

Smoking Cessation

A Report of the Surgeon General



U.S. Department of Health and Human Services

Smoking Cessation: A Report of the Surgeon General

2020

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office of the Surgeon General
Rockville, MD

National Library of Medicine Cataloging-in-Publication Data

Names: United States. Public Health Service. Office of the Surgeon General, issuing body. | National Center for Chronic Disease Prevention and Health Promotion (U.S.). Office on Smoking and Health, issuing body.

Title: Smoking cessation: a report of the Surgeon General.

Other titles: Smoking cessation (Office of the Surgeon General)

Description: Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2020. | Includes bibliographical references.

Subjects: MESH: Smoking Cessation. | United States.

Classification: NLM WM 295



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion
Office on Smoking and Health

For more information

For more information about the Surgeon General's report, visit www.surgeongeneral.gov.

To download copies of this document, go to www.surgeongeneral.gov.

To order copies of this document, go to www.cdc.gov/tobacco and click on Publications Catalog or call 1-800-CDC-INFO (1-800-232-4636); TTY: 1-888-232-6348.

Suggested Citation

U.S. Department of Health and Human Services. *Smoking Cessation. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2020.

Use of trade names is for identification only and does not constitute endorsement by the U.S. Department of Health and Human Services.

Message from Alex M. Azar II

Secretary, U.S. Department of Health and Human Services

Throughout its history, the U.S. Department of Health and Human Services (USDHHS) has led efforts to prevent and reduce the devastating effects of tobacco use, especially the use of combustible tobacco products, as part of its mission to enhance and protect the health and well-being of all Americans. USDHHS has provided critical support in the fields of research and evaluation, program and policy development, public information and education, regulatory activities, systems-level change and management, and clinical practices that has contributed to a dramatic 67% decline in cigarette smoking among U.S. adults since 1965. Support from USDHHS has helped medical and healthcare organizations, government agencies at all levels, and nongovernmental partners create and sustain programs that prevent initiation; help tobacco product users quit; and foster healthy, smokefree environments.

This report is the latest of a longstanding tradition of tobacco prevention and control efforts by USDHHS. Our work includes a comprehensive tobacco control strategic action plan, *Ending the Tobacco Epidemic*, and coordination of tobacco control efforts with related efforts by other federal agencies through the Interagency Committee on Smoking and Health. Reports such as this one from the U.S. Surgeon General give the latest data on tobacco and health to scientists, healthcare professionals, and the public. Research leadership and grant funding through USDHHS's National Institutes of Health contribute to growing knowledge of effective tobacco control strategies and smoking cessation tools. The National Tobacco Control Program, led by the Centers for Disease Control and Prevention (CDC), ensures that these strategies and tools are readily available to state, local, tribal, and territorial public health programs, as well as to partners serving a variety of populations that are disproportionately affected by tobacco use. The U.S. Food and Drug Administration (FDA) regulates the manufacturing, marketing, and sale of tobacco products. Medicare and Medicaid provide smoking cessation tools and support to millions of Americans. Multiple public information campaigns, such as CDC's *Tips From Former Smokers* and FDA's *Every Try Counts*, educate Americans about the significant health risks from smoking and the importance of quitting. Additionally, many agencies in USDHHS provide direct assistance to smokers, including the National Cancer Institute through its Smokefree.gov initiative (<https://smokefree.gov>), and national quitline portal, 1-800-QUIT-NOW.

These and other important efforts are critical to improving the nation's public health. Smoking kills nearly half a million Americans every year, and millions more live with serious chronic diseases caused by smoking. We know that comprehensive interventions at all levels of government and by partners throughout the public health community are extremely effective at preventing and reducing tobacco use. We remain committed to ending the tobacco use epidemic in the United States.

Foreword

Tobacco use remains the number one cause of preventable disease, disability, and death in the United States. Approximately 34 million American adults currently smoke cigarettes, with most of them smoking daily. Nearly all adult smokers have been smoking since adolescence. More than two-thirds of smokers say they want to quit, and every day thousands try to quit. But because the nicotine in cigarettes is highly addictive, it takes most smokers multiple attempts to quit for good.

Today, we know much more about the science of quitting than ever before. Research shows that smokers who use evidence-based tools to help them quit are more likely to succeed than those who do not use such tools, and that using a combination of these tools—for example, calling 1-800-QUIT-NOW and using nicotine replacement therapy, such as the nicotine patch or gum or a prescription medication—raises success rates even higher. Studies also show that policies that prohibit smoking in indoor public places and work spaces and that increase the price of tobacco products promote smoking cessation.

This Surgeon General's report

- Examines the effectiveness of various smoking cessation tools and resources;
- Reviews the health effects of smoking and catalogues the improvements to health that can occur when smokers quit;
- Highlights important new data on populations in which the prevalence of smoking is high and quit rates are low; and
- Identifies gaps in the availability and utilization of programs, policies, and resources that can improve cessation rates and help smokers quit.

Although the benefits of quitting are greater the earlier in life that an individual quits, this report confirms that it is never too late to quit smoking. Even persons who have smoked for many years or who have smoked heavily can realize health and financial benefits from quitting smoking.

The financial toll of smoking is substantial. Each year in the United States, annual healthcare spending attributed to smoking exceeds \$170 billion. Measured against these numbers, comprehensive tobacco prevention and control strategies are extremely cost-effective investments that yield significant returns. For example, the first year of CDC's *Tips From Former Smokers* national campaign prevented thousands of premature deaths in the United States, costing less than \$500 for every smoker who quit.

We know what works to prevent and reduce tobacco use, including how to best help smokers quit for good. Putting this knowledge into action prevents disease, saves lives, and improves the quality of life for all Americans. At CDC, we remain committed to supporting the longstanding national effort to end the tobacco use epidemic and provide all Americans with the opportunity to live tobacco-free.

Robert R. Redfield, M.D.
Director
Centers for Disease Control and Prevention

Preface

from the Surgeon General

One of the most significant public health successes in modern U.S. history has been the reduction in smoking that has occurred during the past half century. Today, the prevalence of cigarette smoking among American adults is at an all-time low, 14%. Although this overall achievement is a source of pride, there is still more work to be done. Today, 16 million Americans are living with a smoking-related disease. In addition to the human costs, smoking places a significant financial burden on Americans, as smoking-attributable healthcare spending exceeds \$170 billion per year.

Research, medical advances, and years of documented experience have given us many tools to tackle the tobacco use epidemic in this country. Although quitting smoking can be a difficult process for many smokers, most say they want to quit, and every year more than half make a serious quit attempt. But only a small portion of smokers who try to quit succeed, and only a small portion use any of the tested and proven aids that will significantly increase their chances of success. This Surgeon General's report on smoking cessation, the 34th report on smoking and health since 1964, examines the most current research on this important issue, identifies barriers to continued success in reducing the prevalence of smoking across all populations, and summarizes evidence-based solutions that can help to eliminate those barriers.

Clinical interventions for smoking cessation are critical if we are to achieve our goal of eliminating the devastating effects of smoking on public health. Primary care physicians, nurses, pharmacists, and other providers in all medical disciplines and in all healthcare environments should take advantage of these opportunities to inform and encourage smokers to quit. Doing so could enable half a million smokers to quit each year.

As a physician, I am acutely aware of the many pressing demands that healthcare providers must address to deliver the highest quality care possible to their patients. At the same time, the evidence in this report clearly points to the tremendous positive impact that healthcare professionals can have on the health and quality of life of their patients and on the public health of our nation—just by helping smokers to quit.

But healthcare professionals alone cannot solve this public health challenge. Everyone has a role in helping to continue to reduce the burden of tobacco use on our society. It is critical that clinical interventions be adopted alongside broader efforts at the health system and population levels to promote and cultivate successful cessation and tobacco-free norms. Even today, with all the gains that have been made over the past few decades, smoking remains the single largest cause of preventable disease and death in the United States. As a nation, we can and must spare no effort to reduce the completely preventable health and financial costs that tobacco smoking has on society.

Jerome M. Adams, M.D., M.P.H.
Vice Admiral, U.S. Public Health Service
Surgeon General of the United States

Acknowledgments

This report was prepared by the U.S. Department of Health and Human Services under the general direction of the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Vice Admiral (VADM) Jerome M. Adams, M.D., M.P.H., Surgeon General, U.S. Public Health Service, Office of the Assistant Secretary for Health, Office of the Surgeon General, Office of the Secretary, U.S. Department of Health and Human Services, Washington, D.C.

Robert R. Redfield, M.D., Director, Centers for Disease Control and Prevention, Atlanta, Georgia.

Dana Shelton, M.P.H., Director (Acting), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Peter A. Briss, M.D., M.P.H., Medical Director, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Rachel Kaufmann, Ph.D., M.P.H., Associate Director for Science, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Corinne Graffunder, Dr.P.H., M.P.H., Director, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Editors of the report were

Rachel A. Grana, Ph.D., M.P.H., Senior Scientific Editor, Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Ann Malarcher, Ph.D., M.S.P.H., Contributing Editor, Consultant, Epidemiologist (Retired), Office on Smoking and Health, National Center for Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Jonathan M. Samet, M.D., M.S., Senior Scientific Editor, Dean and Professor, Colorado School of Public Health, University of Colorado, Aurora, Colorado.

Gillian L. Schauer, Ph.D., M.P.H., Senior Scientific Editor, Senior Consultant (Contractor), Centers for Disease Control and Prevention, Atlanta, Georgia; Clinical Instructor, Department of Health Services, School of Public Health, University of Washington, Seattle, Washington.

Jennifer Unger, Ph.D., Senior Scientific Editor, Professor of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.

Brian A. King, Ph.D. M.P.H., Senior Associate Editor, Deputy Director for Research Translation, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Leslie A. Norman, M.B.A., Managing Editor, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Peter L. Taylor, M.B.A., Technical Editor, Fairfax, Virginia.

Contributing authors were

Robert T. Adsit, M.Ed., Director of Education and Outreach Programs, University of Wisconsin School of Medicine and Public Health, Center for Tobacco Research and Intervention, Madison, Wisconsin.

Anthony J. Alberg, Ph.D., M.P.H., Professor and Chair, Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina.

Erik Augustson, Ph.D., M.P.H., Lead, Smokefree.gov Initiative, Program Director and Health Scientist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Stephen Babb, M.P.H., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Timothy B. Baker, Ph.D., Director of Research, Center for Tobacco Research and Intervention; Professor, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

William Checkley, M.D., Ph.D., Associate Professor of Medicine, Division of Pulmonary and Critical Care, School of Medicine, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland.

Graham A. Colditz, M.D., Dr.P.H., F.A.F.P.H.M., Niess-Gain Professor of Surgery, Professor of Medicine; Chief, Division of Public Health Sciences, Department of Surgery; Associate Director, Prevention and Control, Alvin J. Siteman Cancer Center; Deputy Director, Institute for Public Health, Washington University School of Medicine, St. Louis, Missouri.

MeLisa Creamer, Ph.D., M.P.H., Oak Ridge Institute for Science and Education Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kirsten S. Dorans, Sc.D., Postdoctoral Fellow, Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana.

Lucinda England, M.D., M.S.P.H., Medical Officer, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Brenda Eskenazi, Ph.D., Jennifer and Brian Maxwell Professor of Maternal and Child Health and Epidemiology, Director, Center for Environmental Research and Children's Health, School of Public Health, University of California, Berkeley, California.

Michael C. Fiore, M.D., M.P.H., M.B.A., Hilldale Professor of Medicine, Director, Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Jiang He, M.D., Ph.D., Professor and Joseph S. Copes, M.D. Chair; Department of Epidemiology, School of Public Health and Tropical Medicine; Director, Tulane University Translational Science Institute, Tulane University, New Orleans, Louisiana.

Lauren A. Hunter, M.P.H., Graduate Student Researcher, Division of Epidemiology, School of Public Health, University of California, Berkeley, California.

Eric J. Jacobs, Ph.D., Senior Scientific Director, Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, Georgia.

Ahmed Jamal, M.D., M.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Glenda Lassi, Ph.D., Genomics Project Leader, Centre for Genomics Research, Precision Medicine and Genomics, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Cambridge; Research Fellow, Medical Research Council Integrative Epidemiology Unit, School of Psychological Science, University of Bristol, Bristol, United Kingdom.

Adam M. Leventhal, Ph.D., Director, USC Health, Emotion, and Addiction Laboratory, Professor, Departments of Preventive Medicine and Psychology, University of Southern California, Los Angeles, California.

David T. Levy, Ph.D., Professor, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, D.C.

Maggie Mahoney, J.D., Public Health Analyst, Carter Consulting, Inc. (Contractor), Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Ann Malarcher, Ph.D., M.S.P.H., Contributing Editor, Consultant, Epidemiologist (Retired), Office on Smoking and Health, National Center for Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kristy L. Marynak, M.P.P., Lead Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Tim McAfee, M.D., M.P.H., Senior Medical Officer, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Megan B. Miller, Ph.D., Postdoctoral Fellow, Department of Psychiatry, Yale University, New Haven, Connecticut.

Marcus R. Munafò, Ph.D., Professor of Biological Psychology, School of Psychological Science, University of Bristol, Bristol, United Kingdom.

Christina C. Newton, M.S.P.H., Scientist, Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, Georgia.

Leslie A. Norman, M.B.A., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Michael K. Ong, M.D., Ph.D., Professor in Residence, Division of General Internal Medicine and Health Services Research, Department of Medicine, David Geffen School of Medicine, Department of Health Policy and Management, Jonathan and Karin Fielding School of Public Health, University of California; Chief, Hospitalist Division, Department of Medicine, Veteran's Administration Greater Los Angeles Healthcare System; Chair, State of California Tobacco Education and Research Oversight Committee, Los Angeles, California.

Paul R. Pentel, M.D., Professor of Medicine, Division of Clinical Pharmacology, University of Minnesota; Chief, Pharmacy, Hennepin Healthcare, Minneapolis, Minnesota.

Marina R. Picciotto, Ph.D., Charles B.G. Murphy Professor and Deputy Chair for Basic Science in Psychiatry; Professor of Neuroscience, of Pharmacology, and in the Child Study Center; School of Medicine, Yale University, New Haven, Connecticut.

Judith J. Prochaska, Ph.D., M.P.H., Associate Professor of Medicine, Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, California.

Mays Shamout, M.D., M.P.H., Epidemic Intelligence Service Officer, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sundar Shrestha, Ph.D., Senior Economist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Trishul Siddharthan M.D., Postdoctoral Fellow, Division of Pulmonary and Critical Care Medicine, The Johns Hopkins University, Baltimore, Maryland.

Elliot A. Stein, Ph.D., Chief, Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, Maryland.

Carolyn R. T. Stoll, M.P.H., M.S.W., Staff Scientist, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

Dennis R. Trinidad, Ph.D., M.P.H., Associate Professor, Department of Family Medicine and Public Health, University of California—San Diego, La Jolla, California.

James Tsai, M.D., M.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Michael A. Tynan, Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Rachel F. Tyndale, Ph.D., Canada Research Chair in Pharmacogenomics, Centre for Addiction and Mental Health; Professor, Department of Pharmacology and Toxicology, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.

Graham Warren, M.D., Ph.D., Vice Chairman for Research, Professor, Department of Radiation Oncology, Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston, South Carolina.

Lei Zhang, Ph.D., Health Scientist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Reviewers were

Israel Agaku, D.M.D., Ph.D., M.P.H., Senior Scientist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Brian S. Armour, Ph.D., Associate Director for Science, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Stephen Babb, M.P.H., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

R. Graham Barr, M.D., Dr.P.H., Professor of Medicine and Epidemiology, Columbia University Medical Center, New York, New York.

Neal L. Benowitz, M.D., Professor of Medicine, Bioengineering, and Therapeutic Sciences; Chief, Division of Clinical Pharmacology, University of California, San Francisco, California.

Carla J. Berg, Ph.D., M.B.A., L.P., Associate Professor, Department of Behavioral Sciences and Health Education, Rollins School of Public Health; Associate Director for Population Sciences, Winship Cancer Institute, Emory University Woodruff Health Sciences Center, Atlanta, Georgia.

David Berrigan, Ph.D., M.P.H., Program Director, Health Behaviors Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Michele Bloch, M.D., Ph.D., Chief, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Raymond Boyle, Ph.D., M.P.H., Director of Research Programs, ClearWay Minnesota, Minneapolis, Minnesota.

Thomas H. Brandon, Ph.D., Chair, Department of Health Outcomes and Behavior; Director, Tobacco Research and Intervention Program, Moffitt Cancer Center; Professor, Departments of Psychology and Oncologic Sciences, University of South Florida, Tampa, Florida.

David M. Burns, M.D., Professor Emeritus, Department of Family Medicine and Public Health, University of California—San Diego, School of Medicine, San Diego, California.

Ralph Caraballo, Ph.D., M.P.H., Senior Advisor, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Frank J. Chaloupka, Ph.D., Director, Health Policy Center, Research Professor, Division of Health Policy and Administration, School of Public Health, University of Illinois at Chicago, Chicago, Illinois.

Graham A. Colditz, M.D., Dr.P.H., F.A.F.P.H.M., Niess-Gain Professor of Surgery, Professor of Medicine; Chief, Division of Public Health Sciences, Department of Surgery; Associate Director Prevention and Control, Alvin J. Siteman Cancer Center; Deputy Director, Institute for Public Health, Washington University School of Medicine, St. Louis, Missouri.

Jamie R. Cordova, M.P.H., Cancer Research Training Award Fellow, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

David B. Coultas, M.D., F.A.C.P., Associate Chief of Staff Education, Veterans Affairs Portland Health Care System; Professor of Medicine, Oregon Health and Science University, Portland, Oregon.

Elizabeth Courtney-Long, M.A., M.S.P.H., Deputy Associate Director for Science, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

K. Michael Cummings, Ph.D., M.P.H., Professor, Department of Psychiatry and Behavior Sciences; Co-Leader, Hollings Cancer Center Tobacco Research Program, Medical University of South Carolina, Charleston, South Carolina.

Sue Curry, Ph.D., Interim Executive Vice President and Provost, Distinguished Professor of Health Management and Policy, University of Iowa, Iowa City, Iowa.

Sean P. David, M.D., S.M., D.Phil., Associate Professor of Medicine, Division of Primary Care and Population Health, Stanford University School of Medicine, Palo Alto, California.

Cristine D. Delnevo, Ph.D., M.P.H., Professor and Director, Center for Tobacco Studies, Rutgers School of Public Health, New Brunswick, New Jersey.

Dawn L. DeMeo, M.D., M.P.H., Associate Professor of Medicine, Harvard Medical School; Associate Physician, Channing Division of Network Medicine and the Division of Pulmonary and Critical Care, Brigham and Women's Hospital, Boston, Massachusetts.

Lucinda England, M.D., M.S.P.H., Medical Officer, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Eric J. Feuer, Ph.D., Chief, Statistical Research and Applications Branch, Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Aaron F. Folsom, M.D., M.P.H., Professor, University of Minnesota School of Public Health, Division of Epidemiology and Community Health, Minneapolis, Minnesota.

Neal D. Freedman, Ph.D., M.P.H., Senior Investigator, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland.

Gary A. Giovino, Ph.D., M.S., Professor and Chair, Department of Community Health and Health Behavior, School of Public Health and Health Professions, University at Buffalo, State University of New York (SUNY), Buffalo, New York.

Meredith A. Grady, M.P.H., Co-Lead, Smokefree.gov Initiative, Tobacco Control Research Branch, Behavioral Research Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

David C. Grossman, M.D., M.P.H., Senior Associate Medical Director and Senior Investigator, Kaiser Permanente Washington Health Research Institute; Professor, Department of Health Service; Adjunct Professor, Department of Pediatrics, University of Washington, Seattle, Washington.

Melissa B. Harrell, Ph.D., M.P.H., Associate Professor, The University of Texas Health Science Center at Houston, School of Public Health, Austin Regional Campus, Austin, Texas.

Dorothy K. Hatsukami, Ph.D., Associate Director, Masonic Cancer Center; Professor of Psychiatry, University of Minnesota, Minneapolis, Minnesota.

Stephen T. Higgins, Ph.D., Director, Vermont Center on Behavior and Health, Virginia H. Donaldson Professor of Translational Science, Departments of Psychiatry and Psychological Science; Vice Chair, Department of Psychiatry, University of Vermont, Burlington, Vermont.

Elizabeth S. Holland, M.P.A., Senior Technical Advisor, Quality Measurement and Value-Based Incentives Group, Division of Health Information Technology, Center for Clinical Standards and Quality, Centers for Medicare and Medicaid Services, Baltimore, Maryland.

David Homa, Ph.D., M.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Corinne G. Husten, M.D., M.P.H., Senior Medical Advisor, Office of the Center Director, Center for Tobacco Products, U.S. Food and Drug Administration, Silver Spring, Maryland.

Maki Inoue-Choi, Ph.D., M.S., Staff Scientist, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland.

Prabhat Jha, O.C., M.D., D.Phil., F.C.A.H.S., F.R.S.C., Professor, University of Toronto; Chair in Global Health and Epidemiology, Dalla Lana School of Public Health; Executive Director, Centre for Global Health Research, St. Michael's Hospital, Toronto, Canada.

Michelle C. Kegler, Dr.P.H., M.P.H., Professor, Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, Georgia.

Paul J. Kenny, Ph.D., Ward-Coleman Professor and Chairman, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York.

Chris Kotsen, Psy.D., C.T.T.S., N.C.T.T.P., Lead Psychologist, Tobacco Quitcenter, Lung Cancer Institute, Steeplechase Cancer Center, Robert Wood Johnson Barnabas Health University Hospital Somerset, Somerville, New Jersey.

Thomas E. Kottke, M.D., M.S.P.H., Medical Director for Well-Being and Senior Clinical Investigator, HealthPartners Institute; Professor, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

Stephanie R. Land, Ph.D., Program Director and Statistician, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Frank T. Leone, M.D., M.S., Director, Comprehensive Smoking Treatment Program; Professor, Division of Pulmonary, Allergy and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania.

Douglas E. Levy, Ph.D., Associate Professor of Medicine, Harvard Medical School, Mongan Institute Health Policy Center, Massachusetts General Hospital, Boston, Massachusetts.

Shari M. Ling, M.D., Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services, Baltimore, Maryland.

Jay H. Lubin, Ph.D., National Institutes of Health Scientist Emeritus, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

F. Joseph McClernon, Ph.D., Director, Center for Addiction Science and Technology; Professor, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, North Carolina.

Paul C. Melstrom, Ph.D., Pharm.D., Senior Research Scientist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Glen D. Morgan, Ph.D., Psychologist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Ajay K. Nangia, M.B.B.S., F.A.C.S., Professor and Vice Chair of Urology, Director of Andrology, Department of Urology, University of Kansas Health System, Kansas City, Kansas.

Satomi Odani, M.P.H., Oak Ridge Institute for Science and Education Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

S. Michael Owens, Ph.D., Director, Center for Alcohol and Drug Abuse Studies; Professor, Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Mark Parascandola, Ph.D., M.P.H., Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Terry F. Pechacek, Ph.D., Professor and Interim Division Director of Health Management and Policy, School of Public Health, Georgia State University, Atlanta, Georgia.

Megan E. Piper, Ph.D., Associate Professor, Department of Medicine, School of Medicine and Public Health, University of Wisconsin; Associate Director of Research, University of Wisconsin Center for Tobacco Research and Intervention, Madison, Wisconsin.

Elizabeth A. Platz, Sc.D., M.P.H., Professor, Department of Epidemiology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland.

Elizabeth Reimels, J.D., Associate Director for Policy, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Carolyn Reyes-Guzman, Ph.D., M.P.H., Epidemiologist and Program Director, Tobacco Research Branch, Control Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Nancy A. Rigotti, M.D., Professor of Medicine, Harvard Medical School; Director, Tobacco Research and Treatment Center, Massachusetts General Hospital, Boston, Massachusetts.

Catherine Saucedo, Deputy Director, Smoking Cessation Leadership Center, University of California, San Francisco, California.

Robert Schnoll, Ph.D., Associate Professor and Program Leader, Center for Interdisciplinary Research on Nicotine Addiction, Department of Psychiatry; Associate Director for Population Science and Co-Leader for Tobacco and Environmental Carcinogenesis, Abramson Cancer Center; Senior Fellow, Center for Public Health Initiatives, University of Pennsylvania, Philadelphia, Pennsylvania.

Steven A. Schroeder, M.D., Professor, Distinguished Professorship in Health and Health Care, Department of Medicine; Director, Smoking Cessation Leadership Center, University of California, San Francisco, California.

Donna R. Shelley, M.D., M.P.H., Professor, Department of Population Health; Professor, Department of Medicine, New York University School of Medicine; Co-Director, Section for Tobacco, Alcohol, and Drug Abuse, New York, New York.

Peter G. Shields, M.D., Deputy Director, Comprehensive Cancer Center and James Cancer Hospital; Professor, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio.

Sundar Shrestha, Ph.D., Senior Economist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Lia J. Sorgen, Cancer Research Training Award Fellow, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Frank E. Speizer, M.D., E. H. Kass Distinguished Professor of Medicine, Harvard Medical School, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Margaret R. Spitz, M.D., M.P.H., Professor, Dan L. Duncan Comprehensive Cancer Center, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas.

Meir Stampfer, M.D., Dr.P.H., Professor of Epidemiology and Nutrition, Harvard T.H. Chan School of Public Health, Professor of Medicine, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Linda Topping Streitfeld, M.P.H., Social Science Research Analyst, Center for Medicare and Medicaid Innovation, Centers for Medicare and Medicaid Services, Baltimore, Maryland.

Stephanie Sturgis, M.P.H., Program Analyst, Idoneous Consulting Services (Contractor), Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Van T. Tong, M.P.H., Epidemiologist, Division of Congenital and Developmental Disorders, National Center for Birth Defects and Developmental Disability, Centers for Disease Control and Prevention, Atlanta, Georgia.

Brenna VanFrank, M.D., M.S.P.H., Medical Officer, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Robert E. Vollinger, Jr., Dr.P.H., M.S.P.H., Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Kenneth E. Warner, Ph.D., Avedis Donabedian Distinguished University Professor Emeritus of Public Health and Dean Emeritus, School of Public Health, University of Michigan, Ann Arbor, Michigan.

Gordon B. Willis, Ph.D., Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Shu-Hong Zhu, Ph.D., Director, Center for Research and Intervention in Tobacco Control; Professor, Family Medicine and Public Health, University of California School of Medicine, San Diego, California.

Other contributors were

Katherine J. Asman, M.S.P.H., Statistician, Biostatistics and Epidemiology Division, RTI International, Atlanta, Georgia.

Susan Bratten, Senior Editor, American Institutes for Research, Washington, D.C.

Meghan N. Buran, M.P.H., Senior Professional Research Assistant to Dr. Jonathan M. Samet, Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, Colorado.

Deborah A. Burnette, Expert Consultant, ICF International, Atlanta, Georgia.

Amy de Boynville, Production Design Associate, American Institutes for Research, Washington, D.C.

Phil Esra, Editor, American Institutes for Research, Washington, D.C.

Carolyn Feola Rugamas, Production Design Specialist, American Institutes for Research, Washington, D.C.

Jane Garwood, Senior Editor, American Institutes for Research, Washington, D.C.

Andrea S. Gentzke, Ph.D., M.S., Health Scientist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sondra Hammond, Production Design Associate, American Institutes for Research, Washington, D.C.

William A. Harris, M.M., Northrop Grumman (Contractor), Division of Adolescent and School Health, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sean Hu, M.D., M.S., Dr. P.H., Senior Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Angela Jehle, Director, Publications & Creative Services, American Institutes for Research, Washington, D.C.

Devon LaPoint, Project Associate, American Institutes for Research, Washington, D.C.

Dara L. Ledford, Senior Manager, Production Design, American Institutes for Research, Washington, D.C.

Pamela R. Lemos, M.S., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Yong Liu, M.D., M.S., Statistician, Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Christine C. Maisano, Editor, Prana Enterprises, Inc. (Contractor), American Institutes for Research, Washington, D.C.

Kathleen Major, K Major Editorial Services (Contractor), American Institutes for Research, Washington, D.C.

Kristen N. Mangold, M.S.W., Public Health Advisor, National Cancer Institute, National Institutes of Health, Rockville, Maryland.

Timothy L. McManus, M.S., Lead Health Scientist, Division of Adolescent and School Health, Centers for Disease Control and Prevention, Atlanta, Georgia.

Richard A. Miech, Ph.D., M.P.H., Principal Investigator, Monitoring the Future; Professor, Survey Research Center at the Institute for Social Research, University of Michigan, Ann Arbor, Michigan.

Matthew Mowczko, M.Des., Graphic Design Specialist, American Institutes for Research, Washington, D.C.

Don Mullins, Jr., M.P.H., Project Director, American Institutes for Research, Washington, D.C.

Stephanie Neuben, Editor, American Institutes for Research, Washington, D.C.

Kim O'Brien, Editor, American Institutes for Research, Washington, D.C.

Patrick M. O'Malley, Ph.D., Research Professor, Institute for Social Research, University of Michigan, Ann Arbor, Michigan.

Andrew Peterman, Lead Production Editor, American Institutes for Research, Washington, D.C.

Elyse Phillips, Oak Ridge Institute for Science and Education Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Ketra L. Rice, Ph.D., M.S., M.B.A., Senior Service Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Fatma Romeh Ali, Ph.D., Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Helen A. Sacco, M.S.Ed., Editor, American Institutes for Research, Washington, D.C.

Saida Sharapova, M.D., M.P.H., C.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kathryn E. Szyal, Editorial Assistant, Idoneous Consulting Services (Contractor), Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Wendy E. Theobald, Ph.D., Researcher, University of Wisconsin-Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Stacy Thorne, Ph.D., M.P.H., Health Scientist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sarah Trigger, M.P.H., Social Scientist, Center for Tobacco Products, U.S. Food and Drug Administration, Silver Spring, Maryland.

Katrina Trivers, Ph.D., M.S.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Sharon Wallace, Production Design Specialist, American Institutes for Research, Washington, D.C.

Kimp Walton, M.S., Health Statistician, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Teresa Wang, Ph.D., M.S., Epidemic Intelligence Service Officer, Lieutenant, U.S. Public Health Service, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Karen C. Ward, Production Design Specialist, American Institutes for Research, Washington, D.C.

Xin Xu, Ph.D., Economist, Center for Tobacco Products, U.S. Food and Drug Administration, Silver Spring, Maryland.

Conflict of Interest Disclosures: All senior scientific editors and contributing authors have completed and submitted a conflict of interest disclosure form. Unless otherwise noted below, no potential conflicts of interest were reported. Dr. Glenda Lassi reports being employed by AstraZeneca, a research-based biopharmaceutical company. Dr. Marcus R. Munafò reports receiving grant funding from Pfizer and Rusan Pharma and obtaining products for use in research from GlaxoSmithKline, a company that manufactures smoking cessation products. Dr. Judith J. Prochaska reports having served as an ad hoc advisor to Pfizer Inc, a company that manufactures smoking cessation medications.

Smoking Cessation

Chapter 1 Introduction, Conclusions, and the Evolving Landscape of Smoking Cessation 1

Introduction	3
Organization of the Report	4
Preparation of the Report	5
Scientific Basis of the Report	5
Major Conclusions	6
Chapter Conclusions	7
The Evolving Landscape of Smoking Cessation	12
References	26

Chapter 2 Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth 35

Introduction	37
Data Sources	37
Key Epidemiologic Measures	42
Trends in Current and Former Cigarette Smoking	43
Changing Characteristics of Current Cigarette Smokers	47
Key Disparities in Current Cigarette Smoking Among Adults and Youth	57
Cigarette Smoking Cessation Among Adults and Youth	59
Other Tobacco Products: Use and Cessation	80
Clinical Interventions for Smoking Cessation: Prevalence and Trends	86
Key Disparities in Cessation Among Adults	100
Summary of the Evidence and Implications	102
Conclusions	104
References	105

Chapter 2 Appendices 111

Appendix 2.1: Sources of Data	113
Appendix 2.2: Measures of Cessation	116
References	121

Chapter 3 New Biological Insights into Smoking Cessation 123

Introduction	125
Cell and Molecular Biology of Nicotine Addiction	125
Vaccines and Other Immunotherapies as Treatments for Nicotine Addiction	137
Insights into Smoking Cessation from the Field of Neurobiology	139
Genetic Studies of Smoking Phenotypes	147
Summary of the Evidence	155
Conclusions	157
References	158

Chapter 4 The Health Benefits of Smoking Cessation 173

Introduction	177
Methodologic Challenges	177
Cancer	177
Smoking Cessation After a Cancer Diagnosis	206

Cardiovascular Disease	214
Smoking Cessation After a Diagnosis of Coronary Heart Disease	270
Chronic Respiratory Disease	305
Reproductive Health	320
References	402
Chapter 5 The Benefits of Smoking Cessation on Overall Morbidity, Mortality, and Economic Costs	437
Introduction	439
Benefits of Smoking Cessation on Overall Morbidity	439
Benefits of Smoking Cessation on All-Cause Mortality	461
Benefits of Smoking Cessation on Economic Costs	465
Summary of the Evidence	485
Conclusions	485
References	486
Chapter 6 Interventions for Smoking Cessation and Treatments for Nicotine Dependence	493
Introduction	495
Literature Review Methods	496
Behavioral and Psychological Treatments	496
Pharmacologic Treatments	509
Teachable Moments	532
Considerations for Subpopulations	537
Emerging Intervention Approaches	544
Summary of the Evidence	546
Conclusions	547
References	549
Chapter 7 Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation	577
Introduction	579
Literature Review Methods	579
Clinical- and Health System-Based Strategies on Smoking Cessation	581
Population-Based Strategies on Smoking Cessation	598
Modeling to Assess the Impact of Policy and Regulatory Changes on Cessation	613
Limitations and Methodologic Gaps	617
Summary of the Evidence	618
Conclusions	619
References	620
Chapter 8 A Vision for the Future	641
Introduction	643
Past: Historical Perspective	643
Present: Health Benefits of Cessation	649
Future: Ending the Tobacco Use Epidemic	651
References	661
List of Abbreviations	665
List of Tables and Figures	671

Chapter 1

Introduction, Conclusions, and the Evolving Landscape of Smoking Cessation

Introduction 3

Organization of the Report 4

Preparation of the Report 5

Scientific Basis of the Report 5

Major Conclusions 6

Chapter Conclusions 7

Chapter 2: Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth 7

Chapter 3: New Biological Insights into Smoking Cessation 7

Chapter 4: The Health Benefits of Smoking Cessation 8

Cancer 8

Smoking Cessation After a Cancer Diagnosis 8

Cardiovascular Disease 8

Smoking Cessation After a Diagnosis of Coronary Heart Disease 9

Chronic Respiratory Disease 9

Reproductive Health 9

Chapter 5: The Benefits of Smoking Cessation on Overall Morbidity, Mortality, and Economic Costs 10

Chapter 6: Interventions for Smoking Cessation and Treatments for Nicotine Dependence 10

Chapter 7: Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation 11

The Evolving Landscape of Smoking Cessation 12

Historical Context of Smoking Cessation 12

Addiction Versus Habit 12

Coverage of Smoking Cessation, Nicotine, and Addiction in Surgeon General's Reports 13

Coverage of Smoking Cessation 13

Coverage of Nicotine and Addiction 14

Perspectives on Smoking Cessation 15

Development and Evolution of a Paradigm for Treating Nicotine Addiction 15

Epidemiologic Shifts in Smoking Cessation 16

Changes in the Patterns of Smoking and Population Characteristics of Smokers 16

Changes in the Products Used by Smokers 16

Developments in Approaches to Smoking Cessation at the Individual Level 17

Pharmacotherapy 17

Behavioral Interventions 17

Treating Tobacco Use and Dependence 18

Evolution of Approaches to Smoking Cessation at the Population Level 19

More Intensity Versus Higher Reach of Support Services 19

Population-Based Interventions 20

Quitlines	20
Mass Media Campaigns	20
Healthcare Systems	21
Health Insurance Coverage	22
E-Cigarettes: Potential Impact on Smoking Cessation	23
Implications of E-Cigarette Characteristics for Smoking Cessation	23
Summary	24
References	26

Introduction

Tobacco smoking is the leading cause of preventable disease, disability, and death in the United States (U.S. Department of Health and Human Services [USDHHS] 2014). Smoking harms nearly every organ in the body and costs the United States billions of dollars in direct medical costs each year (USDHHS 2014). Although considerable progress has been made in reducing cigarette smoking since the first U.S. Surgeon General's report was released in 1964 (USDHHS 2014), in 2018, 13.7% of U.S. adults (34.2 million people) were still current cigarette smokers (Creamer et al. 2019). One of the main reasons smokers keep smoking is nicotine (USDHHS 1988). Nicotine, a drug found naturally in the tobacco plant, is highly addictive, as with such drugs as cocaine and heroin; activates the brain's reward circuits; and reinforces repeated nicotine exposure (USDHHS 1988, 2010, 2014; National Institute on Drug Abuse [NIDA] 2018).

The majority of cigarette smokers (68%) want to quit smoking completely (Babb et al. 2017). The 1990 Surgeon General's report, *The Health Benefits of Smoking Cessation*, was the last Surgeon General's report to focus on current research on smoking cessation and to predominantly review the health benefits of quitting smoking (USDHHS 1990). Because of limited data at that time, the 1990 report did not review the determinants, processes, or outcomes of attempts at smoking cessation. Pharmacotherapy for smoking cessation was not introduced until the 1980s. Additionally, behavioral and other counseling approaches were slow to develop and not widely available at the time of the 1990 report because few were covered under health insurance, and programs such as group counseling sessions were hard for smokers to access, even by those who were motivated to quit (Fiore et al. 1990).

The purpose of this report is to update and expand the 1990 Surgeon General's report based on new scientific evidence about smoking cessation. Since 1990, the scientific literature has expanded greatly on the determinants and processes of smoking cessation, informing the development of interventions that promote cessation and help smokers quit (Fiore et al. 2008; Schlam and Baker 2013). This knowledge and other major developments have transformed the landscape of smoking cessation in the United States. This report summarizes this enhanced knowledge and specifically reviews patterns and trends of smoking cessation; biologic mechanisms; various health benefits; overall morbidity, mortality, and economic benefits; interventions; and strategies that promote smoking cessation.

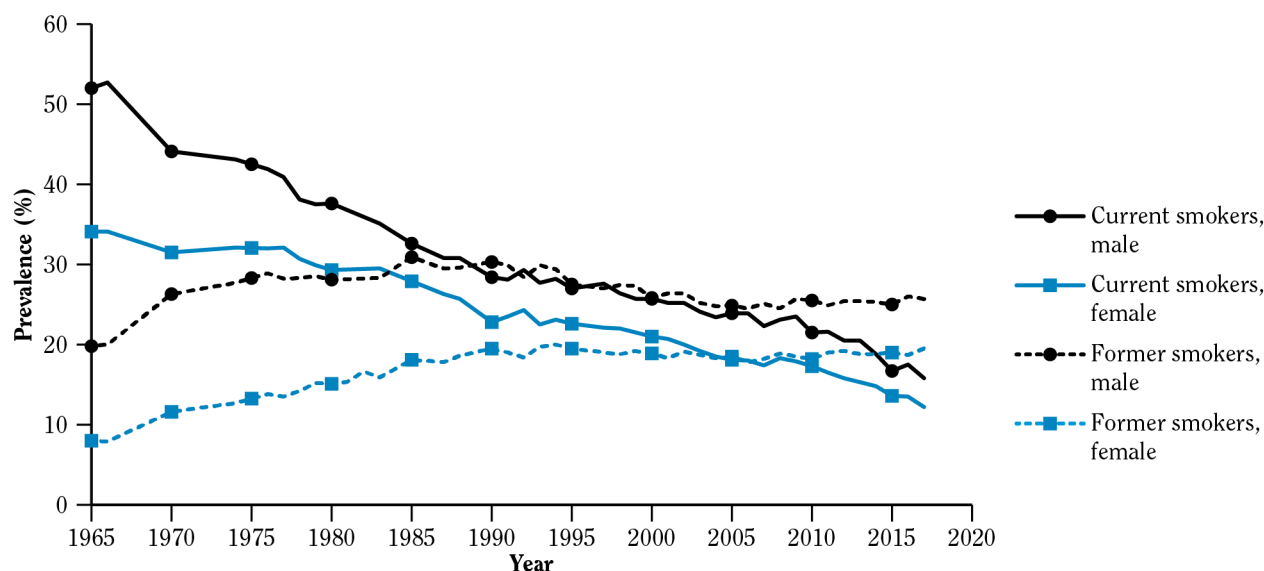
From 1965 to 2017, the prevalence of current smoking declined from 52.0% to 15.8% (relative percent

change: 69.6%) among men and from 34.1% to 12.2% (relative percent change: 64.2%) among women (Figure 1.1). These declines have been attributed, in part, to progress made in smoking cessation since the 1960s, which has continued since the 1990 Surgeon General's report. Specifically, clinical, scientific, and public health communities have increasingly embraced and acted upon the concept of tobacco use and dependence as a health condition that can benefit from treatment in various forms and levels of intensity. Accordingly, a considerable range of effective pharmacologic and behavioral smoking cessation treatment options are now available. As of October 16, 2019, the U.S. Food and Drug Administration (FDA) has approved five nicotine replacement therapies (NRTs) and two non-nicotine oral medications to help smokers quit, and the use of these treatments has expanded, including stronger integration with counseling support (Fiore et al. 2008).

In addition, the reach of smoking cessation interventions has increased substantially since 1990 with the emergence of innovative, population-level interventions and policies that motivate smokers to quit and raise awareness of the health benefits of smoking cessation (McAfee et al. 2013). This includes policies, such as comprehensive smokefree laws, that have been shown to promote cessation at the population level in addition to reducing exposure to secondhand smoke (USDHHS 2014). The development and subsequent expansion of telephone call centers ("quitlines"), mobile phone technologies, Internet-based applications, and other innovations have created novel platforms to provide behavioral and pharmacologic smoking cessation treatments (Ghorai et al. 2014). However, the continued diversification of the tobacco product landscape could have several different potential impacts, ranging from accelerating the rates of complete cessation among adult smokers to erasing progress in reducing all forms of use of tobacco products, especially among youth and young adults. For example, the increasing availability and rapidly increasing use of novel tobacco products, most notably electronic cigarettes (e-cigarettes), raise questions about the potential impact that such products could have on efforts to eliminate disease and death caused by tobacco use at the individual and population levels. Therefore, when considering the impact of e-cigarettes on public health, it is critical to evaluate their effects on both adults and youth.

Collectively, the changes cited in this report provide new opportunities and challenges for understanding and promoting smoking cessation in the United States. However, the evidence-based clinical-, health system-, and population-based tobacco prevention, control, and

Figure 1.1 Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 2017, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

cessation strategies that are outlined in this report are a necessary but insufficient means to end the tobacco epidemic. Reaching the finish line will require coordination across federal government agencies and other government

and non-government stakeholders at the national, state, and local levels. To achieve success, we must work together to maximize resources and coordinate efforts across a wide range of stakeholders.

Organization of the Report

This chapter summarizes the report, identifies its major conclusions, and presents the conclusions from each chapter. It also offers an overview of the evolving landscape of smoking cessation and key developments since the 1990 Surgeon General’s report. Chapter 2 (“Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth”) documents key patterns and trends in cigarette smoking cessation in the United States among adults overall (persons 18 years of age and older), young adults (18–24 years of age), and youth (12–17 years of age). The chapter also reviews the changing demographic- and smoking-related characteristics of cigarette smokers with a focus on how these changes may influence future trends in cessation. Chapter 3 (“New Biological Insights into Smoking Cessation”) reviews several areas of intensive research since the 2010 Surgeon General’s report on how tobacco smoke causes disease: cellular and molecular biology of nicotine addiction; vaccines and other immunotherapies as

treatments for tobacco addiction; neurobiological insights into smoking cessation obtained from noninvasive neuroimaging; and genetics of smoking behaviors and cessation. Chapter 4 (“The Health Benefits of Smoking Cessation”) reviews the more recent findings on disease risks from smoking and benefits after smoking cessation for major types of chronic diseases, including cardiovascular and respiratory systems, cancer, and a wide range of reproductive outcomes. Chapter 5 (“The Benefits of Smoking Cessation on Overall Morbidity, Mortality, and Economic Costs”) discusses general indicators of health that change after smoking cessation, the health benefits of smoking cessation on all-cause mortality, and the economic benefits of smoking cessation. Chapter 6 (“Interventions for Smoking Cessation and Treatments for Nicotine Dependence”) reviews the evidence on current and emerging treatments for smoking cessation, including research that has been conducted since the 2008 U.S. Public Health Service’s

Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update* (Fiore et al. 2008). Chapter 7 (“Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation”) focuses on clinical-, system-, and population-level strategies that combine individual components of treatment for smoking cessation with

routine clinical care, making cessation interventions available and accessible to individual smokers and creating conditions whereby smokers are informed of these interventions and are motivated to use them. Chapter 8 (“A Vision for the Future”) outlines broad strategies to accelerate the progress that has been made in helping smokers quit.

Preparation of the Report

This Surgeon General’s report was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC), which is part of USDHHS. This report was compiled using a longstanding, peer-reviewed, balanced, and comprehensive process designed to safeguard the scientific rigor and practical relevance from influences that could adversely affect impartiality (King et al. 2018). This process helps to ensure that the report’s conclusions are defined by the evidence, rather than the opinions of the authors and editors. In brief, under the leadership of a senior scientific editorial team, 32 experts wrote the initial drafts of the chapters. The experts were selected for their knowledge of the topics addressed. These contributions, which are summarized in Chapters 1–7, were evaluated by 46 peer reviewers. After this initial stage of peer review, more than 20 senior scientists and other

experts examined the scientific integrity of the entire manuscript as part of a second stage of peer review. After each round of peer review, the report’s scientific editors revised each draft based on reviewers’ comments. Chapter 8, which summarizes and is founded upon the preceding content in the report, was written by the senior scientific editorial team once the content in Chapters 1–7 completed peer review. Subsequently, the report was reviewed by various institutes and agencies in the U.S. government, including USDHHS. Throughout the review process, the content of each chapter was revised to include studies and information that were not available when the chapters were first drafted; updates were made until shortly before the report was submitted for publication. These updates reflect the full scope of identified evidence, including new findings that confirm, refute, or refine the initial content. Conclusions are based on the preponderance and quality of scientific evidence.

Scientific Basis of the Report

The statements and conclusions throughout this report are based on an extensive review of the existing scientific literature. Thus, the report focuses primarily on cessation in the context of adults because this is the population for which the preponderance of scientific literature exists on this topic; however, data on youth and young adults are also presented, when available. The report primarily cites peer-reviewed journal articles, including reviews that integrate findings from numerous studies and books that were published between 2000 and 2018, which reflects a period after the last Surgeon General’s report on the topic of cessation. This report also refers, on occasion, to unpublished research, such as presentations at professional meetings, personal communications from researchers, and information available in various media. These references are used when acknowledged by the editors and reviewers as being scientifically valid and reliable, and a critical addition to the emerging literature on a topic. Throughout the writing and review process, highest priority was given to peer-reviewed, scientific research

that is free from tobacco industry interests. As noted in the 2014 Surgeon General’s report, the tobacco industry has a well-documented record of manipulating scientific information about the extent of the harms from cigarette smoking (USDHHS 2014).

Following the model of the 1964 report, this Surgeon General’s report includes comprehensive compilations of the evidence on smoking cessation. The evidence was analyzed to identify causal associations according to enunciated principles, sometimes referred to as the “Surgeon General’s criteria” or the “Hill” criteria (after Sir Austin Bradford Hill) for causality. The criteria, offered in Chapter 3 of the 1964 report, included

- Consistency of the association,
- Strength of the association,
- Specificity of the association,

- Temporal relationship of the association, and
- Coherence of the association (U.S. Department of Health, Education, and Welfare [USDHEW] 1964, p. 20).

In the 2004 Surgeon General's report (USDHHS 2004), the framework for interpreting evidence on smoking and health was revisited in depth for the first time since the 1964 report. The 2004 report provided a four-level hierarchy of categories for interpreting evidence, and this current report follows the same model:

- a. "Evidence is **sufficient** to infer a causal relationship.
- b. Evidence is **suggestive but not sufficient** to infer a causal relationship.
- c. Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
- d. Evidence is **suggestive of no causal relationship**" (USDHHS 2004, p. 18).

Answers to several questions helped to guide judgment toward these categories:

- Do multiple high-quality studies show a consistent association between smoking and disease?

- Are the measured effects large enough and statistically strong?
- Does the evidence show that smoking occurs before the disease occurs (a temporal association)?
- Is the relationship between smoking and disease coherent or plausible in terms of known scientific principles, biologic mechanisms, and observed patterns of disease?
- Is there a dose-response relationship between smoking and disease?
- Is the risk of disease reduced after quitting smoking?

The categories acknowledge that evidence can be "suggestive but not sufficient" to infer a causal relationship, and the categories allow for evidence that is "suggestive of no causal relationship." This framework also separates conclusions about causality from the implications of such conclusions. Inference is sharply and completely separated from policy or research implications of the conclusions, thus adhering to the approach established in the 1964 report. However, consistent with past Surgeon General's reports on tobacco, conclusions are not limited to just causal determinations and frequently include recommendations for research, policies, or other actions.

Major Conclusions

1. Smoking cessation is beneficial at any age. Smoking cessation improves health status and enhances quality of life.
2. Smoking cessation reduces the risk of premature death and can add as much as a decade to life expectancy.
3. Smoking places a substantial financial burden on smokers, healthcare systems, and society. Smoking cessation reduces this burden, including smoking-attributable healthcare expenditures.
4. Smoking cessation reduces risk for many adverse health effects, including reproductive health outcomes, cardiovascular diseases, chronic obstructive pulmonary disease, and cancer. Quitting smoking is also beneficial to those who have been diagnosed with heart disease and chronic obstructive pulmonary disease.
5. More than three out of five U.S. adults who have ever smoked cigarettes have quit. Although a majority of cigarette smokers make a quit attempt each year, less than one-third use cessation medications approved by the U.S. Food and Drug Administration or behavioral counseling to support quit attempts.
6. Considerable disparities exist in the prevalence of smoking across the U.S. population, with higher prevalence in some subgroups. Similarly, the prevalence of key indicators of smoking cessation—quit attempts, receiving advice to quit from a health professional, and using cessation therapies—also varies across the population, with lower prevalence in some subgroups.

7. Smoking cessation medications approved by the U.S. Food and Drug Administration and behavioral counseling are cost-effective cessation strategies. Cessation medications approved by the U.S. Food and Drug Administration and behavioral counseling increase the likelihood of successfully quitting smoking, particularly when used in combination. Using combinations of nicotine replacement therapies can further increase the likelihood of quitting.
8. Insurance coverage for smoking cessation treatment that is comprehensive, barrier-free, and widely promoted increases the use of these treatment services, leads to higher rates of successful quitting, and is cost-effective.
9. E-cigarettes, a continually changing and heterogeneous group of products, are used in a variety of ways. Consequently, it is difficult to make generalizations about efficacy for cessation based on clinical trials involving a particular e-cigarette, and there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation.
10. Smoking cessation can be increased by raising the price of cigarettes, adopting comprehensive smoke-free policies, implementing mass media campaigns, requiring pictorial health warnings, and maintaining comprehensive statewide tobacco control programs.

Chapter Conclusions

Chapter 2: Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth

1. In the United States, more than three out of every five adults who were ever cigarette smokers have quit smoking.
2. Past-year quit attempts and recent and longer term cessation have increased over the past 2 decades among adult cigarette smokers.
3. Marked disparities in cessation behaviors, such as making a past-year quit attempt and achieving recent successful cessation, persist across certain population subgroups defined by educational attainment, poverty status, age, health insurance status, race/ethnicity, and geography.
4. Advice from health professionals to quit smoking has increased since 2000; however, four out of every nine adult cigarette smokers who saw a health professional during the past year did not receive advice to quit.
5. Use of evidence-based cessation counseling and/or medications has increased among adult cigarette smokers since 2000; however, more than two-thirds of adult cigarette smokers who tried to quit during the past year did not use evidence-based treatment.
6. A large proportion of adult smokers report using non-evidence-based approaches when trying to quit smoking, such as switching to other tobacco products.

Chapter 3: New Biological Insights into Smoking Cessation

1. The evidence is suggestive but not sufficient to infer that increasing glutamate transport can alleviate nicotine withdrawal symptoms and prevent relapse.
2. The evidence is suggestive but not sufficient to infer that neuropeptide systems play a role in multiple stages of the nicotine addiction process, and that modulating the function of certain neuropeptides can reduce smoking behavior in humans.
3. The evidence is suggestive but not sufficient to infer that targeting the habenulo-interpeduncular pathway with agents that increase the aversive properties of nicotine are a useful therapeutic target for smoking cessation.
4. The evidence is suggestive but not sufficient to infer that vaccines generating adequate levels of nicotine-specific antibodies can block the addictive effects of nicotine and aid smoking cessation.
5. The evidence is suggestive but not sufficient to infer that dysregulated brain circuits, including prefrontal and cingulate cortical regions and their connections with various striatal and insula loci, can serve as novel therapeutic targets for smoking cessation.
6. The evidence is suggestive but not sufficient to infer that the effectiveness of nicotine replacement therapy may vary across specific genotype groups.

Chapter 4: The Health Benefits of Smoking Cessation

Cancer

1. The evidence is sufficient to infer that smoking cessation reduces the risk of lung cancer.
2. The evidence is sufficient to infer that smoking cessation reduces the risk of laryngeal cancer.
3. The evidence is sufficient to infer that smoking cessation reduces the risk of cancers of the oral cavity and pharynx
4. The evidence is sufficient to infer that smoking cessation reduces the risk of esophageal cancer.
5. The evidence is sufficient to infer that smoking cessation reduces the risk of pancreatic cancer.
6. The evidence is sufficient to infer that smoking cessation reduces the risk of bladder cancer.
7. The evidence is sufficient to infer that smoking cessation reduces the risk of stomach cancer.
8. The evidence is sufficient to infer that smoking cessation reduces the risk of colorectal cancer.
9. The evidence is sufficient to infer that smoking cessation reduces the risk of liver cancer.
10. The evidence is sufficient to infer that smoking cessation reduces the risk of cervical cancer.
11. The evidence is sufficient to infer that smoking cessation reduces the risk of kidney cancer.
12. The evidence is sufficient to infer that smoking cessation reduces the risk of acute myeloid leukemia.
13. The evidence is sufficient to infer that the relative risk of lung cancer decreases steadily after smoking cessation compared with the risk for persons continuing to smoke, with risk decreasing to half that of continuing smokers approximately 10–15 years after smoking cessation and decreasing further with continued cessation.

Smoking Cessation After a Cancer Diagnosis

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking cessation

and improved all-cause mortality in cancer patients who are current smokers at the time of a cancer diagnosis.

Cardiovascular Disease

1. The evidence is sufficient to infer that smoking cessation reduces levels of markers of inflammation and hypercoagulability and leads to rapid improvement in the level of high-density lipoprotein cholesterol.
2. The evidence is sufficient to infer that smoking cessation leads to a reduction in the development of subclinical atherosclerosis, and that progression slows as time since cessation lengthens.
3. The evidence is sufficient to infer that smoking cessation reduces the risk of cardiovascular morbidity and mortality and the burden of disease from cardiovascular disease.
4. The evidence is sufficient to infer that the relative risk of coronary heart disease among former smokers compared with never smokers falls rapidly after cessation and then declines more slowly.
5. The evidence is sufficient to infer that smoking cessation reduces the risk of stroke morbidity and mortality.
6. The evidence is sufficient to infer that, after smoking cessation, the risk of stroke approaches that of never smokers.
7. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of atrial fibrillation.
8. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of sudden cardiac death among persons without coronary heart disease.
9. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of heart failure among former smokers compared with persons who continue to smoke.
10. Among patients with left-ventricular dysfunction, the evidence is suggestive but not sufficient to infer that smoking cessation leads to increased survival and reduced risk of hospitalization for heart failure.

11. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of venous thromboembolism.
12. The evidence is suggestive but not sufficient to infer that smoking cessation substantially reduces the risk of peripheral arterial disease among former smokers compared with persons who continue to smoke, and that this reduction appears to increase with time since cessation.
13. The evidence is suggestive but not sufficient to infer that, among patients with peripheral arterial disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival.
14. The evidence is sufficient to infer that smoking cessation substantially reduces the risk of abdominal aortic aneurysm in former smokers compared with persons who continue to smoke, and that this reduction increases with time since cessation.
15. The evidence is suggestive but not sufficient to infer that smoking cessation slows the expansion rate of abdominal aortic aneurysm.

Smoking Cessation After a Diagnosis of Coronary Heart Disease

1. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and a reduction in all-cause mortality.
2. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reductions in deaths due to cardiac causes and sudden death.
3. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reduced risk of new and recurrent cardiac events.

Chronic Respiratory Disease

Chronic Obstructive Pulmonary Disease

1. Smoking cessation remains the only established intervention to reduce loss of lung function over time

among persons with chronic obstructive pulmonary disease and to reduce the risk of developing chronic obstructive pulmonary disease in cigarette smokers.

2. The evidence is suggestive but not sufficient to infer that airway inflammation in cigarette smokers persists months to years after smoking cessation.
3. The evidence is suggestive but not sufficient to infer that changes in gene methylation and profiles of proteins occur after smoking cessation.
4. The evidence is inadequate to infer the presence or absence of a relationship between smoking cessation and changes in the lung microbiome.

Asthma

1. The evidence is suggestive but not sufficient to infer that smoking cessation reduces asthma symptoms and improves treatment outcomes and asthma-specific quality-of-life scores among persons with asthma who smoke.
2. The evidence is suggestive but not sufficient to infer that smoking cessation improves lung function among persons with asthma who smoke.

Reproductive Health

1. The evidence is sufficient to infer that smoking cessation by pregnant women benefits their health and that of their fetuses and newborns.
2. The evidence is inadequate to infer that smoking cessation before or during early pregnancy reduces the risk of placental abruption compared with continued smoking.
3. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of placenta previa compared with continued smoking.
4. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of premature rupture of the membranes compared with continued smoking.
5. The evidence is inadequate to infer that smoking during early or mid-pregnancy alone, and not during late pregnancy, is associated with a reduced risk of preeclampsia.

6. The evidence is sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than those who continue to smoke.
7. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than nonsmokers.
8. The evidence is inadequate to infer that smoking cessation during pregnancy increases the risk of gestational diabetes.
9. The evidence is sufficient to infer that smoking cessation during pregnancy reduces the effects of smoking on fetal growth and that quitting smoking early in pregnancy eliminates the adverse effects of smoking on fetal growth.
10. The evidence is inadequate to determine the gestational age before which smoking cessation should occur to eliminate the effects of smoking on fetal growth.
11. The evidence is sufficient to infer that smoking cessation before or during early pregnancy reduces the risk for a small-for-gestational-age birth compared with continued smoking.
12. The evidence is suggestive but not sufficient to infer that women who quit smoking before conception or during early pregnancy have a reduced risk of preterm delivery compared with women who continue to smoke.
13. The evidence is suggestive but not sufficient to infer that the risk of preterm delivery in women who quit smoking before or during early pregnancy does not differ from that of nonsmokers.
14. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of stillbirth.
15. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of perinatal mortality among smokers.
16. The evidence is inadequate to infer that women who quit smoking before or during early pregnancy have a reduced risk for infant mortality compared with continued smokers.
17. The evidence is inadequate to infer an association between smoking cessation, the timing of cessation, and female fertility or fecundity.
18. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of earlier age at menopause compared with continued smoking.
19. The evidence is inadequate to infer that smoking cessation reduces the effects of smoking on male fertility and sperm quality.
20. The evidence is suggestive but not sufficient to infer that former smokers are at increased risk of erectile dysfunction compared with never smokers.
21. The evidence is inadequate to infer that smoking cessation reduces the risk of erectile dysfunction compared with continued smoking.

Chapter 5: The Benefits of Smoking Cessation on Overall Morbidity, Mortality, and Economic Costs

1. The evidence is sufficient to infer that smoking cessation improves well-being, including higher quality of life and improved health status.
2. The evidence is sufficient to infer that smoking cessation reduces mortality and increases the lifespan.
3. The evidence is sufficient to infer that smoking exacts a high cost for smokers, healthcare systems, and society.
4. The evidence is sufficient to infer that smoking cessation interventions are cost-effective.

Chapter 6: Interventions for Smoking Cessation and Treatments for Nicotine Dependence

1. The evidence is sufficient to infer that behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment.
2. The evidence is sufficient to infer that behavioral counseling and cessation medications are independently

effective in increasing smoking cessation, and even more effective when used in combination.

3. The evidence is sufficient to infer that proactive quit-line counseling, when provided alone or in combination with cessation medications, increases smoking cessation.
4. The evidence is sufficient to infer that short text message services about cessation are independently effective in increasing smoking cessation, particularly if they are interactive or tailored to individual text responses.
5. The evidence is sufficient to infer that web or Internet-based interventions increase smoking cessation and can be more effective when they contain behavior change techniques and interactive components.
6. The evidence is inadequate to infer that smartphone apps for smoking cessation are independently effective in increasing smoking cessation.
7. The evidence is sufficient to infer that combining short- and long-acting forms of nicotine replacement therapy increases smoking cessation compared with using single forms of nicotine replacement therapy.
8. The evidence is suggestive but not sufficient to infer that pre-loading (e.g., initiating cessation medication in advance of a quit attempt), especially with the nicotine patch, can increase smoking cessation.
9. The evidence is suggestive but not sufficient to infer that very-low-nicotine-content cigarettes can reduce smoking and nicotine dependence and increase smoking cessation when full-nicotine cigarettes are readily available; the effects on cessation may be further strengthened in an environment in which conventional cigarettes and other combustible tobacco products are not readily available.
10. The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation. However, the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine, and the evidence is suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes.
11. The evidence is sufficient to infer that certain life events—including hospitalization, surgery, and

lung cancer screening—can trigger attempts to quit smoking, uptake of smoking cessation treatment, and smoking cessation.

12. The evidence is suggestive but not sufficient to infer that fully and consistently integrating standardized, evidence-based smoking cessation interventions into lung cancer screening increases smoking cessation while avoiding potential adverse effects of this screening on cessation outcomes.
13. The evidence is suggestive but not sufficient to infer that cytisine increases smoking cessation.

Chapter 7: Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation

1. The evidence is sufficient to infer that the development and dissemination of evidence-based clinical practice guidelines increase the delivery of clinical interventions for smoking cessation.
2. The evidence is sufficient to infer that with adequate promotion, comprehensive, barrier-free, evidence-based cessation insurance coverage increases the availability and utilization of treatment services for smoking cessation.
3. The evidence is sufficient to infer that strategies that link smoking cessation-related quality measures with payments to clinicians, clinics, or health systems increase the rate of delivery of clinical treatments for smoking cessation.
4. The evidence is sufficient to infer that tobacco quit-lines are an effective population-based approach to motivate quit attempts and increase smoking cessation.
5. The evidence is suggestive but not sufficient to infer that electronic health record technology increases the rate of delivery of smoking cessation treatments.
6. The evidence is sufficient to infer that increasing the price of cigarettes reduces smoking prevalence, reduces cigarette consumption, and increases smoking cessation.
7. The evidence is sufficient to infer that smokefree policies reduce smoking prevalence, reduce cigarette consumption, and increase smoking cessation.

8. The evidence is sufficient to infer that mass media campaigns increase the number of calls to quitlines and increase smoking cessation.
9. The evidence is sufficient to infer that comprehensive state tobacco control programs reduce smoking prevalence, increase quit attempts, and increase smoking cessation.
10. The evidence is sufficient to infer that large, pictorial health warnings increase smokers' knowledge about the health harms of smoking, interest in quitting, and quit attempts and decrease smoking prevalence.
11. The evidence is suggestive but not sufficient to infer that plain packaging increases smoking cessation.
12. The evidence is suggestive but not sufficient to infer that decreasing the retail availability of tobacco products and exposure to point-of-sale tobacco marketing and advertising increases smoking cessation.
13. The evidence is suggestive but not sufficient to infer that restricting the sale of certain types of tobacco products, such as menthol and other flavored products, increases smoking cessation, especially among certain populations.

The Evolving Landscape of Smoking Cessation

This section of the chapter reviews the history of smoking cessation, from its early origins to the modern era, including the changes that have occurred since publication of the 1990 Surgeon General's report. It also highlights developments that have shaped current initiatives in smoking cessation and will set the stage for the chapters that follow. Finally, this section highlights a broad set of interventions that have been implemented over the past three decades and are proven to be effective at helping people quit successfully. These interventions, which are now being integrated into clinical care and societal policies, include (a) low-intensity interventions, such as telephone quitlines; (b) brief but systematically repeated interventions in primary care settings; (c) over-the-counter medications; and (d) public policy approaches, such as increases in tobacco prices (e.g., through taxation), comprehensive policies to make indoor environments smokefree, and mass media campaigns that increase motivation to quit and may help sustain quit attempts (CDC 2014a; USDHHS 2014).

Historical Context of Smoking Cessation

Addiction Versus Habit

In 2017, a federal court ordered the major U.S. tobacco companies to run television and newspaper ads that tell the American public the truth about the dangers of smoking and secondhand smoke (U.S. Department of Justice 2017b). The ads included several statements related to the addictiveness of nicotine:

- “Smoking is highly addictive. Nicotine is the addictive drug in tobacco”;

- “Cigarette companies intentionally designed cigarettes with enough nicotine to create and sustain addiction”;
- “It’s not easy to quit”; and
- “When you smoke, the nicotine actually changes the brain—that’s why quitting is so hard” (U.S. Department of Justice 2017a; Farber et al. 2018, p. 128).

However, previously secret documents from the tobacco industry reveal that the tobacco industry was aware of the addictive nature of nicotine for decades, long before they publicly acknowledged it or were eventually ordered by the court to publicly acknowledge it (Elias et al. 2018). In fact, the tobacco industry had been engineering cigarettes for decades to improve the rapid delivery of nicotine (Proctor 2011). For years, the tobacco industry coordinated well-financed, systematic efforts to deny the addictiveness of nicotine and the need for users to quit smoking, thereby trivializing the harms of tobacco use while promoting the benefits of nicotine (Hirschhorn 2009; USDHHS 2014). The industry did this using well-documented tactics, including aggressive funding and support for academic, medical, and community organizations that were sympathetic to this perspective (Proctor 2011).

Addiction to any substance often brings on a variety of efforts to overcome or treat it. However, until the late twentieth century, clinical and public health approaches to smoking cessation often treated smoking as a habit rather than as an addiction (USDHEW 1964). The tobacco industry has asserted for many years in public messaging and litigation that smoking is a personal choice (Friedman et al. 2015). Indeed, both smoking and smoking cessation were considered personal choices; the idea was that

if persons started smoking cigarettes, they could quit if they truly wanted to, putting the onus on the individual smoker to quit using his or her own motivation and desire to do so. The Surgeon General first concluded in 1988 that “cigarettes and other forms of tobacco are addicting,” and “nicotine is the drug in tobacco that causes addiction” (USDHHS 1988, p. 9). Eventually, intensive medical treatments and protocols—such as the use of multiple medications for long periods of time, long-term psychological counseling, and inpatient hospitalization—were developed to address the highly addictive nature of nicotine (Fiore et al. 2008). However, between 2000 and 2015, less than one-third of U.S. adult cigarette smokers reported using evidence-based cessation treatments, such as behavioral counseling and/or medication, when trying to quit smoking (Babb et al. 2017).

The first comprehensive clinical practice guideline for smoking cessation was produced by the federal government in 1996 and emphasized the role of health-care providers in providing assessment and treatment interventions for smoking with patients who smoke (Fiore et al. 1996). In 2008, an updated federal guideline, *Treating Tobacco Use and Dependence: 2008 Update* (hereafter referred to as the *Clinical Practice Guideline*), was published (Fiore et al. 2008). This guideline uses language similar to that used in helping persons quit other addictive substances and is discussed in more detail in Chapter 7.

With the shift toward an improved understanding of the nature of nicotine addiction, terminology used to describe tobacco use has also shifted. The *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) is the primary clinical source of diagnostic criteria for mental health disorders. It provides diagnostic criteria for “tobacco use disorder,” which includes physiologic dependence, impaired control, and social impairment, among others (American Psychiatric Association 2013). These diagnostic criteria align with those for other substance use disorders and acknowledge the physical, psychological, and environmental components of addiction. However, as noted in the *Clinical Practice Guideline*, although not all tobacco use results in tobacco use disorder, any tobacco use has risks and, therefore, warrants intervention (Fiore et al. 2008). Accordingly, throughout this report, the term “tobacco use and dependence” is used to be inclusive of all patterns of use and to acknowledge the multifactorial and chronic relapsing nature of nicotine addiction. The term “nicotine dependence” is used specifically to refer to physiologic dependence on nicotine. This terminology aligns with that used in the *Clinical Practice Guideline*, which further details why the term “tobacco use and dependence” is most appropriate when discussing cessation interventions (Fiore et al. 2008).

Coverage of Smoking Cessation, Nicotine, and Addiction in Surgeon General’s Reports

Coverage of cessation, nicotine, and addiction in Surgeon General’s reports has evolved greatly since 1964, reflecting the evolution of scientific understanding of addiction to nicotine and its treatment.

Coverage of Smoking Cessation

Of the 34 Surgeon General’s reports on smoking and health published to date, this is the second to address smoking cessation as the main topic. Even so, beginning with the first report in 1964, evidence reviewed in various reports has supported some conclusions related to the health benefits of smoking cessation. Over time, as the epidemiologic findings from prospective cohort studies became more abundant and covered longer periods of time since quitting smoking, conclusions began to mount on the decline in risks for major smoking-caused diseases after cessation. In fact, declines in risk after cessation figured into the causal inference process presented in the reports, which documented a decrease in health risks after withdrawal of smoking—the presumptive causal agent.

The 1964 Surgeon General’s report reviewed findings from seven prospective cohort studies that had included sufficient numbers of former smokers to provide estimates about cause-specific relative risk for mortality from selected diseases (USDHEW 1964). The data from the cohort studies were complemented by case-control studies for some cancer sites that had also addressed a change in risk after smoking cessation. For all-cause mortality, the 1964 report stated that compared with never smokers, relative mortality was 40% higher among former smokers and 70% higher among current smokers. For lung cancer, quantitative relationships with smoking patterns were described as follows: “The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking” (p. 37). In considering the causal nature of the association between smoking and lung cancer, the report stated, “Where discontinuance, time since discontinuance, and amount smoked prior to discontinuance were considered in either retrospective studies or, with more detail, in prospective studies, these all showed lower risks for ex-smokers, still lower risks as the length of time since discontinuance increased, and lower risks among ex-smokers if they had been light smokers” (p. 188). The report did not conclude that smoking caused cardiovascular disease, but it noted a lower risk of death from cardiovascular disease among former smokers compared with continuing smokers and stated, “Although the causative

role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains” (p. 32).

In ensuing Surgeon General’s reports through the 1970s, the health benefits of smoking cessation did not receive systematic attention, but the results identified a declining risk for some diseases after cessation. The 1979 report offered detailed reviews for major diseases, and it concluded that compared with smokers, risks were lower among former smokers for all-cause mortality, atherosclerosis and coronary heart disease, lung cancer, larynx cancer, lung function, and respiratory symptoms (USDHEW 1979). Three Surgeon General’s reports released in the early 1980s focused on the health consequences of smoking on specific major disease categories: cancer (USDHHS 1982), cardiovascular disease (USDHHS 1983), and chronic lung disease (USDHHS 1984). Each report also examined the impact of smoking cessation on each of those disease categories. In 1988, the report reviewed the evidence to date on nicotine and drew major conclusions that nicotine was addictive (USDHHS 1988).

By 1990, the scope and depth of evidence on smoking cessation was sufficiently abundant to justify a full report, *The Health Benefits of Smoking Cessation*. The report’s conclusions expanded on those of earlier reports, summarizing descriptions of the temporal course of declining risk for many of the diseases caused by smoking (USDHHS 1990). For example, the report concluded, “The excess risk of [coronary heart disease] caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of [coronary heart disease] is similar to that of persons who have never smoked” (p. 11).

Importantly, the 1990 report was the first to address smoking cessation and reproduction. That report offered strong conclusions with clinical implications related to reproduction and offered conclusions about the timing of cessation across gestation and implications for birth-weight (USDHHS 1990).

The 2004 Surgeon General’s report, *The Health Consequences of Smoking*, covered active smoking and disease; and the 2014 Surgeon General’s report, *The Health Consequences of Smoking—Fifty Years of Progress*, again covered the full range of health consequences of smoking, providing conclusions that drew on data from long-running cohort studies that described how risks change in former smokers up to several decades after quitting. For example, the 2004 report concluded, “Even after many years of not smoking, the risk of lung cancer in former smokers remains higher than in persons who have never smoked” (USDHHS 2004, p. 25). In contrast, regarding the effect of smoking in

accelerating the decline of lung function, the report determined “[t]he evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked” (p. 27). The 2014 report updated estimates of relative risks in former smokers, drawing on more contemporary cohorts, and used the estimates to calculate attributable mortality (USDHHS 2014). The extended follow-up of the cohort studies documented the benefits of cessation by early middle age for reducing the risk of death from any cause.

Coverage of Nicotine and Addiction

The 1964 Surgeon General’s report suggested that smoking was a form of habituation, stating that “[e]ven the most energetic and emotional campaigner against smoking and nicotine could find little support for the view that all those who use tobacco, coffee, tea, and cocoa are in need of mental care even though it may at some time in the future be shown that smokers and nonsmokers have different psychologic characteristics” (USDHEW 1964, pp. 351–352). The report used such words as “compulsion” and “habit” but did not consider nicotine to be addicting: “Proof of physical dependence requires demonstration of a characteristic and reproducible abstinence syndrome upon withdrawal of a drug or chemical which occurs spontaneously, inevitably, and is not under control of the subject. Neither nicotine nor tobacco comply with any of these requirements” (USDHEW 1964, p. 352). Correspondingly, the report emphasized habituation and not addiction: “The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacologic actions of nicotine on the central nervous system” (USDHEW 1964, p. 354). In 1977, the National Institute on Drug Abuse began to support studies of cigarette smoking as a “dependence process,” comparing it to other drug addictions (Parascandola 2011). The monograph, *The Behavioral Aspects of Smoking* (Krasnegor 1979), reflected an advancing understanding of the power of nicotine as a pharmacologic agent: “Nicotine has been proposed as the primary incentive in smoking [Jarvik 1973, as cited in Krasnegor 1979] and may be instrumental in the establishment of the smoking habit. Whether or not it is the only reinforcing agent, it is still the most powerful pharmacological agent in cigarette smoke” (p. 12). The 1979 Surgeon General’s report, *Smoking and Health*, devoted considerable attention to the behavioral aspects of smoking, but it still did not use the term “addiction” (USDHEW 1979). That report also concluded that there was general acceptance of the existence of a tobacco withdrawal syndrome, which was more prominent in heavy smokers.

The 1988 Surgeon General’s report explored the clinical and public health implications of smoking, with

several major conclusions serving as an indictment of the addictiveness of nicotine in cigarettes. In fact, this report stated for the first time that cigarettes are addictive and function in a similar fashion to cocaine and heroin use. The three major conclusions of that report were:

- “Cigarettes and other forms of tobacco are addicting”;
- “Nicotine is the drug in tobacco that causes addiction”; and
- “The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine” (USDHHS 1988, p. 9).

Later Surgeon General’s reports on tobacco have addressed the subsequent scientific advances in the area of smoking and addiction, particularly the 2010 report on mechanisms by which smoking causes disease (USDHHS 2010).

Perspectives on Smoking Cessation

In 2015, most smokers stated that they wanted to quit smoking (68%), and about 56% of smokers made a serious attempt to quit; however, only about 7% of smokers reported that they had recently quit (Babb et al. 2017). Despite evidence demonstrating that using smoking cessation pharmacotherapy with behavioral support is more effective than quitting without these treatments, most smokers who had recently quit reported that they did not quit with medication or counseling assistance (see Chapter 6). Proponents of encouraging smokers to quit without treatment, often called quitting “cold turkey,” point to data indicating that most smokers who quit successfully do so without medications or any type of formal assistance, as well as to population surveys suggesting that cold-turkey quitters do as well or better than those who use over-the-counter NRTs. Proponents of this approach also suggest that medicalization may disempower smokers and create artificial barriers to quitting (Alpert et al. 2013; Polito 2013). In contrast, others note that because of a lack of insurance coverage and other barriers, many smokers have little choice but to quit without formal treatment. Selection bias may also play a factor, as the most heavily addicted smokers are those most likely to use NRT, but these smokers also have a lower likelihood of success. In addition, most of those who use NRT do so for short periods of time or at lower-than-recommended doses and do not have adjunctive support available from tobacco cessation quitlines or other interventions (Amodei and

Lamb 2008). There are also issues of recall and attribution bias, which may make smokers more likely to report their most proximal experiences with use or nonuse of pharmacologic smoking cessation aids and/or behavioral supports and not to report previous quit attempts during which they used pharmacologic aids and/or behavioral support.

During most of the twentieth century, smokers who wanted to quit had limited resources to do so, especially smokers with mental health or substance use disorders. For example, the investment in research required for behavioral, pharmacologic, and systems-level interventions that increase successful cessation had been relatively limited given the magnitude of tobacco-related disease burden and the size of the population affected (Dennis 2004; Carter et al. 2015; Hall et al. 2016). Even when interventions developed in the 1980s and 1990s were clearly shown to be effective, most health insurers and health systems showed little interest in providing coverage for or integrating into regular practice any new pharmacologic, behavioral, or systems approaches to cessation (see Chapter 6). Additionally, many medical schools provide only a small amount of time, if any, in their academic curriculum or programs for developing clinical skills to train future physicians in addressing tobacco use and dependence in patients (Ferry et al. 1999; Montalto et al. 2004; Powers et al. 2004; Association of American Medical Colleges 2007; Geller et al. 2008; Richmond et al. 2009; Torabi et al. 2011; Griffith et al. 2013).

Development and Evolution of a Paradigm for Treating Nicotine Addiction

Clinicians’ views on smoking cessation shifted toward the end of the twentieth century. Given the increasing amount of evidence and awareness of the robust and wide-spanning beneficial effects of smoking cessation on various chronic diseases (USDHHS 1990), clinicians began to understand that promoting smoking cessation was among the most powerful interventions for increasing health, while merely advising patients to quit was insufficient in promoting smokers to initiate quitting and sustain abstinence without relapsing. Concurrently, researchers began to better understand the powerfully addictive properties of nicotine and the complexities of the nicotine addiction process (USDHHS 1988). This knowledge was disseminated widely to health professionals and the community (Fiore et al. 1996).

Nicotine addiction is now increasingly emphasized as a main driver of both the initiation and continuation of smoking. Thus, the medical community sees

the morbidity and mortality associated with smoking as clinical endpoints and nicotine addiction as the cause. Correspondingly, a growing number of intensive behavioral and pharmacologic treatments have become available to promote sustained abstinence.

Epidemiologic Shifts in Smoking Cessation

Chapter 2 provides a detailed discussion of key patterns and trends in cigarette smoking cessation in the United States. It also reviews the changing demographic and smoking-related characteristics of cigarette smokers, with a focus on how these changes may influence future trends in cessation.

Changes in the Patterns of Smoking and Population Characteristics of Smokers

The typical profile of the smoker has evolved over the years. The “hardening hypothesis” suggests that adults who continue to smoke cigarettes in the face of strengthening tobacco control policies and the increasing availability of efficacious cessation interventions will tend to be heavier smokers who are more highly addicted, less interested in quitting, and likely to have more difficulty in quitting (National Cancer Institute [NCI] 2003). Only a limited amount of evidence supports this hypothesis (Hughes 2011). Instead of increases over time in the proportion of smokers with frequent or heavy patterns of smoking, as would be predicted by hardening, the proportion has actually decreased (Jamal et al. 2016). Furthermore, from 2005 to 2015, the percentage of current smokers who were daily smokers declined from 80.8% to 75.7%, and the proportion of current smokers who smoked on only some days (i.e., nondaily smokers) increased from 19.2% to 24.3% (Jamal et al. 2016). Similarly, among daily smokers, the average number of cigarettes smoked per day declined from 16.7 in 2005 to 13.8 in 2014. However, when considering other measures of dependence, some modest and preliminary support exists for hardening among treatment-seeking smokers. For example, in a summary review by Hughes and colleagues (2011), two of four studies showed increases in dependence and decreases in quit rates, but similar trends were not found among the general population of smokers who had quit.

Reductions in the frequency and heaviness of smoking do not necessarily suggest that a simple continuation of current approaches to increase smoking cessation will increase or even maintain progress in successful quitting. Nondaily or light smokers would be expected to be less addicted to nicotine and, therefore, when motivated

to make a cessation attempt, would find it easier to quit than heavier smokers. Still, helping light and nondaily smokers to quit presents challenges. For example, some light and nondaily smokers do not self-identify as smokers, do not believe that they are addicted to nicotine, do not feel that they are at risk of smoking-related health effects, and do not expect quitting to be difficult (Berg et al. 2013; Scott et al. 2015; Chaiton et al. 2016). The 2008 *Clinical Practice Guideline* does not recommend cessation medications for use by light smokers, based on insufficient evidence of effectiveness in this population (Fiore et al. 2008). Ten years later, this gap in knowledge about treating light smokers is largely unchanged (Ebbert et al. 2016) (see Chapter 6) and presents a barrier for addressing this growing subpopulation of smokers.

The prevalence of smoking is increasingly concentrated in the United States in populations that may face barriers to quitting. These include persons with behavioral health conditions (including mental health conditions or substance use disorders); persons of low socioeconomic status; persons who are lesbian, gay, bisexual, or transgender; American Indians/Alaska Natives; recent immigrants from countries with a high prevalence of smoking; residents of the South and Midwest; and persons with a disability. Such populations have a markedly higher prevalence of cigarette smoking than their respective counterparts, and the decline in the prevalence of smoking in the United States as a whole has been slower among these groups, particularly those with behavioral health conditions and those of lower socioeconomic status (Grant et al. 2004; Schroeder and Morris 2010; CDC 2013b, 2016; Cook et al. 2014; Szatkowski and McNeill 2015) (see Chapter 2).

Changes in the Products Used by Smokers

The emergence of a wide array of new tobacco products and the increasing use of those products, combined with continued use of other conventional tobacco products, such as menthol cigarettes and smokeless tobacco, could complicate cessation efforts aimed at cigarette smoking (Trinidad et al. 2010; USDHHS 2014; Villanti et al. 2016; Wang et al. 2016). These products include hookahs (water pipes), little cigars and cigarillos, e-cigarettes, and heated tobacco products. Cigarette smokers who also use one or more other tobacco products, generally known as “dual” or “poly” use, have higher dependence on nicotine and greater difficulty quitting (Wetter et al. 2002; Bombard et al. 2007; Soule et al. 2015).

As of July 26, 2019, 11 states and the District of Columbia have passed laws legalizing nonmedical marijuana use (National Conference of State Legislatures [NCSL] 2019). Although not a tobacco product, marijuana is frequently used in combination with conventional

cigarettes or other tobacco products (e.g., cigars, e-cigarettes). For example, approximately 70% of adults who are current users of marijuana are also current users of tobacco (Schauer et al. 2016). Results from population-based surveys and some clinical studies indicate an association between the use of menthol-flavored cigarettes or marijuana and a lower probability of successful quitting (Ford et al. 2002; Patton et al. 2005; Gandhi et al. 2009; Schauer et al. 2017). The available longitudinal evidence from rigorously conducted studies is limited, so it is too soon to determine whether this association is correlational or causal.

Developments in Approaches to Smoking Cessation at the Individual Level

This section summarizes the landmark developments since the 1990 Surgeon General's report that have shaped treatment for tobacco dependence and corresponding breakthroughs in smoking cessation interventions at the individual level. Chapter 6 provides detailed evidence for current and emerging smoking cessation treatments, adding to the evidence presented in the *Clinical Practice Guideline* (Fiore et al. 2008). It also explores approaches to increasing the impact of tobacco cessation treatment through improved efficacy and increased reach.

Pharmacotherapy

The scientific understanding of the neurobiologic impact of chronic exposure to nicotine (USDHHS 2010) has stimulated research and development that focuses on identifying novel medications and improving existing medications. The only FDA-approved smoking cessation medication at the time of the 1990 Surgeon General's report was the gum form of NRT (USDHHS 1990). Since then, several additional NRT formulations (transdermal patch, lozenge, inhaler, and nasal spray) have been developed, with all but the inhaler and spray now approved for over-the-counter sale. Additionally, FDA has approved two non-NRT medications for smoking cessation: bupropion and varenicline (GlaxoSmithKline 2017; FDA 2017; Pfizer 2019).

Adding to the progress seen for individual agents, favorable developments in pharmacologic treatment have been seen in a variety of other areas over the past two decades. For example, because of the modest efficacy of monotherapy and the recognition that persons with nicotine addiction benefit from intensive treatments, a variety of combination pharmacotherapies have been studied (see Chapter 6).

Behavioral Interventions

Discoveries in the behavioral and social sciences have deepened our understanding of psychosocial influences on the nature and treatment of tobacco dependence, which has propelled new approaches to behavioral treatment. The evidence has clarified that during and long after the dissipation of acute pharmacologic withdrawal from nicotine during cessation, several factors—including vacillation of negative emotional states, repeated urges to smoke, diminished motivation, and having less confidence in the ability to successfully quit—can persist throughout the cessation process and undermine quitting (Liu et al. 2013; Ussher et al. 2013). Furthermore, encountering environments and situations previously associated with smoking, such as establishments that serve alcohol or interacting with friends who smoke, has been demonstrated to increase risk of relapse (Conklin et al. 2013). Fortunately, behavioral treatment models for mental health conditions and other substance use disorders have been translated and adapted for nicotine addiction to address these factors and have been shown to improve quit rates (Hall and Prochaska 2009).

In addition to quitlines, which have been a longstanding intervention to deliver population-based behavioral smoking cessation support, technological innovations have opened new service delivery platforms for sophisticated behavioral cessation interventions in other modalities. In the 1990s, computer-tailored, in-depth, personalized mailings based on answers to a lengthy questionnaire were developed and tested on smokers; the tailored or personalized mailings were more effective than mailings with standard text (Prochaska et al. 1993; Strecher et al. 1994). Receipt of personalized written feedback and self-help materials was also found to increase cessation rates (Curry et al. 1991). A systematic review by the U.S. Preventive Services Task Force (USPSTF) (2015) found self-help materials that were tailored to the individual patient to be effective cessation interventions. Interactive program modalities have been developed and tested (USPSTF 2015) for desktop and laptop computers, first via programs operated from a CD-ROM or hard drive, later via Internet downloads, and more recently from “the cloud” (Strecher et al. 2005; Haskins et al. 2017). The current state of science and technology also allows the leveraging of mobile phone technology and applications to deliver cessation interventions (Whittaker et al. 2016). These include applications involving standardized motivation-enhancing texts or quit-promoting strategies—some of which offer real-time, live-peer, or professional advising or counseling within the application (Smokefree.gov n.d.). Preliminary evaluations have suggested that these applications may be beneficial to users (Cole-Lewis et al. 2016; Squiers et al. 2016, 2017; Taber et al. 2016) and that the cost of delivery is low.

Treating Tobacco Use and Dependence

The 2000 and 2008 *Clinical Practice Guidelines* had marked impacts on increasing understanding of and operationalizing the current paradigm of treating tobacco use and dependence (Fiore et al. 2000, 2008). Until the 1990s, synopses of the state of the evidence on smoking cessation usually relied on a somewhat informal aggregation of clinical and population-based studies, an approach that is prone to author bias in the choice of studies included and in their interpretations. Markedly more formal review processes, such as systematic literature reviews, were applied to smoking cessation and treatment in the 1990s and 2000s, as thousands of cessation-related studies accumulated. These more formal reviews systematized the literature review process by using strict criteria for grading studies and employing meta-analyses where appropriate; they also included a more transparent and elaborate process for synthesizing evidentiary findings into conclusions and recommendations.

In addition, the standards and framing of cessation research have evolved over the past several decades, which is consistent with the increased sophistication of pharmaceutical and population-based trials in general. For example, clinical trials have evolved from examining the success rates of persons completing the trial, often examining only the point prevalence of abstinence, into using intent-to-treat, where all persons starting treatment are considered in the denominator and those lost to follow-up are counted as smokers or subject to data imputation techniques (Hall et al. 2001; Mermelstein et al. 2002; SRNT Subcommittee on Biochemical Verification 2002; Hughes et al. 2003; Shiffman et al. 2004). Definitions of successful abstinence often examine smoking status at 1 month, 6 months, and 1 year of abstinence after treatment.

Notably, some definitions of successful abstinence allow for brief lapses in smoking cessation to more accurately reflect the natural course of achieving long-term abstinence (Zhu et al. 1996). Similarly, population-level surveillance and research have evolved to include increasingly more complex questions and techniques to more accurately capture the nature of respondents' use of tobacco products and cessation behavior. For example, sets of questions have been developed to better categorize respondents' use of healthcare services and the nature of cessation support they received. In addition, new technologies have been deployed to better understand the patterns of behavior among smokers, such as ecological momentary assessment, which cues smokers to provide data on their smoking urges and other thoughts, emotions, and behaviors in real time (Shiffman 2009). Large clinical trials have also examined the interplay between multiple factors that affect quit success, such as different medications, dual-medication therapy, and different approaches

and intensities of behavioral interventions (Redmond et al. 2010).

The *Clinical Practice Guidelines* used formal scientific review processes to analyze thousands of studies produced in the 1990s and 2000s—analyses that included detailed evidence reviews that resulted in practical recommendations for clinicians (Fiore et al. 2000, 2008). Unlike most clinical guidelines, they also included recommendations at the health systems and policy levels based on evidence and tools designed specifically for clinicians to use in office practices. In addition, multiple Cochrane reviews have been performed on medications and counseling approaches (Hajek et al. 2013; Stead et al. 2013; Lindson-Hawley et al. 2015), and USPSTF has updated its literature on clinical preventive services (Siu and USPSTF 2015; USPSTF 2015). Based on the findings presented, the current paradigm for smoking cessation conceptualizes nicotine addiction as a chronic, relapsing disorder that benefits from long-term management and intensive treatment approaches, as do other chronic diseases. The major findings have shaped the way cessation is currently viewed:

- Any level of treatment is beneficial, and more intensive and longer behavioral and pharmacologic treatment is generally better.
- Physicians, psychologists, pharmacists, dentists, nurses, and numerous other healthcare professionals can treat nicotine addiction in smokers. Thus, by extension, the various settings in which such professionals work represent appropriate venues for providing these services.
- Behavioral interventions and FDA-approved pharmacotherapies are effective for treating nicotine dependence. A combination of behavioral interventions and pharmacotherapy is the optimal treatment based on overwhelming scientific evidence, with superiority in efficacy over either intervention alone.

Advances in research and technology have shaped how the clinical and scientific communities view and approach treatment for nicotine addiction in smokers, but this progress continues to lag the advances made in treating other chronic diseases. For instance, in cancer, cardiovascular disease, and other illnesses with multifactorial etiologies, major strides have been made toward precision treatment methods, which are based on the premise that clinical outcomes can be enhanced by selecting, adapting, and tailoring treatment on the basis of a patient's specific clinical profile and disease pathogenesis (Collins and Varmus 2015). Such approaches have been endorsed

and promoted as part of the Precision Medicine Initiative (Genetics Home Reference 2018), which reinforces that the future of clinical care lies in basic and clinical research and their translation to optimize health outcomes. Although precision treatment has not advanced for smoking cessation at the same rate as it has for treating certain other illnesses, emerging findings suggest that a personalized, precision approach has the potential to meaningfully improve smoking cessation outcomes (Allenby et al. 2016).

Evolution of Approaches to Smoking Cessation at the Population Level

More Intensity Versus Higher Reach of Support Services

Through the first decades in which cessation interventions were developed, most of the emphasis was on improved efficacy—specifically, increasing the probability that if smokers engaged and fully used an intervention service, their chances of success would be increased. As interventions, both behavioral or pharmacologic therapies and combination therapies have become increasingly effective, but despite the effectiveness of such therapies, they are not being used as designed by substantial numbers of smokers (Zhu et al. 2012). Several theoretical models suggested that efforts to develop interventions need to consider their population impact, not just their individual efficacy for those taking part in the intervention.

In the 1990s, the potential for smoking cessation interventions to make an impact on the tobacco epidemic was overshadowed by the low rate at which smokers actually used interventions. Several factors contributed to this phenomenon, and several other factors initially assumed to be the main drivers were eliminated. One assumption was that smokers were just not very interested in quitting or in accessing help to quit. However, population-level surveys over time and among diverse populations showed that not only were smokers interested in quitting, but more than half planned to quit in the next 6 months and had attempted to quit in the past year (Babb et al. 2017). In addition, when physicians or other healthcare providers systematically offered support for quitting, such as medications or follow-up, a much larger than expected fraction of smokers agreed to accept support. Even so, further examination revealed that helping smokers quit presented unique obstacles. Up to the 1990s,

- Almost no health insurers provided any coverage of smoking treatments—either medications, counseling, or physician intervention.

- Most physicians did not systematically address smoking in the course of clinical practice for multiple reasons, including lack of time, perception that patients are unready to quit, limited resources, and inadequate clinical skills related to cessation.
- Although smokers generally understood that smoking had unfavorable health effects, many did not fully understand or accept the magnitude or personal relevance of smoking's effects on various aspects of health and its dramatic overall effect on longevity (USDHHS 1989; Chapman et al. 1993). Even if smokers accept the theoretical possibility of risk, they often do not believe that the hypothetical future risk from smoking applies to them personally—for example, they believe they have “good genes” or other healthy habits, or they smoke in a less dangerous manner (Oakes et al. 2004).
- Smokers and physicians did not realize that effective treatments were available.
- Even when smokers wanted to quit and were potentially interested in getting help, evidence-based treatments were not readily available to them because of financial and practical barriers.

Thus, during the 1980s and 1990s, a series of system and policy innovations were developed and tested to address these barriers. These innovations included the use of organizational system change and quality improvement theory to systematically address opportunities to influence smokers during routine interactions with healthcare systems (Solberg et al. 1990; Manley et al. 1992); experiments providing different types of insurance coverage for cessation treatments (Curry et al. 1998); the development of more easily accessible treatments, such as phone-based quitlines (Orleans et al. 1991; Zhu et al. 2012); integrated promotion of cessation via mass media campaigns that encouraged the use of cessation services (McAfee et al. 2013); and easily accessible, in-person cessation clinics (Lee et al. 2016).

The lack of accessibility to cessation support was addressed in several ways. One approach attempted to bypass the lack of availability of support within healthcare services by creating easily accessible, low-intensity cessation supports, such as telephone quitlines or in-person clinics, that were generally operated and funded outside the healthcare system. Another approach attempted to integrate very brief but systematic, repeated support for cessation into primary care clinical practices while working to obtain insurance coverage and accessibility to more intense services for those interested in quitting. In

some instances, these approaches were combined synergistically (McAfee et al. 1998). A few U.S. states and some other countries, such as the United Kingdom, successfully developed—through funding from tobacco tax dollars or government healthcare—networks of freestanding, in-person cessation clinics that provided basic cessation counseling and medications (Gibson et al. 2010; West et al. 2013). However, this model has not been sustained in any geographic region of the United States, primarily because of limited resources to maintain it over time. Still, a higher intensity model, which includes more intensive and comprehensive cessation components, has continued to focus on markedly improving the chances of success by treating nicotine addiction via a tertiary treatment delivery model, akin to how a cancer center approaches patients who are referred for its services. For example, the Mayo Clinic and a handful of similar referral clinics use such strategies as in-depth evaluation by multidisciplinary staff; personalized treatment plans; recurrent follow-up; and, in some cases, admission to a residential facility or hospital (Hays et al. 2011). Although such programs often achieve high rates of smoking cessation, their utility is greatly limited by the high cost of implementation, unclear cost-effectiveness, and limited reach. For example, during a 7-year period, in a study of a large outpatient clinic, 2–3% of smokers used the available nicotine dependence services, even when the services were optimally promoted and delivered (Burke et al. 2015).

Population-Based Interventions

Historically, tobacco control efforts have focused on either helping smokers quit at the individual level, such as through clinical interventions, or on providing population-level interventions to decrease the prevalence of smoking. Potential synergies between these two approaches have become increasingly apparent over the past several decades. This section discusses four examples of attempts to combine individually delivered cessation support and population-based strategies to smoking cessation: quitlines, health systems transformation, mass media campaigns, and health insurance coverage of smoking cessation treatment. Chapter 7 provides a more in-depth review of the current literature on each of these topics and on other population-based interventions that have been shown to promote cessation, such as increasing the prices of tobacco products and the implementation of smokefree policies.

Quitlines

In the late 1980s and throughout the 1990s, researchers interested in helping large numbers of smokers quit smoking began to experiment with the provision of

behavioral counseling support via telephone, in the hope of overcoming such barriers to utilization as cost and the reluctance of many smokers to attend face-to-face group or individual sessions. Providing counseling centrally was thought to provide more opportunities for systematically improving the quality of the counseling and the research infrastructures used to answer questions about the cessation process. Protocols were developed and tested in a variety of environments, ranging from academic centers (Ossip-Klein et al. 1991) to health systems (Orleans et al. 1991) to state health departments (Zhu et al. 1996). Multiple large, randomized trials have since established the effectiveness of the telephone modality (Stead et al. 2013). The availability of quitlines grew rapidly during the 1990s and the early 2000s.

The adoption of quitlines by state health departments was initially facilitated by the increased revenue provided to states from the Master Settlement Agreement in 1998 and higher taxes on tobacco products. In 2003, CDC provided supplemental funding to state health departments to establish quitlines in those that did not have them and to enhance quitline services and access in those with existing quitlines (Zhang et al. 2016). In 2004, a national network of state quitlines was created with a single national portal number (1-800-QUIT-NOW), which is serviced by NCI (Cummins et al. 2007; CDC 2014b). By 2006, residents in all 50 states, the District of Columbia, and U.S. territories had access to quitlines, and the North American Quitline Consortium had been developed to help set evaluation standards and enhance the collection of information, including an agreed-upon minimum dataset to be collected from all callers, with a data warehouse funded by CDC (North American Quitline Consortium 2007; Keller et al. 2010). Providers of quitline services grew from modest operations with a few dozen employees to multiple large providers based in a range of organizations, including for-profit and nonprofit national healthcare organizations and academic centers, some employing hundreds of “quit coaches.”

Mass Media Campaigns

Mass media educational campaigns on the hazards of smoking have been used for decades, in part to motivate quit attempts in the general population of current smokers, and a considerable evidence base shows their effectiveness in promoting successful cessation at the population level (NCI 2008; USDHHS 2014). These campaigns are generally thought of as being unrelated to efforts to provide direct assistance and support to individual smokers in healthcare settings or through community initiatives. However, since 1990, numerous efforts have been made to create synergies and efficiencies between mass media campaigns and the provision of individual support for quit attempts. For example, CDC’s *Tips From*

Former Smokers (Tips) media campaign features ads with real people (former smokers) who have suffered the health consequences of smoking to increase awareness of suffering caused by smoking. The ads are also tagged with a quitline number (CDC 2012, 2013a). Tagging the ads with an offer of assistance may help smokers absorb the message of the ad by making it actionable rather than simply negative. Chapter 7 discusses the effectiveness of mass media campaigns, including *Tips*.

Healthcare Systems

Clinic-Based Integration of Health Systems

In the 1980s, NCI funded primary care-based research showing that a systematic approach to addressing tobacco use could help individual smokers in a clinical practice to quit and could lower the prevalence of tobacco use in the population served by a clinic (Solberg et al. 1990; Manley et al. 1992). Out of this research grew the “4 A’s model,” a carefully crafted intervention for transforming the approach of primary care clinics to tobacco cessation that was developed and packaged for widespread dissemination. This model differed from previous efforts in that it emphasized a systems approach to effectively address tobacco use in the context of primary care clinical practice, rather than simply developing an intervention that required for delivery its own separate healthcare or community infrastructure. The model had four components:

- **Ask:** Systematically identify the smoking status of all patients flowing through a practice, usually by an assistant interviewing the patient rather than relying on physician recall of patients’ smoking status at every visit;
- **Advise:** Provide at every encounter very brief, non-threatening recommendations to quit;
- **Assist:** Offer practical help for quitting, including tips to make it through the first few weeks and brief supportive counseling; and
- **Arrange:** Ensure that any smoker planning a quit attempt will receive follow-up (e.g., during future office visits and/or through off-site resources).

Despite being shown to have significant benefits to smokers in clinical practices in the 1980s and 1990s, the adoption, implementation, and subsequent maintenance of this systematic approach was slow and uneven (Ferketich et al. 2006).

Based on an additional review of the evidence (Fiore et al. 2008), a fifth step, “Assess,” was added between the “Advise” and “Assist” components, thereby emphasizing the importance of determining a patient’s level of interest in quitting so that assistance and follow-up could be tailored to that person’s specific circumstances. For example, a brief interaction with a patient not interested in quitting would focus on enhancing motivation rather than providing quit advice.

The 5 A’s model is an example of an intervention designed to maximize the probability of a smoker making a quit attempt and the probability that he or she will be successful during such an attempt. The model seeks to accomplish these two tasks for a population of smokers. Building on the effectiveness of the 5 A’s model, the Ask, Advise, Refer (AAR) model was developed as a shorter alternative to the 5 A’s model in clinical settings where there is less time afforded for the patient encounter (Schroeder 2005). In addition, a different model, termed Ask, Advise, Connect (AAC) (Vidrine et al. 2013) was developed to ameliorate the low rate of participation among persons passively referred to a smoking cessation treatment, usually a quitline, through the AAR model. In the AAC model, smokers who accept the referral are subsequently contacted by the provider of smoking cessation treatment, typically a quitline counselor. The referral or connection services, such as to quitlines, have very strong evidence for effectiveness (Vidrine et al. 2013; Adsit et al. 2014) (also see Chapter 7). However, fewer studies have assessed the overall population impact of the AAR and AAC models compared with the 4 A’s and 5 A’s models.

Although the identification of smoking status is now routine in most healthcare systems, providing assistance and follow-up to smokers occurs in only less than half of primary care visits (King et al. 2013; Bartsch et al. 2016). Health professionals have reported barriers to adopting and implementing these healthcare-based treatment protocols, including

- Lack of time;
- Lack of reliable reimbursement for provision of services;
- Lack of acceptance that addressing tobacco dependence is part of a physician’s job;
- Lack of training and/or comfort addressing problems with substance abuse;
- Lack of reliable, accessible referral resources;

- High prevalence of smoking, meaning that even brief interventions significantly affect clinic flow, as the interventions may need to be implemented with a large number of patients (Vogt et al. 2005; Association of American Medical Colleges 2007; Blumenthal 2007); and
- Privacy concerns, fear of losing patients, the discouraging belief that most patients will not be able to stop, and concern about stigmatizing the smoker (Schroeder 2005).

Responding to these issues, several professional organizations, including the American Academy of Family Physicians, have recommended using the AAR model at the clinical level to address smoking behaviors.

In recent years, increased attention has also been paid to the importance of building linkages between public health and the healthcare system and between community and clinical healthcare resources. This draws on the recognition that public health and healthcare stakeholders have complementary strengths and perspectives; that ultimately achieving lasting improvements in population health will take the combined efforts of both; and that improved coordination efforts will hasten this outcome. As part of this broader trend, national public health organizations and state tobacco control programs have begun to engage with healthcare systems to encourage and help them integrate treatment for tobacco dependence into their workflows (CDC 2006). Some healthcare systems have broadened the scope of their interventions to address upstream factors that shape health outcomes. For example, some healthcare systems have championed evidence-based interventions that go beyond the clinical sphere, such as smokefree and tobacco-free policies, increases in the price of tobacco products, and policies raising the age of sale for tobacco products to 21 years (Campaign for Tobacco-Free Kids 2016). Predicting the evolution of cessation treatment in the United States and the various roles of different segments of the healthcare system is challenging because of the volatility and uncertain future structure of healthcare, especially the nature of healthcare insurance. Regardless of what type of delivery system emerges, efforts should continue to integrate evidence-based tobacco treatment and cessation supports into healthcare settings and expand those supports. This would require further embedding of smoking processes and outcomes in quality measures, adequate funding, and routinization of training. Such services could be provided in the general healthcare system, as well as through specialized cessation clinics. The ability to deliver services effectively would be aided by having sufficient geographic locations for delivering care, promoting services, and removing barriers to services.

Health Insurance Coverage

Comprehensive insurance coverage for evidence-based cessation treatments plays a key role in helping smokers quit by increasing their access to proven treatments that raise their chances of quitting successfully (Fiore et al. 2008; CDC 2014a). Research in multiple healthcare settings in the 1990s (Curry et al. 1998) and 2000s (Joyce et al. 2008; Hamlett-Berry et al. 2009; Smith et al. 2010; Fu et al. 2014; Fu et al. 2016) has demonstrated that comprehensive cessation coverage increases quit attempts, the use of cessation treatments, and successful quitting (Fiore et al. 2008). Accordingly, implementation of comprehensive cessation coverage is important in both private and public health insurance.

Significant milestones in the recognition that comprehensive insurance coverage for smoking cessation plays a key role in helping smokers quit include (a) the Community Preventive Services Task Force's finding that reducing tobacco users' out-of-pocket costs for proven cessation treatments increases the number of tobacco users who quit (Hopkins et al. 2001), and (b) the recommendation in each of the *Clinical Practice Guidelines* that health insurers cover the FDA-approved cessation treatments and the behavioral treatments that the *Guidelines* found to be effective (Fiore et al. 2000, 2008). These recommendations draw on a body of research that has documented the outcomes of insurance coverage for cessation, including its cost-effectiveness. This research has also helped to identify the levels of coverage that influence tobacco cessation. More recently, several studies have examined the utilization of cessation treatments covered by health insurance, especially cessation medications, and how this has changed over time. Initial findings from these analyses suggest that cessation treatments continue to be underused, especially among Medicaid populations, and utilization varies considerably across states (Babb et al. 2017).

Healthcare Insurance Policies

After 2010, several national levers were added to make tobacco use and dependence treatment a part of healthcare. Both Medicare and Medicaid required coverage of certain smoking cessation treatments, and the Affordable Care Act included several provisions that required non-grandfathered commercial health plans to provide in-network smoking cessation medications and counseling without financial barriers because those two treatments had "A" ratings from USPSTF (McAfee et al. 2015). Even with these new regulatory levers, many national plans are not yet providing the required coverage (Kofman et al. 2012). Chapter 7 provides an in-depth discussion of private and public health insurance coverage for the treatment of tobacco use and dependence.

E-Cigarettes: Potential Impact on Smoking Cessation

E-cigarettes (also called electronic nicotine delivery systems [ENDS], vapes, vape pens, tanks, mods, and pod-mods) are battery-powered devices designed to convert a liquid (often called e-liquid)—which contains a humectant (propylene glycol and vegetable glycerin) and also typically contains nicotine, flavorings, and other compounds—into aerosol for inhalation by the user. First introduced in the United States in 2007 (USDHHS 2016), the advent of e-cigarettes into the tobacco product marketplace was seen by some as a potential harm-reduction tool for current adult smokers if the products were used to transition completely from conventional cigarettes (Fagerstrom et al. 2015; Warner and Mendez 2019). E-cigarette aerosol has been shown to contain markedly lower levels of harmful constituents than conventional cigarette smoke (National Academies of Sciences, Engineering, and Medicine 2018). Accordingly, interest remains in policies and approaches that could maximize potential benefits of these devices while minimizing potential pitfalls posed by the devices at the individual and population levels, including concerns about initiation among young people. The 2016 Surgeon General’s report, *E-Cigarette Use Among Youth and Young Adults*, examined many aspects of e-cigarettes related to young people; however, it did not address the potential impact of e-cigarettes on smoking cessation among adult smokers (USDHHS 2016). It is also important to note that the landscape of available e-cigarette products has rapidly diversified since their introduction in the United States in 2007, including the introduction of “pod mod” e-cigarettes that have dominated the e-cigarette marketplace in recent years (Barrington-Trimis and Leventhal 2018; Office of the U.S. Surgeon General n.d.). This section highlights salient issues about how e-cigarettes may influence cessation, which is reviewed in more depth in Chapter 6.

Implications of E-Cigarette Characteristics for Smoking Cessation

Nicotine delivery through inhalation, as is the case with cigarette smoking, results in rapid nicotine absorption and delivery to the brain. The pharmacokinetics of nicotine delivery varies across products and is influenced by user topography, with some, but not all, e-cigarette products providing nicotine delivery comparable to conventional cigarettes (National Academies of Sciences, Engineering, and Medicine 2018). By contrast, the nicotine inhaler, one of several FDA-approved NRTs, delivers nicotine primarily through the buccal mucosa; it is designed to reduce nicotine withdrawal and cravings while minimizing abuse liability (Schneider et al. 2001). For smokers

of conventional cigarettes who seek a product with a rapid delivery of nicotine similar to cigarettes, e-cigarettes that deliver nicotine in a similar way to cigarettes may have greater appeal than NRTs. Although rapid boluses of nicotine could increase the appeal, as well as addiction and potential greater abuse liability, of e-cigarettes relative to NRTs, whether this pharmacokinetic profile produces an effective method of cessation is presently inconclusive from the emerging base of empirical evidence (Shihadeh and Eissenberg 2015).

Other features of e-cigarettes that may enhance their appeal to smokers of conventional cigarettes include the ways in which they mirror some of the sensorimotor features of conventional cigarette smoking, including stimulation of the airways, the sensations and taste of e-cigarette aerosol in the mouth and lungs, the hand-to-mouth movements and puffing in which e-cigarette users engage, and the exhalation of aerosol that may visually resemble cigarette smoking. Given the potentially important role of such sensorimotor factors in the reinforcing and addictive qualities of conventional cigarettes (Chaudhri et al. 2006), the presence of these attributes could make e-cigarettes more appealing to smokers as a substitute for cigarettes than NRTs because the NRTs either lack such sensorimotor features (e.g., the transdermal patch, nicotine gum) or offer only partial approximations (e.g., the inhaler).

However, when considering e-cigarettes as a potential cessation aid for adult smokers, it is also important to take into account factors related to both safety and efficacy. NRT has been proven safe and effective, but there is no safe tobacco product. Although e-cigarette aerosol generally contains fewer toxic chemicals than conventional cigarette smoke, all tobacco products, including e-cigarettes, carry risks.

As noted in the 2016 Surgeon General’s report, many of the characteristics that distinguish e-cigarettes from conventional cigarettes increase the appeal of these new products to youth and young adults, particularly nonsmokers (USDHHS 2016). These factors include appealing flavors, high concentrations of nicotine, concealability of use, and widespread marketing through social media promotion and other channels (Barrington-Trimis and Leventhal 2018). Many e-cigarettes differ markedly in shape and feel compared with conventional cigarettes; e-cigarettes come in a variety of shapes, including rectangular tank-style and USB-shaped devices (as discussed in Chapter 6 and shown in Figure 6.1). For example, JUUL, the top-selling e-cigarette brand in the United States in 2018 (Wells Fargo Securities 2018), is shaped like a USB flash drive and offers high concentrations of nicotine in the cartridges, which are also known as “pods” (Huang et al. 2018). Notably, the novelty, diversity, and customizability of e-cigarettes appeal to youth (Chu et al. 2017; Office of the U.S. Surgeon

General n.d.). For example, there are numerous scientific reports documenting the appeal of, and dramatic rise in, JUUL use among youth and young adults (Chen 2017; Teitell 2017; Beal 2018; Bertholdo 2018; Coughlin 2018; Grigorian 2018; Saggio 2018; Suiters 2018; FDA 2018; Willett et al. 2018; Radding n.d.).

Of note, a growing number of e-cigarettes, including JUUL, also use nicotine salts, which have a lower pH than the freebase nicotine used in most other e-cigarettes and traditional tobacco products, and allow particularly high levels of nicotine to be inhaled more easily and with less irritation. Although this type of product may be appealing to adult smokers seeking e-cigarettes with potentially greater nicotine delivery, the potency and appeal of such products can also make it easier for young people to initiate the use of nicotine and become addicted (Office of the U.S. Surgeon General n.d.).

The final chapter of the 2014 Surgeon General's report concluded that the use of e-cigarettes could have both positive and negative impacts at the individual and population levels (USDHHS 2014). One of its conclusions was that "the promotion of noncombustible products is much more likely to provide public health benefits only in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combusted tobacco products are being rapidly reduced" (USDHHS 2014, p. 874). Therefore, it is important to continue (a) monitoring the findings of research on the potential of e-cigarettes as a smoking cessation aid and (b) evaluating the positive and negative impacts that these products could have at the individual and population levels, so as to ensure that any potential benefits among adult smokers are not offset at the population level by the already marked increases in the use of these products by youth. It is particularly important to evaluate scientific evidence on the impact of e-cigarettes on adult smoking cessation in the current context of the high level of e-cigarette use by youth, which increased at unprecedented levels in recent years following the introduction of JUUL and other e-cigarettes shaped like USB flash drives (Cullen et al. 2019).

Summary

Once erroneously considered a habit that could be broken by simply deciding to stop, nicotine addiction is now recognized as a chronic, relapsing condition. The prevalence of cigarette smoking in the United States has declined steadily since the 1960s; however, as of 2017, there were still more than 34 million adult current cigarette smokers in the United States (Wang et al. 2018).

Proven smoking cessation treatments are widely available today. However, the reach and use of existing

smoking cessation interventions remain low, with less than one-third of smokers using any proven cessation treatments (behavioral counseling and/or medication) (Babb et al. 2017). A majority of smokers still attempt to quit without using such treatments, contributing to a failure rate in excess of 90% (Hughes et al. 2004; Fiore et al. 2008).

Medications and behavioral interventions with increasing levels of efficacy and sophistication are becoming more widely available, but there is considerable room for improvement. Further, the challenge of getting behavioral and pharmacologic interventions to be used concurrently and disseminated more broadly to the public has only been partially solved.

Full integration of treatment for nicotine dependence into all clinical settings—including primary and specialty clinics, hospitals, and cancer treatment settings—can benefit from increases in barrier-free health insurance coverage. Combining health service systems and electronic media platforms for the delivery of smoking cessation interventions has emerged as one promising method to increase reach of smoking cessation treatment to smokers (e.g., evidence-based cessation interventions using phone lines and mobile phone applications, and use of electronic health records to promote more timely referral to cessation support services). Barrier-free health insurance coverage (e.g., copays, coverage limits, prior authorization) and access to services, coupled with the use of quality improvement metrics and methodologies, have been shown to increase smokers' use of evidence-based services.

Clinical-, system-, and population-level strategies are increasingly taking a more holistic approach to decreasing the prevalence of smoking, with interventions designed to increase quit attempts and enhance the chances of success. Examples include the national *Tips From Former Smokers* media campaign, which used ads featuring smokers who had suffered tobacco-related morbidity to increase awareness of individual suffering caused by smoking while simultaneously enhancing the capacity of the national quitline network to respond to upsurges in calls that were generated by tagging the ads with the phone number for the quitline. Millions of smokers made quit attempts as a result of exposure to the ads, and hundreds of thousands have successfully quit smoking. In addition, the development and dissemination of the carefully crafted and research-tested 5 A's model in healthcare settings, combined with public and private policy changes that encourage coverage of cessation, have systematically encouraged more smokers to try to quit and provided them with evidence-based support. Still, the potential of mass media campaigns, quitlines, and clinical support has been tapped only partially, leaving many opportunities for further adoption, dissemination, and extensions of these approaches.

Use of e-cigarettes could have varied impacts on different segments of the population, including potential benefits to current adult cigarette smokers who transition completely; however, potential efficacy may depend on many factors, such as type of devices and e-liquids used, reason for use, and duration of use. Well-controlled, randomized clinical trials and rigorous, large-scale observational studies with long-term follow-ups will be critical to better understand the impact of e-cigarettes on cessation under various conditions and settings. Nevertheless, the

potential benefit of e-cigarettes for cessation among adult smokers cannot come at the expense of escalating rates of use of these products by youth. Accordingly, the current science base supports a number of actions to minimize population risks while continuing to explore the potential utility of e-cigarettes for cessation, including efforts to prevent e-cigarette use among young people, regulate e-cigarette products and marketing, and discourage long-term use of e-cigarettes as a partial substitute for conventional cigarettes rather than completely quitting.

References¹

- Adsit RT, Fox BM, Tsiolis T, Ogland C, Simerson M, Vind LM, Bell SM, Skora AD, Baker TB, Fiore MC. Using the electronic health record to connect primary care patients to evidence-based telephonic tobacco quitline services: a closed-loop demonstration project. *Translational Behavioral Medicine* 2014;4(3):324–32.
- Allenby CE, Boylan KA, Lerman C, Falcone M. Precision medicine for tobacco dependence: development and validation of the nicotine metabolite ratio. *Journal of Neuroimmune Pharmacology* 2016;11(3):471–83.
- Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control* 2013;22(1):32–7.
- American Psychiatric Association. Substance-related and addictive disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington (VA): American Psychiatric Association Publishing, 2013.
- Amodei N, Lamb RJ. Over-the-counter nicotine replacement therapy: can its impact on smoking cessation be enhanced? *Psychology of Addictive Behaviors* 2008;22(4):472–85.
- Association of American Medical Colleges. *Physician Behavior and Practice Patterns Related to Smoking Cessation*. Washington (DC): Association of American Medical Colleges, 2007.
- Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;65(52):1457–64.
- Barrington-Trimis JL, Leventhal AM. Adolescents’ use of “pod mod” e-cigarettes—urgent concerns. *New England Journal of Medicine* 2018;379(12):1099–102.
- Bartsch AL, Harter M, Niedrich J, Brutt AL, Buchholz A. A systematic literature review of self-reported smoking cessation counseling by primary care physicians. *PLoS One* 2016;11(12):e0168482.
- Beal K. JUUL e-cigarettes make their way into local schools, February 8, 2018; <<http://wset.com/news/local/juul-e-cigarettes-make-their-way-into-local-schools>>; accessed: August 9, 2018.
- Berg CJ, Schauer GL, Buchanan TS, Sterling K, DeSisto C, Pinsker EA, Ahluwalia JS. Perceptions of addiction, attempts to quit, and successful quitting in nondaily and daily smokers. *Psychology of Addictive Behaviors* 2013;27(4):1059–67.
- Bertholdo S. Vaping goes mainstream: high tech devices especially popular on local campuses. The Acorn, February 1, 2018; <<https://www.theacorn.com/articles/vaping-goes-mainstream/>>; accessed: August 9, 2018.
- Blumenthal DS. Barriers to the provision of smoking cessation services reported by clinicians in underserved communities. *Journal of the American Board of Family Medicine* 2007;20(3):272–9.
- Bombard JM, Pederson LL, Nelson DE, Malarcher AM. Are smokers only using cigarettes? exploring current polytobacco use among an adult population. *Addictive Behaviors* 2007;32(10):2411–9.
- Burke MV, Ebbert JO, Schroeder DR, McFadden DD, Hays JT. Treatment outcomes from a specialist model for treating tobacco use disorder in a medical center. *Medicine* 2015;94(44):e1903.
- Campaign for Tobacco-Free Kids. Trinity Health and Campaign for Tobacco-Free Kids partner to reduce tobacco use with focus on raising tobacco age to 21 [press release], April 28 2016; <https://www.tobacco-freekids.org/press_releases/post/2016_04_28_trinity>; accessed: September 14, 2017.
- Carter AJ, Delarosa B, Hur H. An analysis of discrepancies between United Kingdom cancer research funding and societal burden and a comparison to previous and United States values. *Health Research Policy and Systems* 2015;13:62.
- Centers for Disease Control and Prevention. *A Practical Guide to Working with Health-Care Systems on Tobacco-Use Treatment*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
- Centers for Disease Control and Prevention. Increases in quitline calls and smoking cessation website visitors during a national tobacco education campaign—March 19–June 10, 2012. *Morbidity and Mortality Weekly Report* 2012;61(34):667–70.
- Centers for Disease Control and Prevention. Impact of a national tobacco education campaign on weekly numbers of quitline calls and website visitors—United States, March 4–June 23, 2013. *Morbidity and Mortality Weekly Report* 2013a;62(37):763–7.
- Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥18 years

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- with mental illness—United States, 2009–2011. *Morbidity and Mortality Weekly Report* 2013b;62:81–7.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014a; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/comprehensive.pdf>; accessed: July 26, 2017.
- Centers for Disease Control and Prevention. Frequently asked questions (FAQ) about 1-800-QUIT-NOW and the National Network of Tobacco Cessation Quitlines, May 2014b; <https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/1800quitnow_faq.pdf>; accessed: April 4, 2018.
- Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States, December 1, 2016; <https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm>; accessed: September 7, 2017.
- Chaiton M, Cohen JE, Bondy SJ, Selby P, Brown KS, Ferrence R, Garcia JM. Perceived addiction as a predictor of smoking cessation among occasional smokers. *Journal of Smoking Cessation* 2016:1–8.
- Chapman S, Wong WL, Smith W. Self-exempting beliefs about smoking and health: differences between smokers and ex-smokers. *American Journal of Public Health* 1993;83(2):215–9.
- Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology* 2006;184(3–4):353–66.
- Chen A. Teenagers embrace JUUL, saying it's discreet enough to vape in class, December 4, 2017; <<https://www.npr.org/sections/health-shots/2017/12/04/568273801/teenagers-embrace-juul-saying-its-discreet-enough-to-vape-in-class>>; accessed: August 9, 2018.
- Chu K, Allem J, Cruz TB, Unger JB. Vaping on Instagram: cloud chasing, hand checks and product placement. *Tobacco Control* 2017;26:575–8.
- Cole-Lewis H, Augustson E, Sanders A, Schwarz M, Geng Y, Coa K, Hunt Y. Analysing user-reported data for enhancement of SmokefreeTXT: a national text message smoking cessation intervention. *Tobacco Control* 2016.
- Collins FS, Varmus H. A new initiative on precision medicine. *New England Journal of Medicine* 2015;372(9):793–5.
- Conklin CA, Salkeld RP, Perkins KA, Robin N. Do people serve as cues to smoke? *Nicotine and Tobacco Research* 2013;15(12):2081–7.
- Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA: the Journal of the American Medical Association* 2014;311(2):172–82.
- Corey CG, Chang JT, Rostron BL. Electronic nicotine delivery system (ENDS) battery-related burns presenting to US emergency departments, 2016. *Injury Epidemiology* 2018;5(1):4.
- Coughlin S. We asked teens to explain Juuling to us & wow, August 9, 2018; <<http://www.refinery29.com/2018/02/190089/what-is-juul-e-cigarette-vaping-teenagers>>.
- Creamer MR, Wang TW, Babb S, Cullen KA, Day H, Willis G. Tobacco product use and cessation indicators among adults—United States, 2018. *Morbidity and Mortality Weekly Report* 2019;68(45):1013–9.
- Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW, Creamer MR, Jamal A, Ambrose BK, King BA. E-cigarette use among youth in the United States, 2019. *JAMA: the Journal of the American Medical Association* 2019.
- Cummins SE, Bailey L, Campbell S, Koon-Kirby C, Zhu SH. Tobacco cessation quitlines in North America: a descriptive study. *Tobacco Control* 2007;16(Suppl 1):i9–i15.
- Curry SJ, Grothaus LC, McAfee T, Pabiniak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *New England Journal of Medicine* 1998;339(10):673–9.
- Curry SJ, Wagner EH, Grothaus LC. Evaluation of intrinsic and extrinsic motivation interventions with a self-help smoking cessation program. *Journal of Consulting and Clinical Psychology* 1991;59(2):318–24.
- Dennis PA. Disparities in cancer funding. *Science* 2004;305(5689):1401–2.
- Ebbert JO, Croghan IT, Hurt RT, Schroeder DR, Hays JT. Varenicline for smoking cessation in light smokers. *Nicotine and Tobacco Research* 2016;18(10):2031–5.
- Elias J, Hendlin YH, Ling PM. Public versus internal conceptions of addiction: an analysis of internal Philip Morris documents. *PLoS Medicine* 2018;15(5):e1002562.
- Fagerstrom K, Etter JF, Unger JB. E-cigarettes: a disruptive technology that revolutionizes our field? *Nicotine and Tobacco Research* 2015;17(2):125–6.
- Farber HJ, Neptune ER, Ewart GW. Corrective statements from the tobacco industry: more evidence for why we need effective tobacco control. *Annals of the American Thoracic Society* 2018;15(2):127–30.
- Ferketich AK, Khan Y, Wewers ME. Are physicians asking about tobacco use and assisting with cessation? Results from the 2001–2004 national ambulatory medical care survey (NAMCS). *Preventive Medicine* 2006;43(6):472–6.
- Ferry LH, Grissino LM, Runfola PS. Tobacco dependence curricula in U.S. undergraduate medical education.

- JAMA: the Journal of the American Medical Association* 1999;282(9):825–9.
- Fiore MC, Bailey WC, Cohen SJ. *Treating Tobacco Use and Dependence: Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, U.S. Public Health Service, 2000.
- Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, Heyman RB, Holbrook J, Jaen CR, Kottke TE, et al. *Smoking Cessation: Clinical Practice Guideline No. 18*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1996. AHCPR Publication No. 96-0692.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Fiore MC, Novotny TE, Pierce JP, Giovino GA, Hatziandreu EJ, Newcomb PA, Surawicz TS, Davis RM. Methods used to quit smoking in the United States. Do cessation programs help? *JAMA: the Journal of the American Medical Association* 1990;263(20):2760–5.
- Ford DE, Vu HT, Anthony JC. Marijuana use and cessation of tobacco smoking in adults from a community sample. *Drug and Alcohol Dependence* 2002;67(3):243–8.
- Friedman LC, Cheyne A, Givelber D, Gottlieb MA, Daynard RA. Tobacco industry use of personal responsibility rhetoric in public relations and litigation: disguising freedom to blame as freedom of choice. *American Journal of Public Health* 2015;105(2):250–60.
- Fu SS, van Ryn M, Nelson D, Burgess DJ, Thomas JL, Saul J, Clothier B, Nyman JA, Hammett P, Joseph AM. Proactive tobacco treatment offering free nicotine replacement therapy and telephone counselling for socioeconomically disadvantaged smokers: a randomised clinical trial. *Thorax* 2016;71(5):446–53.
- Fu SS, van Ryn M, Sherman SE, Burgess DJ, Noorbaloochi S, Clothier B, Taylor BC, Schleder CM, Burke RS, Joseph AM. Proactive tobacco treatment and population-level cessation: a pragmatic randomized clinical trial. *JAMA Internal Medicine* 2014;174(5):671–7.
- Gandhi KK, Foulds J, Steinberg MB, Lu SE, Williams JM. Lower quit rates among African American and Latino menthol cigarette smokers at a tobacco treatment clinic. *International Journal of Clinical Practice* 2009;63(3):360–7.
- Geller AC, Brooks DR, Powers CA, Brooks KR, Rigotti NA, Bogner B, McIntosh S, Zapka J. Tobacco cessation and prevention practices reported by second and fourth year students at U.S. medical schools. *Journal of General Internal Medicine* 2008;23(7):1071–6.
- Genetics Home Reference. What is the Precision Medicine Initiative, June 12, 2018; <<https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative>>; accessed: June 13, 2018.
- Ghorai K, Akter S, Khatun F, Ray P. mHealth for smoking cessation programs: a systematic review. *Journal of Personalized Medicine* 2014;4(3):412–23.
- Gibson JE, Murray RL, Borland R, Cummings KM, Fong GT, Hammond D, McNeill A. The impact of the United Kingdom's national smoking cessation strategy on quit attempts and use of cessation services: findings from the International Tobacco Control Four Country Survey. *Nicotine and Tobacco Research* 2010;12(Suppl):S64–S71.
- GlaxoSmithKline. Medication guide: Wellbutrin (bupropion hydrochloride) tablets, May 2017; <https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Wellbutrin_Tablets/pdf/WELLBUTRIN-TABLETS-PI-MG.PDF>; accessed: July 16, 2019.
- Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* 2004;61(11):1107–15.
- Griffith BN, Montalto NJ, Ridpath L, Sullivan K. Tobacco dependence curricula in U.S. osteopathic medical schools: a follow-up study. *Journal of the American Osteopathic Association* 2013;113(11):838–48.
- Grigorian G. Juuling at Dartmouth: addiction renewed and reimagined. *The Dartmouth*, February 9, 2018; <<http://www.thedartmouth.com/article/2018/02/juuling-at-dartmouth-addiction-renewed-and-reimagined>>; accessed: August 9, 2018.
- Hajek P, Stead LF, West R, Jarvis M, Hartmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub4.
- Hall M, Bogdanovica I, Britton J. Research funding for addressing tobacco-related disease: an analysis of UK investment between 2008 and 2012. *BMJ Open* 2016;6(7):e011609.
- Hall SM, Delucchi KL, Velicer WF, Kahler CW, Ranger-Moore J, Hedeker D, Tsoh JY, Niaura R. Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. *Nicotine and Tobacco Research* 2001;3(3):193–202.
- Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. *Annual Review of Clinical Psychology* 2009;5:409–31.
- Hamlett-Berry K, Davison J, Kivlahan DR, Matthews MH, Hendrickson JE, Almenoff PL. Evidence-based national

- initiatives to address tobacco use as a public health priority in the Veterans Health Administration. *Military Medicine* 2009;174(1):29–34.
- Haskins BL, Lesperance D, Gibbons P, Boudreaux ED. A systematic review of smartphone applications for smoking cessation. *Translational Behavioral Medicine* 2017;7(2):292–9.
- Hays JT, Croghan IT, Schroeder DR, Burke MV, Ebbert JO, McFadden DD, Hurt RD. Residential treatment compared with outpatient treatment for tobacco use and dependence. *Mayo Clinic Proceedings* 2011;86(3):203–9.
- Hirschhorn N. *Evolution of the Tobacco Industry Positions on Addiction to Nicotine: A Report Prepared for the Tobacco Free Initiative, World Health Organization*. Geneva (Switzerland): World Health Organization, 2009; <<http://www.who.int/iris/handle/10665/43988>>; accessed: September 14, 2017.
- Hopkins DP, Husten CG, Fielding JE, Rosenquist JN, Westphal LL. Evidence reviews and recommendations on interventions to reduce tobacco use and exposure to environmental tobacco smoke: a summary of selected guidelines. *American Journal of Preventive Medicine* 2001;20(2 Suppl):67–87.
- Huang J, Duan Z, Kwok J, Binns S, Vera LE, Kim Y, Szczyka G, Emery SL. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the U.S. retail e-cigarette market. *Tobacco Control* 2018.
- Hughes JR. The hardening hypothesis: is the ability to quit decreasing due to increasing nicotine dependence? A review and commentary. *Drug and Alcohol Dependence* 2011;117(2-3):111–7.
- Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;99(1):29–38.
- Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine and Tobacco Research* 2003;5(1):13–25.
- Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, King BA. Tobacco use among middle and high school students—United States, 2011–2016. *Morbidity and Mortality Weekly Report* 2017;66(23):597–603.
- Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005–2015. *Morbidity and Mortality Weekly Report* 2016;65(44):1205–11.
- Jarvik ME. Further observations on nicotine as the reinforcing agent in smoking. In: Dunn WL Jr, editor. *Smoking Behavior: Motives and Incentives*. Washington (DC): V. H. Winston and Sons, 1973:33–49.
- Joyce GF, Niaura R, Maglione M, Mongoven J, Larson-Rotter C, Coan J, Lapin P, Morton S. The effectiveness of covering smoking cessation services for Medicare beneficiaries. *Health Services Research* 2008;43(6):2106–23.
- Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, et al. Tobacco-product use by adults and youths in the United States in 2013 and 2014. *New England Journal of Medicine* 2017;376(4):342–53.
- Keller PA, Feltracco A, Bailey LA, Li Z, Niederdeppe J, Baker TB, Fiore MC. Changes in tobacco quitlines in the United States, 2005–2006. *Preventing Chronic Disease* 2010;7(2):A36.
- King BA, Creamer MR, Harrell M, Kelder S, Norman L, Perry CL. Surgeon General’s reports on tobacco: a continued legacy of unbiased and rigorous synthesis of the scientific evidence. *Nicotine and Tobacco Research* 2018;20(8):1033–6.
- King BA, Dube SR, Babb SD, McAfee TA. Patient-reported recall of smoking cessation interventions from a health professional. *Preventive Medicine* 2013;57(5):715–7.
- Kofman M, Dunton K, Senkewicz MB. *Implementation of Tobacco Cessation Coverage Under the Affordable Care Act: Understanding How Private Health Insurance Policies Cover Tobacco Cessation Treatments*. Washington (DC): Health Policy Institute, Georgetown University, 2012.
- Krasnegor NA, editor. *The Behavioral Aspects of Smoking*. NIDA Research Monograph 26. Rockville (MD): U.S. Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; National Institute on Drug Abuse; Division of Research, August 1979.
- Lee JE, Park EC, Chun SY, Park HK, Kim TH. Socio-demographic and clinical factors contributing to smoking cessation among men: a four-year follow up study of the Korean Health Panel Survey. *BMC Public Health* 2016;16:908.
- Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD006936. DOI: 10.1002/14651858.CD006936.pub3.
- Liu X, Li R, Lanza ST, Vasilenko SA, Piper M. Understanding the role of cessation fatigue in the smoking cessation process. *Drug and Alcohol Dependence* 2013;133(2):548–55.
- Manley MW, Epps RP, Glynn TJ. The clinician’s role in promoting smoking cessation among clinic patients. *Medical Clinics of North America* 1992;76(2):477–94.
- McAfee T, Babb S, McNabb S, Fiore MC. Helping smokers quit—opportunities created by the Affordable Care Act. *New England Journal of Medicine* 2015;372(1):5–7.
- McAfee T, Davis KC, Alexander RL Jr, Pechacek TF, Bunnell R. Effect of the first federally funded U.S. antismoking national media campaign. *Lancet* 2013;382(9909):2003–11.

- McAfee T, Sofian NS, Wilson J, Hindmarsh M. The role of tobacco intervention in population-based health care: a case study. *American Journal of Preventive Medicine* 1998;14(3 Suppl):46–52.
- Mermelstein R, Colby SM, Patten C, Prokhorov A, Brown R, Myers M, Adelman W, Hudmon K, McDonald P. Methodological issues in measuring treatment outcome in adolescent smoking cessation studies. *Nicotine and Tobacco Research* 2002;4(4):395–403.
- Montalto NJ, Ferry LH, Stanhiser T. Tobacco dependence curricula in undergraduate osteopathic medical education. *Journal of the American Osteopathic Association* 2004;104(8):317–23.
- National Academies of Sciences, Engineering, and Medicine. *Public Health Consequences of E-Cigarettes*. Washington (DC): The National Academies Press, 2018.
- National Cancer Institute. *Those Who Continue to Smoke: Is Achieving Abstinence Harder and Do We Need to Change Our Interventions?* Smoking and Tobacco Control Monograph No. 15. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2003.
- National Cancer Institute. *The Role of the Media in Promoting and Reducing Tobacco Use*. Smoking and Tobacco Control Monograph No. 19. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2008. NIH Publication No. 07-6242.
- National Conference of State Legislatures. Marijuana Overview: Legalization, 2016; <<http://www.ncsl.org/research/civil-and-criminal-justice/marijuana-overview.aspx>>; accessed: November 5, 2019.
- National Institute on Drug Abuse. *Research Reports: Tobacco, Nicotine, and E-Cigarettes*. Bethesda (MD): National Institutes of Health, National Institute on Drug Abuse, 2018.
- North American Quitline Consortium. North American quitlines: a profile of reach and services in 2005 across the U.S. and Canada, 2007; <<http://c.y.mcdn.com/sites/www.naquitline.org/resource/resmgr/docs/factsheet-survey2007.pdf>>; accessed: September 14, 2017.
- Oakes W, Chapman S, Borland R, Balmford J, Trotter L. “Bulletproof skeptics in life’s jungle”: which self-exempting beliefs about smoking most predict lack of progression towards quitting? *Preventive Medicine* 2004;39(4):776–82.
- Office of the U.S. Surgeon General. *Surgeon General’s Advisory on E-Cigarette Use Among Youth*, n.d.; <<https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf>>; accessed: January 9, 2019.
- Orleans CT, Schoenbach VJ, Wagner EH, Quade D, Salmon MA, Pearson DC, Fiedler J, Porter CQ, Kaplan BH. Self-help quit smoking interventions: effects of self-help materials, social support instructions, and telephone counseling. *Journal of Consulting and Clinical Psychology* 1991;59(3):439–48.
- Ossip-Klein DJ, Giovino GA, Megahed N, Black PM, Emont SL, Stiggins J, Shulman E, Moore L. Effects of a smoker’s hotline: results of a 10-county self-help trial. *Journal of Consulting and Clinical Psychology* 1991;59(2):325–32.
- Parascandola M. Tobacco harm reduction and the evolution of nicotine dependence. *American Journal of Public Health* 2011;101(4):632–41.
- Patton GC, Coffey C, Carlin JB, Sawyer SM, Lynskey M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. *Addiction* 2005;100(10):1518–25.
- Pfizer. Medication guide: Chantix (varenicline) tablets, February 2019; <<http://labeling.pfizer.com/ShowLabeling.aspx?id=557§ion=MedGuide>>; accessed: July 16, 2019.
- Polito JR. *Freedom from Nicotine: The Journey Home*, 2013; <<http://whyquit.com/ffn/index.html>>; accessed: September 14, 2017.
- Powers CA, Zapka JG, Bogner B, Dube C, Hyder Ferry L, Ferguson KJ, O’Donnell JF, Rigotti N, Conley Thomson C, White M, et al. Evaluation of current tobacco curriculum at 12 U.S. medical schools. *Journal of Cancer Education* 2004;19(4):212–9.
- Prochaska JO, DiClemente CC, Velicer WF, Rossi JS. Standardized, individualized, interactive, and personalized self-help programs for smoking cessation. *Health Psychology* 1993;12(5):399–405.
- Proctor RN. *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition*. Berkeley (CA): University of California Press, 2011.
- Radding B. Pax Juul: the iPhone of e-cigs?, n.d.; <<https://www.mensfitness.com/life/gearandtech/pax-juul-iphone-e-cigs>>; accessed: August 9, 2018.
- Redmond LA, Adsit R, Kobinsky KH, Theobald W, Fiore MC. A decade of experience promoting the clinical treatment of tobacco dependence in Wisconsin. *Wisconsin Medical Journal* 2010;109(2):71–8.
- Richmond R, Zwar N, Taylor R, Hunnisett J, Hyslop F. Teaching about tobacco in medical schools: a worldwide study. *Drug and Alcohol Review* 2009;28(5):484–97.
- Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia (PA): Lippincott-Raven, 1998.
- Saggio J. What is a Juul? It’s a trend parents need to know about. *Florida Today*, 2018; <<https://www.floridatoday.com/story/news/2018/02/02/what-juul-its-trend-parents-need-know/1070088001>>; accessed: August 9, 2018.
- Schauer GL, Berg CJ, Kegler MC, Donovan DM, Windle M. Differences in tobacco product use among past month adult marijuana users and nonusers: findings from the

- 2003–2012 National Survey on Drug Use and Health. *Nicotine and Tobacco Research* 2016;18(3):281–8.
- Schauer GL, King BA, McAfee TA. Prevalence, correlates, and trends in tobacco use and cessation among current, former, and never adult marijuana users with a history of tobacco use, 2005–2014. *Addictive Behaviors* 2017;73:165–71.
- Schlam TR, Baker TB. Interventions for tobacco smoking. *Annual Review of Clinical Psychology* 2013;9:675–702.
- Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clinical Pharmacokinetics* 2001;40(9):661–84.
- Schroeder SA. What to do with a patient who smokes. *JAMA: the Journal of the American Medical Association* 2005;294(4):482–7.
- Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. *Annual Review of Public Health* 2010;31:297–314.
- Scott KA, Mason MJ, Mason JD. I'm not a smoker: constructing protected prototypes for risk behavior. *Journal of Business Research* 2015;68(10):2198–206.
- Shiffman S. Ecological momentary assessment (EMA) in studies of substance use. *Psychological Assessment* 2009;21(4):486–97.
- Shiffman S, West R, Gilbert D. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine and Tobacco Research* 2004;6(4):599–614.
- Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. *Nicotine and Tobacco Research* 2015;17(2):158–62.
- Siu AL. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 2015;163(8):622–34.
- Smith MW, Chen S, Siroka AM, Hamlett-Berry K. Using policy to increase prescribing of smoking cessation medications in the VA healthcare system. *Tobacco Control* 2010;19(6):507–11.
- Smokefree.gov. Sign up for SmokefreeTXT, n.d.; <<https://smokefree.gov/smokefreetxt>>; accessed: August 17, 2017.
- Solberg LI, Maxwell PL, Kottke TE, Gepner GJ, Brekke ML. A systematic primary care office-based smoking cessation program. *Journal of Family Practice* 1990;30(6):647–54.
- Soule EK, Pomeranz JL, Moorhouse MD, Barnett TE. Multiple tobacco use and increased nicotine dependence among people with disabilities. *Disability and Health Journal* 2015;8(2):258–63.
- Squiers L, Brown D, Parvanta S, Dolina S, Kelly B, Dever J, Southwell BG, Sanders A, Augustson E. The SmokefreeTXT (SFTXT) study: web and mobile data collection to evaluate smoking cessation for young adults. *JMIR Research Protocols* 2016;5(2):e134.
- Squiers LB, Augustson E, Brown D, Kelly B, Southwell B, Dever J, Dolina S, Tzeng J, Parvanta S, Holt S, et al. An experimental comparison of mobile texting programs to help young adults quit smoking. *Health Systems* 2017;6(1):1–14.
- SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine and Tobacco Research* 2002;4(2):149–59.
- Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD002850. DOI: 10.1002/14651858.CD002850.pub3.
- Strecher VJ, Kreuter M, Den Boer DJ, Kobrin S, Hoppers HJ, Skinner CS. The effects of computer-tailored smoking cessation messages in family practice settings. *Journal of Family Practice* 1994;39(3):262–70.
- Strecher VJ, Shiffman S, West R. Randomized controlled trial of a web-based computer-tailored smoking cessation program as a supplement to nicotine patch therapy. *Addiction* 2005;100(5):682–8.
- Suiters K. Are your kids JUULing at school? 7 on your side investigates, January 31, 2018; <<http://wjla.com/features/7-on-your-side/are-your-kids-juuling-at-school-7-on-your-side-investigates>>; accessed: August 9, 2018.
- Szatkowski L, McNeill A. Diverging trends in smoking behaviors according to mental health status. *Nicotine and Tobacco Research* 2015;17(3):356–60.
- Taber JM, Klein WM, Ferrer RA, Augustson E, Patrick H. A pilot test of self-affirmations to promote smoking cessation in a national smoking cessation text messaging program. *JMIR mHealth uHealth* 2016;4(2):e71.
- Teitell B. “Juuling”: The most widespread phenomenon you've never heard of. *The Boston Globe*, November 16, 2017; <<https://www.bostonglobe.com/metro/2017/11/15/where-teenagers-are-high-school-bathrooms-vaping/IJ6xYWWIOTKqsUGTtlw4UO/story.html>>; accessed: August 9, 2018.
- Torabi MR, Tao R, Jay SJ, Olcott C. A cross-sectional survey on the inclusion of tobacco prevention/cessation, nutrition/diet, and exercise physiology/fitness education in medical school curricula. *JAMA: the Journal of the American Medical Association* 2011;305(5):400–6.
- Trinidad DR, Perez-Stable EJ, Messer K, White MM, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. *Addiction* 2010;105(Suppl 1):84–94.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service.*

- Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General.* Washington: U.S. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979. DHEW Publication No. (PHS) 79-50066.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1982. DHHS Publication No. (PHS) 82-50179.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1983. DHHS Publication No. (PHS) 84-50204.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984. DHHS Publication No. (PHS) 84-50205.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.
- U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Publication No. (CDC) 89-8411.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
- U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.* Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2016.
- U.S. Department of Justice. Print corrective statements—exhibit 3: newspaper exemplars, October 2, 2017a; <<https://www.justice.gov/opa/press-release/file/1013581/download>>; accessed: April 11, 2019.
- U.S. Department of Justice. Tobacco companies to begin issuing court-ordered statements in tobacco racketeering suit [press release], November 22, 2017b; <<https://www.justice.gov/opa/pr/tobacco-companies-begin-issuing-court-ordered-statements-tobacco-racketeering-suit>>; accessed: April 11, 2019.
- U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on new enforcement actions and a Youth Tobacco Prevention Plan to stop youth use of, and access to, JUUL and other e-cigarettes [press release], April 24, 2018; <<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm605432.htm>>; accessed: August 9, 2018.
- U.S. Food and Drug Administration (FDA). Want to Quit Smoking? FDA-Approved Products Can Help [consumer update], 2017; <<https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198176.htm>>; accessed: August 1, 2018.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions, September 2015;

- <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>>; accessed: May 24, 2017.
- Ussher M, Beard E, Abikoye G, Hajek P, West R. Urge to smoke over 52 weeks of abstinence. *Psychopharmacology* 2013;226(1):83–9.
- Vidrine JI, Shete S, Cao Y, Greisinger A, Harmonson P, Sharp B, Miles L, Zbikowski SM, Wetter DW. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. *JAMA Internal Medicine* 2013;173(6):458–64.
- Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tobacco Control* 2016;25(Suppl 2):ii14–ii20.
- Vogt F, Hall S, Marteau TM. General practitioners' and family physicians' negative beliefs and attitudes towards discussing smoking cessation with patients: a systematic review. *Addiction* 2005;100(10):1423–31.
- Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults—United States, 2017. *Morbidity and Mortality Weekly Report* 2018;67(44):1225–32.
- Wang TW, Kenemer B, Tynan MA, Singh T, King B. Consumption of combustible and smokeless tobacco—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2016;65(48):1357–63.
- Warner KE, Mendez D. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine and Tobacco Research* 2019;21(1):41–7.
- Wells Fargo Securities. *Nielsen: Tobacco “All Channel” Data: Marlboro Vol Weak But Share Pressures Ease*. Equity Research. San Francisco (CA): Wells Fargo Securities, 2018.
- West R, May S, West M, Croghan E, McEwen A. Performance of English stop smoking services in first 10 years: analysis of service monitoring data. *BMJ* 2013;347:f4921.
- Wetter DW, McClure JB, de Moor C, Cofta-Gunn L, Cummings S, Cinciripini PM, Gritz ER. Concomitant use of cigarettes and smokeless tobacco: prevalence, correlates, and predictors of tobacco cessation. *Preventive Medicine* 2002;34(6):638–48.
- Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD006611. DOI: 10.1002/14651858.CD006611.pub4.
- Willett JG, Bennett M, Hair EC, Xiao H, Greenberg MS, Harvey E, Cantrell J, Vallone D. Recognition, use and perceptions of JUUL among youth and young adults. *Tobacco Control* 2018.
- Zhang L, Malarcher A, Mann N, Campbell K, Davis K, Anderson C, Alexander R, Rodes R. The influence of state-specific quitline numbers on call volume during a national tobacco education campaign promoting 1-800-QUIT-NOW. *Nicotine and Tobacco Research* 2016;18(8):1780–5.
- Zhu SH, Lee M, Zhuang YL, Gamst A, Wolfson T. Interventions to increase smoking cessation at the population level: how much progress has been made in the last two decades? *Tobacco Control* 2012;21(2):110–8.
- Zhu SH, Stretch V, Balabanis M, Rosbrook B, Sadler G, Pierce JP. Telephone counseling for smoking cessation: effects of single-session and multiple-session interventions. *Journal of Consulting and Clinical Psychology* 1996;64(1):202–11.

Chapter 2

Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth

Introduction 37

Data Sources 37

Key Epidemiologic Measures 42

Trends in Current and Former Cigarette Smoking 43

Adults 43

Young Adults 45

Youth 45

Changing Characteristics of Current Cigarette Smokers 47

Adults 47

Young Adults 51

Youth 51

Key Disparities in Current Cigarette Smoking Among Adults and Youth 57

Disparities by Behavioral Health Condition 57

Disparities by Chronic Disease Status 57

Disparities by Geographic Location 57

Disparities by Sexual Orientation and Gender Identity 58

Disparities in Smoking in Pregnant Women 58

Disparities in Smoking Among Active Duty Service Members 59

Correlation of Smoking-Related Risk Factors 59

Cigarette Smoking Cessation Among Adults and Youth 59

Recent Successful Cessation 59

Adults 61

Quit Ratio 61

Adults 61

Young Adults 66

Youth 66

Trends in the Cessation Continuum for Current Smokers 66

Attempts to Quit Smoking During the Past Year 67

Trends in Attempts to Quit Smoking During the Past Year 71

Number and Duration of Quit Attempts During the Past Year 71

Interest in Quitting Smoking 78

Trends in Interest in Quitting Smoking 78

History of a Quit Attempt 79

Other Tobacco Products: Use and Cessation 80

Adults 80

Young Adults 84

Youth 84

Clinical Interventions for Smoking Cessation: Prevalence and Trends 86

Screening for Tobacco Use and Receipt of Advice to Quit from Health Professionals 86

Adults 86

Young Adults 90

Youth 93

Use of Counseling and Medications to Quit Smoking 93

Adults 93

Young Adults 95

Youth 95

Use of Other Cessation Strategies 97

Adults 97

Young Adults 100

Youth 100

Key Disparities in Cessation Among Adults 100

Summary of the Evidence and Implications 102

Conclusions 104

References 105

Introduction

This chapter documents key patterns and trends in cigarette smoking cessation in the United States among adults overall (persons 18 years of age and older), young adults (18–24 years of age), and youth (12–17 years of age). The chapter also reviews the changing demographic and smoking-related characteristics of cigarette smokers, with a focus on how these changes may influence future trends in cessation.

This chapter also describes persistent disparities in cessation by age, race/ethnicity, level of education, status of health insurance, and other demographic characteristics. In addition, this chapter highlights trends and recent findings for several different measures, including the quit ratio (the proportion of ever smokers who are former smokers); recent successful cessation; past-year

quit attempts; interest in quitting; receipt of cessation advice from healthcare professionals; and use of effective cessation strategies, such as counseling and medication. As with previous Surgeon General's reports, this chapter focuses primarily on cigarette smoking (U.S. Department of Health and Human Services [USDHHS] 1990, 2014); however, given the shifting patterns of tobacco product use in the United States, it also touches on cessation as it relates to all tobacco products. Monitoring key trends and current patterns in tobacco use and cessation is critical for informing the development and implementation of policies and programs to increase cessation and, as a result, reduce the morbidity, mortality, and associated financial costs caused by tobacco product use in the United States.

Data Sources

A variety of national surveillance systems in the United States collect data on smoking cessation among adults and youth. These systems typically collect an array of information on cigarette smoking history; use of other tobacco products; and various aspects of cessation, such as quit intentions, quit attempts, and successful cessation. These surveys use different data collection methods and may define specific cessation behaviors using comparable, but not identical, approaches. Accordingly, it is important to monitor the results from national surveys that include cessation-related data involving adults, young adults, and youth to create a comprehensive picture of cessation prevalence and patterns.

Appendix 2.1 describes the surveys referenced in this chapter, all of which are cross-sectional except for the Population Assessment of Tobacco and Health (PATH) Study. The primary source for data on adults was the National Health Interview Survey (NHIS), and the primary sources for data on youth were the national Youth Risk Behavior Survey (YRBS), conducted as part of the Youth Risk Behavior Surveillance System (YRBSS), and the National Youth Tobacco Survey (NYTS) (Table 2.1). These surveys were chosen because of their scientific and methodologic reliability and validity and because they are conducted as part of long-standing surveillance systems (Thacker et al. 1988; Centers for Disease Control and Prevention [CDC] 2001). Additionally, most of these surveys have historically been used to track progress toward national cessation goals, including the U.S. Department

of Health and Human Services' *Healthy People* initiative (Office of Disease Prevention and Health Promotion n.d.b).

These data systems have additional strengths, including the timeliness of data releases and proven data collection methodologies, which use anonymous or confidential self-reported surveys that yield relatively high response rates. Self-reported data have been found to adequately reflect patterns of cigarette smoking among adults, including whether a respondent who has smoked in the past is currently not smoking, using scientifically validated biomarkers and other approaches (Connor Gorber et al. 2009; Wong et al. 2012); however, few studies have examined the validity of other cessation-related measures (Brigham et al. 2010; Persoskie and Nelson 2013).

NHIS, which has been a major source of health data among the U.S. adult population since the 1950s, is an annual household interview survey of the civilian, non-institutionalized population. At the time this report was compiled, NHIS data on cigarette smoking among adults 18 years of age and older were available from 1965 to 2017, and data on cigarette smoking cessation for daily smokers and nondaily smokers were available from 1997 to 2017. In addition, since 2000, NHIS has fielded a CCS every 5 years, which includes detailed questions on cigarette smoking cessation; NHIS also fielded the CCS in 1987 and 1992, but the cessation questions were not consistent between these surveys. Therefore, for analyses of adult cessation trends, the present report uses the longest series of years available for each cessation measure. Data on the characteristics of

Table 2.1 Sources of national survey data on smoking cessation used for this report, 1965–2017; United States

	BRFSS	HINTS	MTF	NAMCS	NATS	NHIS	NYTS	PATH	TUS-CPS	YRBS
Sponsoring agency or organization	Centers for Disease Control and Prevention; Health Resources and Services Administration; Administration on Aging; U.S. Department of Veterans Affairs; and Substance Abuse and Mental Health Services Administration	Health Communication and Informatics Research Branch, Division of Cancer Control and Population Sciences, National Cancer Institute	National Institute on Drug Abuse, administered by the University of Michigan's Institute for Social Research	Centers for Disease Control and Prevention	Centers for Disease Control and Prevention and U.S. Food and Drug Administration	National Center for Health Statistics	Centers for Disease Control and Prevention (with support from U.S. Food and Drug Administration since 2011)	U.S. Food and Drug Administration; National Institute on Drug Abuse	National Cancer Institute (2014–2015 wave cosponsored by the U.S. Food and Drug Administration)	Centers for Disease Control and Prevention
Type	Cross-sectional	Cross-sectional	Cross-sectional and longitudinal	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Longitudinal	Cross-sectional and longitudinal	Cross-sectional
Years	2017	2017	2011–2017	2004–2011	2013–2014	1965–2017; Cancer Control Supplements 2000, 2005, 2010, and 2015	1999, 2000, 2002, 2004, 2006, 2009, 2015, and 2017	2013–2014, 2014–2015	2001–2002, 2003, 2006–2007, 2010–2011, and 2014–2015	1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009, 2011, 2013, 2015, and 2017
Mode	Telephone-based questionnaire that state health departments conduct monthly over landline and cellular telephones using a standardized questionnaire and technical and methodologic assistance provided by CDC	Household-based, mailed questionnaire	School-based, self-administered questionnaire	<ul style="list-style-type: none"> Review medical records for information about patient visits Interview physicians and community health center providers 	Telephone-based questionnaire	Computer-assisted personal interview	School-based, self-administered questionnaire (paper-based)	Computer-assisted personal interview	Questionnaire via telephone and in-person interviews	School-based, self-administered questionnaire (paper-based)

Table 2.1 Continued

	BRFSS	HINTS	MTF	NAMCS	NATS	NHIS	NYTS	PATH	TUS-CPS	YRBS
Response rate	2017: 45.9%	<ul style="list-style-type: none"> • 2017: 25.0% • HINTS-FDA: 34.1% (NCI 2017a) • HINTS 5 Cycle 1 (2017): 32.4% (NCI 2017b) 	<ul style="list-style-type: none"> • 2015: <ul style="list-style-type: none"> – 12th-grade RR: 83% – Schools: 382 • 2016: <ul style="list-style-type: none"> – 12th-grade RR: 80% – Schools: 372 • 2017: <ul style="list-style-type: none"> – 12th-grade RR: 79% 	<ul style="list-style-type: none"> • 2009: 62.4% • 2010: 57.3% • 2011: 54.1% • 2012: 39.4% • 2013: 40.4% • 2014: 39.0% • 2015: 29.6% • 2016: 32.7% 	2013–2014: 36.1% overall (47.6% landline and 17.1%, cellular)	<ul style="list-style-type: none"> • 2015^a: <ul style="list-style-type: none"> – Household: 70.1% – Family: 69.3% – Sample adult: 63.4% • 2016^a: <ul style="list-style-type: none"> – Household: 67.9% – Family: 67.1% – Sample adult: 61.9% • 2017^a: <ul style="list-style-type: none"> – Household: 66.5% – Family: 65.7% – Sample adult: 53.0% • For years 1997–2017, the question about a past-year quit attempt was asked of all current cigarette smokers 	<ul style="list-style-type: none"> • 2015: <ul style="list-style-type: none"> – School: 72.6% – Student: 87.4% – Overall: 63.4% • 2016: <ul style="list-style-type: none"> – School: 81.5% – Student: 87.9% – Overall: 71.6% • 2017: <ul style="list-style-type: none"> – School: 76.8% – Student: 88.7% – Overall: 68.1% 	<ul style="list-style-type: none"> • 2013–2014: <ul style="list-style-type: none"> – 74.0% (adult) – 78.4% (youth) • 2014–2015: <ul style="list-style-type: none"> – 83.1% (adult) – 88.4% (youth) 	2014–2015: Average self-response rate (for all waves combined) 54.2%	<ul style="list-style-type: none"> • 2015: <ul style="list-style-type: none"> – School: 69% – Student: 86% – Overall: 60% • 2017: <ul style="list-style-type: none"> – School: 75% – Student: 81% – Overall: 60%

Table 2.1 Continued

	BRFSS	HINTS	MTF	NAMCS	NATS	NHIS	NYTS	PATH	TUS-CPS	YRBS
Sample size	2017: 450,016	<ul style="list-style-type: none"> • 2017: 3,335 • HINTS-FDA: 1,736 • HINTS 5 Cycle 1 (2017): 3,285 	<ul style="list-style-type: none"> • 2015: <ul style="list-style-type: none"> – 12th-grade students: 13,730 – Schools: 382 • 2016: <ul style="list-style-type: none"> – 12th-grade students: 12,600 – Schools: 372 • 2017: <ul style="list-style-type: none"> – 12th-grade students: 13,522 – Schools: 360 	<ul style="list-style-type: none"> • Patient records extracted: <ul style="list-style-type: none"> – 2009: 32,281 from a sample of 3,319 physicians – 2010: 31,229 from a sample of 3,525 physicians – 2011: 30,872 from a sample of 3,819 physicians – 2012: 76,330 from a sample of 15,740 physicians – 2013: 54,873 from a sample of 11,212 physicians – 2014: 45,710 from a sample of 9,989 physicians – 2015: 28,332 from a sample of 8,091 physicians – 2016: 13,165 from a sample of 3,699 physicians 	2013–2014: 75,233 respondents (70% landline and 30% cellular)	<ul style="list-style-type: none"> • Adults >18 years of age: <ul style="list-style-type: none"> – 2015: 33,672 – 2016: 33,028 – 2017: 26,742 • Overall households: <ul style="list-style-type: none"> – 2015: 41,493 – 2016: 30,220 – 2017: 32,617 	<ul style="list-style-type: none"> • Students in grades 6–12: <ul style="list-style-type: none"> – 2015: 17,711 – 2016: 20,675 – 2017: 17,872 • Overall households: <ul style="list-style-type: none"> – 2015: 41,493 – 2016: 30,220 – 2017: 32,617 	<ul style="list-style-type: none"> • 2013–2014: 45,971 (32,320 adults/16,651 youth) • 2014–2015: 40,534 (28,362 adults/12,172 youth) 	2014–2015: 163,920	<ul style="list-style-type: none"> • Students in grades 9–12: <ul style="list-style-type: none"> – 2015: 15,624 – 2017: 14,765

Table 2.1 Continued

	BRFSS	HINTS	MTF	NAMCS	NATS	NHIS	NYTS	PATH	TUS-CPS	YRBS
Cessation measure(s)	Quit ratio	Use of Internet-based programs or tools in quit attempts	Interest in quitting	<ul style="list-style-type: none"> • Screening for tobacco use • Counseling for use of or exposure to tobacco 	Advice to quit	Quit ratio, recent successful cessation, past-year quit attempt, Cancer Control Supplements, interest in cessation, provider advice to quit, and use of effective treatments	Advice to quit and use of counseling and medications to quit ^b	Quit attempts, quit ratio, recent successful cessation; use of NRT, medications, or counseling to quit	Past-year quit attempts, interest in quitting, recent smoking cessation, or receipt of medical doctor's advice to quit	Past-year quit attempt

Notes: **BRFSS** = Behavioral Risk Factor Surveillance System; **CDC** = Centers for Disease Control and Prevention; **HINTS** = Health Information National Trends Survey; **MTF** = Monitoring the Future; **NATS** = National Adult Tobacco Survey; **NAMCS** = National Ambulatory Medical Care Survey; **NHIS** = National Health Interview Survey; **NYTS** = National Youth Tobacco Survey; **PATH** = Population Assessment of Tobacco and Health; **RR** = relative risk; **TUS-CPS** = Tobacco Use Supplement to the Current Population Survey; **YRBS** = National Youth Risk Behavior Survey.

^aRR for household component, and unconditional RR for family and sample adult components.

^bThe measure of advice to quit has changed over time: 2009 (“During the past 12 months, did a medical doctor, dentist, or nurse tell you to stop smoking?”) and 2015 (“During the past 12 months, did any doctor, dentist, or nurse give you advice not to use tobacco that is smoked or put in your mouth?”). In 2017, NYTS did not contain either of these measures (advice to quit; use of counseling/cessation medications). There are other cessation measures that are not listed here (e.g., thinking about quitting during the past 12 months, and stopped using because trying to quit).

cigarette smokers are reviewed beginning with the year 2000 to correspond with the available cessation data.

YRBSS monitors six categories of health-related behaviors that contribute to the leading causes of death and disability among youth and adults. In operation since 1991, the national YRBS is a biennial survey that utilizes probability samples of students in public and private high schools; students anonymously complete questionnaires administered in schools. The survey is nationally representative of the U.S. high school population. This Surgeon General's report uses biennial data from the national YRBS to examine trends in youth cigarette smoking and past-year quit attempts among current cigarette smokers. For trends in cigarette smoking cessation among youth, this report uses biennial data from 1991 to 2015 from the national YRBS. However, this report does not include state and local data from YRBS surveys because (a) only one state and two districts produced weighted data for all years of the YRBS and (b) some of these surveys had small sample sizes for the measures examined in this report (CDC 2013).

NYTS is a cross-sectional, voluntary, school-based, self-administered, pencil-and-paper survey of U.S. middle and high school students. A three-stage cluster sampling procedure is used to generate a nationally representative sample of U.S. students who attend public and private schools in grades 6–12. Because the NYTS is a tobacco-focused survey as opposed to a general health survey, it collects more comprehensive data than YRBS on a variety of tobacco-related measures from middle school and high

school students, including tobacco product use, smoking cessation, exposure to secondhand smoke, tobacco-related knowledge and attitudes, access to tobacco products, and other tobacco-related indicators. The NYTS has been conducted most years since 1999. This chapter examined data from 2000, 2004, 2009, and 2015, corresponding roughly with the years of adult data from the NHIS Cancer Control Supplement (CCS). In 2017, the most recent wave of data available at the time this report was compiled, cessation of all tobacco products was assessed, and separate questions were not asked about cigarette smoking cessation specifically.

As reviewed in more detail in Appendix 2.1, this chapter also considers other sources of data, including the Tobacco Use Supplement to the Current Population Survey (TUS-CPS), the Behavioral Risk Factor Surveillance System (BRFSS), the National Adult Tobacco Survey (NATS), the National Ambulatory Medical Care Survey (NAMCS), the Health Information National Trends Survey (HINTS), and the Monitoring the Future (MTF) Study. Data from Nielsen Retail Management Services were also used to assess sales of over-the-counter nicotine replacement therapy (NRT). The data contain projected NRT sales from two major retail channels: expanded all outlets combined and convenience stores. The former category includes aggregated sales from food stores, drug stores, mass merchandizers, club stores, dollar stores, and military commissaries. In addition, published baseline and longitudinal analyses from the PATH Study are summarized.

Key Epidemiologic Measures

Appendix 2.2 defines the survey measures used in this chapter. In brief, this chapter examines a variety of epidemiologic areas related to cigarette smoking and cessation, including trends in current and former cigarette smoking and the smoking characteristics of adult and youth current cigarette smokers; disparities in current smoking, trends in the quit ratio, recent successful cessation, past-year quit attempts, current interest in quitting, and ever trying to quit smoking cigarettes among adult and youth smokers; tobacco screening and advice to quit delivered by health professionals; counseling and use of Food and Drug Administration (FDA)-approved medications for smoking cessation; use of other strategies for smoking cessation; and disparities in smoking cessation. This chapter also briefly addresses cessation of other tobacco products to the extent possible, given that national surveys include few measures of cessation for noncigarette tobacco products. Patterns of use of noncigarette tobacco products were included in the 2014 Surgeon

General's report (USDHHS 2014). However, because limited cessation information is available for noncigarette tobacco products, this report does not review trends in the use of these products and changes in the characteristics of the populations that use these products.

Data are presented in an order that first highlights the primary public health goal of tobacco use cessation (i.e., successful cessation), including the following three measures: prevalence of former smoking (persons who ever smoked >100 cigarettes who do not currently smoke), quit ratio (the proportion of ever smokers who are former smokers), and prevalence of recent smoking cessation (persons who quit smoking for >6 months in the past year). These measures are then followed by intermediary measures that reflect a smoker's journey to cessation (i.e., the cessation continuum), starting with the most proximate measure (prevalence of past-year quit attempts) and moving backward on the continuum from assessing a smoker's current interest in quitting completely to whether he or she

has ever made a quit attempt (Institute of Medicine 2007). The chapter concludes by examining tobacco screening and cessation interventions provided by health professionals and the utilization of other selected cessation strategies.

For adults overall, the most recent year of data from NHIS is presented for each indicator by key demographic characteristics (e.g., sex, age [18–24, 25–44, and 45–64 years of age and 65 years of age and older], race/ethnicity, level of education, geographic region, and status of health

insurance), followed by trends over time among adults for men and women overall and for non-Hispanic Whites (hereafter referred to as Whites), non-Hispanic Blacks (hereafter referred to as Blacks), and Hispanics. These data on adults are then followed by corresponding sections for analyses on young adults (18–24 years of age) and youth from various data sources. Some measures for young adults are missing, and statistically stable estimates could not be produced because of small sample sizes.

Trends in Current and Former Cigarette Smoking

Tests for linear and quadratic (nonlinear) trends were performed and controlled for variations in sex and race/ethnicity over time. Models for adults overall controlled for age over time, and models for youth controlled for grade level. A test for linear trend is statistically significant if a straight line (indicating a consistent increase or decrease) fits the adjusted data significantly better than no linear trend (i.e., the null hypothesis of no linear trend over time is rejected). Similarly, a test for quadratic trend is statistically significant if a curved line with one bend (indicating an accelerated or decelerated rate of change during the assessed period) fits the adjusted data better than no quadratic trend. Quadratic trends were initially assessed. If the quadratic trend was not statistically significant, then tests for linear trends were performed. Tests for other time functions (i.e., trend shapes) were not assessed; it is possible that other time functions could also fit the data.

Adults

The NHIS definition of current cigarette smoking has changed over time. For the purposes of this report, the definition of current smoking has been standardized. Specifically, current cigarette smokers are defined as those who smoked at least 100 cigarettes in their lifetime and who smoked every day or on some days at the time of the survey. Former cigarette smokers are defined as those who smoked at least 100 cigarettes during their lifetime but were not smoking at the time of the survey.

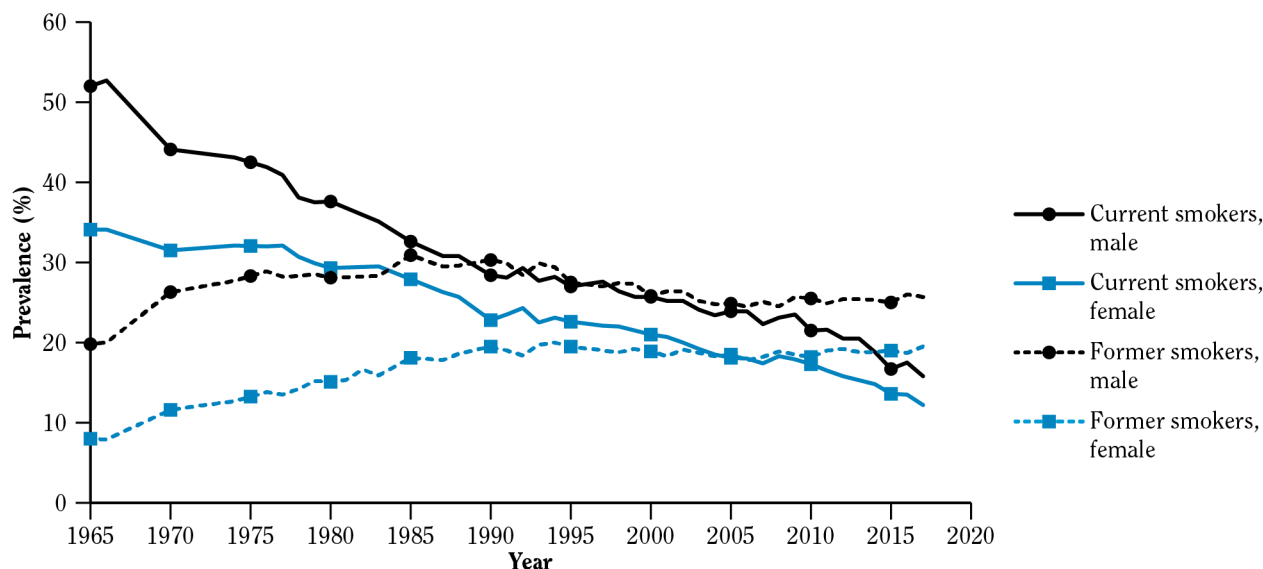
Among adults in 2018, the prevalence of current cigarette smoking was 13.8%, the lowest measured prevalence among U.S. adults since NHIS data collection for this measure began in 1965; the prevalence of former cigarette smoking was 20.9% (NHIS, public use data, 2018) (Blackwell and Villarroel 2018; Wang et al. 2018a). From 1965 to 2017, the prevalence of current smoking declined by 36.2 percentage points (relative percentage change: 69.6%) among men (from 52.0% to 15.8%)

and 21.9 percentage points (relative percentage change: 64.2%) among women (from 34.1% to 12.2%) ($p < 0.001$ for quadratic trend for both groups) (Figure 2.1). The prevalence of former smoking among all men peaked in 1985 (at 30.9%), and the prevalence of former smoking among women peaked in 1994 (at 20.0%) ($p < 0.001$ for quadratic trend for both groups). Among men, 1991 was the first year in which the prevalence of former smoking was higher than the prevalence of current smoking; however, not until 2010–2017 was the prevalence of former smoking consistently greater each year than the prevalence of current smoking. Among women, the prevalence of former smoking first surpassed the prevalence of current smoking in 2011 and remained higher through 2017.

Declines in the prevalence of current smoking were also observed across racial and ethnic subgroups (Figure 2.2) ($p < 0.001$ for linear trend for Whites from 42.2% in 1965 to 15.2% in 2017, Blacks [$p < 0.001$ for linear trend] from 46.0% in 1965 to 14.9% in 2017, and Hispanics [$p < 0.0001$ for linear trend] from 31.6% in 1978 to 9.9% in 2017). Although the prevalence of former smoking exceeded the prevalence of current smoking among Whites during 2002–2017 and among Hispanics during 2014–2017, the prevalence of former smoking among Blacks never exceeded the prevalence of current cigarette smoking during 1965–2017 ($p < 0.001$ for quadratic trends for former smoking among Whites and Blacks and a linear trend [$p < 0.001$] for Hispanics). The pattern of lower prevalence of former smoking than current smoking among Blacks may be the result of both their lower prevalence of initiation and their lower quit ratios compared with other racial/ethnic groups (USDHHS 2014).

It is important to note that the definition of a former smoker is broad and contains both persons who quit many years ago and persons who are actively trying to quit (i.e., they were not smoking at the time of the survey but could have quit for only 1 day). Decreases in the prevalence of former cigarette smoking among adults during the past 20–30 years primarily reflect decreases in

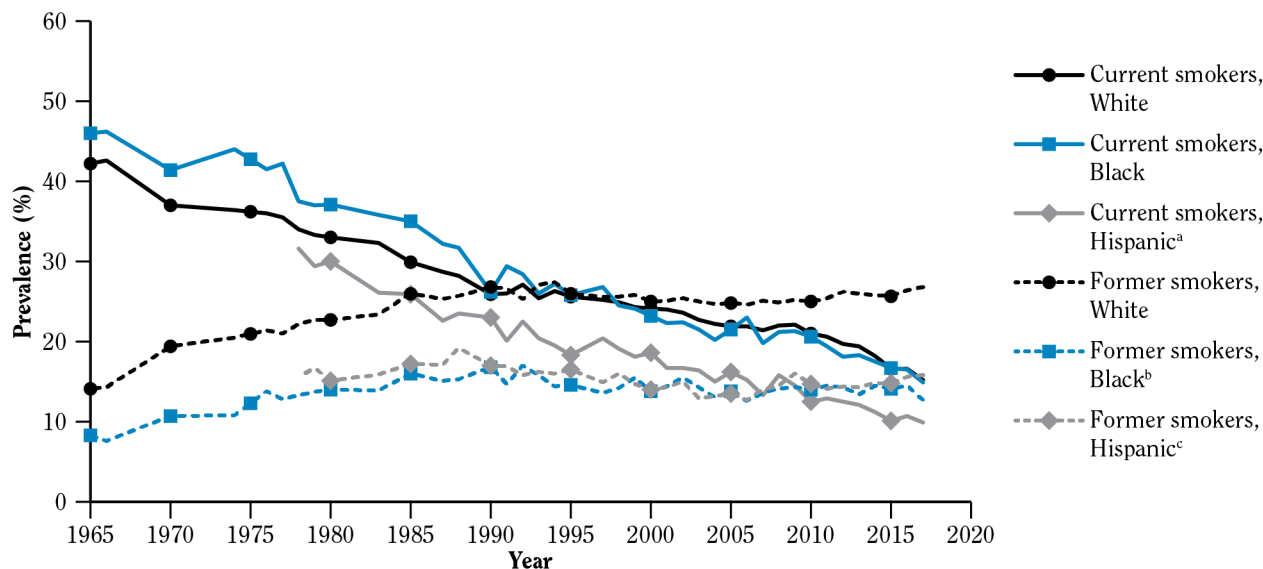
Figure 2.1 Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 2017, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

Figure 2.2 Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 2015, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

^aData were not collected for 1965, 1966, 1970, 1974, 1976, and 1977.

^bData were statistically unreliable (relative standard error >30% or denominator <50 sample cases) for the following years: 1980, 1987, 1992–1995, 2002, 2003, 2005, 2007–2013, and 2015–2017.

^cData were statistically unreliable (relative standard error >30% or denominator <50 sample cases) for 1992 and 2016.

cigarette smoking initiation, as illustrated by data from birth cohorts (USDHHS 2014). Specifically, this means that the prevalence of former smoking has primarily decreased because youth and young adults, in particular, are less likely to initiate cigarette smoking than they might have been in the past. Therefore, the pool of persons who are eligible to quit has decreased over time. Nevertheless, during the past decade, adult former cigarette smokers have become more common than current smokers, with the exception of Black adults.

Young Adults

Current cigarette smokers are defined as those who smoked at least 100 cigarettes in their lifetime and who smoked every day or on some days at the time of the survey. Among U.S. young adults (18–24 years of age) in 2017, the prevalence of current cigarette smoking was 10.4%, and the prevalence of former cigarette smoking was 5.1% (NHIS, public use data, 2017) (Wang et al. 2018a). Similar to data for adults overall, the prevalence of current smoking during 1965–2017 declined by 42.3 percentage points (relative percentage change: 77.9%) among young adult men (from 54.3% in 1965 to 12.0% in 2015; $p < 0.001$ for linear trend) and 29.6 percentage points (relative percentage change: 77.1%) among young adult women (from

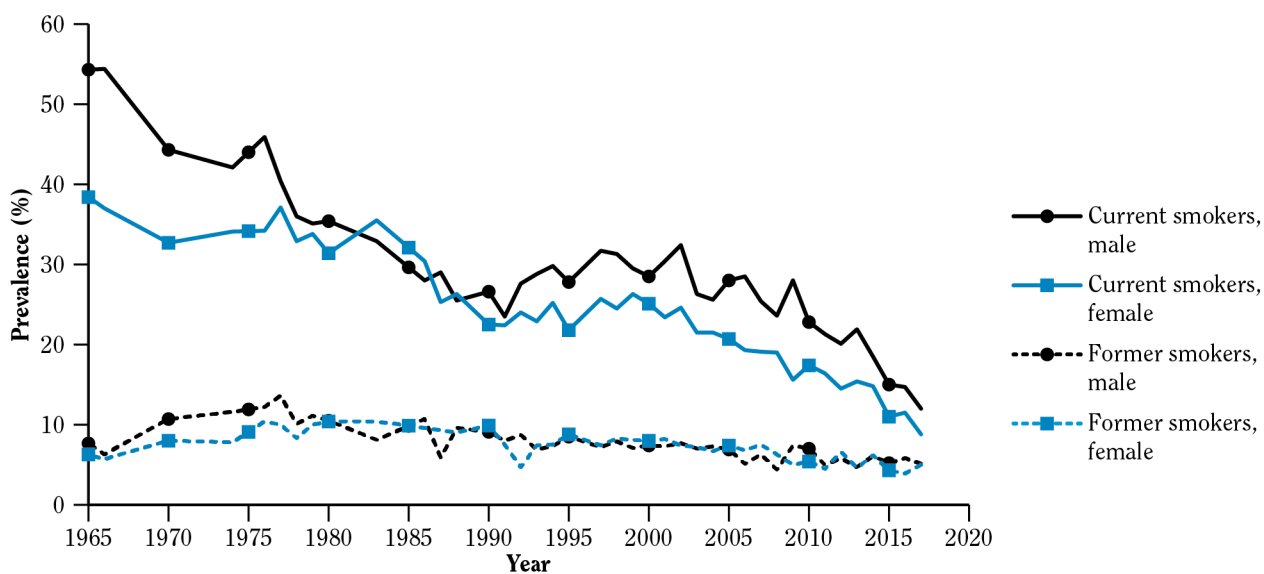
38.4% in 1965 to 8.8% in 2017; $p < 0.001$ for quadratic trend) (Figure 2.3). In contrast to the findings for adults overall, the prevalence of former smoking among young adult men peaked in 1977 (at 13.6%), and the prevalence of former smoking among young adult women peaked in 1978 (at 10.4%). Among young adult men and young adult women, the prevalence of former smoking has never exceeded the prevalence of current smoking (Figure 2.3).

Declines in the prevalence of current smoking among young adults across racial and ethnic subgroups were also similar to those for adults overall (Figure 2.4), declining for young adult Whites from 45.4% in 1965 to 13.5% in 2017 ($p < 0.001$ for quadratic trend), for young adult Blacks from 49.2% in 1965 to 8.6% in 2017 ($p < 0.001$ for quadratic trend), and for young adult Hispanics from 36.1% in 1978 to 5.6% in 2017 ($p < 0.001$ for linear trend) (Figure 2.4). In contrast to the findings for adults overall, the prevalence of former smoking among young adults in any of the three racial/ethnic groups never exceeded the prevalence of current smoking (Figure 2.4).

Youth

Current cigarette smoking in YRBS is defined as having smoked cigarettes on at least 1 day during the 30 days before the survey. In 2017, the prevalence of current

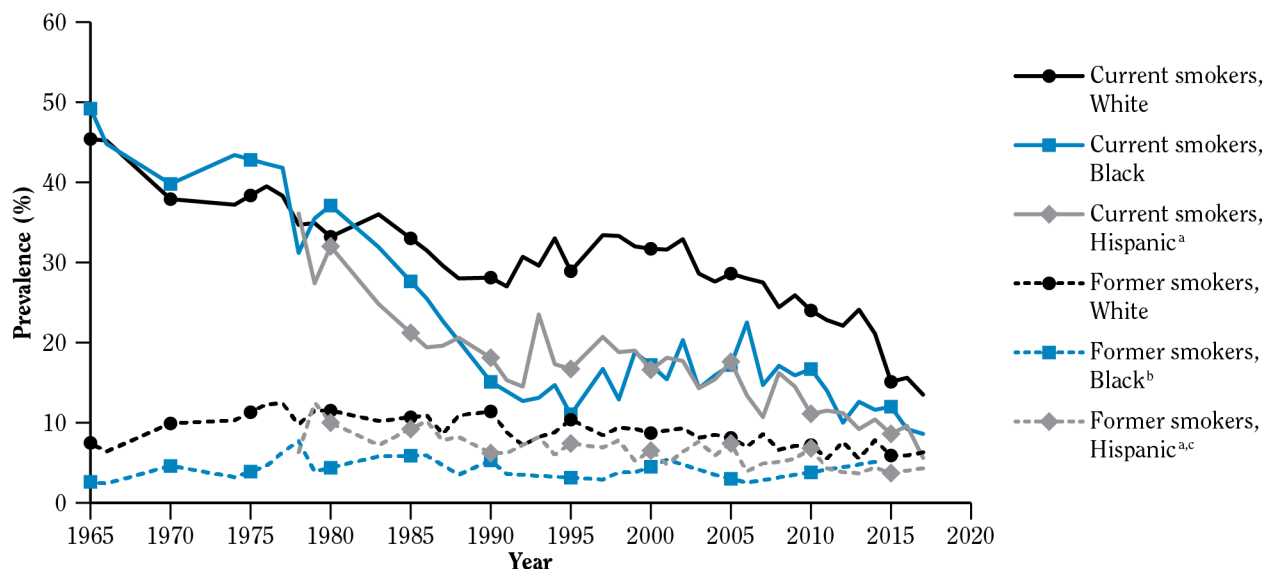
Figure 2.3 Trends in prevalence (%) of current and former cigarette smoking among young adults 18–24 years of age, by sex; National Health Interview Survey (NHIS) 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 2017, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

Figure 2.4 Trends in prevalence (%) of current and former cigarette smoking among young adults 18–24 years of age, by race/ethnicity; National Health Interview Survey (NHIS) 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 2017, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

^aData were not collected for 1965, 1966, 1970, 1974, 1976, and 1977.

^bData were statistically unreliable (relative standard error >30% or denominator <50 sample cases) for the following years: 1980, 1987, 1992–1995, 2002, 2003, 2005, 2007–2013, and 2015–2017.

^cData were statistically unreliable (relative standard error >30% or denominator <50 sample cases) for 1992 and 2016.

smoking among U.S. students in grades 9–12 was 8.8% (Kann et al. 2018). Many youth experiment with cigarette smoking, and some progress to a more established pattern of smoking. Those with a more established pattern may be particularly important to study for future cessation trends, as they are most likely to become adult smokers (USDHHS 2012). Among students in grades 9–12, the prevalence of current frequent cigarette smoking (ever smokers who had smoked 20 or more days during the past 30 days) was 2.7% (Kann et al. 2018). The prevalence of current smoking increased during 1991–1997 (27.5–36.4%) and then decreased during 1997–2017 (36.4–8.8%), and a significant quadratic trend was observed (Kann et al. 2018). Similarly, the prevalence of current frequent smoking increased during 1991–1999 (12.8–17.0%) and then decreased during 2001–2017 (13.9–2.7%), and a significant quadratic trend was also observed (Figure 2.5).

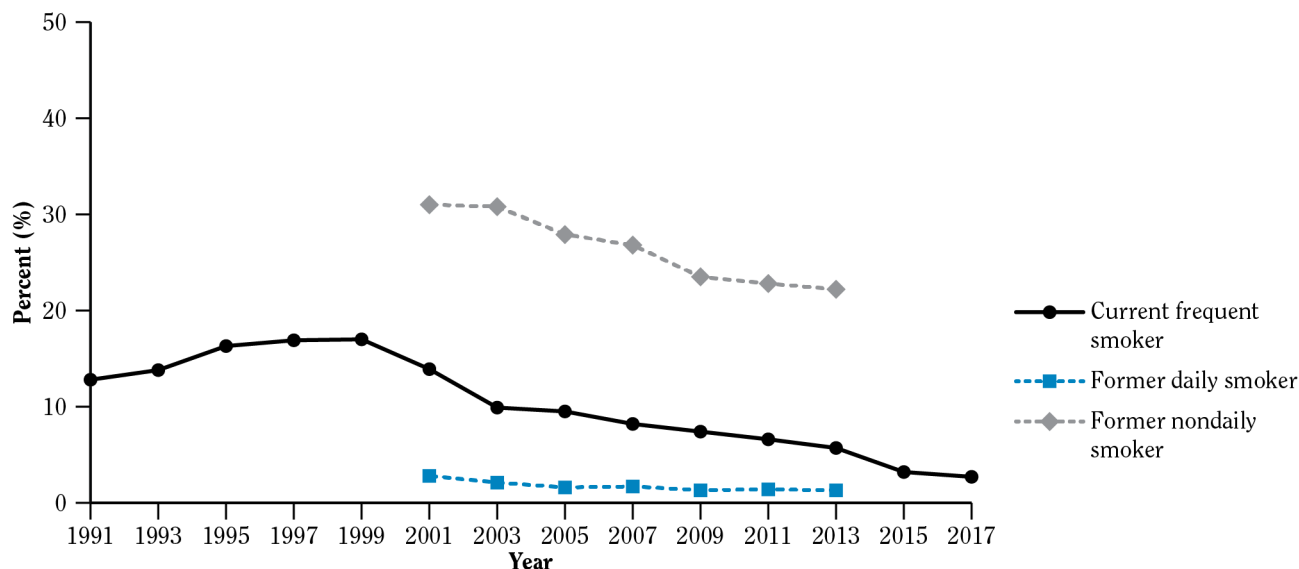
Similar nonlinear trends in these measures over time were observed by sex (YRBS, public use data, 1991–2017) and race/ethnicity (Figures 2.6a and 2.6b). The prevalence of current frequent smoking was consistently and statistically higher in Whites than in Blacks and Hispanics.

The YRBS does not contain a measure of former smoking that is similar to the NHIS measure of former

smoking for adults (i.e., ever smoked at least 100 cigarettes but was not a current smoker at the time of the survey). However, during 2001–2013, the YRBS asked students whether they had ever smoked daily. Students who were former daily smokers (i.e., ever smokers who were not smoking currently but reported smoking daily in the past) presumably include the majority of youth who had smoked at least 100 cigarettes and had since stopped smoking. In 2013, the prevalence of former daily smoking (i.e., ever daily smokers who reported no current smoking) among students in grades 9–12 was 1.3%, and the prevalence of former nondaily smoking was 22.2% (Figure 2.5). From 2001 to 2013, a nonlinear decrease was observed in the prevalence of former daily smoking, and the prevalence of former nondaily smoking decreased linearly. Similar patterns were observed among females (YRBS, public use data, 2001–2013) and Whites (Figure 2.6b). In contrast, males (YRBS, public use data, 2001–2013) and Blacks (Figure 2.6b) had linear decreases for former daily smoking, but changes in this measure were not observed among Hispanics. In addition, nonlinear decreases in former nondaily smoking occurred among Blacks.

For all years, the prevalence of former nondaily smoking was higher than the prevalence of current

Figure 2.5 Trends in prevalence (%) of current frequent^a, former daily^b, and former nondaily^c cigarette smoking among high school students; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States



Source: YRBS, Centers for Disease Control and Prevention, public use data, 1991–2017.

Note: The question about daily smoking was not asked in 2015 and 2017.

^aStudents who answered “yes” to “have you ever smoked” and “yes” to “do you currently smoke?”; and reported smoking on >19 days during the past 30 days.

^bStudents who answered “yes” to “have you ever smoked” and “no” to “do you currently smoke?” and answered “yes” to “ever daily.”

^cStudents who answered “yes” to “have you ever smoked” and “no” to “do you currently smoke?” and answered “no” to “ever daily.”

frequent and former daily smoking (Figure 2.5), indicating high percentages of youth tried (i.e., experimented with), but did not maintain, cigarette smoking. In contrast, the low prevalence of former daily smokers most

likely reflects the low prevalence of daily smoking among students in grades 9–12 and the low prevalence of cessation among those who only recently became daily smokers (Fiore et al. 2008; USDHHS 2014).

Changing Characteristics of Current Cigarette Smokers

Adults

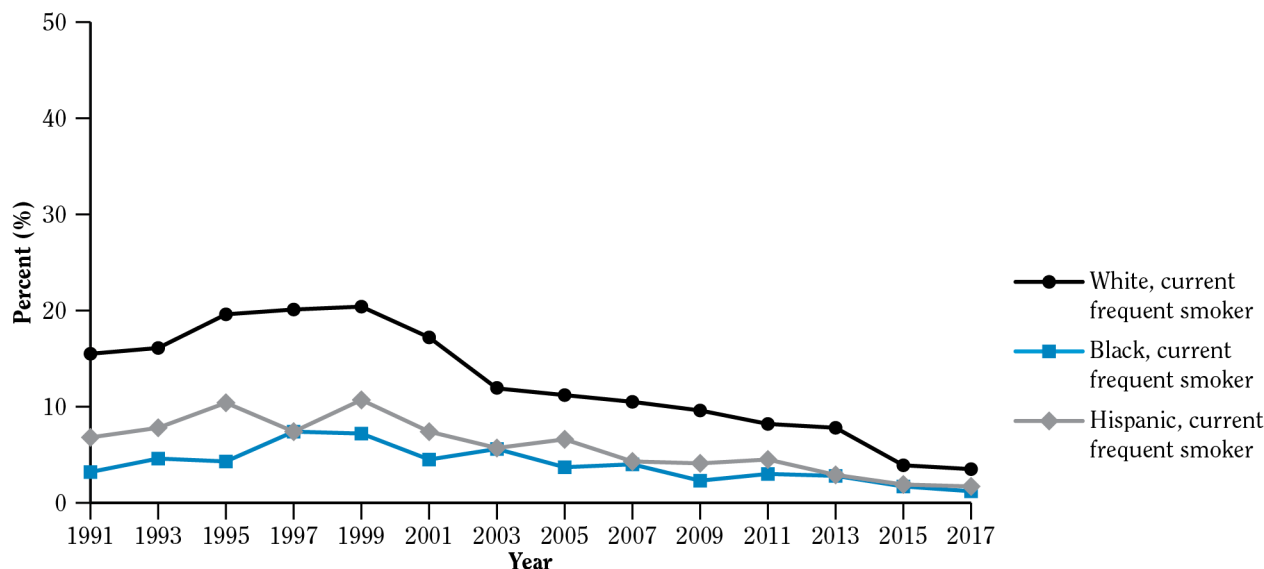
Demographic characteristics of current adult cigarette smokers have changed in recent years, reflecting changes in demographics of the U.S. population and advancements in national and state tobacco prevention and control policies (Howden and Meyer 2011; Humes et al. 2011; Ryan and Bauman 2016; National Center for Health Statistics 2018). These changes may have affected levels of interest in quitting cigarettes, the prevalence of quit attempts, and the prevalence of successful cessation. For example, during 2000–2017, notable changes occurred across several demographic variables (Table 2.2):

- During 2000–2017, the proportion of current smokers who were 45–64 years of age increased

from 30.9% to 39.9%, and the proportion of current smokers who were 65 years of age and older rose from 6.8% to 11.8%. Conversely, during this period, the proportions of current smokers who were 18–24 or 25–44 years of age decreased, reflecting the decreased initiation of smoking among youth since 1997 (USDHHS 2014).

- The proportion of current smokers who were Hispanic increased from 8.4% in 2000 to 11.3% in 2017, and the proportion of current smokers who were White decreased from 76.4% in 2000 to 69.5% in 2017.
- The proportion of current smokers 25 years of age and older whose highest level of education was a high school diploma decreased from 33.4% in

Figure 2.6a Trends in prevalence (%) of current frequent^a cigarette smoking among high school students, by race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States



Source: YRBS, Centers for Disease Control and Prevention, public use data, 1991–2017.

Note: The question about daily smoking was not asked in 2015 and 2017.

^aStudents who answered “yes” to “have you ever smoked” and “yes” to “do you currently smoke?”; and reported smoking on >19 days during the past 30 days.

Figure 2.6b Trends in prevalence (%) of former daily^a and former nondaily^b cigarette smoking among high school students, by race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States



Source: YRBS, Centers for Disease Control and Prevention, public use data, 1991–2017.

Note: The question about daily smoking was not asked in 2015 and 2017.

^aStudents who answered “yes” to “have you ever smoked” and “no” to “do you currently smoke?”; and answered “yes” to “daily.”

^bStudents who answered “yes” to “have you ever smoked” and “no” to “do you currently smoke?”; and answered “no” to “daily.”

Table 2.2 Distribution of selected demographic characteristics of adult current cigarette smokers^a 18 years of age and older; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States

Characteristic	2000: % (95% CI)	2005: % (95% CI)	2010: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Sex (% male)	52.9 (51.6–54.3)	54.9 (53.5–56.4)	53.8 (52.2–55.4)	53.4 (51.5–55.3)	54.7 (52.6–56.8)
Age group (in years)					
18–24	15.2 (14.0–16.3)	15.2 (14.0–16.4)	13.4 (12.1–14.7)	10.6 (9.3–12.0)	8.9 (7.6–10.2)
25–44	47.2 (45.9–48.5)	43.4 (41.9–44.9)	40.3 (38.8–41.9)	40.1 (38.2–42.1)	39.4 (37.5–41.3)
45–64	30.9 (29.7–32.0)	34.8 (33.4–36.2)	38.1 (36.4–39.7)	38.6 (36.7–40.5)	39.9 (38.0–41.8)
≥65	6.8 (6.2–7.3)	6.6 (6.0–7.2)	8.2 (7.4–9.1)	10.6 (9.6–11.7)	11.8 (10.7–12.9)
Race/ethnicity					
White, non-Hispanic	76.4 (75.2–77.7)	74.4 (72.9–76.0)	74.1 (72.6–75.6)	71.3 (69.5–73.1)	69.5 (67.1–71.8)
Black, non-Hispanic	11.1 (10.3–11.9)	11.4 (10.4–12.4)	12.4 (11.2–13.5)	12.9 (11.7–14.2)	12.6 (11.0–14.2)
Hispanic	8.4 (7.7–9.2)	10.0 (9.0–10.9)	9.0 (8.2–9.8)	10.4 (9.3–11.5)	11.3 (9.5–13.1)
American Indian/Alaska Native, non-Hispanic	0.8 (0.5–1.1)	0.8 (0.4–1.1)	0.8 (0.5–1.1)	0.9 (0.6–1.2)	1.2 (0.7–1.8)
Asian, non-Hispanic	2.0 (1.5–2.5)	2.3 (1.8–2.9)	2.2 (1.8–2.6)	2.6 (2.1–3.2)	3.0 (2.3–3.8)
Multiple races, non-Hispanic	1.2 (0.9–1.5)	1.1 (0.8–1.5)	1.5 (1.2–1.9)	1.9 (1.4–2.3)	2.3 (1.8–2.9)
Level of education^b					
≤12 years (no diploma)	21.5 (20.4–22.6)	19.8 (18.5–21.1)	18.4 (17.1–19.8)	19.8 (18.3–21.3)	18.0 (16.4–19.7)
GED certificate	5.5 (4.8–6.1)	5.6 (4.9–6.4)	6.7 (5.8–7.6)	6.1 (5.2–7.0)	7.0 (6.0–8.0)
High school diploma	33.4 (32.0–34.9)	32.0 (30.5–33.5)	29.4 (27.8–31.0)	27.4 (25.7–29.2)	27.2 (25.5–28.9)
Some college (no degree)	18.0 (17.0–19.1)	19.0 (17.8–20.2)	21.2 (19.8–22.5)	20.5 (18.9–22.1)	20.0 (18.4–21.6)
Associate degree	8.7 (7.9–9.5)	10.5 (9.5–11.4)	10.7 (9.6–11.8)	13.0 (11.7–14.2)	12.6 (11.3–13.9)
Undergraduate degree	9.5 (8.6–10.3)	9.6 (8.7–10.5)	10.0 (8.9–11.0)	10.0 (8.8–11.2)	11.1 (9.7–12.4)
Graduate degree	3.4 (2.8–3.9)	3.5 (3.0–4.1)	3.7 (3.0–4.4)	3.2 (2.5–3.8)	4.0 (3.2–4.8)
Poverty status (% below poverty level)	14.8 (13.7–15.8)	16.3 (15.2–17.4)	19.5 (18.2–20.9)	21.0 (19.6–22.5)	19.2 (17.5–20.9)
Geographic region					
Northeast	18.0 (16.7–19.3)	16.8 (15.5–18.2)	15.9 (14.6–17.2)	15.6 (13.9–17.2)	14.7 (12.8–16.6)
Midwest	27.8 (26.4–29.1)	28.7 (27.1–30.2)	26.2 (24.6–27.8)	27.8 (25.6–29.9)	26.4 (24.3–28.6)
South	37.9 (36.2–39.5)	37.7 (35.8–39.5)	38.7 (36.8–40.6)	37.7 (35.7–39.7)	40.3 (37.9–42.6)
West	16.4 (15.2–17.5)	16.8 (15.6–18.1)	19.2 (17.7–20.8)	19.0 (17.3–20.7)	18.6 (16.7–20.5)

Table 2.2 Continued

Characteristic	2000: % (95% CI)	2005: % (95% CI)	2010: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Health insurance coverage					
Private	61.9 (60.5–63.3)	56.4 (54.7–58.1)	48.3 (46.6–50.0)	48.1 (46.1–50.1)	48.7 (46.6–50.8)
Medicaid (includes persons with Medicaid and Medicare)	7.7 (7.0–8.5)	11.0 (10.1–11.9)	13.4 (12.4–14.4)	21.6 (19.9–23.3)	20.9 (19.1–22.7)
Medicare only	1.9 (1.6–2.3)	1.8 (1.5–2.1)	2.8 (2.3–3.2)	4.0 (3.3–4.7)	4.6 (3.9–5.4)
Other coverage	3.7 (3.3–4.2)	4.3 (3.7–4.8)	5.7 (5.0–6.4)	6.7 (5.8–7.6)	7.6 (6.6–8.6)
Uninsured	24.0 (22.9–25.2)	26.3 (24.9–27.7)	29.5 (28.1–30.9)	18.8 (17.2–20.3)	17.7 (16.1–19.2)

Source: NHIS, National Center for Health Statistics, public use data, 2000, 2005, 2010, 2015, and 2017.

Notes: **CI** = confidence interval; **GED** = General Educational Development.

^aPersons who reported smoking ≥ 100 cigarettes during their lifetime and who, at the time of the interview, reported smoking every day or some days.

^bAmong only adults 25 years of age and older.

2000 to 27.2% in 2017; the proportion of current smokers with 12 or fewer years of education (with no diploma) decreased from 21.5% in 2000 to 18.0% in 2017; and the proportion of current smokers with an associate degree increased from 8.7% to 12.6% during the time period.

- The proportion of current smokers living below the poverty level increased from 2000 (14.8%) to 2017 (19.2%).
- The proportion of current smokers covered by Medicaid rose from 7.7% in 2000 to 20.9% in 2017, and the proportion of current smokers with private health insurance decreased from 61.9% in 2000 to 48.7% in 2017.
- The proportion of current smokers covered only by Medicare increased from 1.9% in 2000 to 4.6% in 2017, and the proportion of current smokers who were uninsured increased from 24.0% in 2000 to 29.5% in 2010 but then decreased to 17.7% in 2017.

Tobacco-use characteristics among current adult cigarette smokers also changed during 2000–2017. The proportion of current smokers who did not smoke every day increased from 17.9% in 2000 to 25.1% in 2017 (Table 2.3), and the proportion of current smokers who smoked fewer than 14 cigarettes per day also increased: the proportion of smokers who smoked 1–4 cigarettes per day rose from 4.0% in 2000 to 7.0% in 2017; and the proportion of smokers who smoked 5–14 cigarettes per day rose from 25.4% to 34.9%. The proportion of smokers who usually smoked menthol cigarettes increased from 26.4% in 2005 to 31.6% in 2010 but did not change significantly (31.5%) in 2015 (data on menthol cigarettes were not available in 2017). Use of other tobacco products (cigars, smokeless tobacco, and/or pipes) by current cigarette smokers increased from 10.2% in 2000 to 14.5% in 2017. Current adult cigarette smokers who were also current users of electronic cigarettes (e-cigarettes) decreased from 13.6% in 2015 to 10.0% in 2017 (NHIS, public use data, 2015, 2017). Current e-cigarette users who were also current cigarette smokers decreased from 58.8% in 2015 to 49.6% in 2017 (NHIS, public use data, 2015, 2017).

Young Adults

Trends in demographic characteristics among young adult current smokers (18–24 years of age) were similar to trends among all adults, except that the proportion of young adult smokers living below the poverty level

was the highest in 2010 (29.9%) (Table 2.4), and the proportion of adult current smokers living below the poverty level was highest in 2015 (21.0%) (Table 2.2). The proportion of young adult current smokers who had private insurance was lowest (38.2%) in 2010. Among adult current smokers, the lowest proportion with private insurance (48.1%) was in 2015 (Table 2.2).

Changes in the distribution of tobacco product use over time among young adults are similar to those for all adults (Table 2.5). In 2017, the proportion of cigarette smokers who were some-day smokers was higher among young adults (34.7%) than among adults overall (25.1%) (Table 2.3), and the proportion who smoked 15–24 cigarettes per day was lower among young adults (15.8%) than among adults overall (27.8%). In addition, in 2017, the prevalence of cigar smoking, smokeless tobacco use, and pipe use among current smokers was higher among young adults (19.2%, 9.3%, and 7.7%, respectively) (Table 2.5) than it was among adults overall (10.6%, 3.5%, and 2.7%, respectively) (Table 2.3); the same was also true for the combined category of any cigar, smokeless tobacco, and/or pipe use (28.4% vs. 14.5%).

Youth

Findings from the national YRBS indicate that, among high school students (grades 9–12) who were current frequent cigarette smokers (ever smokers who had smoked >19 days during the past 30 days), the proportion who were White decreased from 84.5% in 2001 to 75.6% in 2005 and remained lower through 2017 (73.7%, $p < 0.001$ for quadratic trend), and the proportion who were Hispanic increased from 6.2% in 2001 to 13.6% in 2015 to 14.5% in 2017 (Table 2.6; $p < 0.001$ for quadratic trend). The proportion who were Black remained statistically unchanged during this period (3.9% in 2001 and 5.3% in 2017).

Use of smokeless tobacco increased during 2001–2015 among frequent youth smokers (from 19.9% to 35.2%) (Table 2.7); comparable data were not available from the 2017 YRBS because the smokeless tobacco question changed. In 2017, the majority of frequent youth smokers (68.0%) also used e-cigarettes. According to NYTS, use of menthol cigarettes among high school students increased among frequent smokers, from 33.7% in 2000 to 52.9% in 2017 (Table 2.8) to 53.0% in 2018 (NYTS, public use data, 2018). Similar findings were observed among current youth cigarette smokers, in a comparison of NYTS data between 1999–2009 and 2010–2013 using a slightly different definition of use of menthol cigarettes (Courtemanche et al. 2017). Of note, caution should be taken when assessing trends among youth or comparing

Table 2.3 Distribution of tobacco use characteristics among adult current cigarette smokers^a 18 years of age and older; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States

Characteristic	2000: % (95% CI)	2005: % (95% CI)	2010: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Cigarette smoking frequency, amount					
Some-day smokers	17.9 (16.8–19.0)	19.4 (18.2–20.6)	21.9 (20.5–23.2)	24.4 (22.8–26.0)	25.1 (23.4–26.9)
Daily smokers, 1–4 cpd	4.0 (3.4–4.4)	4.4 (3.7–5.0)	5.9 (5.2–6.6)	6.6 (5.8–7.5)	7.0 (5.9–8.1)
Daily smokers, 5–14 cpd	25.4 (24.2–26.6)	29.4 (27.9–30.8)	32.5 (31.0–33.9)	34.4 (32.6–36.2)	34.9 (33.1–36.8)
Daily smokers, 15–24 cpd	37.7 (36.4–39.0)	35.4 (33.9–36.9)	32.5 (30.9–34.0)	28.5 (26.7–30.2)	27.8 (26.0–29.6)
Daily smokers, ≥25 cpd	15.1 (14.1–16.1)	11.4 (10.4–12.5)	7.3 (6.4–8.2)	6.1 (5.1–7.0)	5.1 (4.3–5.9)
Usually smokes menthol					
Yes	NA	26.4 (24.9–27.9)	31.6 (30.0–33.3)	31.5 (29.7–33.4)	NA
No	NA	71.3 (69.9–72.7)	66.3 (64.7–67.9)	66.0 (64.1–67.9)	NA
No usual type	NA	2.3 (1.8–2.8)	2.0 (1.6–2.5)	2.4 (1.9–3.0)	NA
Current use of other tobacco products					
Cigars	7.4 (6.7–8.1)	8.0 (7.1–8.9)	10.3 (9.2–11.3)	8.7 (7.6–9.8)	10.6 (9.1–12.0)
Smokeless tobacco	2.7 (2.2–3.2)	3.5 (2.7–4.3)	3.6 (3.0–4.3)	4.0 (3.1–4.9)	3.5 (2.8–4.2)
Pipes	1.4 (1.1–1.7)	1.4 (1.0–1.8)	NA	2.6 (2.0–3.3)	2.7 (2.0–3.3)
Any use of cigars, smokeless tobacco, pipes	10.2 (9.4–11.1)	11.3 (10.3–12.4)	NA	13.3 (11.9–14.6)	14.5 (12.9–16.1)
E-cigarettes	NA	NA	NA	13.6 (12.2–14.9)	10.0 (8.8–11.1)

Source: NHIS, National Center for Health Statistics, public use data, 2000, 2005, 2010, 2015, and 2017.

Notes: **CI** = confidence interval; **cpd** = cigarettes smoked per day; **NA** = not available.

^aPersons who reported smoking ≥100 cigarettes during their lifetime and who, at the time of the interview, reported smoking every day or some days.

Table 2.4 Distribution of selected demographic characteristics of young adult current cigarette smokers^a 18–24 years of age; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States

Characteristic	2000: % (95% CI)	2005: % (95% CI)	2010: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Sex (% male)	53.0 (49.5–56.6)	57.5 (53.0–61.9)	57.2 (51.9–62.5)	58.2 (51.5–64.8)	57.6 (49.9–65.4)
Race/ethnicity					
White, non-Hispanic	77.7 (74.6–80.6)	73.0 (68.9–77.0)	72.7 (68.3–77.1)	64.3 (58.1–70.6)	71.2 (64.2–78.2)
Black, non-Hispanic	8.8 (6.7–10.8)	9.5 (6.9–12.1)	12.0 (8.7–15.4)	12.9 (8.5–17.4)	11.4 (6.6–16.3)
Hispanic	9.5 (7.5–11.5)	12.8 (10.3–15.2)	10.3 (7.5–13.1)	14.5 (10.2–18.9)	12.1 (7.0–17.2)
American Indian/Alaska Native, non-Hispanic	— ^b	— ^b	— ^b	— ^b	— ^b
Asian, non-Hispanic	1.9 (0.9–3.0)	— ^b	2.3 (1.3–3.4)	3.1 (1.3–4.9)	— ^b
Multiple races, non-Hispanic	1.7 (0.8–2.6)	— ^b	— ^b	— ^b	— ^b
Poverty status (% below poverty level)	21.0 (17.7–24.2)	24.2 (19.5–28.9)	29.9 (25.1–34.7)	24.5 (19.3–29.6)	24.5 (17.7–31.3)
Geographic region					
Northeast	17.5 (14.1–20.9)	13.0 (9.8–16.3)	16.7 (12.2–21.2)	16.2 (10.2–22.3)	13.4 (6.5–20.3)
Midwest	32.4 (28.3–36.5)	31.6 (27.5–35.8)	28.1 (23.8–32.5)	30.0 (23.5–36.4)	27.3 (21.2–33.4)
South	35.8 (31.6–39.9)	40.8 (35.8–45.8)	36.8 (31.8–41.7)	33.3 (27.1–39.6)	42.0 (34.3–49.7)
West	14.4 (11.9–16.9)	14.5 (11.9–17.2)	18.4 (14.6–22.2)	20.5 (15.2–25.7)	17.3 (11.7–22.8)
Health insurance coverage					
Private	52.9 (49.0–56.9)	43.5 (39.0–48.0)	38.2 (33.1–43.3)	47.4 (40.3–54.5)	46.5 (39.4–53.6)
Medicaid and persons with Medicaid and Medicare	9.0 (7.0–10.8)	13.7 (10.8–16.5)	16.9 (13.2–20.6)	26.2 (20.3–32.0)	21.5 (15.2–27.8)
Other coverage	— ^b	1.8 (0.8–2.8)	3.0 (1.4–4.7)	— ^b	— ^b
Uninsured	35.6 (31.7–39.5)	40.4 (36.0–44.8)	41.0 (35.9–46.2)	22.0 (17.0–27.0)	28.1 (21.4–34.7)

Source: NHIS, National Center for Health Statistics, public use data, 2000, 2005, 2010, 2015, and 2017.

Notes: **CI** = confidence interval.

^aPersons who reported smoking ≥ 100 cigarettes during their lifetime and who, at the time of the interview, reported smoking every day or some days.

^bPrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

Table 2.5 Distribution of tobacco use characteristics of young adult current cigarette smokers^a 18–24 years of age; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States

Characteristic	2000: % (95% CI)	2005: % (95% CI)	2010: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Cigarette smoking frequency, amount					
Some-day smoker	21.8 (18.5–25.1)	24.4 (20.6–28.3)	30.0 (25.4–34.5)	40.8 (34.1–47.6)	34.7 (28.1–41.2)
Daily smoker, 1–4 cpd	5.4 (3.7–7.0)	7.6 (5.0–10.2)	8.8 (6.0–11.6)	9.5 (5.5–13.6)	8.6 (4.5–12.7)
Daily smoker, 5–14 cpd	36.2 (32.4–40.0)	38.7 (34.6–42.7)	36.6 (31.7–41.6)	36.2 (29.3–43.1)	40.6 (33.0–48.1)
Daily smoker, 15–24 cpd	30.9 (27.5–34.3)	24.0 (20.1–27.9)	21.9 (17.7–26.0)	12.1 (7.8–16.4)	15.8 (10.1–21.5)
Daily smoker, ≥25 cpd	5.8 (3.9–7.6)	— ^b	— ^b	— ^b	— ^b
Usually smokes menthol					
Yes	NA	30.7 (26.1–35.2)	43.8 (38.5–49.0)	35.4 (28.5–42.4)	NA
No	NA	66.3 (61.6–71.1)	52.7 (47.4–58.0)	58.7 (51.4–66.0)	NA
No usual type	NA	3.0 (1.7–4.3)	3.5 (1.6–5.4)	5.9 (2.5–9.2)	NA
Current use of other tobacco products					
Cigars	10.0 (7.6–12.4)	10.8 (7.7–13.9)	15.6 (11.8–19.4)	10.0 (6.0–14.0)	19.2 (13.3–25.1)
Smokeless tobacco	4.6 (2.6–6.5)	8.1 (4.0–12.2)	6.7 (4.1–9.3)	10.6 (5.4–15.7)	9.3 (5.2–13.3)
Pipes	2.5 (1.3–3.6)	2.4 (1.1–3.7)	NA	6.1 (2.8–9.3)	7.7 (4.0–11.5)
Any use of cigars, smokeless tobacco, and pipes	15.0 (12.0–18.1)	17.3 (12.8–21.9)	NA	21.5 (15.3–27.8)	28.4 (21.7–35.0)
E-cigarettes	NA	NA	NA	18.6 (13.1–21.7)	16.1 (11.0–21.1)

Source: NHIS, National Center for Health Statistics, public use data, 2000, 2005, 2010, 2015, and 2017.

Notes: **CI** = confidence interval; **cpd** = cigarettes smoked per day; **NA** = not available.

^aPersons who reported smoking ≥100 cigarettes during their lifetime and who, at the time of the interview, reported smoking every day or some days.

^bPrevalence estimates with a relative standard error ≥30% are not presented due to low precision.

Table 2.6 Distribution of demographic characteristics of high school students who are frequent cigarette smokers^a; National Youth Risk Behavior Survey (YRBS) 2001, 2005, 2009, 2015, and 2017; United States

Characteristic	2001: % (95% CI)	2005: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Sex (% male)	52.0 (48.1–55.9)	50.3 (46.4–54.3)	57.2 (53.2–61.0)	52.0 (47.0–56.9)	49.1 (42.0–56.3)
Grade					
9	19.2 (15.4–23.7)	21.8 (18.5–25.5)	18.1 (15.1–21.6)	17.4 (11.0–26.6)	14.4 (9.9–20.5)
10	23.3 (20.0–26.8)	21.0 (17.3–25.2)	20.6 (17.9–23.6)	22.9 (17.4–29.5)	17.1 (12.1–23.6)
11	25.3 (21.0–30.3)	26.3 (23.0–30.0)	26.9 (23.1–31.0)	23.4 (17.3–30.8)	26.5 (20.0–34.2)
12	32.2 (28.5–36.1)	30.9 (26.8–35.4)	34.4 (31.0–38.1)	36.3 (30.6–42.4)	42.0 (35.2–49.2)
Race/ethnicity^b					
White, non-Hispanic	84.5 (81.1–87.4)	75.6 (69.5–80.8)	78.9 (73.8–83.3)	66.0 (57.6–73.5)	73.7 (67.6–78.9)
Black, non-Hispanic	3.9 (2.7–5.7)	5.4 (3.3–8.6)	4.2 (2.6–7.0)	7.1 (4.1–12.1)	5.3 (2.3–11.9)
Hispanic	6.2 (4.4–8.6)	10.5 (7.6–14.2)	10.2 (7.8–13.1)	13.6 (9.7–18.7)	14.5 (10.8–19.3)

Source: YRBS, Centers for Disease Control and Prevention, public use data, 2001, 2005, 2009, 2015, and 2017.

Notes: **CI** = confidence interval.

^aStudents who answered “yes” to “have you ever smoked?”; and “yes” to “do you currently smoke?”; and reported smoking on >19 days during the past 30 days.

^bEstimates will not add up to 100% because data were not reported for students of other/multiple races/ethnicities.

Table 2.7 Prevalence of use of other tobacco products among high school students who are frequent cigarette smokers^a; National Youth Risk Behavior Survey (YRBS) 2001, 2005, 2009, 2015, and 2017; United States

Other tobacco products	2001: % (95% CI)	2005: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Cigars ^b	44.3 (40.0–48.8)	47.6 (42.7–52.7)	52.7 (45.6–59.7)	54.1 (47.1–61.0)	54.8 (46.7–62.7)
Smokeless tobacco ^c	19.9 (15.9–24.5)	23.5 (19.9–27.6)	35.5 (31.1–40.2)	35.2 (29.2–41.7)	NA
Electronic vapor products ^d	NA	NA	NA	76.4 (70.8–81.2)	68.0 (58.2–76.4)

Source: YRBS, Centers for Disease Control and Prevention, public use data, 2001, 2005, 2009, 2015, and 2017.

Notes: **CI** = confidence interval; **NA** = not available.

^aStudents who answered “yes” to “have you ever smoked?”; “yes” to “do you currently smoke?”; and reported smoking ≥ 20 days during the past 30 days.

^bSmoked cigars, cigarillos, or little cigars on at least 1 day during the 30 days before the survey.

^cUsed chewing tobacco, snuff, or dip on at least 1 day during the 30 days before the survey.

^dUsed e-cigarettes, e-cigars, e-pipes, vape pipes, vaping pens, e-hookahs, or hookah pens during the 30 days before the survey.

Table 2.8 Prevalence of use of menthol cigarettes among high school students who currently smoke cigarettes, by frequency of smoking^a; National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States

Usually smokes menthol cigarettes	2000: % (95% CI)	2004: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Yes	33.7 (28.7–38.7)	47.2 (40.3–54.1)	50.5 (44.1–56.9)	48.8 (39.8–57.8)	52.9 (41.0–64.7)
No	63.7 (58.7–68.6)	52.8 (45.9–59.7)	49.5 (43.1–55.9)	45.2 (36.6–53.8)	42.2 (30.0–54.3)
No usual brand	2.7 (1.9–3.4)	NA	NA	NA	NA
Not sure	NA	NA	NA	6.0 (1.9–10.0)	— ^b

Source: NYTS, Centers for Disease Control and Prevention, public use data, 2000, 2004, 2009, 2015, and 2017.

Notes: **CI** = confidence interval; **NA** = not available;

^aStudents who answered “yes” to “have you ever tried cigarette smoking?” were categorized as (a) current infrequent smokers for smoking 1–19 days during the past 30 days or (b) current frequent smokers for smoking ≥ 20 days during the past 30 days.

^bPrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

the timing of the increases among youth with the increases among adults (Table 2.3) because wording of the question in NYTS changed over time, which may have influenced the likelihood of an affirmative response. For example, in 2000, the question was, “Is the brand of cigarettes you

usually smoked during the past 30 days mentholated?” but in questionnaires in 2015 and 2017, the question changed to, “Menthol cigarettes are cigarettes that taste like mint. During the past 30 days, were the cigarettes that you usually smoked menthol?” (CDC 2018).

Key Disparities in Current Cigarette Smoking Among Adults and Youth

Numerous Surgeon General’s reports have reviewed disparities in the prevalence of current smoking (USDHHS 1998, 2001, 2012, 2014). In 2017, the prevalence of current cigarette smoking was 20.0% or higher in a variety of vulnerable or high-risk groups:

- 36.8% among those who had obtained a General Educational Development (GED) certificate but went no further in their education;
- 35.2% among persons with serious psychological distress, a proxy variable for mental illness;
- 24.7% among persons with no health insurance;
- 24.5% among Medicaid enrollees;
- 24.0% among American Indians/Alaska Natives; and
- 20.3% among lesbian, gay, and bisexual adults (Wang et al. 2018a).

Disparities by Behavioral Health Condition

Data from the U.S. National Survey on Drug Use and Health (NSDUH) from 2005 to 2013 indicate that current smoking among adults reporting anxiety, depression, or substance abuse disorders ranged from 39.6% to 56.3% (Stanton et al. 2016). In the 2014 NSDUH, the prevalence of current smoking among persons who abused or were dependent on illicit drugs other than marijuana was 63.3%, and among those who abused or were dependent on marijuana, it was 51.3% (Weinberger et al. 2018). Data from the 2012 NHIS indicate that the age-adjusted

prevalence of current smoking was 53.0% among those with a lifetime history of bipolar disorder, 31.5% among those with a lifetime history of depression, 30.6% among those with a lifetime history of attention deficit disorder or attention deficit hyperactivity disorder, and 28.3% among those with a lifetime history of phobias or fears (NHIS, public use data, 2012).

Disparities by Chronic Disease Status

Using 2017 NHIS data, the prevalence of current smoking was high among persons with emphysema (35.2%) and those with chronic bronchitis (29.7%). Among those with other smoking-related diseases (lung cancer, other cancers, coronary heart disease, and stroke) (see Chapter 4), the prevalence of current smoking ranged from 13.5% to 35.2% and was 14.8% among those with other chronic diseases¹ and 12.2% among those with no chronic diseases (NHIS, public use data, 2017).

Disparities by Geographic Location

The prevalence of current smoking varies widely by geographic location. Data from the 2017 NHIS indicate that by region, cigarette smoking was higher in the Midwest (16.9%) and South (15.5%) than in the Northeast (11.2%) and West (11.0%) (Wang et al. 2018a). Data from the 2017 BRFSS indicate that by state, West Virginia, Kentucky, and Louisiana had the highest prevalence of current cigarette smoking (26.0%, 24.6%, and 23.1%, respectively), and the states of Utah, California, and Connecticut had the lowest prevalence (8.9%, 11.3%, and 12.7%, respectively) (CDC 2017). Data from the 2013

¹Other chronic diseases are defined as those that are not related to smoking, including hypertension; other heart condition or heart disease; ulcer; and cancers, including blood, bone, brain, breast, gallbladder, lymphoma, melanoma, ovarian, prostate, skin (non-melanoma and other), soft tissue, testicular, thyroid, and other types of cancer.

BRFSS indicate that persons who live in rural counties have a higher prevalence of smoking than persons who live in metropolitan areas, with estimates ranging from a high of 25.1% in rural counties to a low of 16.1% in large metropolitan centers (Matthews et al. 2017). In a multivariate logistic regression model controlling for age, sex, poverty, and geographic region, the 2013–2014 PATH Study observed that, compared with urban residents, rural residents had 25% greater odds of being current cigarette smokers (smoked in the past 30 days) (Roberts et al. 2017).

Disparities by Sexual Orientation and Gender Identity

The prevalence of cigarette smoking among lesbian, gay, bisexual, and transgender (LGBT) individuals is higher than the prevalence of smoking among heterosexual or straight persons. According to NHIS data, in 2017, current cigarette smoking was 20.3% among lesbian, gay, and bisexual adults compared with 13.7% among heterosexual or straight adults (Wang et al. 2018a). Variations in the prevalence of cigarette smoking also exist across sexual orientation and gender minority subgroups. Data from the 2012–2013 NATS indicated that cigarette smoking was particularly high among bisexual women, and that sexual minority women started smoking and transitioned to daily smoking earlier than their heterosexual or straight counterparts (Johnson et al. 2016). Data from the 2009–2010 NATS indicated that menthol cigarette smoking was significantly higher among LGBT adult smokers, particularly among LGBT women, than among their heterosexual counterparts (Fallin et al. 2015). Limited information exists on the prevalence of cigarette smoking by gender identity. A 2013 cross-sectional online survey of U.S. adults found that the prevalence of cigarette smoking was higher among transgender adults than among cisgender adults (Buchting et al. 2017).

Similar disparities in the prevalence of smoking by sexual orientation and gender identity exist among youth. Data from the 2017 YRBS indicated that current cigarette smoking by high school students in grades 9–12 was higher among gay, lesbian, and bisexual students (16.2%) than among heterosexual students (8.1%) and those unsure of their sexual orientation (10.1%) (Kann et al. 2018). Moreover, 2017 YRBS data from 19 states and large urban school districts found that ever use of cigarettes was significantly higher among transgender high school students (32.9%) than among cisgender male (23.2%) and cisgender female (22.0%) students (Johns et al. 2019).

Sexual orientation and gender identity are two separate and distinct measures, and existing surveillance data suggest disparities in smoking prevalence by both sexual orientation and gender identity. Taken together, these findings reinforce the heterogeneity of tobacco product use by sexual orientation and the critical importance of (a) tobacco control efforts designed to reach sexual and gender minorities and (b) tobacco survey measures designed specifically to ask adults and youth about gender identity separately from sexual orientation.

Disparities in Smoking in Pregnant Women

Smoking during pregnancy can have devastating health consequences for the mother, such as the outcome of the pregnancy, and for the future health of the child, making quitting smoking an important part of prenatal care (USDHHS 2014) (also see in this report related sections on smoking cessation and reproductive health in Chapter 4). According to data from birth certificates of children of women who gave birth in 2016, 7.2% of women in the United States reported smoking during pregnancy (Drake et al. 2018).

In a study using the first wave of data from the 2013–2014 PATH Study, the prevalence of current cigarette smoking among women of reproductive age was 20.1%, and current cigarette smoking was highly correlated with the use of other tobacco products (Lopez et al. 2018). Data from the 2013 Pregnancy Risk Assessment Monitoring System (PRAMS) indicated that 21.1% of women had smoked during the 3 months before pregnancy, and 14.0% had smoked postpartum. Estimates of the prevalence of smoking in working women of reproductive age and in working pregnant women from the 2009–2013 NHIS are generally lower than estimates in PRAMS, with 17.3% and 6.8% of these women, respectively, being current smokers (Mazurek and England 2016).

In 2016, disparities in cigarette smoking during pregnancy occurred by age, race/ethnicity, educational level, and geographic location (Drake et al. 2018). For smoking during pregnancy, women 20–24 years of age had the highest prevalence (10.7%) by age group; American Indian/Alaska Native women had the highest prevalence (16.7%) by race/ethnicity; and women with a high school diploma or GED had the highest prevalence by level of education (12.2%). Prevalence of current smoking among pregnant women was highest in West Virginia (25.1%), Kentucky (18.4%), and Montana (16.5%) and lowest in Arizona, California, Connecticut, Hawaii, New Jersey, New York, Nevada, Texas, Utah, and Washington, D.C. (each <5.0%) (Drake et al. 2018).

Disparities in Smoking Among Active Duty Service Members

Tobacco use can negatively impact the readiness and resilience of active duty service members and is a major concern to the Military Health System of the U.S. Department of Defense (Bondurant and Wedge 2009). In June 2019, the Surgeons General of the Air Force, Army, Navy, and United States released an open letter stating tobacco use is a threat to the health and fitness of U.S. military forces and compromises readiness, which is the foundation of a strong national defense (Adams et al. 2019). An estimated 38% of current cigarette smokers in the military initiated smoking after enlisting (Carter 2016), and tobacco use has been associated with higher dropout rates during basic training, poorer visual acuity, higher rates of leaving military service during the first year, and higher rates of absenteeism (Bondurant and Wedge 2009). Factors that may promote tobacco use in the military include stress, peer influence, and easy access to less expensive tobacco products (Haddock et al. 2014). Additionally, the tobacco industry has previously been shown to target marketing toward active duty service members (Smith and Malone 2009).

In addition to the health-related burden, tobacco use also exacts significant financial costs to the military. In 2009, it was estimated that tobacco use costs the U.S. Department of Defense \$1.6 billion a year for medical care, increased hospitalizations, and absenteeism (Bondurant and Wedge 2009). Additionally, in 2010, Veterans Health Administration (VHA) spent \$2.7 billion on smoking-related ambulatory care, prescription drugs, hospitalizations, and home healthcare (Barnett et al. 2015).

According to data from the 2015 Health Related Behaviors Survey (HRBS) from the U.S. Department of Defense, 13.9% of service members currently smoked cigarettes, a prevalence that is two-fold higher among military

personnel who have been deployed (28.0%) (Meadows et al. 2018). Additionally, among active duty service members, disparities exist by branch of service, sex, age group, race/ethnicity, education, and pay grade. For example, cigarette smoking is highest among those in the Marine Corps (20.7%); men (14.4%); persons 17–24 years of age (19.5%); those who reported being Other race/ethnicity (16.1%), White (14.6%), or Hispanic (14.6%); those with a high school education or less (25.1%); and those with low salaries (E1–E4 pay grade) (17.9%).

Correlation of Smoking-Related Risk Factors

As with many health behaviors and chronic diseases, several risk factors for cigarette smoking are highly correlated (Remington et al. 2016). For example, in 2017, the prevalence of serious psychological distress was 9.6% among those who completed grades 9–12 (with neither a high school diploma nor a GED certificate) compared with 2.8% among those with at least a high school education (NHIS, public use data, 2017). Similarly, those who completed grades 9–12 (with neither a diploma or a GED certificate) were more likely than those with more than a high school education to live below the poverty level (27.9% vs. 7.2%, respectively) or to be uninsured (20.3% vs. 7.3%, respectively) (NHIS, public use data, 2017). Persons with multiple risk factors for current smoking had a higher prevalence of smoking than those with a single risk factor. For example, the prevalence of smoking was 58.5% among those with serious psychological distress who completed 9–12 years of education with neither a diploma or a GED certificate, but it was 32.7% among those with serious psychological distress with at least a high school education (Figures 2.7a and 2.7b [NHIS, public use data, 2017]).

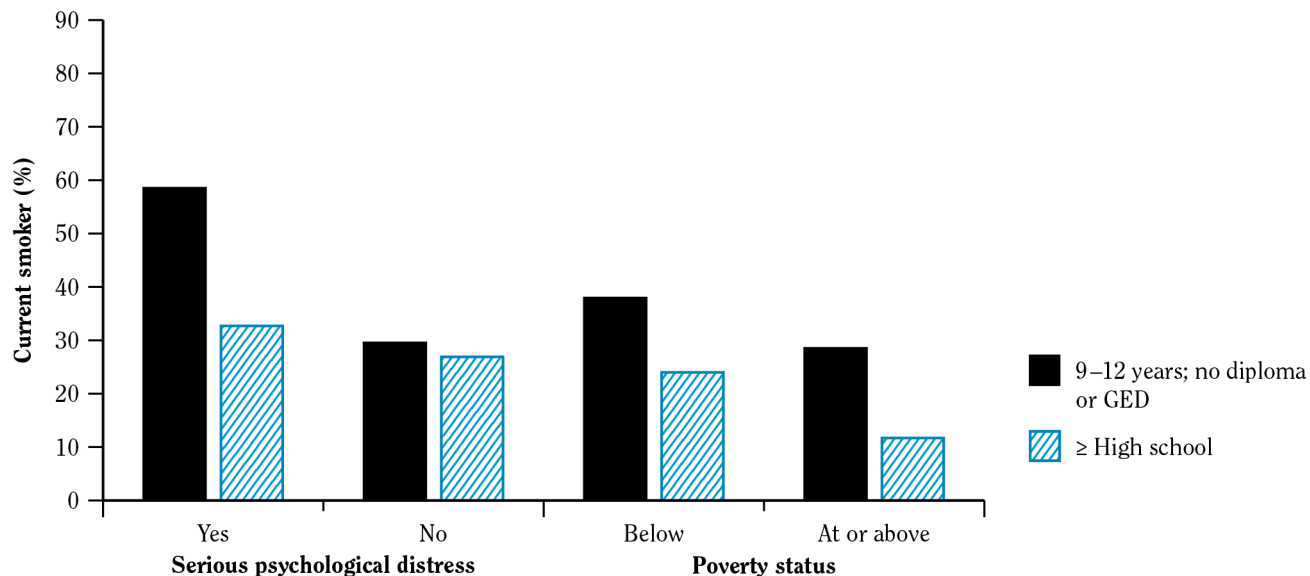
Cigarette Smoking Cessation Among Adults and Youth

Recent Successful Cessation

Recent successful cessation is defined as having smoked during the past year but having quit for at least 6 months at the time of the survey interview. The denominator in the prevalence calculation includes all persons who smoked during the past year (i.e., both current cigarette smokers and former smokers who reported quitting during the past year). Furthermore, to be included in the denominator, current smokers had to have smoked for at

least 2 years—corresponding to the *Healthy People 2020* definition for recent smoking cessation success (measure TU-5.1) (Office of Disease Prevention and Health Promotion n.d.a). Recent smoking cessation gives a more proximate measure of current patterns in smoking cessation than prevalence of former smoking; however, recent smoking cessation may overestimate sustained quitting because some former smokers will relapse to smoking after 6 months (Hughes et al. 2008). Estimates of long-term sustained quit rates using smoking prevalence and initiation

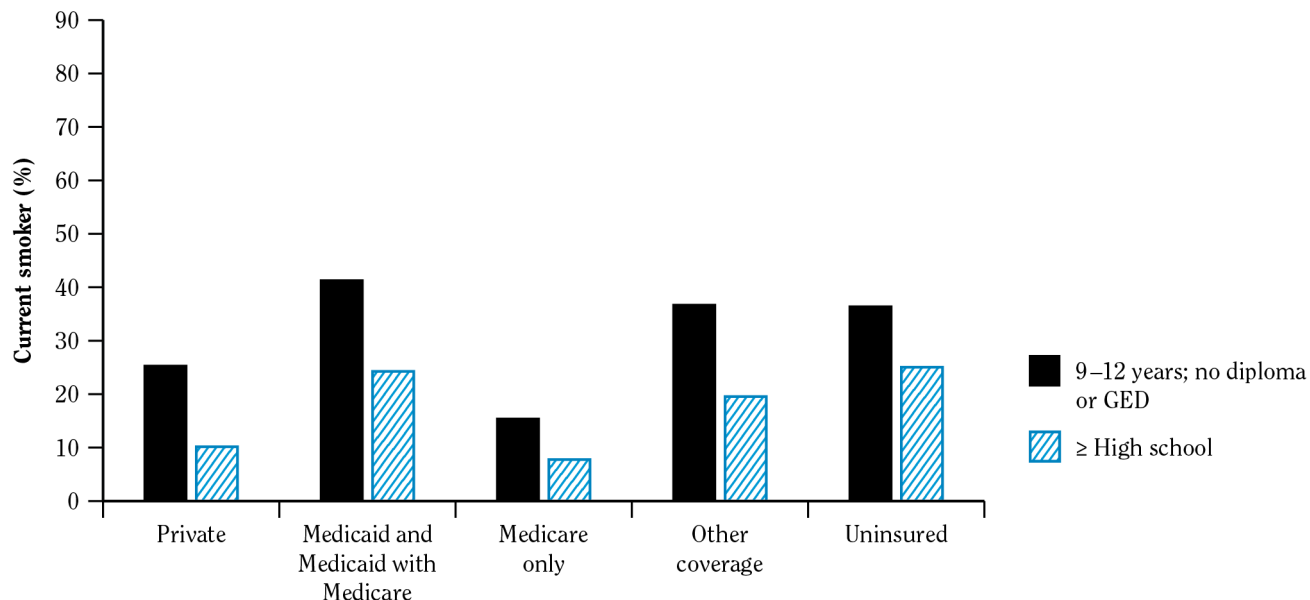
Figure 2.7a Prevalence of current cigarette smoking by level of education and presence or absence of serious psychological distress and poverty status among adults 25 years of age and older: National Health Interview Survey (NHIS) 2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 2017.

Note: GED = General Educational Development.

Figure 2.7b Prevalence of current cigarette smoking by level of education and status of health insurance among adults 25 years of age and older: National Health Interview Survey (NHIS) 2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 2017.

Note: GED = General Educational Development.

data from NHIS and NSDUH, as well as death rates of smokers from the Cancer Intervention and Surveillance Modeling Network, indicate that permanent annual quit rates during 2008–2014 were 4.5% using NHIS data and 4.2% using NSDUH data (Mendez et al. 2017).

Adults

Data from the 2017 NHIS indicate that 7.6% of adults who were ever cigarette smokers reported recent successful cessation (Table 2.9). Recent successful cessation generally decreased with age (14.0% among young adults [18–24 years of age] and 6.3% among adults [65 years of age and older]) (Table 2.9). Among the 50 states, the District of Columbia, Guam, and Puerto Rico, the highest prevalence of recent successful cessation was observed in South Dakota, Connecticut, Minnesota, and the District of Columbia. (7.5–7.9%), and the lowest prevalence was observed in Mississippi, Indiana, Nevada, Pennsylvania, and Tennessee (3.3–3.9%) (Table 2.10). It is important to note that, because the BRFSS does not ask current smokers about the number of years smoked, the BRFSS measure is not restricted to current smokers who smoked for at least 2 years; therefore, this measure is not directly comparable to that used in NHIS (see Appendix 2.2 for more information). The PATH Study observed that (a) 15.5% of current cigarette smokers at Wave 1 (September 2013–December 2014) who reported at Wave 2 (October 2014–October 2015) that they had attempted to quit in the past 12 months were abstinent for 30 or more days at Wave 2 and (b) cigarette smokers with a college degree had a higher prevalence of cessation (i.e., abstinence of >30 days) (20.0%) than those with lower levels of education (14.9%) (Benmarhnia et al. 2018). In a second analysis of the PATH Study, Berry and colleagues (2019) did not limit the analysis to current cigarette smokers who were trying to quit, but instead examined quitting among all current cigarette smokers at Wave 1. Through multivariate logistic regression models, the study observed that (a) daily smokers were less likely (odds ratio [OR] = 0.27; 95% confidence interval [CI], 0.19–0.38) to quit than some-day smokers and (b) daily smokers who had tried to quit during the year before Wave 1 were more likely to quit (OR = 1.25; 95% CI, 1.00–1.57) for 30 or more days at Wave 2 than those who did not attempt to quit during the previous year. In a third analysis of the PATH Study, Rodu and Plurphanswat (2017) examined correlates at Wave 1 of having quit smoking during the past year. The study found that, among cigarette smokers who tried to quit during the past year, the odds of having quit in the past year decreased with increased age, with increased number of quit attempts, and with increased level of education; and odds of having quit in the past year were lower among Blacks than they were among Whites (OR = 0.70; 95% CI, 0.50–0.97).

During 2000–2015, a linear increase in recent successful cessation was observed (from 5.7% to 7.4%), as noted previously (Babb et al. 2017). Using data from NHIS, Mendez and colleagues (2017) also observed an increase in permanent annual quit rates from 2.4% (1990–1995) to 4.5% (2008–2014). No significant trends for this measure were observed among young adults (NHIS, public use data, 2000, 2005, 2010, and 2015).

Quit Ratio

The quit ratio represents the percentage of ever smokers who have quit smoking and is defined as the number of former smokers divided by the number of ever smokers. Similar to the prevalence of former smoking, quit ratio is a broad cessation measure encompassing cigarette smokers who quit many decades ago through those who have quit for 1 day at the time of their survey interview. However, although the denominator for the prevalence of former smoking includes all adults in the United States, the denominator for quit ratio includes only persons who have ever smoked 100 or more cigarettes in their lifetime. Data from the 2017 NHIS show that the quit ratio for U.S. adults was 61.7% (Table 2.9), indicating that there are more former cigarette smokers in the United States than current cigarette smokers (by a ratio of almost 3:2). The quit ratio in 2017 represents a 6-percentage-point increase over the quit ratio in 2012 (55.1%) and reflects a continued increasing trend in the population-based quit ratio since 1965 (USDHHS 2014).

Adults

Data from the 2017 NHIS indicate that the quit ratio increased linearly with age, ranging from 32.7% among 18- to 24-year-olds to 82.9% among those 65 years of age and older (Table 2.9). The quit ratio has been consistently highest among adults 65 years of age and older and consistently lowest among young adults (Figure 2.8a). The quit ratio has increased in all adult age groups since 1965, with some variability from year to year.

Data from the 2017 NHIS indicate that quit ratios were lower among Blacks (46.1%) than Asians (64.3%), Whites (63.9%), and Hispanics (61.5%) (Table 2.9). Persons of multiple races (50.0%) had lower quit ratios than Whites (63.9%). The quit ratio increased among White and Black adults from 1965 to 2017, and it increased between 1980 and 2017 among Hispanics (data on Hispanics were not available before 1980), with variability from year to year (Figure 2.8b).

Data from the 2017 NHIS also indicate that the quit ratio generally increased with level of education.

Table 2.9 Percentage of ever cigarette smokers 18 years of age and older who have recently successfully quit and quit smoking (quit ratio), by selected characteristics; National Health Interview Survey (NHIS) 2017; United States

Characteristic	Recent successful cessation: ^a	
	% (95% CI)	Quit ratio: % (95% CI)
Total	7.6 (6.6–8.6)	61.7 (60.4–63.0)
Sex		
Men	7.2 (5.9–8.5)	61.9 (60.2–63.6)
Women	8.1 (6.5–9.6)	61.5 (59.6–63.3)
Age group (years)		
18–24	14.0 (9.4–18.7)	32.7 (26.6–38.8)
25–44	7.9 (6.5–9.4)	50.7 (48.4–53.0)
45–64	6.1 (4.5–7.6)	59.7 (57.7–61.7)
≥65	6.3 (3.9–8.6)	82.9 (81.3–84.5)
Race/ethnicity		
White, non-Hispanic	7.4 (6.3–8.5)	63.9 (62.5–65.3)
Black, non-Hispanic	7.0 (4.0–10.1)	46.1 (42.3–50.0)
Hispanic	9.1 (5.7–12.5)	61.5 (57.3–65.7)
American Indian/Alaska Native, non-Hispanic	— ^b	— ^b
Asian, non-Hispanic	— ^b	64.3 (57.3–71.2)
Multiple races, non-Hispanic	— ^b	50.0 (41.2–58.8)
Level of education^c		
≤12 years (no diploma)	5.8 (3.7–7.9)	50.6 (47.2–53.9)
GED certificate	6.1 (3.1–9.0)	42.4 (37.1–47.7)
High school diploma	6.1 (4.1–8.0)	58.4 (56.0–60.9)
Some college (no degree)	8.2 (5.6–10.8)	62.4 (59.9–65.0)
Associate degree	5.7 (3.5–8.0)	63.3 (60.2–66.5)
Undergraduate degree	8.7 (5.7–11.7)	76.1 (73.3–78.9)
Graduate degree	11.0 (6.0–16.0)	82.8 (79.8–85.8)
Poverty status		
At or above poverty level	8.0 (6.9–9.2)	64.5 (63.2–65.8)
Below poverty level	5.8 (3.9–7.6)	42.2 (38.7–45.7)
U.S. Census region		
Northeast	8.6 (5.8–11.4)	68.0 (65.0–70.9)
Midwest	6.8 (4.8–8.7)	59.3 (56.7–61.9)
South	7.7 (6.0–9.3)	56.6 (54.5–58.7)
West	7.8 (5.8–9.7)	67.6 (65.1–70.1)
Health insurance coverage		
Private	8.5 (6.9–10.1)	67.9 (66.4–69.4)
Medicaid (includes persons with Medicaid and Medicare)	6.6 (4.6–8.7)	41.1 (37.5–44.6)
Medicare only	— ^b	81.5 (78.6–84.4)
Other coverage	6.6 (3.7–9.5)	60.4 (56.4–64.4)
Uninsured	7.5 (5.0–10.0)	38.7 (35.0–42.5)

Table 2.9 Continued

Source: NHIS, National Center for Health Statistics, public use data, 2017; Babb and colleagues (2017).

Notes: **CI** = confidence interval; **GED** = General Educational Development.

^aThe numerator includes former smokers who quit smoking for ≥ 6 months during the past year. The denominator for this measure includes both current smokers who smoked for ≥ 2 years and former smokers who quit during the past year.

^bPrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

^cAmong only adults 25 years of age and older.

Table 2.10 Percentage of current and ever smokers 18 years of age and older who quit smoking (quit ratio)^a and prevalence of recent successful cessation^b and a past-year quit attempt,^c by state; Behavioral Risk Factor Surveillance System (BRFSS) 2017; United States

State/territory	Quit ratio: % (95% CI)	Recent successful cessation: % (95% CI)	Past-year quit attempt: % (95% CI)
Overall	59.2 (57.0–61.4)	—	—
Alabama	52.8 (50.3–55.3)	4.7 (3.2–6.2)	67.5 (64.1–70.9)
Alaska	54.9 (50.6–59.3)	5.1 (2.8–7.4)	63.6 (57.2–70.0)
Arizona	61.3 (59.7–63.0)	6.3 (5.0–7.6)	66.6 (64.2–69.0)
Arkansas	53.4 (49.7–57.1)	5.2 (2.9–7.5)	66.7 (61.7–71.8)
California	66.3 (63.9–68.7)	7.0 (5.2–8.8)	68.0 (64.2–71.7)
Colorado	63.6 (61.6–65.6)	6.2 (4.5–7.8)	68.2 (65.2–71.1)
Connecticut	67.1 (65.0–69.2)	7.7 (5.6–9.9)	71.6 (68.3–74.9)
Delaware	59.5 (56.2–62.9)	6.3 (3.4–9.2)	71.0 (66.5–75.4)
District of Columbia	56.3 (53.0–59.6)	7.0 (4.7–9.3)	69.3 (64.9–73.8)
Florida	60.8 (58.5–63.1)	5.2 (3.8–6.7)	67.6 (64.4–70.8)
Georgia	53.8 (51.1–56.5)	4.4 (2.9–6.0)	64.3 (60.5–68.1)
Hawaii	67.6 (65.2–70.0)	6.6 (4.2–8.9)	67.0 (63.2–70.8)
Idaho	62.4 (59.3–65.6)	6.0 (3.1–8.9)	62.2 (57.2–67.1)
Illinois	59.8 (57.1–62.6)	5.4 (3.5–7.2)	64.8 (60.7–68.9)
Indiana	52.9 (51.2–54.6)	3.9 (3.0–4.9)	62.0 (59.6–64.3)
Iowa	59.0 (57.0–61.1)	4.7 (3.5–6.0)	59.9 (56.9–63.0)
Kansas	58.3 (57.0–59.7)	5.0 (4.1–6.0)	64.3 (62.4–66.2)
Kentucky	51.0 (48.4–53.5)	4.3 (2.8–5.7)	62.1 (58.7–65.5)
Louisiana	49.9 (47.1–52.7)	5.3 (3.7–7.0)	69.7 (66.3–73.2)
Maine	64.7 (62.5–66.9)	6.1 (4.3–7.9)	62.2 (58.5–66.0)
Maryland	61.4 (59.2–63.6)	5.3 (3.5–7.1)	65.9 (62.4–69.3)
Massachusetts	64.7 (61.7–67.7)	5.0 (3.2–6.9)	64.6 (59.8–69.3)
Michigan	58.1 (56.2–59.9)	4.5 (3.4–5.6)	66.2 (63.6–68.8)
Minnesota	64.5 (63.0–66.0)	7.5 (6.2–8.7)	63.8 (61.5–66.1)
Mississippi	49.3 (46.2–52.4)	3.3 (1.9–4.6)	61.1 (56.8–65.5)
Missouri	55.4 (53.0–57.8)	5.5 (3.9–7.0)	59.7 (56.2–63.1)
Montana	61.4 (58.7–64.0)	4.8 (3.1–6.4)	60.6 (56.6–64.7)
Nebraska	61.5 (59.6–63.5)	5.7 (4.2–7.1)	63.9 (61.0–66.8)
Nevada	57.7 (53.9–61.5)	3.9 (2.2–5.7)	62.7 (57.2–68.2)
New Hampshire	65.9 (63.0–68.8)	5.6 (3.5–7.7)	63.7 (58.8–68.6)

Table 2.10 Continued

State/territory	Quit ratio: % (95% CI)	Recent successful cessation: % (95% CI)	Past-year quit attempt: % (95% CI)
New Jersey	64.8 (62.4–67.2)	5.5 (3.8–7.2)	71.3 (67.7–74.9)
New Mexico	57.7 (55.0–60.5)	5.3 (3.5–7.1)	65.5 (61.7–69.3)
New York	62.1 (60.1–64.1)	6.2 (4.6–7.9)	66.4 (63.4–69.5)
North Carolina	60.1 (57.3–62.9)	4.8 (3.1–6.4)	65.4 (61.3–69.6)
North Dakota	57.7 (55.3–60.2)	4.2 (2.8–5.6)	62.2 (58.7–65.7)
Ohio	53.6 (51.6–55.6)	4.4 (3.1–5.7)	61.7 (58.9–64.6)
Oklahoma	54.9 (52.5–57.3)	5.9 (4.4–7.4)	65.9 (62.5–69.2)
Oregon	61.5 (59.1–64.0)	4.6 (3.1–6.0)	62.5 (58.8–66.2)
Pennsylvania	59.0 (56.6–61.3)	3.9 (2.7–5.1)	64.3 (60.9–67.6)
Rhode Island	65.6 (62.7–68.5)	6.3 (4.0–8.7)	69.6 (64.9–74.3)
South Carolina	58.5 (56.5–60.5)	4.7 (3.2–6.2)	65.8 (62.9–68.7)
South Dakota	57.1 (53.6–60.6)	7.9 (5.0–10.8)	64.5 (59.4–69.6)
Tennessee	51.2 (48.5–54.0)	3.9 (2.4–5.4)	60.3 (56.6–64.0)
Texas	55.8 (52.6–59.1)	5.4 (3.4–7.3)	70.7 (66.6–74.7)
Utah	62.8 (60.3–65.3)	6.1 (4.3–7.9)	66.4 (62.8–70.1)
Vermont	65.1 (62.6–67.6)	6.3 (4.1–8.5)	66.0 (62.0–70.0)
Virginia	59.2 (57.0–61.4)	5.6 (3.9–7.4)	66.4 (63.2–69.6)
Washington	66.8 (65.1–68.6)	6.3 (4.9–7.7)	68.1 (65.4–70.7)
West Virginia	50.2 (47.9–52.5)	5.8 (4.3–7.3)	61.6 (58.5–64.8)
Wisconsin	61.5 (58.8–64.2)	5.1 (3.2–6.9)	58.6 (54.3–62.8)
Wyoming	58.1 (55.2–61.0)	6.7 (4.4–9.1)	65.0 (61.0–69.0)
Guam	43.6 (38.5–48.7)	6.7 (3.8–9.7)	72.3 (66.7–77.9)
Puerto Rico	62.3 (58.5–66.1)	6.3 (2.9–9.6)	67.1 (61.5–72.7)

Source: BRFSS, Centers for Disease Control and Prevention, public use data, 2017.

Notes: **CI** = confidence interval.

^aQuit ratio is calculated as the proportion of current smokers who reported having stopped smoking for >1 day during the past year because they were trying to quit smoking, and former smokers who quit smoking during the past year (numerator), among all current and former smokers who only quit in the past year (denominator).

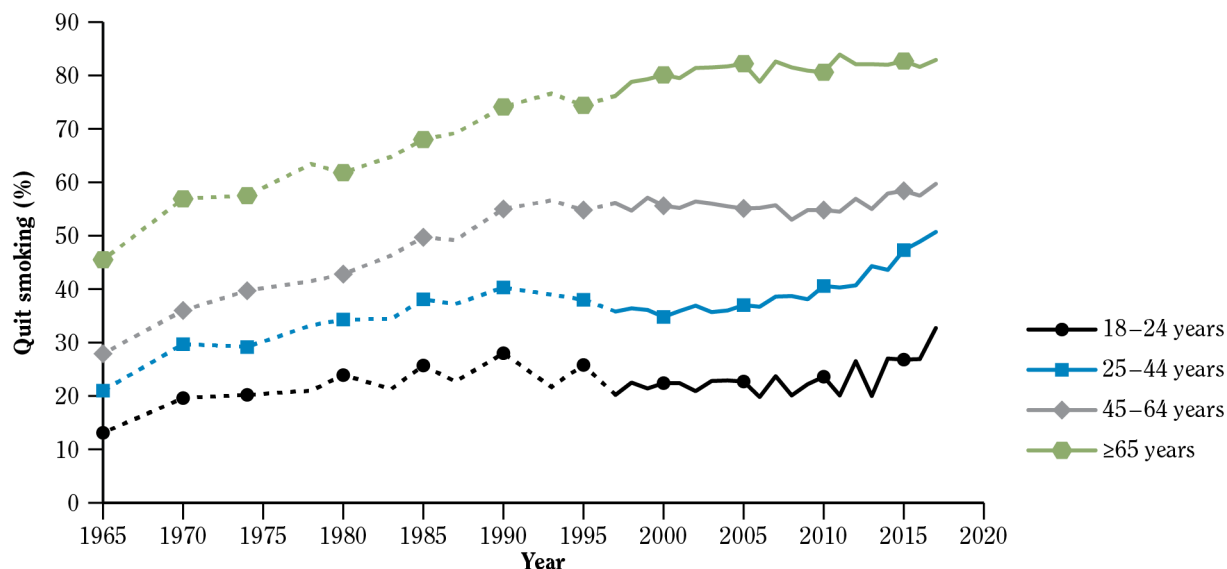
^bThe percentage of former smokers who quit smoking for >6 months during the past year among current smokers and former smokers who quit during the past year.

^cCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

For example, in 2017, the quit ratio among those with a graduate degree (82.8%) was far higher than the quit ratio among those who had 12 or fewer years of education (with no diploma) (50.6%) or a GED certificate (42.4%) (Table 2.9). Those living below the federal poverty level had a much lower quit ratio (42.2%) than persons at or above the poverty level (64.5%). By geographic region, the Northeast (68.0%) and West (67.6%) had higher quit ratios than the Midwest (59.3%) and the South (56.6%). By status of health insurance, those who were uninsured (38.7%) or enrolled in Medicaid (41.1%) had the lowest quit ratios.

Data from the 2017 BRFSS indicate that quit ratios were greater than 50% in every state except Mississippi (49.3%) and Louisiana (49.9%) (Guam also had a prevalence <50%) (Table 2.10). Thus, in the vast majority of states, more than half of the persons who had ever smoked cigarettes had quit smoking. In three states (Hawaii [67.7%], Connecticut [67.1%], and Washington [66.8%]), more than two-thirds of ever smokers had quit smoking, and the quit ratio in 20 other states and Puerto Rico was between 60.1% and 66.3%. These are marked improvements from 2004, when only 34 states had quit ratios

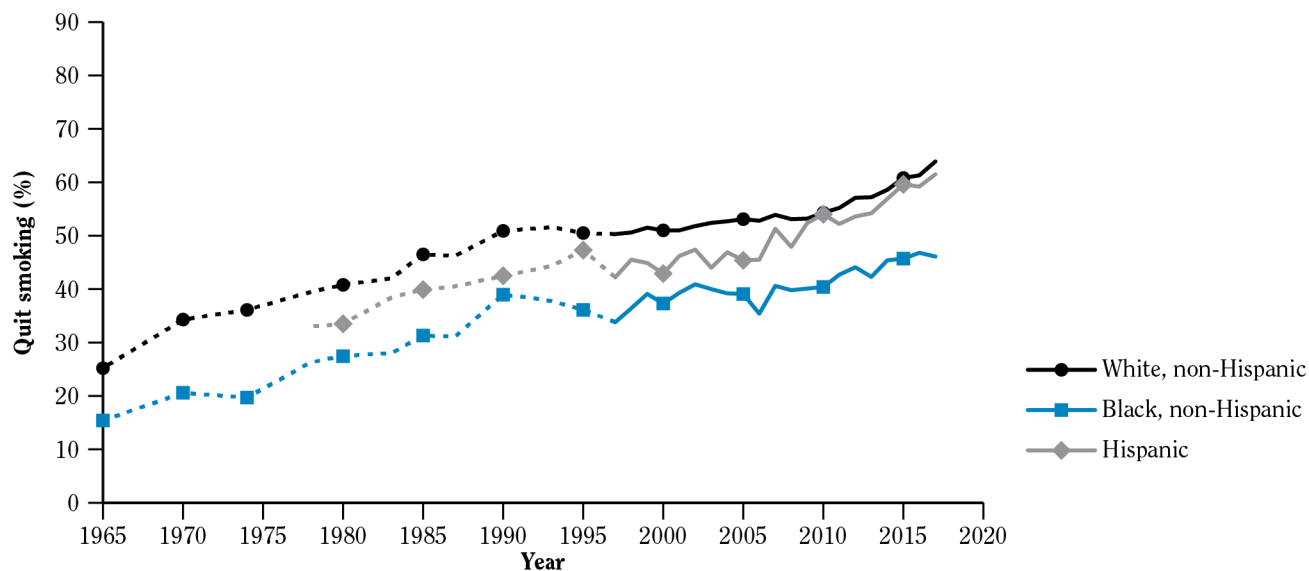
Figure 2.8a Percentage of ever smokers 18 years of age and older who quit smoking (quit ratio), by age group; National Health Interview Survey (NHIS), 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 1996, data were reported for the following years (as indicated by the dotted line): 1965, 1970, 1974, 1978, 1980, 1983, 1985, 1987, 1990, 1993, and 1995. Data were reported annually for years 1997–2017 (as indicated by the solid line).

Figure 2.8b Percentage of ever smokers 18 years of age and older who quit smoking (quit ratio), by race/ethnicity; National Health Interview Survey (NHIS), 1965–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.

Note: From 1965 to 1996, data were reported for the following years (as indicated by the dotted line): 1965, 1970, 1974, 1978, 1980, 1983, 1985, 1987, 1990, 1993, and 1995. Data were reported annually for years 1997–2017 (as indicated by the solid line).

greater than 50% and just 4 states had quit ratios greater than 60% (CDC 2005). In 2004, the median quit ratio across 49 states and the District of Columbia was 52.4%, and in 2017, the median quit ratio for all 50 states and the District of Columbia was 59.2%.

Young Adults

The quit ratio among young adults has consistently been the lowest of all adult age groups since 1965 (Figure 2.8a). The quit ratio among young adult ever smokers has increased since 1965 (from 13.1% in 1965 to 32.7% in 2017); however, little change has occurred since the 1980s. The positive relationship between quit ratio and age is due in part to the accumulation of quitters with age; specifically, the numerator among older ever smokers includes persons who quit many decades ago, but among young adult ever smokers, a decade ago would be when they were 8–14 years of age—a time when many were smoking their first cigarette, not quitting (USDHHS 2012). This positive relationship is also due, in part, to the increased mortality among older current smokers compared with long-term former smokers, which would decrease the denominator among older versus younger ever smokers (USDHHS 2014).

Youth

Compared with adults, smoking behaviors among youth are less established and the prevalence of quitting is much lower (USDHHS 2012). Therefore, quit ratios among youth are not included in this report because they would most likely reflect cessation attributable to both quitting and experimentation, or discontinuation of non-established smoking patterns (USDHHS 2012).

Trends in the Cessation Continuum for Current Smokers

Data from TUS-CPS from 2006–2007, 2010–2011, and 2014–2015 were used to develop a cigarette smoking cessation continuum for adults 18 years of age and older who were current smokers. A cessation continuum was constructed to describe more completely the dynamic process of smoking cessation, including interest in quitting, quitting history, and past-year quit attempts. The continuum included six subgroups of current cigarette smokers:

- Persons who had never tried to quit and who were currently *not interested* in quitting,
- Persons who had never tried to quit but were currently *interested* in quitting,

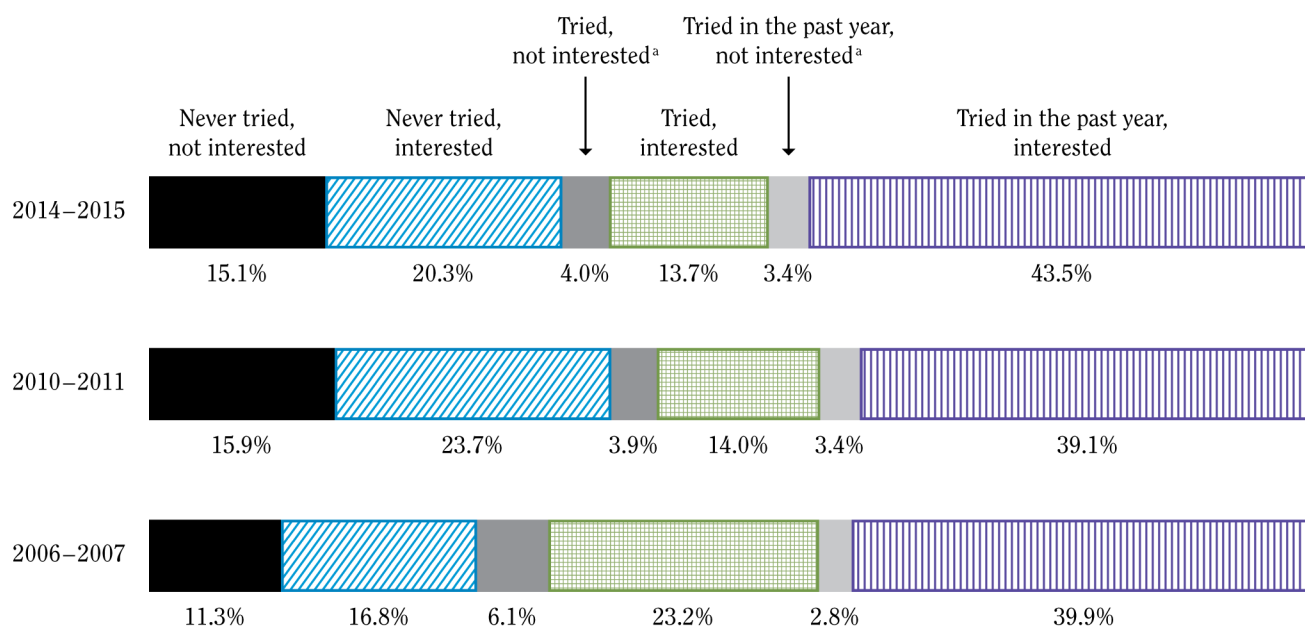
- Persons who had ever tried to quit but did not try in the past year and who were currently *not interested* in quitting,
- Persons who had ever tried to quit but did not try to quit in the past year and who were currently *interested* in quitting,
- Persons who tried to quit in the past year but were currently *not interested* in quitting, and
- Persons who tried to quit in the past year and were currently *interested* in quitting.

It is important to note that, although the definition of those who ever tried to quit includes cigarette smokers whose quit attempt lasted less than 1 day, the definition of trying to quit in the past year includes only quit attempts that lasted for 1 day or longer (i.e., not attempts that lasted for less than 1 day) among current daily smokers and some-day smokers who smoked 12 or more days in the past 30 days—thereby underestimating the prevalence of past-year quit attempts (Hughes et al. 2013). The more conservative definition of past-year quit attempt was selected to match more closely the past-year quit attempt question on NHIS, which has the greatest number of years of data on the prevalence of past-year quit attempts. Appendix 2.2 presents more information about the potential effect of excluding past-year quit attempts of less than 1 day on prevalence estimates.

The proportion of current adult smokers who had never tried to quit but were interested in quitting increased from 16.8% (95% CI, 16.2–17.3) in 2006–2007 to 23.7% (95% CI, 22.9–24.4) in 2010–2011, and then decreased to 20.3% (95% CI, 19.6–21.0) in 2014–2015 (Figure 2.9). From 2006–2007 to 2010–2011, the proportions of three groups changed: (a) the proportion of current adult smokers who had never tried to quit and were not interested in quitting increased from 11.3% (95% CI, 10.8–11.8) to 15.9% (95% CI, 15.3–16.6), (b) the proportion of current adult smokers who had ever tried to quit but did not try during the past year and at the time of the survey were not interested in quitting decreased from 6.1% (95% CI, 5.7–6.4) to 3.9% (95% CI, 3.6–4.2), and (c) the proportion of current adult smokers who had ever tried to quit but did not try during the past year and were interested in quitting decreased from 23.2% (95% CI, 22.6–23.7) to 14.0% (95% CI, 13.5–14.6). The proportion of those who had tried to quit during the past year and were interested in quitting increased from 39.1% (95% CI, 38.3–40.0) in 2010–2011 to 43.5% (95% CI, 42.7–44.3) in 2014–2015.

For all years, the proportion of those who were interested in quitting was greater than the proportion of

Figure 2.9 Cessation continuum for current cigarette smokers 18 years of age and older; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2006–2007, 2010–2011, 2014–2015; United States



Source: TUS-CPS, public use data, 2006–2007, 2010–2011, and 2014–2015.

^aEver tried to quit but did not try to quit during the past year.

those who were not interested in quitting, regardless of quit attempt status. In addition, the ratio between those interested and those not interested in quitting increased across the quit attempt continuum from those who had never tried to quit to those who had tried to quit during the past year. The following sections examine trends and demographic differences in the cessation components of this continuum.

Attempts to Quit Smoking During the Past Year

Adults

According to NHIS, in 2015, 55.4% of adult cigarette smokers had made a past-year quit attempt (Table 2.11). This included current smokers (those who had smoked 100 cigarettes in their lifetime and now smoked some days or every day) who had made a quit attempt lasting at least 1 day during the past year and former smokers who had quit during the past year. Persons younger than 45 years of age had a higher prevalence of quit attempts than those 45 years of age and older. Asians (69.4%) and Blacks (63.4%) had a higher prevalence of quit attempts during the past year compared with Whites (53.3%). Those with Medicare had a lower prevalence of making a quit attempt during the past year compared with those who had private insurance. The prevalence of quit attempts did not change

during 2015–2017 (both 55.4%) (NHIS, public use data, 2017). Also, the prevalence of quit attempts did not change within each of the demographic groups, and the quit attempt patterns by demographic subgroups were similar except for level of education and insurance status. In 2017, the prevalence of past-year quit attempts was higher among persons with graduate degrees (64.9%) than among those with 12 or fewer years of education and no diploma (50.4%) and those with a high school diploma (47.6%); prevalence of past-year quit attempts was higher among those with an associate degree (59.8%) than among those with a high school diploma (47.6%) (NHIS, public use data, 2017). In 2017, the prevalence of past-year quit attempts was lower among both those with Medicare (40.5%) and the uninsured (50.9%) than among those with private insurance (58.6%) (NHIS 2017, public use data, 2017).

In 2015, quit attempts varied by smoking frequency but not by status of smoking menthol cigarettes (Table 2.12). Among adults 18 years of age or older in 2015, nondaily smokers had a higher prevalence of past-year quit attempts (63.6%) compared with daily smokers (44.6%). These findings are similar to those obtained in previous analyses of nationally representative data (Tindle and Shiffman 2011; Schauer et al. 2014b; Keeler et al. 2017) and to data in the 2017 NHIS (NHIS, public use data, 2017). Although quit attempts during the past year did not differ significantly across age groups of nondaily

Table 2.11 Prevalence of a past-year quit attempt^a and interest in quitting smoking^b among adult cigarette smokers 18 years of age and older, by selected characteristics; National Health Interview Survey (NHIS) 2015; United States

Characteristic	Past-year quit attempt: % (95% CI)	Interest in quitting: % (95% CI)
Total	55.4 (53.5–57.3)	68.0 (65.9–70.0)
Sex		
Men	55.3 (52.7–57.9)	66.7 (63.8–69.6)
Women	55.6 (53.0–58.1)	69.4 (66.7–72.1)
Age group (years)		
18–24	66.7 (61.0–72.4)	62.3 (55.7–69.0)
25–44	59.8 (57.3–62.3)	72.7 (69.7–75.7)
45–64	49.6 (46.8–52.5)	68.7 (65.8–71.6)
≥65	47.2 (42.2–52.3)	53.7 (48.4–58.9)
Race/ethnicity		
White, non-Hispanic	53.3 (50.8–55.7)	67.5 (65.0–70.0)
Black, non-Hispanic	63.4 (59.0–67.9)	72.8 (68.2–77.4)
Hispanic	56.2 (51.6–60.9)	67.4 (61.9–72.8)
American Indian/Alaska Native, non-Hispanic	52.1 (32.1–72.2)	55.6 (35.8–75.4)
Asian, non-Hispanic ^c	69.4 (62.1–76.7)	69.6 (59.5–79.8)
Multiple races, non-Hispanic	57.8 (47.2–68.4)	59.8 (45.7–73.9)
Level of education^d		
≤12 years (no diploma)	50.4 (46.2–54.5)	68.0 (63.7–72.2)
GED certificate	48.1 (40.1–56.0)	65.7 (58.0–73.4)
High school diploma	52.2 (48.3–56.2)	65.5 (61.9–69.1)
Some college (no degree)	57.8 (53.6–61.9)	70.2 (66.1–74.4)
Associate degree	57.4 (52.2–62.7)	70.6 (65.3–76.0)
Undergraduate degree	57.6 (51.5–63.8)	73.3 (67.7–78.8)
Graduate degree	55.8 (46.0–65.6)	74.0 (65.1–82.9)
Poverty status		
At or above poverty level	55.5 (53.3–57.7)	68.2 (65.9–70.4)
Below poverty level	55.2 (51.6–58.8)	67.3 (63.4–71.1)
U.S. Census region		
Northeast	58.8 (54.6–63.0)	74.5 (69.0–80.1)
Midwest	54.0 (49.7–58.4)	67.1 (63.1–71.1)
South	54.3 (51.6–57.0)	67.2 (64.0–70.4)
West	56.9 (52.5–61.3)	65.5 (60.7–70.2)
Health insurance coverage		
Private	57.2 (54.6–59.9)	69.0 (66.1–71.8)
Medicaid (includes persons with Medicaid and Medicare)	56.3 (52.5–60.1)	69.2 (65.3–73.2)
Medicare only	42.3 (35.5–49.4)	47.7 (40.3–55.2)
Other coverage	50.7 (43.9–57.4)	63.6 (57.2–69.9)
Uninsured	53.5 (49.7–57.2)	69.5 (65.2–73.9)

Table 2.11 Continued

Source: Babb and colleagues (2017).

Notes: **CI** = confidence interval; **GED** = General Educational Development.^aCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.^bCurrent smokers who reported that they wanted to stop smoking completely.^cDoes not include Native Hawaiians or Other Pacific Islanders.^dAmong only adults 25 years of age and older.**Table 2.12 Prevalence of a past-year quit attempt^a among adult current cigarette smokers 18 years of age and older, by selected smoking-related and demographic characteristics; National Health Interview Survey (NHIS) 2015; United States**

Characteristic	Nondaily: % (95% CI)	Daily: % (95% CI)	Menthol: % (95% CI)	Nonmenthol: % (95% CI)
Total	63.6 (60.2–67.1)	44.6 (42.3–46.9)	51.5 (47.9–55.1)	48.3 (45.6–51.1)
Sex				
Male	60.9 (56.3–65.4)	45.0 (41.7–48.3)	52.7 (47.5–57.9)	49.0 (45.4–52.7)
Female	67.8 (62.6–72.9)	44.2 (41.2–47.1)	50.5 (45.8–55.2)	47.4 (43.8–51.1)
Age group (years)				
18–24	63.5 (53.8–73.3)	58.8 (50.3–67.3)	60.5 (50.2–70.7)	64.8 (54.4–75.1)
25–44	64.1 (59.0–69.2)	49.4 (45.9–52.9)	54.8 (49.7–60.0)	51.9 (48.0–55.8)
45–64	64.5 (59.1–69.9)	39.1 (36.0–42.2)	46.2 (40.7–51.7)	43.1 (39.4–46.8)
≥65	57.4 (46.4–68.4)	37.4 (31.8–43.0)	42.7 (31.8–53.6)	42.1 (35.9–48.3)
Race/ethnicity				
White, non-Hispanic	66.4 (61.6–71.1)	41.9 (39.2–44.7)	47.1 (42.2–52.0)	46.8 (43.7–50.0)
Black, non-Hispanic	70.1 (62.0–78.1)	56.6 (51.0–62.3)	60.0 (54.2–65.8)	62.4 (52.9–72.0)
Hispanic	50.3 (42.3–58.3)	48.0 (41.7–54.3)	48.2 (39.6–56.8)	53.5 (46.6–60.3)
American Indian/Alaska Native, non-Hispanic	— ^b	— ^b	— ^b	— ^b
Asian, non-Hispanic	67.2 (53.0–81.4)	55.9 (43.3–68.5)	— ^b	56.5 (42.7–70.2)
Multiple races, non-Hispanic	— ^b	40.0 (26.6–53.4)	— ^b	42.6 (25.1–60.2)
Level of education^c				
≤12 years (no diploma)	67.4 (57.4–77.3)	40.7 (35.7–45.7)	50.7 (43.1–58.2)	43.4 (38.3–48.5)
GED certificate	— ^b	40.2 (31.8–48.7)	55.3 (42.4–68.2)	39.1 (28.4–49.8)
High school diploma	67.0 (59.0–75.0)	41.5 (37.0–45.9)	49.1 (41.9–56.2)	45.9 (40.8–51.0)
Some college (no degree)	66.4 (59.2–73.7)	47.2 (42.2–52.2)	50.2 (42.5–58.0)	52.3 (46.9–57.7)
Associate degree	56.7 (47.1–66.3)	48.0 (41.6–54.5)	52.5 (41.5–63.5)	48.5 (40.8–56.1)
Undergraduate degree	61.1 (50.9–71.3)	43.2 (35.4–51.0)	53.9 (42.7–65.1)	46.3 (38.2–54.4)
Graduate degree	46.3 (30.4–62.2)	45.6 (31.5–59.7)	— ^b	49.8 (37.2–62.3)
Poverty status				
At or above poverty level	63.7 (59.8–67.6)	43.8 (41.1–46.5)	51.0 (46.7–55.2)	48.1 (44.9–51.3)
Below poverty level	63.5 (55.5–71.4)	47.5 (43.1–51.9)	53.2 (46.9–59.6)	49.5 (44.6–54.4)
U.S. Census region				
Northeast	72.4 (64.1–80.7)	47.2 (41.6–52.8)	58.2 (49.7–66.7)	51.8 (43.7–60.0)

Table 2.12 Continued

Characteristic	Nondaily: % (95% CI)	Daily: % (95% CI)	Menthol: % (95% CI)	Nonmenthol: % (95% CI)
U.S. Census region (continued)				
Midwest	71.2 (63.2–79.3)	41.5 (36.5–46.5)	48.8 (41.0–56.7)	46.5 (40.7–52.4)
South	59.3 (54.2–64.3)	45.0 (41.7–48.2)	50.5 (45.2–55.7)	47.5 (43.9–51.1)
West	56.8 (49.8–63.8)	46.7 (41.1–52.2)	51.8 (43.5–60.0)	49.8 (43.7–55.8)
Health insurance coverage				
Private	63.8 (59.1–68.4)	43.6 (40.4–46.9)	53.3 (48.5–58.1)	47.0 (43.0–51.0)
Medicaid (includes persons with Medicaid and Medicare)	65.2 (57.2–73.2)	48.0 (43.2–52.8)	55.0 (48.2–61.8)	49.9 (44.6–55.2)
Medicare only	— ^b	36.2 (28.0–44.3)	41.2 (24.2–58.1)	38.0 (28.8–47.3)
Other coverage	69.6 (56.1–83.1)	39.9 (32.7–47.0)	37.7 (25.7–49.7)	48.5 (40.5–56.5)
Uninsured	60.9 (52.9–69.0)	45.7 (40.9–50.4)	49.5 (42.2–56.8)	49.9 (44.6–55.2)

Source: NHIS, National Center for Health Statistics, public use data, 2015.

Notes: **CI** = confidence interval; **GED** = General Educational Development.

^aCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

^bPrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

^cAmong only adults 25 years of age and older.

smokers, the prevalence of quit attempts among daily smokers (Table 2.12) was higher among persons younger than 45 years of age than among those 45 years of age and older; in 2017, the prevalence of quit attempts was higher among those younger than 45 years of age than among only those 65 years of age and older. Among daily smokers, Blacks had a higher prevalence of quit attempts compared with Whites (NHIS, public use data, 2017). Among nondaily smokers in 2015, Whites and Blacks were more likely than Hispanics to make a quit attempt (Table 2.12); these racial/ethnic differences were not observed in 2017: Whites (55.9%), Blacks (67.8%), and Hispanics (57.8%) (NHIS, public use data, 2017). Also, among nondaily smokers, for all education levels below a graduate degree, the prevalence of making a past-year quit attempt was greater than 50%, although prevalence across educational groups was not statistically significant. In contrast, among daily smokers, the prevalence of making a past-year quit attempt was greater than 50% in only three groups: those 18–24 years of age, Blacks, and Asians (NHIS, public use data, 2017).

According to findings from the 2017 BRFSS, the prevalence of having a past-year quit attempt among cigarette smokers was greater than 60% in every state except Wisconsin (58.6%), Missouri (59.7%), and Iowa (59.9%) (Table 2.10). The prevalence of having a past-year quit attempt exceeded 70% in four states and one U.S. territory: Connecticut (71.6%), New Jersey (71.3%), Delaware (71.0%), Texas (70.7%), and Guam (72.3%).

Young Adults

Quit attempts among young adults varied significantly across demographic subgroups (NHIS, public use data, 2017). During 1997–2017, significant nonlinear increases in quit attempts among young adults were found among males, females, and Whites ($p < .05$ for quadratic trends), and significant linear increases were found among Hispanics ($p < .05$ for linear trends), but there were no significant changes in quit attempts among Blacks (NHIS, public use data, 1997–2017). Since 2009, across males and females and across Whites, Blacks, and Hispanics, the majority of cigarette smokers had tried to quit smoking during the past year. The prevalence of quit attempts among young adults differed across states; the prevalence of a quit attempt was highest in Vermont (86.5%), Mississippi (85.7%), and Florida (85.5%) and lowest in Oregon (58.9%), District of Columbia (59.6%), and Illinois (60.5%) (BRFSS, public use data, 2017).

Youth

Using data from the 2015 national YRBS, among the 10.8% of students in grades 9–12 who currently smoked cigarettes, 45.4% had tried to quit smoking cigarettes during the 12 months preceding the survey (Kann et al. 2016). The prevalence of having tried to quit smoking cigarettes was higher among female (52.8%) than male (39.7%) students. The prevalence of having tried to quit

smoking cigarettes was higher among 9th-grade (47.8%), 10th-grade (51.6%), and 12th-grade (47.7%) students than among 11th-grade students (37.9%). In contrast to the report from the national YRBS, the analysis of data from NYTS found that, in 2015, the prevalence of having a past-year quit attempt among students in grades 9–12 was 57.8% (NYTS, public use data, 2015), or 12.4 percentage points higher than the YRBS finding (Table 2.13a). Appendix 2.2 discusses factors contributing to this difference and other differences between the two surveys. The analysis of data from the 2017 NYTS also found that the prevalence of a past-year quit attempt was 61.1% among students in grades 9–12 and 67.2% among students in grades 6–8 (Tables 2.13a and 2.13b) (the YRBS did not ask this question in 2017).

Trends in Attempts to Quit Smoking During the Past Year

Adults

According to data from NHIS, from 1997 to 2017, the prevalence of a past-year quit attempt increased significantly among men and women ($p < 0.05$ for quadratic trends) (Figure 2.10). The percentage of female cigarette smokers who made a past-year quit attempt increased from 1997 (49.5%) to 2008 (54.1%); this percentage was 50% or greater from 2005 to 2017 and peaked at 57.7% in 2014; however, percentages from 2008 to 2017 were not statistically significantly different. The prevalence of past-year quit attempts among men also increased from 1997 (48.9%) to 2009 (52.2%) (Figure 2.10); it was 50% or higher every year from 2009 to 2017 and peaked at 55.3% in 2015; however, percentages from 2009 to 2017 were not statistically significantly different.

During 1997–2017, there were significant increasing trends in quit attempts among Whites, Blacks, and Hispanics ($p < 0.05$ for quadratic trends among Whites and Blacks and $p < 0.05$ for linear trend among Hispanics). Among Whites, the prevalence of past-year quit attempts rose from 48.5% in 1997 to 54.4% in 2014; larger increases were observed among Blacks from 1997 (49.0%) to 2016 (63.8%) and among Hispanics from 1997 (53.3%) to 2012 (61.1%) (Figure 2.11); prevalence was not statistically different from 2014 to 2017 for Whites, 2016 to 2017 for Blacks, and 2012 to 2017 for Hispanics. The prevalence of past-year quit attempts peaked in 2016 among Blacks (63.8%), in 2014 among Whites (54.4%), and in 2012 among Hispanics (61.6%). From 2013 (Lavinghousse et al. 2015) to 2017 (Table 2.10), the prevalence of a quit attempt increased in Delaware, decreased in Missouri and Wisconsin, and remained stable in all other states and the District of Columbia.

Young Adults

Among young adults, significant nonlinear increases in quit attempts were found among males, females, and Whites ($p < 0.05$ for quadratic trends), and significant linear increases were observed for Hispanics ($p < 0.05$ for linear trends) (NHIS, public use data, 1997–2017). Peak prevalence of past-year quit attempts occurred in 2013 among young adult males (60.6%), in 2014 among young adult females (65.6%), and in 2015 among young adult Whites (66.6%).

Youth

Data from the national YRBS showed, among high school students who were current cigarette smokers, a significant linear decrease in the prevalence of past-year quit attempts from 2001 to 2015 among males (from 53.4% to 39.7%) and females (from 61.4% to 52.8%) (Figure 2.12). A similar linear decrease occurred in the prevalence of past-year quit attempts among Whites (from 57.2% in 2001 to 44.1% in 2015), but no change occurred among Hispanics (50.3% in 2001 and 49.6% in 2015) (YRBS, public use data, 2001–2015). The sample size for Blacks was insufficient to yield statistically stable estimates.

In contrast, data from the NYTS (Tables 2.13a and 2.13b) suggest a more stable trend in the prevalence of past-year quit attempts among high school students between 2000 (59.3%) and 2017 (61.1%). These differences could be the result of multiple factors, including variations in the length of the questionnaire and its content, time of administration (i.e., spring vs. fall semester), periodicity of the survey (i.e., biennial vs. annual), and sample demographics. Analysis of data from NYTS indicates that the prevalence of a past-year quit attempt among middle school students in grades 6–8 increased from 59.9% in 2000 to 77.0% in 2015 and then remained unchanged in 2017 (67.2%).

Number and Duration of Quit Attempts During the Past Year

Adults

Successfully quitting cigarette smoking usually involves multiple quit attempts. For example, estimates from a longitudinal study of adult smokers in Ontario, Canada, indicated that among those currently trying to quit, the highest probability of successful cessation on a given quit attempt, accounting for self-reported lifetime quit attempts, occurred on quit attempts 4–6 (Chaiton et al. 2016). However, further life table analyses of these smokers estimated that the average number of quit attempts before successfully quitting for at least 1 year was 29.6 (95% CI, 27.6–31.7) (Chaiton et al. 2016). Analysis of

Table 2.13a Quitting behaviors among current cigarette smokers^a in high school (grades 9–12); National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States

Quitting behaviors	2000: % (95% CI)	2004: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Tried to quit cigarettes ≥1 days during the past year	59.3 (57.4–61.2)	57.6 (54.9–60.3)	53.7 (49.8–57.7)	57.8 (53.0–62.6)	61.1 (54.8–67.4)
Number of times tried to quit cigarettes during the past year^b					
1	35.0 (33.3–36.8)	23.7 (20.7–26.8)	22.2 (18.7–25.6)	24.6 (17.8–31.3)	24.8 (19.1–30.5)
2	29.8 (27.8–31.7)	22.0 (19.3–24.6)	22.0 (18.6–25.4)	20.0 (15.0–25.0)	19.5 (14.4–24.7)
3–5	23.7 (22.1–25.4)	26.5 (23.5–29.5)	25.1 (21.5–28.8)	25.2 (20.6–29.8)	18.2 (13.8–22.6)
6–9	4.4 (3.6–5.2)	8.8 (7.2–10.5)	8.8 (6.9–10.8)	7.7 (5.2–10.3)	10.5 (7.1–13.8)
≥10	7.1 (5.9–8.3)	19.0 (15.9–22.1)	21.9 (18.1–25.7)	22.5 (17.7–27.3)	27.0 (22.6–31.5)
Considered quitting cigarettes within					
30 days	NA	41.6 (36.5–46.6)	44.3 (39.8–48.9)	30.1 (25.0–35.1)	33.6 (29.4–37.8)
6 months	NA	30.1 (26.1–34.1)	32.5 (28.6–36.5)	21.5 (15.4–27.5)	18.3 (13.6–23.1)
Not within 6 months	NA	28.3 (24.5–32.2)	23.1 (19.0–27.3)	48.5 (42.3–54.6)	48.1 (42.7–53.5)

Source: NYTS, Centers for Disease Control and Prevention, public use data, 2000, 2004, 2009, 2015, and 2017.

Notes: **CI** = confidence interval; **NA** = not applicable, question not asked in this year.

^aSmoked cigarettes during the past 30 days.

^bAmong those who tried to quit smoking cigarettes during the past year.

Table 2.13b Quitting behaviors among current cigarette smokers^a in middle school (grades 6–8); National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States

Quitting behaviors	2000: % (95% CI)	2004: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)	2017: % (95% CI)
Tried to quit cigarettes ≥1 day during the past year	59.9 (56.8–63.0)	64.7 (60.2–69.2)	63.2 (53.6–72.7)	77.0 (71.0–83.0)	67.2 (58.3–76.1)
Number of times tried to quit cigarettes during the past year^b					
1	35.2 (31.6–38.8)	20.4 (16.4–24.4)	22.8 (17.7–27.8)	21.7 (12.2–31.2)	15.3 (8.6–22.0)
2	27.6 (24.1–31.1)	16.9 (14.1–19.7)	20.0 (14.8–25.2)	— ^c	19.1 (9.3–28.9)
3–5	18.6 (15.8–21.3)	23.3 (19.5–27.1)	21.9 (16.1–27.7)	21.8 (13.3–30.4)	24.0 (12.7–35.3)
6–9	6.3 (3.9–8.8)	10.1 (7.4–12.7)	7.0 (3.8–10.1)	— ^c	— ^c
≥10	12.3 (9.9–14.7)	29.3 (26.0–32.5)	28.4 (22.9–33.8)	23.9 (12.1–35.7)	33.3 (22.7–43.9)
Considered quitting cigarettes within					
30 days	NA	57.8 (51.0–64.6)	56.7 (44.1–69.2)	51.7 (39.0–64.4)	45.5 (31.8–59.1)
6 months	NA	17.6 (13.2–22.1)	25.6 (14.6–36.6)	— ^c	18.4 (9.0–27.8)
Not within 6 months	NA	24.5 (19.5–29.5)	17.8 (10.2–25.3)	38.8 (24.6–53.1)	36.2 (24.6–47.7)

Source: NYTS, Centers for Disease Control and Prevention, public use data, 2000, 2004, 2009, 2015, and 2017.

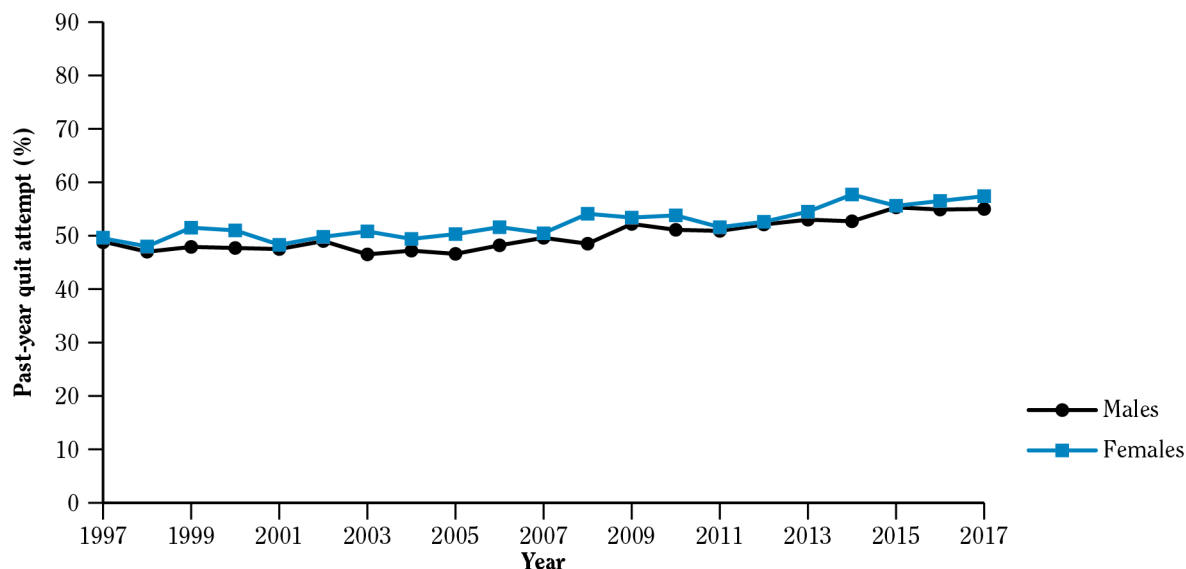
Notes: **CI** = confidence interval; **NA** = not applicable, question not asked in this year.

^aSmoked cigarettes during the past 30 days.

^bAmong those who tried to quit smoking cigarettes during the past year.

^cPrevalence estimates with a relative standard error ≥30% are not presented due to low precision.

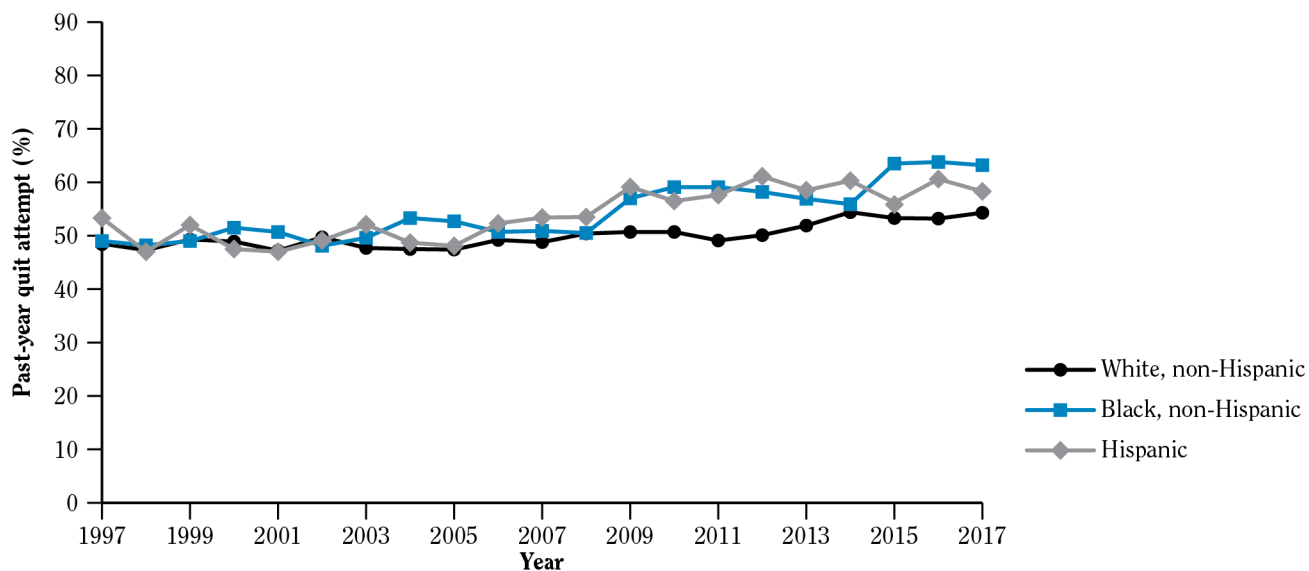
Figure 2.10 Prevalence of past-year quit attempts^a among adult cigarette smokers 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1997–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1997–2017.

^aCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

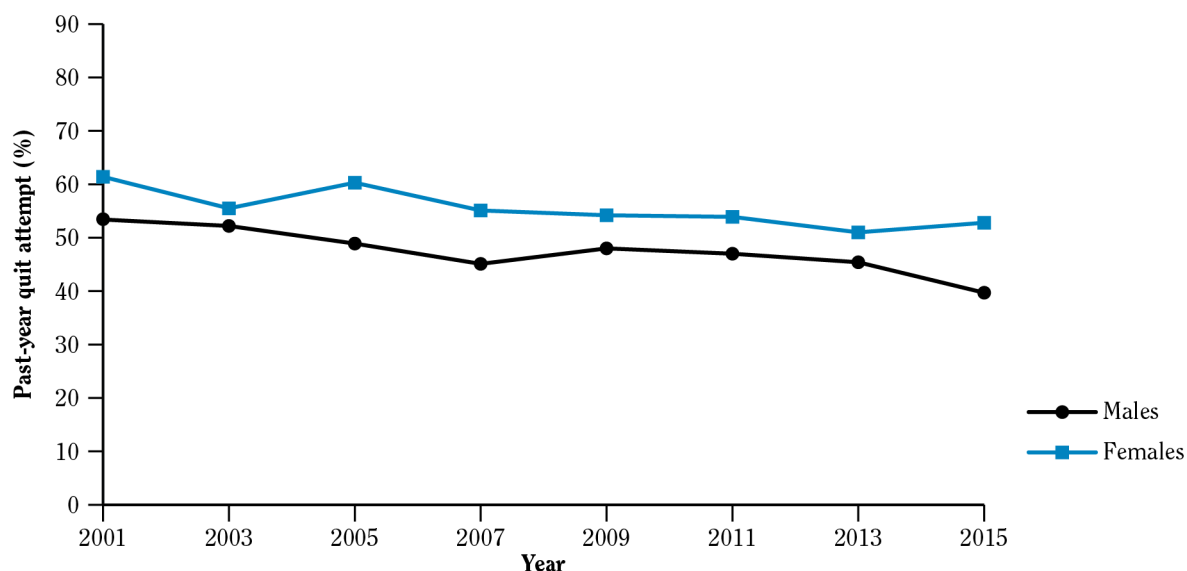
Figure 2.11 Prevalence of past-year quit attempts^a among adult cigarette smokers 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 1997–2017; United States



Source: NHIS, National Center for Health Statistics, public use data, 1997–2017.

^aCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

Figure 2.12 Prevalence of past-year quit attempts among students in grades 9–12 who currently smoke cigarettes^a, by sex; National Youth Risk Behavior Survey (YRBS) 2001–2015; United States



Source: YRBS, Centers for Disease Control and Prevention, public use data, 2001–2015.

^aRespondents who reported that they had smoked cigarettes on at least 1 day during the 30 days before the survey and also reported that they had tried to quit smoking during the past 12 months.

the 2014–2015 TUS-CPS data found that, among current daily smokers or some-day smokers who had smoked on 12 or more days during the past 30 days and had tried to quit during the past year, the most common range of past-year quit attempts was two or three (40.4%). The percentages were 30.7% for one attempt and 28.9% for at least four attempts (Table 2.14).

According to findings using the 2014–2015 TUS-CPS data, for more than one-third of current smokers (daily smokers plus some-day smokers who had smoked for 12 or more days during the past month) who had tried to quit during the past year, their longest quit attempt lasted between 1 and 6 days (35.7%), and 10.7% had a quit attempt of 6 months or longer (Table 2.14). The percentage with a past-year quit attempt lasting 6 months or longer increased from 7.5% in 2001–2002 to 11.1% in 2006–2007 and 14.6% in 2010–2011 but declined to 10.7% in 2014–2015. The percentage with a past-year quit attempt lasting 30 days to less than 6 months also declined from 32.8% in 2010–2011 to 24.4% in 2015, and the percentage with a quit attempt of 1–6 days increased from 21.5% in 2010–2011 to 35.7% in 2014–2015.

Young Adults

Among young adult current cigarette smokers (daily smokers plus some-day smokers who had smoked on 12 or

more days during the past 30 days) who had made a quit attempt during the past year, the distribution of quit attempts was similar to that for all adults (Table 2.15). For all years except 2006–2007, a smaller proportion of young adult smokers (compared with adult smokers overall) reported a longest quit attempt during the past year of 1–6 days. In contrast to adults overall, the prevalence of a long quit attempt—that is, 30 days to less than 6 months or 6 months or longer—did not change significantly over time.

Youth

Findings from the 2017 NYTS indicate that among high school current cigarette smokers who had tried to quit during the past year, more than one-fourth (27.0%) reported trying 10 or more times in the past year and slightly less than one-fourth reported trying to quit one time (24.8%) (Table 2.13a). In addition, approximately one-fifth reported trying to quit two times (19.5%) or three to five times (18.2%), and 10.5% reported trying to quit six to nine times. Among current cigarette smokers in middle school who tried to quit during the past year, one-third (33.3%) reported trying to quit 10 or more times, and a smaller percentage (15.3%) reported trying to quit one time. Although the prevalence of one or two quit attempts decreased from 2000 to 2004 among middle

Table 2.14 Quitting behaviors among current cigarette smokers^a 18 years of age and older, by year; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2001–2002, 2006–2007, 2010–2011, and 2014–2015; United States

Quitting behaviors	2001–2002: % (95% CI)	2006–2007: % (95% CI)	2010–2011: % (95% CI)	2014–2015: % (95% CI)
Ever tried to quit ^b	71.2 (70.5–71.8)	72.2 (71.6–72.9)	60.4 (59.6–61.2)	64.4 (63.6–65.2)
Tried to quit during the past year	NA	42.5 (41.8–43.3)	42.6 (41.8–43.3)	46.7 (45.9–47.5)
Tried to quit >1 days during the past year	50.0 (49.2–50.7)	35.5 (34.7–36.2)	37.2 (36.4–37.9)	41.3 (40.4–42.2)
Number of times tried to quit during the past year^c				
1	31.9 (30.9–33.0)	36.1 (35.0–37.3)	32.3 (31.2–33.4)	30.7 (29.5–31.9)
2–3	40.7 (39.5–41.8)	37.9 (36.7–39.0)	41.2 (40.0–42.4)	40.4 (39.1–41.7)
≥4	27.4 (26.4–28.4)	26.0 (25.0–27.0)	26.5 (25.4–27.6)	28.9 (27.7–30.1)
Duration of longest quit attempt during the past 12 months^c				
1–6 days	35.1 (33.9–36.2)	33.4 (32.3–34.6)	21.5 (18.7–24.3)	35.7 (34.5–37.0)
7–29 days	32.7 (31.7–33.8)	30.0 (28.9–31.0)	31.1 (27.8–34.4)	29.1 (28.0–30.3)
30 days to <6 months	24.7 (23.8–25.6)	25.5 (24.6–26.5)	32.8 (29.4–36.2)	24.4 (23.3–25.6)
>6 months	7.5 (6.9–8.1)	11.1 (10.3–11.8)	14.6 (12.0–17.2)	10.7 (9.8–11.6)
Considered quitting within:^c				
30 days	18.2 (17.6–18.7)	17.9 (17.3–18.5)	16.4 (15.9–16.9)	19.7 (18.9–20.4)
6 months	26.5 (26.0–27.1)	26.5 (25.9–27.1)	24.2 (23.6–24.9)	25.8 (25.1–26.5)
Not within 6 months	55.3 (54.6–56.0)	55.6 (54.9–56.3)	59.4 (58.6–60.2)	54.5 (53.7–55.3)
Level of interest in quitting^c				
1 (not at all interested)	NA	20.2 (19.6–20.8)	23.2 (22.4–24.0)	22.5 (21.7–23.2)
2–5	NA	31.9 (31.3–32.6)	32.2 (31.5–33.0)	30.3 (29.6–31.1)
6–8	NA	23.3 (22.7–23.9)	21.3 (20.7–21.9)	22.5 (21.9–23.2)
9 or 10 (extremely interested)	NA	24.6 (24.0–25.2)	23.3 (22.6–23.9)	24.7 (24.0–25.4)
Think they would be likely to succeed in quitting if tried during the next 6 months^d				
Not likely	NA	11.8 (11.3–12.3)	11.0 (10.4–11.6)	10.8 (10.1–11.4)
A little likely	NA	22.3 (21.6–23.0)	21.8 (21.0–22.5)	21.6 (20.9–22.3)
Somewhat likely	NA	37.1 (36.4–37.9)	37.9 (37.1–38.7)	38.4 (37.5–39.3)
Very likely	NA	28.8 (28.1–29.5)	29.3 (28.5–30.1)	29.3 (28.3–30.2)

Source: TUS-CPS, National Cancer Institute, public use data, 2001–2002, 2006–2007, 2010–2011, and 2014–2015.

Notes: **CI** = confidence interval; **NA** = not applicable.

^aSmoked 12 or more days during the past 30 days and had tried to quit during the past year.

^bFor 2001–2002, estimates are from the question, “Have you ever stopped smoking for one day or longer because you were trying to quit smoking?” In other years, the question for current some-day smokers who smoked less than 12 days during past 30 days included, “Have you ever tried to quit smoking completely?” and for current daily smokers and some-day smokers who smoked 12 or more days during the past 30 days included, “Have you ever made a serious attempt to stop smoking because you were trying to quit—even if you stopped for less than a day?” Also, in 2006–2007, current daily smokers and some-day smokers who smoked less than 12 days/month were asked, “Have you ever stopped smoking one day or longer because you were trying to quit smoking?”

^cAmong current daily smokers and some-day smokers who smoked 12 or more days during the past 30 days who tried to quit during the past year.

^dAmong those who were interested in quitting.

Table 2.15 Quitting behaviors among current cigarette smokers^a 18–24 years of age, by year; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2001–2002, 2006–2007, 2010–2011, 2014–2015; United States

Quitting behaviors	2001–2002: % (95% CI)	2006–2007: % (95% CI)	2010–2011: % (95% CI)	2014–2015: % (95% CI)
Ever tried to quit ^b	67.7 (65.9–69.5)	65.7 (63.7–67.7)	56.7 (54.4–58.9)	61.6 (58.7–64.5)
Tried to quit during the past year	NA	50.1 (47.8–52.4)	47.9 (45.5–50.2)	52.6 (49.6–55.7)
Tried to quit ≥1 day during the past year	69.1 (67.0–71.3)	43.8 (41.5–46.1)	42.9 (40.5–45.4)	50.0 (46.7–53.2)
Number of times tried to quit during the past year^c				
1	30.4 (28.2–32.6)	34.0 (30.8–37.3)	29.4 (25.9–32.9)	30.4 (26.2–34.5)
2–3	41.7 (39.2–44.2)	38.3 (35.2–41.5)	46.4 (42.5–50.2)	42.1 (37.6–46.7)
≥4	27.9 (25.6–30.1)	27.6 (24.8–30.5)	24.2 (20.9–27.6)	27.5 (23.5–31.4)
Duration of longest quit attempt during the past 12 months^c				
1–6 days	30.7 (28.3–33.0)	26.0 (23.1–28.9)	20.1 (12.2–28.0)	25.5 (22.0–29.0)
7–29 days	34.5 (32.0–36.9)	32.9 (29.9–35.8)	32.0 (22.5–41.5)	34.0 (29.8–38.2)
30 days to <6 months	26.9 (24.5–29.3)	28.0 (25.2–30.9)	33.2 (24.2–42.2)	28.3 (24.7–31.8)
≥6 months	7.9 (6.5–9.4)	13.1 (10.8–15.3)	14.7 (8.4–21.1)	12.3 (9.2–15.3)
Considered quitting within:^c				
30 days	20.3 (18.6–22.0)	17.5 (15.8–19.2)	16.6 (14.9–18.3)	19.1 (16.6–21.6)
6 months	27.8 (26.1–29.4)	25.4 (23.7–27.1)	23.8 (21.6–26.0)	24.6 (22.0–27.3)
Not within 6 months	52.0 (50.1–53.8)	57.1 (54.8–59.4)	59.6 (57.0–62.2)	56.3 (53.1–59.5)
Level of interest in quitting^c				
1 (not at all interested)	NA	17.5 (15.9–19.1)	20.5 (18.3–22.7)	19.5 (16.9–22.1)
2–5	NA	37.1 (35.0–39.1)	36.9 (34.5–39.3)	36.9 (33.8–40.0)
6–8	NA	27.6 (25.5–29.7)	24.8 (22.8–26.7)	23.8 (20.9–26.6)
9 or 10 (extremely interested)	NA	17.8 (16.1–19.4)	17.9 (16.0–19.8)	19.8 (17.2–22.4)
Think they would be likely to succeed in quitting if tried during the next 6 months^d				
Not likely	NA	10.8 (9.2–12.5)	11.0 (10.4–11.6)	8.8 (6.7–10.9)
A little likely	NA	22.8 (20.9–24.6)	21.8 (21.0–22.5)	18.4 (16.0–20.9)
Somewhat likely	NA	38.1 (35.9–40.4)	37.9 (37.1–38.7)	39.3 (35.9–42.6)
Very likely	NA	28.3 (26.2–30.3)	29.3 (28.5–30.1)	33.5 (30.3–36.7)

Source: TUS-CPS, National Cancer Institute, public use data, 2001–2002, 2006–2007, 2010–2011, and 2014–2015.

Notes: **CI** = confidence interval; **NA** = not applicable.

^aSmoked 100 cigarettes in their lifetime and currently smoked some days or every day.

^bFor 2001–2002, estimates are from the question, “Have you ever stopped smoking for one day or longer because you were trying to quit smoking?” In other years, questions for current some-day smokers who smoked less than 12 days during the past 30 days included, “Have you ever tried to quit smoking completely?” and for current daily smokers and some-day smokers who smoked 12 or more days during the past 30 days included, “Have you ever made a serious attempt to stop smoking because you were trying to quit—even if you stopped for less than a day?” Also, in 2006–2007, current daily smokers and some-day smokers who smoked less than 12 days/month were asked, “Have you ever stopped smoking one day or longer because you were trying to quit smoking?”

^cAmong current daily smokers and some-day smokers who smoked 12 or more days during the past 30 days who tried to quit during the past year.

^dAmong those who were interested in quitting.

and high school smokers who tried to quit during the past year, the prevalence of one or two quit attempts remained relatively stable from 2004 to 2017. In contrast, the prevalence of 10 or more quit attempts increased during 2000–2004 among current cigarette smokers in both middle school and high school who tried to quit in the past year and increased further among high school students from 19.0% in 2004 to 27.0% in 2017.

Interest in Quitting Smoking

Adults

NHIS data for 2015 indicated that 68.0% of current cigarette smokers were interested in quitting smoking completely (Table 2.11). However, when a 10-point scale was used for the 2014–2015 TUS-CPS (Table 2.14) to determine *any* interest, the estimate was somewhat higher (77.5%). In contrast to the prevalence of quit attempts, the prevalence of interest in quitting was highest among those 25–44 years of age (72.7%) and lowest among those 65 years of age and older (53.7%) and those 18–24 years of age (62.3%) (Table 2.11). This age difference was reflected in the results for health insurance: those with Medicare only were less interested in quitting (47.7) than those with other types of insurance. However, for 29 of the 30 demographic groups that were examined, only the group with Medicare only did not have a majority of current cigarette smokers who wanted to quit smoking completely. A more proximate measure of interest in quitting smoking may be whether the current cigarette smoker is interested in quitting in the next 30 days or 6 months. According to data from the 2014–2015 TUS-CPS, the majority of smokers were not considering quitting within 6 months (54.5%), 25.8% were considering quitting within 6 months, and 19.7% were considering quitting within 30 days (Table 2.14).

Young Adults

In 2015, an estimated 62.3% of young adult (18–24 years of age) current cigarette smokers wanted to stop smoking completely (Table 2.11); this measure did not vary across demographic subgroups (NHIS, public use data, 2015). According to data from the 2014–2015 TUS-CPS, young adult current cigarette smokers (daily smokers plus some-day smokers who had smoked on 12 or more days during the past 30 days) had a lower prevalence (19.8%) of having an extreme interest (determined by a report of “9” or “10” on a 10-point scale) in quitting smoking (Table 2.15) than adults overall (24.7%) (Table 2.14). The distribution of the periods in which young adult current smokers were considering quitting (i.e., within 30 days, within 6 months, or not within 6 months) (Table 2.15) was similar to that for adults overall (Table 2.14).

Youth

In the MTF Study, combined data from 2011 to 2017 (Table 2.16) indicated that 21.8% of high school seniors (12th graders) who were current smokers wanted to stop smoking “now.” Seniors whose parents had the highest level of education were less likely to want to stop smoking immediately (15.0%) than were those whose parental education fell into the second-to-lowest category (26.4%) and the middle category (22.1%). Another measure related to interest in quitting in the MTF Study is whether the smoker thinks that he or she will be smoking in 5 years. The majority of high school seniors who were current smokers thought that they would probably or definitely not be smoking in 5 years (60.3%). The percentage who thought that they would not be smoking in 5 years increased with level of parental education, from 50.7% among those with the lowest level to 68.8% among those with the highest level.

According to NYTS, in 2017, 33.6% of students in grades 9–12 and 45.5% of students in grades 6–8 who were current cigarette smokers were considering quitting smoking in the next 30 days, and 18.3% of students in grades 9–12 and 18.4% of students in grades 6–8 were considering quitting in the next 6 months (Tables 2.13a and 2.13b).

Trends in Interest in Quitting Smoking

Adults

NHIS data showed no significant change from 2000 (70.0%) to 2015 (68.0%) in the prevalence of being interested in completely stopping cigarette smoking among adults 18 years of age and older (Babb et al. 2017). Similarly, during 2000–2015, no significant change was observed in the prevalence of being interested in quitting among men, women, Whites, and Hispanics (NHIS, public use data, 2000–2015). In contrast, interest in quitting increased among Blacks from 2000 (68.4%) to 2010 (75.6%), then remained stable in 2015 (72.8%) ($p < 0.05$ based on linear trend analysis; NHIS, public use data, 2000–2015). However, data from the TUS-CPS indicate that the proportion of current smokers who were considering quitting within the next 30 days may have slightly increased from 2001–2002 (18.2%) to 2014–2015 (19.7%) (Table 2.14).

Young Adults

Similar to changes observed for adults overall, no significant changes were observed from 2000 to 2015 in interest in quitting among young adults overall. Unlike changes observed for adults overall, no significant changes were observed among any demographic subgroups (NHIS, public use data, 2000–2015). As for considering quitting

Table 2.16 Prevalence of cessation behaviors and attitudes among high school seniors who are current cigarette smokers^a; Monitoring the Future (MTF) Study 2011–2017 combined data; United States

Characteristic	Ever tried to quit smoking: % (95% CI)	Tried to stop but could not: % (95% CI)	Wants to stop smoking now: % (95% CI)	Will probably or definitely not smoke in 5 years: % (95% CI)
Total	44.8 (42.8–46.7)	22.1 (20.5–23.7)	21.8 (20.3–23.3)	60.3 (58.5–62.1)
Sex				
Male	43.9 (40.9–46.8)	21.3 (19.0–23.6) ^b	21.4 (19.3–23.5)	60.7 (58.3–63.2)
Female	44.2 (41.2–47.2)	21.3 (19.0–23.7) ^b	22.7 (20.3–25.1)	61.3 (58.6–64.0)
Race/ethnicity				
White, non-Hispanic	43.6 (41.1–46.1)	21.9 (19.9–23.9)	22.8 (20.9–24.8)	61.6 (59.4–63.7)
Black, non-Hispanic	47.7 (40.7–54.6)	24.9 (18.7–31.2)	20.4 (14.5–26.2)	60.7 (52.6–68.7)
Hispanic	42.8 (37.9–47.6)	17.8 (13.5–22.0)	18.0 (13.8–22.2)	59.1 (53.5–64.8)
Parental education^c				
1–2 (low)	44.7 (39.0–50.5)	21.9 (17.0–26.8)	20.7 (16.1–25.4)	50.7 (44.8–56.6)
2.5–3	48.9 (45.2–52.5)	24.9 (21.7–28.2)	26.4 (22.9–30.0)	57.8 (54.0–61.6)
3.5–4	45.1 (41.7–48.4)	21.8 (19.1–24.4)	22.1 (19.2–25.0)	61.1 (58.1–64.1)
4.5–5	39.8 (36.0–43.6)	18.9 (16.0–21.9)	19.8 (16.6–23.0)	65.9 (62.3–69.5)
5–6 (high)	38.8 (32.4–45.2)	15.5 (11.2–19.9)	15.0 (11.1–18.9)	68.8 (62.9–74.8)
U.S. Census region				
Northeast	47.7 (43.9–51.6)	23.2 (20.1–26.3)	24.0 (20.7–27.3)	60.3 (56.2–64.4)
Midwest	43.6 (39.0–48.2)	22.0 (18.5–25.4)	21.7 (18.6–24.8)	61.3 (57.8–64.8)
South	45.2 (42.4–48.1)	23.0 (20.5–25.5)	22.6 (20.1–25.1)	58.5 (55.4–61.6)
West	42.6 (37.9–47.3)	19.2 (14.9–23.6)	18.4 (15.1–21.7)	62.7 (58.4–66.9)

Source: MTF Study, University of Michigan, Institute for Social Research, 2011–2017 (unpublished data).

Notes: **CI** = confidence interval. Data come from a randomly selected 33% of the entire sample (questions on cessation and attitudes were asked on two survey forms out of a total of six). The total weighted N for 30-day smoking is 4,320; variable-specific missing data reduce the sample size slightly overall and in results for each sociodemographic subgroup presented here.

^aBased on responses to the question, “How frequently have you smoked cigarettes during the past 30 days?” Respondents who reported that they had smoked less than 1 cigarette per day or more were classified as current smokers.

^bThe overall percentage does not fall between the sex-specific percentages because of missing values for sex.

^cParental education is the average of a mother’s education and a father’s education based on answers from respondents about the highest level of education achieved by each parent, using the following scale: completed (1) grade school or less, (2) some high school, (3) high school, (4) some college, (5) college, and (6) graduate or professional school after college. Missing data were allowed for one of the two parents.

in the next 30 days, unlike adults overall, data from the TUS-CPS indicated that no significant change occurred over time in the prevalence of young adults who were considering quitting in the next 30 days (Table 2.15).

Youth

According to the MTF Study, the prevalence of high school seniors who were current smokers and wanted to stop smoking “now” decreased from 31.0% in 2000–2004 to 16.5% in 2015–2017 (Table 2.17). The proportion who believed they would probably or definitely not be smoking in 5 years was similar between 2000–2004 (63.2%) and

2015–2017 (65.4%). Using data from the NYTS, among current smokers in grades 9–12, the prevalence of considering quitting within 30 days decreased from 44.3% in 2009 to 33.6% in 2017 (Table 2.13a). Similarly, the prevalence in this group of wanting to quit in the next 6 months decreased from 32.5% in 2009 to 18.3% in 2017.

History of a Quit Attempt

Adults

According to the TUS-CPS, in 2001–2002, 71.2% of current adult cigarette smokers had ever tried to quit

Table 2.17 Prevalence of cessation behaviors and attitudes among high school seniors who are current cigarette smokers^a, by year; Monitoring the Future (MTF) Study 2000–2004, 2005–2009, 2010–2014, and 2015–2017 combined data; United States

Characteristic	2000–2004: % (95% CI)	2005–2009: % (95% CI)	2010–2014: % (95% CI)	2015–2017: % (95% CI)
Ever tried to quit smoking	49.6 (47.2–52.0)	44.2 (42.1–46.3)	45.0 (41.9–48.1)	40.2 (35.6–44.8)
Tried to stop but could not	28.8 (26.6–30.9)	22.3 (20.7–24.0)	22.9 (20.4–25.4)	17.6 (14.2–21.0)
Wants to stop smoking now	31.0 (28.9–33.2)	21.8 (20.2–23.4)	22.9 (20.5–25.2)	16.5 (13.3–19.7)
Will probably or definitely not smoke in 5 years	63.2 (61.0–65.4)	62.5 (60.7–64.4)	58.7 (56.1–61.3)	65.4 (61.0–69.8)

Source: MTF, University of Michigan, Institute for Social Research, 2001–2017 (unpublished data).

Notes: CI = confidence interval.

^aRespondents who reported that they had smoked one cigarette per day or more.

smoking, even just once. This percentage remained relatively stable in 2006–2007 (72.2%), but by 2010–2011 it had decreased by more than 10 percentage points, to 60.4%. Although the percentage increased to 64.4% in 2014–2015, it was lower than in 2001–2002 or 2006–2007 (Table 2.14).

Young Adults

Through 2010–2011, young adult current smokers had a lower prevalence of ever having tried to quit smoking (Table 2.15) than adults overall (Table 2.14). But in 2014–2015, the prevalence among young adults of ever having tried to quit smoking (61.6%) (Table 2.15) was similar to that of adults overall (64.4%, Table 2.14). The patterns of change over time in ever trying to quit smoking were similar between young adult smokers (Table 2.15) and adults overall (Table 2.14).

Youth

The MTF Study found that in 2011–2017, 44.8% of high school seniors who were current smokers had ever tried to quit smoking (Table 2.16). A significant decrease in this percentage was seen from 2000–2004 (49.6%) to 2015–2017 (40.2%) (Table 2.17). Similarly, in 2015–2017, 17.6% of youth had tried to quit smoking but could not, which was lower than in 2000–2004 (28.8%) (Table 2.17). In 2011–2017, high school seniors with parents with the second-lowest level of parental education were more likely than students with parents in the two highest categories of parental education to have ever tried to quit (48.9% vs. 39.8% and 38.8%, respectively) (Table 2.16). In addition, high school seniors with parents with the second-lowest level of parental education were more likely to report that they had tried to quit but could not (24.9%) than those with parents in the highest category of parental education (15.5%).

Other Tobacco Products: Use and Cessation

Adults

Data from the 2017 NHIS indicate that 3.8% of adults currently smoked cigars, cigarillos, or filtered little cigars; 2.8% of U.S. adults currently used e-cigarettes; 2.1% used smokeless tobacco; 1.0% smoked regular pipes, water pipes, or hookahs; and 3.7% used 2 or more types of tobacco products (Wang et al. 2018a). The PATH Study found that in 2013–2014, 17.7% of U.S. adult respondents reported having ever tried e-cigarettes; among those, 3.8% of 18- to 24-year-old respondents reported becoming regular users of e-cigarettes (Kasza et al. 2017). In addition, 5.5% of adults in Wave 1 (2013–2014) of PATH reported currently using e-cigarettes (now uses e-cigarettes every

day or some days); among those who used e-cigarettes, 42.2% reported infrequent use (current some-day use and used 0–2 days in the past 30 days), 36.5% reported moderate use (some-day use and used more than 2 days of the past 30 days), and 21.3% reported daily use (Coleman et al. 2017; Kasza et al. 2017). The 2013–2014 PATH Study also observed that the prevalence of current established use of cigarillos (1.7%; 95% CI, 1.5–1.8) was higher than the prevalence of use of filtered cigars (0.9%; 95% CI, 0.8–1.0), nonpremium cigars (other larger mass-market cigars) (0.8%; 95% CI, 0.7–0.8), and premium cigars (0.7%; 95% CI, 0.6–0.7) (the term “current established users” was defined as persons who had ever heard of the cigar type, ever smoked the cigar type “fairly regularly,”

and now smoked every day or some days) (Corey et al. 2017). In addition, in the 2013–2014 PATH Study, 31.9% of adults reported smoking hookahs during the past year, and among these, 10.7% were daily or weekly users, 13.7% were monthly users, 42.1% used every couple of months, and 33.5% used about once a year (Robinson et al. 2018).

For all four types of tobacco products (i.e., e-cigarettes, cigars, smokeless tobacco, pipes), NHIS 2017 prevalence was higher among men than women, decreased with age and, correspondingly, was lower among those with Medicare only than among those with other types of insurance (Wang et al. 2018a). However, when each type of cigar product was examined separately for the 2013–2014 PATH Study, only use of cigarillos decreased with age; use of filtered cigars increased with age; and prevalence of premium cigars and nonpremium cigars was the highest among persons 35–54 years of age (Corey et al. 2017). Prevalence of cigar smoking was higher among Blacks than among Whites and Hispanics (Wang et al. 2018a); however, for the 2013–2014 PATH Study, prevalence of premium and nonpremium cigar use was higher among Whites than Blacks (Corey et al. 2017).

Data from the 2017 NHIS indicate that smokeless tobacco use was higher among Whites than among Blacks and Hispanics (Wang et al. 2018a). E-cigarette use was also higher among Whites and persons of multiple races than Hispanics and Asians. Prevalence of pipe and/or hookah use was higher among Whites than Hispanics. Cigar use and smokeless tobacco use were higher in the Midwest than in the Northeast and the West, and the Midwest had a higher prevalence of pipe and/or hookah use than the Northeast. Data from the PATH Study suggest that there are urban–rural differences in the use of noncigarette tobacco products—for example, smokeless tobacco use was more prevalent in rural than urban counties; and the use of hookahs, cigarillos among women, and e-cigarettes among men was more prevalent in urban areas than in rural areas (Roberts et al. 2017).

Data from the 2017 NHIS indicate that the prevalence of e-cigarette and smokeless tobacco use was lower among those with a graduate degree than among those with an associate degree or lower level of education. E-cigarette use was higher among those with a GED than among those with any other level of education, and e-cigarette use was lower among those with an undergraduate degree than among those with a GED, a high school diploma, or those with some college and no degree. Smokeless tobacco use was also lower among those with an undergraduate degree than those with a high school diploma (Wang et al. 2018a). For the 2013–2014 PATH Study, use of premium cigars increased as level of education increased, and use of nonpremium cigars, cigarillos, and filtered cigars was greatest among those with some college or an associate

degree (Corey et al. 2017). Among pregnant women in the 2013–2014 PATH Study, 4.9% used e-cigarettes, 2.5% used hookahs, and 2.3% used cigars (Kurti et al. 2017).

Cross-sectional evidence suggests that the majority of adult e-cigarette users in the United States are either current or former cigarette smokers. Among current adult e-cigarette users in the 2017 NHIS, 49.6% were current smokers of conventional cigarettes, 33.5% were former cigarette smokers, and 17.0% had never been cigarette smokers (NHIS, public use data, 2017).

Although significant declines in cigarette smoking have occurred among U.S. adults during the past 5 decades, the use of noncigarette tobacco products has increased in recent years (USDHHS 2014; Hu et al. 2016), making cessation of all tobacco products an important measure. In addition, health risk behaviors, similar to cigarette smokers, also tend to cluster among persons who use other tobacco products. For example, an analysis of patterns of alcohol, marijuana, and tobacco use in the PATH Study revealed that co-use of alcohol, cigarettes, and e-cigarettes was one of the top five use patterns among adults 25 years of age and older (Cohn et al. 2018). In addition, among young adults (18–24 years of age), mental health and substance use problems were associated with higher odds of alcohol and hookah co-use (OR = 1.48; 95% CI, 1.03–2.13; OR = 1.97; 95% CI, 1.04–3.74, respectively) than alcohol-only use. Among adults (25 years of age and older) and compared with alcohol-only users, mental health and substance use problems were associated with higher odds of alcohol, cigarette, and e-cigarette co-use (OR = 1.55; 95% CI, 1.24–1.93; OR = 2.22; 95% CI, 1.43–3.44, respectively) and with higher odds of alcohol and cigar co-use (OR = 1.60; 95% CI, 1.20–2.14; OR = 4.64; 95% CI, 3.10–6.94, respectively) (Cohn et al. 2018).

Data from the 2017 NHIS indicated that 8.0% of adults were former users of smokeless tobacco; 11.6% were former users of e-cigarette; 12.2% were former users of pipes, water pipes, or hookahs; and 23.7% were former users of cigars, cigarillos, or little cigars (NHIS, public use data, 2017). In contrast to the measure of former cigarette smoking, former users of noncigarette tobacco products was defined as persons who ever used the product but were not currently using. The quit ratio (defined as the ratio of former smokers to ever smokers) was 92.1% for pipes, water pipes, and hookahs; 86.2% for cigars, cigarillos, and little cigars; 79.4% for smokeless tobacco; and 80.6% for e-cigarettes (NHIS, public use data, 2017). The 2014–2015 TUS-CPS also examined the use of pipes: the prevalence of former use was 5.4% for a regular pipe and 4.1% for water or hookah pipes, and quit ratios were 93.9% for those who had used a regular pipe and 87.8% for those who had used a water or hookah pipe (TUS-CPS, public use data, 2014–2015). In the 2013–2014 PATH Study, among women

15–44 years of age, prevalence of former use was 3.8% for e-cigarettes, 3.2% for cigars, 6.9% for hookah, 1.2% for pipes, and 0.4% for smokeless tobacco and snus (Lopez et al. 2018). Initial prospective longitudinal evidence from Wave 1 (2013–2014) and Wave 2 (2014–2015) of the PATH Study indicated that 48.8% of U.S. adult e-cigarette users overall at Wave 1 had discontinued their use of e-cigarettes at Wave 2 (Coleman et al. 2018). Cessation of e-cigarettes at Wave 2 decreased with increasing frequency of e-cigarette use at Wave 1. In addition, adjusted prevalence ratios indicated that e-cigarette users who also used combustible tobacco products at Wave 1 and e-cigarette users who used customizable e-cigarette devices were less likely to quit e-cigarette use at Wave 2. Among dual users of e-cigarettes and conventional cigarettes at Wave 1, 44.3% had maintained dual use at Wave 2; 43.5% had discontinued the use of e-cigarettes but maintained smoking conventional cigarettes; 7.0% had discontinued both products; and 5.1% had discontinued conventional cigarettes but continued smoking e-cigarettes (Coleman et al. 2018).

Additional longitudinal data from Kurti and colleagues (2018) from the PATH Study indicated that 1-year quit rates among nonpregnant women 18–44 years of age who were established tobacco users (i.e., used product fairly regularly in the past and currently used) were highest for users of cigars (60.6%), followed by hookah users (45.4%) and e-cigarette users (32.8%). Quit rates for users of these products were higher than the 1-year quit rate (11.5%) among women who had smoked 100 or more cigarettes in their lifetime. In separate multivariate logistic regression models containing data on both established and experimental users (used product in the past but not fairly regularly and used some days or every day at the time of the survey), experimental use was associated with increased odds of quitting e-cigarette use, hookah use, cigar use, and all tobacco use at Wave 2 compared with established use. In addition, respondents who used illicit drugs were more likely to quit e-cigarettes at Wave 2 than those who did not use these drugs, and those who belonged to a racial/ethnic group other than White, Black, or Hispanic were less likely to quit hookah use at Wave 2. Women with lower levels of education were less likely than those with higher levels of education to quit hookah use and all tobacco use. Hispanic women were more likely to quit all tobacco use than White women (Kurti et al. 2018).

Additional key cessation measures for individual tobacco products other than cigarettes generally have not been included in national surveillance systems. The 2014–2015 TUS-CPS assessed past-year quit attempts for other tobacco products, but the population for these questions was limited to persons who used only one product. The 2012–2014 NHIS included a question about trying to quit

all tobacco use during the past year, and the 2013–2014 NATS included a question about interest in quitting all tobacco products. In contrast, the PATH Study has data on interest and intentions to quit all tobacco products and on quit attempts, as well as longitudinal data on quitting, as described previously (Hyland et al. 2017).

In 2012–2014, 39.8% of persons who used two or more tobacco products (cigarettes, cigars, smokeless tobacco, or pipes) had tried to quit all tobacco use during the past year (NHIS, public use data, 2012–2014) (Table 2.18). Among cigarette smokers who also used another tobacco product, the prevalence of attempting to quit all tobacco products during the past year (40.1%) was lower than the prevalence of making an attempt to quit cigarette smoking (48.9%). This lower prevalence of trying to quit all tobacco use versus cigarette smoking was also observed among men; persons 25–64 years of age, Whites, Blacks, those with 12 or fewer years of education or a high school diploma, those living at or above the poverty level, those living in the South, and those without insurance. Similarly, the PATH Study found that adult users of more than one type of combustible tobacco product were less likely to try to quit tobacco use completely during the past year than cigarette-only users (OR = 0.82, $p < 0.05$) (Kypriotakis et al. 2018).

Among those who used two or more tobacco products, the associations between having tried to quit all tobacco product use during the past year and demographic characteristics (Table 2.18) were similar to those for a past-year attempt to quit cigarette smoking (Table 2.11), except for race/ethnicity; specifically, no differences were observed among Whites, Blacks, and Asians (38.8%, 39.5%, and 43.2%, respectively) (Table 2.18). Overall, the prevalence of trying to quit cigarette smoking during the past year did not differ significantly between those who smoked cigarettes only (47.1%) and cigarette smokers who used other tobacco products (48.9%) (Table 2.18). Thus, although cigarette smokers who use other tobacco products (i.e., cigars, smokeless tobacco, and pipes) have a similar prevalence of making a past-year cigarette quit attempt to that of cigarette-only smokers, they have a lower prevalence of trying to quit all tobacco use than trying to quit cigarette smoking during the past year.

The PATH Study, using Wave 1 data, also compared past-year tobacco quit attempts among adult users of various combinations of tobacco products and observed that cigarette-only (OR = 0.59, $p < 0.01$), smokeless tobacco-only (OR = 0.39, $p < 0.001$), and polycombustible tobacco users (OR = 0.48, $p < 0.001$) were less likely to attempt to quit than those who used both e-cigarettes and hookah (Kypriotakis et al. 2018). In addition, smokeless tobacco-only users were less likely to attempt to quit than cigarette-only users (OR = 0.66, $p < 0.001$).

Table 2.18 Prevalence of a past-year quit attempt for cigarette smoking^a and all tobacco use^b by type of tobacco used among adult current tobacco users 18 years of age and older, by selected demographic characteristics; National Health Interview Survey (NHIS) 2012–2014; United States

Characteristic	Attempted to quit cigarette smoking		Attempted to quit all tobacco use	
	Cigarette-only smokers: % (95% CI)	Cigarette smokers who used other tobacco products: % (95% CI)	Cigarette smokers who used other tobacco products: % (95% CI)	Used ≥2 tobacco products: % (95% CI)
Total	47.1 (46.0–48.3)	48.9 (46.3–51.6)	40.1 (37.7–42.6)	39.8 (37.5–42.1)
Sex				
Male	46.0 (44.4–47.7)	47.2 (44.3–50.2)	38.7 (36.0–41.5)	38.5 (36.0–41.1)
Female	48.2 (46.6–49.7)	55.3 (48.9–61.6)	45.2 (38.4–52.1)	45.0 (38.3–51.8)
Age group (years)				
18–24	54.3 (49.5–59.2)	57.6 (51.5–63.7)	50.6 (44.2–56.9)	50.3 (44.4–56.2)
25–44	50.3 (48.6–52.0)	49.7 (46.3–53.1)	40.3 (37.1–43.4)	39.5 (36.6–42.5)
45–64	44.3 (42.7–46.0)	43.0 (38.2–47.8)	33.4 (29.0–37.7)	33.8 (29.6–38.1)
≥65	38.3 (35.3–41.3)	31.4 (23.6–39.2)	23.7 (16.8–30.7)	23.0 (16.3–29.7)
Race/ethnicity				
White, non-Hispanic	45.0 (43.6–46.4)	47.8 (44.7–50.9)	39.3 (36.4–42.3)	38.8 (36.1–41.6)
Black, non-Hispanic	52.9 (50.4–55.5)	50.3 (44.8–55.7)	38.0 (32.6–43.3)	39.5 (34.2–44.8)
Hispanic	52.5 (49.5–55.5)	60.4 (52.6–68.2)	50.1 (42.0–58.1)	49.2 (41.5–56.8)
American Indian/Alaska Native, non-Hispanic	39.7 (28.3–51.2)	— ^c	— ^c	— ^c
Asian, non-Hispanic	51.6 (45.0–58.2)	48.8 (33.1–64.5)	43.4 (28.8–57.9)	43.2 (29.2–57.3)
Multiple races, non-Hispanic	51.1 (43.5–58.7)	39.8 (26.9–52.8)	35.8 (23.0–48.6)	35.3 (22.9–47.8)
Level of education^d				
≤12 years (no diploma)	43.6 (41.3–45.8)	45.8 (39.5–52.0)	33.1 (27.8–38.4)	33.6 (28.3–38.8)
GED certificate	47.3 (42.9–51.4)	48.9 (39.6–58.1)	43.4 (34.3–52.5)	43.4 (34.4–52.4)
High school diploma	43.8 (41.6–46.0)	40.3 (35.9–44.7)	30.2 (26.0–34.4)	31.1 (26.9–35.3)
Some college (no degree)	47.7 (45.2–50.1)	49.6 (44.3–55.0)	39.4 (34.1–44.6)	39.0 (34.0–44.0)
Associate degree	50.6 (47.4–53.9)	51.5 (39.7–63.2)	42.9 (32.9–52.9)	42.4 (33.2–51.5)
Undergraduate degree	50.8 (47.5–54.1)	45.7 (38.6–52.8)	39.6 (32.8–46.3)	35.8 (29.4–42.3)
Graduate degree	47.4 (42.3–52.4)	40.7 (28.9–52.6)	36.3 (24.9–47.7)	35.0 (24.1–45.9)
Poverty status				
At or above poverty level	46.6 (45.2–48.0)	50.4 (47.1–53.8)	41.4 (38.2–44.7)	40.7 (37.7–43.7)
Below poverty level	49.0 (46.9–51.0)	43.9 (39.3–48.5)	35.7 (31.3–40.1)	36.6 (32.3–40.8)
U.S. Census region				
Northeast	48.0 (45.2–50.8)	50.2 (44.2–56.1)	39.9 (33.7–46.0)	37.6 (32.0–43.1)
Midwest	46.8 (44.4–49.3)	49.2 (43.5–55.0)	40.7 (35.5–45.9)	40.8 (35.8–45.9)
South	47.1 (45.3–48.8)	48.7 (44.5–52.9)	39.1 (35.1–43.1)	38.6 (34.8–42.5)
West	46.7 (44.0–49.3)	48.3 (43.5–53.0)	41.2 (37.1–45.3)	41.6 (37.8–45.4)
Health insurance coverage				
Private	47.1 (45.4–48.8)	51.0 (46.5–55.4)	43.1 (38.8–47.4)	41.9 (38.1–45.8)
Medicaid and those with Medicaid and Medicare	50.8 (48.4–53.2)	48.2 (42.5–54.0)	39.2 (33.5–44.8)	38.7 (33.2–44.3)

Table 2.18 Continued

Characteristic	Attempted to quit cigarette smoking		Attempted to quit all tobacco use	
	Cigarette-only smokers: % (95% CI)	Cigarette smokers who used other tobacco products: % (95% CI)	Cigarette smokers who used other tobacco products: % (95% CI)	Used ≥2 tobacco products: % (95% CI)
Health insurance coverage (continued)				
Medicare only	36.5 (31.8–41.3)	31.2 (17.4–45.1)	24.9 (12.2–37.6)	25.7 (13.7–37.8)
Other coverage	47.3 (43.3–51.4)	47.8 (38.9–56.6)	40.0 (31.0–49.0)	39.5 (30.8–48.3)
Uninsured	46.7 (44.5–49.0)	47.4 (43.2–51.6)	36.5 (32.5–40.5)	37.2 (33.2–41.1)

Source: NHIS, National Center for Health Statistics, public use data, 2015.

Notes: **CI** = confidence interval; **GED** = General Educational Development.

^aCurrent cigarette smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking.

^bCurrent users of at least two tobacco products—cigarettes, other smoked tobacco products (including cigars, pipes, water pipes or hookahs, very small cigars, bidis, cigarillos), and smokeless tobacco (including chewing tobacco, snuff, dip, snus, dissolvable tobacco)—who reported that they stopped using all kinds of tobacco products for >1 day during the past 12 months because they were trying to quit using tobacco.

^cPrevalence estimates with a relative standard error ≥30% are not presented due to low precision.

^dAmong only adults 25 years of age and older.

Findings using data from the 2013–2014 NATS indicated that the majority (87.2%) of U.S. adults who used cigarettes and at least one other tobacco product were thinking about quitting all tobacco products for good (NATS, public use data, 2013–2014). This percentage was significantly higher than the comparable estimate for those who used at least two noncigarette tobacco products but no conventional cigarettes, which was 52.8%.

The PATH Study also examined adult tobacco users' intentions to quit at Wave 1 and observed that both polycombustible tobacco users and smokeless tobacco users were somewhat less likely to be interested in quitting (OR = 0.92, $p < 0.01$; and OR = 0.94, $p < 0.01$, respectively) than cigarette-only smokers (Kyriotakis et al. 2018). In addition, polycombustible tobacco users were also less likely than cigarette-only smokers and smokeless tobacco-only users to respond that they planned to quit for good (OR = 0.41, $p < 0.001$; and OR = 0.48, $p < 0.01$, respectively).

Young Adults

Findings using data from the 2017 NHIS indicated that quit ratios for young adults (18–24 years of age) who used other tobacco products ranged from 82.7% for pipes, 79.6% for e-cigarettes, 80.6% for cigars, and 63.4% for smokeless tobacco (NHIS, public use data, 2017). According to the 2014–2015 TUS-CPS, the prevalence of

former use of a regular pipe among young adults was 3.6% (significantly lower than the prevalence among all adults of 5.4%), and the prevalence of former use of a water or hookah pipe was 9.5% (significantly higher than the prevalence among all adults of 4.1%) (TUS-CPS, public use data, 2014–2015). Data from the PATH Study indicated that among women who used tobacco at Wave 1, those 18–24 years of age were more likely to quit all tobacco use at Wave 2 than those 25–44 years of age (Kurti et al. 2018).

Similar to data on adults overall, data from the 2012–2014 NHIS indicated no differences in past-year quit attempts for cigarette smoking among young adult cigarette-only smokers and cigarette smokers who used another tobacco product (i.e., cigars, smokeless tobacco, and pipes) (NHIS, public use data, 2012–2014). In contrast to data on adults overall, no significant differences were observed between the prevalence of trying to quit all tobacco products (50.6%) and trying to quit cigarettes (57.6%) among young adult cigarette smokers who also used another tobacco product (NHIS, public use data, 2012–2014).

Youth

Data from the 2017 YRBS indicate that 13.2% of students in grades 9–12 were current users (used on at least 1 day during the 30 days before the survey) of e-cigarettes; 8.0% currently smoked cigars, cigarillos, or little cigars;

and 5.5% currently used chewing tobacco, snuff, dip, snus, or dissolvable tobacco products (Kann et al. 2018). For all three types of assessed tobacco products (e-cigarettes, cigars, and smokeless tobacco products), prevalence of current use was higher among male than among female students and increased as grade level increased. The prevalence of current e-cigarette and smokeless tobacco use was higher among Whites than among Blacks and Hispanics, and higher among Hispanics than among Blacks. Whites also had a higher prevalence of current cigar use than Hispanics (Kann et al. 2018). Among students in grades 9–12 who used at least two tobacco products (cigarettes, e-cigarettes, cigar products, or smokeless tobacco) (10.5% of students), 52.7% (95% CI, 47.9–57.5) had tried to quit all tobacco product use in the past year (YRBS, public use data, 2017). The prevalence of having tried to quit using all tobacco products in the past year was higher among 12th-grade students (61.9%) than among 9th-grade students (42.0%) (YRBS, public use data, 2017).

According to 2017 data from the NYTS, 9.2% of high school students and 2.4% of middle school students reported using two or more tobacco products, and e-cigarettes were the most commonly used tobacco product among high school (11.7%) and middle school (3.3%) students (Wang et al. 2018b). However, trends in the use of different tobacco products have varied. For example, decreases

in cigarette and cigar smoking during 2011–2016 were offset by increases in hookah and e-cigarette use, resulting in no significant change in any tobacco use (Jamal et al. 2017). E-cigarette use has continued to increase among U.S. youth more recently. During 2017–2018, current use of e-cigarettes among high school students rose 77.8% (from 11.7% to 20.8%) and among middle school students rose 48.5% (from 3.3% to 4.9%) (Gentzke et al. 2019). This increase resulted in a corresponding increase in overall tobacco product use among middle and high school students during 2017–2018: Current use of any tobacco product increased 38.3% (from 19.6% to 27.1%) among high school students and 28.6% (from 5.6% to 7.2%) among middle school students (Gentzke et al. 2019).

The majority of high school and middle school students who used at least two tobacco products had tried to quit all tobacco use for at least 1 day during the past year (55.9% and 62.0%, respectively) (Table 2.19). Among users who had tried to quit all tobacco products during the past year, the distribution of their number of attempts (Table 2.19) was similar to the distribution for quitting cigarettes (Tables 2.13a and 2.13b). Similarly, among those who used at least two tobacco products, the distribution of the timeframes of when they considered quitting all tobacco products (Table 2.19) was similar to the distribution for quitting cigarettes (Tables 2.13a and 2.13b).

Table 2.19 Quitting behaviors among current users of two or more tobacco products,^a by grade in school; National Youth Tobacco Survey (NYTS) 2017; United States

Quitting behaviors	High school (grades 9–12): % (95% CI)	Middle school (grades 6–8): % (95% CI)
Tried to quit all tobacco ≥1 days during the past year	55.9 (51.5–60.4)	62.0 (51.2–72.7)
Number of times tried to quit all tobacco during the past year^b		
1	22.7 (16.8–28.6)	15.6 (7.5–23.7)
2	16.0 (10.2–21.9)	21.9 (9.5–34.4)
3–5	24.1 (17.4–30.9)	22.8 (13.6–32.0)
6–9	12.5 (8.1–16.9)	RSE >30%
>10	24.7 (20.1–29.3)	29.0 (16.2–41.7)
Considered quitting all tobacco within		
30 days	25.3 (19.7–30.9)	43.4 (27.9–58.9)
6 months	17.9 (12.4–23.3)	RSE >30%
Not within 6 months	56.8 (49.8–63.9)	39.4 (26.5–52.3)
Tried to quit cigarettes ≥1 day during the past year	63.1 (57.2–69.0)	68.2 (58.5–78.0)

Source: NYTS, Centers for Disease Control and Prevention, public use data, 2017.

Notes: **CI** = confidence interval; **RSE** = relative standard error.

^aAmong those who used at least two of the following tobacco products: cigarettes, e-cigarettes, cigars, cigarillos, little cigars, chewing tobacco, snuff, dip, bidis, hookahs, waterpipe with tobacco, pipe filled with tobacco, snus, dissolvable tobacco products.

^bAmong those who tried to quit all tobacco products at least once during the past year.

Clinical Interventions for Smoking Cessation: Prevalence and Trends

The *Clinical Practice Guideline for Treating Tobacco Use and Dependence (Clinical Practice Guideline)* recommends that healthcare providers screen all patients for tobacco use and deliver brief advice to quit to all tobacco users at every visit (Fiore et al. 2008). The *Clinical Practice Guideline* specifically recommends following the “5 A’s” model to deliver a brief cessation intervention in the primary care setting (i.e., Ask about tobacco use, Advise to quit, Assess willingness to quit, Assist by offering counseling and medication, and Arrange for follow-up). Chapter 6 of this report provides detailed information about these clinical interventions.

Two types of national data are available to track screening for tobacco use and counseling on tobacco cessation by healthcare professionals. The first type depends on abstracting medical records from a sample of visits to office-based physicians (e.g., NAMCS), which is used to assess screening for tobacco use and the provision of information on tobacco and/or prescriptions or orders for cessation medication to identified users. The second type of national surveillance data involves self-reports and includes assessment by patients of the receipt of advice to quit and the other 5 A’s, use of effective counseling and medications for cessation, and the use of unproven cessation strategies (datasets include NHIS, TUS-CPS, NATS, and NYTS).

Screening for Tobacco Use and Receipt of Advice to Quit from Health Professionals

Adults

Clinical Data from Abstractions of Medical Records

Reports from NAMCS that were based on the abstraction of medical records for outpatient visits to office-based physicians showed that, in 2009–2011, adults 18 years of age and older made an estimated 2.5 billion outpatient visits. NAMCS started including a panel of community health centers in 2006, which included visits to physicians and to non-physician clinicians. Data for office-based and community health center-based physicians were included in analyses for 2009–2011. According to the review, screening for tobacco use was documented

in 66.6% of the outpatient visits (average annual estimate) (Table 2.20), an increase from 62.7% during 2005–2008 (CDC 2012). Of the total documented visits in 2009–2011, 16.4% were made by current tobacco users, a decrease from 17.6% in 2005–2008. Among outpatient visits made by patients who were identified as current tobacco users in 2009–2011, 20.1% reported counseling or education was ordered or provided during their visits, a percentage that reflects no change from 2005–2008 (CDC 2012), and 3.8% received a prescription or an order for cessation medication (Table 2.20).

These estimates were similar to estimates made by screening records for visits to outpatient departments of nonfederal general and short-stay hospitals. From 2005 to 2010, screening for tobacco use occurred in 63.0% of these visits; 24.5% of visits from patients who were identified as current tobacco users included counseling on tobacco, prescriptions or orders for cessation medication, or both (Jamal et al. 2015). No significant changes in these measures occurred in hospital outpatient visits during 2005–2010 (Jamal et al. 2015).

During 2009–2011 (Table 2.20), visits to psychiatrists had a lower proportion that included screening for tobacco use (56.3%) compared with visits to general and family practitioners (69.7%) or to obstetricians and gynecologists” (69.8%). Patients who were identified as current tobacco users varied by status of health insurance, as those with Medicaid/State Children’s Health Insurance Program (SCHIP)/Children’s Health Insurance Program (33.9%), those who were self-payers (23.6%), and those covered by other insurance (25.3%) were more likely to be current tobacco users than those with private insurance (15.3%) or Medicare (11.8%).

For office-based outpatient visits among current tobacco users (i.e., the patient was identified as a current tobacco user during screening), the prevalence of visits that included tobacco counseling was lower among patients 18–24 years of age (14.5%) than among patients 45–64 years of age (22.1%) (Table 2.20).

Visits by tobacco users with other types of insurance (9.4%) were less likely to include counseling than were visits among persons in any of the other insurance subgroups (e.g., worker’s compensation, no charge/charity). Tobacco-using patients who visited their primary care physicians were more likely to receive counseling (25.0% of their visits) than were tobacco-using patients who visited doctors who were not their primary care physicians (16.2% of visits). A similar finding was made in

Table 2.20 Receipt of screening for tobacco use, counseling, and a prescription for a cessation medication during outpatient visits to office-based physicians among adults 18 years of age and older, by patient and physician characteristics; National Ambulatory Medical Care Survey (NAMCS) 2009–2011 combined data; United States

Characteristic	Visits with screening for tobacco use ^a : % (95% CI)	Visits with current tobacco use ^b : % (95% CI)	Visits with current tobacco use and tobacco counseling ^c : % (95% CI)	Visits with current tobacco use and prescription of cessation medication ^d : % (95% CI)
Total	66.6 (64.7–68.5)	16.4 (15.4–17.5)	20.1 (17.9–22.5)	3.8 (3.1–4.7)
Sex				
Male	65.7 (63.2–68.2)	19.8 (18.4–21.2)	19.8 (17.2–22.7)	3.7 (2.9–4.7)
Female	67.2 (64.7–69.6)	14.3 (13.3–15.3)	20.4 (17.9–23.1)	4.0 (3.1–5.1)
Age (in years)				
18–24	67.2 (63.9–70.3)	17.8 (16.0–19.9)	14.5 (10.9–18.9)	— ^e
25–44	68.2 (65.7–70.7)	19.8 (18.1–21.6)	18.7 (15.9–21.8)	4.4 (3.1–6.1)
45–64	66.6 (64.0–69.1)	20.1 (18.7–21.6)	22.1 (19.2–25.2)	4.5 (3.7–5.6)
≥65	65.3 (62.7–67.9)	9.1 (8.3–9.9)	19.9 (16.5–23.8)	1.3 (0.8–2.1)
Race/ethnicity				
White, non-Hispanic	67.8 (65.4–70.1)	17.1 (16.0–18.2)	20.0 (17.4–22.9)	4.1 (3.3–5.1)
Black, non-Hispanic	61.7 (56.2–66.9)	18.2 (16.1–20.5)	23.4 (18.8–28.7)	2.8 (1.5–4.9)
Hispanic	64.3 (60.5–68.0)	11.3 (9.9–12.8)	18.5 (13.8–24.4)	— ^e
Other race/multiple race, non-Hispanic	63.8 (55.8–71.1)	11.2 (8.6–14.5)	14.1 (8.6–22.2)	— ^e
Health insurance coverage				
Private insurance	68.3 (65.8–70.7)	15.3 (14.3–16.3)	20.4 (18.0–23.0)	4.2 (3.3–5.2)
Medicare	66.3 (63.5–69.0)	11.8 (10.8–12.9)	21.3 (18.0–24.9)	3.2 (2.2–4.7)
Medicaid/SCHIP/CHIP	66.1 (61.2–70.8)	33.9 (30.3–37.6)	23.0 (17.6–29.5)	4.5 (3.0–6.7)
Self-pay	61.5 (55.9–66.9)	23.6 (20.6–27.0)	19.3 (14.8–24.8)	4.7 (3.1–7.0)
Other ^f	66.1 (60.4–71.4)	25.3 (21.4–29.5)	9.4 (6.2–14.2)	— ^e
Patient's primary care physician				
Yes	69.9 (66.8–72.8)	18.3 (16.6–20.1)	24.7 (21.4–28.9)	5.1 (3.8–6.7)
No	66.6 (64.2–68.8)	14.8 (14.0–15.8)	16.2 (14.0–18.7)	2.8 (2.2–3.5)
Physician specialty				
General or family practice	69.7 (65.9–73.2)	21.6 (19.9–23.5)	22.1 (18.9–25.7)	4.8 (3.8–6.1)
Internal medicine	67.1 (60.7–72.9)	16.2 (13.9–18.9)	27.8 (22.3–34.1)	4.1 (2.5–6.9)
Obstetrics and gynecology	69.8 (64.4–74.7)	10.6 (9.0–12.5)	16.7 (11.1–24.3)	— ^e
Cardiovascular disease	67.8 (61.7–73.4)	12.3 (10.6–14.2)	38.6 (31.7–46.1)	— ^e
Psychiatry	56.3 (49.4–63.1)	23.9 (19.6–28.8)	28.8 (19.0–41.1)	13.3 (9.9–17.7)
All other specialties	64.8 (61.7–67.8)	14.6 (13.6–15.7)	12.9 (10.5–15.8)	2.1 (1.5–3.1)
Time spent with physician				
<20 minutes	64.8 (61.9–67.7)	15.8 (14.8–16.9)	17.6 (15.3–20.1)	3.3 (2.6–4.2)
≥20 minutes	68.8 (66.4–71.1)	17.0 (15.7–18.5)	22.8 (19.9–26.0)	4.4 (3.4–5.6)

Source: NAMCS, National Center for Health Statistics, public use data, 2009–2011.

Table 2.20 Continued

Note: **CHIP** = Children's Health Insurance Program; **CI** = confidence interval; **SCHIP** = State Children's Health Insurance Program.

^aVisits during which the status (yes, no) of current tobacco use (cigarettes, cigars, or snuff or chewing tobacco) was recorded.

Denominator includes current tobacco use, no current use, unknown, and blanks.

^bDocumented visits during which current tobacco use (smoking cigarettes or cigars or using snuff or chewing tobacco) was recorded.

^cTobacco counseling refers to the provision of any information related to tobacco use in any form, including cigarettes, cigars, snuff, and chewing tobacco, and also includes information about exposure to tobacco in the form of secondhand smoke, smoking cessation, and the prevention of tobacco use; referrals to other healthcare providers for smoking cessation programs are also included.

^dCessation medications include nicotine replacement therapy (nicotine patch, gum, lozenge, nasal spray, and inhaler), bupropion, and varenicline.

^ePrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

^fIncludes response options "Worker's compensation, No charge/Charity, Other."

the examination of the 2005–2010 data on visits to hospital outpatient departments (Jamal et al. 2015). Among patients who used tobacco, those who visited cardiovascular disease specialists were more likely to receive counseling on tobacco use (38.6%) than were patients who visited general and family practitioners (22.0%), obstetricians and gynecologists (16.7%), or all other specialists (12.9%). Similar differences by type of healthcare insurance, primary care physician, and physician specialty were observed in the 2005–2008 NAMCS (CDC 2012).

Among current smokers who visited office-based physicians, the percentage of visits at which tobacco cessation medications were prescribed varied by age group. The percentage was lower for visits by those 65 years of age and older compared with those 25–44 or 45–64 years of age (Table 2.20). Outpatient visits by current cigarette smokers that included a prescription of cessation medication also varied by whether the physician was the patient's primary care physician (5.1% of visits) or was not (2.8% of visits). Visits to psychiatrists had a higher proportion with prescribed medication (13.3%) than visits to all other specialists. These differences by age and physician specialty were also observed in the 2005–2008 NAMCS (CDC 2012).

Self-Reported Data from Cigarette Smokers

According to NHIS data, in 2015, 83.9% of adult cigarette smokers saw a physician or other health professional during the past year, and among this group, 57.2% reported receiving advice to quit smoking (Table 2.21). The prevalence of smokers who received advice to quit was higher among older age groups (45–64 years of age [65.7%] and those aged 65 years of age and older [65.7%]) than among younger age groups (18–24 years of age [44.4%] and 25–44 years of age [49.8%]). Whites were more likely to receive advice to quit (60.2%) than were Asians (34.2%), American Indians/Alaska Natives (38.1%), or Hispanics (42.2%) (Table 2.21). Smokers living in the Northeast were more likely to report being advised to quit

smoking (65.1%) than smokers living in the West (50.6%) or the South (55.2%). In addition, the prevalence of smokers who received advice to quit was lower in the West (50.6%) than it was in the Midwest (60.0%). Uninsured smokers were less likely to report receiving advice to quit (44.1%) than smokers with any type of insurance (range: 56.8–69.2%). There were no significant differences in receipt of advice to quit between persons identifying as lesbian, gay, or bisexual (57.7%) (Table 2.22) and those identifying as heterosexual (57.1%). These demographic differences were similar to those seen in the 2010 NHIS, although sexual orientation was not assessed prior to the 2013 NHIS (CDC 2011).

According to the 2009–2010 NATS, the prevalence of self-reported receipt of advice from a health professional to quit smoking was 65.8% among current cigarette smokers who had seen a health professional during the past year (King et al. 2013). This figure is higher than the estimate using the 2010 NHIS, in which 48.3% of current cigarette smokers and former smokers who quit during the past year reported receiving cessation advice (CDC 2011). Appendix 2.1 discusses NATS and NHIS, and Appendix 2.2 discusses methodologic features that may have contributed to this difference, including that NATS was a tobacco-focused survey that may have contributed to a social desirability bias among cigarette smokers to answer that they received cessation advice. Using data from the 2010–2011 TUS-CPS, 64.8% of current cigarette smokers reported receiving advice to quit (TUS-CPS, public use data, 2010–2011), which was similar to the estimate from the 2009–2010 NATS. Although the TUS-CPS was another tobacco-focused survey and may have been subject to social desirability bias, it is also possible that data from NHIS may underestimate the prevalence of cigarette smokers receiving advice to quit.

Also using the 2009–2010 NATS, 87.9% of current smokers who visited a health professional recalled being asked if they smoked cigarettes, and 42.6% recalled being asked if they wanted to quit (King et al. 2013). Among

Table 2.21 Prevalence of receiving a health professional's advice to quit smoking^a and use of counseling^b and medications^c for cessation among cigarette smokers 18 years of age and older, by selected characteristics; National Health Interview Survey (NHIS) 2015; United States

Characteristic	Received health professional's advice to quit: % (95% CI)	Used counseling: % (95% CI)	Used medication: % (95% CI)	Used counseling and/or medication: % (95% CI)
Overall	57.2 (55.3–59.1)	6.8 (5.7–7.9)	29.0 (26.8–31.2)	31.2 (28.9–33.5)
Sex				
Men	55.2 (52.5–57.9)	5.8 (4.3–7.4)	27.0 (24.0–30.0)	29.1 (26.0–32.2)
Women	59.3 (56.6–61.9)	7.9 (6.4–9.5)	31.3 (28.2–34.3)	33.6 (30.5–36.6)
Age group (in years)				
18–24	44.4 (37.1–51.6)	— ^c	15.6 (9.5–21.7)	16.8 (10.6–23.0)
25–44	49.8 (46.6–53.0)	6.1 (4.5–7.8)	25.5 (22.2–28.7)	27.4 (24.1–30.8)
45–64	65.7 (62.9–68.4)	8.8 (6.9–11.1)	37.7 (34.0–41.4)	40.2 (36.4–43.9)
≥65	65.7 (61.4–70.0)	9.2 (5.3–13.1)	33.7 (27.7–39.7)	37.0 (31.0–43.1)
Race/ethnicity				
White, non-Hispanic	60.2 (58.0–62.4)	6.9 (5.5–8.3)	32.6 (29.8–35.4)	34.3 (31.4–37.2)
Black, non-Hispanic	55.7 (50.2–61.1)	7.6 (4.5–10.8)	25.2 (20.1–30.3)	28.9 (23.5–34.4)
Hispanic	42.2 (37.0–47.5)	5.1 (2.4–7.7)	16.6 (12.4–20.9)	19.2 (14.4–24.0)
American Indian/Alaska Native, non-Hispanic	38.1 (21.4–54.8)	— ^c	— ^c	— ^c
Asian, non-Hispanic ^d	34.2 (24.2–44.3)	— ^c	17.4 (9.4–25.4)	20.5 (12.2–28.8)
Multiple races, non-Hispanic	69.6 (59.2–80.1)	— ^c	22.1 (10.5–33.6)	24.6 (12.7–36.4)
Level of education^e				
≤12 years (no diploma)	60.8 (56.6–65.1)	5.4 (3.1–7.6)	26.5 (21.8–31.2)	28.7 (23.8–33.6)
GED certificate	61.6 (52.4–70.7)	— ^c	30.8 (21.5–40.1)	31.4 (22.0–40.7)
High school diploma	58.1 (53.9–62.3)	7.0 (4.7–9.4)	30.3 (25.5–35.1)	33.1 (28.1–38.1)
Some college (no degree)	59.1 (55.3–63.0)	8.6 (6.0–11.1)	32.5 (28.1–36.9)	34.6 (30.1–39.2)
Associate degree	61.6 (56.4–66.8)	8.6 (5.1–12.2)	33.2 (27.4–39.0)	36.0 (29.8–42.3)
Undergraduate degree	52.6 (46.6–58.5)	7.4 (3.7–11.1)	33.2 (26.5–39.8)	35.1 (28.4–41.7)
Graduate degree	57.7 (48.5–66.8)	— ^c	32.8 (22.9–42.6)	35.9 (25.7–46.0)
Poverty status				
At or above poverty level	57.8 (55.6–60.1)	6.8 (5.6–8.1)	29.5 (27.1–31.8)	31.7 (29.2–34.2)
Below poverty level	54.7 (50.7–58.7)	6.7 (4.6–8.9)	27.0 (21.6–31.6)	29.0 (24.2–33.7)
U.S. Census region				
Northeast	65.1 (60.2–70.1)	8.2 (4.9–11.5)	34.7 (27.9–41.5)	37.6 (30.9–44.2)
Midwest	60.0 (56.1–63.9)	4.9 (3.0–6.8)	28.9 (24.9–32.8)	30.2 (26.1–34.4)
South	55.2 (52.2–58.2)	7.2 (5.3–9.0)	27.2 (23.8–30.6)	29.3 (25.7–33.0)
West	50.6 (46.9–54.4)	7.5 (5.1–9.9)	28.0 (23.1–32.8)	30.7 (25.5–35.9)
Health insurance coverage				
Private	56.8 (54.0–59.5)	6.8 (5.3–8.3)	29.9 (27.0–32.7)	32.1 (29.1–35.1)
Medicaid and dual eligibles	59.9 (55.7–64.1)	8.0 (5.3–10.7)	32.2 (27.3–37.2)	34.5 (29.3–39.6)
Medicare Advantage	66.6 (56.5–76.6)	— ^c	26.5 (15.5–37.4)	31.6 (19.7–43.4)

Table 2.21 Continued

Characteristic	Received health professional's advice to quit: % (95% CI)	Used counseling: % (95% CI)	Used medication: % (95% CI)	Used counseling and/or medication: % (95% CI)
Health insurance coverage (continued)				
Medicare only (excluding Advantage)	62.0 (51.7–72.3)	— ^c	28.5 (15.5–41.5)	35.9 (22.6–49.1)
Other coverage	69.2 (62.8–75.7)	5.2 (2.7–7.7)	34.9 (26.2–43.6)	36.0 (27.3–44.7)
Uninsured	44.1 (38.8–49.3)	4.3 (2.2–6.4)	20.0 (15.6–24.6)	21.4 (17.0–25.8)

Source: Babb and colleagues (2017).

Notes: **CI** = confidence interval; **GED** = General Educational Development.

^aReported receiving advice from a medical doctor, dentist, or other health professional to quit smoking or quit using other kinds of tobacco among current smokers and those who quit during the past year who saw a doctor or other health professional during the past year.

^bUsed one-on-one counseling; attended a stop-smoking clinic, class, or support group; and/or sought a telephone helpline or quitline during the past year among current smokers who tried to quit during the past year or used when stopped smoking among former smokers who quit during the past 2 years.

^cUsed nicotine patch, nicotine gum or lozenge, nicotine-containing nasal spray or inhaler, varenicline (U.S. trade name Chantix), and/or bupropion (including trade names Zyban and Wellbutrin) during the past year among current smokers who tried to quit during the past year or used when they stopped smoking among former smokers who quit during the past 2 years.

^dDoes not include Native Hawaiians or Other Pacific Islanders.

^eAmong only adults 25 years of age and older.

those wanting to quit, 78.2% were offered assistance, and 17.5% were scheduled for follow-up. Among persons who received assistance, 50.6% were provided with access to booklets, videos, websites, or other information; 37.5% were referred to a quitline, class, program, or counseling; and 57.8% received recommendations or prescriptions for cessation medication. Thus, in the 5 A's model of clinician cessation intervention, the prevalence of provider intervention was higher for asking, assessing, and assisting than for more time-comprehensive and time-intensive components, such as scheduling for follow-up.

Trends

For 2000–2015, NHIS data indicate a nonlinear (quadratic) trend in the prevalence of receiving advice to quit smoking. Among adult current cigarette smokers who had visited a healthcare professional during the past year, prevalence of receiving advice to quit smoking increased from 52.4% in 2000 to 57.0% in 2005, decreased to 48.2% in 2010, but then increased again to 57.2% in 2015 (Babb et al. 2017). These trends did not differ by sex (NHIS, public use data, 2000–2015). Similar trends were observed among Whites, Blacks, and Hispanics. However, among Asians, advice from healthcare professionals to quit decreased linearly over time, from 54.7% in 2000 to 34.2% in 2015 (NHIS, public use data, 2000–2015).

Young Adults

Clinical Data Obtained by Abstracting Medical Records

According to combined data for 2004–2010 from NAMCS, an average of 65.7% of physician visits among patients 18–21 years of age included screening for tobacco use; among these, an average of 16.1% visits were made by current tobacco users (Jamal et al. 2014). Among visits made by persons identified as current tobacco users, 19.1% received any assistance with cessation, including counseling on tobacco in the form of health education ordered or provided at the visit, a prescription or order for a cessation medication, or both.

Using 2004–2010 data from NAMCS, Jamal and colleagues (2014) examined physician visits among 11- to 21-year-old patients and found that a higher proportion of visits included screening for tobacco use among patients with private insurance (71.0%) and Medicaid or SCHIP (69.6%) than among patients with other types of insurance (59.9%). In addition, a higher proportion of visits to a patient's primary care physician included screening for tobacco use (72.7%) compared with visits with nonprimary care physicians (67.9%), and a higher proportion of visits to a pediatrician (74.7%) included tobacco screening compared with visits to general or family practitioners

Table 2.22 Prevalence of interest in quitting^a, past-year quit attempt^b, receipt of a health professional's advice to quit^c, use of counseling^d and/or medication^e, quit ratio^f, and recent successful cessation^g among smokers 18 years of age and older, by selected subpopulations; National Health Interview Survey (NHIS) 2015, 2017; United States

Subpopulation	Interested in quitting: % (95% CI) (2015)	Past-year quit attempt: % (95% CI) (2017)	Received health professional's advice to quit: % (95% CI) (2015)	Used counseling and/or medication: % (95% CI) (2015)	Quit ratio: % (95% CI) (2017)	Recent successful cessation: % (95% CI) (2017)
Cigarette smoking frequency^h						
Some-day smokers	71.0 (67.4–74.7)	58.5 (54.5–62.5)	44.6 (40.2–49.0)	24.2 (19.7–28.7)	NA	NA
Daily smokers, 1–4 cpd	71.8 (65.0–78.7)	59.8 (52.0–67.6)	51.3 (43.7–59.0)	33.6 (24.4–42.7)	NA	NA
Daily smokers, 5–14 cpd	68.8 (65.6–72.0)	49.8 (46.5–53.2)	64.5 (61.1–67.8)	36.2 (31.5–41.0)	NA	NA
Daily smokers, 15–24 cpd	66.3 (62.6–70.0)	40.2 (36.7–43.7)	68.4 (64.4–72.3)	42.5 (36.5–48.4)	NA	NA
Daily smokers, ≥25 cpd	55.6 (48.1–63.2)	29.5 (22.6–36.4)	79.3 (73.1–85.6)	46.7 (32.5–60.9)	NA	NA
Usually smokes menthol^h						
Yes	71.3 (68.1–74.5)	NA	58.6 (54.8–62.4)	32.8 (28.4–37.1)	NA	NA
No	67.3 (64.7–69.9)	NA	62.8 (60.4–65.3)	35.9 (31.6–38.7)	NA	NA
No usual type	40.0 (28.2–51.9)	NA	34.1 (21.8–46.4)	— ⁱ	NA	NA
Serious psychological distress						
Yes (Kessler score ^j ≥13)	67.4 (61.3–73.5)	58.2 (51.8–64.6)	70.1 (64.5–75.8)	41.6 (33.7–49.5)	40.7 (35.4–46.1)	7.2 (3.9–10.5)
No (Kessler score <13)	68.2 (66.0–70.3)	55.0 (53.1–56.9)	55.7 (53.7–57.7)	30.1 (27.8–32.5)	63.0 (61.6–64.3)	7.7 (6.7–8.8)
Chronic illness diagnosis						
Any smoking-related chronic disease ^k	67.9 (65.1–70.8)	56.5 (54.0–58.9)	67.3 (64.7–69.8)	35.4 (32.0–38.8)	65.2 (63.6–66.8)	6.8 (5.6–8.0)
Other chronic disease ^l	69.4 (66.6–72.2)	55.8 (53.3–58.3)	66.5 (64.0–69.1)	37.2 (33.6–40.7)	67.6 (66.1–69.1)	6.5 (5.0–7.9)
No chronic disease	69.3 (66.8–71.8)	56.1 (54.0–58.3)	64.8 (62.6–67.1)	36.1 (33.0–39.2)	64.8 (63.4–66.2)	6.7 (5.5–7.8)
Disability/limitation^m						
Yes	66.4 (61.4–71.3)	54.0 (50.0–58.0)	71.8 (67.4–76.2)	39.0 (32.1–45.9)	59.4 (56.7–62.1)	5.4 (3.5–7.4)
No	66.8 (63.5–70.2)	54.6 (51.9–57.2)	53.6 (50.5–56.8)	28.5 (25.1–31.9)	62.6 (60.7–64.4)	8.4 (6.8–9.9)
Sexual orientation						
Heterosexual	68.1 (65.9–70.2)	55.4 (53.4–57.3)	57.1 (55.1–59.1)	31.7 (29.3–34.1)	62.1 (60.8–63.4)	7.5 (6.4–8.5)
Lesbian/gay/bisexual	66.7 (56.9–76.6)	54.6 (46.4–62.9)	57.7 (48.5–66.9)	14.5 (7.9–21.1)	50.6 (44.1–57.0)	— ⁱ

Table 2.22 Continued

Subpopulation	Interested in quitting: % (95% CI) (2015)	Past-year quit attempt: % (95% CI) (2017)	Received health professional's advice to quit: % (95% CI) (2015)	Used counseling and/or medication: % (95% CI) (2015)	Quit ratio: % (95% CI) (2017)	Recent successful cessation: % (95% CI) (2017)
Binge drinking (past month)						
Yes	70.1 (66.0–74.2)	54.8 (51.2–58.4)	53.5 (49.3–57.7)	29.9 (25.2–34.5)	51.5 (48.7–54.4)	6.4 (4.8–8.1)
No	67.2 (64.8–69.6)	55.8 (53.6–58.0)	58.8 (56.6–61.0)	32.1 (29.5–34.7)	64.8 (63.4–66.1)	8.0 (6.7–9.2)

Source: NHIS, National Center for Health Statistics, public use data, 2015, 2017; Babb and colleagues (2017).

Notes: **CI** = confidence interval; **cpd** = cigarettes smoked per day; **NA** = not available.

^aCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

^bCurrent smokers who reported that they wanted to stop smoking completely.

^cReceived advice from a medical doctor, dentist, or other health professional to quit smoking or quit using other kinds of tobacco among current smokers and those who quit during the past year who saw a doctor or other health professional during the past year.

^dUsed one-on-one counseling; attended a stop-smoking clinic, class, or support group; and/or sought a telephone helpline or quitline during the past year among current smokers who tried to quit during the past year or among former smokers who quit during the past 2 years.

^eUsed nicotine patch, nicotine gum or lozenge, nicotine-containing nasal spray or inhaler, varenicline (U.S. trade name Chantix), and/or bupropion (including trade names Zyban and Wellbutrin) during the past year among current smokers who tried to quit during the past year or among former smokers who quit during the past 2 years.

^fThe percentage of ever smokers who have quit smoking. Defined as the number of former smokers divided by the number of ever smokers.

^gHaving smoked during the past year but having been quit for at least 6 months at the time of the survey interview. The denominator in the prevalence calculation includes all persons who smoked during the past year (i.e., both current cigarette smokers and former smokers who reported quitting during the past year).

^hAnalysis limited to current smokers.

ⁱPrevalence estimates with a relative standard error ≥30% are not presented due to low precision.

^jThe Kessler Psychological Distress Scale was developed for mental health screening in population surveys. The 10-item questionnaire is intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4-week period.

^kIncludes lung cancer, other tobacco-related cancers (bladder, cervical, colon, esophageal, kidney, larynx-windpipe, leukemia, liver, mouth/tongue/lip, pancreas, rectum, stomach, throat-pharynx, and uterine), coronary heart disease, stroke, emphysema, chronic bronchitis, asthma, diabetes, and arthritis.

^lIncludes hypertension, other heart condition or heart disease, ulcer, and cancers including blood, bone, brain, breast, gallbladder, lymphoma, melanoma, ovarian, prostate, skin (non-melanoma and other), soft tissue, testicular, thyroid, and other.

^mDefined on the basis of self-reported presence of selected limitations, including vision, hearing, cognition, and movement. Limitations in performing activities of daily living were defined on the basis of responses to the following question: “Does [person] have difficulty dressing or bathing?” Limitations in performing instrumental activities of daily living were defined on the basis of responses to the following question: “Because of a physical, mental, or emotional condition, does [person] have difficulty doing errands alone such as visiting a doctor’s office or shopping?” Any disability was defined as a “yes” response pertaining to at least one of the limitations (vision, hearing, cognition, movement, activities of daily living, or instrumental activities of daily living). Results include responses from a random sample of half of the respondents from the 2017 Person File who were asked about limitations and weights from the Family Disability Questions File.

or internal medicine physicians (68.3%), psychiatrists (62.4%), or physicians in all other specialties, except obstetrics and gynecology (65.0%). A higher proportion of visits in which preventive care was the major reason for the visit (28.9%) included cessation assistance (including counseling, medication, or both) compared with visits for other reasons (16.7%) (Jamal et al. 2014).

Data from Self-Reports of Cigarette Smokers

Among young adult current cigarette smokers (18–24 years of age), differences in the prevalence of receiving a health professional's advice to quit were similar to differences in the advice received by all adults in 2015. However, regional differences were more pronounced, as 28.6% of smokers in the South were advised to quit compared with 66.7% of smokers in the Northeast and 57.3% of smokers in the Midwest (NHIS, public use data, 2015).

Trends

Among adults 18–24 years of age, NHIS data for 2000–2015 indicated that trends in receiving advice from a provider to quit among men were similar to the quadratic trends among all adults (Babb et al. 2017), but there was no significant increase among women from 2010 (42.4%) to 2015 (42.0%) (NHIS, public use data, 2000–2015).

Youth

Clinical Data Obtained by Abstracting Medical Records

According to combined data for 2004–2010 from NAMCS, an average of 71.5% of outpatient visits by patients 11–17 years of age included screening for tobacco use; among these, an average of 3.0% outpatient visits were made by current tobacco users (Jamal et al. 2014). Among visits made by persons identified as current tobacco users, 21.8% included the receipt of any cessation assistance, including tobacco counseling in the form of health education ordered or provided at the visit, a prescription or order for a cessation medication, or both. Using 2004–2010 data from NAMCS, Jamal and colleagues (2014) examined demographic differences in the screening and provision of education and/or medication among visits by patients 11–21 years of age; these were discussed previously in the section on young adults.

Self-Reported Data

In 2015, according to data from the NYTS, 46.2% of high school students and 23.9% of middle school students who had visited a healthcare provider during the past year, were asked at any visit during that year if they had

used tobacco (Tables 2.23a and 2.23b). Twelfth-grade students (54.3%) were more likely than 9th-grade students (40.6%) and 10th-grade students (41.6%) to report being asked about tobacco use. This question was not asked in the 2016 or 2017 NYTS.

According to 2017 data from the NYTS, 31.4% of high school students and 28.1% of middle school students who had smoked cigarettes during the past 30 days had been advised by a doctor, dentist, or nurse not to use tobacco. The prevalence of receiving advice to quit was similar between these students and students who used any type of tobacco (29.5% of high school students and 24.6% of middle school students) (NYTS, public use data, 2017). According to data from the 2011 NYTS, high school students who smoked on more than 19 days during the past 30 days were more likely to receive a health professional's advice to not use tobacco (54.0%) than those who smoked on 1–19 of the past 30 days (33.0%) (Schauer et al. 2014a). According to the 2013 NSDUH, 26.3% of past-30-day tobacco users 12–17 years of age were screened for tobacco use and advised to quit (Collins et al. 2017). Furthermore, males were more likely to be advised to quit than females, and Hispanics were less likely to be advised to quit than Whites.

Use of Counseling and Medications to Quit Smoking

Adults

In 2015, according to data from the NHIS, the use of cessation counseling and/or medication among current smokers who had tried to quit during the past year and former smokers who had successfully quit during the past 2 years was 31.2% (Table 2.21). In all, 6.8% had used counseling, 29.0% had used medications, and 4.7% had used both (Babb et al. 2017). Counseling services (alone or in combination) included a telephone quitline (4.1%); one-on-one counseling (2.8%); and a stop-smoking clinic, class, or support group (2.4%). Medications included the seven FDA-approved medications for smoking cessation (alone or in combination); the prevalence of medication use was 16.6% for the nicotine patch, 12.5% for nicotine gum or lozenges, 2.4% for nicotine nasal spray or inhaler, 7.9% for varenicline, and 2.7% for bupropion.

According to NHIS, in 2015, the use of effective treatment (counseling and/or medications) was lower among persons 18–24 years of age (16.8%) than in any of the other age groups (Table 2.21). In addition, prevalence of the use of counseling and/or medication was lower among smokers 25–44 years of age (27.4%) than among smokers 45–64 years of age (40.2%) or those 65 years of age and

Table 2.23a Prevalence of being asked about tobacco use^a and being advised not to use tobacco^b among high school students (grades 9–12) who saw a healthcare provider during the past year, by grade in school; National Youth Tobacco Survey (NYTS) 2015; United States

Characteristic	Asked about tobacco use: % (95% CI)	Current cigarette smokers advised not to use tobacco: % (95% CI)
Total	46.2 (43.6–48.8)	30.2 (28.0–32.4)
Sex		
Male	45.2 (42.2–48.2)	34.1 (27.3–41.0)
Female	47.4 (44.4–50.4)	32.9 (26.4–39.4)
Grade		
9	40.6 (36.8–44.4)	27.2 (18.9–35.5)
10	41.6 (38.2–45.0)	28.6 (19.7–37.5)
11	49.7 (46.1–53.4)	38.1 (29.8–46.3)
12	54.3 (51.5–57.2)	36.6 (28.8–44.3)
Race/ethnicity		
White, non-Hispanic	47.5 (44.2–50.8)	33.1 (27.8–38.4)
Black, non-Hispanic	45.9 (42.0–49.9)	33.5 (16.8–50.2)
Other, non-Hispanic	44.8 (40.2–49.4)	33.5 (14.9–52.1)
Hispanic	44.3 (40.5–48.1)	35.4 (24.6–46.1)

Source: NYTS, public use data, 2015.

Notes: This question was not asked in the 2016 or 2017 NYTS. **CI** = confidence interval.

^aBeing asked about tobacco use was defined as being asked at any visit to a doctor, dentist, or nurse during the past year if the student used tobacco that is smoked or put in the mouth.

^bBeing advised not to use tobacco was defined as being advised by a doctor, dentist, or nurse during the past 12 months not to use tobacco that is smoked or put in the mouth among current cigarette smokers (smoked cigarettes during the 30 days preceding the survey).

Table 2.23b Prevalence of being asked about tobacco use^a and being advised not to use tobacco^b among middle school students (grades 6–8) who saw a healthcare provider during the past year, by grade in school; National Youth Tobacco Survey (NYTS) 2015; United States

Characteristic	Asked about tobacco use: % (95% CI)	Current cigarette smokers advised not to use tobacco: % (95% CI)
Total	23.9 (21.9–26.0)	22.9 (21.0–24.8)
Sex		
Male	23.4 (21.2–25.5)	31.5 (17.0–46.0)
Female	24.7 (22.1–27.2)	25.6 (14.7–36.5)
Race/ethnicity		
White, non-Hispanic	24.0 (20.9–27.0)	26.5 (17.5–35.4)
Black, non-Hispanic	28.6 (24.0–33.2)	— ^c
Other, non-Hispanic	21.2 (17.4–25.0)	— ^c
Hispanic	23.5 (21.3–25.8)	— ^c

Source: NYTS, public use data, 2015.

Notes: This question was not asked in the 2016 or 2017 NYTS. **CI** = confidence interval; **RSE** = relative standard error.

^aBeing asked about tobacco use was defined as being asked at any visit to a doctor, dentist, or nurse during the past year if the student used tobacco that is smoked or put in the mouth.

^bBeing advised not to use tobacco was defined as being advised by a doctor, dentist, or nurse during the past 12 months not to use tobacco that is smoked or put in the mouth among current cigarette smokers (smoked cigarettes during the 30 days preceding the survey).

^cData are not shown because sample size was <50 and the relative standard error of the estimate was >30%.

older (37.0%). Hispanics used effective treatments less often than Whites (19.2% vs. 34.3%). Uninsured smokers were less likely to use effective treatments (21.4%) than were smokers who were privately insured (32.1%), had Medicaid (34.5%), or had other coverage (36.0%). Use of counseling and/or medication was also lower among lesbian, gay, and bisexual smokers than among heterosexuals (14.5% vs. 31.7%) (Table 2.22).

According to data from the 2014–2015 TUS-CPS, the prevalence of using a telephone quitline for cessation was 3.5% among current cigarette smokers who had tried to quit during the past year (Table 2.24), a figure that was quite similar to the prevalence using the 2015 NHIS for using such a quitline among current smokers who had tried to quit during the past year combined with former smokers who had quit during the past 2 years (4.1%) (Babb et al. 2017). Use of a telephone quitline by current cigarette smokers during the last time they tried to quit within the past year was higher among women (4.2%) than men (2.8%), among those 45–64 years of age (4.4%) than those aged 65 years and older (2.1%), and among those living below the poverty level (5.2%) than among those living at or above the poverty level (3.0%) (Table 2.24).

Young Adults

In 2015, according to data from the NHIS, 16.8% of young adult current smokers 18–24 years of age who had tried to quit during the past year and former smokers who successfully quit during the past 2 years used cessation counseling and/or medications (Table 2.21) (Babb et al. 2017). This included 15.6% who used only medications, but because of small numbers and low precision (relative standard error $\geq 30\%$), the percentages who used either counseling only or both counseling and medication could not be estimated (Babb et al. 2017). Regardless, both percentages were lower than those for smokers 25 years of age and older (Babb et al. 2017). The association between demographic characteristics and treatment use among young adults could not be examined using 2015 NHIS data because of small sample sizes and the low precision of estimates (relative standard error $\geq 30\%$).

Youth

In 2015, according to data from the NYTS, 17.8% of high school current cigarette smokers who had tried to quit during the past year used a program, counseling, and/or medication to quit during the past 12 months, and 69.9% reported that they had “tried to quit on my own or quit cold turkey” (Table 2.25). Among middle school students, 30.4% of current cigarette smokers used a program, counseling, and/or medication to quit, and 81.9%

tried to quit cold turkey. However, caution is warranted in interpreting these results because a large proportion of middle school students reported using both a strategy to quit and quitting cold turkey, suggesting that they had different interpretations of what was meant by “quitting on their own” or quitting cold turkey.

Among high school students who were current cigarette smokers and had attempted to quit during the past year, the use of a program, counseling, and/or medication was higher among males (22.8%; 95% CI, 15.6–30.1) than females (8.9%; 95% CI, 4.2–13.6) (NYTS, public use data, 2015; not shown in Table 2.25). Estimates for other demographic characteristics were of low precision and therefore were not examined (relative standard error $\geq 30\%$).

Trends Among Adults

The prevalence among current cigarette smokers of using effective cessation treatments increased nonlinearly during 2000–2015. A significant increase was observed from 2000 (21.9%) to 2010 (31.7%), but there was no change during 2010–2015 (31.2%) (Babb et al. 2017). A similar trend was observed among women (2000, 22.4%; 2005, 32.7%; 2010, 35.1%; and 2015, 33.6%). Among men, a linear increase in the use of effective treatments was seen from 2000 (21.4%) to 2015 (29.1%) (NHIS, public use data, 2000–2015). Trends in the use of cessation aids also differed by race/ethnicity: Trends among Whites and Hispanics were similar to those for adults overall, but a linear increase was observed for Blacks (Figure 2.13). Data from Nielsen Retail Management Services showed sales of NRT gum, lozenge, and patch totaled \$1.0 billion in 2018 (adjusted for inflation to 2018 dollars) (Figure 2.14). From Quarter 2 of 2014 to Quarter 4 of 2018, NRT gum had the highest sales followed by NRT lozenge and NRT patch. During this time period, sales of NRT gum increased steadily from Quarter 2 of 2014 to Quarter 4 of 2015, peaked in Quarter 2 of 2016 at \$145.6 million, and then decreased through Quarter 4 of 2018 (\$132.0 million). In contrast, sales of NRT lozenge increased fairly steadily from Quarter 2 of 2014 to Quarter 4 of 2018, when sales peaked at \$78.2 million. Sales of NRT patch appeared to have a seasonal pattern from 2014 to 2018, as sales peaked in the first quarter of each year and then generally declined throughout the year. Sales of NRT patch peaked in Quarter 1 of 2016 (\$48.3 million) but then decreased generally through 2018 despite its annual first-quarter peaks.

Trends Among Young Adults

Among young adults 18–24 years of age, trends in the use of effective cessation treatments among female smokers and White smokers were similar to trends among adults overall; but among men, use of effective cessation

Table 2.24 Prevalence of using strategies to quit cigarette smoking^a among current cigarette smokers^b 18 years of age and older who tried to quit during the past year, by selected characteristics; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2014–2015; United States

Characteristic	Used telephone quitline: % (95% CI)	Used Internet or web-based program or tool: % (95% CI)	Used switching to smokeless tobacco: % (95% CI)	Used switching to cigar or pipe: % (95% CI)	Used switching to e-cigarettes: % (95% CI)
Overall	3.5 (3.1–3.9)	2.1 (1.8–2.4)	5.4 (4.8–6.0)	2.7 (2.4–3.1)	34.7 (33.6–35.7)
Sex					
Men	2.8 (2.3–3.4)	1.7 (1.3–2.1)	7.7 (6.7–8.7)	4.0 (3.3–4.6)	32.7 (31.2–34.3)
Women	4.2 (3.6–4.7)	2.5 (2.0–3.0)	3.0 (2.4–3.5)	1.5 (1.0–1.9)	36.8 (35.3–38.3)
Age group (in years)					
18–24	2.7 (1.4–4.0)	2.4 (1.1–3.6)	7.8 (5.6–10.0)	3.7 (2.2–5.1)	39.2 (35.2–43.2)
25–44	3.2 (2.6–3.8)	2.3 (1.7–2.8)	5.8 (4.8–6.7)	2.3 (1.7–2.8)	38.0 (36.3–39.8)
45–64	4.4 (3.7–5.1)	1.9 (1.4–2.4)	4.5 (3.8–5.3)	3.0 (2.4–3.6)	32.2 (30.6–33.7)
≥65	2.1 (1.2–3.0)	1.8 (1.0–2.6)	3.8 (2.5–5.1)	2.5 (1.6–3.5)	23.7 (20.7–26.7)
Race/ethnicity					
White, non-Hispanic	3.2 (2.8–3.7)	2.1 (1.7–2.5)	5.5 (4.8–6.1)	2.5 (2.0–2.9)	38.8 (37.6–40.0)
Black, non-Hispanic	4.0 (2.8–5.2)	2.3 (1.3–3.2)	4.6 (3.3–6.0)	4.0 (2.7–5.3)	23.1 (20.3–25.9)
Hispanic	4.3 (2.6–6.1)	2.2 (1.0–3.3)	4.7 (3.0–6.5)	3.0 (1.5–4.4)	22.8 (19.6–26.0)
American Indian/Alaska Native, non-Hispanic	— ^c	— ^c	— ^c	— ^c	24.5 (16.7–32.2)
Asian, non-Hispanic	— ^c	— ^c	— ^c	— ^c	25.4 (18.1–32.7)
Multiple races, non-Hispanic	— ^c	— ^c	— ^c	— ^c	50.6 (42.4–58.9)
Level of education^d					
≤12 years (no diploma)	4.3 (3.2–5.3)	1.0 (0.6–1.5)	4.5 (3.4–5.7)	3.5 (2.4–4.5)	28.4 (25.9–31.0)
High school diploma	3.0 (2.4–3.7)	1.7 (1.2–2.2)	5.5 (4.6–6.5)	2.6 (2.0–3.2)	34.6 (32.7–36.4)
Some college (no degree)	3.2 (2.5–4.0)	2.5 (1.8–3.2)	5.9 (4.8–7.1)	2.9 (2.1–3.8)	37.8 (35.4–40.2)
Associate degree	4.6 (3.1–6.1)	2.2 (0.9–3.6)	5.2 (3.8–6.7)	2.0 (0.9–3.0)	37.7 (34.8–40.6)
Undergraduate degree	3.5 (2.2–4.8)	4.1 (2.7–5.5)	5.0 (3.4–6.6)	2.0 (0.9–3.1)	35.7 (32.3–39.1)
Graduate degree	3.1 (0.5–5.8)	3.4 (1.2–5.7)	6.2 (2.8–9.6)	3.5 (1.3–5.7)	32.4 (26.3–38.6)
Poverty status					
At or above poverty level	3.0 (2.6–3.4)	2.1 (1.7–2.5)	5.5 (4.9–6.1)	2.4 (2.0–2.8)	35.1 (34.0–36.3)
Below poverty level	5.2 (4.2–6.2)	2.1 (1.5–2.6)	5.1 (4.1–6.1)	3.9 (2.9–4.8)	33.2 (30.7–35.7)
U.S. Census region					
Northeast	3.9 (2.7–5.0)	2.3 (1.4–3.1)	4.7 (3.4–6.1)	3.0 (1.9–4.1)	32.2 (29.2–35.1)
Midwest	3.1 (2.3–3.9)	1.7 (1.2–2.3)	5.6 (4.4–6.8)	2.2 (1.5–2.8)	35.6 (33.5–37.7)
South	3.2 (2.7–3.8)	2.2 (1.6–2.7)	5.3 (4.5–6.2)	3.1 (2.4–3.7)	35.3 (33.5–37.1)
West	4.2 (3.2–5.1)	2.4 (1.6–3.2)	5.9 (4.7–7.2)	2.6 (1.7–3.5)	34.5 (31.7–37.2)

Source: TUS-CPS, National Cancer Institute, public use data, 2014–2015.

Notes: CI = confidence interval.

^aUsed during their last quit attempt among those who tried to quit for at least 1 day during the past 12 months.

^bPersons who reported smoking more than 100 cigarettes during their lifetime and who, at the time of the interview, reported smoking every day or some days.

^cPrevalence estimates with a relative standard error ≥30% are not presented due to low precision.

^dAmong only adults 25 years of age and older.

Table 2.25 Strategies used to quit smoking among high school and middle school current cigarette smokers^a who tried to quit during the past year; National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, and 2015; United States

Quitting behaviors	2000: % (95% CI)	2004: % (95% CI)	2009: % (95% CI)	2015: % (95% CI)
High school (grades 9–12)				
Used a program, counseling, and/or medication ^b	16.5 (15.0–18.0)	11.8 (9.3–14.3)	10.2 (6.7–13.7)	17.8 (12.9–22.7)
Attended a program in my school	4.7 (3.8–5.6)	2.6 (1.2–4.0)	— ^c	— ^c
Used nicotine gum, nicotine patch, or any medicine to quit	12.2 (10.9–13.5)	8.9 (6.9–10.9)	7.8 (5.0–10.7)	10.8 (7.1–14.5)
Tried to quit on my own or quit “cold turkey”	NA	NA	NA	69.9 (58.3–81.5)
Middle school (grades 6–8)				
Used a program, counseling, and/or medication ^b	31.8 (27.8–35.9)	17.4 (13.8–20.9)	26.1 (19.4–32.7)	30.4 (18.4–42.3)
Attended a program in my school	9.9 (7.4–12.5)	3.0 (1.6–4.3)	— ^c	— ^c
Used nicotine gum, nicotine patch, or any medicine to quit	19.7 (16.4–23.0)	13.4 (10.5–16.2)	19.7 (13.1–26.2)	23.7 (13.4–33.9)
Tried to quit on my own or quit “cold turkey”	NA	NA	NA	81.9 (77.4–86.4)

Source: NYTS, Centers for Disease Control and Prevention, public use data, 2000, 2004, 2009, and 2015.

Notes: **CI** = confidence interval; **NA** = not available.

^aSmoked cigarettes during the past 30 days.

^bAttended a program in school or a program in the community; called a telephone helpline or telephone quitline; and/or used nicotine gum, nicotine patch, and/or any medication to quit.

^cPrevalence estimates with a relative standard error $\geq 30\%$ are not presented due to low precision.

treatments increased from 2000 (5.7%) to 2005 (15.9%) and then remained unchanged through 2015 (17.2%) (NHIS, public use data, 2000–2015). Estimates for other racial/ethnic groups are not presented because of low precision (relative standard error $\geq 30\%$).

Trends Among Youth

Use of cessation treatments (e.g., school or community programs, telephone quitlines, nicotine patches, nicotine gum, or any other medications) among high school and middle school students decreased during 2000–2004, and the use of cessation treatments in 2015 was similar to that seen in 2000 (Table 2.25).

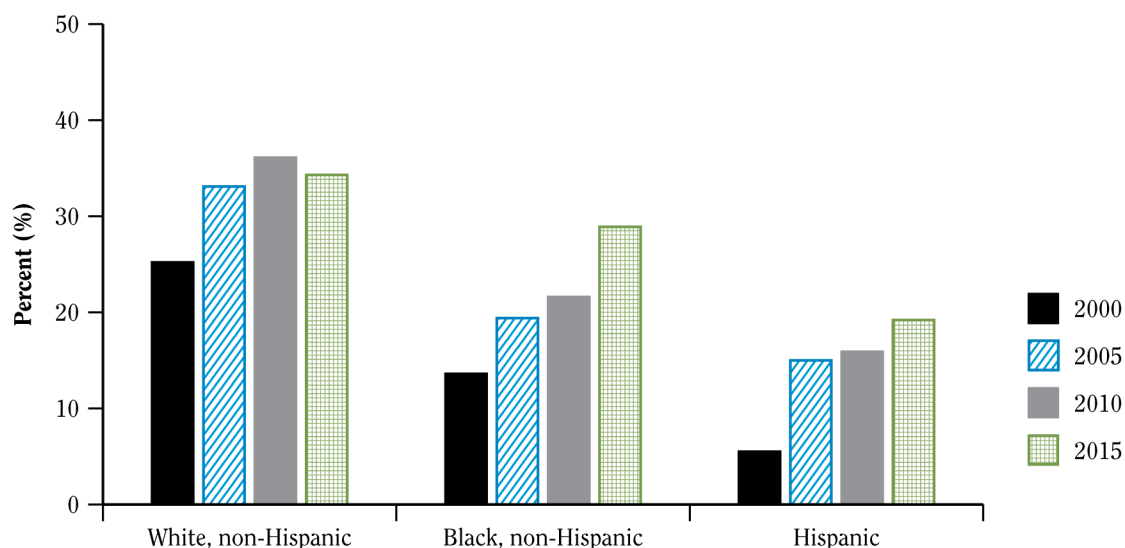
Use of Other Cessation Strategies

Adults

According to the 2014–2015 TUS-CPS, among adult cigarette smokers who tried to quit smoking during the past year, switching to e-cigarettes was the most prevalent

strategy (34.7%) used the last time they tried to quit (Table 2.24), despite inconclusive data on the efficacy of these products for promoting long-term cessation (see Chapter 7) (Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016; Coleman et al. 2017; Verplaetse et al. 2018; Young-Wolff et al. 2018; Berry et al. 2019). The percentage of adult smokers switching to e-cigarettes was similar to the percentage of adult cigarette smokers (as estimated in the 2015 NHIS) who used any evidence-based cessation treatment (31.2%) (Table 2.21). According to the TUS-CPS data, switching to e-cigarettes in an attempt to quit smoking conventional cigarettes was more common among women (36.8%) than men (32.7%). Cigarette smokers younger than 45 years of age were more likely to try to quit by switching to e-cigarettes than were older smokers, and their use of e-cigarettes to try to quit was greater than their use of proven cessation treatments (Table 2.21). Whites (38.8%) and persons of multiple races (50.6%) were more likely than smokers of all other racial/ethnic groups to switch to e-cigarettes in an attempt to quit (Table 2.24), and the percentage of those who switched to e-cigarettes in an attempt to quit was

Figure 2.13 Prevalence of use of counseling or medications for cessation^a among adult smokers 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 2000–2015; United States



Source: NHIS, National Center for Health Statistics, public use data, 2000, 2005, 2010, and 2015.

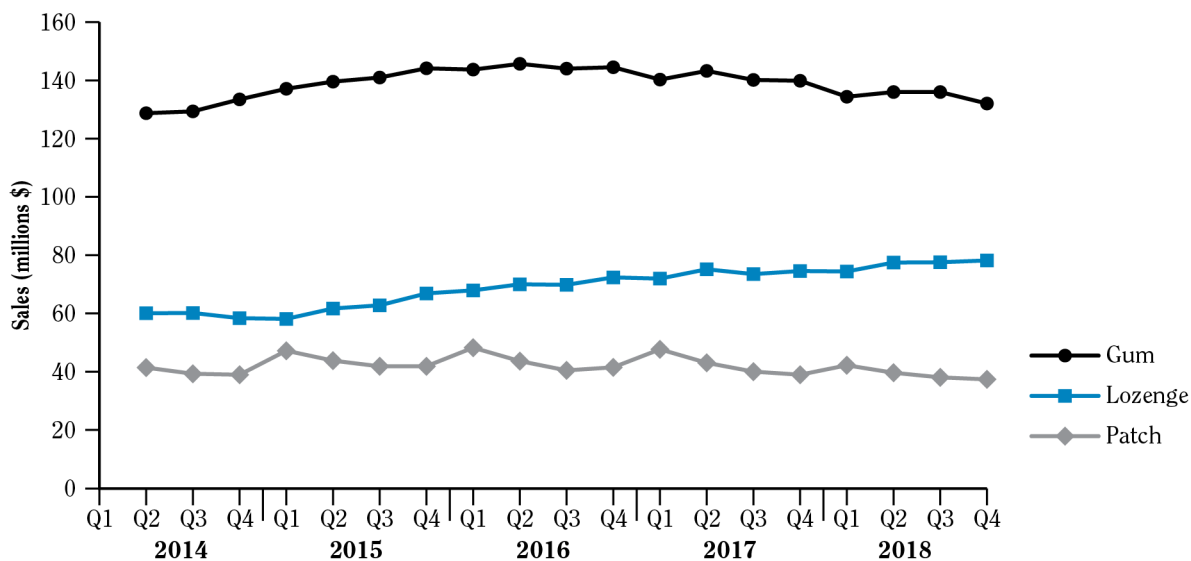
^aFor 2010 and 2015, used one-on-one counseling; a stop-smoking clinic, class, or support group; telephone helpline or quitline; nicotine patch, nicotine gum, or lozenge; nicotine-containing nasal spray or inhaler; or varenicline (U.S. trade name Chantix) and/or bupropion (including trade names Zyban and Wellbutrin) during the past year among current smokers who tried to quit during the past year or among former smokers who quit during the past 2 years. For 2005, the list included a nicotine tablet and excluded varenicline, as that drug was not approved by the Food and Drug Administration until 2006. For 2000, the list included a stop-smoking program and excluded a stop-smoking class or support group, nicotine lozenge (not approved by the Food and Drug Administration until 2002), and varenicline.

higher than the percentage of smokers who used effective cessation treatments (Table 2.21) for both groups. Persons with 12 or fewer years of education (with no high school diploma) were less likely to switch to e-cigarettes in an attempt to quit smoking than those with higher levels of education, with the exception of those with a graduate degree (Table 2.24). The use of e-cigarettes for cessation was also a commonly reported strategy among cigarette smokers in Wave 1 of the PATH Study: 25.2% reported using e-cigarettes to quit, and 23.5% reported using an FDA-approved cessation medication—NRT (18.7%), varenicline (5.7%), or bupropion (3.1%) (Benmarhnia et al. 2018). Similar to the TUS-CPS, younger (18–34 years of age) cigarette smokers in the PATH Study who were trying to quit had a higher prevalence of using e-cigarettes as a cessation aid than those 35 years of age and older (Benmarhnia et al. 2018). In their analysis of data from the PATH Study, Harlow and colleagues (2018) observed that, among cigarette-only smokers at Wave 1, Whites, persons with greater than a high school education, and persons living at or above 200% of the poverty level were more likely to become exclusive e-cigarette users at Wave 2 than Blacks and Hispanics, persons with a high school

education or GED, and persons living below the poverty level, respectively. Whites were also more likely than Blacks and Hispanics to become dual users of e-cigarettes and cigarettes at Wave 2, and Whites were more likely to have quit conventional cigarettes (with no uptake of e-cigarettes) than Blacks at Wave 2. Persons with greater than high school education and those living at or above 200% of the poverty level were also more likely to quit conventional cigarettes (with no uptake of e-cigarettes) than those with lower levels of education and persons with less income, respectively.

According to 2013–2014 data from the NATS, among former smokers who quit during the past year and had ever used e-cigarettes, 45.9% had completely switched to e-cigarettes from conventional cigarettes at some time during the past 12 months (NATS, public use data, 2013–2014). Among the recent former smokers who reported having switched to e-cigarettes during the past year, 66.0% were current e-cigarette users (NATS, public use data, 2013–2014). In contrast, among recent former smokers who had ever used e-cigarettes but did not report switching to e-cigarettes during the past year, just 13.4% were current e-cigarette users (NATS, public use

Figure 2.14 Quarterly, inflation-adjusted^a dollar sales of over-the-counter nicotine replacement therapy, by type; Quarter 2, 2014–Quarter 4, 2018; United States



Source: FDA CTP's licensed Nielsen Retail Measurement Services data.

Note: Nielsen Retail Measurement Services data, including projected sales from expanded all outlet combined and convenience stores. Types of outlets include food and grocery stores, drug stores, mass merchandizers, club stores, dollar stores, military commissaries, and convenience stores. Data do not include food stores with annual sales volume <\$2 million, certain specialty food stores, drug stores with annual volume <\$1 million, certain club stores, certain dollar stores, and Internet sales (including those from point-of-sale retailers). Data do not include the category of "other" NRT, which represented 0.07% of sales during this period. Nielsen did not participate in the data analysis, summary, or interpretation. CTP = Center for Tobacco Products; FDA = U.S. Food and Drug Administration; NRT = nicotine replacement therapy.

^aAdjusted to 2018 dollars using data from the Bureau of Labor Statistics on the Consumer Price Index for all items.

data, 2013–2014). In their analysis of data from the PATH Study, Harlow and colleagues (2018) found that cigarette smokers at Wave 1 who reported new use of e-cigarettes at Wave 2 had almost the same prevalence of quitting cigarettes from Wave 1 to Wave 2 (8.06%) as those who did not begin using e-cigarettes at Wave 2 (8.42%). However, using multivariate logistic regression models, Berry and colleagues (2019) found that adult cigarette smokers who initiated daily e-cigarette use at Wave 1 had 7.88 times the odds of having quit cigarette smoking at Wave 2 than those who did not use e-cigarettes. In contrast, adult cigarette smokers who initiated experimental e-cigarette use (current e-cigarette use but no regular use) were less likely to quit cigarette smoking than those who were not using e-cigarettes (OR = 0.51; 95% CI, 0.26–1.00). Similarly, findings from Wave 1 to Wave 2 of the PATH Study indicated that cigarette smokers who were daily e-cigarette users at Wave 1 had higher odds of quitting cigarette smoking at Wave 2 (OR = 1.56; 95% CI, 1.12–2.18) than never e-cigarette users. But among men, former cigarette smokers who were daily or nondaily e-cigarette users at Wave 1 were more likely than men who were never

e-cigarette users to relapse to cigarette smoking at Wave 2 (OR = 2.96; 95% CI, 1.49–5.86 and OR = 3.05; 95% CI, 1.29–7.17, respectively) (Verplaetse et al. 2018).

According to the 2014–2015 TUS-CPS data, more cigarette smokers reported switching to e-cigarettes (31.2%) in an attempt to quit than switching to smokeless tobacco (5.4%), switching to cigars or pipes (2.7%), or using the Internet or a web-based program or tool (2.1%) (Table 2.24). The estimate for switching to smokeless tobacco in an attempt to quit cigarette smoking is similar to that from the 2013–2014 NATS, where 4.9% of former cigarette smokers who had quit during the past year had switched to smokeless tobacco to quit smoking (NATS, public use data, 2013–2014). According to data from the 2014–2015 TUS-CPS, higher percentages of men than women switched to cigars or pipes in an attempt to quit (4.0% vs. 1.5%) or switched to smokeless tobacco in an attempt to quit (7.7% vs. 3.0%) (Table 2.24). Also, 18- to 24-year-old smokers were more likely to switch to smokeless tobacco in an attempt to quit than smokers who were 45 years of age and older. In addition, persons living below the poverty level were more likely to switch to cigars or

pipes (3.9%) in an attempt to quit than those living at or above the poverty level (2.4%). Finally, smokers with an undergraduate degree (4.1%) were more likely to use the Internet for help with cessation than those with a high school education or less.

Although the estimate for use of specific Internet or web-based programs or tools for quitting smoking was low (2.1%) in the 2014–2015 TUS-CPS (Table 2.24), according to the 2017 HINTS, 43.7% of current cigarette smokers who were 18 years of age and older and were Internet users had used the Internet during the past 12 months to look for information about quitting smoking. Of note, the HINTS did not ask whether they used specific Internet programs or tools in their quit attempt (Graham and Amato 2018).

Data from the 2010–2011 TUS-CPS assessed different cessation strategies from those described above for the 2014–2015 version. According to the 2010–2011 TUS-CPS, the most common cessation strategy among smokers who had tried to quit during the past year was trying to quit abruptly (78.0%), followed by gradually reducing consumption (43.0%) and receiving help from friends and family (32.4%) (Schauer et al. 2015). In the 2013–2014 PATH Study, the three most prevalent cessation methods among current smokers who tried to quit in the past 12 months and former smokers who quit during the past 12 months were unaided quit attempts (i.e., no reported use of support or cessation strategy) (47.1% and 47.7%, respectively), support from friends and family (18.7% and 16.5%, respectively), and use of other tobacco products (18.3% and 24.8%, respectively) (Rodu and Plurphanswat 2017).

Key Disparities in Cessation Among Adults

In addition to the disparities in key measures of cessation by age, race/ethnicity, geographic region, status of health insurance, and sexual orientation that were described previously, important disparities exist by the amount and frequency of cigarette smoking and other health-related and demographic factors (Babb et al. 2017).

With regard to the frequency of cigarette smoking, in 2015, current daily smokers who smoked >25 cigarettes per day had a lower prevalence of being interested in quitting (55.6%) than current some-day smokers (71.0%) and daily smokers of 1–14 cigarettes per day (daily, 1–4 cigarettes per day: 71.8%; daily, 5–14 cigarettes per day: 68.8%) (Table 2.22). In addition, in 2017, current daily smokers who smoked >25 cigarettes per day had a lower prevalence of a past-year quit attempt (29.5%) than some-day smokers (58.5%) and daily smokers of lesser amounts (daily, 1–4 cigarettes per day: 59.8%; daily, 5–14 cigarettes

Young Adults

According to the 2014–2015 TUS-CPS, the prevalence of young adults' (18–24 years of age) use of other cessation strategies, including switching to another tobacco product and using the Internet, was similar to the estimates for adults overall (Table 2.24). Similar to the case with adults overall, no differences in use were observed by race/ethnicity and geographic region among young adults; however, estimates were of low statistical precision for other cessation strategies among young adults, and e-cigarette use could not be examined by poverty status because estimates were of low precision (relative standard error $\geq 30\%$) and statistically unstable (TUS-CPS, public use data, 2014–2015). In contrast to findings for all adults (Table 2.24), the prevalence of switching to e-cigarettes in an attempt to quit cigarette smoking among young adults did not differ by sex (men: 38.7%; 95% CI, 33.1–44.3; women: 39.8%; 95% CI, 33.8–45.8) (TUS-CPS, public use data, 2014–2015).

Youth

Unlike surveillance systems for adults, surveillance systems that focus on youth do not assess whether cigarette smokers in that age group who were trying to quit during the past year had switched to another tobacco product. However, in the 2017 NYTS, among youth who had ever used e-cigarettes, an estimated 5.3% of middle school students (grades 6–8) and 5.6% of high school students (grades 9–12) reported one of the reasons they had used e-cigarettes was to try to quit using other tobacco products (NYTS, public use data, 2017).

per day: 49.8%; daily, 15–24 cigarettes per day: 30.2%). In contrast, in 2017, both the prevalence of having received advice to quit and use of counseling and/or medication for cessation increased with the frequency and amount of smoking. Current some-day smokers had the lowest prevalence of using counseling and/or medications (24.2% vs. 46.7% for daily smokers who smoked 25 or more cigarettes per day), a finding likely related to (a) their lower prevalence of receiving advice from a health professional and (b) the lack of evidence for medication utilization by some-day smokers (Fiore et al. 2008).

Persons who had serious psychological distress, a smoking-related chronic disease, or a disability/limitation were more likely to receive a health professional's advice to quit than those without these conditions (70.1% vs. 55.7%, 67.3% vs. 64.8%, and 71.8% vs. 53.6%, respectively) (Table 2.22). This may be because such persons have more

contact with the healthcare system and because quitting could improve, or avoid exacerbating, conditions that are related to smoking. Those who had serious psychological distress or a disability/limitation were more likely to use cessation treatments than those without such conditions (41.6% vs. 30.1% and 39.0% vs. 28.5%, respectively).

Disparities also exist in rates of quitting smoking while pregnant. In a study based on birth certificates, which included 46 states and the District of Columbia, 10.9% of women who gave birth in 2014 smoked during the 3 months before pregnancy (Curtin and Mathews 2016). Of these women, 24.2% reported smoking no cigarettes during each trimester of pregnancy and thus presumably quit before becoming pregnant, and 20.6% of women who smoked in the first or second trimesters quit by the third trimester. By level of education, cessation during the 3 months before pregnancy was lowest among those with less than a high school education (14.1%) and highest among those with a bachelor's degree or more education (53.7%). By insurance status, cessation was lowest among those with Medicaid insurance or who self-paid (18.9% and 17.3%, respectively) and highest among those with private insurance (38.3%). In addition, Asian women cigarette smokers were more than twice as likely to quit during the 3 months before their pregnancy (45.0%) as American Indian or Alaska Native women (21.8%). In an analysis of data from the PATH Study, Kurti and colleagues (2018)

observed that, among nonpregnant women, 18–44 years of age who used tobacco at Wave 1 and became pregnant at Wave 2, 98.3% had quit hookah use, 88.0% had quit cigar use, 81.3% had quit e-cigarette use, and 58.7% had quit any tobacco use. The prevalence of quitting hookah, cigars, and e-cigarettes was higher than the prevalence of quitting cigarettes (53.4%).

Residing in a rural or nonmetropolitan area as opposed to an urban area or a metropolitan area is also associated with cessation-related disparities. According to the 2017 BRFSS, the quit ratio (see the “Quit Ratio” section earlier in this chapter) and the prevalence of a past-year quit attempt were significantly lower among cigarette smokers who lived in micropolitan (54.8% and 61.1%, respectively) and rural (54.8% and 62.2%, respectively) counties than among those who lived in large fringe (62.8% and 66.2%, respectively) or large central metropolitan areas (59.9% and 68.2%, respectively) (Table 2.26). Quit ratios were also lower among persons in micropolitan and rural counties than among those in small and medium metropolitan counties, and prevalence of a past-year quit attempt was also lower among persons in micropolitan counties than among those in medium metropolitan counties. In addition, recent successful cessation was significantly higher among persons living in large metropolitan fringe areas (5.9%) compared with those living in micropolitan (4.3%) counties.

Table 2.26 Percentage of ever cigarette smokers 18 years of age and older who quit smoking (quit ratio)^a and prevalence of recent successful cessation^b and a past-year quit attempt,^c by urban or rural status; Behavioral Risk Factor Surveillance System (BRFSS) 2017; United States

	Quit ratio: % (95% CI)	Recent successful cessation: % (95% CI)	Past-year quit attempt: % (95% CI)
Overall	59.3 (58.8–59.8)	5.3 (5.0–5.7)	65.5 (64.7–66.2)
Large metropolitan center	59.9 (58.6–61.1)	5.8 (5.0–6.7)	68.2 (66.5–69.9)
Large fringe metropolitan	62.8 (61.8–63.8)	5.9 (5.2–6.7)	66.2 (64.7–67.6)
Medium metropolitan	59.4 (58.5–60.3)	5.1 (4.6–5.8)	65.3 (63.9–66.6)
Small metropolitan	57.5 (56.3–58.7)	5.1 (4.5–5.9)	63.8 (62.0–65.6)
Micropolitan	54.8 (53.6–56.1)	4.3 (3.6–5.1)	61.1 (59.4–62.9)
Noncore	54.8 (53.4–56.2)	4.5 (3.8–5.3)	62.6 (60.7–64.5)

Source: BRFSS, Centers for Disease Control and Prevention, public use data, 2017.

Notes: **CI** = confidence interval. A metropolitan statistical area is defined as a group of counties that contain at least one urbanized area of 50,000 or more inhabitants. A micropolitan statistical area is defined as a group of counties that contain at least one urban cluster of at least 10,000 but less than 50,000 inhabitants.

^aQuit ratio is calculated as the proportion of current smokers who reported having stopped smoking for >1 day during the past year because they were trying to quit smoking, and former smokers who quit smoking during the past year (numerator), among all current and former smokers who only quit in the past year (denominator).

^bThe percentage of former smokers who quit smoking for >6 months during the past year among current smokers and former smokers who quit during the past year.

^cCurrent smokers who reported that they stopped smoking for >1 day during the past 12 months because they were trying to quit smoking and former smokers who quit during the past year.

Summary of the Evidence and Implications

In the United States, 61.7% of adults who have ever been a cigarette smoker have now quit, highlighting the marked progress in smoking cessation observed in this chapter. Among adults, past-year quit attempts and recent (i.e., recent successful cessation) and longer term (i.e., quit ratio) cessation measures have increased over the past 2 decades. Nevertheless, survey data indicate that several subpopulations—including those with less education, racial/ethnic minorities, and those who are older in age—are less likely to try to quit each year than those in the general population. These disparities, in turn, may be affected by other variables, such as receiving advice from a health professional to quit smoking, using evidence-based resources, and patterns and frequency of cigarette smoking.

Disparities across cessation-related variables existed by level of educational attainment, which is closely correlated with income, poverty, overall socioeconomic status, status of health insurance, and geographic location. Notably, smokers with the lowest levels of education (<12 years or GED certificate) had significantly lower quit ratios compared with smokers with the highest levels of education (undergraduate or graduate degree).

These socioeconomic disparities also may be partly explained by emerging geographic disparities, given that rural populations, who tend to have lower socioeconomic status (U.S. Department of the Census 2016), have lower quit ratios and a lower prevalence of recent successful cessation than metropolitan populations, despite having a similar prevalence of past-year quit attempts. In addition, quit ratios and the prevalence of recent successful cessation and past-year quit attempts vary widely across U.S. states and territories. These variations might be linked to differences in state and local tobacco control policies, healthcare coverage and policies, and historical relationships of resident populations with tobacco (e.g., growers of tobacco). Tobacco growing, pervasive tobacco advertising and marketing (e.g., sponsorships of rodeos and auto races), and more prevalent exposure to secondhand smoke in public and private settings may also be influential environmental factors that make quitting more difficult among rural residents compared with urban residents (Chaloupka et al. 2002; Roeseler et al. 2010; USDHHS 2011; Vander Weg et al. 2011). Rural areas may also have fewer resources, including a more limited capacity to implement comprehensive tobacco control programs (American Lung Association 2012).

Persons of lower socioeconomic status, including lower levels of education, have a higher incidence of lung cancer and other tobacco-related diseases than

persons in higher socioeconomic groups (Clegg et al. 2009; Singh et al. 2011), making persons of lower socioeconomic status a critical population for treating nicotine dependence. Challenges to quitting smoking among this subpopulation may include heavier patterns of cigarette smoking and earlier initiation (Siahpush et al. 2010; Ham et al. 2011). In addition, predatory marketing by the tobacco industry, reflected in part by an increased density of retail outlets and more retail and point-of-sale promotions in low-income areas, may contribute to an environment that is challenging for successful cessation (Brown-Johnson et al. 2014; Center for Public Health Systems Science 2014, 2016).

Disparities also exist by race/ethnicity. For example, Black adult smokers have a higher prevalence of past-year quit attempts than White adult smokers. However, prevalence of recent successful cessation does not vary by race/ethnicity, suggesting that a higher percentage of Black adults are trying to quit cigarette smoking than White adults but are less successful. This may also be reflected in the lower quit ratio among Blacks compared with Whites. The use of menthol cigarettes may play a role in this disparity, as Black smokers are more likely to use menthol cigarettes than other racial/ethnic groups (Giovino et al. 2015); however, research findings on the relation between menthol use and successful cessation are mixed (Delnevo et al. 2011; Levy et al. 2011; Keeler et al. 2017). Although data presented in this chapter show that Blacks who smoke menthol cigarettes are just as likely to try to quit smoking as those who do not smoke menthol cigarettes (Table 2.12), menthol use might increase dependence on nicotine and make quitting more difficult (Hoffman and Simmons 2011). In addition, similar to targeting populations with low socioeconomic status, predatory marketing by the tobacco industry is common in geographic areas with large numbers of Black residents, which may negatively influence cessation (Yu et al. 2010; Richardson et al. 2015; Alexander et al. 2016).

Age is another demographic factor with pronounced cessation disparities. To date, both past-year quit attempts and recent successful cessation decrease as adult cigarette smokers' ages increase. Although quitting smoking at any age is beneficial, smokers who quit by the time they are 35–44 years of age avoid most of the risk of dying from a smoking-related disease (Doll et al. 2004; Jha et al. 2013). Continued public health strategies that specifically target adults 45 years of age and older are needed to increase quit attempts, given the inverse relationships between age and both quit attempts and the prevalence of recent successful cessation. In addition, among youth, trends in past-year

quit attempts have remained stable or slightly declined, depending on the data source. More research is needed to better understand how the growing use of other tobacco products will affect cigarette smoking cessation and to assess cessation from other tobacco products that youth and young adults are using regularly.

Factors contributing to the previously noted disparities could also be affected by a health professional's advice to quit tobacco and by the use of evidence-based cessation approaches, such as counseling and medication. For example, receiving advice from a health professional to quit smoking and using evidence-based cessation resources increased from 2000 to 2015; however, 42.8% of cigarette smokers who saw a healthcare professional during the past year did not receive advice to quit, and less than one-third (31.2%) of cigarette smokers who tried to quit during the past year used evidence-based cessation resources. Cigarette smokers younger than 45 years of age were less likely than older cigarette smokers to be advised to quit or to use an evidence-based cessation treatment. One potential explanation for these findings is that young adult cigarette smokers are more likely than older smokers to be some-day smokers (also called intermittent or nondaily smokers) and light daily smokers (smoking <5 cigarettes per day) (Babb et al. 2017).

Data presented previously in this chapter suggest that light daily and some-day smokers are among the most interested in quitting, and they have the highest prevalence of past-year quit attempts. Nevertheless, many do not consider themselves to be smokers (Levinson et al. 2007; Smith et al. 2012) and, thus, may not be identified as a smoker by clinical screening. Furthermore, light daily and nondaily smokers may be able to abstain from cigarettes on some days but continue smoking on other days. As discussed in Chapter 6, existing clinical guidance concludes that there is insufficient evidence for the use of pharmacotherapy to assist with cessation in light smokers (Fiore et al. 2008). Given these challenges and the increasing prevalence of some-day and light daily smokers, new approaches may be needed to help persons in these subgroups quit successfully.

Clinical interventions may also play an important role in helping youth quit smoking cigarettes. Although screening for tobacco use among 11- to 17-year-olds is fairly high in ambulatory care settings (71.5%), only approximately 20% of tobacco users were provided assistance for tobacco cessation (Jamal et al. 2014). The 2008 update of the *Clinical Practice Guideline on Treating Tobacco Dependence* recommends that clinicians provide counseling interventions to aid youth smokers in quitting (Fiore et al. 2008). Far less is known about how to help youth quit compared with how to help adults, and use of effective cessation strategies is lower among youth than

adults (Fiore et al. 2008). Because many youth, like the young adults discussed previously, are some-day smokers, more research is needed on how to address these occasional users and on effective and appropriate clinical interventions for youth overall.

Data presented in this chapter suggest that fewer than 2 of every 3 of adult smokers who saw a healthcare provider in the past year were advised to quit smoking, fewer than 1 of every 3 reported using cessation medications to help them quit, and fewer than 1 of every 10 reported using counseling. Taken together, these findings reinforce the need for the implementation of additional public health interventions that aim to increase cessation counseling in clinical settings and the number of quit attempts among adults and youth (Fiore et al. 2008; The Community Guide 2014).

Encouraging and helping tobacco users to quit remains the quickest approach to reducing tobacco-related disease, death, and healthcare costs (Institute of Medicine 2007), including through both individual (see Chapter 6) and population-based (see Chapter 7) interventions. However, as is noted in this chapter, use of tobacco cessation resources among persons who use tobacco remains low: among adults, 18 years of age and older, only 29.0% used cessation medication, just 6.8% used any counseling, and only 4.1% used a telephone-based quitline, which is a freely available resource in all states (see Chapter 6). Use of counseling and/or medication was lower among young adults (16.6%) than among all adults (31.2%) (Babb et al. 2017). To further increase cessation among adults and youth, public health efforts can continue the aforementioned strategies and encourage healthcare providers to consistently identify smokers, advise them to quit, and offer them cessation treatments (Fiore et al. 2008; U.S. Preventive Services Task Force 2015). Nevertheless, it is also important to recognize that a majority of cigarette smokers who quit do so without using evidence-based treatments. As is described in Chapter 6, identifying ways to continue to promote quit attempts to help cigarette smokers in quitting, even among those who do not intend to use treatment or are not interested in using treatment, is still needed. Furthermore, continuing to include questions in population-based surveys to assess (a) the prevalence of tobacco screening and interventions and (b) the proportion of smokers who use cessation counseling and medication is needed for ongoing tracking of smokers' engagement with evidence-based treatments that can improve the odds of quitting and staying quit.

Importantly, this chapter's review of epidemiologic data focused on cigarette smoking because measures of other tobacco product use and cessation are limited. Therefore, many of the analyses centered on cigarettes may underestimate the impact that the use of other tobacco

products, such as little cigars and e-cigarettes, has on tobacco cessation. Although limited national surveillance data are available on cessation of noncigarette tobacco products, survey data indicate that adult cigarette smokers who use cigars, smokeless tobacco, and/or pipes are less likely to try to quit all tobacco products than to try to quit cigarette smoking; however, this is not the case among young adult cigarette smokers, who are as likely to try to quit all tobacco products as they are to try to quit cigarette smoking (NYTS, public use data, 2017). Poly tobacco use, which is the use of two or more tobacco products, is now common (3.7% in 2017) (Wang et al. 2018a), especially among youth and young adults (USDHHS 2014), and e-cigarettes have been the most prevalent tobacco product used among middle and high school students since 2014 (Wang et al. 2018b). Therefore, enhanced national surveillance of both use and cessation of these tobacco products is warranted (USDHHS 2014). Since the PATH Study is a nationally representative, longitudinal cohort study of adults and youth 12 years of age and older, it will continue to contribute key information on patterns of use of these tobacco products, including initiation, cessation, relapse, and transitions between tobacco products (Hyland et al. 2017; Coleman et al. 2018; Kurti et al. 2018; Kyriotakis et al. 2018; Lopez et al. 2018). However, comprehensive surveillance of all of the diverse tobacco products being used by the American public is essential to effectively inform tobacco control policies, planning, and practices.

In addition, continued surveillance of the use of switching to other tobacco products by smokers who are trying to quit cigarettes is needed. Switching to smokeless

tobacco and cigars as a quit strategy is relatively uncommon (see “Other Tobacco Products: Use and Cessation” in this chapter). However, switching to e-cigarettes in an attempt to quit cigarette smoking (34.7% in 2014–2015) was as popular a cessation strategy among those who tried to quit during the past year as was the use of counseling and/or the seven FDA-approved smoking cessation medications (31.2% in 2015) (Fiore et al. 2008; Babb et al. 2017), even though the efficacy of using e-cigarettes for smoking cessation is inconclusive. For example, switching to e-cigarettes in an attempt to quit cigarette smoking is the most prevalent cessation strategy among all demographic groups, despite the lack of clear evidence for the long-term effectiveness and safety of e-cigarettes as a cessation approach (Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016). More research is needed to better understand the patterns of usage of noncigarette products and their relationship with quitting cigarettes and all tobacco use. In addition, research is needed to understand long-term outcomes among cigarette smokers who report switching to noncigarette products to quit cigarette smoking, including dual usage, the substitution of noncigarette products use for cigarette smoking, and the potential use of noncigarette products as temporary cessation aids with eventual cessation of all tobacco use. The findings on the use of switching to another tobacco product to quit conventional cigarettes underscore the pressing need to (a) consider more effective and efficient ways to reach smokers with evidence-based cessation support and (b) continue to research the efficacy of emerging strategies to reduce combustible tobacco use.

Conclusions

1. In the United States, more than three out of every five adults who were ever cigarette smokers have quit smoking.
2. Past-year quit attempts and recent and longer term cessation have increased over the past 2 decades among adult cigarette smokers.
3. Marked disparities in cessation behaviors, such as making a past-year quit attempt and achieving recent successful cessation, persist across certain population subgroups defined by educational attainment, poverty status, age, health insurance status, race/ethnicity, and geography.
4. Advice from health professionals to quit smoking has increased since 2000; however, four out of every nine adult cigarette smokers who saw a health professional during the past year did not receive advice to quit.
5. Use of evidence-based cessation counseling and/or medications has increased among adult cigarette smokers since 2000; however, more than two-thirds of adult cigarette smokers who tried to quit during the past year did not use evidence-based treatment.
6. A large proportion of adult smokers report using non-evidence-based approaches when trying to quit smoking, such as switching to other tobacco products.

References²

- Adams J, West N, Faison F, Hogg D. Tobacco product use threatens military readiness, July 7, 2019; <<https://www.stripes.com/opinion/tobacco-product-use-threatens-military-readiness-1.589063>>; accessed: July 24, 2019.
- Alexander LA, Trinidad DR, Sakuma KL, Pokhrel P, Herzog TA, Clanton MS, Moolchan ET, Fagan P. Why we must continue to investigate menthol's role in the African American smoking paradox. *Nicotine and Tobacco Research* 2016;18(Suppl 1):S91–S101.
- American Lung Association. *Cutting Tobacco's Rural Roots: Tobacco Use in Rural Communities*. Washington (DC): American Lung Association, 2012; <<http://www.lung.org/assets/documents/research/cutting-tobaccos-rural-roots.pdf>>; accessed: September 25, 2017.
- Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;65(52):1457–64.
- Barnett PG, Hamlett-Berry K, Sung HY, Max W. Health care expenditures attributable to smoking in military veterans. *Nicotine and Tobacco Research* 2015;17(5):586–91.
- Benmarhnia T, Pierce JP, Leas E, White MM, Strong DR, Noble ML, Trinidad DR. Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. *American Journal of Epidemiology* 2018;187(11):2397–404.
- Berry KM, Reynolds LM, Collins JM, Siegel MB, Fetterman JL, Hamburg NM, Bhatnagar A, Benjamin EJ, Stokes A. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013–2015. *Tobacco Control* 2019;28(1):42–9.
- Blackwell DL, Villarroel MA. *Tables of Summary Health Statistics for U.S. Adults: 2017 National Health Interview Survey*. Hyattsville (MD): National Center for Health Statistics, 2018.
- Bondurant S, Wedge R, editors. *Combating Tobacco Use in Military and Veteran Populations*. Washington (DC): The National Academies Press, 2009.
- Brigham J, Lessov-Schlaggar CN, Javitz HS, Krasnow RE, Tildesley E, Andrews J, Hops H, Cornelius MD, Day NL, McElroy M, et al. Validity of recall of tobacco use in two prospective cohorts. *American Journal of Epidemiology* 2010;172(7):828–35.
- Brown-Johnson CG, England LJ, Glantz SA, Ling PM. Tobacco industry marketing to low socioeconomic status women in the U.S.A. *Tobacco Control* 2014;23(e2):e139–e146.
- Buchting FO, Emory KT, Scout, Kim Y, Fagan P, Vera LE, Emery S. Transgender use of cigarettes, cigars, and e-cigarettes in a national study. *American Journal of Preventive Medicine* 2017;53(1):e1–e7.
- Carter A. Policy Memorandum 16-001, Department of Defense Tobacco Policy, April 8, 2016; <<https://www.med.navy.mil/sites/nmcphc/Documents/health-promotion-wellness/tobacco-free-living/INCOMING-CARTER-Tobacco-Policy-Memo.pdf>>; accessed: June 14, 2019.
- Center for Public Health Systems Science. *Point-of-Sale Report to the Nation: The Tobacco Retail and Policy Landscape*. St. Louis (MO): Center for Public Health Systems Science at the Brown School at Washington University in St. Louis and the National Cancer Institute, State and Community Tobacco Control Research Initiative, 2014.
- Center for Public Health Systems Science. *Point-of-Sale Report to the Nation: Realizing the Power of States and Communities to Change the Tobacco Retail and Policy Landscape*. St. Louis (MO): Center for Public Health Systems Science at the Brown School at Washington University in St. Louis and the National Cancer Institute, State and Community Tobacco Control Research Initiative, 2016.
- Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *Morbidity and Mortality Weekly Report* 2001;50(RR13):1–35.
- Centers for Disease Control and Prevention. State-specific prevalence of cigarette smoking and quitting among adults—United States, 2004. *Morbidity and Mortality Weekly Report* 2005;54(44):1124–7.
- Centers for Disease Control and Prevention. Quitting smoking among adults—United States, 2001–2010. *Morbidity and Mortality Weekly Report* 2011;60(44):1513–9.
- Centers for Disease Control and Prevention. Tobacco use screening and counseling during physician office visits among adults—National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005–2009. *Morbidity and Mortality Weekly Report: Supplement* 2012;61(2):38–45.
- Centers for Disease Control and Prevention. Methodology of the Youth Risk Behavior Surveillance

²For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- System—2013. *Morbidity and Mortality Weekly Report Recommendations and Reports* 2013;62(RR-1):1–20.
- Centers for Disease Control and Prevention. BRFSS prevalence and trends data, September 13 2017; <<https://www.cdc.gov/brfss/brfssprevalence/index.html>>; accessed: November 19, 2018.
- Centers for Disease Control and Prevention. National Youth Tobacco Survey, May 9, 2018; <https://www.cdc.gov/tobacco/data_statistics/surveys/nyts/index.htm>; accessed: August 14, 2018.
- Chaiton M, Diemert L, Cohen JE, Bondy SJ, Selby P, Philipneri A, Schwartz R. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open* 2016;6(6):e011045.
- Chaloupka F, Hahn E, Emery S. Policy levers for the control of tobacco consumption. *Kentucky Law Journal* 2002;90:1009–42.
- Clegg LX, Reichman ME, Miller BA, Hankey BF, Singh GK, Lin YD, Goodman MT, Lynch CF, Schwartz SM, Chen VW, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes and Control* 2009;20(4):417–35.
- Cohn AM, Johnson AL, Rose SW, Pearson JL, Villanti AC, Stanton C. Population-level patterns and mental health and substance use correlates of alcohol, marijuana, and tobacco use and co-use in U.S. young adults and adults: results from the Population Assessment for Tobacco and Health. *American Journal on Addictions* 2018;27(6):491–500.
- Coleman B, Rostron B, Johnson SE, Persoskie A, Pearson J, Stanton C, Choi K, Anic G, Goniewicz ML, Cummings KM, et al. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013–2015). *Tobacco Control* 2018.
- Coleman BN, Rostron B, Johnson SE, Ambrose BK, Pearson J, Stanton CA, Wang B, Delnevo C, Bansal-Travers M, Kimmel HL, et al. Electronic cigarette use among U.S. adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Tobacco Control* 2017;26(e2):e117–e126(e2).
- Collins L, Smiley SL, Moore RA, Graham AL, Villanti AC. Physician tobacco screening and advice to quit among U.S. adolescents—National Survey on Drug Use and Health, 2013. *Tobacco Induced Diseases* 2017;15:2.
- Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine and Tobacco Research* 2009;11(1):12–24.
- Corey CG, Holder-Hayes E, Nguyen AB, Delnevo CD, Rostron BL, Bansal-Travers M, Kimmel HL, Koblitz A, Lambert E, Pearson JL, et al. U.S. adult cigar smoking patterns, purchasing behaviors, and reasons for use according to cigar type: findings from the Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Nicotine and Tobacco Research* 2017;20(12):1457–66.
- Courtemanche CJ, Palmer MK, Pesko MF. Influence of the flavored cigarette ban on adolescent tobacco use. *American Journal of Preventive Medicine* 2017;52(5):e139–e146.
- Curtin SC, Mathews TJ. Smoking prevalence and cessation before and during pregnancy: data from the birth certificate, 2014. *National Vital Statistics Reports* 2016;65(1):1–14.
- Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB. Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes. *American Journal of Preventive Medicine* 2011;41(4):357–65.
- Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328(7455):1519.
- Drake P, Driscoll AK, Mathews TJ. *Cigarette Smoking During Pregnancy: United States, 2016*. NCHS Data Brief, Number 305. Hyattsville (MD): National Center for Health Statistics, 2018.
- Fallin A, Goodin AJ, King BA. Menthol cigarette smoking among lesbian, gay, bisexual, and transgender adults. *American Journal of Preventive Medicine* 2015;48(1):93–7.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students, United States, 2011–2018. *Morbidity and Mortality Weekly Report* 2019;68(6):157–64.
- Giovino GA, Villanti AC, Mowery PD, Sevilimedu V, Niaura RS, Vallone DM, Abrams DB. Differential trends in cigarette smoking in the U.S.A.: is menthol slowing progress? *Tobacco Control* 2015;24(1):28–37.
- Graham AL, Amato MS. Twelve million smokers look online for smoking cessation help annually: Health Information National Trends Survey data, 2005–2017. *Nicotine and Tobacco Research* 2018.
- Haddock CK, Hyder ML, Poston WS, Jahnke SA, Williams LN, Lando H. A longitudinal analysis of cigarette prices in military retail outlets. *American Journal of Public Health* 2014;104(4):e82–e87.

- Ham DC, Przybeck T, Strickland JR, Luke DA, Bierut LJ, Evanoff BA. Occupation and workplace policies predict smoking behaviors: analysis of national data from the current population survey. *Journal of Occupational and Environmental Medicine* 2011;53(11):1337–45.
- Harlow A, Stokes A, Brooks D. Socio-economic and racial/ethnic differences in e-cigarette uptake among cigarette smokers: Longitudinal analysis of the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine and Tobacco Research* 2018.
- Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub3.
- Hoffman AC, Simmons D. Menthol cigarette smoking and nicotine dependence. *Tobacco Induced Diseases* 2011;9(Suppl 1):S5.
- Howden LM, Meyer JA. *Age and Sex Composition 2010: 2010 Census Briefs*, May 2011; <<https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>>; accessed: November 19, 2018.
- Hu SS, Neff L, Agaku IT, Cox S, Day HR, Holder-Hayes E, King BA. Tobacco product use among adults—United States, 2013–2014. *Morbidity and Mortality Weekly Report* 2016;65(27):685–91.
- Hughes JR, Peters EN, Naud S. Relapse to smoking after 1 year of abstinence: a meta-analysis. *Addictive Behaviors* 2008;33(12):1516–20.
- Hughes JR, Solomon LJ, Fingar JR, Naud S, Helzer JE, Callas PW. The natural history of efforts to stop smoking: a prospective cohort study. *Drug and Alcohol Dependence* 2013;128(1–2):171–4.
- Humes KR, Jones JA, Ramirez RR. *Overview of Race and Hispanic Origin: 2010: 2010 Census Briefs*, March 2011; <<https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf>>; accessed: November 19, 2018.
- Hyland A, Ambrose BK, Conway KP, Borek N, Lambert E, Carusi C, Taylor K, Crosse S, Fong GT, Cummings KM, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tobacco Control* 2017;26(4):371–8.
- Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington (DC): National Academies Press, 2007.
- Jamal A, Dube SR, Babb SD, Malarcher AM. Tobacco use screening and cessation assistance during physician office visits among persons aged 11–21 years—National Ambulatory Medical Care Survey, United States, 2004–2010. *Morbidity and Mortality Weekly Report Supplement* 2014;63(2):71–9.
- Jamal A, Dube SR, King BA. Tobacco use screening and counseling during hospital outpatient visits among US adults, 2005–2010. *Preventing Chronic Disease* 2015;12:E132.
- Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, King BA. Tobacco use among middle and high school students—United States, 2011–2016. *Morbidity and Mortality Weekly Report* 2017;66(23):597–603.
- Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005–2015. *Morbidity and Mortality Weekly Report* 2016;65(44):1205–11.
- Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *New England Journal of Medicine* 2013;368(4):341–50.
- Johns MM, Lowry R, Andrzejewski J, Barrios LC, Demissie Z, McManus T, Rasberry CN, Robin L, Underwood JM. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students—19 states and large urban school districts, 2017. *Morbidity and Mortality Weekly Report* 2019;68(3):67–71.
- Johnson SE, Holder-Hayes E, Tessman GK, King BA, Alexander T, Zhao X. Tobacco product use among sexual minority adults: findings from the 2012–2013 National Adult Tobacco Survey. *American Journal of Preventive Medicine* 2016;50(4):e91–e100.
- Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respiratory Medicine* 2016;4(2):116–28.
- Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, Lowry R, Chyen D, Whittle L, Thornton J, et al. Youth Risk Behavior Surveillance—United States, 2017. *Morbidity and Mortality Weekly Report Surveillance Summaries* 2018;67(8):1–114.
- Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Hawkins J, Queen B, Lowry R, Olsen EO, Chyen D, et al. Youth Risk Behavior Surveillance—United States, 2015. *Morbidity and Mortality Weekly Report Surveillance Summaries* 2016;65(6):1–174.
- Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, et al. Tobacco-product use by adults and youths in the United States in 2013 and 2014. *New England Journal of Medicine* 2017;376(4):342–53.
- Keeler C, Max W, Yerger V, Yao T, Ong MK, Sung HY. The association of menthol cigarette use with quit attempts, successful cessation, and intention to quit across racial/ethnic groups in the United States. *Nicotine and Tobacco Research* 2017;19(12):1450–64.
- King BA, Dube SR, Babb SD, McAfee TA. Patient-reported recall of smoking cessation interventions from a health professional. *Preventive Medicine* 2013;57(5):715–7.

- Kurti AN, Redner R, Bunn JY, Tang K, Nighbor T, Lopez AA, Keith DR, Villanti AC, Stanton CA, Gaalema DE, et al. Examining the relationship between pregnancy and quitting use of tobacco products in a U.S. national sample of women of reproductive age. *Preventive Medicine* 2018;117:52–60.
- Kurti AN, Redner R, Lopez AA, Keith DR, Villanti AC, Stanton CA, Gaalema DE, Bunn JY, Doogan NJ, Cepeda-Benito A, et al. Tobacco and nicotine delivery product use in a national sample of pregnant women. *Preventive Medicine* 2017;104:50–6.
- Kypriotakis G, Robinson JD, Green CE, Cinciripini PM. Patterns of tobacco product use and correlates among adults in the Population Assessment of Tobacco and Health (PATH) Study: a latent class analysis. *Nicotine and Tobacco Research* 2018;20(Suppl 1):S81–S87.
- Lavinghouze SR, Malarcher A, Jama A, Neff L, Debrot K, Whalen L. Trends in quit attempts among adult cigarette smokers—United States, 2001–2013. *Morbidity and Mortality Weekly Report* 2015;64(40):1129–35.
- Levinson AH, Campo S, Gascoigne J, Jolly O, Zakharyan A, Tran ZV. Smoking, but not smokers: identity among college students who smoke cigarettes. *Nicotine and Tobacco Research* 2007;9(8):845–52.
- Levy DT, Blackman K, Tauras J, Chaloupka FJ, Villanti AC, Niaura RS, Vallone DM, Abrams DB. Quit attempts and quit rates among menthol and nonmenthol smokers in the United States. *American Journal of Public Health* 2011;101(7):1241–7.
- Lopez AA, Redner R, Kurti AN, Keith DR, Villanti AC, Stanton CA, Gaalema DE, Bunn JY, Doogan NJ, Cepeda-Benito A, et al. Tobacco and nicotine delivery product use in a U.S. national sample of women of reproductive age. *Preventive Medicine* 2018;117:61–8.
- Matthews KA, Croft JB, Liu Y, Lu H, Kanny D, Wheaton AG, Cunningham TJ, Khan LK, Caraballo RS, Holt JB, et al. Health-related behaviors by urban-rural county classification—United States, 2013. *Morbidity and Mortality Weekly Report Surveillance Summaries* 2017;66(5):1–8.
- Mazurek JM, England LJ. Cigarette smoking among working women of reproductive age—United States, 2009–2013. *Nicotine and Tobacco Research* 2016;18(5):894–9.
- Meadows SO, Engel CC, Collins RL, Beckman R, Cefalu M, Haws-Dawson J, Doyle M, Kress AM, Sontag-Padilla L, Ramchand R, et al. *2015 Department of Defense Health Related Behaviors Survey (HRBS)*. Santa Monica (CA): RAND Corporation, 2018; <https://www.rand.org/pubs/research_reports/RR1695.html>; accessed: June 14, 2019.
- Mendez D, Tam J, Giovino GA, Tsodikov A, Warner KE. Has smoking cessation increased? An examination of the U.S. adult smoking cessation rate 1990–2014. *Nicotine and Tobacco Research* 2017;19(12):1418–24.
- National Cancer Institute. *Health Information National Trends Survey 4 (HINTS 4): HINTS-FDA2 Methodology Report*, July 2017a; <https://hints.cancer.gov/docs/methodologyreports/HINTS_FDA_Cycle2_Methodology_Rpt.pdf>; accessed: April 30, 2019.
- National Cancer Institute. *Health Information National Trends Survey 5 (HINTS 5): Cycle 1 Methodology Report*, July 2017b; <https://hints.cancer.gov/docs/methodologyreports/HINTS5_Cycle_1_Methodology_Rpt.pdf>; accessed: April 30, 2019.
- National Center for Health Statistics. *Health, United States, 2017: With Special Feature on Mortality*. Hyattsville (MD): National Center for Health Statistics, 2018.
- Office of Disease Prevention and Health Promotion. Tobacco use: objectives, n.d.a; <<https://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use/objectives>>; accessed: July 26, 2017.
- Office of Disease Prevention and Health Promotion. Tobacco use: overview, n.d.b; <<https://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use>>; accessed: May 1, 2017.
- Persoskie A, Nelson WL. Just blowing smoke? Social desirability and reporting of intentions to quit smoking. *Nicotine and Tobacco Research* 2013;15(12):2088–93.
- Remington PL, Brownson RC, Wegner MV. *Chronic Disease Epidemiology, Prevention and Control*. 4th ed. Washington (DC): American Public Health Association, 2016.
- Richardson A, Ganz O, Pearson J, Celcis N, Vallone D, Villanti AC. How the industry is marketing menthol cigarettes: the audience, the message and the medium. *Tobacco Control* 2015;24(6):594–600.
- Roberts ME, Doogan NJ, Stanton CA, Quisenberry AJ, Villanti AC, Gaalema DE, Keith DR, Kurti AN, Lopez AA, Redner R, et al. Rural Versus Urban Use of Traditional and Emerging Tobacco Products in the United States, 2013–2014. *American Journal of Public Health* 2017;107(10):1554–9.
- Robinson JN, Wang B, Jackson KJ, Donaldson EA, Ryant CA. Characteristics of hookah tobacco smoking sessions and correlates of use frequency among U.S. adults: findings from Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine and Tobacco Research* 2018;20(6):731–40.
- Rodu B, Plurphanswat N. Quit methods used by American smokers, 2013–2014. *International Journal of Environmental Research and Public Health* 2017;14(11):E1403.
- Roeseler A, Feighery EC, Cruz TB. Tobacco marketing in California and implications for the future. *Tobacco Control* 2010;19(Suppl 1):i21–i29.

- Ryan CL, Bauman K. *Educational Attainment in the United States: 2015: Population Characteristics*, March 2016; <<https://www.census.gov/content/dam/Census/library/publications/2016/demo/p20-578.pdf>>; accessed: November 19, 2018.
- Schauer GL, Agaku IT, King BA, Malarcher AM. Health care provider advice for adolescent tobacco use: results from the 2011 National Youth Tobacco Survey. *Pediatrics* 2014a;134(3):446–55.
- Schauer GL, Malarcher AM, Babb SD. Gradual reduction of cigarette consumption as a cessation strategy: prevalence, correlates, and relationship with quitting. *Nicotine and Tobacco Research* 2015;17(5):530–8.
- Schauer GL, Malarcher AM, Berg CJ. Differences in smoking and cessation characteristics among adult nondaily smokers in the United States: findings from the 2009–2010 National Adult Tobacco Survey. *Nicotine and Tobacco Research* 2014b;16(1):58–68.
- Siahpush M, Singh GK, Jones PR, Timsina LR. Racial/ethnic and socioeconomic variations in duration of smoking: results from 2003, 2006 and 2007 Tobacco Use Supplement of the Current Population Survey. *Journal of Public Health* 2010;32(2):210–8.
- Singh GK, Williams SD, Siahpush M, Mulhollen A. Socioeconomic, rural-urban, and racial inequalities in U.S. cancer mortality: part I—all cancers and lung cancer and part II—colorectal, prostate, breast, and cervical cancers. *Journal of Cancer Epidemiology* 2011;2011:107497.
- Smith EA, Malone RE. Tobacco promotion to military personnel: “the plums are here to be plucked”. *Military Medicine* 2009;174(8):797–806.
- Smith KH, Stutts MA, Zank GM. An exploratory study of the behavior and perceptions of college students with respect to regular, light, and ultralight cigarettes. *Journal of Public Policy and Marketing* 2012;31(2):206–22.
- Stanton CA, Keith DR, Gaalema DE, Bunn JY, Doogan NJ, Redner R, Kurti AN, Roberts ME, Higgins ST. Trends in tobacco use among U.S. adults with chronic health conditions: National Survey on Drug Use and Health 2005–2013. *Preventive Medicine* 2016;92:160–8.
- Thacker SB, Parrish RG, Trowbridge FL. A method for evaluating systems of epidemiological surveillance. *World Health Statistics Quarterly* 1988;41(1):11–8.
- The Community Guide. Reducing tobacco use and secondhand smoke exposure: comprehensive tobacco control programs—task force finding and rationale statement, September 29, 2014; <<https://www.thecommunityguide.org/sites/default/files/assets/TFFRS-Tobacco-Comprehensive-Control-Programs.pdf>>; accessed: August 29, 2017.
- Tindle HA, Shiffman S. Smoking cessation behavior among intermittent smokers versus daily smokers. *American Journal of Public Health* 2011;101(7):e1–e3.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.
- U.S. Department of Health and Human Services. *Tobacco Use Among U.S. Racial/Ethnic Minority Groups—African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1998.
- U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.
- U.S. Department of Health and Human Services. *The Health and Wellbeing of Children in Rural Areas: A Portrait of the Nation 2007*. Rockville (MD): U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, 2011.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Department of the Census. New census data show differences between urban and rural populations [press release CB16-210], December 08, 2016 2016; <<https://www.census.gov/newsroom/press-releases/2016/cb16-210.html>>; accessed: April 5, 2018.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy

- Interventions, September 2015; <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>>; accessed: May 24, 2017.
- Vander Weg MW, Cunningham CL, Howren MB, Cai X. Tobacco use and exposure in rural areas: Findings from the Behavioral Risk Factor Surveillance System. *Addictive Behaviors* 2011;36(3):231–6.
- Verplaetse TL, Moore KE, Pittman BP, Roberts W, Oberleitner LM, Peltier MR, Hacker R, Cosgrove KP, McKee SA. Intersection of e-cigarette use and gender on transitions in cigarette smoking status: findings across Waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine and Tobacco Research* 2018.
- Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults—United States, 2017. *Morbidity and Mortality Weekly Report* 2018a;67(44):1225–32.
- Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco product use among middle and high school students—United States, 2011–2017. *Morbidity and Mortality Weekly Report* 2018b;67(22):629–33.
- Weinberger AH, Gbedemah M, Wall MM, Hasin DS, Zvolensky MJ, Goodwin RD. Cigarette use is increasing among people with illicit substance use disorders in the United States, 2002–14: emerging disparities in vulnerable populations. *Addiction* 2018;113(4):719–28.
- Wong SL, Shields M, Leatherdale S, Malaison E, Hammond D. Assessment of validity of self-reported smoking status. *Health Reports* 2012;23(1):47–53.
- Young-Wolff KC, Klebaner D, Folck B, Tan ASL, Fogelberg R, Sarovar V, Prochaska JJ. Documentation of e-cigarette use and associations with smoking from 2012 to 2015 in an integrated healthcare delivery system. *Preventive Medicine* 2018;109:113–8.
- Yu D, Peterson NA, Sheffer MA, Reid RJ, Schnieder JE. Tobacco outlet density and demographics: analysing the relationships with a spatial regression approach. *Public Health* 2010;124(7):412–6.

Chapter 2 Appendices

Appendix 2.1: Sources of Data 113

National Health Interview Survey	113
Youth Risk Behavior Surveillance System	113
Tobacco Use Supplement to the Current Population Survey	113
Behavioral Risk Factor Surveillance System	114
National Adult Tobacco Survey	114
National Ambulatory Medical Care Survey	114
Population Assessment of Tobacco and Health Study	114
Health Information National Trends Survey	115
Monitoring the Future Study	115
National Youth Tobacco Survey	115

Appendix 2.2: Measures of Cessation 116

Validity of Measures of Cessation Among Youth	116
Validity of Measures of Tobacco Use Among Adults	116
Definitions	117
Current and Former Cigarette Smoking	117
Quit Ratio	117
Recent Successful Cessation	117
Cessation Continuum	118
Past-Year Quit Attempts	118
Number and Duration of Quit Attempts	118
Interest in Quitting	119
Ever Tried to Quit Smoking	119
Cessation of Other Tobacco Products	119
Screening for Tobacco Use	119
Advice to Quit—Clinical Data from Abstractions of Medical Records	119
Advice to Quit—Self-Reported Data	120
Use of Counseling and Medications to Quit Smoking	120
Use of Other Cessation Strategies	120

References 121

Appendix 2.1: Sources of Data

Data summarized in this chapter come from two national surveys, the National Health Interview Survey (NHIS) and the National Youth Risk Behavior Survey (YRBS) (Table 2.1), which are described below. After descriptions of NHIS and YRBS, brief summaries of other national surveys that provided limited information for this chapter are provided.

National Health Interview Survey

NHIS, a multipurpose survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC), is the principal source of information on the health of the civilian, non-institutionalized population of the United States. NHIS has been conducted continuously since 1957. Questions on smoking have been included in selected survey years since 1965, and detailed items allowing classification by race/ethnicity have been included since 1978. Information on quit attempts among all cigarette smokers has been assessed since 1991. Detailed questions on tobacco use cessation are included in a CCS to NHIS, which was initiated in 1987 and subsequently conducted in 1992, 2000, 2005, 2010, and 2015, with relatively consistent questions on cessation included from 2000 to 2015. Face-to-face interviews are used to collect confidential data from a representative sample of the population using the place of residence of individual respondents.

The sampling plan follows a multistage area probability design that permits the representative sampling of households and noninstitutional group living quarters (e.g., college dormitories) in all 50 states and the District of Columbia. Non-Hispanic African American or Black, Hispanic or Latino, and Asian persons were oversampled during 2006–2015. For each family included in NHIS, one sample child (younger than 18 years of age) and one sample adult are randomly selected, and information on each is collected. For children and those adults not capable of doing so, information is provided by a knowledgeable adult family member. Since 1974, only self-reports of cigarette smoking and use of other tobacco products have been used, and thus no proxy data have been used since that year on questions of importance to this report. Since 1997, NHIS has been conducted using computer-assisted personal interviewing by interviewers from the U.S. Census Bureau; sampling and interviewing are continuous throughout each year. CDC (2017c) has detailed information on NHIS questionnaires and sampling on its website.

Youth Risk Behavior Surveillance System

Developed in 1990 by CDC, the Youth Risk Behavior Surveillance System (YRBSS) monitors priority health risk behaviors, including past-year quit attempts among current cigarette smokers, among high school students in the United States. In addition to the surveys that are conducted by state, local, territorial, and tribal health and education agencies, there is the national YRBS conducted by CDC. The current report includes data from the national YRBS only, which has a sampling frame of all public and private school students in grades 9–12 in the 50 states and the District of Columbia. A three-stage cluster sample design is used to sample (1) large-sized counties or groups of smaller adjacent counties, (2) public and private schools with a probability proportional to the schools' enrollment, and (3) one or two randomly selected classes in each grade. Examples of classes include home-rooms, classes of a required discipline (e.g., English or social studies), and all classes meeting during a required period (e.g., second period). All students in a sampled class are eligible to participate. Oversampling is used to achieve sufficiently large subsamples of Black or African American and Hispanic or Latino students to enable separate analyses of these subgroups. Schools that decline to participate in the original sample are not replaced. Students complete self-administered, paper-and-pencil questionnaires and record their answers directly in the questionnaire booklet (CDC 2013). Local procedures to obtain the permission of parents are followed. Trained personnel administer the questionnaires to students in their classrooms for the national survey. The participation of students is both voluntary and anonymous (CDC 2013).

Tobacco Use Supplement to the Current Population Survey

The Tobacco Use Supplement to the Current Population Survey (TUS-CPS) is a National Cancer Institute-sponsored survey of tobacco use that has been administered as part of the U.S. Census Bureau's Current Population Survey approximately every 3–4 years since 1992–1993 (since 2000, surveys were conducted for 2001–2002, 2003, 2006–2007, 2010–2011, and 2014–2015). In each cycle, the TUS-CPS collects nationally representative data from about 240,000 adults (data collected between

1992 and 2006 also included youth 15–17 years of age). About two-thirds of respondents complete the questionnaire by telephone, and responses for the remaining one-third are obtained through in-person interviews. More detailed information about the TUS-CPS is available from the National Cancer Institute (NCI) (n.d.b).

Behavioral Risk Factor Surveillance System

In 1984, CDC initiated the state-based Behavioral Risk Factor Surveillance System (BRFSS), a cross-sectional telephone survey that state health departments conduct monthly over landline and cellular telephones (included since 2011), using a standardized questionnaire and technical and methodologic assistance provided by CDC. The BRFSS is used to collect data among U.S. adults 18 years of age and older regarding their risk behaviors and preventive health practices that can affect their health status. Data from respondents are forwarded to CDC to be aggregated for each state, returned with standard tabulations, and published at year's end by each state. In 2011, BRFSS adopted new methods, including the addition of cellular telephone households to its sample, and used new methods of weighting to adjust survey data for differences between the demographic characteristics of respondents and the survey population (CDC 2012). As a result of these methodologic changes, data from 2011 to 2017 cannot be compared with years before 2011. In 2017, more than 450,000 interviews were conducted with respondents from all 50 states, the District of Columbia, and participating U.S. territories and other geographic areas. The number of completed interviews at each site ranged from 1,508 to 22,059, and the median response rate was 45.9%. For this Surgeon General's report, data have been weighted to reflect the age, race/ethnicity, and sex distribution of each participating state. CDC (2017a) offers detailed information about the BRFSS.

National Adult Tobacco Survey

The 2013–2014 National Adult Tobacco Survey (NATS)—a stratified, random-digit-dialed (RDD), telephone survey of noninstitutionalized adults 18 years of age and older—was conducted from October 2013 to October 2014. The survey was part of a collaborative effort between CDC and the U.S. Food and Drug Administration (FDA). The survey sought to determine the prevalence and correlates of tobacco use behaviors among a nationally representative sample of U.S. adults. The 2013–2014 NATS

included 75,233 respondents (70% landline, 30% cellular), and the overall response rate was 36.1% (47.6%, landline; 17.1%, cellular). Data were weighted to provide nationally representative estimates of prevalence. Detailed information on NATS is available at CDC (2016).

National Ambulatory Medical Care Survey

The National Ambulatory Medical Care Survey (NAMCS), conducted by CDC's National Center for Health Statistics, is a survey designed to meet the need for objective, reliable information about the provision and use of ambulatory medical care services in the United States. Findings are based on a sample of visits to nonfederal, office-based physicians who are primarily engaged in direct patient care. Abstraction of medical records includes documentation of screening for tobacco use, counseling on tobacco cessation in the form of health education ordered or provided during the visit, and tobacco cessation medications ordered or continued during the visit. In 2009, 32,281 records were abstracted from a sample of 3,319 physicians, with a response rate of 62.4% (in 2010, 31,229 records were abstracted from a sample of 3,525 physicians, with a response rate of 57.3%, and in 2011, 30,872 records were abstracted from a sample of 3,819 physicians, with a response rate of 54.1%). CDC (2017b) offers on its website more detailed information about NAMCS.

Population Assessment of Tobacco and Health Study

The Population Assessment of Tobacco and Health (PATH) Study was launched in October 2011 through a collaboration between the FDA Center for Tobacco Products and the National Institutes of Health, National Institute for Drug Abuse. PATH is a nationally representative, longitudinal cohort study that uses computer-assisted interviews to collect information from approximately 49,000 current, never, and former tobacco users, including noninstitutionalized youth (12–17 years of age) and adults (18 years of age and older). The study also collects biospecimens (i.e., buccal cell, urine, blood) from consenting adults. Wave 1 of data collection was completed in 2014 (September 2013–December 2014), and four subsequent waves have been completed: Wave 2 (October 2014–October 2015), Wave 3 (October 2015–October 2016), Wave 4 (December 2016–November 2017), and an additional wave among only 12- to 17-year-old youth (December 2017 to November 2018).

The goal of the Path Study is to monitor and assess behavioral and biological between-person differences and within-person changes over time in tobacco product use patterns and behaviors, attitudes and risk perceptions, tobacco-related biomarkers of exposure and harm, and health conditions. The findings may inform FDA regulatory activities related to product standards (e.g., toxicity, appeal, abuse liability/addictiveness), health warnings, and the authorization of new and modified risk tobacco products, as well as FDA's public education efforts.

Health Information National Trends Survey

The Health Information National Trends Survey (HINTS) was developed by the Health Communication and Informatics Research Branch of the Division of Cancer Control and Population Sciences of NCI. The HINTS is a biennial, cross-sectional survey that routinely collects data about the use of cancer-related information, including information on quitting smoking, from a nationally representative sample of adults 18 years of age and older in the civilian noninstitutionalized population of the United States. Data from the survey are used to assess the impact of the health information environment. There have been nine iterations of the HINTS: in 2003, 2005, 2007, 2011, 2012, 2013, 2014, 2015, and 2017. The 2017 survey, which was used for this report, was conducted primarily by telephone (95%) with incentives promised of either \$0, \$5, or \$15 upon survey completion (there were 3,335 completed surveys, a 25.0% response rate). More detailed information about the HINTS is available from NCI (n.d.a).

Monitoring the Future Study

The Monitoring the Future (MTF) Study, conducted annually since its inception in 1975, is conducted by the University of Michigan's Institute for Social Research and

supported through grants from the National Institute on Drug Abuse. The MTF—a study of American youth, college students, and adults through 45 years of age—monitors changes in the beliefs, attitudes, and behaviors relevant to drug use and other health and social issues among young persons in the United States. This report presents data on high school seniors from confidential, self-administered paper-and-pencil questionnaires used to survey nationally representative samples of 12th-grade students in public and private schools in 48 of the 50 states (all but Alaska and Hawaii). From 2011 to 2015, the years used in this report, sample sizes for the 12th-grade students (from 121 to 129 schools) who participated in the MTF Study ranged from 13,015 to 14,855, and response rates ranged from 82% to 83% (Miech et al. 2016).

National Youth Tobacco Survey

The National Youth Tobacco Survey (NYTS) was developed by CDC to assist with the evaluation of the National Tobacco Control Program (NTCP) and state tobacco control programs. CDC and FDA have co-administered the survey since 2011. The NYTS, which provides nationally representative data on tobacco-related behaviors among middle school (grades 6–8) and high school (grades 9–12) students, was first conducted in fall 1999 and was subsequently conducted in 2000, 2002, 2004, 2006, 2009, and 2011–2017. The NYTS sampling frame consists of all students enrolled in public, Catholic, and other private middle schools and high schools (grades 6–12) in the 50 states and Washington, D.C. Participation is voluntary and anonymous. Participants complete a self-administered paper-and-pencil questionnaire and record their responses on a computer-scannable questionnaire booklet. For the NYTS years used in this report (2000, 2004, 2009, 2015, and 2017), sample sizes were as low as 17,711 and as high as 35,828; the number of participating schools ranged from 185 to 324; and response rates ranged from 63.4% to 84.8% (Office on Smoking and Health et al. 2001; CDC 2010; Singh et al. 2016).

Appendix 2.2: Measures of Cessation

Validity of Measures of Cessation Among Youth

All of the data on cessation among youth that are presented in this report are based on self-reported responses to questionnaires. Because tobacco use is viewed by many as a socially undesirable behavior, there is a risk of inaccurate or dishonest responses. Because it was not feasible to verify the self-reported data included here, it is important for researchers to interpret these data with some caution and an understanding of possible sources of inaccuracy. Many factors can affect the validity of self-reported data—factors that can be categorized as cognitive or situational. Cognitive processes that affect responses include comprehension of the question, retrieval of relevant information from memory, decision making about the adequacy of the information retrieved, and the generation of a response (Brener et al. 2003). Each of these processes can contribute to errors in responses and, subsequently, to problems with validity.

Situational factors that affect the validity of self-reported data refer to characteristics of the external environment in which the survey is being conducted. These include the setting (i.e., school or home based), the method (i.e., self-administered questionnaire or in-person interview), the social desirability of the behavior being reported, and the perception of privacy and/or confidentiality of responses (U.S. Department of Health and Human Services [USDHHS] 1994; Brener et al. 2003).

Many studies have found that youth are more likely to report engaging in sensitive behaviors when a survey is completed in a school setting rather than in their homes (Gfroerer et al. 1997; Hedges and Jarvis 1998; Kann et al. 2002). A study that compared the school-based National Youth Risk Behavior Survey (YRBS) with the household-based YRBS supplement to the National Health Interview Survey (NHIS) found that the school-based survey produced a significantly higher reporting of many sensitive behaviors, such as driving after drinking alcohol, binge drinking, and current use of marijuana and cocaine (Brener et al. 2006). Four measures of various stages of the smoking uptake process were higher in the school-based survey, but estimates for current cigarette use and frequent cigarette use, although elevated in the school-based survey, did not differ significantly from estimates generated in the household-based survey. Few differences in nonsensitive behaviors were observed. Two other studies (Gfroerer et al. 1997; Brener et al. 2003) indicated that, although estimates based on self-reports of current use of alcohol and illicit drugs were higher in school-based than in household-based

surveys, estimates of current cigarette smoking were quite similar across settings. It is noteworthy that all three of these studies use self-administered rather than interviewer-administered interviews/questionnaires. Nevertheless, the privacy that school surveys provide is important, especially if smoking becomes more socially unacceptable over time. Household-based surveys, however, are more likely to include youth who drop out of school or are frequently absent from school, and youth in these groups are more likely to smoke. In addition, the Population Assessment of Tobacco and Health (PATH) Study (which uses audio, computer-administered self-interviews in a respondent's household) recently conducted a reliability and validity study of current use of a variety of tobacco products among youth 12–17 years of age, finding high levels of agreement across interviews conducted 6–24 days apart (Tourangeau et al. 2018). There was also a high level of agreement between self-reported current tobacco use and salivary cotinine tests among a combined sample of adults and youth (87.5% of the reports and tests agreed).

Overall, the factors described above may affect point estimates of cessation. If these factors remain stable over the years, however, they should not affect the trends seen over time.

Validity of Measures of Tobacco Use Among Adults

All of the data on tobacco use among adults presented in this report were based on self-reported responses to questionnaires. Biochemical validation studies suggest that data on self-reported cigarette smoking are generally valid, except in certain situations, such as when data are collected in conjunction with intense smoking cessation programs or with certain populations, such as pregnant women (Velicer et al. 1992; Kendrick et al. 1995). Misclassification may also be more common among intermittent smokers, who may not classify themselves as smokers because they do not perceive themselves as being addicted or because of social desirability bias. Additionally, smokers may misreport the number of cigarettes they smoke per day because of “digit preference” (a preference for multiples of 10) (Klesges et al. 1995). Although self-reported data have been found to adequately reflect cigarette smoking patterns (including whether a respondent who has smoked in the past is currently not smoking) (Connor Gorber et al. 2009; Wong et al. 2012; Tourangeau et al. 2018), few studies have examined the validity of other cessation measures (Brigham et al. 2010;

Persoskie and Nelson 2013). It should be noted, however, that much of the research literature on the validity of self-reported data is restricted to cigarette smoking—and not measures of cessation or other tobacco products. However, among adult tobacco users, a recent PATH Study found high levels of agreement at initial interview and subsequent re-interview 6–24 days later between self-reported current use of cigarettes, electronic nicotine products, traditional cigars, cigarillos, filtered cigars, pipes, snus, hookahs, and smokeless tobacco (Tourangeau et al. 2018). High agreement was also found for self-reported information on current tobacco use and salivary cotinine among a combined sample of youth and adults (Tourangeau et al. 2018). Thus, a discussion of the factors that may affect validity is important so that the data presented in this report are interpreted with some caution and an understanding of possible sources of inaccuracy. Clearly, many factors can affect the validity of self-reported data, such as response biases and the particular methodologic features of the surveys. For example, methodologic differences in survey administration include but are not limited to timing, order of survey questions, sampling, mode of data collection (e.g., computer-assisted personal interviewing vs. computer-assisted telephone interviewing), participation rates, and operational definitions (Ryan et al. 2012). In addition, responses to questions may be subject to more social desirability biases in surveys that are focused solely on tobacco use versus those where tobacco use is just one of several health behaviors being assessed, as research has found that the context in which sensitive questions are asked can effect responses to survey questions (Tourangeau and Yan 2007; Krumpal 2013).

Definitions

Measures of cessation differ between surveys of youth and those focused on adults. Three surveys (NHIS, Behavioral Risk Factor Surveillance System [BRFSS], and Tobacco Use Supplement to the Current Population Survey [TUS-CPS]) included in this chapter provide information about cessation among adults and young adults, while three other surveys (YRBS, Monitoring the Future [MTF] Study, and National Youth Tobacco Survey [NYTS]) provide information about smoking among youth. For each smoking measure, the definitions used in the various surveys are summarized below.

Current and Former Cigarette Smoking

Adults and Young Adults

In NHIS from 1965 to 1991, current cigarette smokers were defined as respondents who had smoked at

least 100 cigarettes and who answered “yes” to the question, “Do you smoke cigarettes now?” Beginning in 1992, NHIS assessed whether respondents smoked cigarettes every day, some days, or not at all. Persons who smoked every day or some days were classified as current cigarette smokers.

Also in NHIS, former cigarette smokers were those who reported smoking at least 100 cigarettes during their lifetime but currently did not smoke.

Youth

The YRBS defines current cigarette smoking among students as having smoked cigarettes on at least 1 day during the 30 days before the survey. To be classified as a current smoker, students had to answer “yes” to questions about ever smoking and current smoking. In addition, students who were current smokers and reported smoking on 20 or more of the past 30 days were categorized as current frequent cigarette smokers. This measure was examined for youth because current frequent cigarette smokers most likely have a more established pattern of use and are more likely to smoke as adults, thereby potentially representing the future group of adult smokers who are trying to quit.

Former smoking among youth in the YRBS was categorized as either (a) former daily smokers, representing those who had an established pattern of smoking daily but were not currently smoking and perhaps reflecting youth who had quit smoking; and (b) former nondaily smokers, who may contain a higher proportion of youth who experimented with smoking, in addition to those who quit smoking. Students who answered “yes” to ever smoke and “no” to currently smoke were categorized as (a) former daily smokers, if they answered “yes” to ever daily; or (b) former nondaily smokers, if they answered “no” to ever daily.

Quit Ratio

Adults

In NHIS, the quit ratio is defined as the ratio of former smokers to ever smokers; ever smokers were those who had smoked at least 100 cigarettes in their lifetimes. Former smokers were defined as ever smokers who did not currently smoke at the time of the survey. Because smoking behaviors are less established among youth and young adults, this measure was not examined for those groups.

Recent Successful Cessation

Adults and Young Adults

In NHIS, the recent smoking cessation percentage includes in the numerator only former smokers who quit smoking 6–12 months ago (i.e., persons who reported

having smoked 100 cigarettes in their life but were not smoking at time of interview and had quit smoking 6–12 months prior). The denominator for this measure includes both current smokers who smoked for at least 2 years and former smokers who quit during the past year. This measure was not examined for youth. Because the BRFSS did not include a question about the length of time that current cigarette smokers had smoked, the estimate from BRFSS does not include this restriction in its denominator and, therefore, is not comparable to the estimate from NHIS. Nevertheless, when the restriction of having smoked for at least 2 years is removed from the denominator in NHIS, the resulting estimate of the prevalence of recent successful cessation is 7.4% (95% CI, 6.4–8.4%) (NHIS, NCHS, public use data, 2017), which is similar to the estimate with this restriction (7.6%, 95% CI, 6.6–8.6%) (Table 2.13).

Cessation Continuum

Using TUS-CPS data, a cessation continuum was constructed to more completely describe the dynamic process of smoking cessation. This measure was examined only for adult current smokers. The continuum included the proportion of current smokers who had ever tried to quit smoking, whether they had attempted to quit during the past year, and their current interest in quitting.

Past-Year Quit Attempts

Adults and Young Adults

NHIS defines past-year quit attempts among current smokers as those who answer “yes” to, “During the past 12 months, have you quit smoking for one day or longer?” In the 1998 NHIS, the question was revised to, “During the past 12 months, have you stopped smoking for more than one day because you were trying to quit smoking?” This measure also includes former smokers who quit during the past year. It is important to note that in addition to excluding those who may have quit for 1 day during the past year, this measure does not include past-year quit attempts of less than 1 day. Therefore, the measure may underestimate quit-attempt prevalence. Data from the 2014–2015 TUS-CPS indicated that among current cigarette smokers, the prevalence of past-year quit attempts increased by 5.4 percentage points from 41.3% to 46.7% when self-reported quit attempts of less than 1 day were included (Table 2.14). Questions defining past-year quit attempts in the 2014–2015 TUS-CPS included asking some-day smokers who smoked fewer than 12 days in the past 30 days, “During the past 12 months, have you tried to quit smoking completely?” and asking daily smokers and some-day smokers who smoked on 12 or more days

during the past 30 days, “During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?” Those who answered “no” to this question were asked, “During the past 12 months, have you made a serious attempt to stop smoking because you were trying to quit—even if you stopped for less than a day?” Quit attempts of less than 1 day comprised 12.9% of past-year quit attempts among current daily smokers and some-day smokers who smoked on 12 or more days during the past 30 days (TUS-CPS, public use data, 2014–2015).

It is also important to note that Table 2.14 estimates past-year quit attempt prevalence in 2014–2015 TUS-CPS only among current smokers and does not include former smokers who quit in the past year; therefore, the quit attempt prevalence in Table 2.14 (41.3%) is much lower than the quit attempt prevalence in Table 2.11, which is estimated from the 2015 NHIS and includes former smokers who quit during the past year (55.4%). However, the absence of former smokers who quit during the past year from the 2014–2015 TUS-CPS estimate does not entirely explain the difference in prevalence. In the combined 2014–2015 NHIS among current smokers only, the quit attempt prevalence was 48.9% (NHIS, public use data, 2014–2015), which was still above the quit attempt prevalence of 41.3% among the same group in the 2014–2015 TUS-CPS.

Youth

In the YRBS, students were asked the question, “During the past 12 months, did you ever try to quit smoking cigarettes?”

The NYTS defines past-year quit attempts as those made by current smokers who reported having tried to quit smoking for a day or longer during the past year.

Number and Duration of Quit Attempts

Adults and Young Adults

In the 2014–2015 TUS-CPS, among current daily smokers and some-day smokers who smoked at least 12 or more days during the past 30 days, the question, “How many TIMES during the past 12 months have you stopped smoking for one day or longer because you were trying to quit smoking?” was asked of those who responded “yes” to the question, “During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?”

Duration of quit attempts was examined with the questions, “During the past 12 months, what is the length of time of this single quit attempt where you stopped smoking because you were trying to quit smoking” and “Thinking of those attempts during the past 12 months,

what was the length of time of the one attempt that lasted the longest?”

Youth

In the 2017 NYTS, middle and high school students who were current smokers and had tried to quit smoking during the past year were asked, “During the past 12 months, how many times have you stopped using all tobacco products for one day or longer because you were trying to quit all tobacco products for good?” The response options were “I did not smoke cigarettes during the past 12 months,” “I did not try to quit during the past 12 months,” “1 time,” “2 times,” “3 to 5 times,” “6 to 9 times,” and “10 or more times.”

Interest in Quitting

Adults and Young Adults

In the 2014–2015 TUS-CPS, among current daily and some-day smokers, interest in quitting was assessed using a 10-point scale. Participants were asked, “Overall, on a scale from 1 to 10, where 1 is not at all interested and 10 is extremely interested, how interested are you in quitting smoking?”

NHIS defines interest in quitting as current smokers who reported that they wanted to stop smoking completely.

Youth

In the 2011–2015 MTF Study, interest in quitting was assessed by asking high school seniors who were current smokers whether they wanted to stop smoking “now.” Another measure included in this survey concerned whether the smoker thought that he or she would be smoking in 5 years.

In the 2015 NYTS, interest in quitting was assessed by asking current smokers, “Are you seriously thinking about quitting cigarettes?”

Ever Tried to Quit Smoking

Adults and Young Adults

In the 2001–2002 TUS-CPS, estimates for ever trying to quit smoking relied on one question, “Have you ever stopped smoking for one day or longer because you were trying to quit smoking?” In other years, questions for current some-day smokers who had smoked fewer than 12 days during the past 30 days were asked, “Have you ever tried to quit smoking completely?” and current daily smokers and some-day smokers who had smoked 12 or more days during the past 30 were asked, “Have you ever made a serious attempt to stop smoking because you were

trying to quit—even if you stopped for less than a day?” For the 2006–2007 TUS-CPS, current daily smokers and some-day smokers who smoked 12 or more days during the past 30 days were also asked, “Have you ever stopped smoking one day or longer because you were trying to quit smoking?”

Youth

In the MTF Study, high school seniors who were current smokers were asked if they had ever tried to quit smoking.

Cessation of Other Tobacco Products

Adults and Young Adults

In NHIS, cessation of other tobacco products was examined using past-year quit attempts (“During the past 12 months, have you stopped using all kinds of tobacco products for more than one day because you were trying to quit using tobacco?” “All kinds” meant trying to quit using tobacco completely, including smoking cigarettes, smoking products other than cigarettes, and using smokeless tobacco products.). This question was asked of current cigarette smokers who used another tobacco product or who used two or more tobacco products.

Screening for Tobacco Use

Adults and Young Adults

Screening for tobacco use was examined using 2009–2011 NAMCS data, based on abstraction of medical records for visits to office-based physicians during which current tobacco use (smoked cigarettes or cigars or used snuff or chewing tobacco) or no current use was recorded. The same measure was used for youth. Because of methodologic changes, this chapter does not report the most recent NAMCS data (2012–2013).

Advice to Quit—Clinical Data from Abstractions of Medical Records

Adults and Young Adults

Using 2009–2011 NAMCS data, receipt of advice to quit was based on abstraction of medical records for visits to office-based physicians by identified current tobacco users (i.e., the patient was identified as a current tobacco user during screening). Receipt of advice is defined as visits where tobacco counseling was recorded. Tobacco counseling refers to any information provided that related to tobacco use in any form, including cigarettes, cigars, snuff, and chewing tobacco, and on exposure to tobacco

in the form of secondhand smoke, smoking cessation, and prevention of tobacco use, as well as referrals to other healthcare providers for smoking cessation programs. The same measure was used for youth. Because of methodologic changes, this chapter does not report the most recent NAMCS data (2012–2013).

Advice to Quit—Self-Reported Data

Adults and Young Adults

In the 2015 NHIS, receipt of advice to quit was assessed among current smokers and former smokers who quit during the past year and also saw a doctor or other health professional during the past year. Receipt of advice to quit was defined as having been given advice from a medical doctor, dentist, or other health professional to quit smoking or to quit using other kinds of tobacco among current cigarette smokers and former smokers who quit during the past year.

Youth

In the 2013 NYTS, high school and middle school students were asked whether at any visit to a doctor, dentist, or nurse during the time covered by the survey, they had been asked by the provider whether they used tobacco that is smoked or put in the mouth. A separate measure, being advised not to use tobacco, was defined using current cigarette smokers (smoked cigarettes during the 30 days preceding the survey) as being advised by a doctor, dentist, or nurse during the past 12 months not to use tobacco that is smoked or put in the mouth.

Use of Counseling and Medications to Quit Smoking

Adults and Young Adults

To define the use of counseling, NHIS considers two groups, current smokers who tried to quit during the past year and former smokers who quit during the past 2 years. Counseling is defined as having used one-on-one counseling; a stop-smoking clinic, class, or support group; and/or a telephone helpline or quitline during the past year, among current smokers who tried to quit in the past year and among former smokers who quit in the past 2 years. The 2014–2015 TUS-CPS asked current smokers who tried

to quit during the past year about their use of a telephone helpline or quitline the last time they tried to quit.

NHIS defines use of medications as having used during the past year the nicotine patch, nicotine gum or lozenge, a nicotine-containing nasal spray or inhaler, varenicline (U.S. trade name Chantix), and/or bupropion (including trade names Zyban and Wellbutrin).

Youth

The 2000, 2004, and 2009 NYTS asked high school and middle school students if they did any of the following during the past 12 months to help themselves stop smoking: attend a program in their school, attend a program in their community, call a helpline or quitline, use nicotine gum or lozenge, use a nicotine patch, and/or use any medication. (In 2000, the strategies of using nicotine gum and using a nicotine patch were asked together as one strategy.) The same cessation strategies were assessed in the 2015 NYTS but the question changed to, “In the past 12 months, did you do any of the following to help you quit using tobacco of any kind for good?” and the word “telephone” was added before “helpline” and “quitline.”

Use of Other Cessation Strategies

Adults and Young Adults

The 2014–2015 TUS-CPS asked current smokers who tried to quit during the past year about their use of the Internet or a web-based program or tool the last time they tried to quit. Current smokers were also asked if they did any of the following the last time they tried to quit: tried to quit by switching to (a) smokeless tobacco, such as chewing tobacco, snuff, or snus; (b) regular cigars, cigarillos, little filtered cigars, or any pipes filled with tobacco, and (c) electronic or e-cigarettes. The survey did not operationalize what switching meant (i.e., completely switching vs. dual use while reducing cigarette smoking).

Youth

The 2015 NYTS asked high school and middle school students if they had tried to quit “on my own” or cold turkey during the past 12 months to help themselves quit using tobacco of any kind for good. The 2015 NYTS also asked if one of the reasons why they had used e-cigarettes was to try to quit using tobacco products, such as cigarettes.

References¹

- Brener ND, Billy JO, Grady WR. Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature. *Journal of Adolescent Health* 2003;33(6):436–57.
- Brener ND, Eaton DK, Kann L, Grunbaum JA, Gross LA, Kyle TM, Ross JG. The association of survey setting and mode with self-reported health risk behaviors among high school students. *Public Opinion Quarterly* 2006;70(3):354–74.
- Brigham J, Lessov-Schlaggar CN, Javitz HS, Krasnow RE, Tildesley E, Andrews J, Hops H, Cornelius MD, Day NL, McElroy M, et al. Validity of recall of tobacco use in two prospective cohorts. *American Journal of Epidemiology* 2010;172(7):828–35.
- Centers for Disease Control and Prevention. Tobacco use among middle and high school students—United States, 2000–2009. *Morbidity and Mortality Weekly Report* 2010;59(33):1063–8.
- Centers for Disease Control and Prevention. Methodologic changes in the Behavioral Risk Factor Surveillance System in 2011 and potential effects on prevalence estimates. *Morbidity and Mortality Weekly Report* 2012;61(22):410–3.
- Centers for Disease Control and Prevention. Methodology of the Youth Risk Behavior Surveillance System—2013. *Morbidity and Mortality Weekly Report Recommendations and Reports* 2013;62(RR-1):1–20.
- Centers for Disease Control and Prevention. 2013–2014 National Adult Tobacco Survey (NATS) Sample Design and Methodology Report, January, 2016; <https://www.cdc.gov/tobacco/data_statistics/surveys/nats/pdfs/2014-methodology-report-tag508.pdf>; accessed: August 15, 2017.
- Centers for Disease Control and Prevention. 2015 BRFSS survey data and documentation, 2017a; <https://www.cdc.gov/brfss/annual_data/annual_2015.html>; accessed: August 15, 2017.
- Centers for Disease Control and Prevention. Ambulatory health care data, 2017b; <https://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm>; accessed: August 15, 2017.
- Centers for Disease Control and Prevention. NHIS data, questionnaires and related documentation, 2017c; <<https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm>>; accessed: August 15, 2017.
- Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine and Tobacco Research* 2009;11(1):12–24.
- Gfroerer J, Wright D, Kopstein A. Prevalence of youth substance use: the impact of methodological differences between two national surveys. *Drug and Alcohol Dependence* 1997;47(1):19–30.
- Hedges B, Jarvis M. Cigarette smoking. In: Prescott-Clark P, Primatesta P, editors. *Health Survey for England: The Health of Young People, '95–97*. London: The Stationery Office, 1998:191–221.
- Kann L, Brener ND, Warren CW, Collins JL, Giovino GA. An assessment of the effect of data collection setting on the prevalence of health risk behaviors among adolescents. *Journal of Adolescent Health* 2002;31(4):327–35.
- Kendrick JS, Zahniser SC, Miller N, Salas N, Stine J, Gargiullo PM, Floyd RL, Spierto FW, Sexton M, Metzger RW, et al. Integrating smoking cessation into routine public prenatal care: the Smoking Cessation in Pregnancy project. *American Journal of Public Health* 1995;85(2):217–22.
- Klesges RC, Debon M, Ray JW. Are self-reports of smoking rate biased? Evidence from the Second National Health and Nutrition Examination Survey. *Journal of Clinical Epidemiology* 1995;48(10):1225–33.
- Krumpal I. Determinants of social desirability bias in sensitive surveys: a literature review. *Quality and Quantity* 2013;47(4):2025–47.
- Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. *Monitoring the Future national survey results on drug use, 1975–2015: Volume I, Secondary school students*. Ann Arbor (MI): Institute for Social Research, The University of Michigan, 2016.
- National Cancer Institute. Dispelling myths about nicotine replacement therapy, n.d.a; <<https://smokefree.gov/sites/default/files/pdf/mythsaboutNRTfactsheet.pdf>>; accessed: March 20, 2019.
- National Cancer Institute. Survey instruments, n.d.b; <<https://hints.cancer.gov/instrument.aspx>>; accessed: August 15, 2017.
- Office on Smoking and Health, American Legacy Foundation, CDC Foundation, Macro International, State Youth Tobacco Survey Coordinators. Youth tobacco surveillance—United States, 2000. *Morbidity and Mortality Weekly Report Surveillance Summaries* 2001;50(4):1–84.
- Persoskie A, Nelson WL. Just blowing smoke? Social desirability and reporting of intentions to quit smoking. *Nicotine and Tobacco Research* 2013;15(12):2088–93.

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- Ryan H, Trosclair A, Gfroerer J. Adult current smoking: differences in definitions and prevalence estimates—NHIS and NSDUH, 2008. *Journal of Environmental and Public Health* 2012;2012:918368.
- Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, King BA. Tobacco use among middle and high school students—United States, 2011–2015. *Morbidity and Mortality Weekly Report* 2016;65(14):361–7.
- Tourangeau R, Yan T. Sensitive questions in surveys. *Psychological Bulletin* 2007;133(5):859–83.
- Tourangeau R, Yan T, Sun H, Hyland A, Stanton CA. Population Assessment of Tobacco and Health (PATH) reliability and validity study: selected reliability and validity estimates. *Tobacco Control* 2018.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1994.
- Velicer WF, Prochaska JO, Rossi JS, Snow MG. Assessing outcome in smoking cessation studies. *Psychological Bulletin* 1992;111(1):23–41.
- Wong SL, Shields M, Leatherdale S, Malaisson E, Hammond D. Assessment of validity of self-reported smoking status. *Health Reports* 2012;23(1):47–53.

Chapter 3

New Biological Insights into Smoking Cessation

Introduction 125

Cell and Molecular Biology of Nicotine Addiction 125

Literature Review Methods 125

Neurobiology of Nicotine Addiction 125

 Nicotinic Acetylcholine Receptors 126

 Nicotine Reward 128

 Nicotine Withdrawal and Relapse 128

 Animal Models of Nicotine Addiction 129

Molecular Targets of Current Pharmacotherapies 129

Novel Targets for Smoking Cessation 131

 Glutamatergic Signaling 131

 Neuropeptide Systems 132

 The Habenulo-Interpeduncular Pathway 135

Vaccines and Other Immunotherapies as Treatments for Nicotine Addiction 137

Literature Review Methods 137

Design and Mechanism of Action 137

Examining Data from Animals to Confirm Vaccine Activity 138

Clinical Trials of Nicotine Vaccines 138

Next-Generation Vaccines 138

Combining Vaccines with Medications 139

Passive Immunization with Monoclonal Antibodies or Gene Transfer 139

Summary 139

Insights into Smoking Cessation from the Field of Neurobiology 139

Literature Review Methods 140

Methodology of Neuroimaging Studies 141

Differences in Brain Circuitry and Cognitive Constructs in Nicotine Dependence 141

Smoking Cues and Craving Provocation 142

Reward 143

Cognition and Cognitive Control 143

Insights from Neuroimaging for Antismoking Messages 144

Neuronal Circuits and Networks 144

Molecular Imaging 146

Summary 147

Genetic Studies of Smoking Phenotypes 147

Literature Review Methods 148

Candidate Gene Studies 148

Genomewide Association Studies 148

 Examples of Biologically Promising Candidate Genes (*DRD2* and *DAT1*) 148

 Associations Between the *DRD2* and *DAT1* Genes and Smoking Behavior 149

The Moderating Effect of <i>DRD2</i> and <i>DAT1</i> on the Efficacy of Treatment for Smoking Cessation	149
Genetic Risk Scores	149
Examples of Biologically Promising Genes That May Help Optimize Treatment	150
The <i>CHRNA5-A3-B4</i> Gene Cluster	150
Associations with Nicotine Dependence and Smoking Intensity	150
<i>CHRNA5-A3-B4</i> Variants and Smoking Cessation in Absence of Treatment	151
<i>CHRNA5-A3-B4</i> Variants and Smoking Cessation with Pharmacotherapy	151
The <i>CYP2A6</i> Gene and the Nicotine Metabolite Ratio	153
Nicotine Metabolite Ratio and Smoking Behavior	153
Nicotine Metabolite Ratio and Smoking Cessation in Absence of Treatment	154
Smoking Cessation in Treatment Seekers	154
Summary	154
Summary of the Evidence	155
Conclusions	157
References	158

Introduction

The 1988 Surgeon General's report on nicotine addiction was the first in this series to conclude that "[n]icotine is the drug in tobacco that causes addiction" (U.S. Department of Health and Human Services [USDHHS] 1988, p. 9). The biologic mechanisms underlying nicotine addiction continue to be a subject of great research interest, and several promising pharmacotherapeutic targets have emerged. For example, acquisition of basic knowledge about the function of nicotinic acetylcholine receptors (nAChRs) led to the development of targeted smoking cessation medications currently in use, and research would benefit from an additional understanding of molecular mechanisms (USDHHS 2010). The 2010 Surgeon General's report on how tobacco causes disease described the pharmacokinetics of nicotine, the behavioral pharmacology of nicotine addiction, and the known genotypes and receptor subtypes that contribute to nicotine addiction (USDHHS 2010). This chapter focuses on how biology can influence smoking cessation and reviews four areas of intensive research since the publication of the 2010 Surgeon General's report.

1. **Cell and molecular biology of nicotine addiction** focuses on the nAChRs as the primary target of currently available medications and on the following potential targets for medication development: glutamatergic signaling, neuropeptide systems, habenulo-interpeduncular pathway, and noradrenergic system. This section describes the preclinical basis for

understanding nicotine addiction and the ways that this knowledge could be used to enhance smoking cessation.

2. **Vaccines and other immunotherapies as treatments for tobacco addiction** focuses on the conceptual basis of vaccine treatment, vaccine mechanistic design, and vaccine animal studies; progress made and barriers encountered with the early generation vaccines; and approaches to next-generation treatments and passive immunization.
3. **Insights into smoking cessation from the field of neurobiology** describes the brain circuitry involved in nicotine dependence, as understood primarily through advances in brain imaging techniques; the role of stress, craving, and reward; and changes in cognitive control. Findings provide insight into the effects of smoking on the brain and the potential to identify new types of targets for smoking cessation.
4. **Genetic studies of smoking phenotypes** focuses on the further mechanistic understanding gained from the interindividual differences that genetics creates and from some of the methodologic approaches that can be used to examine genetics in humans. Findings provide insight into distinct classes of genes that represent potential targets for novel smoking cessation therapeutics and optimizing choice of treatment.

Cell and Molecular Biology of Nicotine Addiction

Literature Review Methods

For this section of the chapter, PubMed was searched in January 2017 for studies published between 2010 and 2017 that focused on the neurobiologic mechanisms underlying nicotine addiction in model organisms and in human subjects. Such search teams included "nACh" and "nicotinic receptor," and these terms were combined with such terms as "addiction" and "behavior." Studies about nicotinic acetylcholine receptor mechanisms that were cited in these articles were also reviewed to identify primary research articles. These studies and a current search of clinical trials websites were used to identify molecular targets for the development of novel smoking cessation

aids and ongoing clinical trials of relevant therapeutic agents. One reviewer conducted a full review and identified 76 articles for this section. The cited references for preclinical work represent a compilation of the current knowledge base obtained from rodent studies, but the base cannot be considered completely comprehensive because of the large volume of studies in this area.

Neurobiology of Nicotine Addiction

Nicotine, the main addictive constituent of cigarette smoke, binds to nAChRs, a class of ligand-gated ion channels that, following the binding of acetylcholine or

nicotine, open and allow the trafficking of cations (positive ions [e.g., Ca^{++} , Na^+ , K^+]) (USDHHS 2010). nAChRs play an important role in transmitter release, cell excitability, and neuronal integration. Through these processes, nicotine stimulates the release of many different neurotransmitters throughout the brain. In particular, nicotine activates the mesocorticolimbic dopamine system, which can induce both reward or aversion (USDHHS 2010).

The mesocorticolimbic system, which is characterized by the ventral tegmental area (VTA) located in the midbrain, transmits dopamine to two main targets: one cortical, the prefrontal cortex (PFC); and one limbic, the nucleus accumbens (NAc) in the ventral striatum (Figure 3.1). Nicotine increases extracellular dopamine in all of these structures but mainly in the NAc. The reward associated with the release of dopamine is one of the underlying mechanisms of the development of nicotine dependence. In fact, the dopaminergic pathway is targeted by existing pharmacotherapies for smoking cessation. At present, the approved pharmacologic treatments in the United States or Europe are nicotine replacement therapy (NRT), varenicline, and bupropion (U.S. Food and Drug Administration [FDA] 2016). Varenicline (trade names: Chantix, Champix) partially blocks the $\alpha 4\beta 2$ nAChRs, and bupropion (trade names: Wellbutrin, Zyban) is a norepinephrine/dopamine reuptake inhibitor that also can decrease the function of nAChRs by acting as an antagonist of the receptors (Mansvelder et al. 2007). These two medications act indirectly and directly on the dopamine pathway.

Nicotinic Acetylcholine Receptors

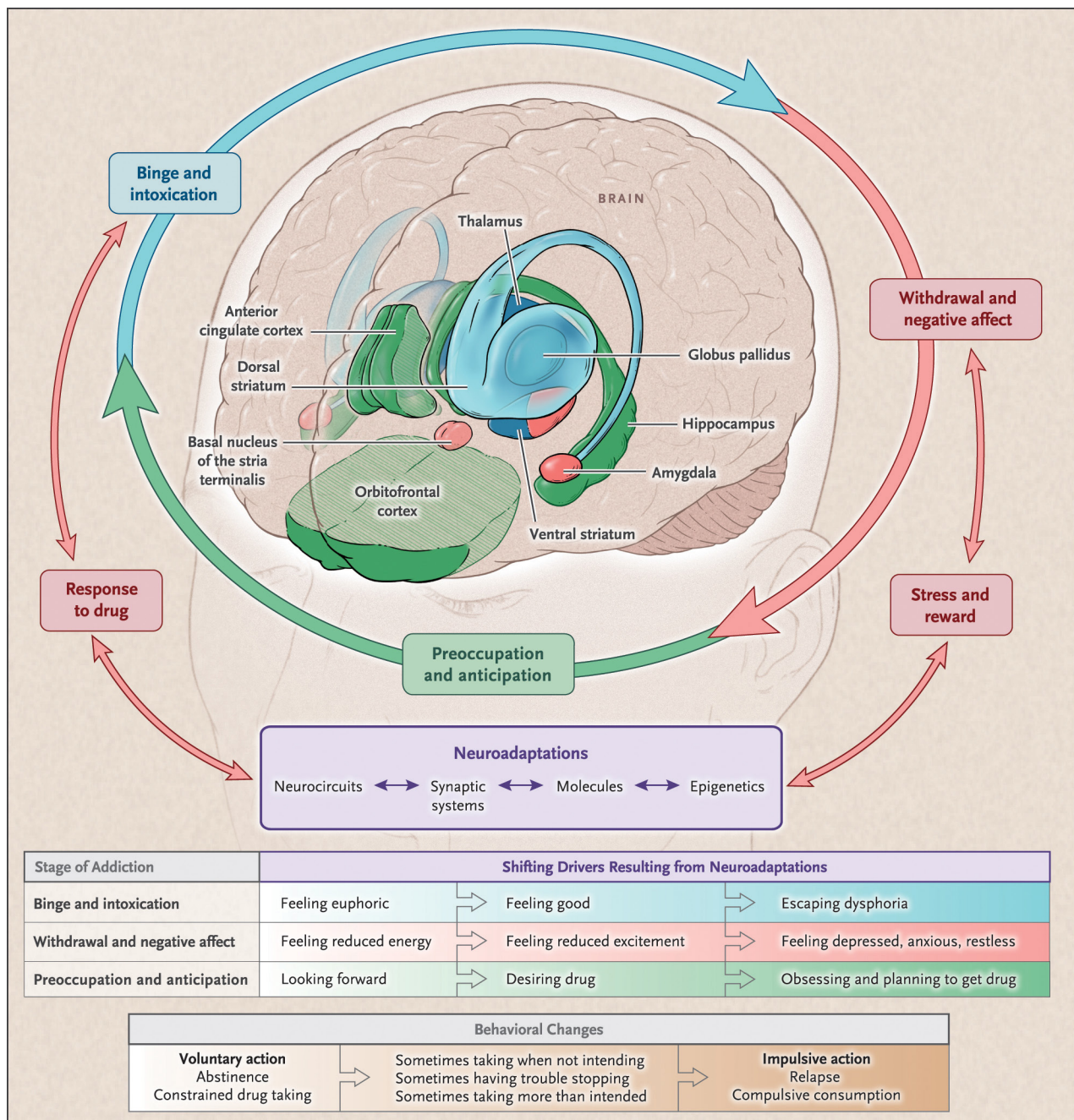
nAChRs are ion channels that normally are activated by the neurotransmitter acetylcholine, but the nicotine in tobacco products “hijacks” nAChRs. In humans, these receptors are assembled from combinations of 17 known subunits, 12 of which are expressed in the brain ($\alpha 2$ – $\alpha 10$ and $\beta 2$ – $\beta 4$) (Picciotto et al. 2008; Picciotto and Kenny 2013). Importantly, co-assembly of specific combinations of subunits results in a set of nAChR subtypes that vary in their properties, location in the brain, and sensitivity to nicotine (Figure 3.2). For example, $\alpha 7$ can form a functional nAChR on its own [$(\alpha 7)^5$], while all other nAChRs contain at least one α subunit and one β subunit [e.g., $(\alpha 4)^2(\beta 2)^3$]. The $\alpha 4$ and $\beta 2$ subunits, which are expressed throughout the brain and body in many types of cells, nearly always assemble together, sometimes with additional subunits, and their interface forms a high-affinity nicotine binding site (Kutlu and Gould 2016). Activation of these $\alpha 4$ - and $\beta 2$ -containing receptors is required for many of the neurobiologic and behavioral effects associated with nicotine reward. The $\alpha 6$ subunit also can associate selectively with

these receptors in dopamine and norepinephrine neurons (Kutlu and Gould 2016).

Nicotine and the endogenous ligand acetylcholine bind to the extracellular interface between two nAChR subunits. Upon binding of either nicotine or acetylcholine, the receptors undergo a structural change that causes the ion channel to open, permitting the influx of cations and membrane depolarization. Cellular responses to nicotine depend on the composition of nAChR subunits and their subcellular localization. For example, activation of nAChRs located on nerve terminals stimulates the release of neurotransmitters, and activation of cell body receptors increases neuronal excitability and can induce action potentials. Nicotine also binds to intracellular receptors in the endoplasmic reticulum and promotes their assembly and trafficking. Long-term exposure to nicotine increases the surface expression of nAChRs, particularly the high-affinity $\alpha 4$ - and $\beta 2$ -containing receptors. Cells in the brains of smokers, therefore, have an increased capacity for nicotine binding, which may result in altered neuronal signaling once nicotine is cleared from the brain and these nAChRs become available for acetylcholine signaling. In fact, heightened expression of nAChRs is observed in the brains of smokers for weeks following cessation; this might contribute to craving and withdrawal symptoms (Cosgrove et al. 2012). Although low levels of nicotine activate nAChRs, leading to nicotine reinforcement, continued exposure to nicotine desensitizes the receptors, which contributes to tolerance. The extent of desensitization varies with the composition of receptors and concentration of nicotine. $\beta 2$ subunit-containing nAChRs, which are required for the rewarding effects of nicotine, desensitize rapidly in response to very low concentrations of nicotine (Picciotto et al. 2008). $\alpha 7$ receptors, however, will continue to respond in the presence of sustained low concentrations of nicotine.

The physiologic consequences of nAChR desensitization are complex and not entirely understood, but chronic exposure to nicotine in the brains of users of tobacco products likely results in phases of activation and desensitization of nAChRs that contribute to nicotine reinforcement and tolerance, respectively. The variability in this balance also may contribute to individual differences in susceptibility to nicotine addiction. In addition, receptors are reactivated once nicotine is removed from the system. Thus, increases in the number of nAChRs and receptor reactivation when nicotine is cleared from the system that last at least 4 weeks after cessation (Cosgrove et al. 2012) result in robust potentiation of nAChR signaling following abstinence, which then contributes to withdrawal symptoms (Millar and Harkness 2008; Picciotto et al. 2008; Changeux 2010).

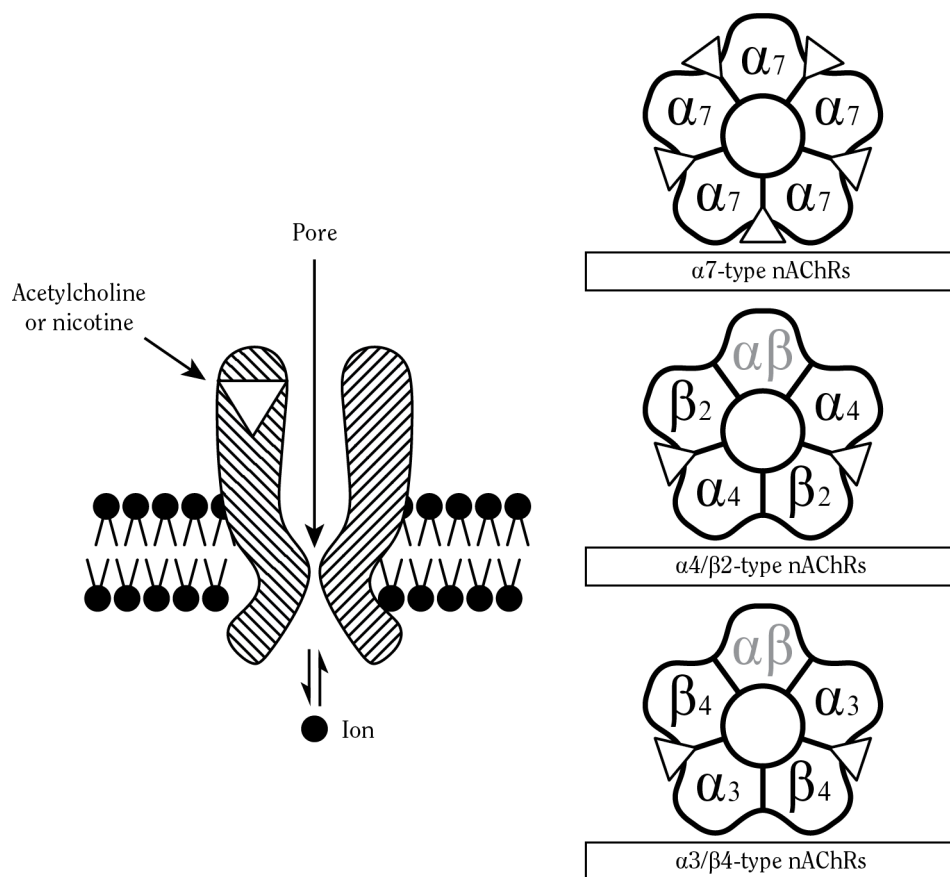
Figure 3.1 Stages of the addiction cycle



Source: From Volkow and colleagues (2016, p. 365). Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Notes: “Binge and intoxication” and “feeling euphoric” are not relevant to nicotine. “During intoxication, drug-induced activation of the brain’s reward regions (in blue) is enhanced by conditioned cues in areas of increased sensitization (in green). During withdrawal, the activation of brain regions involved in emotions (in pink) results in negative mood and enhanced sensitivity to stress. During pre-occupation, the decreased function of the prefrontal cortex leads to an inability to balance the strong desire for the drug with the will to abstain, which triggers relapse and reinitiates the cycle of addiction. The compromised neurocircuitry reflects the disruption of the dopamine and glutamate systems and the stress-control systems of the brain, which are affected by corticotropin-releasing factor and dynorphin. The behaviors during the three stages of addiction change as a person transitions from drug experimentation to addiction as a function of the progressive neuroadaptations that occur in the brain” (Volkow et al. 2016, p. 365).

Figure 3.2 Structure and properties of nAChRs



Source: Created by Marina Picciotto and Megan Miller, Yale University School of Medicine, for this Surgeon General’s report.

Notes: α = alpha; β = beta; nAChR = nicotinic acetylcholine receptor. nAChRs in the brain assemble as pentameric (5-member) structures from 12 subunits: $\alpha 2$ – $\alpha 10$ and $\beta 2$ – $\beta 4$. The most common combinations are formed as homomers (all subunits the same) of the $\alpha 7$ subunit, or heteromers of the $\alpha 4$ and $\beta 2$, or $\alpha 3$ and $\beta 4$ subunits. Many subunit combinations with different properties are possible, with variability particularly at the fifth position in the receptor (indicated in grey as a choice of α or β subunit in this figure). Assembled receptors form a channel through the membrane, with a pore that is closed under resting conditions. The neurotransmitter acetylcholine normally binds to interfaces between subunits in the assembled nAChRs, activating the receptors and allowing ions to flow through the opened pore into cells expressing them. Nicotine binds to the same site in the nAChR as acetylcholine and can open the channel, although with different open times and likelihood of desensitization.

Nicotine Reward

As for all drugs of abuse, the primary reinforcing (i.e., initial rewarding or addictive) effects of nicotine are driven by its activation of the mesolimbic dopamine system, commonly known as the brain’s reward circuit. Nicotine promotes phasic firing of dopamine neurons in the VTA through several nAChR-mediated mechanisms (USDHHS 2010). Activation of $\alpha 4$ - and $\beta 2$ -containing nAChRs on dopamine cell bodies increases their excitability and is required for the reinforcing properties of nicotine. Nicotine also acts through $\alpha 7$ nAChRs located on glutamatergic terminals in the VTA to promote glutamate

release onto dopamine neurons, further enhancing their excitation (USDHHS 2010). Similarly, nicotine stimulation of nAChRs made of the $\alpha 4$, $\beta 2$, and $\alpha 6$ subunits that are found on dopamine terminals promotes the release of dopamine in NAc and other regions (Picciotto and Kenny 2013; Wickham et al. 2013; Picciotto and Mineur 2014).

Nicotine Withdrawal and Relapse

Chronic nicotine use can induce a physical dependence severe enough that cessation induces a series of negative withdrawal symptoms in humans and in laboratory animals (Picciotto et al. 2008; USDHHS 2010). Thus,

in addition to being drawn to the primary reinforcing properties of nicotine, many persons return to smoking to avoid negative effects of abstinence, such as irritability, anxiety, depression, insomnia, and difficulty concentrating. Additionally, environmental cues (sights, sounds, or other sensations) associated with nicotine often elicit drug cravings that can be sufficient to induce relapse to regular smoking after a quit attempt (USDHHS 2010). For example, former smokers who used to have a cigarette with their morning coffee may experience intense nicotine cravings at the smell of coffee, which could trigger relapse to smoking (Bevins and Palmatier 2004). Importantly, drug-paired cues (things in the environment that are associated with nicotine being on board) can become themselves reinforcing after repeated pairings, and this conditioned reinforcement may be at least partially responsible for continuing drug use and relapse. Mechanistically, perseverative drug use and high relapse rates happen because of persistent neurobiologic adaptations (tolerance), particularly within the mesocorticolimbic dopamine system. Thus, although developing therapies aimed at reducing the reinforcing properties of nicotine itself is reasonable, this strategy is unlikely to be completely effective in combating relapse to smoking (USDHHS 2010). For this reason, several research efforts have focused on elucidating the neurobiologic underpinnings of relapse.

Animal Models of Nicotine Addiction

Studies of animal models of disease have contributed to much of our understanding of the neurobiologic basis of nicotine addiction. Although animal models cannot capture the full range of human addiction, mice and rats do develop addiction-like behaviors, and several reliable paradigms have been established to measure specific aspects of the disease in animals. The drugs that animals self-administer correspond well with drugs that have high abuse liability in humans (Carter and Griffiths 2009). As described in detail below, nicotine-dependent animals will work to obtain nicotine and to relieve nicotine withdrawal symptoms (Koob and Simon 2009). Therefore, animal models are useful for measuring the abuse liability of addictive drugs, such as nicotine, and identifying pharmacotherapies that make addictive drugs less reinforcing or that mitigate withdrawal symptoms.

Modeling Nicotine Reward

The conditioned place preference (CPP) and self-administration paradigms are two common models used to evaluate nicotine reinforcement and drug-seeking behavior. CPP is established by repeatedly pairing nicotine administration with exposure to a particular environmental

context. Over time, the animal learns to associate the context with nicotine and develops a preference for that environment over an adjacent, similar environment that is not paired with nicotine. The development of such a preference is considered to be an indication of the rewarding effects of the drug.

In the self-administration model, animals are trained to complete an operant task, such as pressing a lever to receive an infusion of nicotine. Once the task is learned, changes in operant behavior are thought to indicate changes in drug reinforcement or craving. Variations of this task also can be used to measure motivation (i.e., how hard an animal is willing to work for nicotine), extinction, and relapse. Interestingly, self-administration of nicotine is more robust if infusion is paired with a cue versus with the drug alone (Caggiula et al. 2001).

Modeling Nicotine Withdrawal and Relapse

Human smokers often relapse in response to one of three stimuli: exposure to environmental cues associated with nicotine, aversive or stressful life events, or a small amount of the drug (i.e., a “lapse”) (USDHHS 2010). Each of these types of stimuli is also sufficient to induce reinstatement of nicotine-seeking behavior in rodents after forced extinction of the behavior. In the cue-induced reinstatement model, animals are trained to self-administer nicotine that is paired with an innocuous cue, such as a light or a tone. After self-administration of nicotine is acquired, the operant behavior can be extinguished by placing the animals in the same context but in the absence of the drug and the associated cue. Following extinction, animals will resume responding to the cue alone, even in the absence of nicotine. Similar paradigms have been developed to model stress-induced reinstatement and drug-induced reinstatement in animals, all of which may be valid for nicotine relapse in humans (Mantsch et al. 2016). Preclinical studies using these paradigms have been useful in identifying cellular and molecular processes that contribute to drug reinstatement, as discussed in this section.

Molecular Targets of Current Pharmacotherapies

As a consequence of our understanding of the neurobiology of nicotine addiction, several successful pharmacotherapies have been developed to aid in smoking cessation (Table 3.1) (Cochrane Tobacco Addiction Group n.d.), most of which alter nAChR signaling (Cahill et al. 2013, 2016). These include varenicline (a partial agonist of nAChRs) and bupropion (an atypical antidepressant with the ability to block nAChRs). Various forms of NRT—including

Table 3.1 Current pharmacotherapies for smoking cessation

Line	Trade name(s)	Target	Action	FDA approved for smoking cessation: Yes/no	Other information
First-line					
Bupropion	<ul style="list-style-type: none"> Wellbutrin Elontril Zyban 	Catecholamine system/nAChRs (multiple subtypes)	Norepinephrine or dopamine reuptake inhibitor/nAChR antagonist	Yes	Atypical antidepressant; also approved for ADHD and obesity
NRT	<ul style="list-style-type: none"> Nicoderm Commit Nicorette Others 	nAChRs (multiple subtypes)	Agonist	Yes	—
Varenicline	<ul style="list-style-type: none"> Chantix Champix 	nAChRs (multiple subtypes)	Partial agonist	Yes	—
Second-line					
Nortriptyline	<ul style="list-style-type: none"> Sensoval Aventyl Pamelor Norpress Allegron Noritren Nortrilen 	Serotonin and norepinephrine systems	Serotonin or norepinephrine reuptake inhibitor	No	Tricyclic antidepressant
Clonidine	<ul style="list-style-type: none"> Catapres Kapvay Duraclon Nexiclon 	Adrenergic receptors	Agonist	No	Also indicated for high blood pressure, ADHD, anxiety, migraine, withdrawal (opiates, alcohol, and nicotine), and other
Others					
Cytisine	<ul style="list-style-type: none"> Tabex 	nAChR	Partial agonist	No	Popular in Eastern Europe but not available in the United States; relatively inexpensive
Naltrexone	<ul style="list-style-type: none"> Revia Vivitrol 	Opioid receptors (μ , κ)	Antagonist	No	Commonly used to treat alcoholism and opioid dependence

Notes: κ = kappa; μ = mu; **ADHD** = attention-deficit/hyperactivity disorder; **FDA** = U.S. Food and Drug Administration; **nAChR** = nicotinic acetylcholine receptor; **NRT** = nicotine replacement therapy.

the patch, gums, lozenges, and nasal sprays—also act on nAChRs. Varenicline activates nAChRs, although to a lesser extent than nicotine, and blocks the binding of nicotine from tobacco to the nAChR, thereby resulting in reduced withdrawal symptoms and less reward from a lapse to smoking. Although not currently approved for use in the United States, cytisine is another nAChR partial agonist and has been used as an herbal smoking cessation aid for decades in Eastern European countries and Canada (Gómez-Coronado et al. 2018). Repeated efficacy

studies, including a Phase 3 clinical trial in New Zealand, have found cytisine to be effective for smoking cessation at levels similar to varenicline (Etter 2006). Because cytisine is a naturally occurring compound, it is less expensive than currently available cessation aids, making it a potentially promising tool for reducing smoking rates in certain populations, including low-income individuals. With withdrawal-induced negative affect a major problem for smokers trying to quit, antidepressants are often prescribed, and several of these drugs have shown efficacy

in reducing smoking (Hughes et al. 2014). Bupropion can alleviate withdrawal symptoms and reduce the severity of nicotine cravings. Overall, its efficacy for cessation is about double that of placebo (Wu et al. 2006). Notably, bupropion is also an nAChR antagonist that alters nicotine-mediated dopamine responses, which likely contributes to its efficacy in reducing smoking (Mansvelder et al. 2007). Although it has not been approved by FDA for smoking cessation, nortriptyline (trade names: Sensoval, Pamelor, Aventyl, and others), a tricyclic antidepressant and serotonin/norepinephrine reuptake inhibitor, also has shown off-label efficacy in improving rates of smoking cessation (Hughes et al. 2005).

Novel Targets for Smoking Cessation

Glutamatergic Signaling

Although enhanced dopamine signaling is critical for the initial reinforcing properties of nicotine, both the maintenance and reinstatement of nicotine-seeking behavior require long-lasting alterations in the actions of glutamate, the major excitatory neurotransmitter in the brain (Knackstedt and Kalivas 2009; Li et al. 2014; Marchi et al. 2015). Glutamate levels are elevated in both the NAc and the VTA after exposure to nicotine, and glutamate inputs to the VTA mediate the increases in the activity of dopamine neurons in response to nicotine. Repeated exposure to nicotine results in a long-term potentiation (or long-lasting increase in activation) of these synapses, which contributes to elevated excitability of dopamine neurons. Furthermore, sustained low levels of nicotine, as would be observed in the brains of smokers, can desensitize nAChRs located on inhibitory nerve terminals in the VTA. This may reduce the inhibition of dopamine neurons, further shifting the excitatory–inhibitory balance in the VTA. Nicotine dependence also is associated with long-term potentiation of glutamate synapses in the NAc, and disruption of glutamate signaling in this region alters nicotine-mediated physiology and behavior. Thus, chronic use of nicotine causes long-lasting changes to the mesolimbic dopamine system, many of which are driven by alterations in glutamate transmission. Behaviorally, these adaptations sustain drug cravings and contribute to a vulnerability to relapse. Glutamate binds to and activates two types of receptors: ionotropic, which are ion channels that allow current to pass through and activate cell membranes; and metabotropic, which are G-protein-coupled receptors that activate downstream cell signaling cascades. Neuroadaptive mechanisms in the glutamate system, perhaps on both types of glutamate receptors, may be targets for pharmacologic intervention.

Ionotropic Glutamate Receptors

Glutamate signaling through the ionotropic glutamate receptors N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is implicated in the neurobiologic mechanisms of nicotine dependence (Li et al. 2014; D'Souza 2015). Pharmacologic blockade of both NMDA and AMPA receptors in the VTA attenuates nicotine-induced dopamine release in the NAc, and inhibition of NMDA receptors impairs nicotine-seeking behaviors (Kenny et al. 2009; Mao et al. 2011). Conversely, blockade of NMDA receptors in the shell region of the NAc increases the self-administration of nicotine, suggesting that glutamatergic transmission in this region may offset the rewarding effects of nicotine (D'Souza and Markou 2014). The mechanisms underlying this effect are not fully understood, but one hypothesis is that medium spiny neurons in the shell region of the NAc are activated by glutamate, and these medium spiny neurons project to and inhibit dopamine neurons in the VTA (Yang et al. 2018). Regardless, glutamatergic signaling in mesocorticolimbic regions clearly contributes to nicotine reinforcement.

Gipson and colleagues (2013) demonstrated that long-lasting changes in glutamate signaling are central to post-withdrawal reinstatement of nicotine-seeking behavior in rats. Long-term potentiation of glutamatergic synapses in the NAc was apparent after 2 weeks of nicotine withdrawal, with further strengthening observed following cue-induced reinstatement of nicotine seeking. Furthermore, blocking the function of NMDA receptors in the core region of the NAc prevented cue-induced reinstatement of nicotine-seeking behavior. Similar observations have been made with other drugs of abuse, such as cocaine and alcohol. These data suggest that dampening mesolimbic glutamate signaling, potentially by inhibiting the function of NMDA receptors in the core of the NAc, may be a useful strategy for reducing vulnerability to smoking relapse in humans.

Although blockade of ionotropic glutamate receptors is effective in reducing addiction-like behaviors in animal models, systemic use of these drugs in humans is likely not feasible using current pharmacologic agents, given the crucial role of glutamate in the function of the nervous system. Also, because glutamate plays different roles in different regions of the brain, a more targeted, region-specific approach is warranted.

Metabotropic Glutamate Receptors

Metabotropic glutamate receptors (mGluRs) are widely expressed, G-protein-coupled receptors that use second-messenger systems (key distributors of an external signal) to modulate neuronal excitability. Two of these receptors, mGluR5 and mGluR2, have been implicated in

the neurobiology of nicotine addiction. Because pharmacologic manipulation of metabotropic glutamate signaling may have a more subtle effect on the function of the nervous system than do ionotropic drugs, targeting these receptors may be a more feasible clinical approach for smoking cessation (D'Souza 2015; Mihov and Hasler 2016; Acri et al. 2017; Chiamulera et al. 2017). Table 3.2 summarizes novel pharmacologic targets for smoking cessation.

mGluR5. mGluR5 is localized postsynaptically where it signals through the excitatory G-protein $G\alpha_s$, to enhance neuronal excitability. Reducing the function of mGluR5 with MPEP (2-methyl-6-(phenylethynyl pyridine), a negative allosteric modulator (NAM) in the NAc shell, attenuates nicotine self-administration and dopamine release (Paterson et al. 2003; Tronci et al. 2010), suggesting a role for this receptor in the primary reinforcing properties of nicotine. Additionally, both drug- and cue-induced reinstatement of nicotine-seeking behavior are reduced in animals that have been pretreated with mGluR5 antagonists (Bespalov et al. 2005). In humans, studies using selective mGluR5 radiotracers have revealed a significant reduction of binding sites in the brains of persons addicted to nicotine, which is normalized after cessation (Akkus et al. 2013; Hulka et al. 2014). The mechanism for this reduction is not entirely understood, but it may be a compensatory action meant to limit aberrant glutamate signaling in the brains of smokers.

The preclinical efficacy of mGluR5 NAMs in reducing drug-seeking behavior is well documented, but higher doses of the same drugs also have been reported to impair food-seeking behaviors in animals (Mihov and Hasler 2016). Although the curbing of appetite during smoking cessation may seem like an appealing side effect, such overly generalized effects may be dangerous or undesirable. mGluR5 NAMs also have been shown to increase the severity of nicotine withdrawal symptoms (Chiamulera et al. 2017), which could limit their feasibility for clinical use.

mGluR2. In contrast to mGluR5, mGluR2 is expressed on presynaptic glutamate terminals, acting as an autoreceptor that inhibits the release of this neurotransmitter. Therefore, dopamine neurons can be inhibited by the activation of mGluR2 receptors on glutamatergic inputs to the VTA.

Stimulation with the nonselective mGluR2/3 agonist LY379268 can reduce drug- and cue-induced reinstatement of nicotine responding, and these effects can be blocked by an mGluR2 antagonist (Justinova et al. 2016). mGluR2/3 stimulation also can reduce the primary reinforcing properties of nicotine, but these effects are smaller and less consistent than the effects on reinstatement. In nicotine-experienced rats, LY379268 reduced nicotine-induced increases in dopamine levels in the NAc only in the presence of drug-predicting cues (D'Souza et al. 2011),

supporting the hypothesis that mGluR2/3 stimulation is more effective at reducing the conditioned effects of nicotine than its primary reinforcing effects.

Although a selective mGluR2 positive allosteric modulator (PAM) was not shown to improve schizophrenia symptoms in a Phase 2 clinical trial, it has been repurposed as a possible therapy for nicotine addiction because of its good safety profile and preclinical efficacy in reducing nicotine reinstatement (Justinova et al. 2015). A Phase 2 clinical trial of this drug for smoking cessation was completed in January 2017, but results are not yet available. This study enrolled 210 female cigarette smokers and evaluated abstinence from nicotine as a primary endpoint. Although GluR5 and GluR2 have been linked to addiction-like behaviors in animals, Acri and colleagues (2017) argued that mGluR2 may be a more feasible drug target because of its relatively mild side-effect profile compared with mGluR5 antagonists.

Glutamate Transporters

Alterations in the function of glutamate transporters also contribute to nicotine-mediated disruptions in the excitatory–inhibitory balance. Mesocorticolimbic expression of glutamate transporter 1 (GLT-1), the cystine/glutamate exchanger, and excitatory amino acid transporter 3 are all decreased after chronic administration of nicotine in rodents (Knackstedt and Kalivas 2009; Knackstedt et al. 2009; Yoon et al. 2014). In addition, reinstatement of nicotine-seeking behavior is associated with decreased expression of GLT-1 and elevated concentration of extracellular glutamate (Gipson et al. 2013). In mice, upregulation of GLT-1 with ceftriaxone had no effect on CPP acquisition but reduced withdrawal symptoms and significantly attenuated nicotine-primed reinstatement of nicotine CPP (Alajaji et al. 2013). Stimulating cystine/glutamate exchanger activity with N-acetylcysteine also may be effective in reducing nicotine consumption. An open-label pilot study of a combination therapy of varenicline and N-acetylcysteine showed a favorable safety profile. Although the study was not designed to evaluate differences in cessation efficacy, patients receiving both therapies smoked fewer cigarettes than those receiving only varenicline (McClure et al. 2015). In addition, a double-blind, randomized controlled trial (RCT) found that, in combination with group behavioral therapy, N-acetylcysteine was effective in reducing the number of cigarettes smoked and in increasing quit rates versus a placebo control group (Prado et al. 2015).

Neuropeptide Systems

Neuropeptides are a class of short-chain polypeptides that serve as neurotransmitters (Table 3.2). Acting

Table 3.2 Novel pharmacologic targets for smoking cessation

Target	Pharmacology	Expected neurobiologic effect	Expected behavioral outcome	Stage of drug development	Other information
Glutamate system					
mGluR5	NAM	<ul style="list-style-type: none"> Decreased Glu transmission 	<ul style="list-style-type: none"> Decreased nicotine intake Decreased relapse vulnerability 	Preclinical	—
mGluR2	PAM	<ul style="list-style-type: none"> Decreased Glu transmission 	<ul style="list-style-type: none"> Decreased relapse vulnerability Decreased nicotine intake 	Phase 2	—
GLT-1	Agonist	<ul style="list-style-type: none"> Decreased Glu transmission 	<ul style="list-style-type: none"> Decreased relapse vulnerability 	Preclinical	—
xCT	Agonist (N-acetylcysteine)	<ul style="list-style-type: none"> Decreased Glu transmission 	<ul style="list-style-type: none"> Decreased nicotine intake 	Phase 2	—
Neuropeptides					
CRF-1	Antagonist (Paxacerfont)	<ul style="list-style-type: none"> Decreased reactivity to withdrawal Decreased dopamine response 	<ul style="list-style-type: none"> Decreased relapse vulnerability Decreased nicotine intake 	Preclinical	Failed Phase 2 anxiety trial
DOR	Antagonist	<ul style="list-style-type: none"> Decreased dopamine response 	<ul style="list-style-type: none"> Decreased nicotine intake 	Preclinical	Naltrexone is a non-selective opioid receptor antagonist used to treat alcoholism and opioid dependence
KOR	Antagonist	<ul style="list-style-type: none"> Decreased reactivity to withdrawal 	<ul style="list-style-type: none"> Decreased relapse vulnerability 	Preclinical	Naltrexone is a non-selective opioid receptor antagonist used to treat alcoholism and opioid dependence
MHb-IPN pathway					
α 5	PAM	<ul style="list-style-type: none"> Increased nicotine-mediated MHb-IPN activation 	<ul style="list-style-type: none"> Decreased nicotine intake 	Preclinical	—
Noradrenergic system					
α 1	Antagonist	<ul style="list-style-type: none"> Decreased norepinephrine signaling 	<ul style="list-style-type: none"> Decreased nicotine intake Decreased relapse vulnerability 	—	—
α 2	Agonist (clonidine)	<ul style="list-style-type: none"> Decreased norepinephrine signaling 	<ul style="list-style-type: none"> Decreased relapse vulnerability 	Off-label use	Potent side effects include sedation and low blood pressure

Notes: α = alpha; **CRF** = corticotropin-releasing factor; **DOR** = delta (δ) opioid receptor; **GLT** = glutamate transporter; **KOR** = kappa (κ) opioid receptor; **mGluR** = metabotropic glutamate receptor; **MHb-IPN** = medial habenulo-interpeduncular nucleus; **NAM** = negative allosteric modulator; **PAM** = positive allosteric modulator; **xCT** = cystine/glutamate exchanger.

on designated G-protein-coupled receptors, these molecules can modulate neuronal activities. As outlined in the upcoming sections of this chapter, a substantial amount of preclinical evidence suggests that multiple neuropeptide systems can contribute to the development of nicotine dependence. Additionally, because several neuropeptides can modulate mood, manipulating these systems may be an effective strategy for improving success rates for cessation by reducing the severity of negative withdrawal symptoms. Although at least a dozen neuropeptides have been linked to nicotine dependence, this section focuses on two primary promising targets: corticotropin-releasing factor (CRF) and the opioid system.

Corticotropin-Releasing Factor

CRF is a peptide hormone known best for its role in the stress response. Chronic nicotine administration increases CRF levels in the VTA of rats, and genetic knockdown of this peptide attenuates self-administration of nicotine (Grieder et al. 2014). In addition, blockade of the peptide's receptor, CRF1, in rats prevented the normally observed increase in nicotine self-administration following a period of forced abstinence and prevented the aversive effects of withdrawal (Cohen et al. 2015). In an intracranial self-stimulation paradigm, the sensitivity of the brain reward pathway can be assessed by measuring the intensity of a stimulus required to elicit self-stimulation behavior, such that higher stimulation thresholds indicate a less sensitive reward system. Exposure to nicotine (or other drugs of abuse) causes animals to perform for much less intense stimulation (i.e., they have lower thresholds), indicating a drug-induced potentiation of the reward system. Conversely, a period of abstinence from a drug elicits a large increase in the intracranial self-stimulation threshold, indicating reduced excitability of the reward system and signifying a depression-like brain state (reflected in elevations of brain reward thresholds) (Stoker et al. 2012).

In nicotine-dependent animals, withdrawal-induced increases in the intracranial self-stimulation threshold are absent in animals treated systemically with CRF1 receptor antagonists, or only in the central amygdala, a brain region known to regulate mood (Marcinkiewicz et al. 2009; Bruijnzeel et al. 2012). Similarly, withdrawal-induced, anxiety-like behavior is exacerbated by infusion of CRF into the interpeduncular nucleus (IPN), and blockade of CRF1 alleviates this behavior (Zhao-Shea et al. 2015). Thus, CRF signaling, particularly in the amygdala and IPN, contributes to the negative affect associated with nicotine withdrawal. Lastly, inhibition of the CRF1 receptor can block both stress-induced potentiation of nicotine CPP and stress-induced reinstatement of self-administration (Zislin et al. 2007). Together, these studies suggest that CRF

signaling is central to changes in nicotine-seeking behavior in response to stress. Although clinical data regarding the role of CRF in smoking behavior are not available, many studies in animal models of nicotine dependence suggest that CRF antagonists may be useful for reducing smoking in humans (Bruijnzeel 2017).

Notably, several small-molecule CRF ligands can cross the blood–brain barrier. Although most are being used only for preclinical research, several have been evaluated clinically to treat anxiety and depression. In a clinical trial of 260 patients, Paxacerfont (a CRF1 receptor agonist) was no more effective than placebo for treating generalized anxiety disorder (Coric et al. 2010); however, this drug has not been evaluated for smoking cessation.

The Opioid System

Mounting evidence has implicated the endogenous opioid system in both neurobiologic and behavioral responses to nicotine. The opioid system consists of three G-protein-coupled opioid receptors that are activated by endogenous peptide ligands. Delta (δ) opioid receptors (DORs) are activated primarily by enkephalins; kappa (κ) opioid receptors (KORs) are activated by dynorphins; and mu (μ) opioid receptors (MORs) are activated by β -endorphins. Each of these receptor–ligand pairs appears to play a role in nicotine addiction. Nicotine-induced dopamine release is attenuated in mice lacking DORs, and these animals do not acquire a CPP for nicotine (Berrendero et al. 2012). Genetic ablation or pharmacologic blockade of DORs with naltrindole also substantially reduces self-administration of nicotine (Berrendero et al. 2012). Although DORs do not appear to play an important role in the somatic responses to nicotine (Berrendero et al. 2012), animals treated with the KOR antagonist JDTic have diminished physical and affective nicotine withdrawal symptoms (Jackson et al. 2010a).

Interestingly, KOR activity does not appear to be necessary for the initial reinforcing properties of nicotine (Jackson et al. 2010a), but pharmacologic blockade of the receptor reduces the anxiogenic effects of nicotine withdrawal and prevents stress-induced reinstatement of nicotine-seeking behavior (Jackson et al. 2010a; Nygard et al. 2016). In addition, withdrawal-mediated activation of the amygdala was reduced in mice pretreated with the KOR antagonist norbinaltorphimine (Nygard et al. 2016). Together, these data suggest that DORs and KORs play discrete roles in the physiological and behavioral responses to nicotine. Although DOR contributes to dopamine release and nicotine reinforcement, KOR appears to be more involved in the physiologic effects of nicotine withdrawal.

In humans, MORs have been linked to craving and addiction severity among smokers. Compared with

nonsmoking controls, smokers had fewer available MOR-binding sites in the basal ganglia and thalamus, and the number of binding sites in the basal ganglia was negatively associated with baseline craving levels (Nuechterlein et al. 2016). Additionally, the availability of MOR-binding sites in both the basal ganglia and temporal cortex was inversely correlated with the severity of physical dependence on nicotine, as assessed by the Fagerström Test for Nicotine Dependence (FTND) (Kuwabara et al. 2014; Nuechterlein et al. 2016). Interestingly, a MOR gene variant (OPRM1 A118G) was found to be potentially associated with reduced availability of MOR binding (Nuechterlein et al. 2016).

Naltrexone (trade names: Revia, Vivitrol), a nonselective opioid receptor antagonist, is commonly used to treat alcoholism and opioid dependence. A clinical trial of 121 smokers found that combining naltrexone with bupropion was associated with higher rates of abstinence from smoking after 7 weeks of treatment compared with bupropion alone, but these rates did not differ significantly between the bupropion-plus-placebo group and the bupropion-plus-naltrexone group at 6 months (Mooney et al. 2016). Similarly, a Cochrane review of eight trials showed no effect of naltrexone alone or as an adjunct to NRT (David et al. 2013a).

Finally, preclinical studies have implicated orexin/hypocretin peptides, originally thought to be involved mainly in feeding and arousal but now shown to modulate the rewarding effects of nicotine, as potential therapies for smoking cessation (Plaza-Zabala et al. 2010; Hollander et al. 2012). An orexin/hypocretin receptor 2 polymorphism has been associated with nicotine dependence in human smokers (Nishizawa et al. 2015), and in rats the selective receptor 2 antagonist (2-SORA 18) can block both cue-induced reinstatement of nicotine self-administration and motivation to respond to nicotine cues, as determined by a progressive ratio experiment in which animals had to press a lever exponentially more times to receive each successive nicotine-paired cue (Uslaner et al. 2014). Similarly, the orexin/hypocretin receptor 1 antagonist SB-334867 decreased the reward-enhancing effects of nicotine in rats, as well as their cue-induced reinstatement of nicotine-seeking behaviors (Hollander et al. 2008; Plaza-Zabala et al. 2013). Interestingly, stimulation of nAChRs increased the activity of orexin/hypocretin neurons (Zhou et al. 2015), suggesting that stimulation of this system may contribute to the physiologic effects of nicotine.

Summary

Neuropeptide systems play a role in multiple stages of the addiction process. Experiments in animals have shown that CRF and the opioid system, neuropeptide Y,

hypocretin, galanin, ghrelin, and vasopressin and additional peptides not discussed here are associated with nicotine dependence (Bruijnzeel 2017). Thus, modulating the function of neuropeptides may effectively reduce smoking behavior in humans. Even so, the role that neuropeptide systems play in human addiction should be investigated further. Several drugs targeting neuropeptide receptors are already in use for treatment of other disorders, but none are approved by FDA for use in smoking cessation.

The Habenulo-Interpeduncular Pathway

Aversive Effects of Nicotine

As discussed previously, nicotine stimulates dopamine pathways to generate the rewarding effects that contribute to addiction. At the same time, activation of nAChRs in the brain and elsewhere results in highly aversive effects, such as nausea, dizziness, and irregular heartbeat. In fact, most first-time smokers report a largely unpleasant experience with nicotine, and sensitivity to the aversive effects of cigarette smoke is inversely correlated with the likelihood of developing habitual smoking (Sartor et al. 2010).

Animal studies of nicotine withdrawal and aversion have identified a crucial role for the habenulo-interpeduncular pathway in mediating these responses. The medial habenula (MHb) is composed mostly of cholinergic neurons that also express Substance P and co-release glutamate. MHb neurons project to the IPN, and activation of this circuit is required for many of the negative effects associated with exposure to nicotine, including the sedative effects induced by high concentrations of this chemical and negative symptoms of withdrawal. Furthermore, stimulation of the MHb or IPN reduces the reinforcing properties of nicotine, but disrupting neuronal signaling in these connected brain regions has the opposite effect—resulting in increased self-administration of nicotine in rodents (Fowler and Kenny 2014).

Potential Molecular Targets

Nicotinic receptors are highly expressed on MHb and IPN neurons, and these regions have the highest expressions of $\alpha 3$, $\beta 4$, and $\alpha 5$ nAChR subunits in the brain. Several human genomewide association studies (GWAS) have linked variants in the *CHRNA3-CHRNA5-CHRNB4* gene cluster (genes that encode the $\alpha 3$, $\alpha 5$, and $\beta 4$ nAChR subunits, respectively) to susceptibility to tobacco use, and preclinical studies in rodents have revealed an important role for these subunits in moderating nicotine intake. $\alpha 5$ knockout mice lacking the $\alpha 5$ nAChR subunit acquired a CPP for high doses of nicotine, but such doses were aversive to their wild-type littermates (Jackson et al.

2010b). Similarly, $\alpha 5$ knockout animals failed to titrate their responses in a self-administration paradigm when increasing doses of nicotine were offered, and this effect was rescued by expression of $\alpha 5$ in MHb (Fowler et al. 2011). Interestingly, $\alpha 5$ knockout mice were indistinguishable from controls at low doses of nicotine in both CPP and self-administration paradigms (Jackson et al. 2010b; Fowler et al. 2011), indicating that the $\alpha 5$ nAChR subunit is not required for the rewarding properties of nicotine. Furthermore, overexpression of the $\beta 4$ nAChR subunit in MHb resulted in increased aversion to nicotine (Frahm et al. 2011). Mice overexpressing $\beta 4$ nAChRs—with or without a $\beta 4$ mutation, which is associated with decreased risk of smoking in humans—displayed larger nicotine-evoked current amplitudes and enhanced aversive behavior (Slimak et al. 2014). Together, these studies suggest that $\alpha 5$ - and $\beta 4$ -containing nAChRs in the MHb are essential for encoding the aversive properties of nicotine, and they likely serve to limit nicotine intake.

Characterization of the MHb to IPN aversive circuit offers a novel and intriguing approach to addiction pharmacotherapy, in which the goal is to enhance the aversive effects of nicotine rather than to reduce its reinforcing effects. $\alpha 5$ - and $\beta 4$ -containing nAChRs are obvious targets. Unfortunately, continuous stimulation of this aversive pathway likely will warrant the use of full agonists of these receptors and is, therefore, clinically unrealistic, because the $\beta 4$ -containing nAChRs are also highly expressed in the autonomic ganglia and a full agonist would likely be poorly tolerated. Instead, the use of PAMs that would enhance signaling only in the presence of an agonist may be more feasible (Fowler and Kenny 2014). Recent findings show that galantamine, which acts as a positive allosteric modulator of $\alpha 5$ subunit-containing nAChRs at low doses, can reduce nicotine intake in rats and smoking in humans (Ashare et al. 2016), supporting the rationale for developing $\alpha 5$ PAMs as novel smoking cessation agents. Notably, other brain regions and neuronal systems, including the mesocorticolimbic dopamine pathway and autonomic nervous system, also contribute to the aversive effects of nicotine. However, the specific mechanisms by which aversive pathways communicate with reward pathways are uncertain.

The Noradrenergic System

Norepinephrine (also known as noradrenaline) is a monoamine neurotransmitter that signals through $\alpha 1$, $\alpha 2$, and β G-protein-coupled adrenoceptors. Like other neuromodulators, norepinephrine receptors are found throughout the brain, and norepinephrine is well known for its role in arousal and the stress response. The noradrenergic system has also been implicated in neurobiologic

responses to nicotine, contributing to both nicotine reward and reinstatement (Fitzgerald 2013). Nicotine increases activity of adrenergic neurons in the locus coeruleus, resulting in increased levels of norepinephrine in the brain. In animal models of nicotine addiction, blocking the transmission of norepinephrine with prazosin, the $\alpha 1$ receptor antagonist, reduced nicotine-induced dopamine signaling and attenuated nicotine self-administration and reinstatement (Forget et al. 2010). In other studies, reducing the tone of norepinephrine by stimulating $\alpha 2$, an inhibitory autoreceptor, with clonidine or dexmedetomidine diminished stress-induced reinstatement of nicotine-seeking behavior in rats (Zislis et al. 2007; Yamada and Bruijnzeel 2011).

In humans, long-term smoking is associated with reduced expression of $\alpha 2$ - and β -adrenergic receptors, which normalize after a period of abstinence (Klimek et al. 2001). In addition, guanfacine, the $\alpha 2$ agonist, reduced stress-induced nicotine craving and smoking in a study of 33 smokers (McKee et al. 2015). Thus, both clinical and preclinical evidence suggest that nicotine increases noradrenergic activity and that correction of this increase may be an effective strategy for reducing smoking.

Clonidine (trade names: Catapres, Kapvay, Nexiclon), the $\alpha 2a$ receptor agonist, has consistently shown some efficacy in improving cessation rates by alleviating negative withdrawal symptoms (Gourlay et al. 2004), but clonidine is not an FDA-approved cessation aid, and prominent adverse side effects, mainly sedation and low blood pressure, limit its practicality. Notably, bupropion and nortriptyline, the antidepressant smoking cessation aids, are norepinephrine reuptake inhibitors.

Summary

Although current pharmacotherapies are effective in reducing smoking in some persons, many are unable to maintain abstinence. With continued interest in the neurobiologic mechanisms of addiction, preclinical advances have improved considerably our understanding of the pathophysiology of nicotine dependence, withdrawal, and relapse. Correspondingly, dozens of novel targets for pharmacologic intervention have emerged, and further investigation into the role of these targets in human smoking is warranted.

Moving forward, the need to develop individualized, multifaceted approaches to smoking cessation is becoming apparent. For instance, drugs that reduce the initial rewarding properties of nicotine are unlikely to normalize the long-lasting neuroadaptations associated with persistent drug use, which underlie craving, withdrawal, and vulnerability to relapse. Another approach may be combination therapy that targets multiple aspects

of addiction behavior, such as a combination of bupropion with NRT or varenicline, which has been successful in human clinical trials. Current evidence is conclusive that current pharmacotherapies for smoking cessation, including such combination therapies as bupropion with NRT or varenicline, improve quit rates (see Chapter 6) but many persons still relapse to smoking (see Chapter 2).

Finally, the pathophysiology underlying addiction to other drugs of abuse, particularly stimulants like cocaine, is similar to that of nicotine. Thus, research that leads to improved smoking cessation therapies also may benefit the treatment of other addictions. The literature should be mined to identify novel targets for interventions that promote smoking cessation.

Vaccines and Other Immunotherapies as Treatments for Nicotine Addiction

Nicotine vaccines are a new class of medication being developed for smoking cessation; interest in these vaccines stems from their novel mechanism of action. Unlike existing cessation medications that act on neurotransmitter receptors in the brain to reduce the reinforcement or withdrawal associated with the use of tobacco products, vaccines act directly on nicotine, the principal addictive constituent of tobacco (Pentel and LeSage 2014). Vaccines stimulate the immune system to produce antibodies that can bind and retain nicotine in the blood, thereby reducing or slowing its delivery to the brain (LeSage et al. 2006b; Esterlis et al. 2013). Interrupting nicotine delivery to its site of action blocks or reduces its behavioral effects (Jefferson et al. 2004; Goniewicz and Delijewski 2013; Maglione et al. 2014). If it proves feasible for nicotine vaccines to produce very high levels of antibodies in blood, efficacy for this approach to smoking cessation should be possible. Because vaccines act in a different manner than existing medications for smoking cessation, such as varenicline or bupropion, combining a nicotine vaccine with those medications to enhance overall efficacy may be possible. An additional potential benefit of nicotine vaccines is that their effects last for many months (Cornuz et al. 2008; Hatsukami et al. 2011), avoiding the need to take a medication each day or, for some products, even more often (Prochaska and Benowitz 2016).

Literature Review Methods

For this section of the chapter, PubMed was searched in January 2017 for studies published between January 1966 and January 2017 about active or passive immunization against nicotine *in vitro* in animals or humans. The following terms were searched alone or in combination: nicotine, tobacco, smoking, cigarette, vaccine, vaccination, immunogen, immunization, antibody, linker, hapten, conjugate, adjuvant, addiction, dependence, cessation,

and monoclonal. Articles identified in this manner were also reviewed to find additional primary references. One reviewer conducted a full review and identified 35 articles for this section.

Design and Mechanism of Action

The human immune system can recognize foreign (nonhuman) proteins present on infectious agents, such as bacteria or viruses, and can form antibodies to help defend against them. Nicotine is a much smaller molecule than a protein and lacks the structure needed to be recognized as foreign. Even so, nicotine can be chemically linked to a foreign carrier protein to stimulate the production of antibodies against it (Pentel et al. 2000; Isomura et al. 2001; Maurer et al. 2005). This nicotine–protein immunogen is typically administered with an adjuvant, a chemical or mix of chemicals that generally enhances immune responsiveness. Administration of such a vaccine results in the production of antibodies that circulate in the blood and bind nicotine tightly and with high specificity. Because these antibodies do not bind appreciably to anything other than nicotine, they might not disrupt the actions of other drugs or medications, and they might not interfere with normal physiologic functions.

Nicotine vaccines have not shown any serious side effects in animals and humans (Hatsukami et al. 2005; Fahim et al. 2013). Autoimmune reactions from vaccine-generated antibodies have not been observed (Hatsukami et al. 2005). Nicotine-specific antibodies do not bind acetylcholine (the endogenous ligand that nicotine mimics), and nicotine itself is a small molecule that should not be able to cross-link antibodies and form immune complexes (Pentel et al. 2000).

Nicotine-specific antibodies in blood cannot enter the brain because of their large size (Satoskar et al. 2003). In addition, nicotine that binds to an antibody cannot enter the brain to interact with the receptors that mediate its

actions. As a consequence, vaccination can attenuate many of the effects of nicotine, provided a sufficient amount of antibody is present (Lindblom et al. 2002; LeSage et al. 2006a). After vaccination, levels of nicotine-specific antibodies in blood decline slowly, over months, and periodic booster doses of vaccine are needed to maintain high levels of antibody (Cornuz et al. 2008; Hatsukami et al. 2011). Because smoking cessation medications generally are required for only 3–6 months, vaccine efficacy should be obtainable after an initial three or four monthly doses of vaccine to achieve high serum antibody concentrations and perhaps a booster dose 3–6 months after that (Hatsukami et al. 2011).

After vaccination, nicotine in blood exists as an equilibrium between a large amount of nicotine bound to antibody and a much smaller amount that remains unbound. Nicotine that is bound to antibody cannot be metabolized, but the unbound nicotine is metabolized normally. As the concentration of unbound nicotine in blood is reduced by metabolism, bound nicotine dissociates from the antibody to re-establish equilibrium and is, in turn, metabolized. In this manner, nicotine can be eliminated even in the presence of antibody, albeit more slowly than otherwise. For example, in rats, immunization doubled the elimination half-life of nicotine from 1 hour in controls to 2 hours in rats vaccinated against nicotine (Keyler et al. 2005). This process frees the antibody of its bound nicotine so that it is once again available to bind newly delivered nicotine (e.g., from the next cigarette).

Examining Data from Animals to Confirm Vaccine Activity

In rats and mice, nicotine vaccination reduces by up to 80% the delivery of single doses of clinically relevant nicotine (equivalent to one or two cigarettes) to the brain (Cerny et al. 2002; Maurer et al. 2005; Pravetoni et al. 2011). Vaccine efficacy is lower with chronic doses of nicotine that approximate regular smoking, but the entry of nicotine into the brain is still slowed (Hieda et al. 2000). In rats, which are thought to provide the best animal models for smoking behavior in humans, vaccination markedly reduces addiction-relevant behaviors, such as nicotine self-administration (Lindblom et al. 2002; LeSage et al. 2006a). Animal studies consistently show that vaccine efficacy is greatest when the level of nicotine-specific antibodies in the blood is high, maximizing the nicotine-binding capacity provided in relation to the amount of nicotine present (Maurer et al. 2005; Pravetoni et al. 2011). For the same reason, vaccination is more effective in blocking the effects of fewer or lower doses of

nicotine than against regular or higher doses (Keyler et al. 1999). Extrapolating these findings to humans, it appears that nicotine vaccines will be most useful for preventing relapse, which is often triggered by taking just a few puffs or smoking just a few cigarettes, and may be less effective for encouraging smoking cessation among regular smokers who are not motivated to quit.

Clinical Trials of Nicotine Vaccines

Several nicotine vaccines have progressed through Phase 2 or 3 clinical trials (i.e., have been tested for safety, efficacy, and effectiveness relative to other treatments), in combination with standard behavioral counseling (Cornuz et al. 2008; Hatsukami et al. 2011; Fahim et al. 2013; Tonstad et al. 2013). All of these studies provide preliminary evidence of safety, but levels of antibody in the blood have been substantially lower than those achieved in rats or mice. Mean levels of antibody in participants in human studies have reached approximately 40 micrograms per milliliter ($\mu\text{g/mL}$), but levels of 200–500 $\mu\text{g/mL}$ can be produced in mice or rats (Maurer et al. 2005; Keyler et al. 2008). Part of this difference comes from the ability to administer higher doses of immunogens and stronger adjuvants in animals than would be tolerated in humans without producing side effects. Not surprising, therefore, is that the overall efficacy of vaccines for enhancing smoking cessation has not been demonstrated. In several studies, however, participants with the highest levels of serum antibody also had higher rates of smoking cessation compared with those who received a placebo vaccine (Cornuz et al. 2008; Hatsukami et al. 2011). This key observation suggests that the vaccine strategy has merit and has the potential to be effective. At this time, FDA has not approved any nicotine vaccines.

Next-Generation Vaccines

Next-generation vaccines hold promise for producing higher levels of antibody than those studied to date; several approaches are being evaluated:

- Improving the way in which nicotine is attached to its carrier protein to provide tighter binding to the immune cells that initiate antibody production (Moreno et al. 2012);
- Using more immunogenic carrier proteins or designing and synthesizing carrier proteins that are optimized to enhance the interaction of nicotine

with immune cells (McCluskie et al. 2013; Rosenberg et al. 2013; Miller et al. 2014; Jacob et al. 2016);

- Mixing or combining the nicotine–protein immunogen with newer adjuvants (e.g., CpG oligonucleotides, water/lipid emulsions) that enhance the production of antibodies by activating novel molecular pathways, or using combinations of adjuvants that provide additive efficacy (McCluskie et al. 2013; Jacob et al. 2016); and
- Attaching nicotine to synthetic nanoparticle scaffolds that are designed to more precisely control and optimize interactions between nicotine and the immune system (Lockner et al. 2013; Desai and Bergman 2015; Liu et al. 2016).

Combining Vaccines with Medications

Nicotine vaccines can be designed to display different surfaces of the nicotine molecule to the immune system. Because the immune system sees each surface as a distinct stimulus, two or three suitably designed nicotine vaccines can be co-administered to get an additive antibody response (Keyler et al. 2008; de Villiers et al. 2013). Nicotine vaccines also can be combined with small-molecule medications because those drugs act by separate mechanisms. For example, nicotine-specific antibodies can be combined with mecamylamine, a nicotine antagonist that blocks the action of nicotine on its receptors in the brain and has been used experimentally to promote smoking cessation. This combination is more effective in rats than either of these treatments alone for blocking nicotine discrimination, a measure of whether the animal recognizes that it has received nicotine (LeSage et al. 2012). However, a clinical trial of a nicotine vaccine combined with another drug for smoking cessation, varenicline, found no additional effect from vaccination compared with the drug alone (Hoogsteder et al. 2014).

Passive Immunization with Monoclonal Antibodies or Gene Transfer

The amount of antibody produced by vaccination is limited by the capacity of the immune system. Thus, it could be possible to produce nicotine-specific monoclonal antibodies in bacterial cultures or other *in vitro* systems and bypass the need for vaccination by administering the preformed antibodies directly (passive immunization). In animals, this approach mimics vaccination, but greater efficacy is possible because very large doses of antibody can be safely administered (Carrera et al. 2004; Keyler et al. 2005). The main limitations to this approach in humans are its high cost and the likely need to administer the antibodies intravenously (Skolnick 2015). An alternative approach to passive immunization is to administer a harmless virus (not capable of replication) that contains DNA coding for the production of the desired antibody. This virus can take up temporary residence in tissues and produce nicotine-specific antibodies that are independent of the host's immune system. In rodents, extremely high levels of antibody have been achieved using this strategy for periods of up to several months (Hicks et al. 2012). This approach holds promise for human therapies if measures to ensure its safety can be established.

Summary

Animal studies and early clinical trials have provided proof-of-principle that drug-specific antibodies can block the addictive effects of nicotine and serve as an adjunct to smoking cessation. The main benefit of this approach may be preventing relapse. Anticipated progress in vaccine design and enhancement of the immune response should (a) provide substantially more effective vaccines and other approaches to providing nicotine-specific antibodies and (b) create opportunities to better explore their therapeutic potential.

Insights into Smoking Cessation from the Field of Neurobiology

Smokers trying to quit often can maintain abstinence for short periods, ranging from days to weeks. However, quitting smoking usually requires several attempts (USDHHS 2000, 2010; García-Rodríguez et al. 2013). Evidence shows that smokers often require multiple quit attempts (even more than 20, depending on the

metrics used) and many years to obtain long-term (greater than 1 year) smoking abstinence (Chaiton et al. 2016). This clinical observation highlights the often-mistaken assumption made by both practitioners and smokers trying to quit that the absence of the behavior (smoking) reflects the absence of the disease (dependence). Thus, to

enhance treatment outcomes, a better understanding of the neurobiologic basis of the disease is required. Until the development of noninvasive brain imaging (initially positron emission tomography [PET] and more recently and prominently, functional magnetic resonance imaging [fMRI]), such an understanding of affected humans has been difficult to obtain. In contrast, considerable preclinical data (Leslie et al. 2013) have convincingly supported the proposition that chronic self-administration of nicotine—like that of other dependence-producing drugs, including stimulants and opiates—alters specific long-term regional neurobiologic processes that have been hypothesized to explain the high rates of recidivism in persons who are trying to quit smoking (Sutherland and Stein 2018).

During the past two decades, noninvasive brain imaging has repeatedly demonstrated differences in brain structure and function in smokers compared with matched, never-smoking, healthy persons. Thus, it is plausible that such differences might be applied usefully and clinically to develop better behavioral interventions and pharmacologic treatment strategies to improve the current rates of cessation. There are, however, no currently available brain-based neuroimaging biomarkers of treatment outcome, and much of the historic behavioral and personality characterizations that have been shown to differ between smokers and nonsmokers have failed to serve as accurate predictors of treatment success.

Why, after consistent demonstrations of differences in brain and behavior between groups, have these data not been effective in predicting treatment outcomes? One working hypothesis is that the differences are not a result of the addiction process, but rather that they reflect a predispositional trait that preceded drug use and dependence and are more likely to reflect risk factors for addiction than consequences of drug use. If so, it would seem unlikely that differences identified from cross-sectional population studies would or should signal outcome changes in brain circuits.

The alternative hypothesis is that the aforementioned brain differences are indeed caused by chronic drug use and reflect dependence-induced, neuroplastic brain changes. If so, this would suggest that longitudinal, within-participant neuroimaging data collected along the trajectory from the onset of treatment through short- and long-term recovery might serve as a biomarker of current disease severity and, importantly, be predictive of disease remission. Such a biomarker also could determine the possible liability risk for addiction of potential novel pharmacologic agents and help match treatment options with the highest probability of aiding the individual smoker. A review of the neuroimaging literature reveals a miniscule number of studies performed on former smokers

(Neuhaus et al. 2006; Nestor et al. 2011, 2018a,b; Krönke et al. 2015; Zanchi et al. 2015, 2016; Weywadt et al. 2017; Ono et al. 2018), leaving mostly unknown the answer to the question of what a former smoker's brain actually looks like.

Once the data become available in greater numbers, noninvasive brain imaging could:

- Identify differences in brain structure and function between smokers and nonsmokers;
- Follow persons along the course of treatment to identify brain circuits and networks that uniquely change in those whose treatments induce prolonged abstinence versus those who relapse (i.e., whether the above-group differences return to a [presumed] pre-addicted state vs. whether other neurobiological systems strengthen to compensate for the dysregulated brain system and networks);
- Make post hoc predictions of treatment outcomes by using pretreatment data and posttreatment outcomes;
- Develop brain-based biomarkers in clinical trials that predict treatment outcomes;
- Identify intermediate phenotypes of brain circuits and networks that can be used to fractionate the phenotype of the individual smoker to allow for personalized medicine and identify treatments with the highest probability of successful outcomes.

The ultimate goal of this strategy is to develop a system to individualize predictions of health outcomes on the basis of a model developed from group studies (Gabrieli et al. 2015).

Literature Review Methods

For this section of the chapter, PubMed was searched in January 2017 for articles that were published between 2014 and 2017 about studies that focused on the intersection of human neuroimaging and nicotine addiction. The following terms were searched: fMRI, PET, MRI, nicotine, and nicotine addiction. The references cited represent publications in this domain since the 2014 Surgeon General's report. From these articles, some studies conducted between the publication of the 2010 and 2014 Surgeon General's reports were also included. One reviewer conducted a full review and identified 77 articles for this section. Articles were omitted if the studies were

considered to be underpowered or if quality could not be assessed because of incomplete descriptions.

Methodology of Neuroimaging Studies

In contrast to PET technology, which is best suited to identify molecular changes in neurotransmitter systems (for a review, see Lameka et al. 2016), MRI can be used to study brain structure, including gray matter density and cortical thickness, and the microstructure and integrity of white matter tracts (diffusion tensor imaging). MRI also can measure certain biochemical constituents of the brain using magnetic resonance spectroscopy. Finally, fMRI measures changes in brain activity (as inferred from changes in blood flow, blood volume, and oxygenation). The strength of fMRI is that it can measure brain activity while persons perform various cognitive and emotionally laden tasks, linking the behavioral performance of such nicotine addiction-related processes as working memory, attention, cue reactivity, and inhibitory (cognitive) control to the localization and magnitude of brain activity (for a review, see Huettel et al. 2014).

Data from fMRI also can be acquired in the absence of a directed task (i.e., the participant is at rest) (Biswal et al. 1995). Studies using resting-state fMRI have demonstrated that specific brain connections (i.e., circuits and networks) are apparent in the absence of a directed task, with the strength of connections at rest sufficient to predict the strength of subsequent task activation and behavioral performance (Kelly et al. 2008; Baldassarre et al. 2012). Differences in resting-brain circuits may reflect neuropsychiatric disease, including nicotine dependence (Fedota and Stein 2015).

Despite their increasing applicability, neuroimaging studies are inherently correlative. Nevertheless, designs that include a pharmacologic intervention and incorporate a parametric manipulation of the task or drug (dose-response) enable more precise interpretations. Finally, the advent of noninvasive brain stimulation (NIBS) (e.g., transcranial magnetic stimulation and transcranial direct [or alternating] current stimulation) may enable more direct probes of and interventions directed at putative neural circuit plasticity. The rationale for applying NIBS in addiction is that it could enhance circuits related to cognitive control or weaken circuits that are sensitive to provocations from cues. Although these circuits are also targets for many of the behavioral therapies applied in addiction (e.g., cognitive behavioral therapy), brain electrical stimulation has the potential to improve the efficacy of the treatment intervention by directly engaging the

affected circuits. Having achieved some modest success, transcranial magnetic stimulation, an FDA-approved treatment for depression, has been proposed as a treatment for addiction in general (Barr et al. 2008; Gorelick et al. 2014; Dunlop et al. 2017) and for smoking in particular (Fraser and Rosen 2012; Li et al. 2013b; Dinur-Klein et al. 2014; Pripfl et al. 2014). However, the data for NIBS are too preliminary to evaluate its efficacy in smoking cessation.

Differences in Brain Circuitry and Cognitive Constructs in Nicotine Dependence

The neuroimaging studies reviewed in this section have examined the effects of chronic cigarette smoking, acute versus extended abstinence, treatment interventions, and smoking cessation on the major cognitive and affective constructs hypothesized to be involved in nicotine addiction (for a general review of addiction neurobiology, see earlier discussion, Koob and Volkow 2016, and USDHHS 2010). Although different drugs of abuse initially bind to receptors specific to that drug's pharmacology (e.g., opiate receptors [opioids]; psychostimulants [monoamine transporters]; tobacco [various nicotinic receptor subtypes]), the "downstream" neurobiologic circuits and mechanisms generally are believed to share a common substrate across all (or most) addictions. The cyclic nature of addiction and the underlying circuitry and neuroplastic consequences of chronic drug administration provide a theoretical framework to discuss the circuitry of nicotine addiction (Koob and Volkow 2016; Volkow et al. 2016). A better understanding of these neurobiologic mechanisms may yield more effective tools to aid in smoking cessation and also may be achievable using many fewer participants than are necessary in a behavior-only-based clinical trial, because the effect size of a brain response, which is more proximal to the causative mechanism, is significantly greater than the more distal behavioral response (Rasetti and Weinberger 2011). A review of the literature by Menossi and colleagues (2013) summarized the role of neuroimaging in pharmacologic treatment for smoking and nicotine dependence. They identified multiple brain regions—including the anterior and posterior cingulate cortex, orbitofrontal cortex, ventral striatum, amygdala, thalamus, and insula—that are involved in both the maintenance of smoking and processes related to nicotine withdrawal, such that two reasonably efficacious drugs used to treat nicotine dependence, varenicline and bupropion, modulated activity in these areas. In contrast, although NRT improves cognitive symptoms related to withdrawal, it does not generally alter the activity of neural circuits that are associated with nicotine addiction.

Smoking Cues and Craving Provocation

Exposure to cues related to smoking is thought to activate brain circuits related to the salience (i.e., of immediate relevance) of the stimuli and to engage memory, affective, and cognitive processes that promote drug seeking and, in most cases, drug taking. Moreover, smoking cues can directly interfere with the abstinent person's ability to concentrate and to focus attention on performing a task or on a therapeutic intervention that involves behavioral change (Luijten et al. 2011). Accordingly, a better understanding of the brain circuits and neurobiologic mechanisms engaged by cues might lead to novel targets for treatment interventions and potentially the development of a biomarker of outcome efficacy. For example, treatment with bupropion is associated with improved ability to resist cue-induced cravings and a reduction in cue-induced activation of limbic and prefrontal brain regions, including the ventral striatum, medial orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) (Culbertson et al. 2011). Similarly, responses to varenicline in the medial OFC (as a function of reward) and in the lateral OFC (during reward evaluation) may play a role in a diminished response to smoking cues, which may contribute to the drug's clinical efficacy (Franklin et al. 2011). Consistent with these findings, Hartwell and colleagues (2013) found that successful smoking cessation with varenicline was associated with increased activation, before a quit attempt, in brain areas related to attentiveness and memory while the person resisted the urge to smoke, suggesting the drug may exert its effects by reducing craving and enhancing resistance to urges to smoke during cue-elicited craving.

More mechanistically, activation in the amygdala—a structure long associated with stress processing, reinforcement learning, and risk of relapse—is dampened by both varenicline and nicotine, but a report by Sutherland and colleagues (2013b) found that this was only in a subset of smokers who appeared most susceptible to the negative consequences of nicotine abstinence for behavioral performance (in this case, forced choice reaction time). This finding on individual difference may provide a useful step toward fractionating the smoker phenotype by discrete neurobiologic characteristics, which in turn could lead to differential treatment algorithms. Furthermore, the functional connectivity between the amygdala and insula and, in turn, of the insula to components of the default mode network (DMN) (which is composed of the ventromedial PFC, parahippocampal gyrus, and posterior cingulate cortex [PCC] and is thought to process interoceptive states, ruminations, reflective thoughts, and similar phenomena) is downregulated by both varenicline and nicotine in abstinent (but not sated) smokers, and the circuit

reduction is linked to reduced symptoms of nicotine withdrawal, which may help to promote cessation (Sutherland et al. 2013a).

Consistent with a role for the amygdala and insula in cessation, 3 months of mindfulness treatment was found to reduce both behavioral reactivity and responsivity in both brain regions and to predict successful cessation (Kober et al. 2017). In another study, 2 weeks of meditation training (vs. a relaxation control) resulted in an average 60% reduction in smoking that correlated with increased activity in the ACC and PFC, which are brain areas related to self-control (Tang et al. 2013). Taken together, these studies suggest that reducing DMN-insula-amygdala circuit activity (via pharmacologic or behavioral interventions) may promote abstinence by modulating the interoceptive, negative affective, and ruminatory consequences (i.e., cravings) of cessation and point toward reduced strength of discrete circuit connectivity, contributing in turn to the amelioration of subjective withdrawal symptoms.

Sutherland and colleagues (2012) hypothesized that the balance between various large-scale brain networks modulates both normal and addiction-related behaviors. The three major large-scale brain networks in this model were (1) the DMN; (2) the executive control network, primarily composed of the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex and thought to be engaged during the cognitive processing of exteroceptive signals; and (3) the salience network, which is anchored by the dorsal anterior cingulate cortex (dACC) and anterior insula and is thought to attribute salience to stimuli and the selection of action during times of conflict. In a test of this hypothesis, Lerman and colleagues (2014) demonstrated that the dynamic interrelationship among these three major large-scale networks is altered during acute 24-hour abstinence (vs. satiety) and predicts the (a) difference in abstinence-induced changes in craving to smoke and (b) reduced cognitive performance and brain activation seen during a working memory task. Independently, a study by Zhang and colleagues (2011) positively correlated cue-elicited activity in the dlPFC with the strength of functional connectivity between the dlPFC and rostral anterior cingulate cortex.

If acute abstinence in fact modulates the circuits and networks described above, intervention strategies aimed at changing their activities might prove efficacious. One such potential cessation treatment uses real-time feedback of the fMRI signal to facilitate volitional control over regions of the brain that regulate craving. In a proof-of-concept study, modulating the strength of functional connectivity between the ACC and medial PFC via feedback was associated with a reduction in craving among heavy smokers (Kim et al. 2015). Furthermore, feedback from the ACC but not the dorsomedial PFC (dmPFC),

which is thought to be more involved in resisting craving, reduced activation to smoking cues, especially in persons with less severe nicotine dependence (Canterberry et al. 2013; Hanlon et al. 2013; Hartwell et al. 2016).

The amount of nicotine presented to the brain via smoking is directly related to the severity of nicotine dependence, which in turn is linked to the severity of cravings during abstinence. Emergent data suggest a genetic link between the rate of nicotine metabolism, success in smoking cessation, pharmacologic efficacy, and brain activity (see “Genetic Studies of Smoking Phenotypes” later in this chapter for a discussion about the influence of nicotine metabolism on dependence). For example, compared with slow metabolizers, persons who are fast nicotine metabolizers demonstrate significantly greater responses to cigarette cues in the amygdala, hippocampus, striatum, insula, and cingulate cortex—supporting the importance of cue-induced craving in relapse and helping to explain why fast metabolizers have lower cessation rates (Tang et al. 2012). In one study, greater activation in the caudate and frontal pole in fast versus normal metabolizers predicted abstinence-induced subjective cravings in response to smoking cues, suggesting that adjunctive behavioral cessation treatment, such as desensitization to repeated exposures to cues, may be useful in faster metabolizing persons (Falcone et al. 2016).

Reward

Like other abused drugs, nicotine, by virtue of its ability to interact with components of the mesocorticolimbic system and to enhance levels of dopamine (Volkow et al. 2015), modulates reward processes in ways that may help perpetuate smoking and limit successful cessation. For example, 24-hour abstinence is associated with increased striatal activation during anticipation of a smoking reward and decreased activation in anticipation of a monetary reward, and greater abstinence-induced decrements in striatal activation during monetary reward are associated with a greater likelihood of relapse (Sweitzer et al. 2016b). Consistently, administration of nicotine during abstinence reduces activity in the ventral striatum when the person is anticipating a win or loss (i.e., reward valence) and increases activity in the dorsal striatum when the person is anticipating the magnitude of a rewarded outcome (Rose et al. 2013; Fedota et al. 2015), suggesting a mechanism influencing the observed continued motivation to smoke and difficulty with cessation when trying to quit. Importantly, chronic dependence on nicotine, but not acute nicotine administration (i.e., NRT), reduced the ventral striatal temporal difference error signal (a learning mechanism construct related to dopamine release) in a

classical conditioning reward paradigm, which is consistent with the inability of NRT to alter reward-related functional properties and perhaps explains its only modest ability to aid in smoking cessation (Rose et al. 2012). In contrast, varenicline blunts the magnitude of mesocorticolimbic dopamine activity when a smoker is processing a reward, likely contributing to the drug’s greater efficacy as pharmacotherapy for smoking cessation (Fedota et al. 2015).

Practically speaking, smokers who show lower prequit brain reactivity to pleasant stimuli than to cigarette-related cues are less likely to be abstinent 6 months after their quit attempt. Therefore, an important factor underlying relapse may be the lack of alternative forms of reinforcement when someone is deprived of nicotine (Versace et al. 2014). Indeed, ambivalence about treatment negatively correlates with cue-related activation in brain areas linked to reward processing, motivation, and attention—including the rostral ACC, medial PFC, and caudate nucleus—thus, supporting the importance of both motivation to quit and expectancy to smoke (Wilson et al. 2012, 2013).

Cognition and Cognitive Control

Cognitive performance and control processes have long been known to regulate so-called top-down control over behaviors, such as the ability to resist the drug-seeking drive following cue presentation, subsequent drug craving, and ultimately drug taking. Such processes may serve as potential markers of sustained abstinence and treatment efficacy. For example, in a study by Krönke and colleagues (2015), former smokers exhibited less Stroop interference, indicating superior cognitive control, compared with current smokers. (Stroop interference is a behavioral task designed to induce a conflict in cognitive processing that leads to a reduction in reaction time to perform the task. One example of this effect requires individuals to identify the color of a word that is incongruent with the word itself [e.g., the word green written in red ink] [Stroop 1935].) Furthermore, when more demanding incongruent trials were contrasted with easier congruent trials in this study, former smokers showed stronger activity in the superior frontal gyrus and ACC than current smokers, suggesting successful smoking cessation may be mediated by enhanced cognitive control (Krönke et al. 2015). Elsewhere, in a study by Froeliger and colleagues (2017), differences in baseline corticothalamic function were predictive of inhibitory control processing and vulnerability to smoking relapse. In another study, greater activation in the inferior frontal gyrus, presupplementary motor area, and basal ganglia during a response inhibition task at pretreatment baseline was associated

with an attenuated association between cravings and subsequent smoking (Berkman et al. 2011).

Externalizing tendencies and/or compromised error processing among subsets of smokers may be relevant factors for the success of smoking cessation. Specifically, higher externalizing tendencies correlated with more performance errors and predicted less recruitment of the insula and dACC following the commission of errors in smokers, and smaller error-related insula activity and less dACC activity correlated with higher craving during abstinence (Carroll et al. 2015). In support of these regional alterations, reduced density of gray matter in the dlPFC of smokers, a structure long implicated in working memory, was associated with cue-elicited activity in the same brain area, suggesting a neurobiologic mechanism for the impaired cognitive control associated with chronic drug use (Zhang et al. 2011). Finally, smoking is associated with a diffuse cortical thinning that accelerates normal age-induced thinning and cognitive decline, which requires approximately 25 years post-cessation for complete cortical recovery (Karama et al. 2015). Although the amount of cortical thinning was related to the amount of nicotine used, as an association, the causation of the thinning is not known. Similarly, Power and colleagues (2015) observed a dose-dependent relationship between smoking and white matter hyperintensities.

Working memory is a sensitive biomarker of nicotine dependence and acute withdrawal (Loughead et al. 2010). Relapse to smoking was highly predictive by decreased dlPFC and increased PCC activation during acute abstinence versus smoking satiety (Loughead et al. 2015). Moreover, acute smoking abstinence was sufficient to reduce dmPFC activity and performance on a working memory task, and because smoking a low-nicotine cigarette did not ameliorate the deficit, NRT may be sufficient to resolve cognitive function during smoking abstinence. In contrast, an attempt to improve withdrawal-induced cognitive deficits by using tolcapone (to inhibit dopamine metabolism) only modestly improved the performance of working memory (Ashare et al. 2013). Similarly, a nicotine vaccine that blocks binding to nicotinic receptors in the brain did not block effectively either cue responsivity or brain activity during a working memory task (Havermans et al. 2014). Thus, like most vaccines, a nicotine vaccine may prove more effective in preventing a disease (i.e., nicotine addiction) because brain circuits that have been modified or dysregulated as a result of nicotine dependence are not likely to return to their pre-addiction state simply by blocking new nicotine from reaching the brain. Indeed, that smoking relapses occur months or even years after smoking cessation suggests that the absence of nicotine alone is insufficient to reverse dependence-induced circuit neuroadaptations.

Insights from Neuroimaging for Antismoking Messages

In addition to providing a salient stimulus to seek out or enhance drug use (Wang et al. 2013), smoking cues could serve, together with appropriate messaging, as a negative reinforcement. For example, analyses using neuroimaging of responses to antismoking ads that were intended to change attitudes toward smoking appeared to predict the severity of subsequent smoking and treatment outcomes (Camenga and Klein 2016). Most persons begin using nicotine and often become nicotine dependent during adolescence (USDHHS 2012; Camenga and Klein 2016). Compared with adult smokers, adolescent smokers exhibited greater craving reduction and greater blunted recruitment of insula and dlPFC in response to package warning labels (Do and Galván 2015). Furthermore, greater dlPFC regulation of limbic regions predicted cigarette craving. These data underscore the prominent role of fronto-insular circuitry in predicting the efficacy of graphic warning labels for reducing craving in adult and adolescent smokers. In adult smokers, activation in the dmPFC in response to persuasive advertisements predicted urine cotinine levels 1 month later (Wang et al. 2013). In smokers trying to quit, the amygdala's response to smoking cessation messages was modulated by genetic variation in the serotonin transporter and was predictive of quitting outcome (Jasinska et al. 2012). Genetic alterations in the dopamine D4 receptor also modulated responsiveness of the amygdala to cues (Xu et al. 2014). A study by Chua and colleagues (2011) supports the hypothesis that tailored health interventions are more effective at eliciting positive behavior change than generic interventions. For example, messages tailored to the individual increased activation of the dmPFC, a region known to be involved in self-related processing, and predicted quitting during a 4-month follow-up. Taken together, these data suggest that fMRI may aid the prerelease evaluation of televised public health ads.

Neuronal Circuits and Networks

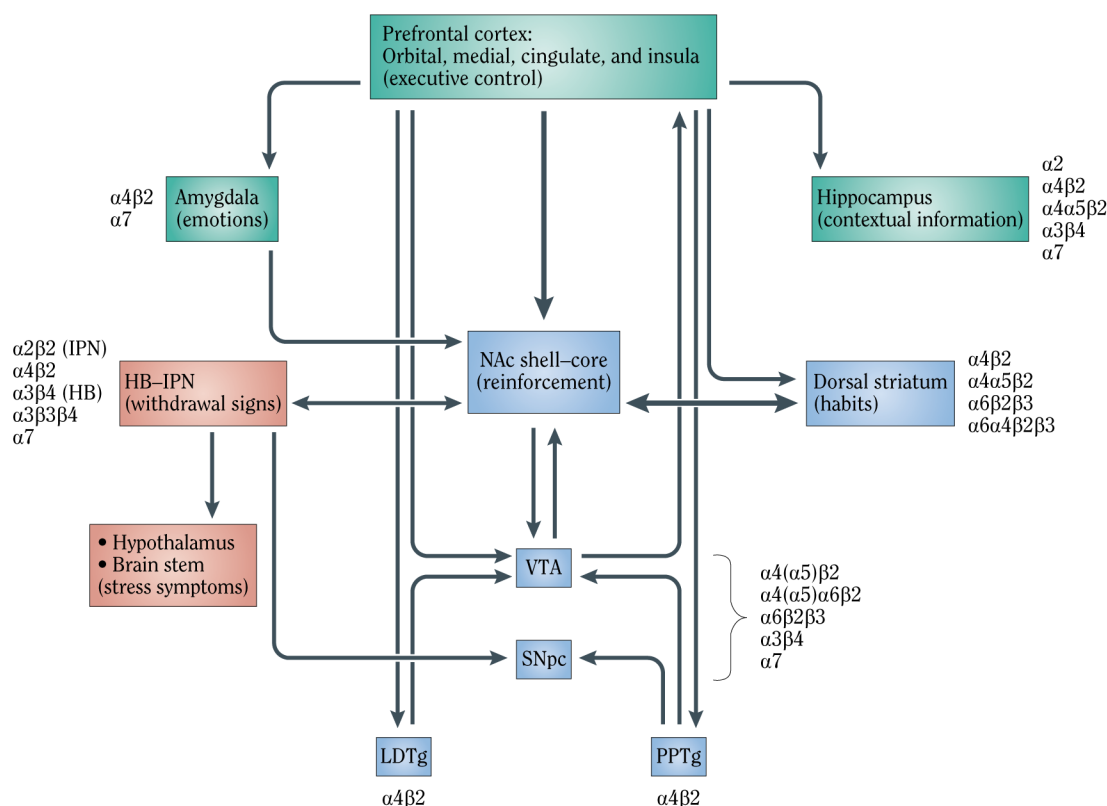
Studies of resting-state functional connectivity have revealed that the ACC, PCC, medial and lateral OFC, ventral striatum, amygdala, thalamus, and insula are all heavily involved in the maintenance of smoking and nicotine withdrawal (Figure 3.3). Varenicline and bupropion modulate activities in these brain areas, providing mechanistic support for their abilities to alleviate withdrawal symptoms and help with smoking cessation. For example, among non-lapsed smokers who were making a 3-week quit attempt,

Sweitzer and colleagues (2016a) observed abstinence-induced increases in connectivity strength between the ventral striatum and a network of regions implicated in addictive disorders, including the insula, superior temporal gyrus, and ACC; the opposite pattern was observed for those who later lapsed. Also in this study, following 24-hour abstinence, decreased connectivity between the dorsal striatum and the medial PFC, PCC, hippocampus, and supplemental motor area was observed across both successful and unsuccessful cessation groups. These findings suggest that modulation of striatal connectivity with

the cingulo-insular network during early withdrawal may be associated with outcomes for smoking cessation.

This potential association is particularly important because a high density of nAChRs has been found in the cingulo-insular network (Picard et al. 2013), and this salience network has been implicated in the switching of cognitive resources during abstinence (vs. satiety) toward more internal bodily processing and nicotine craving (Sutherland et al. 2012; Lerman et al. 2014). Moran-Santa Maria and colleagues (2015) found a psychophysiological interaction between the anterior insula and the

Figure 3.3 Neuronal mechanisms involved in nicotine addiction: A model



Source: Changeux (2010, p. 391), with permission.

Notes: α = alpha; β = beta; **HB-IPN** = habenula–interpeduncular; **LDTg** = laterodorsal tegmental nucleus; **NAc** = nucleus accumbens; **nAChR** = nicotinic acetylcholine receptor; **PPTg** = pedunculopontine tegmental nucleus; **SNpc** = substantia nigra pars compacta; **VTA** = ventral tegmental area. “Many brain areas contain nAChR subunits and are involved in nicotine addiction. First, the somata of the dopaminergic neurons that contribute to nicotine intake and reinforcement are in the VTA of the midbrain: they project to the prefrontal cortex and to limbic areas, in particular the hippocampus and NAc in the striatum [Balfour et al. 2000; Di Chiara 2000; Maskos et al. 2005; Balfour 2009]. These VTA neurons receive cholinergic innervation from the PPTg and the adjacent LDTg [Picciotto and Corrigall 2002; Maskos 2008]. Second, the emergence of a negative emotional state and withdrawal syndrome following smoking cessation—or nicotine deprivation—mobilizes distinct neural circuits that can include the extended amygdala and brain stress systems [Koob 2008], the hypothalamus, hippocampus [Davis and Gould 2009], SNpc, and/or the HB-IPN system [Salas et al. 2009]. Third, the ‘switch’ from voluntary nicotine use to compulsive drug use may represent a global top-down ‘gating’ transition from control by a prefrontal (cortical and insular) global neuronal workspace (BOX 1) to subcortical (striatal) control [Grace 2000; Changeux and Dehaene 2008; Naqvi and Bechara 2009]” (Changeux 2010, p. 391).

precuneus (a part of the DMN)—which are regions known to be involved in self-awareness and interoception, or the sense of internal bodily states—during the presentation of smoking cues. According to Zelle and colleagues (2017), connectivity strength between the anterior insula and dlPFC following provocation from smoking cues predicts the ability to resist smoking after acute abstinence.

Vulnerability to relapse after a quit attempt was associated with weaker connectivity between the posterior insula and primary sensorimotor cortex, suggesting that greater connectivity in this network improves the ability to inhibit a motor response to cigarette cravings when those cravings conflict with the goal to remain abstinent (Addicott et al. 2015). Elsewhere, research has consistently shown that the insula and basal ganglia play a role in addiction to smoking, as revealed by localized stroke lesions in these regions (Naqvi and Bechara 2010; Gaznick et al. 2014), and that local connectivity coherence within the PCC, a key DMN region, can predict the success of cessation (Wang et al. 2017).

In contrast to the insula-based circuits related to the state of nicotine withdrawal and the positive effects of NRT on cognitive processing, NRT does not alter the activity in an ACC-ventral striatal neural circuit that is associated with the severity of trait nicotine addiction (Hong et al. 2009). Further speaking to the role of the ACC and striatum in trait addiction, slow nicotine metabolizers, which presumably have relatively higher nicotine levels in the brain, showed greater functional connectivity in the dACC and ventral striatum, which is negatively associated with the severity of nicotine dependence (Li et al. 2017). Critically, the dACC and ventral striatum are biased by inputs from the insula. Moreover, a similar gene–environment reduction was seen in the dACC and ventral striatum during smoking abstinence when study participants performed a cognitive control response inhibition task and a reward task to probe their function, which were both normalized following NRT. These data suggest that the inherited rate of nicotine metabolism fundamentally changes brain circuits and function, which may, in turn, influence the outcomes of smoking cessation (Li et al. 2017).

The findings that both nicotine trait addiction (long standing) and current state (transient) engage distinct neural mechanisms (dACC and ventral striatum) and circuits (amygdala, insula, and DMN) and that NRT appears to improve cognitive symptoms related to withdrawal but does not alter a measure of disease severity (the FTND), suggest that both nicotinic and non-nicotinic pharmacotherapy may reduce smoking via distinct neural mechanisms of action and thereby endorse the potential value of neuroimaging in the development of new medications and discovery of brain-based biomarkers of early therapeutic response in cigarette smokers (Menossi et al. 2013).

Molecular Imaging

PET imaging has contributed to a better understanding of the biochemical and molecular alterations in nicotine addiction and smoking cessation. Clearly, understanding the mechanisms of action of effective pharmacotherapies for nicotine dependence is critical to the development of better treatments. A PET study using [(11)C]-(+)-PHNO demonstrated that varenicline, the most effective pharmacotherapy currently available, increases levels of striatal dopamine, much as smoking does (Cosgrove et al. 2014), which may contribute to the drug's efficacy (Di Ciano et al. 2016).

An important public health question is whether documented changes in brain structure and function in persons who are dependent on nicotine can be reversed or normalized following extended abstinence. Notably, smoking cessation is accompanied by a decrease in the density of $\alpha 4\beta 2^*$ nAChRs across the brain, suggesting a normalization of the receptors that primarily bind nicotine following intake (Brody et al. 2013). Additionally, smokers with less upregulation of $\alpha 4\beta 2^*$ were found to have a greater probability of quitting smoking than those with greater upregulation, providing a potential biomarker of cessation success (Brody et al. 2014). In a different study (Akkus et al. 2016), compared with recent former smokers, long-term former smokers showed higher mGluR5 binding, most prominently in the frontal cortex and thalamus, suggesting that downregulation of these receptors may be a mechanism underlying nicotine dependence and the high rate of relapse seen in those previously exposed to nicotine. Accordingly, mGluR5 receptor binding may serve as an effective smoking biomarker and a potential target for future medications (Akkus et al. 2016). In contrast, binding at the GABA(A) receptor, a component of the principal brain inhibitory system, does not seem to normalize with sustained abstinence (Stokes et al. 2013).

Sex differences in smoking behavior and brain molecular mechanisms have been reported (Sieminska and Jassem 2014). Consistent with the notions that men smoke cigarettes for their reinforcing properties and women smoke for such reasons as mood regulation and cue reactivity (Perkins et al. 2001; Xu et al. 2008), Cosgrove and colleagues (2014) found, in an analysis of smoking in a PET scanner, that smoking resulted in rapid increases in dopamine in the ventral striatum of men, while dopamine release in women was faster than in men in a subregion of the dorsal putamen. Moreover, smoking-induced alterations in nAChR binding appeared to differ by sex, with receptor upregulation seen in male but not female smokers (vs. nonsmokers, respectively). In contrast, nAChRs are negatively correlated with levels of progesterone, which in turn are positively correlated with symptoms of depression and intensities of cigarette craving and withdrawal (Cosgrove et al. 2012). These data

suggest that female smokers may be best treated by medications that do not interact directly with nicotinic mechanisms. Additionally, a study using fMRI indicated higher reactivity to smoking cues (vs. neutral cues) in males compared with females in specific reward-related regions of the brain (the ventral striatum/ventral pallidum and the ventral medial prefrontal cortex) (Dumais et al. 2017). Brain activation during smoking cues correlated positively with cue-induced subjective craving in males but not in females. These data suggest that, compared with women, men have greater reward-related brain activation to drug cues.

Although these small studies may have been underpowered to definitively distinguish smoking-related, sex-specific differences in the neurochemistry and circuitry in the brain, they add to a growing and important base of literature on sex differences in nicotine addiction. They also underscore the need for more research on sex-specific neurobiology of the etiology and treatment of nicotine dependence.

Summary

The data presented in this section highlight new biologic insights into smoking cessation gained from multiple neuroimaging modalities, including PET and fMRI.

These studies highlight the neurobiologic complexities of nicotine dependence and, in their totality, are sufficient to support the multiple cognitive and affective systems that are dysregulated in persons with this disease, suggesting why persons who are addicted to nicotine are so resistant to treatment even with multiple FDA-approved medications. On a more positive note, these neuroimaging findings have begun to reveal neurobiologic mechanisms and cognitive constructs that may serve as novel targets for future therapeutic developments, including reward processing, cognitive control, and executive functions (such as working memory and inhibitory control processes and affective responses to internal and external cues and stressors). These studies are suggestive of dysregulated brain regions, including various prefrontal and cingulate cortical regions, and their corresponding circuits and interactions with various striatal and insula loci. Almost all studies were cross-sectional—not longitudinal. Therefore, specific causal relationships are difficult to infer in the absence of repeated measurements within subjects. Nevertheless, outcomes for smoking cessation may be improved by using pre- and posttreatment, multimodal neuroimaging measures that are coupled with recent computational advances (e.g., machine learning) to create objective, quantifiable biomarkers that can be used to assess disease severity and treatment efficacy.

Genetic Studies of Smoking Phenotypes

Studies of twins suggest that smoking behaviors are moderately to highly heritable. For example, according to earlier studies, genetic factors explain an estimated 46–84% of the variability in smoking initiation and smoking persistence, up to 75% of the variability in nicotine dependence (Kendler et al. 1999; Vink et al. 2005), and 50–58% of the variability in smoking cessation (Xian et al. 2003; Broms et al. 2006). Two broad approaches to molecular genetics exist: Candidate gene studies identify a specific gene to investigate, on the basis of biologic plausibility, and test the association between the selected genetic variants and the phenotype of interest. In contrast, GWAS are not restricted to individual genes. Instead, they assess the association between hundreds of thousands of variants (and, more recently, several million variants) across the genome with the phenotype of interest.

The 2010 Surgeon General's report summarized studies of candidate genes involved in the dopamine pathway, which at the time was considered a promising target for genetic dissection, with the *DRD2 Taq1A* polymorphism being one focus of interest (USDHHS 2010). Early studies suggested that the A1 allele at this locus was

associated with increased short-term effectiveness of NRT and bupropion. Subsequent studies, however, have not confirmed an association with smoking status (Tobacco and Genetics Consortium 2010) or with response to pharmacotherapy for smoking cessation (Choi and Shin 2015). The 2010 Surgeon General's report also reviewed studies of candidate genes (e.g., *CYP2A6* and *CYP2E1*) involved in nicotine metabolism in relation to smoking phenotypes, but it concluded that findings were not consistent, possibly because of differences in samples across studies (USDHHS 2010). Two later studies used the nicotine metabolite ratio (NMR), which is the ratio of 3'-hydroxycotinine (the product of *CYP2A6* activity) to cotinine, as a phenotypic biomarker for *CYP2A6* activity and concluded that NMR predicts the outcomes of treatment for smoking (Kaufmann et al. 2015; Lerman et al. 2015). This conclusion likely results from better measurement of nicotine metabolism activity gained using a phenotype instead of a genotype, as this gene locus is very complicated and results can be inconsistent because of the different variants being tested. Since the 2010 Surgeon General's report, considerable progress has been made in understanding the genetic basis of smoking phenotypes,

particularly through GWAS. Candidate gene studies and GWAS have identified variants in the *CHRNA5-CHRNA3-CHRNA4* region as promising targets for the study of nicotine dependence and smoking intensity.

Literature Review Methods

For this section of the chapter, MEDLINE was searched for articles that were published between 2000 and 2018 about studies that focused on genetic associations with smoking behavior (including cessation). A combination of controlled vocabulary and keyword terms was used for each of the concepts: smoking cessation, smoking behavior, smoking phenotype, genetics, and precision medicine. Studies were excluded if they did not focus on the underlying biology of smoking behavior and/or smoking cessation. Conclusions were formulated from evidence cited in the 2014 Surgeon General's report on smoking and any newly available evidence. Search results were limited to studies published in English and to original research. Duplicates were deleted, and unique hits were screened. Two independent reviewers conducted a full review and identified 47 articles for this section. From these articles, seven more articles about studies conducted in the 1990s were also included.

Candidate Gene Studies

Candidate gene approaches require some theoretical knowledge of the biologic mechanism underlying the phenotype of interest that points to specific genes. Typically, these approaches focus on genetic variants that result in functional changes (Kwon and Goate 2000). The selected variant is tested for its occurrence in cases and controls (e.g., assigned by smoking status) or for its association with a continuously distributed trait (e.g., nicotine dependence) (Patnala et al. 2013).

Findings from candidate gene studies are difficult to reproduce. This is likely because of the typically small samples used in these studies, the small effect sizes associated with common genetic variants and complex behavioral traits, and the relatively liberal alpha threshold used (Chang et al. 2014). Despite these limitations, candidate gene studies have produced some robust associations, as discussed later in this section.

Genomewide Association Studies

GWAS adopt the same approach as candidate gene studies, but rather than testing the association of one or

a small number of genetic variants with a phenotype of interest, GWAS simultaneously test hundreds of thousands of genetic variants (typically single nucleotide polymorphisms [SNPs]) across the genome. The multiple testing burden implicit in GWAS has led to a consensus that signals have to achieve a very stringent threshold for statistical significance (typically $p < 5 \times 10^{-8}$). This, in turn, requires very large samples or the pooling of data across multiple studies to achieve the necessary sample size to robustly identify the small effects associated with the common genetic variants. Most GWAS also report results from discovery and replication datasets. This combination of large sample sizes, statistical stringency, and replication means that GWAS have been extremely successful in identifying genetic variants associated with a range of complex phenotypes, including variants that would not have been considered previously on the basis of biological function. GWAS have identified novel genetic associations with smoking behaviors, such as *BDNF* for smoking initiation, the *CHRNA5-A3-B4* gene cluster for intensity of smoking, and *DBH* for smoking cessation (Berrettini et al. 2008; Bierut et al. 2008; Thorgeirsson et al. 2008; Tobacco and Genetics Consortium 2010).

As would be expected, one of the limitations of GWAS is their limited ability to detect low-frequency variants. For example, Lindquist and colleagues (2013) estimated the first GWAS to have detected less than 20% of all independent GWAS-detectable SNPs in chronic diseases. More recent GWAS have employed imputation to expand genomic coverage to better capture low-frequency variants. To impute genotypes, data for the microarray are matched to a genome reference panel, which consists of densely sequenced genomic data from multiple persons (e.g., 1,000 Genomes Project Consortium et al. 2010).

Microarrays designed in this manner cover a large portion of all SNPs in the human genome by directly measuring high- and low-frequency variants and by measuring SNPs in linkage disequilibrium (Lindquist et al. 2013). Even so, another limitation of GWAS is that the phenotypes are relatively crude because they are tested in large samples and in the case of smoking behavior, often rely on retrospective self-reports. Carefully defined and well-characterized phenotypes offer greater precision of measurement, increase the genetic signal, and improve the likelihood of replication (Munafò et al. 2012).

Examples of Biologically Promising Candidate Genes (*DRD2* and *DAT1*)

The mesolimbic dopamine system is particularly important in addictive behaviors and is activated by nicotine. As a consequence, genes encoding proteins involved in the neurotransmission of dopamine have been considered plausible candidate genes for nicotine dependence

and smoking cessation, and they have been widely investigated in candidate gene studies. Variations of the dopamine receptor D2 (*DRD2*) and the dopamine transporter *SLC6A3* (also known as *DAT1*) genes have received particular attention (Sullivan and Kendler 1999; Dani 2003; Duan et al. 2003; Li et al. 2003; Dahl et al. 2006; Lerman et al. 2006a; Schnoll et al. 2007).

Associations Between the *DRD2* and *DAT1* Genes and Smoking Behavior

In the *DRD2* gene, rs1800497 (Taq1A) is one polymorphism that is located downstream and in the neighboring ankyrin repeat and kinase domain containing 1 (*ANKKI*) gene (Neville et al. 2004). This polymorphism, which is involved in inhibiting the synthesis and release of dopamine, leads to decreased density of the dopamine receptor (Noble et al. 1991, 1997; Pohjalainen et al. 1998; Jonsson et al. 1999) and, therefore, reduced dopamine binding in the brain (Thompson et al. 1997). Various studies have reported that the A1 allele of the *DRD2* Taq1A polymorphism is associated with being a former or current smoker (Noble et al. 1994; Morton et al. 2006); with age of smoking initiation and duration of abstinence (Comings et al. 1996); and with smoking intensity (Connor et al. 2007). In addition, meta-analyses have reported suggestive evidence of an association of the A1 allele with increased likelihood of smoking persistence (Munafò 2004; Munafò et al. 2004, 2009). Other studies, however, did not yield similar findings (Batra et al. 2000; Bierut et al. 2000).

Other studies have investigated whether *DAT1* variants are associated with smoking behavior. *DAT1* has a polymorphic variable number of tandem repeats sequence that varies from 3 to 11 copies, of which only the 9- and 10-repeat alleles are common (Chen and Reith 2000). *DAT1* plays a key role in regulating the transport of dopamine by regulating its reuptake (Choi and Shin 2015). Timberlake and colleagues (2006) reported that the absence of the 9-repeat allele in *DAT1* (*DAT-9*) was associated with being less likely to be a smoker; other studies have suggested that this association is stronger if the person was also carrying the *DRD2* A2 allele (Lerman et al. 1999), had a later onset of smoking (Lerman et al. 1999; Schmid et al. 2009), had longer quitting attempts (Lerman et al. 1999), or had formally tried smoking cessation (Sabol et al. 1999). However, these associations have not been found in other studies (Bierut et al. 2000; Jorm et al. 2000; Vandenbergh et al. 2002).

Meta-analyses of GWAS conducted by the Tobacco and Genetic Consortium (2010), using data from three GWAS of smoking consortia to evaluate a number of phenotypes, did not find evidence of an association between loci in either *DRD2* or *DAT1* and smoking behavior. Despite these equivocal results, several pharmacogenetic studies

have suggested an association between genes involved in the dopaminergic pathway and response to pharmacotherapy that is aimed at smoking cessation (David and Munafò 2008).

The Moderating Effect of *DRD2* and *DAT1* on the Efficacy of Treatment for Smoking Cessation

Some studies have found that the A1 allele of the *DRD2* gene is associated with better response to NRT (Johnstone et al. 2004; Yudkin et al. 2004; Lerman et al. 2006b), and others have found an association between A2 and better response to bupropion for specific nicotine withdrawal symptoms (David et al. 2003; Swan et al. 2005; David et al. 2007). In contrast, Berlin and colleagues (2005) did not find an association between the *DRD2* genotype and smoking cessation. Additionally, Choi and Shin (2015) did not find an association between *DRD2* polymorphisms and response to therapy for smoking cessation. Finally, in a randomized, placebo-controlled, smoking cessation study of bupropion, Lerman and colleagues (2003) did not find an association between the *DRD2* and *DAT1* genotypes and either the abstinence rate or response to treatment.

These findings suggest that many genes likely play a role in the efficacy of treatment for smoking cessation (David et al. 2013b). Each genetic variant probably explains only a small fraction of the variation in response to medication and success in quitting, and most studies have investigated only a single variant or just a small number of them. A combination of genetic variants in a single genetic risk score may reveal stronger associations with the outcomes of therapies for smoking cessation and support personalized therapy on the basis of a person's score.

Genetic Risk Scores

Additive genetic scores (AGS) are an alternative approach to evaluate the effects of multiple susceptible SNPs for a single phenotype. These scores take into account the collective impact of several variants, on the basis of theoretical knowledge of those included, and provide greater statistical power than single-variant studies (David et al. 2013b). Early approaches developed AGS on the basis of candidate genes of theoretical interest, and recent approaches have generated scores from variants identified via GWAS.

In two randomized clinical trials of bupropion for smoking cessation, David and colleagues (2013b) used an AGS from genes in the dopaminergic system, including *COMT*, *DRD2*, *DRD4*, and *DAT1*. The score was calculated on the basis of the number of alleles considered to promote smoking cessation through bupropion and was estimated

for each participant. The score was not associated with the number of days to first lapse, but evidence from this study indicated that bupropion (vs. placebo) counteracts the propensity to lapse in persons with a higher additive genetic efficacy score.

Uhl and colleagues (2014) studied smokers by using the “v1.0 score,” which is based on 12,058 SNPs (Uhl et al. 2010). Using a randomized controlled clinical trial in which dose of NRT was matched to the smoking intensity of each participant, the study found that the v1.0 score can predict success of quitting.

More recently, Chenoweth and Tyndale (2017) suggested that including environmental effects (e.g., use of estrogen-containing hormonal therapy) into AGS approaches would improve the ability to predict the outcomes of treatment for smoking cessation. At the same time, evaluative tools, such as biomarkers, could lead to tailored or personalized treatment (Bough et al. 2013). Regardless, early approaches to AGS, which used candidate genes, need to be treated with caution in light of the poor reproducibility of many findings for candidate genes.

Examples of Biologically Promising Genes That May Help Optimize Treatment

Both genetic and metabolic biomarkers have the potential to predict outcomes for different treatments for smoking cessation and individual responses to medication. Particularly promising genetic variants include those in the *CHRNA5-A3-B4* gene cluster on chromosome 15 (at 15q25) that encodes 3 (α 3, α 5, β 4) of the 11 (α 2– α 7, α 9, α 10, β 2– β 4) neuronal nAChR subunits (Gold and Lerman 2012). Multiple candidate gene studies and GWAS have verified the small but robust association of this cluster of genes with smoking intensity and nicotine dependence (Saccone et al. 2007; Bierut et al. 2008; Thorgeirsson et al. 2010). Importantly, smoking intensity and nicotine dependence predict the success of cessation (Piper et al. 2006; Transdisciplinary Tobacco Use Research Center on Tobacco and Dependence et al. 2007), and thus the relationship between the *CHRNA5-A3-B4* gene cluster and cessation phenotypes has been investigated (Munafò et al. 2011; Bergen et al. 2013; Tyndale et al. 2015).

NMR is a metabolic predictive biomarker that captures activity of the *CYP2A6* gene. *CYP2A6* plays an important role in nicotine metabolism; up to 80% of nicotine is inactivated to cotinine by the hepatic enzyme cytochrome P450 (CYP) 2A6, with a small contribution (10%) from *CYP2B6*. Most of the cotinine is further metabolized to 3'-hydroxycotinine. NMR is used as a proxy of *CYP2A6* activity and is preferred over assessing the gene itself because *CYP2A6* is characterized by dozens of polymorphisms. A faster NMR reflects higher *CYP2A6* activity and is associated with several smoking phenotypes.

The *CHRNA5-A3-B4* Gene Cluster

Associations with Nicotine Dependence and Smoking Intensity

Saccone and colleagues (2007) authored the first candidate gene study to report an association between the SNP rs16969968 in *CHRNA5* and nicotine dependence. The following year, GWAS conducted separately by Berrettini and colleagues (2008) and Thorgeirsson and colleagues (2008) reported that rs1051730 at the same locus but in *CHRNA3* (and strongly correlated with rs16969968 in samples of European ancestry) was associated with the number of cigarettes smoked per day. *CHRNA5* was not considered a strong candidate gene at the time, given what was then known about the neurobiology of nicotine dependence. Animal experiments had implicated the α 4 and β 2 nicotinic receptor subunits as critical to nicotine's reinforcing effects (Picciotto et al. 1998; Tapper et al. 2004), and α 4 β 2* partial agonists are now known to be one of the most effective treatments available for smoking cessation (Fowler and Kenny 2014). Findings from GWAS have made variants in the *CHRNA5-A3-B4* region promising targets for the study of nicotine dependence and smoking intensity, given their association with response to nicotine and its consequent consumption.

In particular, the rs1051730 SNP in *CHRNA3* is a coding-synonymous variant that does not result in an altered protein, and thus it likely does not have any functional significance. However, the highly correlated variant rs16969968 in *CHRNA5* is functional and presents with a missense mutation that results in an amino acid substitution of aspartate to asparagine in the α 5 subunit protein. Both in vitro and in vivo studies have further characterized the role of the rs16969968 variant. In in vitro studies, α 5 receptor complexes featuring the aspartic acid variant, when exposed to a nicotine agonist, have exhibited a substantially greater maximal response than the α 5 receptor complexes containing the asparagine variant (i.e., the risk variant associated with the number of cigarettes smoked per day and nicotine dependence) (Bierut et al. 2008). A series of animal studies has established the role of the α 5 nAChR subunit by investigating the phenotype via an α 5 knockout mouse model, which is analogous to a reduced α 5 receptor function in humans (i.e., carriers of the rs16969968 risk allele) (Salas et al. 2009; Fowler et al. 2011; Frahm et al. 2011). Salas and colleagues (2009) showed that α 5 knockout mice, when exposed to chronic infusions of nicotine, exhibited withdrawal symptoms comparable to those of saline-infused mice (i.e., a lack of withdrawal symptoms relative to wild-type mice). In the experiment conducted by Fowler and colleagues (2011), both wild-type and mutant mice were trained to press a lever

to obtain nicotine intravenously. All the mice showed the expected inverted U-shaped dose-response curve, with the difference that knockout mice responded more vigorously at high doses. Knockout mice consumed a greater amount of nicotine, and the wild-type mice appeared to titrate the delivery of nicotine to achieve a desired level. Although knockout mice appeared to experience rewarding effects of nicotine similar to those experienced by wild-type mice, the inhibitory effects of the high doses of nicotine on the activity of the rewarding circuitry seemed to be largely altered. The injection of a lentivirus vector into the MHB in $\alpha 5$ knockout mice rescued the expression of $\alpha 5$ subunits in this region and the phenotype.

Similarly, a study by Jackson and colleagues (2010b) showed differential effects of nicotine dose on reward between $\alpha 5$ knockout and wild-type mice using a CPP task. Later, in a study of humans, Jensen and colleagues (2015) found an attenuated aversive response to nicotine administered intravenously in overnight-abstinent smokers who were carriers of the *CHRNA5* rs16969968 risk allele genotype. In summary, high doses of nicotine seem to stimulate the MHB–IPN tract through nAChRs containing $\alpha 5$ subunits and elicit aversion, limiting further intake. This does not happen when the $\alpha 5$ signaling is deficient and, consequently, the negative effects of nicotine are attenuated. Similarly, smokers carrying the rs16969968 risk allele are more likely to smoke more heavily than their counterparts without the risk allele.

Evidence from in vitro and in vivo studies further indicates that the MHB acts as a gatekeeper for nicotine intake. Frahm and colleagues (2011) manipulated the concentration of $\alpha 5$ and $\beta 4$ subunits in vitro, while $\alpha 3$ was kept constant. Nicotine-evoked currents in MHB neurons of wild-type and transgenic Tabac mice (characterized by an overexpression of $\beta 4$) led to a dramatically higher firing rate in the neurons of the Tabac mice. Those mice exhibited a reduced nicotine intake and a strong preference for water rather than low-nicotine-concentration solutions in a two-bottle choice test that compared them with wild-type mice presented with the same volumes of water and the low-nicotine solution. When the expression of the $\alpha 5$ risk variant was elicited by injecting a lentivirus vector into MHB neurons in the Tabac mice, the latter restored their nicotine consumption and their two-bottle choice behavior to a level comparable to that of the wild-type mice. These animal studies show that $\alpha 5$ and $\beta 4$ play an important role and compete in regulating nicotine intake.

In humans, Hong and colleagues (2010) used resting-state functional connectivity to understand the mechanistic link between variation at the *CHRNA5-A3-B4* locus and nicotine addiction. Their study identified a circuit between the dorsal anterior cingulate and the ventral striatum/extended amygdala that distinguished smokers

from nonsmokers and predicted nicotine dependence. Both smokers and nonsmokers with the risk allele had a weaker circuit than those with the more common allele (although the circuit strength was even weaker in smokers), suggesting a trait-like circuit biomarker. A nearly identical circuit was described previously in smokers (Hong et al. 2009) as a function of nicotine dependence. Critically, in that study, circuit strength did not change following NRT, suggesting that it reflected chronic dependence.

***CHRNA5-A3-B4* Variants and Smoking Cessation in Absence of Treatment**

The genetic risk variants associated with nicotine dependence and smoking intensity also were associated with smoking cessation. Interestingly, persons who smoke a greater number of cigarettes per day seem to quit at a later age (Chen et al. 2015). Some studies have shown that *CHRNA5*, in particular the rs16969968 risk variant, has potential clinical significance in predicting delayed smoking cessation. Chen and colleagues (2015) conducted a large meta-analysis to investigate whether rs16969968 plays a role in the age of smoking cessation among smokers without smoking-related disease and patients with lung cancer, chronic obstructive pulmonary disease, or coronary heart disease. Results from 24 datasets in their study showed evidence for an association only for the smokers without a smoking-related disease and the rs16969968 risk allele, with a median delay of 4 years. The heterogeneity of the studies in this meta-analysis shows that a number of factors may moderate genetic risk, such as the presence of disease, use of medication, and environmental risk factors (e.g., having a partner or friend who smokes).

Freathy and colleagues (2009) assessed smoking cessation in a large cohort of women of European ancestry, over the course of their pregnancies. Carriers of the risk variant rs1051730 showed a reduced likelihood of stopping smoking. The effect did not appear to be solely mediated by intensity of smoking, as adjusting the analysis for that variable did not affect the results, although this may have been because the number of cigarettes smoked per day does not fully capture intensity of smoking (e.g., given interindividual differences in depth of smoke inhalation and other measures of smoking topography). Thorgeirsson and Stefansson (2010) replicated this finding in a retrospective study of pregnant women, which found an association between the risk variant rs1051730 and continuing smoking during pregnancy.

***CHRNA5-A3-B4* Variants and Smoking Cessation with Pharmacotherapy**

Several studies have examined whether personalized smoking cessation treatments based on genotype

can improve cessation success. Such treatments require knowledge of whether genetic variants moderate the effects of the available pharmacotherapies for smoking cessation.

Baker and colleagues (2009) studied the effect of haplotypes on the basis of five tagging SNPs (rs680244, rs569207, rs16969968, rs578776, and rs1051730) in the *CHRNA5-CHRNA3-CHRNA4* locus. For participants receiving either bupropion or placebo, the haplotypes were associated with tolerance, craving, and loss of control, but only among persons who had started smoking early in life.

Elsewhere, Munafò and colleagues (2011) found evidence for a weak association between the same locus, looking at the risk variant rs1051730 in *CHRNA3* and at the short-term ability to quit smoking in heavy smokers receiving either the placebo or NRT. Interestingly, the effect size reported in this study was comparable to the effects found in the studies of pregnant women (Freathy et al. 2009; Thorgeirsson and Stefansson 2010) and the study by Baker and colleagues (2009).

Chen and colleagues (2012) conducted a large study to examine genetic associations with age of cessation. *CHRNA5-A3-B4* risk haplotypes (rs16969968 and rs680299, both in *CHRNA5*) were associated with the number of cigarettes smoked per day and a later quitting age; the latter was no longer associated with the haplotypes when the analysis was adjusted for the number of cigarettes smoked per day. This study suggested that intensity of smoking, measured as the number of cigarettes smoked per day, impedes cessation. Furthermore, carriers of the medium- to high-risk haplotypes found abstinence more difficult, but if carriers received pharmacologic treatment (e.g., nicotine patch, nicotine lozenge, bupropion), they showed an increased rate of quitting success.

A meta-analysis by Bergen and colleagues (2013), which included eight RCTs, found that 6 months after a quit attempt, the risk allele rs1051730 was associated with higher rates of abstinence in the NRT group compared with the placebo group. The authors of this study assessed the association of four SNPs with smoking cessation and response to medication at the end of the treatment (8- to 12-weeks post-quit) and after 6 months. The genetic variants were rs1051730, rs578776, and rs588765 in *CHRNA5* and *CHRNA3*, and rs2072661 in *CHRNA2*. *CHRNA2* has been associated with a number of smoking cessation phenotypes, such as abstinence, FTND, and nausea among treatment-seeking smokers randomized to behavioral therapies and prescribed varenicline (Ehringer et al. 2007; Conti et al. 2008; Wessel et al. 2010; Swan et al. 2012). The eight RCTs considered in the meta-analysis employed placebo, NRT, bupropion, varenicline, or a combination of NRT and bupropion (along with a variety of counseling options). Although rs2072661 and rs578776 were not associated with smoking cessation, rs1051730 and, to a

lesser degree, rs588765 were associated with quitting success in persons randomized to NRT and in those who received the placebo. Participants in the placebo conditions were less likely to be abstinent after 6 months, but those who received NRT were more likely to achieve abstinence after that time. Mediation analysis indicated that rs1051730 increased nicotine dependence—a variable that decreases the success of abstinence—and that a further mechanism (speculated to be abstinence-induced impairment in cognitive function) increased abstinence in the NRT group at the 6-month follow-up from the end of drug administration.

Two subsequent studies—a meta-analysis of four studies and a clinical trial—did not confirm these findings. The meta-analysis revealed no evidence at the end of NRT that rs16969968 or rs1051730 were associated with cessation (Leung et al. 2015). The clinical trial, conducted by Tyndale and colleagues (2015), examined the association between *CHRNA5-A3-B4* haplotypes and smoking abstinence, finding no associations between rs16969968, rs578776, and rs588765 and abstinence at 6- or 12-month follow-up in participants who received placebo, NRT, or varenicline.

An important factor in smoking cessation is adherence to treatment. Ware and colleagues (2015), who studied this phenotype in a secondary analysis of data from an RCT of smoking cessation, found an association between rs1051730 and adherence to NRT after 7 days of the quit attempt but not after 28 days. Each copy of the minor allele corresponded to a 2.9% decrease in adherence to the prescribed dose of NRT over 7 days. This association was robust to adjustments made for age, sex, socioeconomic status, trial condition, body mass index at baseline, and daily cigarette consumption at baseline.

Most studies to date have used samples of European ancestry, but a few have examined samples from other populations, including African Americans. For example, in a small deep-sequencing discovery study of African Americans, Hamidovic and colleagues (2011) reported an association between rs12915366 in *CHRNA5* and rs12914385 in *CHRNA3* and smoking persistence. David and colleagues (2012), who performed a genomewide meta-analysis of 13 studies of African Americans, found that rs2036527, which is in linkage disequilibrium with rs1051730, was significantly associated genomewide with the number of cigarettes smoked per day. In another study of African Americans, Zhu and colleagues (2014) failed to find an association between rs16969968 and smoking abstinence in either the placebo or NRT group. In contrast, the minor allele of rs588765 was associated with lower abstinence in the placebo group and greater abstinence in the group receiving NRT during treatment but not after 6 months.

The study by Zhu and colleagues (2014) also reported an association, both during and at the end of treatment, between the risk allele of rs2036527 in *CHRNA5* and lower smoking abstinence in those who received NRT but not in the placebo group. Interestingly, adjusting the analyses for the number of cigarettes smoked per day had a negligible effect. The rs2036527 SNP was in high linkage disequilibrium with rs1051730, and these findings are consistent with the association reported by Munafò and colleagues (2011) for rs1051730 and short-term smoking cessation in their study of a European population. These findings suggest that linkage disequilibrium structures differ between European and African American populations.

Overall, although the association between the *CHRNA5-A3-B4* gene cluster and smoking intensity is robust, its role in smoking cessation needs further investigation, and currently no clear evidence exists that it influences responses to specific pharmacotherapies. Some of the inconsistent results may be due to differences in methods and sampling or to environmental factors that influence each study. AGS could be employed to explore the collective genetic influence of several variants that may exert a role in complex phenotypes, such as smoking behaviors, but more work is required to understand the role of these genes in ethnic groups other than those of European ancestry.

The *CYP2A6* Gene and the Nicotine Metabolite Ratio

Nicotine from cigarette smoke is distributed in the body via the bloodstream (Benowitz et al. 2009). Its elimination half-life is around 2 hours, and up to 90% of nicotine is converted to cotinine, mainly by the metabolic enzyme *CYP2A6*, which, in turn, is solely responsible for the metabolism of cotinine to 3'-hydroxycotinine (Benowitz and Jacob 3rd 1994; Tanner and Tyndale 2017). Nicotine is also metabolized to more minor metabolites by additional enzymes, including *FMO3* and *UGT2B10* (Benowitz et al. 2009). NMR is the ratio of 3'-hydroxycotinine to cotinine; studies of twins have estimated that about 60% of the variation in NMR is due to genetic factors (Swan et al. 2004). Importantly, *CYP2A6* enzyme activity is reflected by NMR (Dempsey et al. 2004; Johnstone et al. 2006; Malaiyandi et al. 2006a). *CYP2A6* is a highly polymorphic gene (with >30 genetic variants), and its numerous variants have an impact on NMR. Grouping variants, however, is possible according to the impact of *CYP2A6* on the rate of NMR (i.e., faster or slower). Importantly, NMR also captures environmental influences (e.g., hormonal therapies and body mass index). Furthermore, NMR values are stable across time and exhibit high test-retest reliability

when measured 2 to 3 weeks apart (Hamilton et al. 2015). Despite no consensus on the cut-off point between faster and slower metabolizers, several studies have used the lowest 25–50% of the NMR distribution to classify slower metabolizers (Lerman et al. 2006b; Ray et al. 2009; Schnoll et al. 2009; Dubroff et al. 2015).

Nicotine Metabolite Ratio and Smoking Behavior

The GWAS by Thorgeirsson and colleagues (2010) found an association between reduced smoking quantity, measured as the number of cigarettes smoked per day, and variants in or near *CYP2A6* that reduce the enzymatic activity of *CYP2A6* (in particular, rs4105144). Later, Loukola and colleagues (2015) conducted a GWAS meta-analysis of current smokers using data from three Finnish cohorts and identified novel genetic variants associated with NMR. Their study detected three strong independent signals in the immediate vicinity of *CYP2A6*: SNPs rs56113850, rs113288603, and rs2663194. Although the functional consequences of the first two SNPs are unknown, the third one is associated with a decreased clearance rate, and the three SNPs captured up to 31% of the total variance in NMR.

NMR has been assessed in several studies to further characterize smoking behavior. In one study, slower metabolizers smoked an average of 6 to 7 fewer cigarettes per day and had an earlier smoking onset by about 1 year (Schoedel et al. 2004). Other studies found slower metabolizers to be less dependent on nicotine, as measured by the FTND (Malaiyandi et al. 2006b; Wassenaar et al. 2011; Sofuoglu et al. 2012), and slower metabolizers took longer to become dependent on nicotine (Audrain-McGovern et al. 2007; Al Koudsi et al. 2010). Fast metabolizers exhibited a higher total cigarette puff volume (Strasser et al. 2011). This finding is consistent with the observation that fast metabolizers require higher levels of nicotine intake than those with a slower nicotine clearance, which is consistent with self-titration by smokers to achieve the desired circulating level of nicotine (Strasser et al. 2007). Adolescents who were slow metabolizers, however, had a higher risk of becoming nicotine dependent compared with fast metabolizers (Chenoweth et al. 2013, 2016). It is not clear if adolescent smokers titrate their level of nicotine intake according to their NMR to maintain desired levels, but Chenoweth and colleagues (2013) found that once adolescents who were slow metabolizers became dependent on nicotine, they smoked fewer cigarettes and were more likely to become adult smokers (Chenoweth et al. 2013). In fact, slow metabolizers who were adults were more likely than fast metabolizers to successfully quit smoking in the absence of pharmacotherapy (Gu et al. 2000; Patterson et al. 2008; Chenoweth et al. 2013).

In a study of mice, Bagdas and colleagues (2014) used an inhibitor of CYP2A5, the mouse ortholog of human CYP2A6, to mimic the slower nicotine metabolism of humans. The effects of this manipulation were illustrated using a CPP task. A low dose of nicotine administered on one side of a box, versus saline administered on the other side, did not induce a CPP in mice in the control group. In contrast, mice treated with the CYP2A5/6 inhibitor before being exposed to nicotine developed a CPP for the nicotine side and showed increased levels of plasma nicotine. Thus, it appears that the treated mice had become more sensitive to the effects of nicotine. Li and colleagues (2013a) reported similar results from a study that measured CPP in *CYP2A4/5* knockout mice that were exposed to nicotine. In addition, Bagdas and colleagues (2014) administered nicotine to naïve mice across 5 days and pretreated half of the mice with the CYP2A5/6 inhibitor; they then tested the somatic signs of withdrawal after nicotine abstinence. The pretreated mice showed a potentiation of the intensity of somatic signs of withdrawal and higher levels of plasma nicotine. In summary, the mice tested in these studies experienced a decrease of nicotine clearance, similar to human slow metabolizers, and a greater exposure to nicotine in these mice enhanced nicotine dependence and affected nicotine withdrawal behaviors.

Nicotine Metabolite Ratio and Smoking Cessation in Absence of Treatment

Gu and colleagues (2000), who compared the likelihood of quitting smoking between slow and fast metabolizers, found that slow metabolizers were almost twice as successful in quitting smoking. Later, in a prospective cohort of adolescents, Chenoweth and colleagues (2016) also assessed the hypothesis that slow metabolizers are more likely to quit smoking than fast metabolizers and found a linear relationship between *CYP2A6* activity and quit rate: slow metabolizers were more than twice as likely as fast metabolizers to quit smoking.

Smoking Cessation in Treatment Seekers

Compared with slow metabolizers, fast metabolizers have a higher NMR and inactivate nicotine quickly. A higher NMR results in lower levels of nicotine in the blood. Lerman and colleagues (2006b) found that a lower NMR was associated with increased odds of abstinence, both at the end of treatment and after 6 months, in persons who received a nicotine patch but not in those who received nicotine in the form of nasal spray, suggesting that, in contrast with transdermal nicotine (for which the dose is fixed), users of nicotine nasal spray may titrate their intake of nicotine. Furthermore, cravings for cigarettes after 1 week of abstinence were more severe in fast

metabolizers who received the transdermal patch. A subsequent study by Lerman and colleagues (2010) found that slow metabolizers benefitted from using the transdermal nicotine patch for an extended period of time (i.e., 6 months vs. the standard 8 weeks).

Some evidence suggests that bupropion enhances the quit success of fast metabolizers and that the nicotine patch enhances the quit success of slow metabolizers. Patterson and colleagues (2008) assessed the baseline NMR in smokers who subsequently participated in a 10-week randomized trial of bupropion versus placebo with counseling support. With placebo, quit rates were lower among fast metabolizers than slow metabolizers, but with bupropion, quit rates were similar between fast and slow metabolizers.

Because slow metabolizers showed no difference in the likelihood of relapse in either the placebo or bupropion conditions, Lerman and colleagues (2015) conducted an NMR-stratified, placebo-controlled, randomized trial of nicotine patch versus varenicline to test whether varenicline had a superior effect compared with placebo. On the basis of evidence for an interaction of NMR by treatment, fast metabolizers receiving varenicline had higher odds of being abstinent. These studies suggest that NMR may be a predictive biomarker that can be used to personalize treatments for smoking cessation.

Summary

This section examined the role in smoking cessation played by candidate genes in the dopamine system (dopamine receptor D2, *DRD2*, and the dopamine transporter, *DAT1*) and variants in the *CHRNA5-A3-B4* gene cluster and the *CYP2A6* gene. Despite early evidence for associations between genetic variation in *DRD2* or *DAT1* and smoking cessation and response to smoking cessation therapy, subsequent studies have failed to replicate these findings. In contrast, the small but robust association between the *CHRNA5-A3-B4* gene cluster and smoking intensity and nicotine dependence has been replicated in several candidate gene studies and GWAS, and smoking intensity and nicotine dependence predict the success of cessation. Whether variants in this gene cluster influence responses to specific pharmacotherapies is still not clear. Investigating polygenic risk scores may better capture the quitting success and variations in responses to medication.

More consistent results have been provided by studies assessing *CYP2A6* or related biomarkers, such as NMR, and smoking cessation (both with and without pharmacologic treatment). A linear relationship exists between *CYP2A6* activity and quit rate: slow nicotine

metabolizers are more likely than fast metabolizers to quit smoking. In addition, studies suggest that bupropion and varenicline enhance the quit success of fast metabolizers, and the nicotine patch enhances the quit success of slow metabolizers.

Schuit and colleagues (2017) published the first Cochrane systematic review and meta-analyses of pharmacogenetic biomarkers for smoking cessation, which included clinical trials with available genetic or NMR data for all approved smoking cessation pharmacotherapies, all genomewide significant SNPs for number of cigarettes smoked per day or smoking cessation, non-SNP polymorphisms with replication, and NMR. Data were available for 18 clinical trials and the following gene variants: nine SNPs (rs1051730 [*CHRNA3*]; rs16969968, rs588765, and rs2036527 [*CHRNA5*]; rs3733829 and rs7937 [in *EGLN2*, near *CYP2A6*]; rs1329650 and rs1028936 [LOC100188947]; and rs215605 [*PDE1C*]), two variable number tandem repeats (*DRD4* and *SLC6A4*), and the NMR biomarker.

The meta-analyses indicated that genotype groups within certain ethnic groups may benefit more from NRT than from placebo (non-Hispanic Black individuals at 6-months with rs16969968 GG genotype, slow metabolizers, non-Hispanic White and non-Hispanic Black individuals at the end of treatment with rs1051730 GA or AA genotype, and rs16969968 GG genotype) and from NRT (non-Hispanic Black individuals with rs2036527 GG genotype), or may benefit less from a combination of bupropion with NRT (non-Hispanic White individuals with rs1329650 TT genotype and non-Hispanic Black individuals with

rs3733829 AG or GG genotype). These results should be interpreted with caution because none of the statistically significant meta-analyses from placebo-controlled trials included more than two trials per genotype comparison, many confidence intervals were wide, and the quality of this evidence was generally moderate. Although evidence existed of superior NRT efficacy for NMR of normal versus slow metabolizers, the authors could not conclude that NRT is more effective in slow metabolizers. Given the number of trials and investigators who did not provide or publish meta-analyzable data, access to additional data is needed, particularly for comparisons of different pharmacotherapies to improve the reliability of meta-analysis and the potential clinical utility of genomic testing to guide treatment choice for smoking cessation.

Benefits may be derived from personalized precision tailoring of interventions based on genetic approaches. The efficacy of treatment could be improved by assigning patients to a specific treatment based on the results of genetic or biomarker testing. However, for a pharmacogenetic approach to be cost-effective, the effect size must be substantially larger in one stratum compared with another stratum. Other considerations, such as the proportion of the population that falls into each stratum, are also relevant. In particular, before pharmacogenetic or biomarker stratification becomes routine in clinical practice, an RCT should be conducted to determine whether this approach improves overall cessation outcomes. Ideally, the RCT would also include a health economic analysis to help determine the cost-effectiveness of this approach.

Summary of the Evidence

Although current pharmacotherapies are effective in increasing quitting, many current smokers want to quit but have been unable to sustain abstinence, so smoking remains one of the leading causes of preventable disease and death globally. Decades of preclinical advances have improved our understanding of the neurobiologic mechanisms underlying nicotine addiction. Although more remains to be understood, this information has identified dozens of novel and promising targets for pharmacologic intervention that remain to be evaluated in humans. Preclinical studies suggest that targeting multiple stages of addiction may be the most effective way to reduce smoking.

Immunotherapies for nicotine dependence offer an alternative therapeutic mechanism, producing antibodies that bind nicotine in blood and reduce nicotine delivery to the brain (see “Vaccines and Other Immunotherapies as Treatments for Tobacco Addiction”). This approach

involves targeting the drug rather than the brain, potentially reducing the side effects of existing medications to treat nicotine dependence and perhaps treating a limited repertoire of smoking behaviors (see “Insights into Smoking Cessation from the Field of Neurobiology”). Immunotherapies are highly effective in animal models for blocking nicotine reinforcement, but they have not yet been effective in Phase 3 clinical trials for smoking cessation, at least in part because of insufficient and variable antibody concentrations in humans.

Multiple cognitive systems (e.g., attention, reward, inhibitory control) and affective processes (negative and positive emotion) are dysregulated in nicotine dependence, which might help to explain poor treatment outcomes. Regions of the brain involved in the maintenance of smoking and nicotine withdrawal include the anterior and posterior cingulate, amygdala, insula, striatum, and orbitofrontal cortex. Large-scale brain networks altered as

a result of nicotine dependence include the default mode, salience, and executive control networks. Circuit and network connections may serve as predictive biomarkers to personalize treatment choices and as predictors of the outcomes of cessation treatment. More longitudinal neuroimaging studies are needed to understand brain alterations as a function of sustained abstinence. Neuroimaging and genetic analyses to fractionate the nicotine addiction phenotype would help to identify novel therapeutic targets. Transcranial magnetic stimulation, an FDA-approved treatment for depression, has been proposed as a treatment for addiction in general, but further evaluation is needed to determine its efficacy for smoking cessation.

Large GWAS are identifying molecular genetic influences on smoking phenotypes. The greater sensitivity of these large studies allows signals to be identified that may inform the search for potential therapeutic targets, but the studies require somewhat blunt phenotypes. The strongest evidence on potential therapeutic targets to date points to variants related to nAChRs (*CHRNA5-A3-B4* gene cluster) and nicotine metabolism (*CYP2A6* gene). Variation in these genes influences intensity of smoking and nicotine dependence, and an increasing amount of evidence suggests that such variation may influence smoking cessation and be useful for personalized optimization of therapeutic choice. Genetic variants associated with smoking behaviors also provide tools that can be used to support stronger causal inference in observational studies—for example, by treating these genetic variants as instrumental variables (a method known as Mendelian randomization, which is predicated on the assumption that because genotype is assigned randomly at meiosis it should not be associated with potential confounders at a population level) (Gage et al. 2016). Emerging evidence suggests that genetic variants may influence responses to smoking cessation treatments, offering the potential for personalized or stratified approaches to treatment. However, this approach requires a randomized clinical trial to determine its efficacy and cost-effectiveness. Future research should focus on assessing smoking cessation outcomes prospectively

(e.g., by routinely collecting genetic data at baseline in RCTs of smoking cessation interventions) and using intermediate phenotypes (e.g., brain circuits that are relevant to nicotine dependence) through modern genetic approaches. Research should also investigate genetic predictors of responses to behavioral and pharmacologic interventions.

From a public health perspective, interventions to achieve smoking cessation must be developed that are more effective than the current options. The development of biologically based biomarkers for diseases involving organ systems has led to the development of successful therapies for a variety of these diseases. However, such biomarker research lags behind in the fields of addiction (in general) and of nicotine dependence (in particular). It will be important to invest in continued efforts to translate findings and observations from animal models of nicotine addiction and apply them to clinical settings to provide novel, mechanistically sound therapies for humans.

Limited ecologic validity and questions about subsequent predictability are limitations to almost all studies summarized in this chapter. Smoking is frequently comorbid with other neuropsychiatric diseases, including schizophrenia, depression, and anxiety disorders. Moreover, persons who abuse nicotine also use other drugs, including alcohol and marijuana. And yet, most research cohorts involving drugs are only on the basis of smoking. Therefore, a better understanding of the connections between nicotine dependence and neuropsychiatric comorbidity dual-drug dependence is warranted. Similarly, responses to smoking pharmacotherapies clearly differ by sex, but to date, little work has focused on these differences, whether in basic neurobiology or in the interactions with pharmacogenetics. For example, some studies suggest that female smokers may be best treated by medications that do not interact directly with nicotinic mechanisms; this should be explored further. Sex differences also should be evaluated further in the pathophysiology of nicotine addiction and be considered when treating patients. A shift toward developing individualized, multifaceted approaches to smoking cessation is critical.

Conclusions

1. The evidence is suggestive but not sufficient to infer that increasing glutamate transport can alleviate nicotine withdrawal symptoms and prevent relapse.
2. The evidence is suggestive but not sufficient to infer that neuropeptide systems play a role in multiple stages of the nicotine addiction process, and that modulating the function of certain neuropeptides can reduce smoking behavior in humans.
3. The evidence is suggestive but not sufficient to infer that targeting the habenulo-interpeduncular pathway with agents that increase the aversive properties of nicotine are a useful therapeutic target for smoking cessation.
4. The evidence is suggestive but not sufficient to infer that vaccines generating adequate levels of nicotine-specific antibodies can block the addictive effects of nicotine and aid smoking cessation.
5. The evidence is suggestive but not sufficient to infer that dysregulated brain circuits, including prefrontal and cingulate cortical regions and their connections with various striatal and insula loci, can serve as novel therapeutic targets for smoking cessation.
6. The evidence is suggestive but not sufficient to infer that the effectiveness of nicotine replacement therapy may vary across specific genotype groups.

References¹

- Acri JB, Cross AJ, Skolnick P. From bench to bedside: mGluR2 positive allosteric modulators as medications to treat substance use disorders. *Psychopharmacology* 2017;234(9–10):1347–55.
- Addicott MA, Sweitzer MM, Froeliger B, Rose JE, McClernon FJ. Increased functional connectivity in an insula-based network is associated with improved smoking cessation outcomes. *Neuropsychopharmacology* 2015;40(11):2648–56.
- Akkus F, Ametamey SM, Treyer V, Burger C, Johayem A, Umbrecht D, Gomez Mancilla B, Sovago J, Buck A, Hasler G. Marked global reduction in mGluR5 receptor binding in smokers and ex-smokers determined by [11C]ABP688 positron emission tomography. *Proceedings of the National Academy of Sciences of the United States of America* 2013;110(2):737–42.
- Akkus F, Treyer V, Johayem A, Ametamey SM, Mancilla BG, Sovago J, Buck A, Hasler G. Association of long-term nicotine abstinence with normal metabotropic glutamate receptor-5 binding. *Biological Psychiatry* 2016;79(6):474–80.
- Al Koudsi N, Hoffmann EB, Assadzadeh A, Tyndale RF. Hepatic CYP2A6 levels and nicotine metabolism: impact of genetic, physiological, environmental, and epigenetic factors. *European Journal of Clinical Pharmacology* 2010;66(3):239–51.
- Alajaji M, Bowers MS, Knackstedt L, Damaj MI. Effects of the beta-lactam antibiotic ceftriaxone on nicotine withdrawal and nicotine-induced reinstatement of preference in mice. *Psychopharmacology* 2013;228(3):419–26.
- Ashare RL, Kimmey BA, Rupprecht LE, Bowers ME, Hayes MR, Schmidt HD. Repeated administration of an acetylcholinesterase inhibitor attenuates nicotine taking in rats and smoking behavior in human smokers. *Translational Psychiatry* 2016;6:e713.
- Ashare RL, Wileyto EP, Ruparel K, Goelz PM, Hopson RD, Valdez JN, Gur RC, Loughhead J, Lerman C. Effects of tolcapone on working memory and brain activity in abstinent smokers: a proof-of-concept study. *Drug and Alcohol Dependence* 2013;133(3):852–6.
- Audrain-McGovern J, Al Koudsi N, Rodriguez D, Wileyto EP, Shields PG, Tyndale RF. The role of CYP2A6 in the emergence of nicotine dependence in adolescents. *Pediatrics* 2007;119(1)e264–e274.
- Bagdas D, Muldoon PP, Zhu AZ, Tyndale RF, Damaj MI. Effects of methoxsalen, a CYP2A5/6 inhibitor, on nicotine dependence behaviors in mice. *Neuropharmacology* 2014;85:67–72.
- Baker TB, Weiss RB, Bolt D, von Niederhausern A, Fiore MC, Dunn DM, Piper ME, Matsunami N, Smith SS, Coon H, et al. Human neuronal acetylcholine receptor A5-A3-B4 haplotypes are associated with multiple nicotine dependence phenotypes. *Nicotine and Tobacco Research* 2009;11(7):785–96.
- Baldassarre A, Lewis CM, Committeri G, Snyder AZ, Romani GL, Corbetta M. Individual variability in functional connectivity predicts performance of a perceptual task. *Proceedings of the National Academy of Sciences of the United States of America* 2012;109(9):3516–21.
- Balfour DJ. The neuronal pathways mediating the behavioral and addictive properties of nicotine. *Handbook of Experimental Pharmacology* 2009;(192):209–33.
- Balfour DJ, Wright AE, Benwell ME, Birrell CE. The putative role of extra-synaptic mesolimbic dopamine in the neurobiology of nicotine dependence. *Behavioural Brain Research* 2000;113(1–2):73–83.
- Barr MS, Fitzgerald PB, Farzan F, George TP, Daskalakis ZJ. Transcranial magnetic stimulation to understand the pathophysiology and treatment of substance use disorders. *Current Drug Abuse Reviews* 2008;1(3):328–39.
- Batra A, Gelfort G, Bartels M, Smolczyk H, Buchkremer G, Riess O, Schols L. The dopamine D2 receptor (DRD2) gene—a genetic risk factor in heavy smoking? *Addiction Biology* 2000;5(4):429–36.
- Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handbook of Experimental Pharmacology* 2009;(192):29–60.
- Benowitz NL, Jacob P 3rd. Metabolism of nicotine to cotinine studied by a dual stable isotope method. *Clinical Pharmacology and Therapeutics* 1994;56(5):483–93.
- Bergen AW, Javitz HS, Krasnow R, Nishita D, Michel M, Conti DV, Liu J, Lee W, Edlund CK, Hall S, et al. Nicotinic acetylcholine receptor variation and response to smoking cessation therapies. *Pharmacogenetics and Genomics* 2013;23(2):94–103.
- Berkman ET, Falk EB, Lieberman MD. In the trenches of real-world self-control: neural correlates of breaking the link between craving and smoking. *Psychological Science* 2011;22(4):498–506.
- Berlin I, Covey LS, Jiang H, Hamer D. Lack of effect of D2 dopamine receptor Taq1A polymorphism on smoking cessation. *Nicotine and Tobacco Research* 2005;7(5):725–8.
- Berrendero F, Plaza-Zabala A, Galeote L, Flores A, Bura SA, Kieffer BL, Maldonado R. Influence of delta-opioid receptors in the behavioral effects of nicotine. *Neuropsychopharmacology* 2012;37(10):2332–44.

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- Berrettini W, Yuan X, Tozzi F, Song K, Francks C, Chilcoat H, Waterworth D, Muglia P, Mooser V. Alpha-5/alpha-3 nicotinic receptor subunit alleles increase risk for heavy smoking. *Molecular Psychiatry* 2008;13(4):368–73.
- Bespalov AY, Dravolina OA, Sukhanov I, Zakharova E, Blokhina E, Zvartau E, Danysz W, van Heeke G, Markou A. Metabotropic glutamate receptor (mGluR5) antagonist MPEP attenuated cue- and schedule-induced reinstatement of nicotine self-administration behavior in rats. *Neuropharmacology* 2005;49(Suppl 1):167–78.
- Bevins RA, Palmatier MI. Extending the role of associative learning processes in nicotine addiction. *Behavioral and Cognitive Neuroscience Reviews* 2004;3(3):143–58.
- Bierut LJ, Rice JP, Edenberg HJ, Goate A, Foroud T, Cloninger CR, Begleiter H, Conneally PM, Crowe RR, Hesselbrock V, et al. Family-based study of the association of the dopamine D2 receptor gene (DRD2) with habitual smoking. *American Journal of Medical Genetics* 2000;90(4):299–302.
- Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Gruzca RA, Xuei X, Saccone NL, Saccone SF, Bertelsen S, Fox L, et al. Variants in nicotinic receptors and risk for nicotine dependence. *American Journal of Psychiatry* 2008;165(9):1163–71.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine* 1995;34(4):537–41.
- Bough KJ, Lerman C, Rose JE, McClernon FJ, Kenny PJ, Tyndale RF, David SP, Stein EA, Uhl GR, Conti DV, et al. Biomarkers for smoking cessation. *Clinical Pharmacology and Therapeutics* 2013;93(6):526–38.
- Brody AL, Mukhin AG, Mamoun MS, Luu T, Neary M, Liang L, Shieh J, Sugar CA, Rose JE, Mandelkern MA. Brain nicotinic acetylcholine receptor availability and response to smoking cessation treatment: a randomized trial. *JAMA Psychiatry* 2014;71(7):797–805.
- Brody AL, Mukhin AG, Stephanie S, Mamoun MS, Kozman M, Phuong J, Neary M, Luu T, Mandelkern MA. Treatment for tobacco dependence: effect on brain nicotinic acetylcholine receptor density. *Neuropsychopharmacology* 2013;38(8):1548–56.
- Broms U, Silventoinen K, Madden PA, Heath AC, Kaprio J. Genetic architecture of smoking behavior: a study of Finnish adult twins. *Twin Research and Human Genetics* 2006;9(1):64–72.
- Brujinzeel AW. Neuropeptide systems and new treatments for nicotine addiction. *Psychopharmacology* 2017;234(9–10):1419–37.
- Brujinzeel AW, Ford J, Rogers JA, Scheick S, Ji Y, Bishnoi M, Alexander JC. Blockade of CRF1 receptors in the central nucleus of the amygdala attenuates the dysphoria associated with nicotine withdrawal in rats. *Pharmacology, Biochemistry and Behavior* 2012;101(1):62–8.
- Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, Hoffman A, Perkins KA, Sved AF. Cue dependency of nicotine self-administration and smoking. *Pharmacology, Biochemistry and Behavior* 2001;70(4):515–30.
- Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub7.
- Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD009329. DOI: 10.1002/14651858.CD009329.pub2.
- Camenga DR, Klein JD. Tobacco use disorders. *Child and Adolescent Psychiatric Clinics of North America* 2016;25(3):445–60.
- Canterberry M, Hanlon CA, Hartwell KJ, Li X, Owens M, LeMatty T, Prisciandaro JJ, Borckardt J, Saladin ME, Brady KT, et al. Sustained reduction of nicotine craving with real-time neurofeedback: exploring the role of severity of dependence. *Nicotine and Tobacco Research* 2013;15(12):2120–4.
- Carrera MR, Ashley JA, Hoffman TZ, Isomura S, Wirsching P, Koob GF, Janda KD. Investigations using immunization to attenuate the psychoactive effects of nicotine. *Bioorganic and Medicinal Chemistry* 2004;12(3):563–70.
- Carroll AJ, Sutherland MT, Salmeron BJ, Ross TJ, Stein EA. Greater externalizing personality traits predict less error-related insula and anterior cingulate cortex activity in acutely abstinent cigarette smokers. *Addiction Biology* 2015;20(2):377–89.
- Carter LP, Griffiths RR. Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug and Alcohol Dependence* 2009;105(Suppl 1):S14–S25.
- Cerny EH, Levy R, Mauer J, Mpandi M, Mutter M, Henzlin-Nkubana C, Patiny L, Tuchscherer G, Cerny T. Preclinical development of a vaccine “against smoking”. *Onkologie* 2002;25(5):406–11.
- Chaiton M, Diemert L, Cohen JE, Bondy SJ, Selby P, Philipneri A, Schwartz R. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open* 2016;6(6):e011045.
- Chang CQ, Yesupriya A, Rowell JL, Pimentel CB, Clyne M, Gwinn M, Khoury MJ, Wulf A, Schully SD. A systematic review of cancer GWAS and candidate gene meta-analyses reveals limited overlap but similar effect sizes. *European Journal of Human Genetics* 2014;22(3):402–8.

- Changeux J, Dehaene S. The neuronal workspace model: conscious processing and learning. In: Byrne L, editor. *Learning and Memory: A Comprehensive Reference*. Oxford, United Kingdom: Elsevier, 2008:729–58.
- Changeux JP. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. *Nature Reviews: Neuroscience* 2010;11(6):389–401.
- Chen LS, Baker TB, Piper ME, Breslau N, Cannon DS, Doheny KF, Gogarten SM, Johnson EO, Saccone NL, Wang JC, et al. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRNA4) and cessation treatments in smoking cessation success. *American Journal of Psychiatry* 2012;169(7):735–42.
- Chen LS, Hung RJ, Baker T, Horton A, Culverhouse R, Saccone N, Cheng I, Deng B, Han Y, Hansen HM, et al. CHRNA5 risk variant predicts delayed smoking cessation and earlier lung cancer diagnosis—a meta-analysis. *Journal of the National Cancer Institute* 2015;107(5):dju100.
- Chen N, Reith ME. Structure and function of the dopamine transporter. *European Journal of Pharmacology* 2000;405(1–3):329–39.
- Chenoweth MJ, O’Loughlin J, Sylvestre MP, Tyndale RF. CYP2A6 slow nicotine metabolism is associated with increased quitting by adolescent smokers. *Pharmacogenetics and Genomics* 2013;23(4):232–5.
- Chenoweth MJ, Sylvestre MP, Contreras G, Novalen M, O’Loughlin J, Tyndale RF. Variation in CYP2A6 and tobacco dependence throughout adolescence and in young adult smokers. *Drug and Alcohol Dependence* 2016;158:139–46.
- Chenoweth MJ, Tyndale RF. Pharmacogenetic optimization of smoking cessation treatment. *Trends in Pharmacological Sciences* 2017;38(1):55–66.
- Chiamulera C, Marzo CM, Balfour DJK. Metabotropic glutamate receptor 5 as a potential target for smoking cessation. *Psychopharmacology* 2017;234(9–10):1357–70.
- Choi HD, Shin WG. Lack of association between DRD2 Taq1A gene polymorphism and smoking cessation therapy: a meta-analysis. *International Journal of Clinical Pharmacology and Therapeutics* 2015;53(6):415–21.
- Chua HF, Ho SS, Jasinska AJ, Polk TA, Welsh RC, Liberzon I, Strecher VJ. Self-related neural response to tailored smoking-cessation messages predicts quitting. *Nature Neuroscience* 2011;14(4):426–7.
- Cochrane Tobacco Addiction Group. Our reviews, n.d.; <<http://tobacco.cochrane.org/our-reviews>>; accessed: March 30, 2018.
- Cohen A, Treweek J, Edwards S, Leao RM, Schulteis G, Koob GF, George O. Extended access to nicotine leads to a CRF1 receptor dependent increase in anxiety-like behavior and hyperalgesia in rats. *Addiction Biology* 2015;20(1):56–68.
- Comings DE, Ferry L, Bradshaw-Robinson S, Burchette R, Chiu C, Muhleman D. The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. *Pharmacogenetics* 1996;6(1):73–9.
- Connor JP, Young RM, Lawford BR, Saunders JB, Ritchie TL, Noble EP. Heavy nicotine and alcohol use in alcohol dependence is associated with D2 dopamine receptor (DRD2) polymorphism. *Addictive Behaviors* 2007;32(2):310–9.
- Conti DV, Lee W, Li D, Liu J, Van Den Berg D, Thomas PD, Bergen AW, Swan GE, Tyndale RF, Benowitz NL, et al. Nicotinic acetylcholine receptor beta2 subunit gene implicated in a systems-based candidate gene study of smoking cessation. *Human Molecular Genetics* 2008;17(18):2834–48.
- Coric V, Feldman HH, Oren DA, Shekhar A, Pultz J, Dockens RC, Wu X, Gentile KA, Huang SP, Emison E, et al. Multicenter, randomized, double-blind, active comparator and placebo-controlled trial of a corticotropin-releasing factor receptor-1 antagonist in generalized anxiety disorder. *Depression and Anxiety* 2010;27(5):417–25.
- Cornuz J, Zwahlen S, Jungi WF, Osterwalder J, Klingler K, van Melle G, Bangala Y, Guessous I, Muller P, Willers J, et al. A vaccine against nicotine for smoking cessation: a randomized controlled trial. *PLoS One* 2008;3(6):e2547.
- Cosgrove KP, Esterlis I, McKee SA, Bois F, Seibyl JP, Mazure CM, Krishnan-Sarin S, Staley JK, Picciotto MR, O’Malley SS. Sex differences in availability of beta2*-nicotinic acetylcholine receptors in recently abstinent tobacco smokers. *Archives of General Psychiatry* 2012;69(4):418–27.
- Cosgrove KP, Wang S, Kim SJ, McGovern E, Nabulsi N, Gao H, Labaree D, Tagare HD, Sullivan JM, Morris ED. Sex differences in the brain’s dopamine signature of cigarette smoking. *Journal of Neuroscience* 2014;34(50):16851–5.
- Culbertson CS, Bramen J, Cohen MS, London ED, Olmstead RE, Gan JJ, Costello MR, Shulenberg S, Mandelkern MA, Brody AL. Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. *Archives of General Psychiatry* 2011;68(5):505–15.
- D’Souza MS. Glutamatergic transmission in drug reward: implications for drug addiction. *Frontiers in Neuroscience* 2015;9:404.
- D’Souza MS, Liechti ME, Ramirez-Nino AM, Kuczenski R, Markou A. The metabotropic glutamate 2/3 receptor agonist LY379268 blocked nicotine-induced increases in nucleus accumbens shell dopamine only in the presence of a nicotine-associated context in rats. *Neuropsychopharmacology* 2011;36(10):2111–24.

- D'Souza MS, Markou A. Differential role of N-methyl-D-aspartate receptor-mediated glutamate transmission in the nucleus accumbens shell and core in nicotine seeking in rats. *European Journal of Neuroscience* 2014;39(8):1314–22.
- Dahl JP, Jepsen C, Levenson R, Wileyto EP, Patterson F, Berrettini WH, Lerman C. Interaction between variation in the D2 dopamine receptor (DRD2) and the neuronal calcium sensor-1 (FREQ) genes in predicting response to nicotine replacement therapy for tobacco dependence. *Pharmacogenomics Journal* 2006;6(3):194–9.
- Dani JA. Roles of dopamine signaling in nicotine addiction. *Molecular Psychiatry* 2003;8(3):255–6.
- David SP, Brown RA, Papandonatos GD, Kahler CW, Lloyd-Richardson EE, Munafò MR, Shields PG, Lerman C, Strong D, McCaffery J, et al. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. *Nicotine and Tobacco Research* 2007;9(8):821–33.
- David SP, Hamidovic A, Chen GK, Bergen AW, Wessel J, Kasberger JL, Brown WM, Petruzella S, Thacker EL, Kim Y, et al. Genome-wide meta-analyses of smoking behaviors in African Americans. *Translational Psychiatry* 2012;2:e119.
- David SP, Lancaster T, Stead LF, Evins AE, Prochaska JJ. Opioid antagonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2013a, Issue 6. Art. No.: CD003086. DOI: 10.1002/14651858.CD003086.pub3.
- David SP, Munafò MR. Genetic variation in the dopamine pathway and smoking cessation. *Pharmacogenomics* 2008;9(9):1307–21.
- David SP, Niaura R, Papandonatos GD, Shadel WG, Burkholder GJ, Britt DM, Day A, Stumpff J, Hutchison K, Murphy M, et al. Does the DRD2-Taq1 A polymorphism influence treatment response to bupropion hydrochloride for reduction of the nicotine withdrawal syndrome? *Nicotine and Tobacco Research* 2003;5(6):935–42.
- David SP, Strong DR, Leventhal AM, Lancaster MA, McGeary JE, Munafò MR, Bergen AW, Swan GE, Benowitz NL, Tyndale RF, et al. Influence of a dopamine pathway additive genetic efficacy score on smoking cessation: results from two randomized clinical trials of bupropion. *Addiction* 2013b;108(12):2202–11.
- de Villiers SH, Cornish KE, Troska AJ, Pravetoni M, Pentel PR. Increased efficacy of a trivalent nicotine vaccine compared to a dose-matched monovalent vaccine when formulated with alum. *Vaccine* 2013;31(52):6185–93.
- Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. *Clinical Pharmacology and Therapeutics* 2004;76(1):64–72.
- Desai RI, Bergman J. Effects of the nanoparticle-based vaccine, SEL-068, on nicotine discrimination in squirrel monkeys. *Neuropsychopharmacology* 2015;40(9):2207–16.
- Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *European Journal of Pharmacology* 2000;393(1–3):295–314.
- Di Ciano P, Guranda M, Lagzdins D, Tyndale RF, Gamaledin I, Selby P, Boileau I, Le Foll B. Varenicline induced elevation of dopamine in smokers: a preliminary [(11)C]-(+)-PHNO PET study. *Neuropsychopharmacology* 2016;41(6):1513–20.
- Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, Zangen A. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. *Biological Psychiatry* 2014;76(9):742–9.
- Do KT, Galván A. FDA cigarette warning labels lower craving and elicit fronto-insular activation in adolescent smokers. *Social Cognitive and Affective Neuroscience* 2015;10(11):1484–96.
- Duan J, Wainwright MS, Comeron JM, Saitou N, Sanders AR, Gelernter J, Gejman PV. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Human Molecular Genetics* 2003;12(3):205–16.
- Dubroff JG, Doot RK, Falcone M, Schnoll RA, Ray R, Tyndale RF, Brody AL, Hou C, Schmitz A, Lerman C. Decreased nicotinic receptor availability in smokers with slow rates of nicotine metabolism. *Journal of Nuclear Medicine* 2015;56(11):1724–9.
- Dumais KM, Franklin TR, Jagannathan K, Hager N, Gawrysiak M, Betts J, Farmer S, Guthrie E, Pater H, Janes AC, et al. Multi-site exploration of sex differences in brain reactivity to smoking cues: Consensus across sites and methodologies. *Drug and Alcohol Dependence* 2017;178:469–76.
- Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. *Annals of the New York Academy of Sciences* 2017;1394(1):31–54.
- Ehringer MA, Clegg HV, Collins AC, Corley RP, Crowley T, Hewitt JK, Hopfer CJ, Krauter K, Lessem J, Rhee SH, et al. Association of the neuronal nicotinic receptor beta2 subunit gene (CHRNA2) with subjective responses to alcohol and nicotine. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics* 2007;144B(5):596–604.
- Esterlis I, Hannestad JO, Perkins E, Bois F, D'Souza DC, Tyndale RF, Seibyl JP, Hatsukami DM, Cosgrove KP, O'Malley SS. Effect of a nicotine vaccine on nicotine binding to beta2*-nicotinic acetylcholine receptors in

- vivo in human tobacco smokers. *American Journal of Psychiatry* 2013;170(4):399–407.
- Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. *Archives of Internal Medicine* 2006;166(15):1553–9.
- Fahim RE, Kessler PD, Kalnik MW. Therapeutic vaccines against tobacco addiction. *Expert Review of Vaccines* 2013;12(3):333–42.
- Falcone M, Cao W, Bernardo L, Tyndale RF, Loughhead J, Lerman C. Brain responses to smoking cues differ based on nicotine metabolism rate. *Biological Psychiatry* 2016;80(3):190–7.
- Fedota JR, Stein EA. Resting-state functional connectivity and nicotine addiction: prospects for biomarker development. *Annals of the New York Academy of Sciences* 2015;1349:64–82.
- Fedota JR, Sutherland MT, Salmeron BJ, Ross TJ, Hong LE, Stein EA. Reward anticipation is differentially modulated by varenicline and nicotine in smokers. *Neuropsychopharmacology* 2015;40(8):2038–46.
- Fitzgerald PJ. Elevated norepinephrine may be a unifying etiological factor in the abuse of a broad range of substances: alcohol, nicotine, marijuana, heroin, cocaine, and caffeine. *Substance Abuse* 2013;7:171–83.
- Forget B, Wertheim C, Mascia P, Pushparaj A, Goldberg SR, Le Foll B. Noradrenergic alpha1 receptors as a novel target for the treatment of nicotine addiction. *Neuropsychopharmacology* 2010;35(8):1751–60.
- Fowler CD, Kenny PJ. Nicotine aversion: neurobiological mechanisms and relevance to tobacco dependence vulnerability. *Neuropharmacology* 2014;76(Part B):533–44.
- Fowler CD, Lu Q, Johnson PM, Marks MJ, Kenny PJ. Habenular alpha5 nicotinic receptor subunit signalling controls nicotine intake. *Nature* 2011;471(7340):597–601.
- Frahm S, Slimak MA, Ferrarese L, Santos-Torres J, Antolin-Fontes B, Auer S, Filkin S, Pons S, Fontaine JF, Tsetlin V, et al. Aversion to nicotine is regulated by the balanced activity of beta4 and alpha5 nicotinic receptor subunits in the medial habenula. *Neuron* 2011;70(3):522–35.
- Franklin T, Wang Z, Suh JJ, Hazan R, Cruz J, Li Y, Goldman M, Detre JA, O'Brien CP, Childress AR. Effects of varenicline on smoking cue-triggered neural and craving responses. *Archives of General Psychiatry* 2011;68(5):516–26.
- Fraser PE, Rosen AC. Transcranial direct current stimulation and behavioral models of smoking addiction. *Frontiers in Psychiatry* 2012;3:79.
- Freathy RM, Ring SM, Shields B, Galobardes B, Knight B, Weedon MN, Smith GD, Frayling TM, Hattersley AT. A common genetic variant in the 15q24 nicotinic acetylcholine receptor gene cluster (CHRNA5-CHRNA3-CHRNA4) is associated with a reduced ability of women to quit smoking in pregnancy. *Human Molecular Genetics* 2009;18(15):2922–7.
- Froeliger B, McConnell PA, Bell S, Sweitzer M, Kozink RV, Eichberg C, Hallyburton M, Kaiser N, Gray KM, McClernon FJ. Association between baseline corticothalamic-mediated inhibitory control and smoking relapse vulnerability. *JAMA Psychiatry* 2017;74(4):379–86.
- Gabrieli JD, Ghosh SS, Whitfield-Gabrieli S. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron* 2015;85(1):11–26.
- Gage SH, Munafo MR, Davey Smith G. Causal inference in developmental origins of health and disease (DOHaD) research. *Annual Review of Psychology* 2016;67:567–85.
- García-Rodríguez O, Secades-Villa R, Flórez-Salamanca L, Okuda M, Liu SM, Blanco C. Probability and predictors of relapse to smoking: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence* 2013;132(3):479–85.
- Gaznick N, Tranel D, McNutt A, Bechara A. Basal ganglia plus insula damage yields stronger disruption of smoking addiction than basal ganglia damage alone. *Nicotine and Tobacco Research* 2014;16(4):445–53.
- Gipson CD, Reissner KJ, Kupchik YM, Smith AC, Stankeviciute N, Hensley-Simon ME, Kalivas PW. Reinstatement of nicotine seeking is mediated by glutamatergic plasticity. *Proceedings of the National Academy of Sciences of the United States of America* 2013;110(22):9124–9.
- Gold AB, Lerman C. Pharmacogenetics of smoking cessation: role of nicotine target and metabolism genes. *Human Genetics* 2012.
- Gómez-Coronado N, Walker AJ, Berk M, Dodd S. Current and emerging pharmacotherapies for cessation of tobacco smoking. *Pharmacotherapy* 2018;38(2):235–58.
- Goniewicz ML, Delijewski M. Nicotine vaccines to treat tobacco dependence. *Human Vaccines & Immunotherapeutics* 2013;9(1):13–25.
- Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. *Annals of the New York Academy of Sciences* 2014;1327:79–93.
- Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation (2008 review). *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD000058. DOI: 10.1002/14651858.CD000058.pub2.
- Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Research: Brain Research Reviews* 2000;31(2–3):330–41.

- Grieder TE, Herman MA, Contet C, Tan LA, Vargas-Perez H, Cohen A, Chwalek M, Maal-Bared G, Freiling J, Schlosburg JE, et al. VTA CRF neurons mediate the aversive effects of nicotine withdrawal and promote intake escalation. *Nature Neuroscience* 2014;17(12):1751–8.
- Gu DF, Hinks LJ, Morton NE, Day IN. The use of long PCR to confirm three common alleles at the CYP2A6 locus and the relationship between genotype and smoking habit. *Annals of Human Genetics* 2000;64(Part 5):383–90.
- Hamidovic A, Kasberger JL, Young TR, Goodloe RJ, Redline S, Buxbaum SG, Benowitz NL, Bergen AW, Butler KR, Franceschini N, et al. Genetic variability of smoking persistence in African Americans. *Cancer Prevention Research* 2011;4(5):729–34.
- Hamilton DA, Mahoney MC, Novalen M, Chenoweth MJ, Heitjan DF, Lerman C, Tyndale RF, Hawk LW Jr. Test-retest reliability and stability of the nicotine metabolite ratio among treatment-seeking smokers. *Nicotine and Tobacco Research* 2015;17(12):1505–9.
- Hanlon CA, Hartwell KJ, Canterbury M, Li X, Owens M, Lematty T, Prisciandaro JJ, Borckardt J, Brady KT, George MS. Reduction of cue-induced craving through realtime neurofeedback in nicotine users: the role of region of interest selection and multiple visits. *Psychiatry Research* 2013;213(1):79–81.
- Hartwell KJ, Hanlon CA, Li X, Borckardt JJ, Canterbury M, Prisciandaro JJ, Moran-Santa Maria MM, LeMatty T, George MS, Brady KT. Individualized real-time fMRI neurofeedback to attenuate craving in nicotine-dependent smokers. *Journal of Psychiatry and Neuroscience* 2016;41(1):48–55.
- Hartwell KJ, Lematty T, McRae-Clark AL, Gray KM, George MS, Brady KT. Resisting the urge to smoke and craving during a smoking quit attempt on varenicline: results from a pilot fMRI study. *American Journal of Drug and Alcohol Abuse* 2013;39(2):92–8.
- Hatsukami DK, Jorenby DE, Gonzales D, Rigotti NA, Glover ED, Oncken CA, Tashkin DP, Reus VI, Akhavan RC, Fahim RE, et al. Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. *Clinical Pharmacology and Therapeutics* 2011;89(3):392–9.
- Hatsukami DK, Rennard S, Jorenby D, Fiore M, Koopmeiners J, de Vos A, Horwith G, Pentel PR. Safety and immunogenicity of a nicotine conjugate vaccine in current smokers. *Clinical Pharmacology and Therapeutics* 2005;78(5):456–67.
- Havermans A, Vuurman EF, van den Hurk J, Hoogsteder P, van Schayck OC. Treatment with a nicotine vaccine does not lead to changes in brain activity during smoking cue exposure or a working memory task. *Addiction* 2014;109(8):1260–7.
- Hicks MJ, Rosenberg JB, De BP, Pagovich OE, Young CN, Qiu JP, Kaminsky SM, Hackett NR, Worgall S, Janda KD, et al. AAV-directed persistent expression of a gene encoding anti-nicotine antibody for smoking cessation. *Science Translational Medicine* 2012;4(140):140ra87.
- Hieda Y, Keyler DE, Ennifar S, Fattom A, Pentel PR. Vaccination against nicotine during continued nicotine administration in rats: immunogenicity of the vaccine and effects on nicotine distribution to brain. *International Journal of Immunopharmacology* 2000;22(10):809–19.
- Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. *Proceedings of the National Academy of Sciences of the United States of America* 2008;105(49):19480–5.
- Hollander JA, Pham D, Fowler CD, Kenny PJ. Hypocretin-1 receptors regulate the reinforcing and reward-enhancing effects of cocaine: pharmacological and behavioral genetics evidence. *Frontiers in Behavioral Neuroscience* 2012;6:47.
- Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Archives of General Psychiatry* 2009;66(4):431–41.
- Hong LE, Hodgkinson CA, Yang Y, Sampath H, Ross TJ, Buchholz B, Salmeron BJ, Srivastava V, Thaker GK, Goldman D, et al. A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. *Proceedings of the National Academy of Sciences of the United States of America* 2010;107(30):13509–14.
- Hoogsteder PH, Kotz D, van Spiegel PI, Viechtbauer W, van Schayck OC. Efficacy of the nicotine vaccine 3'-AmNic-rEPA (NicVAX) co-administered with varenicline and counselling for smoking cessation: a randomized placebo-controlled trial. *Addiction* 2014;109(8):1252–9.
- Huettel S, Song AW, McCarthy G. *Functional Magnetic Resonance Imaging*. 3rd ed. Cary (NC): Oxford University Press, 2014.
- Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub4.
- Hughes JR, Stead LF, Lancaster T. Nortriptyline for smoking cessation: a review. *Nicotine and Tobacco Research* 2005;7(4):491–9.
- Hulka LM, Treyer V, Scheidegger M, Preller KH, Vonmoos M, Baumgartner MR, Johayem A, Ametamey SM, Buck A, Seifritz E, et al. Smoking but not cocaine use is associated with lower cerebral metabotropic glutamate receptor 5 density in humans. *Molecular Psychiatry* 2014;19(5):625–32.

- Isomura S, Wirsching P, Janda KD. An immunotherapeutic program for the treatment of nicotine addiction: hapten design and synthesis. *Journal of Organic Chemistry* 2001;66(12):4115–21.
- Jackson KJ, Carroll FI, Negus SS, Damaj MI. Effect of the selective kappa-opioid receptor antagonist JDTC on nicotine antinociception, reward, and withdrawal in the mouse. *Psychopharmacology* 2010a;210(2):285–94.
- Jackson KJ, Marks MJ, Vann RE, Chen X, Gamage TF, Warner JA, Damaj MI. Role of alpha5 nicotinic acetylcholine receptors in pharmacological and behavioral effects of nicotine in mice. *Journal of Pharmacology and Experimental Therapeutics* 2010b;334(1):137–46.
- Jacob NT, Lockner JW, Schlosburg JE, Ellis BA, Eubanks LM, Janda KD. Investigations of enantiopure nicotine haptens using an adjuvanting carrier in anti-nicotine vaccine development. *Journal of Medicinal Chemistry* 2016;59(6):2523–9.
- Jasinska AJ, Chua HF, Ho SS, Polk TA, Rozek LS, Strecher VJ. Amygdala response to smoking-cessation messages mediates the effects of serotonin transporter gene variation on quitting. *Neuroimage* 2012;60(1):766–73.
- Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infectious Diseases* 2004;4(2):84–90.
- Jensen KP, DeVito EE, Herman AI, Valentine GW, Gelernter J, Sofuoglu M. A CHRNA5 smoking risk variant decreases the aversive effects of nicotine in humans. *Neuropsychopharmacology* 2015;40(12):2813–21.
- Johnstone E, Benowitz N, Cargill A, Jacob R, Hinks L, Day I, Murphy M, Walton R. Determinants of the rate of nicotine metabolism and effects on smoking behavior. *Clinical Pharmacology and Therapeutics* 2006;80(4):319–30.
- Johnstone EC, Yudkin P, Griffiths SE, Fuller A, Murphy M, Walton R. The dopamine D2 receptor C32806T polymorphism (DRD2 Taq1A RFLP) exhibits no association with smoking behaviour in a healthy UK population. *Addiction Biology* 2004;9(3-4):221–6.
- Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry* 1999;4(3):290–6.
- Jorm AF, Henderson AS, Jacomb PA, Christensen H, Korten AE, Rodgers B, Tan X, Easteal S. Association of smoking and personality with a polymorphism of the dopamine transporter gene: results from a community survey. *American Journal of Medical Genetics* 2000;96(3):331–4.
- Justinova Z, Le Foll B, Redhi GH, Markou A, Goldberg SR. Differential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on nicotine versus cocaine self-administration and relapse in squirrel monkeys. *Psychopharmacology* 2016;233(10):1791–800.
- Justinova Z, Panlilio LV, Secci ME, Redhi GH, Schindler CW, Cross AJ, Mrzljak L, Medd A, Shaham Y, Goldberg SR. The novel metabotropic glutamate receptor 2 positive allosteric modulator, AZD8529, decreases nicotine self-administration and relapse in squirrel monkeys. *Biological Psychiatry* 2015;78(7):452–62.
- Karama S, Ducharme S, Corley J, Chouinard-Decorte F, Starr JM, Wardlaw JM, Bastin ME, Deary IJ. Cigarette smoking and thinning of the brain's cortex. *Molecular Psychiatry* 2015;20(6):778–85.
- Kaufmann A, Hitsman B, Goetz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Tyndale RF, Schnoll RA. Rate of nicotine metabolism and smoking cessation outcomes in a community-based sample of treatment-seeking smokers. *Addictive Behaviors* 2015;51:93–9.
- Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. *Neuroimage* 2008;39(1):527–37.
- Kendler KS, Neale MC, Sullivan P, Corey LA, Gardner CO, Prescott CA. A population-based twin study in women of smoking initiation and nicotine dependence. *Psychological Medicine* 1999;29(2):299–308.
- Kenny PJ, Chartoff E, Roberto M, Carlezon WA Jr, Markou A. NMDA receptors regulate nicotine-enhanced brain reward function and intravenous nicotine self-administration: role of the ventral tegmental area and central nucleus of the amygdala. *Neuropsychopharmacology* 2009;34(2):266–81.
- Keyler DE, Hieda Y, St Peter J, Pentel PR. Altered disposition of repeated nicotine doses in rats immunized against nicotine. *Nicotine and Tobacco Research* 1999;1(3):241–9.
- Keyler DE, Roiko SA, Benlhabib E, LeSage MG, St Peter JV, Stewart S, Fuller S, Le CT, Pentel PR. Monoclonal nicotine-specific antibodies reduce nicotine distribution to brain in rats: dose- and affinity-response relationships. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 2005;33(7):1056–61.
- Keyler DE, Roiko SA, Earley CA, Murtaugh MP, Pentel PR. Enhanced immunogenicity of a bivalent nicotine vaccine. *International Immunopharmacology* 2008;8(11):1589–94.
- Kim DY, Yoo SS, Tegethoff M, Meinlschmidt G, Lee JH. The inclusion of functional connectivity information into fMRI-based neurofeedback improves its efficacy in the reduction of cigarette cravings. *Journal of Cognitive Neuroscience* 2015;27(8):1552–72.
- Klimek V, Zhu MY, Dilley G, Konick L, Overholser JC, Meltzer HY, May WL, Stockmeier CA, Ordway GA. Effects of long-term cigarette smoking on the human

- locus coeruleus. *Archives of General Psychiatry* 2001;58(9):821–7.
- Knackstedt LA, Kalivas PW. Glutamate and reinstatement. *Current Opinion in Pharmacology* 2009;9(1):59–64.
- Knackstedt LA, LaRowe S, Mardikian P, Malcolm R, Upadhyaya H, Hedden S, Markou A, Kalivas PW. The role of cystine-glutamate exchange in nicotine dependence in rats and humans. *Biological Psychiatry* 2009;65(10):841–5.
- Kober H, Brewer JA, Height KL, Sinha R. Neural stress reactivity relates to smoking outcomes and differentiates between mindfulness and cognitive-behavioral treatments. *Neuroimage* 2017;151:4–13.
- Koob GF. A role for brain stress systems in addiction. *Neuron* 2008;59(1):11–34.
- Koob GF, Simon EJ. The neurobiology of addiction: where we have been and where we are going. *Journal of Drug Issues* 2009;39(1):115–32.
- Koob GF, Volkow ND. Neurobiology of addiction: a neuro-circuitry analysis. *Lancet Psychiatry* 2016;3(8):760–73.
- Krönke KM, Wolff M, Benz A, Goschke T. Successful smoking cessation is associated with prefrontal cortical function during a Stroop task: a preliminary study. *Psychiatry Research* 2015;234(1):52–6.
- Kutlu MG, Gould TJ. Nicotinic modulation of hippocampal cell signaling and associated effects on learning and memory. *Physiology and Behavior* 2016;155:162–71.
- Kuwabara H, Heishman SJ, Brasic JR, Contoreggi C, Cascella N, Mackowick KM, Taylor R, Rousset O, Willis W, Huestis MA, et al. Mu opioid receptor binding correlates with nicotine dependence and reward in smokers. *PLoS One* 2014;9(12):e113694.
- Kwon JM, Goate AM. The candidate gene approach. *Alcohol Research and Health* 2000;24(3):164–8.
- Lameka K, Farwell MD, Ichise M. Positron emission tomography. *Handbook of Clinical Neurology* 2016;135:209–27.
- Lerman C, Caporaso NE, Audrain J, Main D, Bowman ED, Lockshin B, Boyd NR, Shields PG. Evidence suggesting the role of specific genetic factors in cigarette smoking. *Health Psychology* 1999;18(1):14–20.
- Lerman C, Gu H, Loughhead J, Ruparel K, Yang Y, Stein EA. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry* 2014;71(5):523–30.
- Lerman C, Jepson C, Wileyto EP, Epstein LH, Rukstalis M, Patterson F, Kaufmann V, Restine S, Hawk L, Niaura R, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. *Neuropsychopharmacology* 2006a;31(1):231–42.
- Lerman C, Jepson C, Wileyto EP, Patterson F, Schnoll R, Mroziewicz M, Benowitz N, Tyndale RF. Genetic variation in nicotine metabolism predicts the efficacy of extended-duration transdermal nicotine therapy. *Clinical Pharmacology and Therapeutics* 2010;87(5):553–7.
- Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, Swan GE, Benowitz NL, Heitjan DF, Tyndale RF, et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. *Lancet Respiratory Medicine* 2015;3(2):131–8.
- Lerman C, Shields PG, Wileyto EP, Audrain J, Hawk LH Jr, Pinto A, Kucharski S, Krishnan S, Niaura R, Epstein LH. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. *Health Psychology* 2003;22(5):541–8.
- Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, Pinto A, Benowitz N. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clinical Pharmacology and Therapeutics* 2006b;79(6):600–8.
- LeSage MG, Keyler DE, Hieda Y, Collins G, Burroughs D, Le C, Pentel PR. Effects of a nicotine conjugate vaccine on the acquisition and maintenance of nicotine self-administration in rats. *Psychopharmacology* 2006a;184(3–4):409–16.
- LeSage MG, Keyler DE, Pentel PR. Current status of immunologic approaches to treating tobacco dependence: vaccines and nicotine-specific antibodies. *AAPS Journal* 2006b;8(1):E65–E75.
- LeSage MG, Shelley D, Pravetoni M, Pentel PR. Enhanced attenuation of nicotine discrimination in rats by combining nicotine-specific antibodies with a nicotinic receptor antagonist. *Pharmacology, Biochemistry and Behavior* 2012;102(1):157–62.
- Leslie FM, Mojica CY, Reynaga DD. Nicotinic receptors in addiction pathways. *Molecular Pharmacology* 2013;83(4):753–8.
- Leung T, Bergen A, Munafò MR, De Ruyck K, Selby P, De Luca V. Effect of the rs1051730-rs16969968 variant and smoking cessation treatment: a meta-analysis. *Pharmacogenomics* 2015;16(7):713–20.
- Li L, Jia K, Zhou X, McCallum SE, Hough LB, Ding X. Impact of nicotine metabolism on nicotine's pharmacological effects and behavioral responses: insights from a Cyp2a(4/5)bgs-null mouse. *Journal of Pharmacology and Experimental Therapeutics* 2013a;347(3):746–54.
- Li MD, Cheng R, Ma JZ, Swan GE. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction* 2003;98(1):23–31.
- Li S, Yang Y, Hoffmann E, Tyndale RF, Stein EA. CYP2A6 genetic variation alters striatal-cingulate circuits,

- network hubs, and executive processing in smokers. *Biological Psychiatry* 2017;81(7):554–63.
- Li X, Hartwell KJ, Owens M, Lematty T, Borckardt JJ, Hanlon CA, Brady KT, George MS. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biological Psychiatry* 2013b;73(8):714–20.
- Li X, Semenova S, D’Souza MS, Stoker AK, Markou A. Involvement of glutamatergic and GABAergic systems in nicotine dependence: implications for novel pharmacotherapies for smoking cessation. *Neuropharmacology* 2014;76(Part B):554–65.
- Lindblom N, de Villiers SH, Kalayanov G, Gordon S, Johansson AM, Svensson TH. Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats. *Respiration* 2002;69(3):254–60.
- Lindquist KJ, Jorgenson E, Hoffmann TJ, Witte JS. The impact of improved microarray coverage and larger sample sizes on future genome-wide association studies. *Genetic Epidemiology* 2013;37(4):383–92.
- Liu X, Wang L, Yan H, Chang Y. Assembly and assessment of DNA scaffolded vaccines. *Methods in Molecular Biology* 2016;1404:301–11.
- Lockner JW, Ho SO, McCague KC, Chiang SM, Do TQ, Fujii G, Janda KD. Enhancing nicotine vaccine immunogenicity with liposomes. *Bioorganic and Medicinal Chemistry Letters* 2013;23(4):975–8.
- Loughead J, Ray R, Wileyto EP, Ruparel K, Sanborn P, Siegel S, Gur RC, Lerman C. Effects of the alpha-4beta2 partial agonist varenicline on brain activity and working memory in abstinent smokers. *Biological Psychiatry* 2010;67(8):715–21.
- Loughead J, Wileyto EP, Ruparel K, Falcone M, Hopson R, Gur R, Lerman C. Working memory-related neural activity predicts future smoking relapse. *Neuropsychopharmacology* 2015;40(6):1311–20.
- Loukola A, Buchwald J, Gupta R, Palviainen T, Hallfors J, Tikkanen E, Korhonen T, Ollikainen M, Sarin AP, Ripatti S, et al. A genome-wide association study of a biomarker of nicotine metabolism. *PLoS Genetics* 2015;11(9):e1005498.
- Luijten M, Veltman DJ, van den Brink W, Hester R, Field M, Smits M, Franken IH. Neurobiological substrate of smoking-related attentional bias. *Neuroimage* 2011;54(3):2374–81.
- Maglione MA, Das L, Raaen L, Smith A, Chari R, Newberry S, Shanman R, Perry T, Goetz MB, Gidengil C. Safety of vaccines used for routine immunization of U.S. children: a systematic review. *Pediatrics* 2014;134(2):325–37.
- Malaiyandi V, Goodz SD, Sellers EM, Tyndale RF. CYP2A6 genotype, phenotype, and the use of nicotine metabolites as biomarkers during ad libitum smoking. *Cancer Epidemiology, Biomarkers and Prevention* 2006a;15(10):1812–9.
- Malaiyandi V, Lerman C, Benowitz NL, Jepson C, Patterson F, Tyndale RF. Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. *Molecular Psychiatry* 2006b;11(4):400–9.
- Mansvelder HD, Fagen ZM, Chang B, Mitchum R, McGehee DS. Bupropion inhibits the cellular effects of nicotine in the ventral tegmental area. *Biochemical Pharmacology* 2007;74(8):1283–91.
- Mantsch JR, Baker DA, Funk D, Lê AD, Shaham Y. Stress-induced reinstatement of drug seeking: 20 years of progress. *Neuropsychopharmacology* 2016;41(1):335–56.
- Mao D, Gallagher K, McGehee DS. Nicotine potentiation of excitatory inputs to ventral tegmental area dopamine neurons. *Journal of Neuroscience* 2011;31(18):6710–20.
- Marchi M, Grilli M, Pittaluga AM. Nicotinic modulation of glutamate receptor function at nerve terminal level: a fine-tuning of synaptic signals. *Frontiers in Pharmacology* 2015;6:89.
- Marcinkiewicz CA, Prado MM, Isaac SK, Marshall A, Rylkova D, Bruijnzeel AW. Corticotropin-releasing factor within the central nucleus of the amygdala and the nucleus accumbens shell mediates the negative affective state of nicotine withdrawal in rats. *Neuropsychopharmacology* 2009;34(7):1743–52.
- Maskos U, Molles BE, Pons S, Besson M, Guiard BP, Guilloux JP, Evrard A, Cazala P, Cormier A, Mameli-Engvall M, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature* 2005;436(7047):103–7.
- Maurer P, Jennings GT, Willers J, Rohner F, Lindman Y, Roubicek K, Renner WA, Muller P, Bachmann MF. A therapeutic vaccine for nicotine dependence: preclinical efficacy, and Phase I safety and immunogenicity. *European Journal of Immunology* 2005;35(7):2031–40.
- McClure EA, Baker NL, Gipson CD, Carpenter MJ, Roper AP, Froeliger BE, Kalivas PW, Gray KM. An open-label pilot trial of N-acetylcysteine and varenicline in adult cigarette smokers. *American Journal of Drug and Alcohol Abuse* 2015;41(1):52–6.
- McCluskie MJ, Pryde DC, Gervais DP, Stead DR, Zhang N, Benoit M, Robertson K, Kim IJ, Tharmanathan T, Merson JR, et al. Enhancing immunogenicity of a 3’aminomethylnicotine-DT-conjugate anti-nicotine vaccine with CpG adjuvant in mice and non-human primates. *International Immunopharmacology* 2013;16(1):50–6.
- McKee SA, Potenza MN, Kober H, Sofuoglu M, Arnsten AF, Picciotto MR, Weinberger AH, Ashare R, Sinha R. A translational investigation targeting stress-reactivity and prefrontal cognitive control with guanfacine for smoking cessation. *Journal of Psychopharmacology* 2015;29(3):300–11.

- Menossi HS, Goudriaan AE, de Azevedo-Marques Perico C, Nicastrì S, de Andrade AG, D'Elia G, Li CS, Castaldelli-Maia JM. Neural bases of pharmacological treatment of nicotine dependence—insights from functional brain imaging: a systematic review. *CNS Drugs* 2013;27(11):921–41.
- Mihov Y, Hasler G. Negative allosteric modulators of metabotropic glutamate receptors subtype 5 in addiction: a therapeutic window. *International Journal of Neuropsychopharmacology* 2016;19(7):pyw002.
- Millar NS, Harkness PC. Assembly and trafficking of nicotinic acetylcholine receptors (review). *Molecular Membrane Biology* 2008;25(4):279–92.
- Miller KD, Roque R, Clegg CH. Novel anti-nicotine vaccine using a trimeric coiled-coil hapten carrier. *PLoS One* 2014;9(12):e114366.
- Mooney ME, Schmitz JM, Allen S, Grabowski J, Pentel P, Oliver A, Hatsukami DK. Bupropion and naltrexone for smoking cessation: a double-blind randomized placebo-controlled clinical trial. *Clinical Pharmacology and Therapeutics* 2016;100(4):344–52.
- Moran-Santa Maria MM, Hartwell KJ, Hanlon CA, Canterberry M, Lematty T, Owens M, Brady KT, George MS. Right anterior insula connectivity is important for cue-induced craving in nicotine-dependent smokers. *Addiction Biology* 2015;20(2):407–14.
- Moreno AY, Azar MR, Koob GF, Janda KD. Probing the protective effects of a conformationally constrained nicotine vaccine. *Vaccine* 2012;30(47):6665–70.
- Morton LM, Wang SS, Bergen AW, Chatterjee N, Kvale P, Welch R, Yeager M, Hayes RB, Chanock SJ, Caporaso NE. DRD2 genetic variation in relation to smoking and obesity in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Pharmacogenetics and Genomics* 2006;16(12):901–10.
- Munafò M. Replication validity of genetic association studies of smoking behavior: what can meta-analytic techniques offer? *Nicotine and Tobacco Research* 2004;6(2):381–2.
- Munafò M, Clark T, Johnstone E, Murphy M, Walton R. The genetic basis for smoking behavior: a systematic review and meta-analysis. *Nicotine and Tobacco Research* 2004;6(4):583–97.
- Munafò MR, Johnstone EC, Walther D, Uhl GR, Murphy MF, Aveyard P. CHRNA3 rs1051730 genotype and short-term smoking cessation. *Nicotine and Tobacco Research* 2011;13(10):982–8.
- Munafò MR, Timofeeva MN, Morris RW, Prieto-Merino D, Sattar N, Brennan P, Johnstone EC, Relton C, Johnson PC, Walther D, et al. Association between genetic variants on chromosome 15q25 locus and objective measures of tobacco exposure. *Journal of the National Cancer Institute* 2012;104(10):740–8.
- Munafò MR, Timpson NJ, David SP, Ebrahim S, Lawlor DA. Association of the DRD2 gene Taq1A polymorphism and smoking behavior: a meta-analysis and new data. *Nicotine and Tobacco Research* 2009;11(1):64–76.
- Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends in Neurosciences* 2009;32(1):56–67.
- Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Structure & Function* 2010;214(5–6):435–50.
- Nestor L, McCabe E, Jones J, Clancy L, Garavan H. Differences in “bottom-up” and “top-down” neural activity in current and former cigarette smokers: evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *Neuroimage* 2011;56(4):2258–75.
- Nestor LJ, McCabe E, Jones J, Clancy L, Garavan H. Shared and divergent neural reactivity to non-drug operant response outcomes in current smokers and ex-smokers. *Brain Research* 2018a;1680:54–61.
- Nestor LJ, McCabe E, Jones J, Clancy L, Garavan H. Smokers and ex-smokers have shared differences in the neural substrates for potential monetary gains and losses. *Addiction Biology* 2018b;23(1):369–78.
- Neuhaus A, Bajbouj M, Kienast T, Kalus P, von Haebler D, Winterer G, Gallinat J. Persistent dysfunctional frontal lobe activation in former smokers. *Psychopharmacology* 2006;186(2):191–200.
- Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation* 2004;23(6):540–5.
- Nishizawa D, Kasai S, Hasegawa J, Sato N, Yamada H, Tanioka F, Nagashima M, Katoh R, Satoh Y, Tagami M, et al. Associations between the orexin (hypocretin) receptor 2 gene polymorphism Val308Ile and nicotine dependence in genome-wide and subsequent association studies. *Molecular Brain* 2015;8:50.
- Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Archives of General Psychiatry* 1991;48(7):648–54.
- Noble EP, Gottschalk LA, Fallon JH, Ritchie TL, Wu JC. D2 dopamine receptor polymorphism and brain regional glucose metabolism. *American Journal of Medical Genetics* 1997;74(2):162–6.
- Noble EP, St Jeor ST, Ritchie T, Sydulko K, St Jeor SC, Fitch RJ, Brunner RL, Sparkes RS. D2 dopamine receptor gene and cigarette smoking: a reward gene? *Medical Hypotheses* 1994;42(4):257–60.
- Nuechterlein EB, Ni L, Domino EF, Zubieta JK. Nicotine-specific and non-specific effects of cigarette smoking on endogenous opioid mechanisms. *Progress in*

- Neuro-Psychopharmacology and Biological Psychiatry* 2016;69:69–77.
- Nygaard SK, Hourguettes NJ, Sobczak GG, Carlezon WA, Bruchas MR. Stress-induced reinstatement of nicotine preference requires dynorphin/kappa opioid activity in the basolateral amygdala. *Journal of Neuroscience* 2016;36(38):9937–48.
- Ono M, Kochiyama T, Fujino J, Sozu T, Kawada R, Yokoyama N, Sugihara G, Murai T, Takahashi H. Self-efficacy modulates the neural correlates of craving in male smokers and ex-smokers: an fMRI study. *Addiction Biology* 2018;23(5):1179–88.
- Paterson NE, Semenova S, Gasparini F, Markou A. The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice. *Psychopharmacology* 2003;167(3):257–64.
- Patnala R, Clements J, Batra J. Candidate gene association studies: a comprehensive guide to useful in silico tools. *BMC Genetics* 2013;14:39.
- Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, Shields PG, Hawk LW, Tyndale RF, Benowitz N, Lerman C. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Clinical Pharmacology and Therapeutics* 2008;84(3):320–5.
- Pentel PR, LeSage MG. New directions in nicotine vaccine design and use. *Advances in Pharmacology* 2014;69:553–80.
- Pentel PR, Malin DH, Ennifar S, Hieda Y, Keyler DE, Lake JR, Milstein JR, Basham LE, Coy RT, Moon JW, et al. A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. *Pharmacology, Biochemistry and Behavior* 2000;65(1):191–8.
- Perkins KA, Gerlach D, Vender J, Grobe J, Meeker J, Hutchison S. Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine and Tobacco Research* 2001;3(2):141–50.
- Picard F, Sadaghiani S, Leroy C, Courvoisier DS, Maroy R, Bottlaender M. High density of nicotinic receptors in the cingulo-insular network. *Neuroimage* 2013;79:42–51.
- Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not “either/or”: activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Progress in Neurobiology* 2008;84(4):329–42.
- Picciotto MR, Kenny PJ. Molecular mechanisms underlying behaviors related to nicotine addiction. *Cold Spring Harbor Perspectives in Medicine* 2013;3(1):a012112.
- Picciotto MR, Mineur YS. Molecules and circuits involved in nicotine addiction: the many faces of smoking. *Neuropharmacology* 2014;76(Pt B):545–53.
- Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, Fuxe K, Changeux JP. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature* 1998;391(6663):173–7.
- Piper ME, McCarthy DE, Baker TB. Assessing tobacco dependence: a guide to measure evaluation and selection. *Nicotine and Tobacco Research* 2006;8(3):339–51.
- Plaza-Zabala A, Flores Á, Martín-García E, Saravia R, Maldonado R, Berrendero F. A role for hypocretin/orexin receptor-1 in cue-induced reinstatement of nicotine-seeking behavior. *Neuropsychopharmacology* 2013;38(9):1724–36.
- Plaza-Zabala A, Martín-García E, de Lecea L, Maldonado R, Berrendero F. Hypocretins regulate the anxiogenic-like effects of nicotine and induce reinstatement of nicotine-seeking behavior. *Journal of Neuroscience* 2010;30(6):2300–10.
- Pohjalainen T, Rinne JO, Nagren K, Lehtikoinen P, Anttila K, Sivalahti EK, Hietala J. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Molecular Psychiatry* 1998;3(3):256–60.
- Power MC, Deal JA, Sharrett AR, Jack CR Jr, Knopman D, Mosley TH, Gottesman RF. Smoking and white matter hyperintensity progression: the ARIC-MRI Study. *Neurology* 2015;84(8):841–8.
- Prado E, Maes M, Piccoli LG, Baracat M, Barbosa DS, Franco O, Dodd S, Berk M, Vargas Nunes SO. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. *Redox Report* 2015;20(5):215–22.
- Pravetoni M, Keyler DE, Raleigh MD, Harris AC, Lesage MG, Mattson CK, Pettersson S, Pentel PR. Vaccination against nicotine alters the distribution of nicotine delivered via cigarette smoke inhalation to rats. *Biochemical Pharmacology* 2011;81(9):1164–70.
- Pripfl J, Tomova L, Rieckensky I, Lamm C. Transcranial magnetic stimulation of the left dorsolateral prefrontal cortex decreases cue-induced nicotine craving and EEG delta power. *Brain Stimulation* 2014;7(2):226–33.
- Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. *Annual Review of Medicine* 2016;67:467–86.
- Rasetti R, Weinberger DR. Intermediate phenotypes in psychiatric disorders. *Current Opinion in Genetics and Development* 2011;21(3):340–8.
- Ray R, Tyndale RF, Lerman C. Nicotine dependence pharmacogenetics: role of genetic variation in nicotine-metabolizing enzymes. *Journal of Neurogenetics* 2009;23(3):252–61.
- Rose EJ, Ross TJ, Salmeron BJ, Lee M, Shakleya DM, Huestis M, Stein EA. Chronic exposure to nicotine is associated with reduced reward-related activity in the

- striatum but not the midbrain. *Biological Psychiatry* 2012;71(3):206–13.
- Rose EJ, Ross TJ, Salmeron BJ, Lee M, Shakleya DM, Huestis MA, Stein EA. Acute nicotine differentially impacts anticipatory valence- and magnitude-related striatal activity. *Biological Psychiatry* 2013;73(3):280–8.
- Rosenberg JB, De BP, Hicks MJ, Janda KD, Kaminsky SM, Worgall S, Crystal RG. Suppression of nicotine-induced pathophysiology by an adenovirus hexon-based antinicotinic vaccine. *Human Gene Therapy* 2013;24(6):595–603.
- Sabol SZ, Nelson ML, Fisher C, Gunzerath L, Brody CL, Hu S, Sirota LA, Marcus SE, Greenberg BD, Lucas FR 4th, et al. A genetic association for cigarette smoking behavior. *Health Psychology* 1999;18(1):7–13.
- Saccone SF, Hinrichs AL, Saccone NL, Chase GA, Konvicka K, Madden PA, Breslau N, Johnson EO, Hatsukami D, Pomerleau O, et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Human Molecular Genetics* 2007;16(1):36–49.
- Salas R, Sturm R, Boulter J, De Biasi M. Nicotinic receptors in the habenulo-interpeduncular system are necessary for nicotine withdrawal in mice. *Journal of Neuroscience* 2009;29(10):3014–8.
- Sartor CE, Lessov-Schlaggar CN, Scherrer JF, Bucholz KK, Madden PA, Pergadia ML, Grant JD, Jacob T, Xian H. Initial response to cigarettes predicts rate of progression to regular smoking: findings from an offspring-of-twins design. *Addictive Behaviors* 2010;35(8):771–8.
- Satoskar SD, Keyler DE, LeSage MG, Raphael DE, Ross CA, Pentel PR. Tissue-dependent effects of immunization with a nicotine conjugate vaccine on the distribution of nicotine in rats. *International Immunopharmacology* 2003;3(7):957–70.
- Schmid B, Blomeyer D, Becker K, Treutlein J, Zimmermann US, Buchmann AF, Schmidt MH, Esser G, Banaschewski T, Rietschel M, et al. The interaction between the dopamine transporter gene and age at onset in relation to tobacco and alcohol use among 19-year-olds. *Addiction Biology* 2009;14(4):489–99.
- Schnoll RA, Johnson TA, Lerman C. Genetics and smoking behavior. *Current Psychiatry Reports* 2007;9(5):349–57.
- Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. *Pharmacology, Biochemistry and Behavior* 2009;92(1):6–11.
- Schoedel KA, Hoffmann EB, Rao Y, Sellers EM, Tyndale RF. Ethnic variation in CYP2A6 and association of genetically slow nicotine metabolism and smoking in adult Caucasians. *Pharmacogenetics* 2004;14(9):615–26.
- Schuit E, Panagiotou OA, Munafo MR, Bennett DA, Bergen AW, David SP. Pharmacotherapy for smoking cessation: effects by subgroup defined by genetically informed biomarkers. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD011823. DOI: 10.1002/14651858.CD011823.pub2.
- Sieminska A, Jassem E. The many faces of tobacco use among women. *Medical Science Monitor* 2014;20:153–62.
- Skolnick P. Biologic approaches to treat substance-use disorders. *Trends in Pharmacological Sciences* 2015;36(10):628–35.
- Slimak MA, Ables JL, Frahm S, Antolin-Fontes B, Santos-Torres J, Moretti M, Gotti C, Ibanez-Tallon I. Habenular expression of rare missense variants of the beta4 nicotinic receptor subunit alters nicotine consumption. *Frontiers in Human Neuroscience* 2014;8:12.
- Sofuoglu M, Herman AI, Nadim H, Jatlow P. Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. *Neuropsychopharmacology* 2012;37(6):1509–16.
- Stoker AK, Olivier B, Markou A. Involvement of metabotropic glutamate receptor 5 in brain reward deficits associated with cocaine and nicotine withdrawal and somatic signs of nicotine withdrawal. *Psychopharmacology* 2012;221(2):317–27.
- Stokes PR, Benecke A, Myers J, Erritzoe D, Watson BJ, Kalk N, Barros DR, Hammers A, Nutt DJ, Lingford-Hughes AR. History of cigarette smoking is associated with higher limbic GABA_A receptor availability. *NeuroImage* 2013;69:70–7.
- Strasser AA, Benowitz NL, Pinto AG, Tang KZ, Hecht SS, Carmella SG, Tyndale RF, Lerman CE. Nicotine metabolite ratio predicts smoking topography and carcinogen biomarker level. *Cancer Epidemiology, Biomarkers and Prevention* 2011;20(2):234–8.
- Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug and Alcohol Dependence* 2007;86(2–3):294–300.
- Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 1935;18(6):643–62.
- Sullivan PF, Kendler KS. The genetic epidemiology of smoking. *Nicotine and Tobacco Research* 1999;1(Suppl 2):S51–S57. discussion S69–S70.
- Sutherland MT, Carroll AJ, Salmeron BJ, Ross TJ, Hong LE, Stein EA. Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. *Biological Psychiatry* 2013a;74(7):538–46.
- Sutherland MT, Carroll AJ, Salmeron BJ, Ross TJ, Hong LE, Stein EA. Individual differences in amygdala reactivity following nicotinic receptor stimulation in abstinent smokers. *Neuroimage* 2013b;66:585–93.

- Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. Resting state functional connectivity in addiction: Lessons learned and a road ahead. *Neuroimage* 2012;62(4):2281–95.
- Sutherland MT, Stein EA. Functional neurocircuits and neuroimaging biomarkers of tobacco use disorder. *Trends in Molecular Medicine* 2018;24(2):129–43.
- Swan GE, Benowitz NL, Jacob P, 3rd, Lessov CN, Tyndale RF, Wilhelmsen K, Krasnow RE, McElroy MR, Moore SE, Wambach M. Pharmacogenetics of nicotine metabolism in twins: methods and procedures. *Twin Research* 2004;7(5):435–48.
- Swan GE, Benowitz NL, Lessov CN, Jacob P, 3rd, Tyndale RF, Wilhelmsen K. Nicotine metabolism: the impact of CYP2A6 on estimates of additive genetic influence. *Pharmacogenetics and Genomics* 2005;15(2):115–25.
- Swan GE, Javitz HS, Jack LM, Wessel J, Michel M, Hinds DA, Stokowski RP, McClure JB, Catz SL, Richards J, et al. Varenicline for smoking cessation: nausea severity and variation in nicotinic receptor genes. *Pharmacogenomics Journal* 2012;12(4):349–58.
- Sweitzer MM, Geier CF, Addicott MA, Denlinger R, Raiff BR, Dallery J, McClernon FJ, Donny EC. Smoking abstinence-induced changes in resting state functional connectivity with ventral striatum predict lapse during a quit attempt. *Neuropsychopharmacology* 2016a;41(10):2521–9.
- Sweitzer MM, Geier CF, Denlinger R, Forbes EE, Raiff BR, Dallery J, McClernon FJ, Donny EC. Blunted striatal response to monetary reward anticipation during smoking abstinence predicts lapse during a contingency-managed quit attempt. *Psychopharmacology* 2016b;233(5):751–60.
- Tang DW, Hello B, Mroziowicz M, Fellows LK, Tyndale RF, Dagher A. Genetic variation in CYP2A6 predicts neural reactivity to smoking cues as measured using fMRI. *Neuroimage* 2012;60(4):2136–43.
- Tang YY, Tang R, Posner MI. Brief meditation training induces smoking reduction. *Proceedings of the National Academy of Sciences of the United States of America* 2013;110(34):13971–5.
- Tanner JA, Tyndale RF. Variation in CYP2A6 activity and personalized medicine. *Journal of Personalized Medicine* 2017;7(4):pii:E18.
- Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Labarca C, Whiteaker P, Marks MJ, Collins AC, Lester HA. Nicotine activation of $\alpha 4^*$ receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004;306(5698):1029–32.
- Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, Morris CM, Perry RH, Ferrier IN, Court JA. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics* 1997;7(6):479–84.
- Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, Manolescu A, Thorleifsson G, Stefansson H, Ingason A, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008;452(7187):638–42.
- Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F, Sulem P, Rafnar T, Esko T, Walter S, et al. Sequence variants at CHRN3-CHRNA6 and CYP2A6 affect smoking behavior. *Nature Genetics* 2010;42(5):448–53.
- Thorgeirsson TE, Stefansson K. Commentary: gene-environment interactions and smoking-related cancers. *International Journal of Epidemiology* 2010;39(2):577–9.
- Timberlake DS, Haberstick BC, Lessem JM, Smolen A, Ehringer M, Hewitt JK, Hopfer C. An association between the DAT1 polymorphism and smoking behavior in young adults from the National Longitudinal Study of Adolescent Health. *Health Psychology* 2006;25(2):190–7.
- Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nature Genetics* 2010;42(5):441–7.
- Tonstad S, Heggen E, Giljam H, Lagerback PA, Tonnesen P, Wikingsson LD, Lindblom N, de Villiers S, Svensson TH, Fagerstrom KO. Nicotine(R), a nicotine vaccine, for relapse prevention: a phase II, randomized, placebo-controlled, multicenter clinical trial. *Nicotine and Tobacco Research* 2013;15(9):1492–501.
- Transdisciplinary Tobacco Use Research Center on Tobacco and Dependence, Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim SY, Colby S, Conti D, Giovino GA, et al. Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. *Nicotine and Tobacco Research* 2007;9(Suppl 4):S555–S570.
- Tronci V, Vronskaya S, Montgomery N, Mura D, Balfour DJ. The effects of the mGluR5 receptor antagonist 6-methyl-2-(phenylethynyl)-pyridine (MPEP) on behavioural responses to nicotine. *Psychopharmacology* 2010;211(1):33–42.
- Tyndale RF, Zhu AZ, George TP, Cinciripini P, Hawk LW Jr, Schnoll RA, Swan GE, Benowitz NL, Heitjan DF, Lerman C, et al. Lack of associations of CHRNA5-A3-B4 genetic variants with smoking cessation treatment outcomes in Caucasian smokers despite associations with baseline smoking. *PLoS One* 2015;10(5):e0128109.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National

- Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.
- U.S. Department of Health and Human Services. *Reducing Tobacco Use. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2000.
- U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.
- U.S. Food and Drug Administration. FDA 101: Smoking Cessation Products, 2016; <<https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198176.htm>>; accessed: May 24, 2017.
- Uhl GR, Drgon T, Johnson C, Walther D, David SP, Aveyard P, Murphy M, Johnstone EC, Munafò MR. Genome-wide association for smoking cessation success: participants in the Patch in Practice trial of nicotine replacement. *Pharmacogenomics* 2010;11(3):357–67.
- Uhl GR, Walther D, Musci R, Fisher C, Anthony JC, Storr CL, Behm FM, Eaton WW, Ialongo N, Rose JE. Smoking quit success genotype score predicts quit success and distinct patterns of developmental involvement with common addictive substances. *Molecular Psychiatry* 2014;19(1):50–4.
- Uslaner JM, Winrow CJ, Gotter AL, Roecker AJ, Coleman PJ, Hutson PH, Le AD, Renger JJ. Selective orexin 2 receptor antagonism blocks cue-induced reinstatement, but not nicotine self-administration or nicotine-induced reinstatement. *Behavioural Brain Research* 2014;269:61–5.
- Vandenbergh DJ, Bennett CJ, Grant MD, Strasser AA, O'Connor R, Stauffer RL, Vogler GP, Kozlowski LT. Smoking status and the human dopamine transporter variable number of tandem repeats (VNTR) polymorphism: failure to replicate and finding that never-smokers may be different. *Nicotine and Tobacco Research* 2002;4(3):333–40.
- Versace F, Engelmann JM, Robinson JD, Jackson EF, Green CE, Lam CY, Minnix JA, Karam-Hage MA, Brown VL, Wetter DW, et al. Prequit fMRI responses to pleasant cues and cigarette-related cues predict smoking cessation outcome. *Nicotine and Tobacco Research* 2014;16(6):697–708.
- Vink JM, Willemsen G, Boomsma DI. Heritability of smoking initiation and nicotine dependence. *Behavior Genetics* 2005;35(4):397–406.
- Volkow ND, Koob G, Baler R. Biomarkers in substance use disorders. *ACS Chemical Neuroscience* 2015;6(4):522–5.
- Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine* 2016;374(4):363–71.
- Wang AL, Ruparel K, Loughhead JW, Strasser AA, Blady SJ, Lynch KG, Romer D, Cappella JN, Lerman C, Langleben DD. Content matters: neuroimaging investigation of brain and behavioral impact of televised anti-tobacco public service announcements. *Journal of Neuroscience* 2013;33(17):7420–7.
- Wang C, Shen Z, Huang P, Qian W, Yu X, Sun J, Yu H, Yang Y, Zhang M. Altered spontaneous activity of posterior cingulate cortex and superior temporal gyrus are associated with a smoking cessation treatment outcome using varenicline revealed by regional homogeneity. *Brain Imaging and Behavior* 2017;11(3):611–18.
- Ware JJ, Aveyard P, Broderick P, Houlston RS, Eisen T, Munafò MR. The association of rs1051730 genotype on adherence to and consumption of prescribed nicotine replacement therapy dose during a smoking cessation attempt. *Drug and Alcohol Dependence* 2015;151:236–40.
- Wassenaar CA, Dong Q, Wei Q, Amos CI, Spitz MR, Tyndale RF. Relationship between CYP2A6 and CHRNA5-CHRNA3-CHRNA4 variation and smoking behaviors and lung cancer risk. *Journal of the National Cancer Institute* 2011;103(17):1342–6.
- Wessel J, McDonald SM, Hinds DA, Stokowski RP, Javitz HS, Kennemer M, Krasnow R, Dirks W, Hardin J, Pitts SJ, et al. Resequencing of nicotinic acetylcholine receptor genes and association of common and rare variants with the Fagerstrom test for nicotine dependence. *Neuropsychopharmacology* 2010;35(12):2392–402.
- Weywadt CR, Kiehl KA, Claus ED. Neural correlates of response inhibition in current and former smokers. *Behavioural Brain Research* 2017;319:207–18.
- Wickham R, Solecki W, Rathbun L, McIntosh JM, Addy NA. Ventral tegmental area alpha6beta2 nicotinic acetylcholine receptors modulate phasic dopamine release in the nucleus accumbens core. *Psychopharmacology* 2013;229(1):73–82.
- Wilson SJ, Creswell KG, Sayette MA, Fiez JA. Ambivalence about smoking and cue-elicited neural activity in quitting-motivated smokers faced with an opportunity to smoke. *Addictive Behaviors* 2013;38(2):1541–9.

- Wilson SJ, Sayette MA, Fiez JA. Quitting-unmotivated and quitting-motivated cigarette smokers exhibit different patterns of cue-elicited brain activation when anticipating an opportunity to smoke. *Journal of Abnormal Psychology* 2012;121(1):198–211.
- Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. *BMC Public Health* 2006;6:300.
- Xian H, Scherrer JF, Madden PA, Lyons MJ, Tsuang M, True WR, Eisen SA. The heritability of failed smoking cessation and nicotine withdrawal in twins who smoked and attempted to quit. *Nicotine and Tobacco Research* 2003;5(2):245–54.
- Xu J, Azizian A, Monterosso J, Domier CP, Brody AL, Fong TW, London ED. Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. *Nicotine and Tobacco Research* 2008;10(11):1653–61.
- Xu X, Clark US, David SP, Mulligan RC, Knopik VS, McGeary J, MacKillop J, McCaffery J, Niaura RS, Sweet LH. Effects of nicotine deprivation and replacement on BOLD-fMRI response to smoking cues as a function of DRD4 VNTR genotype. *Nicotine and Tobacco Research* 2014;16(7):939–47.
- Yamada H, Bruijnzeel AW. Stimulation of alpha2-adrenergic receptors in the central nucleus of the amygdala attenuates stress-induced reinstatement of nicotine seeking in rats. *Neuropharmacology* 2011;60(2–3):303–11.
- Yang H, de Jong JW, Tak Y, Peck J, Bateup HS, Lammel S. Nucleus accumbens subnuclei regulate motivated behavior via direct inhibition and disinhibition of VTA dopamine subpopulations. *Neuron* 2018;97(2):434–49.e4.
- Yoon HJ, Lim YJ, Zuo Z, Hur W, Do SH. Nicotine decreases the activity of glutamate transporter type 3. *Toxicology Letters* 2014;225(1):147–52.
- Yudkin P, Munafò M, Hey K, Roberts S, Welch S, Johnstone E, Murphy M, Griffiths S, Walton R. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. *BMJ* 2004;328(7446):989–90.
- Zanchi D, Brody A, Borgwardt S, Haller S. Sex effects on smoking cue perception in non-smokers, smokers, and ex-smokers: a pilot study. *Frontiers in Psychiatry* 2016;7:187.
- Zanchi D, Brody AL, Montandon ML, Kopel R, Emmert K, Preti MG, Van De Ville D, Haller S. Cigarette smoking leads to persistent and dose-dependent alterations of brain activity and connectivity in anterior insula and anterior cingulate. *Addiction Biology* 2015;20(6):1033–41.
- Zelle SL, Gates KM, Fiez JA, Sayette MA, Wilson SJ. The first day is always the hardest: functional connectivity during cue exposure and the ability to resist smoking in the initial hours of a quit attempt. *Neuroimage* 2017;151:24–32.
- Zhang X, Salmeron BJ, Ross TJ, Gu H, Geng X, Yang Y, Stein EA. Anatomical differences and network characteristics underlying smoking cue reactivity. *Neuroimage* 2011;54(1):131–41.
- Zhao-Shea R, DeGroot SR, Liu L, Vallaster M, Pang X, Su Q, Gao G, Rando OJ, Martin GE, George O, et al. Increased CRF signalling in a ventral tegmental area-interpeduncular nucleus-medial habenula circuit induces anxiety during nicotine withdrawal. *Nature Communications* 2015;6:6770.
- Zhou WL, Gao XB, Picciotto MR. Acetylcholine acts through nicotinic receptors to enhance the firing rate of a subset of hypocretin neurons in the mouse hypothalamus through distinct presynaptic and postsynaptic mechanisms. *eNeuro* 2015;2(1):e0052.
- Zhu AZ, Zhou Q, Cox LS, David SP, Ahluwalia JS, Benowitz NL, Tyndale RF. Association of CHRNA5-A3-B4 SNPs rs2036527 with smoking cessation therapy response in African-American smokers. *Clinical Pharmacology and Therapeutics* 2014;96(2):256–65.
- Zislis G, Desai TV, Prado M, Shah HP, Bruijnzeel AW. Effects of the CRF receptor antagonist D-Phe CRF(12-41) and the alpha2-adrenergic receptor agonist clonidine on stress-induced reinstatement of nicotine-seeking behavior in rats. *Neuropharmacology* 2007;53(8):958–66.

Chapter 4

The Health Benefits of Smoking Cessation

Introduction 177

Methodologic Challenges 177

Cancer 177

Conclusions from Previous Surgeon General's Reports 177

Biological Mechanisms 178

Literature Review Methods 178

Epidemiologic Evidence 179

 Cancers for Which Previous Surgeon General's Reports Have Concluded That Smoking Cessation Reduces Risk 179

 Cancers for Which Previous Reports Have Not Concluded That Smoking Cessation Reduces Risk 182

Synthesis of the Evidence 205

Conclusions 206

Implications 206

Smoking Cessation After a Cancer Diagnosis 206

Conclusions from Previous Surgeon General's Reports 206

Literature Review Methods 207

Smoking Cessation and All-Cause Mortality in Cancer Patients 207

Evaluation of the Evidence 207

 Temporality 212

 Consistency 212

 Strength of Association 212

 Coherence 212

Synthesis of the Evidence 212

Conclusion 213

Implications 213

Cardiovascular Disease 214

Conclusions from Previous Surgeon General's Reports 214

Literature Review Methods 214

Relevant Mechanistic Data 214

 Mechanisms Through Which Smoking Cessation Could Affect Cardiovascular Disease 216

 Summary of the Evidence 219

Smoking Cessation and Subclinical Atherosclerosis 219

 Summary of the Evidence 220

Smoking Cessation and Cardiovascular Disease 220

 Intervention Studies 226

 Observational Studies 226

 Summary of the Evidence 234

Smoking Cessation and Coronary Heart Disease 234

 Summary of the Evidence 239

Smoking Cessation and Cerebrovascular Disease	239
Stroke Subtypes	243
Prognosis of Cerebrovascular Disease	249
Summary of the Evidence	250
Smoking Cessation and Atrial Fibrillation	250
Summary of the Evidence	250
Smoking Cessation and Sudden Cardiac Death	250
Summary of the Evidence	251
Smoking Cessation and Heart Failure	251
Summary of the Evidence	255
Smoking Cessation and Venous Thromboembolism	255
Summary of the Evidence	255
Smoking Cessation and Lower-Extremity Peripheral Artery Disease	255
Prognosis of PAD	259
Summary of the Evidence	260
Smoking Cessation and Abdominal Aortic Aneurysm	260
Prognosis of AAA	265
Summary of the Evidence	265
Summary of the Evidence	265
Evaluation of the Evidence	266
Consistency	266
Strength of Association	266
Temporality	266
Specificity	266
Experiment and Biologic Gradient	266
Coherence, Plausibility, and Analogy	267
Synthesis of the Evidence	267
Conclusions	270
Implications	270
Smoking Cessation After a Diagnosis of Coronary Heart Disease	270
Conclusions from Previous Surgeon General's Reports	271
Biological Basis	271
Literature Review Methods and Other Methodologic Considerations	271
Epidemiologic and Clinical Evidence	272
Smoking Cessation and All-Cause Mortality in Patients with Coronary Heart Disease	272
Smoking Cessation and Cause-Specific Mortality in Cardiac Patients	299
Smoking Cessation and Risk of Recurrence or New Cardiac Events in Cardiac Patients	299
Summary of the Evidence	302
Methodologic Considerations	302
Evaluation of the Evidence	302
Causal Criteria	302
Temporality	302
Consistency	302
Strength of Association	303
Experiment	303
Specificity	303
Coherence	304
Synthesis of the Evidence	304
Conclusions	304
Implications	305

Chronic Respiratory Disease 305

Conclusions from Previous Surgeon General's Reports 305

Literature Review Methods 306

Chronic Obstructive Pulmonary Disease 306

Smoking Cessation and Chronic Obstructive Pulmonary Disease 308

Epidemiology of Mortality from Chronic Obstructive Pulmonary Disease in Relation to Tobacco Cessation 308

How Smoking Cessation Affects the Decline of Lung Function in Smokers 308

Novel Diagnostics for Assessing the Impact of Smoking Cessation on the Progression of Chronic Obstructive Pulmonary Disease 313

Synthesis of the Evidence 316

Conclusions 317

Asthma 317

Smoking as a Risk Factor for Asthma 317

Smoking Cessation, Asthma Symptoms, and Lung Function 317

Smoking Cessation Biomarkers and the Microbiome in Asthma 319

Synthesis of the Evidence 320

Conclusions 320

Implications 320

Reproductive Health 320

Conclusions from Previous Surgeon General's Reports 321

Literature Review Methods 321

Sources of Bias in Observational Studies of Smoking and Reproductive Health 321

Pregnancy Complications 323

Ectopic Pregnancy 323

Spontaneous Abortion 323

Placental Abruption 324

Placenta Previa 324

Premature Rupture of Membranes 325

Preeclampsia 326

Gestational Weight Gain 327

Gestational Diabetes 339

Birth Outcomes 340

Birth Defects 340

Fetal Growth and Birth Weight 340

Stillbirth, Perinatal Mortality, and Infant Mortality 385

Stillbirth 386

Perinatal Mortality 386

Infant Mortality 386

Female Reproductive Health 390

Fertility 390

Age at Menopause 393

Male Reproductive Health 395

Fertility and Sperm Quality 395

Erectile Dysfunction 395

Synthesis of the Evidence 399

Conclusions 399

Implications 400

References 402

Introduction

Evidence on the health benefits of smoking cessation continues to expand and evolve since the topic was last covered comprehensively in the 1990 report of the Surgeon General. This chapter primarily reviews the findings published between 2000 and 2017 on disease risks from smoking and how these risks change after smoking cessation for major types of chronic diseases, including cancer, the cardiovascular and respiratory systems, and a wide range of reproductive outcomes. The more recent studies expand the observational evidence documenting the benefits of smoking cessation and provide insights into the mechanisms underlying these benefits. The review of the effects of smoking cessation on reproductive outcomes documents health benefits of maternal smoking cessation across all phases of reproduction, from pre-conception to birth, and also for male reproductive health.

Chapter 5 summarizes the health benefits of smoking cessation for all-cause mortality in the general population; thus, that topic is not discussed here.

This chapter also addresses the clinically relevant benefits of cessation for mitigating the effects of diseases, particularly in persons with cancer and coronary heart disease. This general topic received mention in previous Surgeon General's reports (U.S. Department of Health and Human Services [USDHHS] 1982, 1983, 1990, 2004), and the consequences of smoking following a diagnosis of cancer received specific attention in the 2014 Surgeon General's report, leading to a conclusion that cigarette smoking has adverse causal effects on persons already diagnosed with cancer (USDHHS 2014). This chapter also reviews cessation and cardiovascular disease and the implications of cessation for the natural history of chronic obstructive pulmonary disease.

Methodologic Challenges

There are methodologic challenges related to assessing smoking cessation and its links to health outcomes in both observational and intervention studies. Risks in former smokers should be compared with those of current or never smokers, thus necessitating a precise definition of former smoking (Lindstrom 2010); the same is true for time since cessation, cumulative smoking (e.g., pack-years [which is defined as the number of packs of cigarettes smoked per day multiplied by the number of years smoked], which incorporates both smoking intensity and duration), and changes in smoking status during follow-up.

Observational studies should consider factors that might differ between those who quit smoking and those who continue to smoke. Some persons may quit smoking because they are sick, and health-conscious persons may be more motivated to quit. In an effort to address bias attributable to “sick quitters,” those with preexisting diseases can be excluded from analyses. This strategy also addresses “reverse causation,” or quitting because of the development of symptoms or a disease. Whenever possible, observational analyses should also adjust for other risk factors that may confound the relationship between smoking habits and disease risk.

Cancer

This section reviews evidence from epidemiologic studies about the impact of smoking cessation on the risk of 12 cancers caused by smoking, as concluded in previous Surgeon General's reports (U.S. Department of Health and Human Services [USDHHS] 2004, 2014). The types of cancers reviewed for this section include cancers of the lung, larynx, oral cavity and pharynx, esophagus, pancreas, bladder, stomach, liver, colon and rectum, kidney, and cervix and acute myeloid leukemia (AML).

Conclusions from Previous Surgeon General's Reports

At the time of release of the 1990 Surgeon General's report, the U.S. Surgeon General and/or the International Agency for Research on Cancer (IARC) classified six cancers as causally associated with cigarette smoking: cancer of the lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder (USDHHS 1990). The 1990 Surgeon

General’s report concluded that smoking cessation reduced the risk of these six cancers. That report set forth nine conclusions about smoking cessation and cancer (Table 4.1). The 2004 and 2014 Surgeon General’s reports concluded that smoking causes at least six additional cancers beyond those for which the associations were considered causal in 1990: cancer of the stomach, liver, colon and rectum, kidney, cervix, and AML (USDHHS 2004, 2014). However, the 2004 and 2014 Surgeon General’s reports did not explicitly conclude that smoking cessation reduces the risk of these six additional cancers.

Biological Mechanisms

Smoking contributes to carcinogenesis through multiple biological mechanisms, including direct genotoxicity, hypermethylation of gene promoters, receptor-mediated pathways, and inflammation (USDHHS 2010, 2014; Hecht 2012). In addition, smoking has been shown to increase the somatic mutation load (Alexandrov et al. 2016). Collectively, these mechanisms can act at the early and late stages of carcinogenesis, implying that smoking cessation could have short- and long-term effects on the risk of cancer. Regardless of the specific mechanisms, smoking cessation ends further increments to cumulative exposure to tobacco smoke and, therefore, is expected to reduce the risk of cancers caused by smoking, since cumulative exposure does not increase further, allowing repair processes to come into play (USDHHS 2010). The particular

mechanisms that are most important in smoking-induced carcinogenesis likely vary by site, as described below.

Literature Review Methods

For this report, systematic literature reviews were not conducted for the six cancers (lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder) for which the 1990 Surgeon General’s report (USDHHS 1990) concluded that smoking cessation reduces risk. Instead, for these sites, this report summarizes new evidence from large pooled analyses or meta-analyses that were determined to clarify the consequences of smoking cessation.

For the six smoking-attributable cancer sites for which smoking cessation has not previously been concluded to lower risk (stomach, liver, colon and rectum, kidney, cervix, and AML), epidemiologic evidence was reviewed in great detail (USDHHS 1990, 2004, 2014). The evidence review focused on whether relative risks (RRs) (a) are lower for former smokers than for current smokers and (b) decrease in former smokers with increasing number of years since cessation. Summary RRs for former and current smokers of cigarettes, compared with never smokers, were identified from the most recent sufficiently comprehensive meta-analyses, as found through literature searches conducted in January 2017 of the National Library of Medicine’s PubMed service. For some papers, current cigarette smokers were the comparison group for former smokers.

Table 4.1 Conclusions from the 1990 Surgeon General’s report on the health benefits of smoking cessation and cancer

Conclusions
1. Smoking cessation reduces the risk of lung cancer compared with continued smoking. For example, after 10 years of abstinence, the risk of lung cancer is about 30 to 50 percent of the risk for continuing smokers: with further abstinence, the risk continues to decline.
2. The reduced risk of lung cancer among former smokers is observed in males and females, in smokers of filter and nonfilter cigarettes, and for all histologic types of lung cancer.
3. Smoking cessation lowers the risk of laryngeal cancer compared with continued smoking.
4. Smoking cessation reduces the severity and extent of premalignant histologic changes in the epithelium of the larynx and lung.
5. Smoking cessation halves the risks for cancers of the oral cavity and esophagus, compared with continued smoking, as soon as 5 years after cessation, with further reduction over a longer period of abstinence.
6. Smoking cessation reduces the risk of pancreatic cancer, compared with continued smoking, although this reduction in risk may only be measurable after 10 years of abstinence.
7. Smoking is a cause of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking.
8. The risk of cervical cancer is substantially lower among former smokers in comparison with continuing smokers, even in the first few years after cessation. This finding supports the hypothesis that cigarette smoking is a contributing cause of cervical cancer.
9. Neither smoking nor smoking cessation are associated with the risk of cancer of the breast.

Source: U.S. Department of Health and Human Services (1990, p. 10).

The literature searches for the six sites for which smoking cessation has not been previously tied to risk at the casual level used the term “smoking or tobacco,” a term for the specific cancer of interest (e.g., “colorectal neoplasms” or “liver neoplasms”), and limited the publication types to “meta-analysis.” The same terms were used in literature searches of PubMed to identify, for each cancer, individual studies published after the time period covered by the most recent comprehensive meta-analysis. All studies identified through meta-analyses or literature searches were examined to determine whether they included results by the number of years since cessation. Results by years since cessation were tabulated in summary tables. Because there were many studies of cessation in relation to stomach and colorectal cancer, summary tables for these cancers include only results from cohort studies, which generally have less potential for bias than case-control studies.

Epidemiologic Evidence

Cancers for Which Previous Surgeon General’s Reports Have Concluded That Smoking Cessation Reduces Risk

Lung

The 2004 Surgeon General’s report added to the conclusions of the 1990 Surgeon General’s report by noting that, while the risk of lung cancer declines with increasing numbers of years since cessation, the risk remains higher in former smokers than in never smokers, even after many years of not smoking (USDHHS 2004). The 2014 Surgeon General’s report covered findings from more recent reports documenting a rise of RR in smokers (USDHHS 2014). For this report, epidemiologic studies of smoking cessation and risk of lung cancer were reviewed in detail in publications by IARC, including two monographs (International Agency for Research on Cancer 2004, 2012) and a cancer prevention handbook that focused specifically on the effects of smoking cessation (IARC 2007). In the handbook, IARC (2007) included meta-analyses with separate estimates of summary RRs for smoking cessation grouped by gender and global region. In most groups, estimates of summary RRs for former smokers were about 0.7–0.8 compared with continuing current smokers up to 10 years after cessation, about 0.3 from 10 to 19 years after cessation, and even lower with longer periods of successful quitting.

There is an ongoing need to examine the relationship between smoking cessation and lung cancer for the following reasons: (a) In the United States, lung cancer due

to smoking still accounts for the majority of lung cancer deaths (U.S. Cancer Statistics Working Group 2019), and (b) changes have occurred over time in the epidemiologic relationship between smoking and lung cancer (USDHHS 2014). This report includes data from three large U.S. cohorts: the Cancer Prevention Study-II (CPS-II) (lung cancer mortality follow-up, 1982–1988) and two cohorts with follow-up for the incidence of lung cancer from the 1990s and 2000s—the CPS-II Nutrition Cohort (Calle et al. 2002) and the Prostate, Lung, Colorectal, and Ovarian cancer screening cohort (PLCO) (Pinsky et al. 2015) (Figure 4.1). The American Cancer Society provided, specifically for this report, analyses of the CPS-II cohort and CPS-II Nutrition Cohort. RRs by the number of years since cessation, analyzed as a time-varying variable in 5-year categories, were similar in the three cohorts (Figure 4.1, Table 4.2). As shown, a former cigarette smoker’s risk of lung cancer decreases to half that of a similarly aged continuing smoker about 10–15 years after cessation. RRs continue to decline as time since cessation increases, but RRs remain higher in former smokers than in persons who have never smoked (Table 4.2). Results by histologic subtype from the PLCO cohort suggest that RRs may decline somewhat more slowly for adenocarcinoma than for squamous cell carcinoma (Pinsky et al. 2015). Table 4.3 provides results using never cigarette smokers as the reference group rather than current smokers.

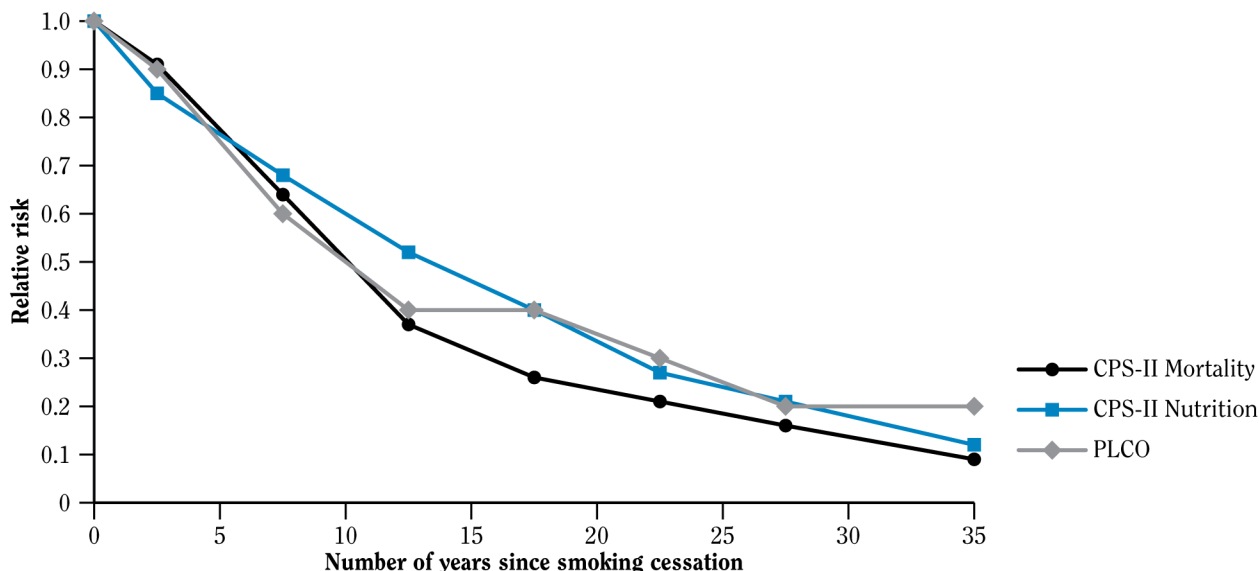
A few studies that examined age at smoking cessation, rather than number of years since cessation, consistently showed that compared with continued smoking, the earlier the age at quitting, the lower the risk of lung cancer (International Agency for Research on Cancer 2004) (Peto et al. 2000; Jha et al. 2013; Pirie et al. 2013; Thun et al. 2013a). Notably, results of these studies indicate that quitting smoking by age 40, rather than continuing to smoke, will eliminate most of the excess risk of developing lung cancer faced by long-term smokers later in life.

Since the 1990 Surgeon General’s report, substantial research has addressed the genetic determinants of risk for lung cancer among cigarette smokers (Chen et al. 2016; Liu et al. 2017). Genetic variation in the $\alpha 5$ nicotinic cholinergic receptor subunit (*CHRNA5*) has been linked to risk for lung cancer, as low- and high-risk genotypes have been identified. Chen and colleagues (2016), who carried out a meta-analysis involving cohort and case-control studies from two collaborative groups, found that the number of years by which a diagnosis of lung cancer was delayed following cessation was the same for the two genotypes.

Larynx, Oral Cavity, and Pharynx

Previous Surgeon General’s reports have concluded that smoking is a cause of laryngeal cancer (U.S. Department of Health, Education, and Welfare [USDHEW]

Figure 4.1 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with continued smoking, in three large U.S. cohorts



Source: American Cancer Society, unpublished data.

Note: **CPS** = Cancer Prevention Study; **PLCO** = Prostate, Lung, Colorectal, and Ovarian cancer screening cohort.

1964), cancer of the oral cavity (USDHEW 1979b), and cancers of the oral cavity and pharynx (USDHHS 2004). The 1990 Surgeon General’s report concluded that “smoking cessation lowers the risk of laryngeal cancer compared with continued smoking [and] . . . halves the risk for cancer of the oral cavity and esophagus . . . as soon as 5 years after cessation” (USDHHS 1990, p. 10).

Results of studies published since the 1990 Surgeon General’s report (IARC 2004, 2012; Marron et al. 2010) have strengthened the evidence that risks of both laryngeal cancer and cancer of the oral cavity and pharynx are approximately halved within 10 years of cessation. Further, the International Head and Neck Cancer Epidemiology Consortium, which conducted a very large pooled analysis of data on smoking cessation from 17 case-control studies (Marron et al. 2010) that included a total of 12,040 cases and 16,884 controls, found gradients of declining RR with increasing numbers of years since cessation. The findings were similar for cancers of the larynx, oral cavity, and pharynx. Compared with continued cigarette smokers, reductions in RR in former smokers were approximately 30% within 5 years of cessation, 50% from 5 to 9 years after cessation, and 80% 20 or more years after cessation. These estimates for RR may actually underestimate the decline in this measure resulting from smoking cessation because they were adjusted for pack-years of smoking (USDHHS 1990).

Esophagus

The 1979 Surgeon General’s report concluded that smoking is a cause of esophageal cancer (USDHEW 1979b), and the 1990 Surgeon General’s report concluded that smoking cessation halves the risk of esophageal cancer as soon as 5 years after cessation (USDHHS 1990). In addition, the 2004 Surgeon General’s report concluded that smoking causes squamous cell carcinoma of the esophagus, historically the predominant histologic type of cancer at this site, as well as adenocarcinoma (USDHHS 2004), which is currently the most common type of esophageal cancer in the United States (Hur et al. 2013; Xie et al. 2017). Studies of esophageal squamous cell carcinoma have revealed declining risks with increasing number of years since cessation among former smokers (IARC 2004, 2007, 2012), and most studies of esophageal adenocarcinoma have also found lower risk in former cigarette smokers than in current smokers (IARC 2012). Notably, a large pooled analysis of esophageal adenocarcinoma and esophageal gastric junction adenocarcinoma from 11 studies, including 10 case-control studies and 1 cohort study, found an approximate 30% reduction in relative risk among former cigarette smokers who had quit for at least 10 years compared with continuing smokers, even after adjusting for pack-years of smoking (Cook et al. 2010).

Table 4.2 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with continued smoking, in three large U.S. cohorts

	CPS-II 1982–1988 (mortality) ^a		CPS-II Nutrition Cohort 1992–2011 (incidence) ^b		PLCO 1993–2009 (incidence) ^c	
	Deaths	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Current smokers	2,571	1.00 (referent)	880	1.00 (referent)	271	1.00 (referent)
Never smokers	332	0.05 (0.046–0.059)	358	0.04 (0.035–0.045)	253	0.03 (0.02–0.03)
Former smokers, by number of years since smoking cessation	—	—	—	—	—	—
≤5	193	0.91 (0.78–1.06)	293	0.85 (0.74–0.97)	83	0.86 (0.67–1.10)
>5–10	360	0.64 (0.57–0.72)	411	0.68 (0.60–0.74)	90	0.62 (0.48–0.78)
>10–15	220	0.37 (0.32–0.42)	400	0.52 (0.46–0.58)	151	0.41 (0.33–0.51)
>15–20	179	0.26 (0.22–0.30)	361	0.40 (0.35–0.45)	236	0.38 (0.30–0.47)
>20–25	137	0.21 (0.18–0.25)	277	0.27 (0.24–0.31)	173	0.28 (0.22–0.35)
>25–30	82	0.16 (0.13–0.20)	241	0.21 (0.18–0.24)	101	0.23 (0.17–0.30)
>30	97	0.09 (0.07–0.11)	648	0.12 (0.11–0.13)	111	0.18 (0.14–0.23)

Source: American Cancer Society, unpublished data.

Notes: **CI** = confidence interval; **CPS** = Cancer Prevention Study; **PLCO** = Prostate, Lung, Colorectal, and Ovarian cancer screening cohort; **RR** = relative risk.

^aAnalyses of the CPS-II mortality cohort were restricted to those 55 years of age and older and excluded ever pipe/cigar smokers, those with prevalent cancer, and those with unknown smoking status. Data were adjusted for race, sex, and level of education.

^bAnalyses of the CPS-II Nutrition Cohort were restricted to those 55 years of age and older and excluded those with prevalent cancer. Data were adjusted for race, sex, and level of education.

^cAnalyses of participants in the PLCO were restricted to those 55 years of age and older and excluded ever smokers with more than 30 pack-years of cigarette smoking. RRs provided in the published analysis (Pinsky et al. 2015) used never smokers as the referent group. Using current smokers as the referent group, Paul Pinsky, Ph.D., of the National Cancer Institute provided equivalent results for this report.

Pancreas

The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of pancreatic cancer, but noted that "this reduction in risk may only be measurable after 10 years of abstinence" (USDHHS 1990, p. 10). In a meta-analysis performed by Iodice and colleagues (2008) of 14 studies with analyses by number of years since cessation, the summary RRs, compared with never smokers, were 1.74 (95% confidence interval [CI], 1.61–1.87) for current cigarette smokers, 1.48 (95% CI, 1.25–1.76) for persons with less than 10 years since smoking cessation, 1.15 for persons with 10 or more years since cessation, and 0.95 for persons with 20 or more years since cessation. In other large pooled analyses of cohort studies (Lynch et al. 2009) and case-control studies (Bosetti et al. 2012), RRs declined with increased time since cessation, and no excess risk (compared with never smokers) was observed among former smokers with 20 or more years since quitting (Bosetti et al. 2012). Thus, collectively, the available scientific evidence indicates that the RR for

pancreatic cancer declines steadily with increased time since cessation and approaches that of never smokers approximately 20 years after quitting smoking.

Bladder

The 1990 Surgeon General's report concluded that "[smoking] cessation reduces risk [of bladder cancer] by about 50 percent after only a few years in comparison with continued smoking" (USDHHS 1990, p. 10). Since that report, many studies have provided more evidence that RRs for bladder cancer are lower in former cigarette smokers than in current smokers and that they decline steadily as the number of years since cessation increases (IARC 2004, 2012; Freedman et al. 2011; Jiang et al. 2012). In comparisons with continued smoking, most studies have observed measurable reductions in risk for bladder cancer within 10 years of smoking cessation. In the three largest studies (Hartge et al. 1987; Brennan et al. 2000; Freedman et al. 2011), however, each of which included more than 2,500 cases of bladder cancer in their

Table 4.3 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with never smokers, in three large U.S. cohorts

	CPS-II 1982–1988 (mortality) ^a		CPS-II Nutrition Cohort 1992–2011 (incidence) ^b		PLCO 1993–2009 (incidence) ^c	
	Deaths	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Never smokers	332	1.00 (referent)	358	1.00 (referent)	253	1.00 (referent)
Current smokers	2,571	19.21 (17.09–21.59)	880	24.96 (22.02–28.28)	271	35.9 (29.0–44.5)
Former smokers, by number of years since smoking cessation	—	—	—	—	—	—
≤5	193	17.48 (14.58–20.96)	293	21.08 (18.03–24.64)	83	30.8 (23.4–40.5)
>5–10	360	12.30 (10.57–14.32)	411	16.96 (14.69–19.56)	90	22.1 (16.9–28.9)
>10–15	220	7.08 (5.96–8.41)	400	12.94 (11.20–14.94)	151	14.8 (11.9–18.2)
>15–20	179	4.93 (4.10–5.92)	361	9.90 (8.54–11.47)	236	13.5 (11.3–16.2)
>20–25	137	4.02 (3.29–4.92)	277	6.73 (5.75–7.88)	173	9.9 (8.1–12.0)
>25–30	82	3.13 (2.46–3.99)	241	5.21 (4.42–6.14)	101	8.1 (6.4–10.2)
>30	97	1.65 (1.32–2.07)	648	2.90 (2.55–3.31)	111	6.4 (5.1–8.0)

Source: American Cancer Society, unpublished data.

Notes: **CI** = confidence interval; **CPS** = Cancer Prevention Study; **PLCO** = Prostate, Lung, Colorectal, and Ovarian cancer screening cohort; **RR** = relative risk.

^aAnalyses of the CPS-II mortality cohort were restricted to those 55 years of age and older and excluded ever pipe/cigar smokers, those with prevalent cancer, and those with unknown smoking status. Data were adjusted for race, sex, and level of education.

^bAnalyses of the CPS-II Nutrition Cohort were restricted to those 55 years of age and older and excluded those with prevalent cancer. Data were adjusted for race, sex, and level of education.

^cAnalyses of participants in the PLCO were restricted to those 55 years of age and older and excluded ever smokers with more than 30 pack-years of cigarette smoking. Results are from Pinsky and colleagues (2015).

analyses, more than 10 years since cessation was required before risk fell in former cigarette smokers to half that of continuing smokers.

Cancers for Which Previous Reports Have Not Concluded That Smoking Cessation Reduces Risk

Stomach

The 2004 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between smoking and stomach cancer (USDHHS 2004). The association between smoking and this type of cancer is independent of *Helicobacter pylori* infection, an established risk factor for stomach cancer (Moy et al. 2010; IARC 2012). Potential biological mechanisms include chronic inflammation in the stomach and exposure to carcinogens in tobacco smoke, including tobacco-specific nitrosamines (Li et al. 2014).

A meta-analysis of more than 30 studies of cigarette smoking and risk for stomach cancer published through 2003 (Gandini et al. 2008) found that risk was lower for former cigarette smokers (RR = 1.31; 95% CI, 1.17–1.46)

than for current smokers (RR = 1.64; 95% CI, 1.37–1.95) when compared with never smokers. Similar results were reported in studies published in 2003 or later (Gonzalez et al. 2003; Jee et al. 2004; Koizumi et al. 2004; Wen et al. 2004; Doll et al. 2005; Fujino et al. 2005; Lindblad et al. 2005; Sauvaget et al. 2005; Tran et al. 2005; Kurosawa et al. 2006; Freedman et al. 2007; Kim et al. 2007; Ozasa 2007; Sjordahl et al. 2007; Sung et al. 2007; Batty et al. 2008; Shikata et al. 2008; Zendehdel et al. 2008; Moy et al. 2010; Steevens et al. 2010; Nomura et al. 2012; Blakely et al. 2013; Tabuchi et al. 2013; Buckland et al. 2015; Chen et al. 2015; Eom et al. 2015; Jayalekshmi et al. 2015; Charvat et al. 2016).

Risk for stomach cancer by time elapsed since quitting among former cigarette smokers has been examined in nine cohort studies (Chao et al. 2002; Koizumi et al. 2004; Sauvaget et al. 2005; Freedman et al. 2007; Ozasa 2007; Zendehdel et al. 2008; Moy et al. 2010; Steevens et al. 2010; Ordonez-Mena et al. 2016). These studies are summarized in Table 4.4, but the table does not include studies that may underestimate the effect of smoking cessation (USDHHS 1990). For example, Table 4.4 does not include a small study from India that included many dual users

Table 4.4 Cohort studies of stomach cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Chao et al. (2002)	<ul style="list-style-type: none"> • Cohort study (Cancer Prevention Study II) • Men and women ≥30 years of age • 1,055,841 participants and 1,505 deaths from stomach cancer • United States • Follow-up period: 1982–1996 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.16 (1.75–2.67) ○ Former smoker: 1.55 (1.28–1.88) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ ≤10: 1.92 (1.50–2.47) ○ 11–19: 1.64 (1.26–2.14) ○ ≥20: 1.23 (0.95–1.59) – P for trend among former smokers: 0.0015 • Women <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.49 (1.18–1.88) ○ Former smoker: 1.36 (1.08–1.71) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ ≤10: 1.31 (0.91–1.87) ○ 11–19: 1.46 (1.00–2.13) ○ ≥20: 1.34 (0.95–1.89) – p trend among former smokers: 0.68 	Adjusted for age; race; level of education; family history of stomach cancer; consumption of high-fiber grain foods, vegetables, and citrus fruits or juices; and use of vitamin C, multivitamins, and aspirin
Koizumi et al. (2004)	<ul style="list-style-type: none"> • Two population-based cohort studies • Men ≥40 years of age • Cohort 1: 9,980 men and 228 cases of stomach cancer • Cohort 2: 19,412 men and 223 cases of stomach cancer • Northern Japan • Follow-up period: <ul style="list-style-type: none"> – Cohort 1: 1984–1992 – Cohort 2: 1990–1997 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.84 (1.39–2.43) – Former smoker: 1.77 (1.29–2.43) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – <5: 1.72 (1.12–2.64) – 5–14: 2.08 (1.41–3.07) – ≥15: 1.31 (0.77–2.21) 	<p>Results from the two cohorts were pooled</p> <p>Adjusted for age, BMI, history of peptic ulcer, parental history of stomach cancer, type of health insurance, alcohol use, daily intake of pickled vegetables, and intake of bean-paste soup</p> <p>Cohort 1 also adjusted for intake of green or yellow vegetables and other vegetables and fruits</p> <p>Cohort 2 also adjusted for intake of spinach, carrots, pumpkin, cabbage, lettuce, Chinese cabbage, and oranges and other fruits</p>

Table 4.4 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Sauvaget et al. (2005)	<ul style="list-style-type: none"> • Cohort study (Life Span Study) • 38,576 men and women who were in Hiroshima or Nagasaki (Japan) at the time of the atomic bombings in August 1945 • 1,280 cases of stomach cancer • Japan • Follow-up period: 1980–1999 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.50 (1.28–1.76) – Former smoker: 1.37 (1.13–1.66) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – 1–5: 1.29 (0.90–1.85) – 6–10: 1.32 (0.88–1.96) – 11–15: 1.06 (0.67–1.67) – ≥16: 0.74 (0.54–1.00) 	Adjusted for city, sex, sex-specific age, calendar period, level of education, and radiation dose
Freedman et al. (2007)	<ul style="list-style-type: none"> • Cohort study (NIH-AARP Diet and Health Study) • 474,606 men and women ≥50 years of age who were members of AARP • 188 cases of stomach cardia and 187 cases of stomach non-cardia • Six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two U.S. metropolitan areas (Atlanta, Georgia; and Detroit, Michigan) • Follow-up period: 1995–2000 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Cardia: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.87 (1.75–4.73) ○ 1–4: 2.39 (1.16–4.92) ○ 5–9: 2.73 (1.55–4.82) ○ ≥10: 2.01 (1.32–3.07) – Non-cardia: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.05 (1.33–3.18) ○ 1–4: 1.18 (0.54–2.62) ○ 5–9: 1.79 (1.05–3.05) ○ ≥10: 1.12 (0.78–1.63) 	Adjusted for age, fruit intake, vegetable intake, total energy intake, sex, BMI, education level, alcohol intake, and physical activity Analyses of non-cardia cancer additionally adjusted for race/ethnicity

Table 4.4 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Ozasa (2007)	<ul style="list-style-type: none"> • Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 1,048 deaths from stomach cancer • Japan • Follow-up period: starting in 1988 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.47 (1.19–1.80) ○ Former smoker: 1.22 (0.97–1.53) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 1.19 (0.84–1.67) ○ 5–14: 1.25 (0.94–1.67) ○ ≥15: 1.14 (0.84–1.55) • Women: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 0.86 (0.50–1.48) ○ Former smoker: 1.07 (0.50–2.28) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 0.61 (0.08–4.37) ○ 5–14: 1.35 (0.43–4.23) ○ ≥15: 0.56 (0.07–4.02) 	Adjusted for age and area of study

Table 4.4 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Zendehdel et al. (2008)	<ul style="list-style-type: none"> • Cohort study • 336,381 men in the Swedish building industry who had records of at least one preventive health checkup between 1971 and 1993 • 276 cases of stomach cardia and 1,109 cases of stomach non-cardia • Nord-Trondelag County, Norway • Follow-up period: from date of initial checkup to 2004 	<ul style="list-style-type: none"> • Cardia: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.3 (1.6–3.3) ○ Former smoker: 1.8 (1.2–2.7) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ <5: 1.9 (1.1–3.4) ○ ≥5: 1.7 (1.1–2.6) – p trend among former smokers: 0.7 • Non-cardia: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.4 (1.2–1.6) ○ Former smoker: 1.3 (1.1–1.5) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ <5: 1.2 (0.9–1.6) ○ ≥5: 1.3 (1.1–1.6) – p trend among former smokers: 0.6 	<p>Adjusted for age and BMI</p> <p>Definition of smoking included pipe/cigar smoking, but study population predominantly smoked cigarettes</p>
Moy et al. (2010)	<ul style="list-style-type: none"> • Cohort study (Shanghai Cohort Study) • 18,244 men 45–64 years of age • 391 cases of stomach cancer • Shanghai, China • Follow-up period: 1986–2005 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.55 (1.23–1.96) – Former smoker: 1.79 (1.25–2.57) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.30 (0.82–2.05) – <5: 1.24 (0.66–2.34) – 5–9: 0.91 (0.49–1.66) – ≥10: 0.64 (0.51–0.81) 	<p>Adjusted for age, year, and neighborhood</p>

Table 4.4 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Steevens et al. (2010)	<ul style="list-style-type: none"> • Cohort study (Netherlands Cohort Study) • 120,852 men and women (3,962 in the subcohort for the case-cohort design) 55–70 years of age • 164 cases of cardia and 491 cases of non-cardia • The Netherlands • Follow-up period: 1986–2002 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Cardia: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.61 (0.97–2.66) ○ <10: 1.72 (0.97–3.05) ○ 10–19: 1.43 (0.81–2.52) ○ ≥20: 1.00 (0.53–1.91) – Non-cardia: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.86 (1.39–2.47) ○ <10: 1.81 (1.30–2.52) ○ 10–19: 1.41 (0.98–2.02) ○ ≥20: 1.13 (0.77–1.67) 	<p>Cases in the case-cohort approach derived from entire cohort and number of person-years at risk for entire cohort estimated from a subcohort of 5,000 men and women who were randomly sampled from the total cohort at baseline</p> <p>Adjusted for age; sex; alcohol use; BMI; level of education; energy intake; and intake of fruits, vegetables, and fish</p>
Ordonez-Mena et al. (2016)	<ul style="list-style-type: none"> • Collaboration of 19 prospective cohort studies • 897,021 men and women • 1,866 cases of stomach cancer and 1,396 deaths from stomach cancer • Europe and United States 	<ul style="list-style-type: none"> • Incidence of stomach cancer: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.74 (1.50–2.02) ○ Former smoker: 1.18 (0.95–1.46) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤9: 0.85 (0.60–1.20) ○ 10–19: 0.68 (0.41–1.12) ○ ≥20: 0.69 (0.51–0.93) – p trend among former smokers: 0.0461 • Death from stomach cancer: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.73 (1.36–2.19) ○ Former smoker: 1.31 (1.02–1.68) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤9: 1.13 (0.80–1.58) ○ 10–19: 0.72 (0.46–1.14) ○ ≥20: 0.87 (0.64–1.19) – p trend among former smokers: 0.2355 	<p>Analyses of number of years since smoking cessation included only cohorts with these data and therefore included substantially fewer participants</p> <p>Adjusted for sex, age, BMI, level of education, vigorous physical activity, history of diabetes, and alcohol consumption</p>

Notes: **AARP** = formerly American Association of Retired Persons; **BMI** = body mass index; **CI** = confidence interval; **NIH** = National Institutes of Health; **RR** = relative risk.

^aStudies are of cancer incidence unless number of cancer deaths is identified.

^bp trend values are shown only if described as being among former smokers.

of cigarettes and bidis (Jayalekshmi et al. 2015), a study in which the highest category of number of years since quitting was only ≥ 3 years (Guo et al. 1994), or studies where the number of years since quitting was adjusted for duration or pack-years of smoking (Gonzalez et al. 2003; Sjordahl et al. 2007; Nomura et al. 2012). In general, risk estimates for the highest category of number of years since cessation (ranging from >10 years to >20 years) were lower than those for categories with fewer numbers of years since cessation (Table 4.4).

Colon and Rectum

The 2014 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and colorectal cancer (USDHHS 2014). For example, Botteri and colleagues (2008), in a meta-analysis of 26 studies of the incidence of colorectal cancer published through 2008, reported RRs of 1.17 (95% CI, 1.11–1.22) for former cigarette smokers and 1.07 (95% CI, 0.99–1.16) for current smokers, both compared with never smokers. Although the excess risk of colorectal cancer associated with current smoking overall was relatively small in this meta-analysis, there were statistically significant trends for increasing risk with increasing years of smoking duration, number of cigarettes smoked per day, and number of pack-years. In studies of colorectal cancer mortality that were included in the meta-analysis, summary RRs were 1.28 (95% CI, 1.15–1.42) for current smokers based on 14 studies, and 1.23 (95% CI, 1.14–1.32) for former smokers based on 12 studies (Botteri et al. 2008). Since 2008, four cohort studies that each included more than 1,000 incident cases of colorectal cancer (Hannan et al. 2009; Limsui et al. 2010; Leufkens et al. 2011) or deaths (Parajuli et al. 2014) have been published that provide RRs for both current and former cigarette smokers. In general, the RRs for current smokers were above those for former smokers:

- 1.27 (95% CI, 1.06–1.52) for current smokers and 1.23 (95% CI, 1.11–1.36) for former smokers (Hannan et al. 2009);
- 1.22 (95% CI, 1.04–1.41) for current smokers and 1.18 (95% CI, 1.02–1.36) for former smokers (Limsui et al. 2010);
- 1.31 (95% CI, 1.06–1.64) and 1.25 (1.04–1.50) for current and former smokers, respectively, with proximal colon cancer; and 0.91 (95% CI, 0.73–1.14) and 1.13 (95% CI 0.95–1.36) for current and former smokers, respectively, with distal colon cancer (Leufkens et al. 2011); and

- 1.27 (95% CI, 1.10–1.46) and 1.20 (95% CI, 1.03–1.38) for current and former smokers, respectively, who were men; and 1.30 (95% CI, 1.12–1.52) and 1.08 (95% CI, 0.90–1.30) for current and former smokers, respectively, who were women (Parajuli et al. 2014).

Taken together, these four studies provide evidence that former smokers have somewhat lower risk for colorectal cancer than do current smokers. Twelve cohort studies have examined risk of colorectal cancer by time since cessation, as summarized in Table 4.5 (Chao et al. 2000; Rohan et al. 2000; Limburg et al. 2003; Ozasa 2007; Kenfield et al. 2008; Weijenberg et al. 2008; Gram et al. 2009; Hannan et al. 2009; Leufkens et al. 2011; Gong et al. 2012; Nishihara et al. 2013; Ordonez-Mena et al. 2016). In most of these studies (Chao et al. 2000; Rohan et al. 2000; Limburg et al. 2003; Kenfield et al. 2008; Weijenberg et al. 2008; Hannan et al. 2009; Leufkens et al. 2011; Gong et al. 2012; Ordonez-Mena et al. 2016), the RR point estimates for the categories with the greatest number of years since smoking cessation (ranging from ≥ 10 years to ≥ 40 years) were lower than those for categories with fewer number of years since cessation.

The influence of smoking cessation on the risk of colorectal cancer may be most clearly observable in analyses that focus on smoking-related molecular subtypes, including colorectal tumors with microsatellite instability (MSI-high) and the cytosine-phosphate-guanine (CpG) island methylator phenotype (CIMP-high). Several studies have associated smoking with about a two-fold increase in risk of MSI-high and CIMP-high colorectal cancer, but not with risk of other subtypes of colorectal cancer (Campbell et al. 2017). To date, only Nishihara and colleagues (2013) have examined time since smoking cessation by molecular subtype. In their study, smoking cessation, compared with continued smoking, was associated with considerably lower risk of MSI-high and CIMP-high colorectal cancer starting 10–20 years after cessation, but risk of other subtypes of colorectal cancer was similar in current and former smokers and did not change with number of years since smoking cessation.

Liver

The 2014 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and liver cancer (USDHHS 2014). Potential biological mechanisms include long-term direct exposure of the liver to carcinogens in tobacco smoke and smoking-induced fibrosis and cirrhosis (USDHHS 2014).

A meta-analysis of 23 studies was carried out for the 2014 Surgeon General's report. The meta-analysis provided estimates of the RR for liver cancer for current and former cigarette smokers compared with never

Table 4.5 Cohort studies of colorectal cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Chao et al. (2000)	<ul style="list-style-type: none"> • Cohort study (Cancer Prevention Study II) • 781,351 men and women ≥30 years of age • 4,432 deaths from colorectal cancer • United States • Follow-up period: 1982–1996 	<ul style="list-style-type: none"> • Current smoker: <ul style="list-style-type: none"> – Men: 1.32 (1.16–1.49) – Women: 1.41 (1.26–1.58) • Number of years since smoking cessation (men and women): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – ≤10: 1.32 (1.19–1.47) – 11–19: 1.20 (1.08–1.35) – ≥20: 1.04 (0.94–1.16) – p trend among former smokers: 0.0001 	<p>Adjusted for age; race; level of education; family history of colorectal cancer; exercise; aspirin and multivitamin use; alcohol use; and intake of vegetables, high-fiber grain foods, and fatty meats</p> <p>Models among women also included hormone replacement therapy</p> <p>Presented only sex-specific RRs for current smokers compared with never smokers</p>
Rohan et al. (2000)	<ul style="list-style-type: none"> • Cohort study (Canadian National Breast Screening Study) • 56,837 women 40–59 years of age • 90 deaths from colorectal cancer • Canada • Follow-up period: 1982–1993 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.15 (0.61–2.16) – Former smoker: 1.52 (0.91–2.56) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – 1–10: 1.74 (0.91–3.33) – ≥11: 1.33 (0.70–2.57) 	<p>Adjusted for age; BMI; hours per week of vigorous activity; and intake of dietary fiber, calcium, and alcohol; and energy level</p>
Limburg et al. (2003)	<ul style="list-style-type: none"> • Cohort study (Iowa Women's Health Study) • 34,467 women 55–69 years of age • 869 cases of colorectal cancer • Iowa • Follow-up period: 1986–1999 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.10 (0.89–1.37) – Former smoker: 1.21 (1.01–1.45) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – <10: 1.21 (0.93–1.56) – 10–19: 1.08 (0.77–1.51) – 20–29: 1.51 (1.09–2.09) – >30: 1.07 (0.71–1.62) – p trend among former smokers: 0.14 	<p>Adjusted for age; BMI; waist-to-hip ratio; physical activity; alcohol consumption; hormone replacement therapy; and intake of methionine, total calories, total fat, sucrose, red meat, calcium, folate, and vitamin E</p>

Table 4.5 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Ozasa (2007)	<ul style="list-style-type: none"> • Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 381 deaths from colon cancer and 226 deaths from rectal cancer • Japan • Follow-up period: starting in 1988 	<ul style="list-style-type: none"> • Men, colon: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.18 (0.80–1.72) ○ Former smoker: 1.27 (0.85–1.91) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 2.05 (1.23–3.42) ○ 5–14: 0.96 (0.55–1.68) ○ ≥15: 1.27 (0.74–2.17) • Men, rectum: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.31 (0.85–2.01) ○ Former smoker: 0.95 (0.58–1.53) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 0.50 (0.19–1.31) ○ 5–14: 1.16 (0.64–2.10) ○ ≥15: 1.00 (0.51–1.96) • Women, colon: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 0.67 (0.29–1.53) ○ Former smoker: 2.05 (0.95–4.41) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 3.74 (1.19–11.8) ○ 5–14: 0.77 (0.10–5.56) ○ ≥15: 2.14 (0.52–8.68) • Women, rectum: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.31 (0.52–3.29) ○ Former smoker: 0.68 (0.09–4.95) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <5: 2.93 (0.40–21.3) ○ 5–14: Not reported ○ ≥15: Not reported 	Adjusted for age and area of study

Table 4.5 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Kenfield et al. (2008)	<ul style="list-style-type: none"> • Cohort study (Nurses' Health Study) • 104,519 women 30–55 years of age • 578 deaths from colorectal cancer • United States (11 states) • Follow-up period: 1980–2004 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.63 (1.29–2.05) – Former smoker: 1.23 (1.02–1.49) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 0.76 (0.55–1.05) – <10: 0.95 (0.70–1.29) – 10–19: 0.70 (0.53–0.93) – ≥20: 0.62 (0.49–0.77) – p trend among former smokers: 0.40 	<p>Adjusted for age; follow-up period; history of hypertension, diabetes, and high cholesterol; BMI; change in weight from 18 years of age to baseline; alcohol intake; physical activity; use of oral contraception; hormone replacement therapy and menopausal status; parental history of myocardial infarction before 60 years of age; number of cigarettes smoked per day; age started smoking; servings of beef, pork, lamb, or processed meat; total calcium and folate intake; and duration of aspirin use</p> <p>All covariates updated until diagnosis</p>
Weijenberg et al. (2008)	<ul style="list-style-type: none"> • Case-cohort study (subset of the Netherlands Cohort Study) • Men and women 55–69 years of age • 4,083 persons in subcohort and 648 cases of colorectal cancer • The Netherlands • Follow-up period: 1989–1994 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 0.81 (0.62–1.05) – Former smoker: 1.22 (0.97–1.53) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – <10: 0.96 (0.76–1.22) – 10–30: 1.24 (0.96–1.61) – >30: 0.78 (0.45–1.33) – p = 0.33 	<p>Adjusted for age, sex, family history of colorectal cancer, BMI, and alcohol and coffee consumption</p>
Gram et al. (2009)	<ul style="list-style-type: none"> • Cohort study (The Norwegian Women and Cancer study) • 68,160 women 30–69 years of age • 425 cases of colorectal cancer • Norway • Follow-up period: 1996–2005 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – Current smoker: 1.2 (0.9–1.5) – Former smoker: 1.3 (1.0–1.6) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – Current smoker: 1.2 (1.0–1.5) – 1–9: 1.1 (0.8–1.7) – 10–19: 1.5 (1.1–2.1) – ≥20: 1.1 (0.8–1.5) 	<p>Adjusted for age, menopausal status, use of hormonal contraceptives and postmenopausal hormonal therapy, BMI, and alcohol consumption</p>

Table 4.5 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Hannan et al. (2009)	<ul style="list-style-type: none"> • Cohort study (CPS-II Nutrition Cohort) • 124,751 men and women, most 50–74 years of age • 1,962 cases of colorectal cancer • United States (21 states) • Follow-up period: 1992–2005 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.27 (1.06–1.52) – Former smoker: 1.23 (1.11–1.36) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – 1–10: 1.48 (1.27–1.73) – 11–20: 1.33 (1.14–1.55) – 21–30: 1.28 (1.10–1.49) – ≥31: 1.03 (0.89–1.19) – p trend among former smokers: 0.0003 	Adjusted for age, BMI, level of education, family history of colorectal cancer, physical activity, race, aspirin use, alcohol use, vegetable consumption, fiber and whole grain consumption, red and processed meat consumption, and history of endoscopy
Leufkens et al. (2011)	<ul style="list-style-type: none"> • Cohort study (European Prospective Investigation into Cancer and Nutrition) • 465,879 men and women, most 35–70 years of age • 2,741 cases of colorectal cancer • 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom) • Follow-up period: 1991–2000 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.08 (0.96–1.21) – Former smoker: 1.17 (1.07–1.29) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – ≤4: 1.15 (0.95–1.40) – 5–9: 1.16 (0.95–1.40) – 10–14: 1.24 (1.03–1.49) – 15–19: 1.34 (1.12–1.60) – 20–24: 1.11 (0.91–1.35) – ≥25: 1.08 (0.92–1.26) – p trend among former smokers: 0.52 	Adjusted for center, age, sex, weight, height, physical activity, level of education, intake of energy from fat and nonfat, fiber, fruit, vegetables, red meat, processed meat, alcohol, and fish
Gong et al. (2012)	<ul style="list-style-type: none"> • Pooled analysis of eight studies from the Genetics and Epidemiology of Colorectal Cancer Consortium (Health Professionals Follow-up Study; Nurses' Health Study; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; VITamins and Lifestyle Study; Women's Health Initiative; Colon Cancer Family Registry; Diet, Activity, and Lifestyle Survey; and Ontario Familial Colorectal Cancer Registry) • Men and women • 6,796 cases of colorectal cancer and 7,770 controls 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.36 (1.12–1.64) – <15: 1.47 (1.21–1.78) – 15–24: 1.31 (1.07–1.60) – 25–34: 1.15 (0.85–1.55) – ≥35: 0.74 (0.47–1.18) 	Adjusted for age, sex, BMI, level of education, alcohol intake, and study site Number of years since smoking cessation additionally adjusted for pack-years of smoking

Table 4.5 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Nishihara et al. (2013)	<ul style="list-style-type: none"> • Two cohort studies: <ul style="list-style-type: none"> – Men from the Health Professionals Follow-up Study – Women from the Nurses' Health Study • 134,204 men and women • 1,260 cases of colorectal cancer with available tumors • United States • Follow-up period: <ul style="list-style-type: none"> – Nurses' Health Study: 1980–2008 – Health Professionals Follow-up Study: 1986–2008 	<ul style="list-style-type: none"> • Colorectal cancer (all): <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.17 (0.96–1.43) ○ Former smoker: 1.18 (1.05–1.34) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ 1–4: 0.99 (0.73–1.34) ○ 5–9: 1.30 (0.99–1.71) ○ 10–19: 0.96 (0.75–1.23) ○ 20–39: 0.92 (0.74–1.14) ○ ≥40: 1.05 (0.80–1.37) • CIMP-high: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.08 (1.35–3.20) ○ Former smoker: 1.30 (0.95–1.76) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ 1–4: 1.09 (0.58–2.02) ○ 5–9: 0.89 (0.48–1.66) ○ 10–19: 0.52 (0.29–0.93) ○ 20–39: 0.52 (0.32–0.84) ○ ≥40: 0.48 (0.26–0.90) 	<p>Adjusted for calendar year, age, sex, BMI, family history of colorectal cancer, regular use of aspirin, physical activity level, alcohol consumption, total caloric intake, and intake of red meat</p> <p>Focused on molecular subtypes of colorectal cancer previously established to be smoking related, including CIMP-high</p>

Table 4.5 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI) ^b	Comments
Ordonez-Mena et al. (2016)	<ul style="list-style-type: none"> • Collaboration of 19 prospective cohort studies • 897,021 men and women • 12,696 cases of colorectal cancer and 4,878 deaths from colorectal cancer • Europe and United States 	<ul style="list-style-type: none"> • Incidence of colorectal cancer: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.20 (1.07–1.34) ○ Former smoker: 1.20 (1.15–1.25) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤9: 1.00 (0.87–1.16) ○ 10–19: 1.11 (0.97–1.27) ○ ≥20: 0.88 (0.78–1.00) • Mortality from colorectal cancer: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.35 (1.16–1.58) ○ Former smoker: 1.22 (1.13–1.31) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤9: 1.07 (0.86–1.32) ○ 10–19: 1.07 (0.87–1.31) ○ ≥20: 0.76 (0.63–0.93) 	<p>Analyses of number of years since smoking cessation included only cohorts with these data and therefore included substantially fewer participants</p> <p>Adjusted for sex, age, BMI, level of education, vigorous physical activity, history of diabetes, and alcohol consumption</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **CIMP-high** = cytosine-phosphate-guanine island methylator phenotype; **CpG** = cytosine-phosphate-guanine; **CPS** = Cancer Prevention Study; **RR** = relative risk.

^aStudies are of cancer incidence unless number of cancer deaths is identified.

^bp trend values are shown only if described as being among former smokers.

smokers. This meta-analysis reported a lower summary RR for former smokers (1.4; 95% CI, 1.1–1.7) than for current smokers (1.7; 95% CI, 1.5–1.9). Seven other studies published in 2014 or later found similar results (Everatt et al. 2014; Moura et al. 2014; Chen et al. 2015; Meyer et al. 2015; Pang et al. 2015; Chiang et al. 2016; Niu et al. 2016). Of the 30 studies overall, only 4 (all case-control studies) reported information on risk by number of years since smoking cessation (Table 4.6) (Choi and Kahyo 1991; Goodman et al. 1995; Ozasa 2007; Hassan et al. 2008). Results from these studies are inconsistent and are limited by small samples, as the largest (Hassan et al. 2008) included only 154 cases of liver cancer among former smokers.

Cervix

The 1990 Surgeon General's report concluded that "risk of cervical cancer is substantially lower among former smokers in comparison with continuing smokers, even in the first few years after cessation" (USDHHS 1990, p. 10). However, it did not explicitly conclude that smoking cessation reduced risk of cervical cancer. The 2004 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between cigarette smoking and cervical cancer (USDHHS 2004). The association between smoking and higher risk of cervical cancer persists when adjusted for measures of infection with the human papillomavirus (HPV) (IARC 2012; Roura et al. 2014). Potential biological mechanisms include direct genotoxic effects of nitrosamines and polyaromatic hydrocarbons from tobacco smoke and suppression of the immune system, including reduced ability to clear infection caused by HPV (Fonseca-Moutinho 2011; Gadducci et al. 2011).

In a meta-analysis of more than 20 studies published through 2003 that used never smokers as the reference group, Gandini and colleagues (2008) found that RRs for cervical cancer were lower for former smokers (1.26; 95% CI, 1.11–1.42) than for current smokers (1.83; 95% CI, 1.51–2.21) (Roura et al. 2014). Earlier, the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC) (2006) conducted a large pooled analysis of 23 studies (8 cohort, 15 case control) that included data from most of the studies published up to that time. In that analysis, summary RRs for squamous cell carcinoma, by far the most common histologic type of cervical cancer (American Cancer Society 2016), were lower for former smokers (1.12; 95% CI, 1.01–1.25) than for current smokers (1.60; 95% CI, 1.48–1.73). Smoking was not associated with adenocarcinoma of the cervix (0.89; 95% CI, 0.74–1.06), which accounts for a small proportion of cervical cancers (American Cancer Society 2016). RRs have also been greater for current smokers than for former smokers in studies published after 2006 (Odongua et al. 2007; Madsen et al. 2008; Roura et al. 2014).

Using data from a subset of studies in its pooled analysis, ICESCC (2006) reported on the risk of cervical cancer by number of years since smoking cessation. Table 4.7 summarizes these results and results from two other studies published since 2004, including a case-control study (Shields et al. 2004) and a cohort study (Roura et al. 2014). In the pooled analysis, estimates of RR were slightly lower for having quit 10 or more years ago versus having done so more recently, although trends by number of years since smoking cessation were not statistically significant. The cohort study (Roura et al. 2014), which was conducted in Europe among 308,036 women, included 261 cases of invasive cervical cancer and 804 cases of carcinoma in situ (CIS) or cervical intraepithelial cancer grade 3 (CIN3). For both invasive cancer and CIS/CIN3, Roura and colleagues (2014) found statistically significant decreases in risk as the number of years since quitting increased, with risk reaching less than or about half that in current smokers among women who had quit smoking 20 or more years earlier. Finally, Shields and colleagues (2004), in a case-control study conducted in five U.S. cities, did not find any trends related to number of years since quitting; however, their study included relatively few former smokers.

Kidney

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and kidney cancer (USDHHS 2004). Biological mechanisms for such a relationship may include oxidative stress (Patel et al. 2015) and exposure to nitrosamines and other carcinogens in tobacco smoke (USDHHS 2004; Clague et al. 2009).

In a meta-analysis of more than 20 studies of smoking and incident kidney cancer, Cumberbatch and colleagues (2016) found that the RR for kidney cancer, in comparisons with never smokers, was lower for former smokers (RR = 1.16; 95% CI, 1.08–1.25) than for current smokers (RR = 1.36; 95% CI, 1.19–1.56). Finally, 10 studies, all case-control, examined risk for kidney cancer by time since quitting among former smokers (Table 4.8) (McLaughlin et al. 1984, 1995; La Vecchia et al. 1990; McCredie and Stewart 1992; Kreiger et al. 1993; Muscat et al. 1995; Yuan et al. 1998; Parker et al. 2003; Hu et al. 2005; Cote et al. 2012). In most of these studies, the odds ratio (OR) for the highest category of number of years since quitting (ranging from >10 to >30 years) was lower than the OR for categories with fewer years since quitting.

Acute Myeloid Leukemia

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between smoking and AML (USDHHS 2004). Potential

Table 4.6 Studies of liver cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population ^a	Exposure estimates: RR (95% CI)	Comments
Choi et al. (1991)	<ul style="list-style-type: none"> • Case-control, hospital-based study • 216 cases of liver cancer in males and 648 male controls • Korea • Time period in which cases were diagnosed: 1986–1990 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.01 (0.65–1.57) – Former smoker: 0.65 (0.35–1.19) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – 1–4: 0.76 (0.31–1.89) – 5–9: 0.43 (0.15–1.26) – ≥10: 0.44 (0.11–1.82) 	Adjusted for age, marital status, level of education, serum hepatitis B virus surface antigen, and alcohol consumption
Goodman et al. (1995)	<ul style="list-style-type: none"> • Cohort study (Life Span Study) • 36,133 men and women who were in Hiroshima or Nagasaki at the time of the atomic bombings in August 1945 • 242 cases of liver cancer • Japan • Follow-up period: 1980–1989 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 4.26 (1.87–9.72) ○ Former smoker: 4.56 (1.95–10.7) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <14: 5.60 (2.15–14.6) ○ 14–23: 4.11 (1.58–10.7) ○ ≥24: 4.04 (1.54–10.6) • Women: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.58 (0.86–2.88) ○ Former smoker: 1.66 (0.76–3.63) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ <10: 10.4 (2.51–43.5) ○ 10–24: 1.03 (0.25–4.24) ○ ≥25: 2.31 (0.72–7.43) 	Adjusted for city, age at time of the atomic bombings, attained age, and radiation dose to the liver

Table 4.6 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI)	Comments
Ozasa (2007)	<ul style="list-style-type: none"> • Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 620 deaths from liver cancer • Japan • Follow-up period: starting in 1988 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.59 (1.20–2.12) ○ Former smoker: 1.48 (1.09–2.00) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ <5: 1.27 (0.81–1.98) ○ 5–14: 1.54 (1.06–2.23) ○ ≥15: 1.54 (1.05–2.27) • Women: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.95 (1.19–3.19) ○ Former smoker: 0.76 (0.24–2.39) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ <5: 1.05 (0.14–7.51) ○ 5–14: 1.40 (0.34–5.69) ○ ≥15: Not reported 	Adjusted for age and area of study
Hassan et al. (2008)	<ul style="list-style-type: none"> • Case-control, hospital-based study • 319 cases of liver cancer among men and women treated at MD Anderson Cancer Center, and 1,061 controls who were relatives of the patients • Houston, Texas • Time period in which cases were diagnosed: 2000–2006 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – ≤10: 1.7 (1.0–3.1) – >10: 1.3 (0.8–1.9) 	Adjusted for age, race, level of education, marital status, state of residency, hepatitis B virus, hepatitis C virus, diabetes, heavy alcohol consumption, and family history of cancer Did not present results by smoking status

Notes: **CI** = confidence interval; **RR** = relative risk.

^aStudies are of cancer incidence unless the number of cancer deaths is identified.

Table 4.7 Studies of cervical cancer incidence by years since smoking cessation

Study	Design/population ^a	Exposure estimates: RR (95% CI)	Comments
International Collaboration of Epidemiological Studies of Cervical Cancer (2006)	<ul style="list-style-type: none"> • Collaborative analysis of 23 cohort and case-control studies (The International Collaboration of Epidemiological Studies of Cervical Cancer) • 9,052 cases of invasive cancer (7,498 with data on number of years since smoking cessation), 4,489 cases of carcinoma in situ or cervical intraepithelial neoplasia III, and 23,017 controls • Studies from Algeria, Brazil, Chile, Colombia, Costa Rica, Denmark, India, Italy, Mali, Mexico, Morocco, Norway, Panama, Paraguay, Peru, Philippines, South Africa, Spain, Sweden, Thailand, United Kingdom, and United States 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Invasive cancer: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (0.94–1.06) ○ Current smoker: 1.46 (1.35–1.58) ○ 1–4: 1.05 (0.87–1.28) ○ 5–9: 1.08 (0.85–1.38) ○ ≥10: 0.99 (0.83–1.18) – Carcinoma in situ or cervical intraepithelial neoplasia III: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (0.91–1.10) ○ Current smoker: 1.83 (1.68–1.99) ○ 1–4: 1.35 (1.05–1.74) ○ 5–9: 1.35 (0.99–1.83) ○ ≥10: 1.19 (0.85–1.66) 	<p>Cohort studies analyzed as nested case-control studies, with up to four controls selected randomly per case according to age</p> <p>Adjusted for study, study center, age, age at first intercourse, duration and use of oral contraception, number of full-term pregnancies, and lifetime number of sexual partners</p>
Shields et al. (2004)	<ul style="list-style-type: none"> • Case-control, population-based study • Women 20–74 years of age • 235 cases of squamous cell carcinoma and 209 controls with seropositive human papillomavirus • Controls obtained from random-digit dialing • Time period in which cases were diagnosed: 1982–1984 • Five U.S. cities (Birmingham, Chicago, Denver, Miami, and Philadelphia) 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – Current smoker: 1.9 (1.2–2.8) – Former smoker: 1.4 (0.8–2.4) • Number of years since smoking cessation: <ul style="list-style-type: none"> – 1–5: 1.0 (referent) – 6–14: 0.6 (0.2–2.0) – ≥15: 0.8 (0.3–2.5) 	Cases restricted to squamous cell carcinoma

Table 4.7 Continued

Study	Design/population ^a	Exposure estimates: RR (95% CI)	Comments
Roura et al. (2014)	<ul style="list-style-type: none"> • Cohort study (European Prospective Investigation into Cancer and Nutrition) • 308,036 women, most 35–70 years of age • 261 cases of ICC and 804 cases of CIS or CIN3 • 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom) • Follow-up period: 1992–2006 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – ICC: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.9 (1.4–2.5) ○ Former smoker: 1.5 (1.1–2.1) – CIS or CIN3: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.1 (1.8–2.5) ○ Former smoker: 1.5 (1.2–1.8) – p trend among former smokers: 0.02 • Number of years since smoking cessation: <ul style="list-style-type: none"> – ICC: <ul style="list-style-type: none"> ○ Current smoker: 1.0 (referent) ○ ≤4: 1.2 (0.7–2.0) ○ 5–9: 0.9 (0.5–1.7) ○ 10–19: 0.8 (0.5–1.3) ○ ≥20: 0.4 (0.2–0.8) – CIS or CIN3: <ul style="list-style-type: none"> ○ Current smoker: 1.0 (referent) ○ ≤4: 0.8 (0.6–1.1) ○ 5–9: 1.0 (0.7–1.3) ○ 10–19: 0.5 (0.4–0.8) ○ ≥20: 0.5 (0.3–0.7) • Statistically significant p trends for the association between smoking-related variables and the risk of CIN3/CIS and ICC by risk factor: <ul style="list-style-type: none"> – Smoking duration (years); p trends among ever smokers: <0.0001 (CIN3/CIS), 0.08 (ICC) – Lifetime smoking intensity (cig/day); p trend among ever smokers: 0.07 (ICC) – Smoking pack years; p trends among ever smokers: 0.001 (CIN3/CIS); 0.07 (ICC) – Time since quitting; p trends among past smokers: 0.02 (CIN3/CIS); 0.02 (ICC) 	Adjusted for BMI, marital status, level of education, physical activity, number of full-term pregnancies, and use and duration of oral contraception

Notes: **BMI** = body mass index; **CI** = confidence interval; **CIN3** = cervical intraepithelial neoplasia III; **CIS** = carcinoma in situ; **ICC** = invasive cervical cancer; **RR** = relative risk.

^aStudies are of cancer incidence unless the number of cancer deaths is identified.

Table 4.8 Studies of kidney cancer incidence by number of years since smoking cessation

Study	Design/population ^a	Exposure estimates: OR (95% CI)	Comments
McLaughlin et al. (1984)	<ul style="list-style-type: none"> • Case-control, population-based study • White men and women 30–85 years of age • 495 cases of kidney cancer and 697 controls • Time period in which cases were diagnosed: 1974–1979 • Minneapolis-St. Paul, Minnesota, metropolitan area 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent): ○ ≤10 prior to 1974: 1.7 ○ >10 prior to 1974: 1.1 ○ Current smoker: 1.8 – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ ≤10 prior to 1974: 1.7 ○ >10 prior to 1974: 1.6 ○ Current smoker: 2.0 	Adjusted for age Confidence intervals not provided
LaVecchia et al. (1990)	<ul style="list-style-type: none"> • Case-control, hospital-based study • Cases: Men and women <75 years of age • Controls: Admitted for acute conditions • 131 cases of kidney cancer and 394 controls • Time period in which cases were diagnosed: 1985–1989 • Northern Italy 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – <10: 2.2 (1.1–4.4) – ≥10: 1.3 (0.6–2.7) 	Adjusted for age, sex, area of residence, level of education, and BMI Did not present results for current smoking status
McCredie et al. (1992)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 20–79 years of age • 489 cases of kidney cancer and 523 controls • Time period in which cases were diagnosed: 1989–1990 • New South Wales, Australia 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 2.17 (1.55–3.02) – Former smoker: 1.41 (1.03–1.95) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – 1–12: 0.85 (0.53–1.38) – 13–24: 0.89 (0.52–1.53) – ≥25: 0.47 (0.22–1.00) 	Adjusted for age, sex, method of interview, and BMI Number of years since smoking cessation additionally adjusted for duration of cigarette smoking and number of cigarettes smoked per day

Table 4.8 Continued

Study	Design/population ^a	Exposure estimates: OR (95% CI)	Comments
Kreiger et al. (1993)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 25–69 years of age • 518 cases of kidney cancer and 1,381 controls • Time period in which cases were diagnosed: 1994–1997 • Ontario, Canada 	<ul style="list-style-type: none"> • Number of years since smoking cessation: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.3 (1.5–3.4) ○ 1–4: 2.1 (1.2–3.8) ○ 5–9: 1.8 (1.0–3.3) ○ 10–19: 2.1 (1.3–3.4) ○ ≥20: 1.3 (0.8–2.1) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.2 (1.5–3.2) ○ 1–4: 1.4 (0.6–2.9) ○ 5–9: 1.6 (0.7–3.7) ○ 10–19: 1.9 (0.8–4.2) ○ ≥20: 1.5 (0.7–3.1) 	Adjusted for age and BMI
McLaughlin et al. (1995)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 20–79 years of age • 1,732 cases of kidney cancer and 2,309 controls • Time period in which cases were diagnosed: 1989–1991 • Six study centers in five countries: Australia (Sydney), Denmark, Germany (Berlin and Heidelberg), Sweden (Uppsala), and United States (Minnesota) 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.0 (referent) – Current smoker: 1.4 (1.2–1.7) – Former smoker: 1.2 (1.0–1.4) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Current smoker: 1.0 (referent) – ≤5: 0.90 (0.7–1.2) – 6–15: 0.84 (0.7–1.1) – 16–25: 0.75 (0.6–1.0) – >25: 0.85 (0.6–1.1) 	Adjusted for age, sex, study center, and BMI Number of years since smoking cessation additionally adjusted for number of cigarettes smoked per day

Table 4.8 Continued

Study	Design/population ^a	Exposure estimates: OR (95% CI)	Comments
Muscat et al. (1995)	<ul style="list-style-type: none"> • Case-control, hospital-based study • Cases: Men and women diagnosed at hospitals in the study areas • Controls: Hospitalized for conditions unrelated to tobacco use • 788 cases of kidney cancer and 779 controls • Time period in which cases were diagnosed: 1977–1993 • Multicenter hospitals in New York (New York City and New Hyde Park), Illinois (Chicago and Hines), Michigan (Detroit), and Pennsylvania (Philadelphia) 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.4 (1.02–2.0) ○ Former smoker: 0.9 (0.7–1.5) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ 1–5: 1.6 (0.9–2.6) ○ 6–10: 2.2 (1.2–4.4) ○ >10: 0.7 (0.5–0.9) • Women <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.0 (0.7–1.6) ○ Former smoker: 1.1 (0.7–1.7) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ 1–5: 1.0 (0.4–2.2) ○ 6–10: 1.3 (0.3–6.0) ○ >10: 1.1 (0.6–1.8) 	Adjusted for age and level of education
Yuan et al. (1998)	<ul style="list-style-type: none"> • Case-control, population-based study • Non-Asian men and women 25–74 years of age • 1,204 cases of kidney cancer and 1,204 controls • Time period in which cases were diagnosed: 1986–1994 • Los Angeles, California 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Current smoker: 1.53 (1.23–1.90) – Former smoker: 1.24 (1.02–1.50) • Number of years since smoking cessation: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – 1–9: 1.33 (1.02–1.74) – 10–19: 1.25 (0.94–1.64) – ≥20: 1.15 (0.89–1.50) 	Adjusted for level of education
Parker et al. (2003)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 40–85 years of age • 387 cases of kidney cancer and 2,333 controls • Time period in which cases were diagnosed: 1985–1987 • Iowa 	<ul style="list-style-type: none"> • Number of years of smoking cessation: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Never smoker: 0.6 (0.4–0.9) – <10: 0.7 (0.4–1.1) – 10–19: 0.8 (0.5–1.2) – 20–29: 0.7 (0.4–1.1) – ≥30: 0.5 (0.3–1.0) 	Adjusted for age, sex, BMI, history of hypertension, and pack-years of smoking

Table 4.8 Continued

Study	Design/population ^a	Exposure estimates: OR (95% CI)	Comments
Hu et al. (2005)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 20 years of age and older • 1,279 cases of kidney cancer and 5,370 controls • Time period in which cases were diagnosed: 1994–1997 • Eight Canadian provinces: Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 0.9 (0.7–1.2) ○ Former smoker: 1.2 (1.0–1.5) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ ≤10: 1.5 (1.0–2.3) ○ 11–20: 1.1 (0.8–1.5) ○ 21–30: 1.2 (0.8–1.6) ○ ≥31: 1.0 (0.7–1.4) • Women: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ Current smoker: 0.9 (0.7–1.2) ○ Former smoker: 1.3 (1.0–1.6) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Never smoker: 1.0 (referent) ○ ≤10: 1.5 (0.8–2.6) ○ 11–20: 0.6 (0.4–1.1) ○ ≥20: 1.1 (0.7–1.6) 	<p>Adjusted for age; Canadian province; level of education; BMI; alcohol use; and consumption of meats, vegetables, and fruits</p> <p>Number of years since smoking cessation additionally adjusted for pack-years of smoking</p>

Table 4.8 Continued

Study	Design/population ^a	Exposure estimates: OR (95% CI)	Comments
Cote et al. (2012)	<ul style="list-style-type: none"> • Case-control, population-based study • Men and women 20–79 years of age • 1,217 cases of kidney cancer and 1,235 controls • Time period in which cases were diagnosed: 2002–2007 • Detroit (Michigan) and Chicago (Illinois) 	<ul style="list-style-type: none"> • White: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.46 (1.05–2.04) ○ Former smoker: 0.99 (0.78–1.25) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤5: 1.34 (0.83–2.17) ○ 6–15: 0.82 (0.53–1.25) ○ 16–25: 0.61 (0.39–0.94) ○ ≥25: 0.62 (0.39–1.01) • Black: <ul style="list-style-type: none"> – Smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.16 (0.81–1.65) ○ Former smoker: 0.81 (0.56–1.18) – Number of years since smoking cessation: <ul style="list-style-type: none"> ○ Current smoker: 1.00 (referent) ○ ≤5: 0.97 (0.51–1.85) ○ 6–15: 0.73 (0.42–1.26) ○ 16–25: 0.72 (0.38–1.37) ○ ≥25: 0.47 (0.25–0.88) 	<p>Adjusted for age, study site, sex, BMI, education level, family history of kidney cancer, and hypertension</p> <p>Number of years since smoking cessation additionally adjusted for pack-years of smoking</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **OR** = odds ratio.

^aStudies are of cancer incidence unless number of cancer deaths is identified.

mechanisms include inhalation of benzene, a known cause of leukemia, and radioactive substances in tobacco smoke (Thomas and Chelghoum 2004; USDHHS 2004; Lichtman 2007).

In a meta-analysis of 5 cohort and 12 case-control studies of smoking and AML, Colamesta and colleagues (2016) reported separate summary RRs for cohort and case-control studies. For the cohort studies, summary RR estimates were 1.45 (95% CI, 1.08–1.94) for former smokers and 1.52 (95% CI, 1.10–2.14) for current smokers. For the case-control studies, summary RRs were 1.21 (95% CI, 1.03–1.41) for former smokers and 1.36 (95% CI, 1.11–1.66) for current smokers. This meta-analysis also pooled data that included information on number of years since cessation from three case-control studies (Severson et al. 1990; Kane et al. 1999; Musselman et al. 2013). In the pooled analysis, risk declined with increasing time since smoking cessation, with no statistically significant reduction in risk among former smokers who had quit within 10 years compared with continuing smokers (OR = 1.01; 95% CI, 0.60–1.72). The risk was lower for those who had quit for 10–20 years (OR = 0.74; 95% CI, 0.53–1.03) and even lower for those who had quit for more than 20 years (OR = 0.59; 95% CI, 0.45–0.78).

Synthesis of the Evidence

The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of six cancers: lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder (USDHHS 1990). Results of studies published since 1990 expand the role of smoking as a cause of cancer and support the reduction of cancer risk following smoking cessation.

The 2004 and 2014 Surgeon General's reports concluded that smoking causes at least six additional cancers beyond those for which the associations were considered causal in 1990: stomach, liver, colon and rectum, kidney, cervix, and AML (USDHHS 2004, 2014). The 12 types of cancer reviewed in this section have all been judged to be caused by cigarette smoking in reports of the U.S. Surgeon General (USDHHS 2014) and IARC (IARC 2012)—based on evaluating the evidence against criteria for causality utilized in Surgeon Generals' reports, including consistency across studies, temporal relationship of association, strength of association, and biological plausibility (USDHHS 2004).

These same criteria have been used to evaluate the evidence on smoking cessation. Because smoking cessation reduces cumulative exposure to tobacco smoke across the life course, biological plausibility alone, coupled with appropriate temporality, supports the conclusion that smoking cessation reduces the risk of all 12 cancers

that have been causally linked to cigarette smoking. Additionally, epidemiological evidence documents that the risk for most of these cancers drops progressively as the time since successful quitting lengthens, and findings are generally consistent across studies.

The effect of smoking cessation on risk for lung cancer is particularly important because lung cancer is the largest contributor to smoking-attributable cancer mortality in the United States and the number of new cases continues to increase (U.S. Cancer Statistics Working Group 2019). Since 1990, many studies have been published characterizing how risk for lung cancer changes with time since smoking cessation. As noted previously, results from many studies (Calle et al. 2002; IARC 2007; Pinsky et al. 2015) indicate that, in comparison with smokers who do not quit, RRs for lung cancer decline steadily after smoking cessation, with RRs for former smokers falling to half those of RRs for continuing smokers after approximately 10–15 years of cessation.

While the 2004 and 2014 Surgeon General's reports concluded that smoking causes cancers of the stomach, colon and rectum, kidney, and cervix and AML (USDHHS 2004, 2014), the two reports did not explicitly conclude that smoking cessation reduces the risk for these cancers. For four of these malignancies (stomach, kidney, cervix, and AML), RRs are consistently lower among former cigarette smokers than among current smokers, supporting a causal association between smoking cessation and lower risk for these cancers. Similarly, the 2004 and 2014 Surgeon General's reports also concluded that smoking causes cancer of the liver (USDHHS 2004, 2014). This report considered four specific studies showing that RRs decline in former smokers with time since smoking cessation. These findings were consistent with the meta-analysis of 29 studies conducted for the 2014 Surgeon General's report that documented a much lower RR in former smokers than in current smokers, compared with never smokers (USDHHS 2014). Taken together, these epidemiological findings support a causal association between smoking cessation and lower risk for liver cancer.

In studies of colorectal cancer, RRs for former smokers have not been consistently lower than those for current smokers. However, in many of the studies where lower RRs have not been observed for former smokers, current smokers likely did not have sufficiently long induction periods to fully reflect the long-term effects of smoking. In addition to the studies where lower RRs were observed, other evidence supports the hypothesis that smoking cessation reduces risk of colorectal cancer. This evidence includes studies that document substantially lower RRs for colorectal adenoma, an established precursor lesion for colorectal cancer, among former smokers than among current smokers. These studies have also found declining RRs

for colorectal cancer among former smokers with increased time since smoking cessation, particularly for specific molecular subtypes that are associated with smoking. Taken together, these epidemiological findings, including those of incident colorectal cancer and established precursor lesions for colorectal cancer, support a causal association between smoking cessation and lower risk for colorectal cancer.

Conclusions

1. The evidence is sufficient to infer that smoking cessation reduces the risk of lung cancer.
2. The evidence is sufficient to infer that smoking cessation reduces the risk of laryngeal cancer.
3. The evidence is sufficient to infer that smoking cessation reduces the risk of cancers of the oral cavity and pharynx
4. The evidence is sufficient to infer that smoking cessation reduces the risk of esophageal cancer.
5. The evidence is sufficient to infer that smoking cessation reduces the risk of pancreatic cancer.
6. The evidence is sufficient to infer that smoking cessation reduces the risk of bladder cancer.
7. The evidence is sufficient to infer that smoking cessation reduces the risk of stomach cancer.
8. The evidence is sufficient to infer that smoking cessation reduces the risk of colorectal cancer.

9. The evidence is sufficient to infer that smoking cessation reduces the risk of liver cancer.
10. The evidence is sufficient to infer that smoking cessation reduces the risk of cervical cancer.
11. The evidence is sufficient to infer that smoking cessation reduces the risk of kidney cancer.
12. The evidence is sufficient to infer that smoking cessation reduces the risk of acute myeloid leukemia.
13. The evidence is sufficient to infer that the relative risk of lung cancer decreases steadily after smoking cessation compared with the risk for persons continuing to smoke, with risk decreasing to half that of continuing smokers approximately 10–15 years after smoking cessation and decreasing further with continued cessation.

Implications

The evidence that smoking cessation reduces cancer risk has long been an important part of the rationale for efforts—including educational, clinical, health systems, community, and population-based interventions and initiatives to make evidence-based, barrier-free cessation services widely available—to motivate and help smokers to quit. This report's conclusion that smoking cessation reduces the risk of several additional types of cancer further strengthens that rationale and provides an opportunity for broadening and intensifying messages about the important role that smoking cessation plays in cancer prevention.

Smoking Cessation After a Cancer Diagnosis

This section reviews evidence of the health benefits of smoking cessation at the time of a cancer diagnosis or after that diagnosis compared with continuing to smoke. At the time of cancer diagnosis, approximately 20–30% of all cancer patients self-reported current cigarette smoking (Warren and Simmons 2018); however, self-reported rates of smoking were typically lower than biochemically confirmed smoking, as smokers with cancer may misrepresent their smoking. Among long-term cancer survivors, the smoking prevalence is approximately 9% (Warren and Simmons 2018). This review is limited to all-cause mortality, an integrative indicator, and does not explore

disease progression or recurrence, cancer-specific mortality, second primary cancer, quality of life, or treatment toxicity as outcomes of interest.

Conclusions from Previous Surgeon General's Reports

Previous reports of the Surgeon General have not evaluated the health benefits of smoking cessation after a cancer diagnosis, but smoking is causally associated with diseases of every major organ system and is therefore

strongly linked with all-cause mortality (USDHHS 2014). The 2014 Surgeon General's report concluded that smoking increases all-cause mortality. The 2014 report was also the first to conclude that continued smoking after a cancer diagnosis causes adverse health outcomes among cancer patients or survivors (i.e., persons who have been diagnosed with cancer) (U.S. Department of Health and Human Services [USDHHS] 2014). Smoking cessation has been shown to reduce all-cause mortality in the general population (USDHHS 2014), providing strong justification for the hypothesis that cessation after a cancer diagnosis will result in improved survival compared with continued smoking. Given the conclusions in the 2014 Surgeon General's report about the adverse health effects that cancer patients who smoke can experience, a review of the evidence on smoking cessation after a cancer diagnosis is important.

Literature Review Methods

The literature search for this section followed the strategy used in the 2014 Surgeon General's report (USDHHS 2014), which queried the National Library of Medicine's MEDLINE database for "smoking" and "cancer." Studies were considered for inclusion if they met three criteria:

- They were original reports that compared all-cause mortality between (a) current smokers who were diagnosed with cancer but continued smoking and (b) patients who had quit smoking within 1 year of a cancer diagnosis or patients who had quit smoking after a cancer diagnosis;
- They had a baseline and final cohort size of at least 100 cancer patients, including cigarette smokers and quitters; and
- They were published from 2000 to 2016.

Studies were excluded if they reported findings on only continued smoking after a cancer diagnosis versus quitting smoking substantially before a cancer diagnosis.

Smoking Cessation and All-Cause Mortality in Cancer Patients

Ten studies (seven prospective cohort studies and three retrospective cohort studies) reporting on 10,975 patients met the inclusion criteria (Table 4.9). The

studies are grouped in the table by their reference group: never smokers, current smokers who did not stop smoking with diagnosis (referred to as persistent smokers), and quitters. The cohorts were composed of patients with lung cancer (four studies), with head/neck cancer (three studies), with breast cancer (one study), and with multiple types of cancer (two studies). Eight studies did not specify the treatment modality (surgery, radiotherapy, chemotherapy), and two patient cohorts were composed exclusively of patients treated with radiotherapy (Al-Mamgani et al. 2014; Roach et al. 2016).

Three prospective cohort studies (Al-Mamgani et al. 2014; Choi et al. 2016; Passarelli et al. 2016) compared continued smoking and quitting smoking with never smoking. In all three studies, continued smoking after a cancer diagnosis significantly increased risk of mortality compared with never smoking, and the risk of mortality for quitters was greater than that for never smokers but not as great as that for continuing smokers.

Three studies (Sardari Nia et al. 2005; Sandoval et al. 2009; Chen et al. 2010) compared quitting smoking with persistent smoking using persistent smokers as the referent. Quitting was significantly associated with reduced all-cause mortality in two studies, with associations that were significant in patients with non-small cell lung cancer (relative risk [RR] = 0.34; 95% CI, 0.16–0.71) (Sardari Nia et al. 2005) and in patients with small cell lung cancer (hazard ratio [HR] = 0.55; 95% CI, 0.38–0.79) (Chen et al. 2010), but not in a study of patients with oral cavity cancer (RR = 0.92; 95% CI, 0.46–1.84) (Sandoval et al. 2009).

Four studies compared continued cigarette smoking with quitting, using quitters as the referent (Tao et al. 2013; Al-Mamgani et al. 2014; Dobson Amato et al. 2015; Roach et al. 2016). In all four studies, continued smoking was associated with increased all-cause mortality relative to quitting. For a group of 1,632 male cancer patients from the Shanghai Cancer Cohort (Tao et al. 2013), results by disease site showed (a) a significantly increased risk of all-cause mortality in persistent (continued) smokers for lung cancer (HR = 1.89; 95% CI, 1.18–3.02), colorectal cancer (HR = 3.46; 95% CI, 1.69–7.10), and bladder cancer (HR = 17.29; 95% CI, 2.25–132.64) and (b) indication of increased mortality in other cancers (HR = 1.49; 95% CI, 0.92–2.40).

Evaluation of the Evidence

This is the first review in a report of the Surgeon General on the potential health benefits of smoking cessation after a cancer diagnosis. This section considers scientific evidence with reference to five key guidelines for

Table 4.9 Cohort studies that compared all-cause mortality in persons who were smokers at the time of a cancer diagnosis but had quit smoking after the diagnosis with those who continued smoking after the diagnosis

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Never smokers					
Yang et al. (2015a)	<ul style="list-style-type: none"> • Prospective cohort • 2,548 patients with colorectal cancer from CPS II • 153 current smokers at baseline 	<ul style="list-style-type: none"> • Every 2 years from 1997 to December 31, 2010 	<ul style="list-style-type: none"> • Quitters • Persistent smokers 	<ul style="list-style-type: none"> • Never smokers: Those who never smoked • Quitters: Those who had quit smoking after a cancer diagnosis • Persistent smokers: Those who continued to smoke after a cancer diagnosis 	<ul style="list-style-type: none"> • Adjusted RR: <ul style="list-style-type: none"> – Never smokers: 1.0 (referent) – Quitters: 1.94 (95% CI, 1.29–2.91) – Persistent smokers: 2.33 (95% CI, 1.62–3.34) • RR for quitters vs. persistent smokers: 0.833 (p = 0.37, 1.94 vs. 2.33)
Choi et al. (2016)	<ul style="list-style-type: none"> • Prospective cohort • 590 patients with head or neck cancer • 146 persistent smokers at any time after a cancer diagnosis • 99 quitters • University of Michigan 	<ul style="list-style-type: none"> • Every 3 months for 2 years • Annually after the first 2 years until 8 years of follow-up or September 11, 2011, whichever came first 	<ul style="list-style-type: none"> • Quitters • Persistent smokers 	<ul style="list-style-type: none"> • Never smokers: Those who never smoked • Quitters: Those who had quit within the first 3 months of diagnosis of squamous cell carcinoma (head or neck) and remained a quitter through the first 2 years after the diagnosis • Persistent smokers: Those who smoked at any time after a cancer diagnosis (defined as continuing smokers in the study) 	<ul style="list-style-type: none"> • Adjusted HR: <ul style="list-style-type: none"> – Never smokers: 1.0 (referent) – Quitters: 2.38 (95% CI, 1.29–4.36) – Persistent smokers: 2.71 (95% CI, 1.48–4.98) • RR for quitters vs. persistent smokers: 0.877 (2.38 vs. 2.71, calculated)
Passarelli et al. (2016)	<ul style="list-style-type: none"> • Prospective cohort • 4,562 patients with breast cancer, as a part of the Collaborative Breast Cancer Study and Collaborative Women’s Longevity Study • 424 persistent smokers • 352 quitters 	<ul style="list-style-type: none"> • Median follow-up of 6 years after diagnosis 	<ul style="list-style-type: none"> • Quitters • Persistent smokers 	<ul style="list-style-type: none"> • Never smokers: Those who never smoked • Quitters: Those who had quit smoking during the year before the cancer diagnosis and remained a quitter after the diagnosis • Persistent smokers: Those who reported actively smoking during the year before the cancer diagnosis and after the diagnosis 	<ul style="list-style-type: none"> • Adjusted HR: <ul style="list-style-type: none"> – Never smokers: 1.0 (referent) – Quitters: 2.34 (95% CI, 1.85–2.96) – Persistent smokers: 2.57 (95% CI, 2.06–3.21) • RR for quitters vs. persistent smokers: 0.911 (2.34 vs. 2.57, calculated)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Persistent smokers					
Sardari Nia et al. (2005)	<ul style="list-style-type: none"> • Prospective cohort • 321 patients with non-small cell lung cancer • 169 persistent smokers • 35 quitters • Belgium 	<ul style="list-style-type: none"> • Every 4 months in Years 1 and 2 • Every 6 months in Year 3 • Annually from Years 4 to 6 through January 2003 	<ul style="list-style-type: none"> • Quitters 	<ul style="list-style-type: none"> • Persistent smokers: Patients who continued smoking (defined as current smokers in the study) • Quitters: Patients who had stopped smoking between the cancer diagnosis and the surgery. (1 week to more than 19 years) 	<ul style="list-style-type: none"> • Persistent smokers: 1.0 (referent) • Quitters: unadjusted RR = 0.34 (95% CI, 0.16–0.71)
Chen et al. (2010)	<ul style="list-style-type: none"> • Retrospective cohort • 284 patients with limited-stage, small cell lung cancer • 76 persistent smokers • 87 quitters • Mayo Clinic 	<ul style="list-style-type: none"> • At 6 months after diagnosis, then annually until December 2003 	<ul style="list-style-type: none"> • Quitters 	<ul style="list-style-type: none"> • Persistent smokers: Those who never quit smoking • Quitters: Those who had quit smoking at the time of or after the cancer diagnosis 	<ul style="list-style-type: none"> • Persistent smokers: 1.0 (referent) • Quitters: adjusted HR = 0.55 (95% CI, 0.38–0.79)
Sandoval et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort • 146 patients with oral cavity cancer • 101 patients who were current smokers at baseline • 30 persistent smokers at 1-year follow-up • 55 quitters • Spain 	<ul style="list-style-type: none"> • At 1 year and 2 years after diagnosis 	<ul style="list-style-type: none"> • Quitters 	<ul style="list-style-type: none"> • Persistent smokers: Those who were classified as current smokers at diagnosis of oral cancer and continued to smoke after the diagnosis • Quitters: Those who had quit smoking after the diagnosis, defined as quitting smoking at 1-year follow-up 	<ul style="list-style-type: none"> • Persistent smokers: 1.0 (referent) • Quitters: unadjusted RR = 0.92 (95% CI, 0.46–1.84)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Quitters					
Tao et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort • Shanghai Cohort Study • 1,632 male patients with cancer <ul style="list-style-type: none"> – 288 with lung cancer – 362 with stomach cancer – 248 with colorectal cancer – 107 with bladder cancer – 132 with prostate cancer – 492 with other cancer • 197 persistent smokers • 214 quitters 	<ul style="list-style-type: none"> • Annually for 25 years through 2010 	<ul style="list-style-type: none"> • Persistent smokers 	<ul style="list-style-type: none"> • Quitters: Those who had quit smoking after a cancer diagnosis and remained quit throughout follow-up • Persistent smokers: Those who continued to smoke after a cancer diagnosis throughout follow-up 	<ul style="list-style-type: none"> • Adjusted HR: <ul style="list-style-type: none"> – Quitters: 1.0 (referent) – Persistent smokers: 1.76 (95% CI, 1.37–2.27) • RR for quitters vs. persistent smokers: 0.568 (95% CI, 0.441–0.730)
Al-Mamgani et al. (2014)	<ul style="list-style-type: none"> • Retrospective cohort • 549 patients with T1a glottic cancer • 52 persistent smokers after radiotherapy • 215 quitters 	<ul style="list-style-type: none"> • At the end of radiotherapy: <ul style="list-style-type: none"> – Weeks 4 and 6 – Months 3, 6, 12, 18, and 24 • Year 1: Every 2 months • Years 2 and 3: Every 3 months • Year 4 and beyond: Every 6 months 	<ul style="list-style-type: none"> • Persistent smokers 	<ul style="list-style-type: none"> • Quitters: Those who had stopped smoking after radiotherapy for T1a glottic cancer • Persistent smokers: Those who continued to smoke after radiotherapy for T1a glottic cancer 	<ul style="list-style-type: none"> • Surviving percentage (not defined, but implied as 10-year survival): <ul style="list-style-type: none"> – Persistent smokers: 36% – Quitters: 70% (p <0.001) • RR for quitters vs. persistent smokers: 0.190 (95% CI, 0.126–0.288, calculated)
Dobson Amato et al. (2015)	<ul style="list-style-type: none"> • Prospective cohort • 224 patients with lung cancer, all of whom were enrolled in a telephone-based tobacco treatment program • 129 persistent smokers at last follow-up • 95 quitters at last follow-up • Roswell Park Cancer Institute 	<ul style="list-style-type: none"> • Survival duration was assessed in May 2014 	<ul style="list-style-type: none"> • Persistent smokers 	<ul style="list-style-type: none"> • Quitters: Those who reported having at least 24 hours' abstinence since the previous contact or follow-up assessment, or who had quit before the initial contact • Persistent smokers: Current smokers found at every contact not to have quit 	<ul style="list-style-type: none"> • Adjusted HR: <ul style="list-style-type: none"> – Quitters: 1.0 (referent) – Persistent smokers: 1.79 (95% CI, 1.14–2.82) • RR for quitters vs. persistent smokers: 0.558 (95% CI, 0.355–0.877)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Quitters (continued)					
Roach et al. (2016)	<ul style="list-style-type: none"> Retrospective cohort 119 patients with lung cancer who were current smokers and treated with SBRT 87 persistent smokers 32 quitters 	<ul style="list-style-type: none"> Physical exam every 3 months for Years 1 and 2 Chest CT scan every 3 months for Years 1 and 2, then every 6 months thereafter Follow-up from 2004 to 2013 	<ul style="list-style-type: none"> Persistent smokers 	<ul style="list-style-type: none"> Quitters: Those who had quit smoking after SBRT Persistent smokers: Those who smoked during and after SBRT 	<ul style="list-style-type: none"> Adjusted HR: <ul style="list-style-type: none"> – Quitters: 1.0 (referent) – Persistent smokers: 2.07 (95% CI, 1.02–4.2) RR for quitters vs. persistent smokers: 0.483 (95% CI, 0.238–0.980)

Notes: **CI** = confidence interval; **CPS** = Cancer Prevention Study; **CT** = computed tomography; **HR** = hazard ratio; **RR** = risk ratio; **SBRT** = stereotactic body radiation therapy.

causal inference set out in the 1964 and 2004 Surgeon General's reports (U.S. Department of Health, Education, and Welfare 1964; USDHHS 2004).

Temporality

All studies evaluated the effects of smoking cessation after a cancer diagnosis. In all the studies, the temporal relationship was appropriate for causation because evaluation of smoking status, including smoking cessation, preceded the outcome of all-cause mortality.

Consistency

Six of the seven studies that directly compared smoking cessation with continued smoking observed significant improvements in all-cause mortality (Sardari Nia et al. 2005; Sandoval et al. 2009; Chen et al. 2010; Tao et al. 2013; Al-Mamgani et al. 2014; Dobson Amato et al. 2015). In the three studies that compared the risks of continued smoking or smoking cessation after a cancer diagnosis with never smoking, quitting smoking reduced risk compared with continued smoking (Yang et al. 2015a; Choi et al. 2016; Passarelli et al. 2016). The consistency of the observations extended across multiple types of cancer: head/neck, lung, breast, colorectal, bladder, and prostate. Observations spanned treatments with surgery, chemotherapy, or radiotherapy. Studies varied in geographic location and time span and in methodologic definitions for smoking status. Thus, in the broad range of the studies across cancer sites, treatments, and definitions of changes in smoking status, evidence consistently showed an improvement in all-cause mortality as a result of smoking cessation.

Strength of Association

The 2014 Surgeon General's report observed a 51% median increase in risk of all-cause mortality among cancer patients who were smokers compared with those who were never smokers (USDHHS 2014). For comparison, a review of 22 population-based cohorts from the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) found a doubled risk of all-cause mortality in current smokers and a 30% increased risk in former smokers compared with never smokers, reflecting an approximately 50% higher risk for current smokers compared with those who had quit smoking (Müezzinler et al. 2015). In the seven cohorts reviewed for this report that compared the effects of continued smoking and smoking cessation on all-cause mortality, the median relative risk of all-cause mortality was 1.82. Thus, with regard to all-cause mortality, the strength of the association between smoking and the reduction in

risk for quitters is similar among cancer survivors and the general population.

Existing scientific evidence indicates that cancer patients substantially underreport their smoking: approximately 30% of patients who were smokers based on cotinine level reported themselves as nonsmokers (Khuri et al. 2001; Warren et al. 2012; Morales et al. 2013; Alberg et al. 2015). Thus, the associations between self-reported smoking and all-cause mortality, as reported in the 2014 Surgeon General's report, may be conservative.

Coherence

Smoking cessation at any age reduces all-cause mortality (USDHHS 2010, 2014; Thun et al. 2013b; Müezzinler et al. 2015). The adverse effects of smoking and the benefits of smoking cessation are well established for many diseases in the general population, including coronary heart disease, pulmonary disease, stroke, and other chronic health conditions. Smoking cessation reduces the risk of developing multiple types of cancer. Cigarette smoking by cancer patients increases all-cause mortality and cancer-specific mortality (USDHHS 2014). Much is known about the mechanisms by which smoking causes cancer (USDHHS 2010). Among these mechanisms, smoking appears to increase tumor progression. In experimental systems, constituents of cigarette smoke promote more aggressive phenotypes in cancer cells (Sobus and Warren 2014; Warren et al. 2014). A body of experimental evidence suggests that nicotine may promote all proliferation and tumor progression and increase risk for metastasis (Schaal and Chellappan 2014). Thus, smoking cessation among cancer patients would be anticipated to reduce all-cause mortality by reducing both noncancer-related mortality and cancer-related mortality. The 2014 Surgeon General's report identified a 51% median increased risk of all-cause mortality among cancer patients who smoked compared with cancer patients who quit smoking.

Synthesis of the Evidence

Ten studies in this section met the inclusion criteria, all including participants who were current smokers at the time of cancer diagnosis and who were evaluated for smoking cessation after diagnosis. The findings showed a benefit of cessation across a variety of cancer diagnoses and treatments. The magnitude of the observed associations is consistent with established reductions in all-cause mortality for smoking cessation in the general population. Given the relatively small body of evidence, limitations in the quality of the evidence, and the breadth of cancer

diagnoses and treatments, current evidence is suggestive but not sufficient to conclude that the observed reductions in all-cause mortality following smoking cessation generalize to all types of malignancies and modalities of treatment. The 2014 Surgeon General’s report concluded that “quitting smoking improves the prognosis of cancer patients” (USDHHS 2014, p. 9). This cancer-specific conclusion contrasts with nonspecific, all-cause mortality, as considered above.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking cessation and improved all-cause mortality in cancer patients who are current smokers at the time of a cancer diagnosis.

Implications

The evidence suggests that smoking cessation after a cancer diagnosis can significantly reduce all-cause mortality relative to continued smoking. This evidence is consistent with the known reduction in all-cause mortality due to smoking cessation in the general population. Thus, smoking cessation likely reduces all-cause mortality in cancer patients.

These conclusions strengthen the scientific basis for existing recommendations that emphasize the importance of quitting smoking after a cancer diagnosis. Many large national and international cancer organizations recommend addressing tobacco use among cancer patients. The American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR)—two of the largest clinical oncology and research organizations—maintain updated recommendations for addressing tobacco use in cancer patients. These organizations advocate for tobacco control, development of methods to facilitate smoking cessation, and practical approaches to enhance clinical care and research (AACR n.d.; ASCO n.d.). The International Association for the Study of Lung Cancer (IASLC) offers advanced recommendations for addressing tobacco use, particularly in the context of cancer care and lung cancer screening (IASLC n.d.). Recognizing the importance of addressing tobacco use and the lack of standardized approaches to screening, the National Cancer Institute (NCI) and the AACR developed standardized approaches for assessing tobacco use in clinical cancer research trials (Land et al. 2016). Similar standardized approaches to screening

recommended by the NCI and AACR can also be applied to clinical care. Using these approaches, the National Comprehensive Cancer Network (NCCN) initiated the first series of recommendations to address tobacco use in all cancer patients who report having smoked during the past 30 days (NCCN n.d.). These guidelines follow the same format and approach as other clinical cancer guidelines, offering a resource to facilitate support for smoking cessation in a format that oncologists are familiar with. Although guidelines are available, they are not always implemented completely (Goldstein et al. 2013; Toll et al. 2013; Gritz et al. 2014; Gallaway et al. 2019), and tobacco treatment/cessation programs are not always offered in all cancer centers (Gallaway et al. 2019), suggesting a need to identify and address barriers to adoption of guidelines.

At present there is no standard format to promote smoking cessation in cancer patients. The context of addressing tobacco use in cancer patients is different from the context of addressing tobacco use in the general population of persons who do not have cancer because cancer patients are commonly presented with life-changing diagnoses and will regularly return for treatment for several months or years (Warren et al. 2014). The change in clinical care patterns associated with a new cancer diagnosis can affect frequency of follow-up with clinical providers and the perceived urgency of addressing tobacco use. Recognizing the clinical importance of tobacco use and tobacco cessation with the importance of developing approaches across a wide spectrum of clinical settings, NCI initiated in 2017 a Cancer Center Cessation Initiative (C3I) to fund the development of dedicated tobacco cessation approaches in 22 NCI Designated Cancer Centers (NCI 2018). In 2018, an additional 20 centers received funding at the same level (Croyle et al. 2019). Results from these centers are expected to help refine standardized approaches to screening for tobacco use and providing evidence-based support for smoking cessation. Furthermore, Warren and colleagues (2019) modeled the incremental costs due to failure of first-line cancer treatments because of continued smoking. Compared with nonsmokers, the attributable costs were estimated as \$2.1 million per 1,000 patients or \$10,700 per patient. These estimates strengthen the rationale for encouraging cessation among persons being treated for cancer.

The evidence reviewed in the 2014 Surgeon General’s report documented the harm of smoking by persons with a cancer diagnosis, and this report builds on that finding by showing that such harm is reduced to some extent by smoking cessation. The conclusions of this report strengthen the rationale for aggressively promoting and supporting smoking cessation in cancer patients and survivors.

Cardiovascular Disease

Approximately 92.1 million American adults 20 years of age or older (more than 1 in 3 adults) have one or more types of cardiovascular disease (CVD), and by 2030 almost 44% of the population will have some form of CVD (Benjamin et al. 2017). In 2014, coronary heart disease (CHD) was listed on the death certificate for approximately 1 of every 7 deaths (Benjamin et al. 2017; National Center for Health Statistics 2017). The CVDs comprise some of the most common causes of death: CHD, congestive heart failure (CHF), cerebrovascular disease (including stroke), atherosclerosis (including aortic aneurysm), and hypertension. In the United States, CVD has accounted for more deaths since 1919 than any other major cause of death (Benjamin et al. 2019). CHD (43.2%) is the leading cause of death attributable to CVD, followed by stroke (16.9%), heart failure (9.3%), high blood pressure (9.8%), diseases of the arteries (3.0%), and other CVDs (Benjamin et al. 2019). In 2015, CVD was the leading cause (41.2%) of smoking-attributable age-standardized disability-adjusted life-years (DALYs), a combined indicator of smoking-attributable mortality and disease burden (GBD 2015 Tobacco Collaborators 2017). Since the first Surgeon General's report in 1964, the rates of age-adjusted CVD mortality have declined greatly; a reduction in smoking has been a major contributing factor to the decline in CHD mortality in particular (USDHHS 2014).

From 2014 to 2015, the average annual direct (medical) plus indirect costs of heart disease were estimated to total \$218.7 billion (Benjamin et al. 2019). Heidenreich and colleagues (2011) projected that the direct (medical) cost of CHD in the United States would increase by approximately 200%, from \$272.2 billion in 2010 to \$818.1 billion in 2030.

Surgeon General's reports published since 1990 have not systematically covered the benefits of smoking cessation with regard to risk and outcomes for men and women with CVD. This section expands on previous reports by summarizing current knowledge of the effects of smoking cessation on risk of CVD and the natural history of this disease. This is not a systematic update, given the scope of the literature, and it does not cover all topics. Instead, this section provides examples of new findings that expand our understanding of conclusions from previous reports. Because of the wide range of research on this topic, this review focuses, where relevant, on summarizing results from meta-analyses or pooled analyses of findings from multiple cohorts and clinical trials.

Conclusions from Previous Surgeon General's Reports

The 1990 Surgeon General's report on the health benefits of smoking cessation (U.S. Department of Health and Human Services [USDHHS] 1990) provided several conclusions on smoking cessation and CVD (Table 4.10) that were updated in subsequent reports. Table 4.10 summarizes the major conclusions related to smoking cessation and CVD from the 1990, 2001, 2004, and 2010 Surgeon General's reports.

Literature Review Methods

For this Surgeon General's report, a literature review was conducted to update the cessation-specific findings from the 1990, 2001, 2004, 2006, 2010, and 2014 Surgeon General's reports. The search was restricted to English-language papers available on PubMed and published between January 2000 and August 31, 2017. Medical Subject Headings (MeSH) in PubMed were used to capture relevant articles. Retrieved articles included at least one term related to smoking cessation (e.g., "former smokers") and at least one term related to CVD (e.g., "coronary heart disease" [CHD]) or a term to describe the mechanism of disease (e.g., "thrombosis"). Citations from relevant retrieved articles and previous Surgeon General's reports and targeted searches were used to identify articles not captured by the search.

Relevant Mechanistic Data

Previous Surgeon General's reports have provided detailed reviews of potential mechanisms underlying how smoking and smoking cessation could affect the development of CVD (USDHHS 1983, 1990, 2004, 2006, 2010, 2014). This section reviews the links between smoking cessation and the following CVDs: CHD, cerebrovascular diseases, atrial fibrillation (AF), sudden cardiac death (SCD), heart failure, venous thromboembolism (VTE), lower-extremity peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA). These diseases share some underlying mechanisms, and multiple risk factors contribute to each disease; for example, atherosclerosis and thrombosis are important for most of these diseases (International Agency for Research on Cancer [IARC] 2007).

Table 4.10 Conclusions from previous Surgeon General's reports on smoking cessation and cardiovascular disease

Year of report (page numbers)	Conclusions
USDHHS (1990, pp. 10–11)	<ol style="list-style-type: none"> 1. Compared with continued smoking, smoking cessation substantially reduces risk of CHD among men and women of all ages. 2. The excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked. 3. Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies, this reduction in risk of recurrence or premature death has been 50% or more. 4. Smoking cessation substantially reduces the risk of peripheral artery occlusive disease compared with continued smoking. 5. Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival. 6. Smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking. After smoking cessation, the risk of stroke returns to the level of never smokers; in some studies this has occurred within 5 years, but in others as long as 15 years of abstinence were required.
USDHHS (2001, pp. 13–14)	<ol style="list-style-type: none"> 1. The risk for coronary heart disease among women is substantially reduced within 1 or 2 years of smoking cessation. This immediate benefit is followed by a continuing but more gradual reduction in risk to that among nonsmokers by 10 to 15 or more years after cessation. 2. In most studies that include women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5 to 15 years of abstinence, the risk approaches that of women who have never smoked. 3. Smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women. Smoking cessation appears to slow the rate of progression of carotid atherosclerosis. 4. Women who are current smokers have an increased risk for peripheral vascular atherosclerosis. Smoking cessation is associated with improvements in symptoms, prognosis, and survival.
USDHHS (2004, p. 25)	<ol style="list-style-type: none"> 1. Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general.
USDHHS (2010, p. 11)	<ol style="list-style-type: none"> 1. Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without coronary heart disease. 2. The use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease produces far less risk than the risk of continued smoking.

Notes: **CHD** = coronary heart disease.

Atherosclerosis is the key underlying pathophysiologic process leading to most clinical manifestations of CVD, including CHD, cerebrovascular disease, and PAD. Atherosclerosis involves the hardening and narrowing of arteries because of deposition of lipids in the inner layers of arteries, fibrosis, and thickening of the arterial wall. This complex process involves the deposition of lipids, inflammatory and immune responses to oxidized lipids, and endothelial dysfunction. When the processes involved in atherosclerosis culminate in thrombosis, this can lead to myocardial infarction (MI) or ischemic stroke (Nagareddy and Smyth 2013).

Key mechanisms through which smoking and smoking cessation affect atherogenesis and thrombosis include endothelial function and injury, oxidative stress, hemostatic factors (platelet function, fibrinogen,

and d-dimer), fibrinolysis, inflammation, lipid modification, and vasomotor function (IARC 2007). Smoking and smoking cessation may also influence CVD risk through the effect of oxygen demand and supply on cardiovascular function (USDHHS 2004) and through effects on occurrence of arrhythmias and coronary artery spasm (USDHHS 1990).

The 1990 Surgeon General's report focused primarily on how smoking affects or may affect mechanisms leading to CVD and described mechanisms that could come into play when smokers quit (USDHHS 1990). The report concluded that some CVD effects of smoking appeared to be reversed within days or weeks of quitting (e.g., increased platelet activation, changes in clotting factors, level of carboxyhemoglobin, occurrence of coronary artery spasm and ventricular arrhythmias), but that other effects (e.g., advance of atherosclerosis, proliferation of smooth

muscle cells, lipid deposition) may be irreversible or only slowly reversible.

The 2004 Surgeon General's report provided a detailed overview of mechanisms linking smoking with CVD development. That report concluded that smoking (1) promotes endothelial injury and cell dysfunction; (2) produces a substantial shift in hemostatic balance at the endothelium, leading to atherosclerosis and thrombotic complications; (3) diminishes the ability of the blood to carry oxygen; and (4) increases physiologic demands of the myocardium (USDHHS 2004). Through these mechanisms, smoking results in substantial adverse alterations in the cardiovascular system's hemostatic balance, explaining the relationship between smoking and the subclinical and clinical manifestations of atherosclerosis. The 2010 Surgeon General's report reviewed in detail the mechanisms through which cigarette smoking causes CHD (USDHHS 2010), concluding that smoking produces insulin resistance that could, in tandem with chronic inflammation, accelerate the development of macrovascular and microvascular complications, such as nephropathy.

The 2014 Surgeon General's report expanded on the research related to the mechanisms through which cigarette smoking affects cardiovascular function, focusing on how smoking affects atherogenesis, endothelial function, thrombosis, and inflammation (USDHHS 2014). The year before, Csordas and Bernard (2013) reviewed the biology of the atherothrombotic effects of smoking. Elsewhere, Messner and Bernhard (2014) reviewed how smoking causes endothelial dysfunction and initiates atherogenesis. The next sections highlight some of the findings related to mechanisms through which smoking cessation could alter the development and progression of CVD.

Mechanisms Through Which Smoking Cessation Could Affect Cardiovascular Disease

As described in the 2010 Surgeon General's report, there are multiple mechanisms by which cigarette smoking contributes to acute cardiovascular events and increases the risk for developing CVDs over the long term (USDHHS 2010). Smoking cessation terminates exposure to the constituents and metabolites in tobacco smoke that drive some of these mechanisms, leading to both rapid and more delayed reduction of risk.

Carbon Monoxide and Nicotine

Several specific components of cigarette smoke are directly relevant to the benefits of smoking cessation: carbon monoxide (CO), nicotine, and oxidant gases, which contribute to inflammation. Tobacco smoke contains high concentrations of CO, which is a gas (USDHHS 2010). The mechanisms by which CO may contribute to acute

cardiovascular events are well characterized. CO binds to hemoglobin, reducing oxygen-carrying capacity, and also shifts the oxyhemoglobin desaturation curve so that less oxygen is released to tissues from hemoglobin. The half-life of CO is brief: smoking-related CO in the body is cleared within several days of cessation (USDHHS 2010).

Nicotine is pharmacologically active and sympathomimetic in its action, causing release of catecholamines from the neurons and from the adrenal gland. This release of catecholamines transiently increases heart rate and blood pressure and results in vasoconstriction, which can contribute to myocardial hypoxia and, hence, increase risk for acute cardiovascular events. Successful smoking cessation ends exposure to nicotine and provides an immediate benefit in terms of reducing risk for acute cardiac events.

Hemodynamic Effects

Smoking impairs vascular endothelial function and activates the sympathetic nervous system. In combination with underlying atherosclerosis, these hemodynamic consequences of smoking increase the risk for CVD events. Alterations in vasomotor function because of smoking appear to be substantially reversible, suggesting the important role that smoking cessation and smokefree environments can play in reducing the burden of CVDs (USDHHS 2010).

Endothelial Effects

The endothelium plays a role in vascular tone, growth, thrombogenicity, and inflammation (Lerman and Zeiher 2005). Dysfunction and injury of the endothelium affects atherogenesis initiation and the development of acute CVD events, and endothelial dysfunction is an independent risk factor for CVD morbidity and mortality (USDHHS 2010). Smoking may impair regeneration of the endothelium; however, 2–4 weeks of cessation has been associated with increases in the number of progenitor cells, which is indicative of repair of the endothelium (Kondo et al. 2004).

Both active smoking and exposure to secondhand smoke can alter coronary and peripheral arterial vasomotion among persons with or without CHD (Czernin and Waldherr 2003). Correspondingly, evidence suggests that smoking cessation can improve endothelial functioning. Smoking cessation leads to improved endothelial-dependent vasodilation in veins in the human hand within 24 hours of cessation (Moreno Jr et al. 1998). Reduced altered brachial artery flow-mediated dilation (FMD) is an early marker for endothelial dysfunction and a risk factor for CVD. Smoking is associated with reduced FMD. This relationship is dose related and may be reversible, as a weaker association has been observed in former smokers

(Celermajer et al. 1993; Raitakari et al. 1999). Johnson and colleagues (2010) reported on a clinical trial that assessed smoking cessation pharmacotherapies in 1,504 smokers; among the 36% of participants who quit smoking, FMD increased by 1% (from 6.2% +/- 4.4% to 7.2% +/- 4.2%) after 1 year—a relative gain of approximately 15%. In contrast, FMD did not change among those who continued to smoke. Results were similar after adjusting for artery diameter, reactive hyperemia, low-density lipoprotein cholesterol, and the presence of a smokefree rule in the home.

In another study, smoking “light” cigarettes (a type of cigarette that was claimed by manufacturers to produce less tobacco tar than a regular cigarette when smoked) was not associated with improved FMD relative to smoking regular cigarettes, providing evidence that “light” cigarettes are not a less harmful alternative to higher yield cigarettes for reducing CVD risk (Amato et al. 2013). In cross-sectional adjusted analyses of data from the Bogalusa Heart Study, former cigarette smokers, compared with current smokers, had higher small-artery compliance, as estimated by radial artery pressure pulse contour analysis, and decreased systemic vascular resistance, with a trend of improvement with increased time since cessation (Li et al. 2006). In the U.S.-based Multi-Ethnic Study of Atherosclerosis (MESA), McEvoy and colleagues (2015b) did not find consistent associations between smoking status (current, former, or never) and measures of vascular dynamics and function (carotid distensibility, aortic distensibility, or FMD). In addition, time since cessation was not associated with these outcomes, possibly because of the older ages of the participants.

Studies have also found that smoking cessation is associated with changes in biomarkers of endothelial function, dysfunction, or activation. In an intervention study focused on lifestyle changes in young adults with family histories of premature CHD, those who quit smoking had significantly lower concentrations of intercellular adhesion molecule-1 (ICAM-1), a biomarker of endothelial activation, compared with those continuing to smoke (Tonstad et al. 2005). Elsewhere, in a small study of a smoking cessation intervention among persons at high risk of CVD, ICAM-1 decreased among quitters after 1 year of cessation but increased among persons who continued to smoke (Halvorsen et al. 2007). Other markers related to endothelial function, thrombotic state, or inflammation (E-selectin, interleukin 6, sCD40 ligand, tumor necrosis factor α , von Willebrand factor, and C-reactive protein [CRP]) did not change during the study period. In a small study of young, healthy smokers, coronary vasomotor abnormality appeared to improve after 1 month of smoking cessation (Morita et al. 2006). Later, Huang and colleagues (2016) examined two Swedish cohorts to assess the relationships of smoking with 80 protein markers

known to be related to CVD risk. In replication analyses, current cigarette smoking was associated with 10 proteins representing endothelial dysfunction, inflammation, neointimal formation, foam cell formation, and plaque instability (Huang et al. 2016). Among former smokers, no consistent associations were observed.

A systematic review of the literature concluded that the evidence was uncertain as to whether smoking cessation leads to a reversal in arterial stiffness (Doonan et al. 2010). In the Atherosclerosis Risk in Communities (ARIC) study of older adults, among women, femoral-ankle pulse wave velocity, a measure of arterial stiffness, was lower in current smokers and former smokers than in never smokers, and lower in former smokers than in current smokers (Camplain et al. 2016). Among women, both smoking status and cumulative smoking exposure were associated with lower peripheral arterial stiffness. Among men, this study did not find a relationship between smoking cessation and a reversal in arterial stiffness, and it did not reveal an association with time since smoking cessation or with carotid-femoral pulse wave velocity.

Thrombogenic Effects

The 2010 Surgeon General’s report noted that smoking-mediated thrombosis appears to be a major factor in the pathogenesis of acute cardiovascular events and described how smoking leads to alterations in the blood and in the blood vessels that promote thrombosis, a pathologic reaction that can result in smoking-related MI or stroke (USDHHS 2010). The report summarized how the hypercoagulable state associated with both active smoking and exposure to secondhand smoke is evident in the epidemiology of related cardiovascular events and in the rapid decline in risk of such events after smoking cessation (USDHHS 2010).

In cross-sectional analyses of 19,600 participants from the Third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994), cigarette smoking was strongly and positively associated with elevated levels of fibrinogen and homocysteine, which are markers of a hypercoagulable state (fibrinogen is also a marker of inflammation) (Bazzano et al. 2003). In addition, there was a dose-response relationship with these markers. Compared with never smokers, former smokers (median of 10 years since cessation) had higher odds of elevated fibrinogen but not of elevated homocysteine. Additionally, current smokers had higher odds of elevated fibrinogen compared with former smokers. Further analyses of data from the NHANES III showed a trend of lower levels of fibrinogen with increasing time since smoking cessation: After approximately 5 years of cessation, levels were similar to those of never smokers (Bakhru and Erlinger 2005).

Among 174 smokers who underwent an intensive 12-month smoking cessation program, levels of von Willebrand factor (a marker of circulating endothelial-coagulative activation) decreased significantly 2, 6, and 12 months after smoking cessation compared with baseline among those who maintained cessation at each follow-up (Caponnetto et al. 2011). In those who quit smoking, concentrations of d-dimer, prothrombin fragment 1 + 2, platelet factor-4, and β -thromboglobulin (all markers of circulating endothelial-coagulative activation) were significantly lower 6 and 12 months after cessation compared with baseline. In a nicotine replacement therapy trial among 197 men, those who quit smoking had improved plasma fibrinogen, reactive capillary flow, and transcutaneous partial oxygen tension (three parameters of blood flow) after 6 months of cessation compared with levels measured at baseline (Haustein et al. 2002). Hematocrit levels and white blood cell counts were lower in quitters compared with those who relapsed; this suggests decreased inflammation in these individuals, as white blood cells play an important role in the inflammatory process. Changes in plasma viscosity and erythrocyte deformability were inconclusive.

Other studies have also found that circulating levels of fibrinogen are higher in smokers and decrease with cessation, with one study finding a decreased rate of fibrinogen synthesis and lower plasma fibrinogen concentrations just 2 weeks after cessation (Hunter et al. 2001). Blann and colleagues (1997) found decreases in many hematologic and coagulation indices in former smokers who used nicotine gum or patches to quit smoking; there were few additional changes after the participants no longer used any nicotine replacement products. Lúdvíksdóttir and colleagues (1999) observed similar results for atherogenic and thrombogenic factors in a smoking cessation trial involving a nicotine nasal spray versus placebo.

Inflammation

Research suggests that smoking leads to a chronic inflammatory state, activates monocytes, and enhances the recruitment and adhesion of leukocytes to blood vessel walls, an important step in vascular inflammation (USDHHS 2010). Evidence indicates that vascular inflammation, in turn, appears to play a role in atherogenesis; and markers of inflammation, such as CRP, predict the risk of future CVD events (Libby et al. 2002).

Several studies have explored the relationships between smoking and markers of inflammation, such as CRP (Bermudez et al. 2002; Bazzano et al. 2003; Bakhru and Erlinger 2005; Helmersson et al. 2005; Ohsawa et al. 2005; Madsen et al. 2007; Hastie et al. 2008; Levitzky et al. 2008; Lao et al. 2009; Reichert et al. 2009; Asthana et al. 2010; Zatu et al. 2011; Golzarand et al. 2012; Marano et al.

2015; McEvoy et al. 2015b; Kianoush et al. 2017; King et al. 2017). In most of these studies, current and former smokers had higher levels of inflammatory markers than nonsmokers (Bermudez et al. 2002; Bazzano et al. 2003; Helmersson et al. 2005; Madsen et al. 2007; Hastie et al. 2008; Levitzky et al. 2008; Lao et al. 2009; Golzarand et al. 2012; Marano et al. 2015; McEvoy et al. 2015b; Kianoush et al. 2017), and in five of the studies inflammatory levels decreased in former smokers with increasing time since smoking cessation (Bakhru and Erlinger 2005; Ohsawa et al. 2005; Reichert et al. 2009; McEvoy et al. 2015b; Kianoush et al. 2017).

In the cross-sectional analyses of data from NHANES III (described previously), cigarette smoking was independently and positively associated with elevated levels of CRP, and there was a dose-response relationship (Bazzano et al. 2003). In analyses of the odds of having either a detectable CRP or a clinically elevated CRP level, former smokers had higher odds compared with never smokers but lower odds compared with current smokers. Additional analyses showed a trend of decreasing white blood cell counts and clinically detectable CRP with increased time since smoking cessation: Approximately 5 years after cessation, white blood cell counts and the odds of detectable CRP did not differ significantly from those of never smokers (Bakhru and Erlinger 2005).

In the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), among 4,121 former smokers, time since cessation was inversely related to levels of high-sensitivity CRP (Kianoush et al. 2017). Similarly, in the U.S.-based MESA cohort, levels of high-sensitivity CRP were higher in current smokers than in former smokers, and levels of high-sensitivity CRP decreased with increased time since cessation (McEvoy et al. 2015b). Notably, this study used cotinine to classify smoking status. In a cross-sectional study by Hastie and colleagues (2008), levels of CRP were similar in never and former smokers approximately 5 years after cessation. In that study, extent of lifetime smoking (assessed by number of pack-years) was a predictor of levels of CRP after smoking cessation, independent of time since cessation, suggesting that levels of CRP may be higher in smokers because of a secondary effect, such as tissue damage caused by inflammation.

In observational analyses of 1,504 smokers enrolled in a smoking cessation trial in which 36% of participants had abstained for 1 year, smoking cessation was not associated with level of CRP (Asthana et al. 2010). There was also no relationship of smoking intensity to CRP, although smoking intensity was associated with increased white blood cell counts. The authors suggested that the effects of adiposity on levels of CRP may have masked the relationship between smoking and CRP. A study by King and colleagues (2017) of 1,652 smokers attempting to quit

examined six inflammatory markers of CVD risk: CRP, D-dimer, fibrinogen, urinary F2 isoprostane:creatinine (F2:Cr) ratio, white blood cell count, and myeloperoxidase. After 1 year, 21% of participants had successfully quit. Cessation was associated with an improved F2:Cr ratio and decreased white blood cell counts independent of weight change but not with other inflammatory markers. Smoking intensity was associated with the F2:Cr ratio, myeloperoxidase, and white blood cell counts. The authors concluded that smoking cessation may have led to reduced inflammation by lowering oxidative stress.

Lipid Abnormalities

Cigarette smoking is associated with lipid profiles that are likely to contribute to the development of atherosclerosis and CVD risk, a topic reviewed in depth in the 2010 Surgeon General's report (USDHHS 2010). Much evidence supports the conclusion that smoking is associated with higher levels of triglycerides (which in turn are associated with levels of very-low-density lipoproteins, total triglycerides, and apolipoprotein B [APO B]), with modestly higher levels of low-density lipoproteins cholesterol (LDL-C), and with lower levels of plasma high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (APO A-I) (USDHHS 2010). The 2010 Surgeon General's report also found that plasma lipid and lipoprotein levels among former cigarette smokers were typically similar to those of nonsmokers.

In a meta-analysis of articles published from 1966 to 2000, Maeda and colleagues (2003) concluded that, based on analyses from 27 prospective studies, smoking cessation is associated with beneficial increases in HDL-C. In this analysis, changes in the levels of total cholesterol, LDL-C, and triglycerides were not significant. Later, Forey and colleagues (2013), in a meta-analysis of 45 studies, found that levels of HDL-C increased rapidly (within weeks) after cessation, but there was no clear pattern after that time.

In a study conducted by Gepner and colleagues (2011), a clinical trial of cessation pharmacotherapies in 1,504 smokers that was included in the meta-analysis by Forey and colleagues (2013), those who successfully quit (36% of participants) had, at 1-year follow-up, higher levels of HDL-C, total HDL, and large HDL particles compared with baseline. Smoking cessation was not, however, associated with changes in LDL-C or LDL size. These results were similar to those reported in the meta-analysis by Maeda and colleagues (2003). Importantly, smokers in the study by Gepner and colleagues (2011) generally had a higher body mass index (BMI) than those in previous studies and thus were more representative of the contemporary U.S. population. Elsewhere, in two reports based on a study in which participants were on the nicotine patch for 32 days and then taken off it for 45 days,

HDL-C levels did not increase significantly among former smokers on the patch, but those levels increased quickly after they stopped using the patch (Moffatt et al. 2000; Chelland Campbell et al. 2008). Of note, nicotine products were used in some arms of the trial by Gepner and colleagues (2011), but that trial did observe higher levels of total HDL at 1-year follow-up.

Summary of the Evidence

Substantial evidence shows that smoking cessation is associated with an improvement in many pathogenetic factors involved in processes through which cigarette smoking causes CVD. Some effects appear to be rapidly reversible with smoking cessation, but other effects may reverse much more slowly or not at all. Evidence indicates that smoking cessation (1) leads to a reduction in markers of inflammation and hypercoagulability and to rapid changes in levels of HDL-C in a favorable direction and (2) may lead to improved endothelial function.

Smoking Cessation and Subclinical Atherosclerosis

According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis (USDHHS 2004). That report addressed the implications of this conclusion, finding that cigarette smoking has a causal relationship with the full natural history of atherosclerosis—from the early stages that are detected by subclinical markers to the late, often fatal, stages. Findings presented at that time indicated the potential for smoking cessation (including quitting and then maintaining cessation) to prevent more advanced, clinically symptomatic disease.

The 2001 Surgeon General's report concluded that smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women and that smoking cessation appears to slow the rate at which carotid atherosclerosis progresses (USDHHS 2001). Since this report appeared, additional approaches have been developed to measure subclinical atherosclerosis, and more evidence has been published indicating that smoking cessation can slow the progression of atherosclerosis.

As described in the 2004 Surgeon General's report, examining measures of subclinical atherosclerosis facilitates assessment of the relationship between smoking and the earlier, preclinical stages of the atherosclerotic disease process. In studies of subclinical measures among healthy persons, findings may be less susceptible to reverse causation, as there is no onset of symptoms that could lead to cessation and distort the temporal relationship between

smoking and CVD. The possibility of reverse causation (for clinical and subclinical outcomes) is of particular concern for cross-sectional analyses in which it may not be possible to ascertain temporality.

Table 4.11 describes findings from 12 studies that have assessed the relationships between smoking cessation and subclinical atherosclerosis (Kiechl et al. 2002; Baldassarre et al. 2009; Jöckel et al. 2009; Liang et al. 2009; Jiang et al. 2010; Kweon et al. 2012; Lehmann et al. 2014; McEvoy et al. 2015b; Yang et al. 2015b; Hansen et al. 2016; Hisamatsu et al. 2016; Kianoush et al. 2017). Studies in many different populations have found, generally, that smoking is positively associated with the presence, extent, and progression of atherosclerosis measured in different vascular beds. Compared with never cigarette smokers, both current and former smokers tend to have more extensive atherosclerosis, although former smokers generally have less extensive atherosclerosis than current smokers. Studies in other populations and studies of other markers for atherosclerosis have reported similar findings (Fowkes et al. 2013; Yi et al. 2015; Pacheco et al. 2016). Time since smoking cessation is also related to the extent of atherosclerosis, with less atherosclerotic burden as time since cessation increases (Jiang et al. 2010; Kweon et al. 2012; McEvoy et al. 2015b; Hansen et al. 2016; Hisamatsu et al. 2016; Kianoush et al. 2017).

Hansen and colleagues (2016) conducted one of several studies assessing the relationship between smoking cessation and the progression of atherosclerosis. This study examined a subcohort of the prospective Malmö Diet and Cancer study in Sweden and found that, compared with never smokers, former smokers had an adjusted difference in the yearly progression rate of 0.0074 millimeters (mm) per year (95% confidence interval [CI], 0.0018–0.0129) in maximal intimal-media thickness (IMT) in the carotid bifurcation (Table 4.11). But compared with never smokers, moderate smokers had an adjusted difference of 0.0106 mm (95% CI, 0.0038–0.0175) and heavy smokers had an adjusted difference of 0.0146 mm (95% CI, 0.0016–0.0230). Among former smokers, as time since smoking cessation increased, there was a reduction in yearly progression of IMT in the carotid bifurcation and in the rate of lumen reduction, with a distinct lowering in progression rates more than 5 years after cessation. In a study of 127 smokers in the Netherlands, successful smoking cessation for 2 years did not result in slowing of the increase in carotid IMT or a reduction in the thickening of the carotid artery, a finding potentially attributable to the study's small size and relatively short follow-up (data not shown in table) (van den Bergmortel et al. 2004). Carotid IMT is a predictor of future CVD events (Lorenz et al. 2007), although its measurement may have no added value for predicting cardiovascular risk (Den Ruijter et al. 2012).

Results from cross-sectional analyses in 2000–2003 of the Heinz Nixdorf Recall Study in Germany were used to estimate the slowing by cessation of coronary artery calcification (CAC), compared with continued smoking (Table 4.11). Compared with continued smoking, smoking cessation at 45, 55, and 65 years of age was estimated to slow CAC progression at 75 years of age by 9, 6, and 3 years, respectively (Jöckel et al. 2009). CAC is a predictor of future CVD events (Pletcher et al. 2004; Chaikriangkrai et al. 2017). Although the findings from Jöckel and colleagues (2009) were based on modeling assumptions and cross-sectional data, their results suggest that smoking cessation may reduce the progression of atherosclerosis, which could potentially reduce the risk of future clinical CVD.

Several studies (Table 4.11) have assessed associations between smoking and the ankle-brachial index (ABI), which is also known as the ankle-arm index (McEvoy et al. 2015b; Hisamatsu et al. 2016; Kianoush et al. 2017). The ABI is the ratio of blood pressure in the lower leg to that in the upper arm. A low ABI is associated with an increased risk of CHD and of CVD (Lin et al. 2013). The ABI has been used as a way to assess the presence of PAD, but it does not assess which blood vessels are narrow or blocked. In two studies (Table 4.11), former smoking was associated with higher odds of a low ABI compared with never smoking (McEvoy et al. 2015b; Kianoush et al. 2017), and in three studies, increased time since quitting was associated with lower odds of having a low ABI (McEvoy et al. 2015b; Hisamatsu et al. 2016; Kianoush et al. 2017). For example, in the MESA cohort, the odds ratio (OR) for an ABI <1.0 was 0.91 (95% CI, 0.86–0.96) for every 5-year increment since smoking cessation (McEvoy et al. 2015b). The relationship between smoking cessation and clinical manifestations of PAD is discussed in more detail in a later section.

Summary of the Evidence

Evidence indicates that smoking cessation reduces the development and progression of markers of subclinical atherosclerosis, with the degree of reduction increasing as time since cessation increases. This pattern of change in markers provides mechanistic background on the evidence of how smoking cessation reduces risk of CVD.

Smoking Cessation and Cardiovascular Disease

The 2010 Surgeon General's report concluded that smoking cessation reduces the risk of cardiovascular morbidity and mortality for cigarette smokers with or without CHD (USDHHS 2010). This report also found that there

Table 4.11 Studies on the association between smoking cessation and subclinical atherosclerosis

Study	Design/population	Main results	Comments
Kiechl et al. (2002)	<ul style="list-style-type: none"> • Prospective cohort (Bruneck Study) • 826 healthy or sick participants, 40–79 years of age, 50% men, 26% former smokers • 1990–1995 • Italy • Follow-up: 5 years • Outcome: carotid IMT, early atherogenesis (nonstenotic plaques), advanced atherogenesis (stenosis >40%) 	<ul style="list-style-type: none"> • Current and former smokers had increased risk of early atherogenesis only if they had chronic infections; risks were similar in never, former, and current smokers without chronic infection • Advanced atherogenesis developed independently of chronic infection; risk returned to normal soon after cessation 	Impact of smoking on atherosclerosis appears to be partially mediated by chronic infections
Baldassarre et al. (2009)	<ul style="list-style-type: none"> • Cross-sectional study • 1,804 consecutive patients' first visit to lipid clinic, 21–85 years of age, 48% men, 21% former smokers • 2000–2003 • Italy • Outcome: carotid IMT (mean, total, and maximum) 	<ul style="list-style-type: none"> • Carotid IMT was highest in current smokers, then former smokers, then never smokers • Only after adjusting for risk factors was carotid IMT significantly higher among current smokers than former smokers • Carotid IMT was positively associated with pack-years of smoking among both former and current smokers 	Results may not be generalizable to populations without dyslipidemia
Liang et al. (2009)	<ul style="list-style-type: none"> • Cross-sectional and prospective analyses (Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology) • 1,132 participants, 35–64 years of age; 34% men; 3% former smokers at baseline; free of myocardial infarction, stroke, and diabetes • Scanned in 1993–1994 and 2002 • China • Exposure: smoking status at baseline and consistency during follow-up • Outcome: mean common carotid IMT 	<ul style="list-style-type: none"> • Mean adjusted IMT was 0.72 mm for consistent current smokers, 0.71 mm for former and inconsistent smokers, and 0.70 mm for consistent never smokers (p for trend <0.01) • Compared with consistent never smokers, consistent current smokers had higher adjusted odds of carotid plaques; a similar pattern was observed among former smokers and former/inconsistent smokers, but the results were not significant 	—
Jöckel et al. (2009)	<ul style="list-style-type: none"> • Cross-sectional study (Heinz Nixdorf Recall Study) • 4,078 participants, 45–75 years of age, 50% men, without manifest CHD (myocardial infarction or coronary revascularization) or stroke • Scanned in 2000–2003 • Germany • Outcome: CAC 	<ul style="list-style-type: none"> • Smoking cessation at 45, 55, or 65 years of age was associated with CAC at the age of 75 years that would have been reached 9, 6, or 3 years earlier, respectively, had smoking continued • CAC accumulation slowed after cessation, but advanced CAC persisted for a long time 	Results are based on predictions from regression models run separately by smoking status; models were not run separately for men and women

Table 4.11 Continued

Study	Design/population	Main results	Comments
Jiang et al. (2010)	<ul style="list-style-type: none"> • Cross-sectional study • 959 men, 50–85 years of age, 26% former smokers • Scanned in 2006–2007 • China • Outcome: mean common carotid IMT, presence of CCA plaques; CCA atherosclerosis defined as CCA-IMT ≥ 1.0 mm or with a stenosis diameter $\geq 20\%$ 	<ul style="list-style-type: none"> • IMT and number of plaques increased from never, to former, to current smokers • Longer duration since cessation was associated with decreased odds of the presence and severity of atherosclerosis in CCA (explored in categories of 1–9, 10–19, ≥ 20 years since cessation; observed benefit compared with current smokers for ≥ 10 years since quitting) 	—
Kweon et al. (2012)	<ul style="list-style-type: none"> • Cross-sectional study (Dong-gu Study) • 2,503 men, ≥ 50 years of age, 51% former smokers • Scanned in 2007–2009 • Korea • Outcome: CCA-IMT, carotid plaque, CCA diameter 	<ul style="list-style-type: none"> • Compared with never smokers, current smokers had greater CCA IMT, CCA diameter, and odds of carotid plaque • Among former smokers, CCA IMT and CCA diameter decreased with years since cessation; not observed for carotid plaque • For current smokers, but not for former smokers, a dose-response relationship was observed between pack-years of smoking and CCA IMT 	Only men were included in analysis because of a very low prevalence of smoking among women
Lehmann et al. (2014)	<ul style="list-style-type: none"> • Prospective study (Heinz Nixdorf Recall Study) • 1,261 participants, 45–75 years of age, 27% men, no detectable CAC at first scan, no history of CHD or stroke • Scanned in 2000–2003, rescanned 5 years later • Germany • Outcome: onset of detectable CAC 	<ul style="list-style-type: none"> • Compared with never smokers, onset of detectable CAC occurred approximately 10 years earlier among current smokers and 5 years earlier among former smokers • Among women, in adjusted analyses, current smokers had higher odds of progression to detectable CAC than never smokers; no association for former smokers • Among men, smoking was not related to CAC onset 	Unclear whether there was adjustment for other factors in the analysis of time to detectable CAC

Table 4.11 Continued

Study	Design/population	Main results	Comments
McEvoy et al. (2015b)	<ul style="list-style-type: none"> • Cross-sectional study (Multi-Ethnic Study of Atherosclerosis) • 6,796 multiethnic participants, 45–84 years of age, 47% men, 38% former smokers, free of CVD • 2000–2002 • United States (six centers) • Outcomes: mean internal carotid IMT, CAC, and ABI 	<ul style="list-style-type: none"> • Difference in log(IMT)_a (95% CI): <ul style="list-style-type: none"> – Never smoker: 0.00 (referent) – Former smoker: 0.05 (0.03–0.07) – Current smoker: 0.09 (0.06–0.12) • Odds ratio of CAC >0 (95% CI): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.28 (1.21–1.57) – Current smoker: 1.79 (1.49–2.14) • Odds ratio of CAC >75th percentile (95% CI): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.18 (0.99–1.41) – Current smoker: 1.38 (1.08–1.77) • Odds ratio of ABI <1 (95% CI): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.24 (1.02–1.50) – Current smoker: 2.22 (1.74–2.83) • Time since quitting was independently associated with atherosclerosis; for example, OR of CAC >0 was 0.94 (95% CI, 0.90–0.97) for each 5 years since quitting 	—
Yang et al. (2015b)	<ul style="list-style-type: none"> • Cross-sectional study (Northern Manhattan Study) • 1,743 multiethnic participants, ≥39 years of age, 40% men, 38% former smokers, free of stroke • Years of data collection: not provided • New York, New York (northern Manhattan) • Outcome: carotid plaque echodensity divided into quintiles 	<ul style="list-style-type: none"> • Compared with never smokers, current smokers were more likely to have soft or calcified plaques • Compared with never smokers, former smokers were more likely to have echodense plaques 	More research is needed to understand whether plaque morphology mediates the relationship between smoking and clinical CVD

Table 4.11 Continued

Study	Design/population	Main results	Comments
Hansen et al. (2016)	<ul style="list-style-type: none"> • Prospective cohort (Malmö Diet and Cancer cardiovascular cohort) • 2,992 middle-aged participants, 41% men, 35% former smokers, free of CVD • 1991–1994 baseline and 2007–2012 visit (subcohort of those born 1926–1945) • Sweden • Outcomes: mean common carotid IMT and maximum carotid bifurcation, degree of lumen diameter reduction 	<ul style="list-style-type: none"> • Difference in IMT progression (mm/year) (95% CI): <ul style="list-style-type: none"> – CCA: <ul style="list-style-type: none"> ○ Never smoker, unexposed to secondhand smoke: 1.00 (referent) ○ Former smoker: 0.0014 (0.0001–0.0028) ○ Moderate smoker (1–15 cigarettes smoked per day): 0.0027 (0.0010–0.0044) ○ Heavy smoker (>15 cigarettes smoked per day): 0.0041 (0.0020–0.0062) – Carotid bifurcation: <ul style="list-style-type: none"> ○ Never smoker, unexposed to secondhand smoke: 1.00 (referent) ○ Former smoker: 0.0074 (0.0018–0.0129) ○ Moderate smoker: 0.0106 (0.0038–0.0175) ○ Heavy smoker: 0.0146 (0.0061–0.0230) • Differences in rate of diameter reduction (%/year) (95% CI): <ul style="list-style-type: none"> – Never smoker, unexposed to secondhand smoke: 1.00 (referent) – Former smoker: 0.25 (0.001–0.36) – Moderate smoker: 0.25 (0.11–0.38) – Heavy smoker: 0.43 (0.26–0.59) • Stronger associations for current smokers • With >5 years since cessation, rate of IMT bifurcation progression decreased; similar pattern for lumen reduction 	<p>Similar results when adjusted for inflammatory markers</p>

Table 4.11 Continued

Study	Design/population	Main results	Comments
Hisamatsu et al. (2016)	<ul style="list-style-type: none"> • Cross-sectional study (Shiga Epidemiological Study of Subclinical Atherosclerosis) • 1,019 Japanese men, 40–79 years of age, 50% former smokers, free of CVD • 2006–2008 • Japan • Outcomes: ABI <1.1; mean carotid IMT; AoAC and CAC 	<ul style="list-style-type: none"> • Former smoking was associated with higher carotid IMT (IMT >1.0 mm, OR = 1.94 [95% CI, 1.13–3.34]) and AoAC (AoAC >0, OR = 2.55 [95% CI, 1.45–4.49]) compared to never smokers • Current smoking was positively associated with all four outcomes: <ul style="list-style-type: none"> – CAC >0, OR = 1.79 (95% CI, 1.16–2.79) – Carotid IMT >1.0 mm, OR = 1.88 (95% CI, 1.02–3.47) – AoAC >0, OR = 4.29 (95% CI, 2.30–7.97) – ABI <1.1, OR = 1.78 (95% CI, 1.16–2.74) • For most outcomes, a dose-response relationship was observed between pack-years of smoking and daily consumption for current and former smokers. Time since cessation was linearly associated with less atherosclerotic burden for all four outcomes • p for trend <0.05 	—
Kianoush et al. (2017)	<ul style="list-style-type: none"> • Cross-sectional study (Brazilian Longitudinal Study of Adult Health) • 14,103 civil servants, 35–74 years of age; 45% men; multiethnic (52% White, 28% Brown [mixed], 16% Black, and 4% Asian or other); 30% former smokers, free of prevalent disease (including CVD) • 2008–2010 • Brazil (multicenter cohort, six cities) • Outcomes: mean carotid IMT, ABI, and CAC 	<ul style="list-style-type: none"> • Compared with never smokers, former smokers had higher IMT and odds of ABI ≤1.0 (p = <.001) • Compared with never smokers, current smokers had higher IMT, odds of ABI ≤1.0, and odds of CAC >0 (p = <.001) • Among former smokers, time since quitting was negatively associated with carotid IMT, ABI ≤1.0, and CAC >0 (p = <.001) 	—

Notes: **ABI** = ankle-brachial index; **AoAC** = aortic artery calcium; **CAC** = coronary artery calcification; **CCA** = common carotid artery; **CHD** = coronary heart disease; **CVD** = cardiovascular disease; **IMT** = intimal-media thickness; **mm** = millimeters.

^aNatural log-transformed IMT.

was not enough evidence to conclude that reducing the number of cigarettes smoked per day reduces the risk for CVD. Among current smokers, however, a dose-response relationship has been observed between the number of cigarettes smoked per day and the incidence of CVD (USDHHS 2010; Benjamin et al. 2017). The next section briefly summarizes the evidence that supports these conclusions.

Intervention Studies

Much of the evidence linking smoking cessation to reduced risk of CVD morbidity and mortality is based on observational studies, but the link has also been observed in intervention studies directed at increasing cessation. The 1990 Surgeon General's report, which summarized results from several clinical trials, found that, overall, such interventions tend to decrease risk of CHD or CVD mortality. Among these studies, some had interventions directed at only smoking cessation, and others addressed risk factors in addition to smoking (USDHHS 1990). For some of these studies, findings from long-term follow-up have been reported subsequently.

One example is the Lung Health Study, a clinical trial started in 1986 that compared a 10-week smoking cessation program with usual care among 5,887 smokers with asymptomatic airway obstruction (Anthonisen et al. 2005). The intervention involved strong messaging by a physician and a total of twelve 2-hour group sessions using behavior modification and nicotine gum. Those who quit smoking entered a maintenance program that focused on coping skills; this group was described as the special-intervention group.

Part of the intervention group received ipratropium, a treatment for chronic obstructive pulmonary disease and asthma, and the rest of that group received a placebo inhaler. A separate group (controls) received care as usual. Over 14 years of follow-up, the all-cause mortality rate was higher in the usual-care group than in the special-intervention group (hazard ratio [HR] = 1.18; 95% CI, 1.02–1.37). The benefit of cessation was most pronounced among the 21.7% of the special-intervention group who had quit smoking at 5 years (only 5.4% of usual-care participants had quit). Although there were no significant differences in rates of CHD mortality or CVD mortality, these rates were lower in the special-intervention group than in the usual-care group. Finally, in observational analyses comparing sustained quitters, intermittent quitters, and continuing smokers in this study, smoking status was significantly related to unadjusted risk of CHD and CVD, with the highest risk among those who continued to smoke.

In the Oslo cardiovascular study, which began in 1972, 1,232 men free of CVD and diabetes—with total

serum cholesterol levels of 6.9–8.9 millimoles/liter (mmol/L) (80% were smokers)—participated in a 5-year intervention study (Hjermann et al. 1981). At clinical visits every 6 months, those in the intervention group received dietary advice, and smokers in the intervention group were advised to quit. At 40-year follow-up, the intervention group had a reduced risk of death from MI versus the control group (HR = 0.71; 95% CI, 0.51–1.00). Most of the reduction in MI risk occurred during the first 15 years of follow-up; the survival curves for MI were parallel after that point (Holme et al. 2016). There was no significant difference in all-cause mortality from MI at 40 years, although there was a reduction in risk of dying among the intervention group across the first 15 years that was statistically significant at follow-up. At 5-year follow-up, the rate of CHD, MI, and SCD combined was 47% lower in the intervention group than in the control group, with an estimated 25% of the benefit attributable to smoking cessation (Hjermann et al. 1981). Follow-up at 8.5 years found a significant reduction in CHD incidence, similar to that found at 5 years, among the intervention group compared with the control group; this analysis also observed increases in the rate of smoking in the intervention group after the end of the trial (Hjermann et al. 1986).

In the Multiple Risk Factor Intervention Trial (MRFIT), which was initiated in 1973, 12,866 men at high risk of CHD were randomized to usual care or to a multifactor special intervention aimed at lowering serum cholesterol and blood pressure and promoting smoking cessation. Over follow-up averaging 7 years (during the active-intervention period), the rates of the composite outcomes of fatal or nonfatal CHD and of fatal or nonfatal CVD were significantly lower in the special-intervention group than in the usual-care group, by 14% (95% CI, 3–24%) for CHD and by 11% (95% CI, 1–21%) for CVD (Stamler et al. 2012). Rates of a priori defined endpoints (CHD death, CHD death or nonfatal MI, CVD death, and all-cause death), however, did not differ significantly between the two groups, possibly because of inadequate statistical power (Multiple Risk Factor Intervention Trial Research Group 1982; Gotto Jr 1997). Importantly, because the interventions in the MRFIT and the Oslo cardiovascular study did not focus solely on smoking cessation, the effects of the smoking cessation intervention cannot be readily separated from the effects of the other interventions.

Observational Studies

Much evidence from observational studies supports previous conclusions that smoking cessation decreases risk of CVD. Based on analyses of mortality in two historical cohorts (Cancer Prevention Study I [CPS I, 1959–1965] and II [CPS II, 1982–1988]) and five contemporary cohorts followed from 2000 to 2010, Thun and colleagues

(2013a) concluded that smoking cessation at any age reduces the risk of smoking-related death, including death from CVD; that much of the excess risk of all-cause mortality can be avoided by quitting smoking before 40 years of age, with additional benefit from quitting earlier (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013); and that quitting smoking completely is much more beneficial than reducing the number of cigarettes smoked per day. For example, an analysis of data from the National Health Interview Survey found that, on average, smokers who quit at 25–34 years of age gained 10 years of life compared with those who continued to smoke; smokers who quit at 35–44 years of age gained 9 years; and smokers who quit at 45–54 years of age gained 6 years (Jha et al. 2013). Similarly, the 50-year analysis of the British Doctors' Study showed that, among men born close to 1920, long-term cigarette smoking beginning in early adulthood tripled age-specific mortality rates, while quitting at 50 years of age halved the hazard and quitting at 30 years of age avoided most of the hazard (Doll et al. 2004).

Mons and colleagues (2015), who performed a pooled analysis of individual-level data from European and U.S. cohorts (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States [CHANCES]), assessed the relationship between smoking cessation and risk of cardiovascular mortality in women and men 60 years of age and older. Smoking was strongly related to increased cardiovascular mortality; compared with current smokers, the adjusted HR of cardiovascular mortality in former smokers was lower by 0.85 for each 10 years of smoking cessation (95% CI, 0.82–0.89), providing evidence of the benefit of smoking cessation among adults 60 years of age and older. Former smokers had a higher risk of cardiovascular mortality than never smokers (Table 4.12 and Figures 4.2a and 4.2b), but the evidence suggests a trend of decreasing excess risk as the number of years since cessation increases (Table 4.12).

Mons and colleagues (2015) also measured the relationships between smoking cessation and risk advancement periods, which are the average periods of time by which the occurrence of an outcome (such as death) attributable to a risk factor is advanced in exposed versus nonexposed persons (Brenner et al. 1993; Mons et al. 2015). In general, the risk advancement period decreased as time since smoking cessation increased. For instance, risk advancement periods ranged from 3.75 years (95% CI, 2.78–4.71) among those who had quit more than 5 years earlier to -0.79 years (95% CI, -0.12–1.69) among those who had quit 20 or more years earlier.

Many studies have assessed the relationships between time since cessation or cumulative exposure and CVD risk. For example, in the Nurses' Health Study, former cigarette smokers had an increased risk of vascular mortality

compared with never smokers (adjusted HR = 1.32; 95% CI, 1.20–1.44) (Kenfield et al. 2008), and compared with current smokers, the risk of vascular mortality trended downward with increased time since cessation (from <5 years to ≥ 20 years). In the ARIC study of Whites and African Americans, former smokers had a 17% significantly greater risk of CVD (defined as MI or stroke) compared with never smokers, with similar elevations observed by race and sex (Table 4.13) (Huxley et al. 2012). The benefit of smoking cessation increased as time since cessation increased; those who had quit 10 or more years earlier had a 33% lower risk of CVD than those who continued to smoke (Table 4.13). In the MESA cohort, former smokers (median cessation at 22 years of age [+/- 13 years]) did not have a significantly higher adjusted HR for all-cause CVD compared with never smokers (Table 4.13) (McEvoy et al. 2015a). Among current smokers in that same cohort, there was a dose-response relationship, as more pack-years were associated with a higher risk of CVD, but this trend was not observed among former smokers. Another analysis of data from the MESA cohort found that former smokers—regardless of duration, intensity, or recency of cessation—were not at increased risk of CVD compared with never smokers (Nance et al. 2017).

Similar findings have been observed in many different populations. For example, in a cohort in China, deaths attributable to tobacco-related causes trended downward with increased time since smoking cessation (He et al. 2014). A similar pattern was observed in that study for deaths attributable to vascular causes (CHD or stroke), where compared with current smokers, those who had quit for 2–7 years had 0.82 times (95% CI, 0.46–1.47) the risk and those who had quit for 8 or more years had 0.71 times (95% CI, 0.42–1.20) the risk. This pattern did not hold for all subtypes of vascular disease, but there were limited cases within these categories. In Japan, in a cohort of healthy, young, and middle-aged persons, adjusted risk of CVD events decreased as time since cessation increased, with risk being significantly lower 4 or more years after cessation (data not shown) (Kondo et al. 2011).

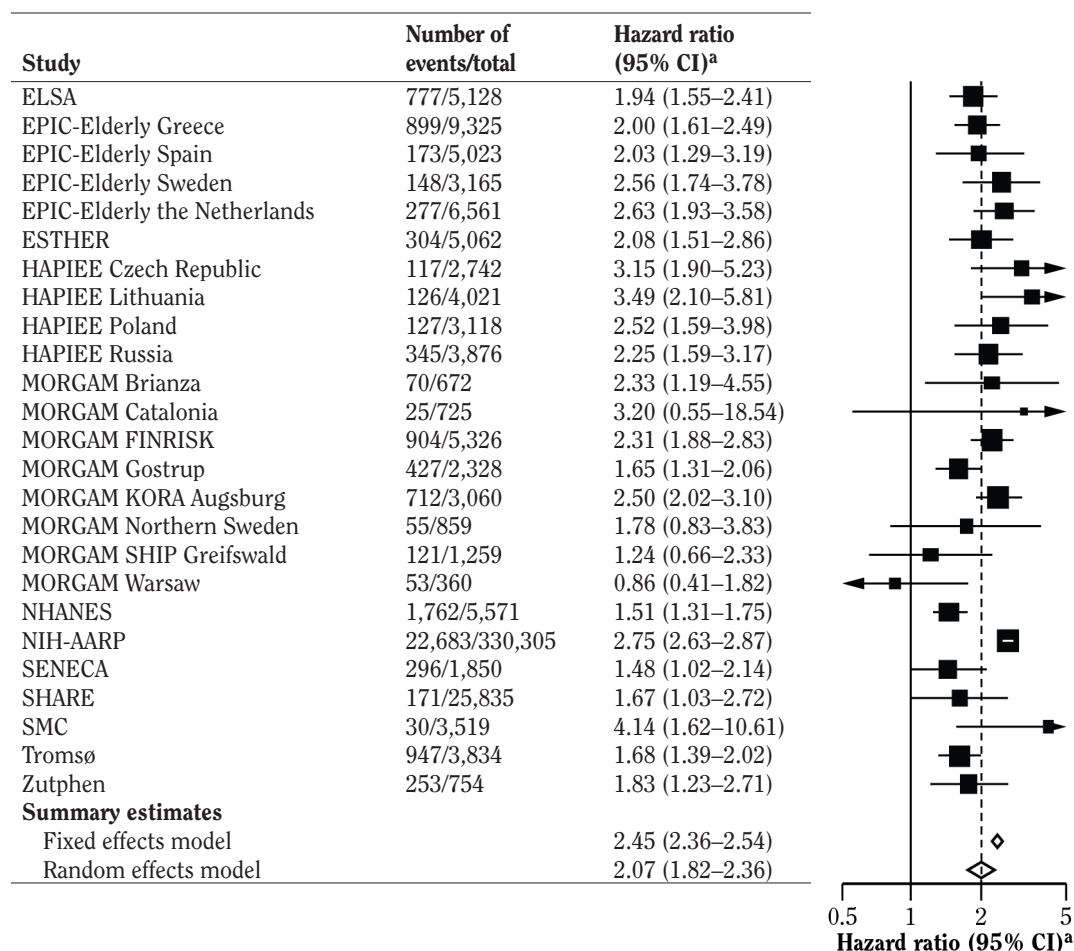
Similar results have been found among persons with diabetes. In a meta-analysis of persons with diabetes, former smokers had an increased risk of CVD, CVD mortality (Table 4.12), and total mortality compared with never smokers (Pan et al. 2015). In the Framingham Offspring Cohort (included in the meta-analysis by Pan and colleagues [2015]), among persons without diabetes, nonsmokers, those who had quit for 4 or fewer years, and those who had quit for more than 4 years, all had lower adjusted risks of CVD than current smokers (Table 4.13) (Clair et al. 2013). Similar patterns were observed among those with diabetes, but results were not statistically significant.

Table 4.12 Meta-analyses of observational studies on smoking cessation and incidence of total cardiovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015) ^a	<ul style="list-style-type: none"> Individual-level meta-analysis 434,278 men and women, ≥60 years of age, 47% former smokers 31,802 CVD deaths 25 prospective cohorts Data collected from different cohorts in various years from the 1980s to the 2010s Europe and North America Mean follow-up: 1.6–14.8 years (approximately 8–13 years for most studies) Outcome: CVD mortality 	<ul style="list-style-type: none"> Smoking status: <ul style="list-style-type: none"> Never smoker: 1.00 (referent) Former smoker: 1.37 (1.25–1.49) Current smoker: 2.07 (1.82–2.36) Years since smoking cessation (never vs. former smoker): <ul style="list-style-type: none"> Never smoker: 1.00 (referent) Former smoker: <ul style="list-style-type: none"> <5: 1.74 (1.51–2.01) 5–9: 1.60 (1.36–1.88) 10–19: 1.43 (1.24–1.64) ≥20: 1.15 (1.02–1.30) Years since smoking cessation (current vs. former smoker): <ul style="list-style-type: none"> Current smoker: 1.00 (referent) Former smoker: <ul style="list-style-type: none"> <5: 0.90 (0.81–1.00) 5–9: 0.84 (0.73–0.95) 10–19: 0.78 (0.71–0.85) ≥20: 0.61 (0.54–0.69) 	Figure 1 in Mons and colleagues (2015) provides more details on results by smoking status
Pan et al. (2015) ^a	<ul style="list-style-type: none"> Meta-analysis Men and women, >18 years of age with type 1 or type 2 diabetes mellitus Prospective cohort studies: <ul style="list-style-type: none"> CVD: 7 studies for former smokers, 16 studies for current smokers CVD mortality: 8 studies for former smokers, 13 studies for current smokers Sample: <ul style="list-style-type: none"> CVD: n = 1,028,982; cases = 94,929 CVD mortality: n = 37,550; cases = 3,163 United States, Europe, China, New Zealand, Australia, and other international collaborations Studies included in the meta-analysis were published between 1989 and 2015 Outcomes: CVD and CVD mortality 	<ul style="list-style-type: none"> CVD: <ul style="list-style-type: none"> Never smoker: 1.00 (referent) Former smoker: 1.09 (1.05–1.13) Current smoker: 1.44 (1.34–1.54) CVD mortality: <ul style="list-style-type: none"> Never smoker: 1.00 (referent) Former smoker: 1.15 (1.00–1.32) Current smoker: 1.49 (1.29–1.71) 	—

Notes: **CI** = confidence interval; **CVD** = cardiovascular disease; **RR** = risk ratio.

^aSome overlap exists between the cohorts included in these publications.

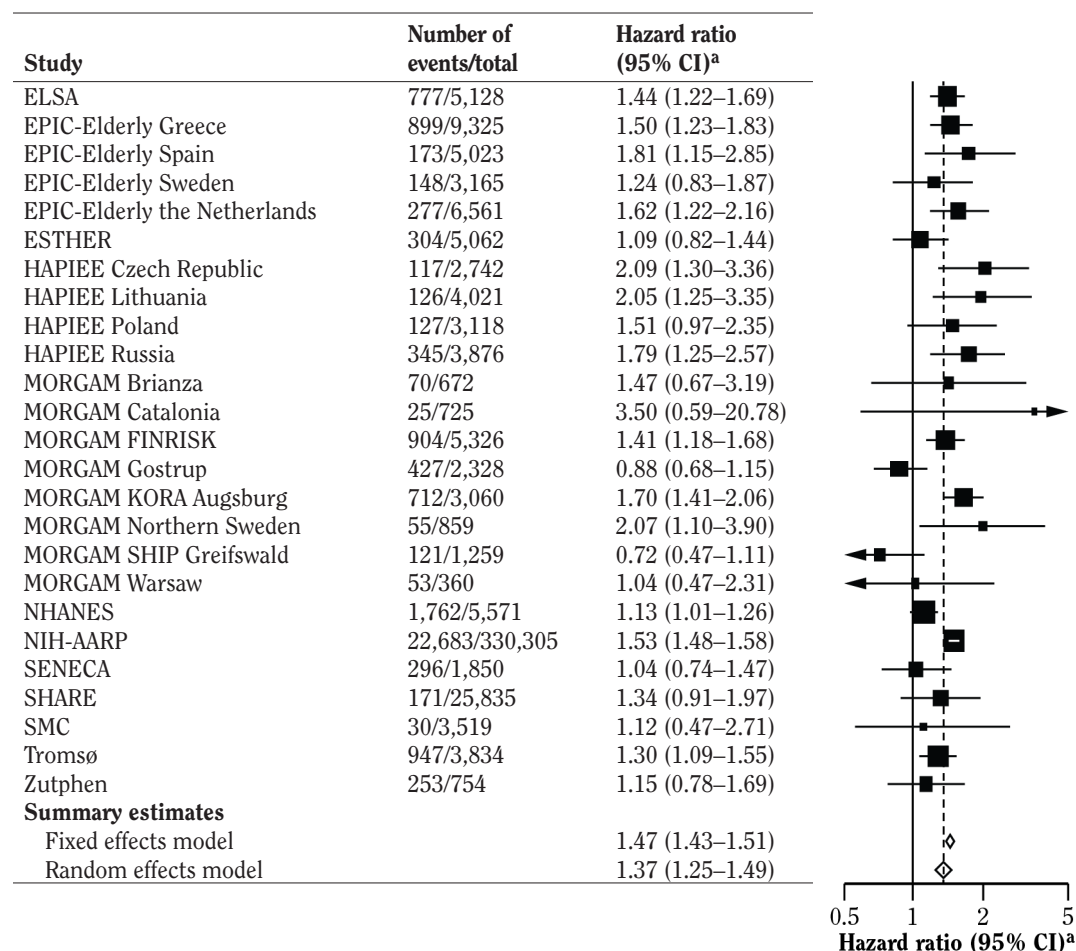
Figure 4.2a Results from the meta-analyses of the association between current and never smoking status and cardiovascular mortality

Source: Mons et al. (2015), with permission.

Note: **CI** = confidence interval; **ELSA** = English Longitudinal Study of Aging; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **ESTHER** = Epidemiological Investigations on Opportunities for Prevention, Early Detection and Optimised Treatment of Chronic Diseases in the Elderly Population; **FINRISK** = a large Finnish population survey on risk factors on chronic, noncommunicable diseases; **HAPIEE** = Health, Alcohol, and Psychosocial factors In Eastern Europe; **KORA** = Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region); **MORGAM** = Monica Risk Genetics Archiving and Monograph; **NHANES** = National Health and Nutrition Examination Survey; **NIH-AARP** = National Institutes of Health–American Association of Retired Persons; **SENECA** = Survey Europe on Nutrition in the Elderly; **SHARE** = Survey of Health, Aging, and Retirement in Europe; **SMC** = Swedish Mammography Cohort.

^aTest for heterogeneity: $\tau^2 = 0.023$, $p < 0.001$, $I^2 = 68.7\%$.

Figure 4.2b Results from the meta-analyses of the association between former and never smoking status and cardiovascular mortality



Source: Mons and colleagues (2015).

Notes: **CI** = confidence interval; **ELSA** = English Longitudinal Study of Aging; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **ESTHER** = Epidemiological Investigations on Chances of Preventing, Recognizing Early and Optimally Treating Chronic Diseases in an Elderly Population; **HAPIEE** = Health, Alcohol, and Psychosocial factors In Eastern Europe; **KORA** = Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region); **MORGAM** = Monica Risk Genetics Archiving and Monograph; **NHANES** = National Health and Nutrition Examination Survey; **NIH-AARP** = National Institutes of Health-American Association of Retired Persons; **SENECA** = Survey Europe on Nutrition in the Elderly; **SHARE** = Survey of Health, Aging, and Retirement in Europe; **SMC** = Swedish Mammography Cohort.

^aTest for heterogeneity: $\tau^2 = 0.067$, $P < 0.001$, $I^2 = 82.3\%$.

Table 4.13 Observational studies on smoking cessation and cardiovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Kondo et al. (2004)	<ul style="list-style-type: none"> • Case-control study • 29 men • Mean age: <ul style="list-style-type: none"> – Nonsmokers: 43.9 years of age – Smokers: 38.9 years of age • Nagoya, Japan (years not reported) 	<ul style="list-style-type: none"> • Smoking cessation led to rapid restoration of progenitor cells and endothelial progenitor cell levels • Circulating progenitor cells and endothelial progenitor cells increased rapidly after cessation ($p < 0.0001$) and decreased after resumption of smoking to a level similar to that before cessation ($p = 0.0031$) 	—
He et al. (2006)	<ul style="list-style-type: none"> • Cross-sectional study • 2,334 participants • 60 years of age or older • 2001–2002 • Beijing, China 	<ul style="list-style-type: none"> • Smoking cessation was associated with decreased risks of PAD. Excess risk of PAD was nearly eliminated after stopping smoking for 10 or more years: <ul style="list-style-type: none"> – Never smoker (referent) – Current smoker 1.57 (1.16–2.13), $p < 0.01$ – Former smoker: 1.42 (1.02–1.98), $p < 0.05$ 	—
Kenfield et al. (2008)	<ul style="list-style-type: none"> • Prospective cohort (Nurses' Health Study) • 104,519 women • 1980–2004 • United States 	<ul style="list-style-type: none"> • Compared with never smokers, former cigarette smokers had an increased risk of vascular mortality (adjusted HR = 1.32; 95% CI, 1.20–1.44) 	Most of the excess risk of vascular mortality due to smoking can be eliminated rapidly upon cessation and within 20 years for lung diseases
Huxley et al. (2012) ^{a,b}	<ul style="list-style-type: none"> • Prospective cohort (Atherosclerosis Risk in Communities Study) • 14,200 participants with 2,777 CVD events, 45–64 years of age, 43% men, 31% former smokers at baseline, 15% quit during follow-up, African Americans (27%) and Whites, free of CHD or stroke • 1987–2007 • United States (four communities) • Mean follow-up: 17.1 years • Outcome: CVD events (myocardial infarction, stroke) 	<ul style="list-style-type: none"> • Compared with never smokers, former smokers had a 17% higher risk of CVD • Compared with never smokers, current smokers had: <ul style="list-style-type: none"> – Men: 70% higher risk of CVD – Women: >200% higher risk of CVD • Years since smoking cessation (overall): <ul style="list-style-type: none"> – Continuous smokers: 1.00 (referent) – 1–3: 0.87 (0.67–1.14) – 4–9: 0.90 (0.69–1.16) – ≥ 10: 0.67 (0.45–1.01) – p trend: 0.061 (0.69 in African Americans, 0.044 in Whites) 	—

Table 4.13 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Clair et al. (2013) ^{a,b}	<ul style="list-style-type: none"> • Prospective cohort (Framingham Offspring) • 3,251 participants and 631 CVD events • Baseline: mean age = 47.8 years, 48% men, mostly White, 26% quit for >4 years and 9% quit for ≤4 years, free of CVD • 1984–2011 • United States • Mean follow-up: 25 years • Outcome: CVD (defined as CHD, cerebrovascular events, PAD, or congestive heart failure) 	<ul style="list-style-type: none"> • Among participants without diabetes mellitus: <ul style="list-style-type: none"> – Current smokers: 1.00 (referent) – Former smokers (quit ≤4 years): 0.47 (0.23–0.94) – Former smokers (quit >4 years): 0.46 (0.34–0.63) – Nonsmokers: 0.30 (0.21–0.44) • Similar results in those with diabetes, but not significant (included in the meta-analysis by Pan and colleagues [2015] in Table 4.13) 	—
McEvoy et al. (2015) ^a	<ul style="list-style-type: none"> • Prospective cohort (Multi-Ethnic Study of Atherosclerosis) • 6,814 multiethnic participants with 638 CVD events, 45–84 years of age, 47% men, 38% former smokers, free of CVD • 1996–2011 • United States • Median follow-up 10.2 years • Outcome: all-cause CVDc 	<ul style="list-style-type: none"> • Risk of CVD by smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.07 (0.89–1.29) – Current smoker: 1.70 (1.32–2.18) 	Median cessation among former smokers was 22 (+/-13) years; smoking exposure confirmed by levels of urinary cotinine
Nance et al. (2017)	<ul style="list-style-type: none"> • Multi-Ethnic Study of Atherosclerosis cohort • 6,814 participants free of clinical heart disease at baseline • 45–84 years of age • 47% men, 53% women • 2000–2002 • United States 	<ul style="list-style-type: none"> • Former smokers—regardless of duration, intensity, or recency—were not at increased risk for suggesting that risk may drop precipitously from the time of quitting • Current smoker: <ul style="list-style-type: none"> – CVDH: HR = 1.98 (1.51–2.60), p <0.0005 – CVDA: HR = 1.80 (1.42–2.29), p <0.0005 – CHDH: HR = 1.94 (1.38–2.74), p <0.0005 – CHDA: HR = 1.66 (1.23–2.22), p = 0.001 • Former smoker: <ul style="list-style-type: none"> – CVDH: HR = 0.89 (0.72–1.11), p = 0.308 – CVDA: HR = 1.06 (0.89–1.27), p = 0.496 – CHDH: HR = 0.91 (0.69–1.20), p = 0.507 – CHDA: HR = 1.13 (0.92–1.40), p = 0.251 	—

Notes: **CHD** = coronary heart disease; **CHDA** = CHDH, definite angina, probable angina if followed by revascularization; **CHDH** = coronary heart disease hard (myocardial infarction, resuscitated cardiac arrest, CHD death); **CI** = confidence interval; **CVD** = cardiovascular disease; **CVDA** = CVDH, CHDH, atherosclerotic death, CVD death; **CVDH** = CHDH, stroke death, stroke; **HR** = hazard ratio; **PAD** = peripheral artery disease; **RR** = risk ratio.

Table 4.13 Continued

^aMeasure(s) of association adjusted for covariate(s).

^bPooled logistic regression analyses.

^cAll-cause CVD events defined as all-cause CHD events plus cerebrovascular accident (CVA), transient ischemic attack, or ischemic or hemorrhagic stroke; CVA death; and other CVD death.

Summary of the Evidence

The additional evidence reviewed in this section strengthens the basis for previous conclusions that smoking cessation reduces the risk of CVD morbidity and mortality. For those who quit, there are short-term benefits in terms of reduced risk for CVD and a continued decline over the long term as time since cessation increases.

Smoking Cessation and Coronary Heart Disease

CHD, the most common form of heart disease in the United States, results in part from the buildup of plaque (atherosclerosis) on the walls of coronary arteries (Centers for Disease Control and Prevention [CDC] 2015). MI, or heart attack, occurs when the flow of blood to part of the heart muscle is reduced or blocked, damaging that part of the heart muscle or causing it to die. The main cause of MI is plaque in the coronary arteries; a less common cause is severe spasm or contraction of a coronary artery (CDC 2017).

In the United States, someone has an MI once every 40 seconds (Benjamin et al. 2017). Approximately 7.9 million adults (20 years of age or older) have had an MI, and 8.7 million have angina pectoris (Benjamin et al. 2017).

In the CHANCES study of women and men 60 years of age or older, cigarette smoking was strongly associated with acute coronary events (confirmed fatal and nonfatal coronary events, such as acute MI, unstable angina pectoris, or coronary death) (Mons et al. 2015). Overall, risk of acute coronary events was higher in former smokers than in never smokers, and compared with risk among current smokers, risk of acute coronary events in former smokers decreased greatly as the number of years since cessation increased (Table 4.14). Compared with current smokers, the adjusted HR of acute coronary events decreased by 0.83 for every 10 years of smoking cessation (95% CI, 0.78–0.89).

Similarly, in pooled analyses of two older cohorts and five contemporary cohorts that were restricted to men and women 55 years of age or older, smoking cessation was associated with lower rates of death from CHD compared with the rate of current smokers, but risk of CHD death was higher among former smokers compared with never smokers (Table 4.14) (Thun et al. 2013a). Among the five contemporary cohorts in that study, benefits generally increased among those who had quit at younger ages or who had quit for longer periods of time, but compared with the risk among never smokers, risks remained elevated for many years. Among women who had quit for 30 or more years and among men who had quit for 40 or

more years, risk of CHD death was similar to that of never smokers. Risks of CHD mortality were not elevated among men and women who had quit before they were 40 years of age. Similar results, showing that the greatest benefit occurred among those who had quit at younger ages, were observed in a large cohort study of women in the United Kingdom (Table 4.15) (Pirie et al. 2013).

The 2014 Surgeon General's report (USDHHS 2014) noted that the pattern of declining CHD risk with increasing time since cessation was not as strong among the contemporary cohorts analyzed by Thun and colleagues (2013a) as with earlier observational analyses (including the Lung Health Study and MRFIT cohorts) that reported a larger decline in CVD risk as time since cessation increased. The report attributed this difference to the fact that analyses by Thun and colleagues (2013a) focused on older adults.

In a meta-analysis of studies comparing smoking as a risk factor for CHD in women and men, the adjusted relative risk (RR) of CHD was higher in women than in men for current cigarette smokers compared with nonsmokers, but the risk did not differ between women and men who were former smokers (Huxley and Woodward 2011).

Pujades-Rodriguez and colleagues (2015) reported on the relationship between smoking and initial presentations of CVD in the CALIBER (Clinical research using Linked Bespoke studies and Electronic health Records) (University College London n.d.), drawing on linked electronic health records of 1.93 million persons 30 years of age or older in England. In age-adjusted analyses (stratified by sex and general practice), the hazards of stable angina, unstable angina, MI, and sudden coronary death decreased gradually with increasing time since smoking cessation (Table 4.15). After 10 years of cessation, former smokers tended to have the same hazard of CHD outcomes as never smokers (not shown in table), although the HR for sudden coronary death in women (HR = 2.74; 95% CI, 1.36–5.51) remained elevated. The main analysis imputed smoking status for 523,611 participants. Results were similar for complete case analyses (1.41 million persons with smoking status) and when adjusting for other variables. It is unclear, however, how many persons in this study had missing covariates and whether any analyses were run without imputed covariates, which could have influenced the validity of the findings.

In the Nurses' Health Study (included in the pooled analysis by Thun and colleagues [2013]), former smokers had an increased risk of CHD mortality compared with never smokers (adjusted HR = 1.24; 95% CI, 1.09–1.42) (Kenfield et al. 2008). Compared with current smokers, former smokers showed a trend of decreased risk of CHD mortality with increased time since cessation (from fewer than 5 years to 20 or more years). In this study, former smoking was also associated with risk of all CHD events

Table 4.14 Meta-analyses and a pooled analysis of observational studies on smoking cessation and incidence of coronary heart disease

Study	Design/population	Findings: RR (95% CI)	Comments
Thun et al. (2013a) ^{a,b}	<ul style="list-style-type: none"> • Pooled analysis • Men and women, ≥55 years of age • Two historical cohorts (CPS I and II) and five contemporary cohorts:^b <ul style="list-style-type: none"> – CPS I: n = 518,982; cases = 17,809 – CPS II: n = 746,485; cases = 16,308 – Contemporary cohorts: n = 956,756; cases = 22,622 • United States • Follow-up: <ul style="list-style-type: none"> – CPS I: 1959–1965 – CPS II: 1982–1988 – Contemporary cohorts: 2000–2010 • Outcome: CHD deaths 	<ul style="list-style-type: none"> • CPS I: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.28 (1.21–1.36) ○ Current smoker: 1.69 (1.61–1.77) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.39 (1.22–1.59) ○ Current smoker: 1.56 (1.46–1.67) • CPS II: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.27 (1.21–1.33) ○ Current smoker: 1.78 (1.69–1.88) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.27 (1.19–1.36) ○ Current smoker: 2.00 (1.88–2.13) • Contemporary cohorts: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.43 (1.37–1.48) ○ Current smoker: 2.50 (2.34–2.66) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.44 (1.38–1.51) ○ Current smoker: 2.86 (2.65–3.08) 	—

Table 4.14 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015) ^{a,b}	<ul style="list-style-type: none"> Individual-level meta-analysis of 19 prospective cohorts 64,221 men and women, ≥60 years of age, 47% former smokers, excluded those with a history of acute coronary events Europe Studies included data collected from different cohorts from various years from the 1980s to the 2010s Mean follow-up: 1.6–14.8 years (approximately 8–13 years for most studies) Outcome: acute coronary events 	<ul style="list-style-type: none"> Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.18 (1.06–1.32) – Current smoker: 1.98 (1.75–2.25) Years since smoking cessation: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – <5: 0.84 (0.72–0.98) – 5–9: 0.86 (0.72–1.02) – 10–19: 0.69 (0.58–0.82) – ≥20: 0.58 (0.46–0.72) 	—
Pan et al. (2015) ^a	<ul style="list-style-type: none"> Meta-analysis of prospective cohort studies: <ul style="list-style-type: none"> – 13 studies of former smokers – 21 studies of current smokers 1,009,457 men and women, >18 years of age with diabetes mellitus (type 1 or 2), 38,752 cases Studies in the meta-analysis were published between 1989 and 2015 United States, Europe, China, New Zealand, and other international collaborations Outcome: CHD 	<ul style="list-style-type: none"> Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.14 (1.00–1.30) – Current smoker: 1.51 (1.41–1.62) 	—

Notes: **CHD** = coronary heart disease; **CI** = confidence interval; **CPS** = Cancer Prevention Study; **RR** = risk ratio.

^aThere was some overlap between cohorts included in two or more of these publications in this table.

^bHistorical cohorts: CPS I (1959–1965) and CPS II (1982–1988). Contemporary cohorts (2000–2010): National Institutes of Health–American Association of Retired Persons Diet and Health Study, CPS II Nutrition Cohort, Women’s Health Initiative (women only), Nurses’ Health Study (women only), and Health Professionals Follow-Up Study (men only).

Table 4.15 Observational studies on smoking cessation and incident coronary heart disease

Study	Design/population	Findings: RR (95% CI)	Comments
Song and Cho (2008) ^a	<ul style="list-style-type: none"> • Prospective cohort • 475,734 men, 30–58 years of age in 1990, 6% quitters,^b 16% ex-smokers,^b free of stroke or myocardial infarction, 2,164 cases of CHD • 1992–2001 • Korea • Mean follow-up: 8.83 years • Outcome: myocardial infarction • Nonreducing heavy smoker (>20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day); reducer from heavy to moderate smoking; reducer from heavy to light smoking; reducer from moderate to light smoking; quitter from any smoking status; sustained ex-smoker; and sustained never smoker. 	<ul style="list-style-type: none"> • Smoking status:^b <ul style="list-style-type: none"> – Current smoker (by smoking intensity): <ul style="list-style-type: none"> ○ Non-reducing heavy smoker 1.00 (referent) ○ Moderate smoker: 0.74 (0.65–0.85) ○ Light smoker: 0.65 (0.57–0.75) – Quitter: 0.43 (0.34–0.53) – Sustained ex-smoker: 0.37 (0.32–0.44) – Never smoker: 0.29 (0.25–0.34) 	Women not included because of their low percentage of smoking
Pirie et al. (2013) ^a	<ul style="list-style-type: none"> • Prospective cohort (Million Women Study) • 1.2 million women; 55 years of age (median) at baseline; 28% former smokers; free of prior cancer (other than nonmelanoma skin cancer), heart disease, stroke, and current respiratory disease treatment; 4,458 cases of CHD among never or current smokers • 1996–2011 • United Kingdom • Mean follow-up: 12 years • Outcome: CHD mortality 	<ul style="list-style-type: none"> • Age (in years) quit smoking: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – <25: 0.8 – 25–34: 1.0 – 35–44: 1.4^c – 45–54: 1.9^c 	Exact CIs not reported for these results; total number of CHD cases not provided
McEvoy et al. (2015a) ^a	<ul style="list-style-type: none"> • Prospective cohort (Multi-Ethnic Study of Atherosclerosis) • 6,814 participants, 45–84 years of age, 47% men, multiethnic, 38% former smokers, free of CVD at baseline; 284 hard CHD events and 449 all-cause CHD events • 1996–2011 • United States • Median follow-up: 10.2 years • Outcomes: hard CHD and all-cause CHD^d 	<ul style="list-style-type: none"> • Hard CHD events: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 0.93 (0.70–1.24) – Current smoker: 1.70 (1.18–2.45) • All-cause CHD events: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.14 (0.91–1.42) – Current smoker: 1.55 (1.14–2.10) 	Median length of cessation among former smokers was 22 (+/-13) years; smoking exposure confirmed by urinary cotinine

Table 4.15 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015)	<ul style="list-style-type: none"> • Prospective cohort • 1.93 million participants, ≥30 years of age, 49% men, predominantly White (also South Asian and Black), 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD, 4,253 cases of myocardial infarction in former smokers • 1997–2010 • England • Median follow-up: 6 years 	<ul style="list-style-type: none"> • Myocardial infarction by smoking status (age-adjusted): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <2: 0.55 (0.34–0.88) ○ 2–9: 0.52 (0.41–0.65) ○ ≥10: 0.45 (0.38–0.55) • Stronger association with more time since cessation for outcomes of unheralded coronary death and unstable angina <ul style="list-style-type: none"> – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <2: 1.01 (0.60–1.71) ○ 2–9: 0.76 (0.47–1.23) ○ ≥10: 0.61 (0.41–0.89) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <2: 1.05 (0.55–1.99) ○ 2–9: 0.86 (0.63–1.18) ○ ≥10: 0.63 (0.52–0.77) • Weaker trend for outcome of stable angina <ul style="list-style-type: none"> – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <2: 1.03 (0.66–1.60) ○ 2–9: 0.88 (0.69–1.12) ○ ≥10: 0.81 (0.81–0.99) 	<p>Imputed smoking status in the main analyses, as smoking data were missing in 523,611 participants; results were similar for complete case analysis (1.41 million participants with smoking status) and when adjusted for other potential confounders; unclear how many persons had missing covariates and whether analyses were run without imputed covariates, which might have influenced validity of findings</p>

Notes: **CALIBER** = Clinical research using LInked Bespoke studies and Electronic health Records; **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **RR** = risk ratio.

^aMeasure(s) of association adjusted for covariate(s).

^bSmoking categories based on smoking status in 1990 baseline exam and change in status from 1990 to 1992 exams: non-reducing heavy smoker (≥20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day), reducer from heavy to moderate, reducer from heavy to light, reducer from moderate to light, quitter from any smoking status, sustained ex-smoker, sustained never smoker. Results for reducers not shown in table.

^cLower boundary of 95% CI >1.0.

^dHard CHD events defined as myocardial infarction or death from CHD. All-cause CHD events defined as hard CHD events plus definite angina, probable angina resulting in revascularization, and resuscitation after cardiac arrest.

(fatal and nonfatal), but there was a stronger association for current smokers than for former smokers (Hu et al. 2000; Stampfer et al. 2000). In the MESA cohort, former smokers (median cessation: 22 years [\pm 13 years]) did not have a higher adjusted hazard for either a more strictly defined or a more broadly defined CHD outcome (Table 4.15) (McEvoy et al. 2015a). Despite a positive dose-response relationship between pack-years of smoking and CHD among current smokers, the dose-response relationship was null among former smokers (data not shown). Both a high-sensitivity CRP ≥ 3 mg/L and, particularly, a CAC >100 identified current smokers with a higher RR of CHD. In a large cohort of Korean men, both those who quit smoking within 2 years before the start of follow-up and those who had quit for a longer period had a lower adjusted hazard of MI compared with current heavy smokers (Table 4.15) (Song and Cho 2008).

Lee and colleagues (2012) used a negative exponential distribution to quantitatively estimate how rapidly the risk of CHD declines following smoking cessation. Estimates from this approach were used to inform a special report from the American Heart Association and the American College of Cardiology on the longitudinal risks and benefits of therapies to prevent cardiovascular problems among Medicare patients (Lloyd-Jones et al. 2017). Based on a literature search and on consultation within their own team and with biostatistical and content experts, Lloyd-Jones and colleagues (2017) concluded that the approach set forth by Lee and colleagues (2012) was the most rigorous methodology for estimating the longitudinal reduction in MI risk associated with tobacco cessation. The quantitative review by Lee and colleagues (2012) had estimated that the excess risk of CHD associated with smoking decreased by 50% at 4.40 years after cessation (95% CI, 3.26–5.95), but there was a substantial range in the estimate of the time required to achieve a 50% decrease in CHD risk across the studies, from less than 2 years to greater than 10 years. The cohort studies considered by Lee and colleagues (2012) had little follow-up time after 2000, and alternative models to the negative exponential model were not considered. It should be noted that Philip Morris funded the research for this paper.

In line with IARC (2007), the risk of MI appears to decrease asymptotically as time since cessation increases, eventually reaching the risk among never smokers. In another modeling paper, Hurley (2005) also observed a rapid decrease in the risk of acute MI within 1–2 years of cessation, followed by a slower decline thereafter.

Summary of the Evidence

Building on evidence reviewed in previous Surgeon General's reports, additional studies have added to the evidence base indicating that smoking cessation reduces

the risk of CHD. The risk declines rapidly in the period immediately following cessation and then declines at a slower rate in the longer term. In some studies, the risk for CHD in former smokers eventually decreases to that of never smokers.

Smoking Cessation and Cerebrovascular Disease

Cerebrovascular disease results from interruptions in the flow of arterial blood to the brain, resulting in a syndrome of mild-to-severe neurologic deficits. Deficits can be temporary (transient ischemic attack) or permanent (stroke). In the United States, cerebrovascular disease is the fifth leading cause of death (Kochanek et al. 2016), responsible for approximately 140,000 deaths each year (Yang et al. 2017). In 2017 it was estimated that 7.7 million U.S. adults 18 years of age or older have had a stroke (Benjamin et al. 2017). Ischemic stroke, which results from an obstruction in a blood vessel that blocks the supply of blood to the brain, accounts for an estimated 87% of strokes in the United States (Benjamin et al. 2017). Hemorrhagic stroke occurs when a weakened blood vessel ruptures and causes either an intracerebral (within the brain) hemorrhage (ICH) or a subarachnoid hemorrhage (SAH). From 2014 to 2015, the annual direct (medical) plus indirect costs of stroke in the United States was estimated to be \$45.5 billion (Benjamin et al. 2019). Heidenreich and colleagues (2011) projected that the direct (medical) cost of stroke will increase by 238% from 2010 to 2030.

Previous Surgeon General's reports (USDHHS 1989, 2004) have concluded that smoking is a cause of stroke. The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of both ischemic stroke and SAH compared with continued smoking, and that the risk of stroke returns to that of never smokers 5–15 years after quitting (USDHHS 1990) (Table 4.10). Similarly, the 2001 Surgeon General's report concluded that in most studies including women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5–15 years of abstinence, the risk among former smokers approaches that of women who have never smoked (USDHHS 2001) (Table 4.10).

Several pooled studies or meta-analyses have found that smoking cessation is associated with a reduced risk of stroke or stroke mortality (Table 4.16) (Feigin et al. 2005; Peters et al. 2013; Thun et al. 2013a; Mons et al. 2015; Pan et al. 2015). Peters and colleagues (2013), in a meta-analysis of prospective cohort studies from around the world that were published between January 1, 1966, and

Table 4.16 Observational studies (meta-analyses and pooled analyses) on smoking cessation and cerebrovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Feigin et al. (2005) ^a	<ul style="list-style-type: none"> • Meta-analysis of five longitudinal studies and three case-control studies • Men and women • Number of cases for analysis of current smoking: <ul style="list-style-type: none"> – Longitudinal studies: 453 – Case-control studies: 607 • Follow-up: 5–22 years • Studies included in the meta-analysis were published between 1966 and 2015 • United States, Europe, and Asia-Pacific region • Outcome: subarachnoid hemorrhage 	<ul style="list-style-type: none"> • Longitudinal studies: <ul style="list-style-type: none"> – Never smoker vs. former smoker: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.9 (1.5–2.3) – Nonsmoker vs. current smoker: <ul style="list-style-type: none"> ○ Nonsmoker: 1.00 (referent) ○ Current smoker: 2.2 (1.3–3.6) • Case-control studies: <ul style="list-style-type: none"> – Never smoker vs. former smoker: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 2.3 (2.2–2.4) – Nonsmoker vs. former smoker: <ul style="list-style-type: none"> ○ Nonsmoker: 1.00 (referent) ○ Current smoker: 3.1 (2.7–3.5) 	—

Table 4.16 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Thun et al. (2013a) ^{a,b}	<ul style="list-style-type: none"> • Pooled analysis • Men and women, ≥55 years of age • Two historical cohorts (CPS I and II) and five contemporary cohorts^c • Sample: <ul style="list-style-type: none"> – CPS I: n = 518,982; 5,890 deaths from stroke – CPS II: n = 746,485; 4,037 deaths from stroke – Contemporary cohorts: 956,756; 7,536 • United States • Follow-up: <ul style="list-style-type: none"> – CPS I: 1959–1965 – CPS II: 1982–1988 – Contemporary cohorts: 2000–2010 • Outcome: deaths from stroke 	<ul style="list-style-type: none"> • CPS I: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 0.95 (0.83–1.09) ○ Current smoker: 1.38 (1.26–1.52) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.46 (1.19–1.78) ○ Current smoker: 1.51 (1.35–1.69) • CPS II: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.07 (0.95–1.20) ○ Current smoker: 1.97 (1.74–2.23) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.16 (1.03–1.31) ○ Current smoker: 2.19 (1.96–2.44) • Contemporary cohorts: <ul style="list-style-type: none"> – Men: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.16 (1.07–1.25) ○ Current smoker: 1.92 (1.66–2.21) – Women: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.15 (1.07–1.22) ○ Current smoker: 2.10 (1.87–2.36) 	—
Peters et al. (2013) ^a	<ul style="list-style-type: none"> • Meta-analysis of prospective cohorts <ul style="list-style-type: none"> – Current smokers: 76 cohorts – Former smokers: 72 cohorts • Men and women, ≥18 years of age: <ul style="list-style-type: none"> – Current smokers: n = 3,817,289; 39,042 cases of stroke – Former smokers: n = 3,534,330; 36,449 cases of stroke • Studies in the meta-analysis were published between January 1, 1996, and January 26, 2013 • United States, Europe, and Asia-Pacific region • Outcome: fatal and nonfatal stroke 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.08 (1.03–1.13) – Nonsmoker: 1.00 (referent) – Current smoker: 1.67 (1.49–1.88) • Women: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.17 (1.12–1.22) – Nonsmoker: 1.00 (referent) – Current smoker: 1.83 (1.58–2.12) 	—

Table 4.16 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015) ^{a,b}	<ul style="list-style-type: none"> • Individual-level meta-analysis of 19 prospective cohorts • 66,136 men and women, ≥60 years of age, approximately 47% former smokers, excluded those with a history of stroke, 4,052 cases of stroke • Years of data collection: not provided • Europe • Mean follow-up: 1.6–14.8 years (8–13 years for most studies) • Outcome: stroke 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.17 (1.07–1.26) – Current smoker: 1.58 (1.40–1.78) • Years since quitting: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ <5: 0.97 (0.79–1.19) ○ 5–9: 0.98 (0.74–1.31) ○ 10–19: 0.79 (0.69–0.92) ○ ≥20: 0.67 (0.60–0.76) 	—
Pan et al. (2015)	<ul style="list-style-type: none"> • Meta-analysis of prospective cohort studies: <ul style="list-style-type: none"> – 9 studies of former smokers – 15 studies of current smokers • 1,013,724 men and women >18 years of age with diabetes mellitus (type 1 or 2); 33,170 cases of stroke • Studies in the meta-analysis were published between 1989 and 2015 • United States, Europe, China, and other international collaborations • Outcome: stroke 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.04 (0.87–1.23) – Current smoker: 1.54 (1.41–1.69) 	—

Notes: **CI** = confidence interval; **CPS** = Cancer Prevention Study; **RR** = risk ratio.

^aThere was some overlap between cohorts that were included in two or more of the publications in this table.

^bHistorical cohorts: CPS I (1959–1965) and CPS II (1982–1988).

^cContemporary cohorts (2000–2010): National Institutes of Health–American Association of Retired Persons Diet and Health Study, CPS II Nutrition Cohort, Women’s Health Initiative (women only), Nurses’ Health Study (women only), and Health Professionals Follow-Up Study (men only).

January 26, 2013, found that, compared with nonsmokers (who were either never smokers or former smokers), the risk of stroke in current smokers was 83% higher (95% CI, 1.58–2.12) for women and 67% higher for men (95% CI, 1.49–1.88) (Table 4.16) (Peters et al. 2013). Compared with never smoking, former smoking was associated with a 17% higher risk of stroke among women (95% CI, 1.12–1.22) and an 8% higher risk among men (95% CI, 1.03–1.13). There was no evidence of a difference in the benefit of smoking cessation between women and men. This analysis did not evaluate the relationships between risk of stroke and smoking duration or time since quitting.

Mons and colleagues (2015) examined individual data from the CHANCES study (European and North American cohorts) to assess the relationship between smoking cessation and risk of stroke in women and men 60 years of age or older, and found that smoking was strongly associated with increased risk of stroke. Overall, former smokers had a higher risk of stroke than never smokers. Compared with current smokers, there was a dose-response relationship, with risk decreasing among former smokers as years since cessation increased (Table 4.16). In this comparison, the adjusted HR of stroke was 0.87 for every 10 years of smoking cessation (95% CI, 0.84–0.91). Similarly, Thun and colleagues (2013a) reported that smoking cessation reduced rates of death from stroke in two older and five contemporary cohorts restricted to men and women 55 years of age or older (Table 4.16), with a greater benefit generally found among those who had quit at younger ages. Risk of stroke mortality among former smokers tended to decrease as time since cessation increased.

Similarly, in a large cohort study of women in the United Kingdom, most of the benefit from cessation occurred among those who had quit at younger ages (Table 4.17) (Pirie et al. 2013). Elsewhere, in the Nurses' Health Study (included in the pooled analysis by Thun and colleagues [2013]), former smokers had an increased risk of cerebrovascular mortality compared with never smokers (adjusted HR = 1.27; 95% CI, 1.06–1.51) (Kenfield et al. 2008). Compared with current smokers, risk of cerebrovascular-disease mortality decreased among former smokers with increased time since cessation (from fewer than 5 years to 20 or more years). In contrast to the Nurses' Health Study, the British Regional Heart Study found that former light smokers (1–19 cigarettes per day) did not have an increased risk of stroke when compared with never smokers; current heavy smokers (≥ 21 cigarettes per day), however, had an increased risk (Wannamethee et al. 1995). In that study, compared with never smokers, former smokers had 1.7 times the adjusted hazard of stroke (95% CI, 0.9–4.8); there was not a consistent pattern of decreasing risk with increased time since cessation, but this pattern was seen in some categories.

Similar findings have been reported by many other studies (Table 4.17). In a case-control study of young women (15–40 years of age) with ischemic stroke, former smokers did not have an increased risk of stroke compared with never smokers, but this study had the potential limitation of recall bias (Bhat et al. 2008). The Strong Heart Study, a population-based cohort recruited from 13 American Indian tribes/communities, found that current and former smokers had an increased adjusted hazard of stroke compared with never smokers (Zhang et al. 2008). For this study, former smoking was defined as having smoked 100 or more cigarettes in one's lifetime, having smoked cigarettes regularly in the past, and not smoking currently. In a meta-analysis of persons with diabetes mellitus, former smokers did not have an increased risk of stroke compared with never smokers (Pan et al. 2015).

In an analysis similar to the one of CHD, Lee and colleagues (2014) quantitatively estimated reduction in stroke risk following smoking cessation. In a fixed-effects model, they estimated that the excess risk of stroke associated with smoking decreased by 50% after 4.78 years of smoking abstinence (95% CI, 2.17–10.50), which is similar to the time needed to realize a 50% reduction in risk that they had estimated for CHD. There was considerable unexplained heterogeneity in the results, however, making a definitive conclusion challenging; the random-effects estimate for a 50% reduction was 3.08 years (95% CI, 1.32–7.16). Hurley (2005), in another modeling paper, observed a rapid decrease in risk of stroke shortly after cessation (within 1–2 years), followed by a slower decline.

Stroke Subtypes

Several studies have assessed relationships between smoking cessation and subtypes of stroke (SAH, ICH, and ischemic stroke) (Kawachi et al. 1993; Kurth et al. 2003a,b; Feigin et al. 2005; Sturgeon et al. 2007; Song and Cho 2008; Pujades-Rodriguez et al. 2015; Lindbohm et al. 2016).

In a meta-analysis of longitudinal and case-control studies by Feigin and colleagues (2005), former smoking was associated with twice the risk of SAH compared with never smoking (Table 4.16). Some of the studies in this meta-analysis assessed amount smoked or time since cessation or examined subtypes of stroke. Kurth and colleagues (2003a,b) assessed associations between smoking and hemorrhagic stroke subtypes in men (Physician's Health Study) and women (Women's Health Study) (Table 4.17). In both studies, former smokers and never smokers had no significant difference in risk of total hemorrhagic stroke, ICH, and SAH (Table 4.17). Earlier, Kawachi and colleagues (1993) reported that, in women in the Nurses' Health Study, the excess risk for total strokes decreased within approximately 2–4 years after smoking cessation compared with the risk among current smokers. Those

Table 4.17 Observational studies on smoking cessation and cerebrovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Kurth (2003a) ^a	<ul style="list-style-type: none"> • Prospective cohort (observational analyses of Women’s Health Study, a randomized controlled trial) • 39,783 women, 40–84 years of age at entry, 95% White, apparently healthy and free of stroke at baseline, seven hemorrhagic strokes • 1993–2003 • United States • Mean follow-up: 9 years • Outcome: hemorrhagic stroke (and subtypes) 	<ul style="list-style-type: none"> • Total hemorrhagic stroke: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 0.97 (0.55–1.72) – Current smoker (<20 cigarettes smoked per day): 1.93 (0.75–5.02) – Current smoker (≥20 cigarettes smoked per day): 3.29 (1.72–6.29) • Similar patterns for subtype analysis of intracerebral hemorrhage and subarachnoid hemorrhage 	—
Kurth (2003b) ^a	<ul style="list-style-type: none"> • Prospective cohort (observational analyses of Physicians’ Health Study, a randomized controlled trial) • 22,022 male physicians, 40–84 years of age at entry, 92% White, apparently healthy and free of stroke at baseline, 139 cases of stroke • 1982–2002 • United States • Mean follow-up: 17.8 years • Outcome: hemorrhagic stroke (and subtypes) 	<ul style="list-style-type: none"> • Total hemorrhagic stroke: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 0.76 (0.53–1.09) – Current smoker (<20 cigarettes smoked per day): 1.65 (0.61–4.50) – Current smoker (≥20 cigarettes smoked per day): 2.36 (1.38–4.02) • Similar patterns for subtype analysis of intracerebral hemorrhage and subarachnoid hemorrhage 	—
Bhat et al. (2008) ^a	<ul style="list-style-type: none"> • Case-control (Stroke Prevention in Young Women Study) • Females, 15–40 years of age, 466 cases of stroke and 604 controls (random-digit dialing; matched by age and geographic region of residence) • Recruited in 1992–1996 and 2001–2003 • United States (greater Baltimore–Washington, D.C., area) • Outcome: ischemic stroke 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.0 (0.6–1.4) – Current smoker (cigarettes smoked per day): <ul style="list-style-type: none"> ○ All: 2.6 (1.9–3.6) ○ 1–10: 2.2 (1.5–3.3) ○ 11–20: 2.5 (1.6–3.8) ○ 21–39: 4.3 (1.8–10) ○ ≥40: 9.1 (3.2–26) 	Potential for recall bias

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Song and Cho (2008) ^a	<ul style="list-style-type: none"> • Prospective cohort • 475,734 men, 30–58 years of age in 1990, 6% quitters,^b 16% ex-smokers,^b free of stroke or myocardial infarction, 6,092 cases of stroke • 1992–2001 • Korea • Mean follow-up: 8.83 years • Outcome: total stroke 	<ul style="list-style-type: none"> • Smoking status:^b <ul style="list-style-type: none"> – Current smoker: <ul style="list-style-type: none"> ◦ Non-reducing heavy smoker (≥20 cigarettes per day): 1.00 (referent) ◦ Moderate smoker: (10–19 cigarettes per day): 0.86 (0.78–0.93) ◦ Light smoker (<10 cigarettes per day): 0.84 (0.77–0.93) – Quitter: 0.70 (0.62–0.80) – Ex-smoker: 0.53 (0.48–0.58) – Never smoker: 0.57 (0.52–0.63) • Similar patterns observed for stroke subtypes (ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage): <ul style="list-style-type: none"> – Hemorrhagic stroke: lighter smokers and quitters did not have a significantly different risk vs. heavy smokers – Subarachnoid hemorrhage: moderate smokers (10–19 cigarettes per day) did not have a lower risk than heavy smokers (≥20 cigarettes per day) 	—
Zhang et al. (2008) ^a	<ul style="list-style-type: none"> • Prospective cohort (Strong Heart Study) • 4,507 participants from 13 American Indian tribes/communities, 45–74 years of age, 41% men, no history of stroke, 306 events of stroke • 1989–2004 • Arizona, North Dakota, Oklahoma, and South Dakota • Mean follow-up: 13.4 years • Outcome: stroke 	<ul style="list-style-type: none"> • Smoking status:^c <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.6 (1.14–2.25) – Current smoker: 2.38 (1.69–3.36) 	—

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Kim et al. (2012a) ^a	<ul style="list-style-type: none"> • Case-control study (multicenter) • Participants, 30–84 years of age (mean age: 50.7 years); 39% men; 426 cases and 426 age–sex-matched controls (recruited from siblings, friends, or neighbors of controls); free of stroke, dementia, or other neurological diseases • Recruited in 2002–2004 • Korea • Outcome: subarachnoid hemorrhage 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 1.79 (0.86–3.75) – Current smoker: 2.84 (1.63–4.97) • Years since quitting (current vs. former smoker): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker <ul style="list-style-type: none"> ○ <5: 0.94 (0.41–2.16) ○ ≥5: 0.41 (0.17–0.97) • Years since quitting (never vs. former smoker): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ <5: 2.71 (1.07–6.81) ○ ≥5: 1.17 (0.46–3.00) • Smoking intensity (current vs. former smoker): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ 1–19 cigarettes per day: 0.36 (0.13–1.01) ○ ≥20 cigarettes per day: 0.84 (0.40–1.78) • Smoking intensity (never vs. former smoker): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ 1–19 cigarettes per day: 0.99 (0.32–3.06) ○ ≥20 cigarettes per day: 2.34 (1.02–5.36) 	<p>Potential for bias because of recall and selection of controls from siblings, friends, or neighbors</p>

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Tse et al. (2012) ^a	<ul style="list-style-type: none"> • Prospective cohort (extension of 7-5 China Stroke Prevention Project) • 26,607 participants ≥35 years of age, 47% men, free of stroke; former smokers included 7.2% of men and 1.5% of women; 1,108 cases of stroke • 1986–2000 • China • Mean follow-up: 9.5 years • Outcomes: total stroke, ischemic stroke, and hemorrhagic stroke 	<ul style="list-style-type: none"> • Men <ul style="list-style-type: none"> – Total stroke: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.35 (1.00–1.81) ○ Current smoker: 1.39 (1.15–1.67) – Similar patterns for ischemic and hemorrhagic stroke • Women: <ul style="list-style-type: none"> – Total stroke: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 0.86 (0.45–1.65) ○ Current smoker: 1.34 (1.06–1.69) – Similar patterns for ischemic and hemorrhagic stroke 	Limited power to detect associations because of few former smokers
Pirie et al. (2013) ^a	<ul style="list-style-type: none"> • Prospective cohort (Million Women’s Study) • 1.2 million women; stopped smoking before 55 years of age (at baseline); 28% former smokers, and free of prior cancer (other than nonmelanoma skin cancer), heart disease, stroke, and current respiratory disease treatment; 2,986 cases of cerebrovascular disease among never or current smokers • 1996–2011 • United Kingdom • Mean follow-up: 12 years • Outcome: cerebrovascular disease mortality 	<ul style="list-style-type: none"> • Age (in years) quit smoking <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – <25: 0.9 – 25–34: 0.9 – 35–44: 1.1 – 45–54: 1.3^d 	Exact CIs not reported for these results; total cases of cerebrovascular disease not provided
Pujades-Rodriguez et al. (2015)	<ul style="list-style-type: none"> • Prospective cohort • 1.93 million participants; ≥30 years of age; 49% men, predominantly White (also South Asian and Black), and 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD; and 1,558 cases of ischemic stroke in former smokers • 1997–2010 • England • Median follow-up: 6 years 	<ul style="list-style-type: none"> • Ischemic stroke by smoking status (age-adjusted): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (<2 years): 0.62 (0.32–1.22) – Former smoker (2–9 years): 0.63 (0.45–0.87) – Former smoker (≥10 years): 0.51 (0.43–0.61) • Reduced risk for longer time since cessation for outcomes of transient ischemic attack, subarachnoid hemorrhage, and intracerebral hemorrhage 	See Table 4.17 for concerns about validity

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Lindbohm et al. (2016) ^a	<ul style="list-style-type: none"> • Prospective cohort (FINRISK Survey) • 65,521 participants, 45 years of age (median), 48% men, no prior subarachnoid hemorrhage at baseline, 492 cases of subarachnoid hemorrhage • 1972–2011 • Finland • Median follow-up: 21.1 years (full cohort) and 14.8 years (cases) • Outcome: subarachnoid hemorrhage 	<ul style="list-style-type: none"> • Age quit smoking: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Recent quitter (<6 months): 1.93 (0.98–3.79) – Former smoker (quit for >6 months): 1.34 (0.98–1.82) – Current smoker (cigarettes per day): <ul style="list-style-type: none"> ○ 1–10: 2.54 (1.90–3.40) ○ 11–20: 2.82 (2.14–3.70) ○ 21–30: 3.79 (2.51–5.71) ○ ≥31: 3.91 (1.97–7.75) 	—

Notes: **CALIBER** = Clinical research using LInked Bespoke studies and Electronic health Records; **CI** = confidence interval; **FINRISK** = a large Finnish population survey on risk factors on chronic, noncommunicable diseases; **RR** = risk ratio.

^aMeasure(s) of association adjusted for covariate(s).

^bSmoking categories based on smoking status in 1990 exam and change from 1990 to 1992: non-reducing heavy smoker (≥20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day), quitter from any smoking status, sustained ex-smoker, sustained never smoker. Results in reducers not shown in table.

^cFormer smoking defined as having smoked ≥100 cigarettes, having smoked cigarettes regularly in the past, and not smoking currently.

^dLower boundary of 95% CI >1.0 (CIs not provided).

researchers found a similar pattern of decreasing risk as time since cessation increased for ischemic stroke and SAH (Kawachi et al. 1993). Elsewhere, in a case-control study, the adjusted odds of SAH due to ruptured intracranial aneurysm were higher among current cigarette smokers than former smokers (Kissela et al. 2002).

More recent research has produced similar findings, but associations have been less consistent for ICH than for SAH (Table 4.17). In the FINRISK study cohort (a large Finnish population survey on risk factors for chronic, non-communicable diseases) (Lindbohm et al. 2016), former smokers had a decreased risk of SAH compared with current smokers. In a nationwide, multicenter, case-control study in Korea (Kim et al. 2012a), former smokers who had quit for 5 or more years had a lower adjusted risk of SAH than current smokers. This study also found a pattern of lower risk for former smokers with lower levels of prior smoking intensity. The study, however, may have been biased because of faulty recall of smoking history and selection of controls who were siblings, friends, or neighbors. Earlier, in a large cohort of Korean men, in a comparison with heavy smokers, former smokers who quit smoking 2 years or less before the start of follow-up had a lower adjusted hazard of total stroke, ischemic stroke, and SAH (Song and Cho 2008). A similar pattern, although not statistically significant, was observed for hemorrhagic stroke. Compared with heavy smokers, former smokers who had stopped smoking for a longer period of time had lower adjusted hazards of all types of strokes. Elsewhere, in a pooled analysis of the ARIC study and the Cardiovascular Health Study, there was no clear relationship between smoking status and ICH (not shown in tables) (Sturgeon et al. 2007).

In a hospital-based case-control study comparing patients with ruptured aneurysms against controls with unruptured aneurysms, the adjusted odds of ruptured cerebral aneurysm were 1.26 (95% CI, 0.98–1.61) in current smokers versus former smokers (Can et al. 2017). In that study, former smokers had higher adjusted odds of ruptured aneurysm than never smokers (OR = 1.56; 95% CI, 1.31–1.86). These findings are in line with those in the meta-analysis performed by Feigin and colleagues (2005) that compared SAH cases with healthy controls. In this analysis, current smokers had a two- to three-fold increase in risk of SAH compared with never smokers, and the risk was approximately twice as great in former smokers as it was in never smokers.

In the electronic health records-based CALIBER program (Table 4.17), the age-adjusted hazards of transient ischemic attack, ischemic stroke, SAH, and ICH gradually decreased with increased time since smoking cessation (Pujades-Rodriguez et al. 2015). After 10 years of cessation, former smokers tended to have the same hazard of

these cerebrovascular-disease outcomes as never smokers (not shown in table). Note that the section on CHD in this chapter discussed concerns about the validity of this study.

In a multicenter, population-based prospective cohort study in China (Table 4.17), men who were former smokers had a higher risk of stroke than those who were never smokers (HR = 1.35; 95% CI, 1.00–1.81) (Tse et al. 2012). Among women, there was no significant difference in this comparison (HR = 0.86; 95% CI, 0.45–1.65), but there were only 11 cases of stroke. Further, power was limited because of the low prevalence of former smokers.

Prognosis of Cerebrovascular Disease

Among four randomized controlled trials that assessed the rate of smoking cessation following cerebrovascular disease with follow-ups ranging from 6 months to 3.5 years, the overall cessation rate was 23.9% (42 of 176) among those who received a smoking cessation intervention and 20.8% (37 of 178) for those who did not receive one (Edjoc et al. 2012). Elsewhere, in a single study of 110 patients with acute stroke, 40% had stopped smoking 1 year after hospital admission; the best predictors of cessation were insular damage and a prestroke intention to stop (Suner-Soler et al. 2012). Finally, in a study of 198 patients, 21.7% gave up smoking within 6 months after their first stroke (Bak et al. 2002).

Among persons with cerebrovascular disease, findings from several studies suggest that former cigarette smokers have a lower risk of morbidity or mortality compared with those who continue to smoke after developing cerebrovascular disease. For example, in a literature review, Straus and colleagues (2002) estimated that smoking cessation would reduce the risk of a new stroke by 33% (95% CI, 29–38%) in survivors of stroke.

In a British study that followed 308 men and women with a history of stroke for an average of 7.5 years, current smokers had 2.27 times the adjusted risk of mortality (95% CI, 1.12–4.57) of never smokers, and former smokers had 1.46 times the risk (95% CI, 0.87–2.43) (Myint et al. 2006). In an Australian cohort of 1,589 cases of first-ever and recurrent stroke, among those who survived 28 days after the index event, the adjusted hazard of death or a nonfatal vascular event was higher for current smokers than former smokers (HR = 1.23; 95% CI, 1.00–1.50) (Kim et al. 2012b). In addition, former smokers had a higher adjusted hazard for such an outcome than never smokers (HR = 1.18; 95% CI, 1.01–1.39). Using data from the Registry of the Canadian Stroke Network, Edjoc and colleagues (2013) reported that, among patients with stroke, former smoking was associated with a reduced risk of the presenting stroke's severity, of mortality at 30 days, and of a prolonged stay in the hospital when compared with current smoking; the results varied by stroke subtype.

Summary of the Evidence

Building on evidence reviewed in previous Surgeon General's reports, the additional studies reviewed in this report further strengthen the evidence that smoking cessation reduces the risk of stroke morbidity and mortality and that the risk of such outcomes decreases with increased time since cessation.

Smoking Cessation and Atrial Fibrillation

Atrial fibrillation (AF) is a condition in which the atria (upper chambers of the heart) beat irregularly. Earlier estimates of the prevalence of AF in the United States ranged from approximately 2.7 to 6.1 million persons (Go et al. 2001; Miyasaka et al. 2006), but it is estimated that prevalence will increase to approximately 12.1 million in 2030 (Colilla et al. 2013). AF is associated with an increased risk of mortality, including mortality attributable to CVD and non-CVD causes (Benjamin et al. 2017).

Zhu and colleagues (2016) found in a meta-analysis of 16 prospective studies (286,217 patients and 11,878 cases of AF) that cigarette smoking was associated with a higher risk of AF (RR = 1.23; 95% CI, 1.08–1.39). Findings on AF related to current, former, and never smokers were available from 8 of the 16 studies. Former smokers had 1.16 times the risk of AF (95% CI, 1.00–1.36), and current smokers had 1.39 times the risk (95% CI, 1.11–1.36) compared with never smokers. Time since cessation was not assessed in any of the studies. Among persons with AF, smoking has also been associated with an increased risk of adverse events (Albertsen et al. 2014; Kwon et al. 2016). In the cohorts of the ARIC study and the Cardiovascular Health Study, current, but not former, smoking was associated with an increased risk of CVD deaths or ischemic stroke among persons with AF (Kwon et al. 2016). In the Danish Diet and Cancer study, former smoking was associated with an increased risk of thromboembolism or death among women with AF but not among men with AF (Albertsen et al. 2014).

Summary of the Evidence

A meta-analysis found that current and former cigarette smoking is associated with a higher risk of AF than never smoking, and the pooled estimate for former smokers was lower than that for current smokers. Findings from other studies regarding AF-related adverse events are mixed. No additional evidence is currently available on how the risk of AF changes with smoking cessation or with time since cessation.

Smoking Cessation and Sudden Cardiac Death

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation (Jacobs et al. 2004). Although it is a leading cause of death, the absence of nationwide surveillance standards makes it difficult to understand the epidemiology of cardiac arrest in the United States (Benjamin et al. 2017). Sudden cardiac death (SCD) is an unexpected death without an obvious noncardiac cause that occurs, if witnessed, within 1 hour of symptom onset or, if not witnessed, within 24 hours of the person's last being observed in normal health, although it is challenging to apply these criteria in practice (Benjamin et al. 2017). SCD can be attributable to cardiac or noncardiac causes; it is usually presumed to be attributable to cardiac causes unless another explanation can be identified. Based on the Resuscitation Outcomes Consortium registry of all emergency management system (EMS)-attended calls in 2015 for out-of-hospital cardiac arrests in eight U.S. and three Canadian regions, the incidence of out-of-hospital cardiac arrests assessed by EMS was estimated to be 110.8 persons per 100,000 (95% CI, 108.9–112.6) (Benjamin et al. 2019). Based on this registry, the rate of survival to hospital discharge for EMS-treated out-of-hospital cardiac arrest was 11.4% (95% CI, 10.4–12.4%) in adults, and survival after bystander-witnessed ventricular fibrillation was 37.4% (95% CI, 32.7–42.0%) for patients of any age (Benjamin et al. 2017).

The 2014 Surgeon General's report reviewed epidemiologic evidence from several studies showing that cigarette smoking is associated with SCD of all types. During 30 years of follow-up of 101,018 women without known CHD, stroke, or cancer at the 1980 baseline in the Nurses' Health Study, there were 351 SCD events, of which 148 occurred in former smokers (Sandhu et al. 2012). Overall, compared with never smokers, the adjusted hazard of SCD was higher among current smokers (HR = 2.44; 95% CI, 1.80–3.31) and former smokers (HR = 1.40; 95% CI, 1.10–1.79). Compared with current cigarette smokers, former smokers had a lower risk of SCD (HR = 0.58; 95% CI, 0.43–0.77). The risk of SCD decreased linearly over time after quitting smoking (p for trend <0.0001). After 15 years of cessation, the risk was significantly lower in former smokers than in current smokers; after 20 years of cessation, the risk was similar in former smokers and never smokers. In analyses stratified by CHD status, women with CHD who quit smoking tended to have a higher risk of SCD than never smokers, while increased risk of SCD dropped within 5 years and did not decline further among those who quit and did not have CHD (p -value interaction = 0.15). Among women who quit,

those without CHD had a more rapid reduction in SCD risk than those with CHD (p-value interaction = 0.03).

Similar findings have been observed among populations with known CHD (Vlietstra et al. 1986; Peters et al. 1995; Goldenberg et al. 2003) or with prior cardiac arrest (Hallstrom et al. 1986). For example, among 3,122 patients with previous MI or stable angina, smoking was associated with an increased risk of SCD, and those who quit smoking had a decreased risk of SCD (Goldenberg et al. 2003). Compared with never smokers (43 cases of SCD), current smokers had 2.47 times (95% CI, 1.46–4.49, 30 cases) the adjusted risk of SCD, while former smokers did not have an elevated adjusted risk (HR = 1.06; 95% CI, 0.70–1.62, 83 cases).

In a study of data from the CALIBER program in England, which uses electronic health records, there was no pattern of decreased age-adjusted risk of cardiac arrest or SCD with increasing time since smoking cessation (not shown) (Pujades-Rodriguez et al. 2015). In this study, however, current smoking also was not associated with increased hazard of this outcome compared with never smoking; the section on CHD discusses concerns about the validity of this study.

Summary of the Evidence

Several studies show that smoking cessation is associated with a reduced risk of SCD. The majority of these studies were carried out among patients with prior CHD. A large study in women found a similar association; however, among those with and without CHD, results show a quicker benefit from smoking cessation among those without known CHD. In this study, the risk of SCD returned to that of never smokers after approximately 20 years of cessation.

Smoking Cessation and Heart Failure

Heart failure results from the inability of the heart to pump sufficient blood and deliver enough oxygen to support other organs in the body. An estimated 6.5 million U.S. adults have heart failure (Benjamin et al. 2017); in 2014, heart failure was mentioned on the death certificate for one in every eight deaths (Benjamin et al. 2017; National Center for Health Statistics 2017). Approximately half of those with heart failure die within 5 years of diagnosis (Roger et al. 2004; Benjamin et al. 2017). In 2012, heart failure cost the United States an estimated \$30.7 billion in direct and indirect costs; this figure is projected to increase to \$69.8 billion by 2030 (Heidenreich et al. 2013). The prevalence of heart failure is projected to increase to

approximately 46% by 2030; thus, more than 8 million persons 18 years of age or older are expected to have heart failure in that year (Heidenreich et al. 2013).

The 1990 Surgeon General's report did not address smoking cessation and risk for heart failure. The 2004 Surgeon General's report suggested that CHD caused by smoking may contribute to heart failure and that this contribution is likely mediated by CHD (USDHHS 2004). Regardless, the pathophysiologic mechanisms underlying the development of heart failure overlap with the effects of cigarette smoking on the cardiovascular system (Suskin et al. 2001). This section briefly reviews the literature on smoking cessation and the development and prognosis of heart failure.

Ahmed and colleagues (2015) reported on the relationships in the Cardiovascular Health Study between prolonged smoking cessation (>15 years) and risk of heart failure and death among 4,482 adults 65 years of age or older who were free of heart failure at baseline. During the 13-year follow-up, former smokers had risks for incident heart failure (adjusted HR = 0.99; 95% CI, 0.85–1.16) and all-cause mortality (adjusted HR = 1.08; 95% CI, 0.96–1.20) that were similar to those of never smokers (Table 4.18). In another cohort study of older adults, both current and former smokers had elevated risk of heart failure compared with the risk among never smokers (Table 4.18) (Gopal et al. 2012).

In the Cardiovascular Health Study, compared with never smokers, former heavy smokers (≥ 32 pack-years) had a higher risk of heart failure (multivariable-adjusted HR = 1.31; 95% CI, 1.03–1.65) and mortality (multivariable-adjusted HR = 1.26; 95% CI, 1.06–1.49 [not shown in table]) (Ahmed et al. 2015). Compared with current smokers, however, former heavy smokers had a lower risk of mortality (age-, sex-, and race-adjusted HR = 0.64; 95% CI, 0.53–0.77) but not of heart failure (age-, sex-, and race-adjusted HR = 0.97; 95% CI, 0.74–1.28). Overall, this study found that after prolonged smoking cessation the risk of heart failure was similar between former smokers and never smokers, but not for former heavy smokers with cumulative consumption of 32 or more pack-years.

In the CALIBER program in England, the age-adjusted HR for heart failure decreased with increased time since smoking cessation (Table 4.18); 2 years after cessation, the age-adjusted hazard of heart failure was not elevated compared with never smokers (not shown in table) (Pujades-Rodriguez et al. 2015). In a study of 267,010 Australian men and women 45 years of age or older with self-reported smoking status that had been linked to administrative hospital data, former smokers and current smokers had a higher adjusted hazard of heart failure hospitalization compared with never smokers (Tran et al. 2015). Risks of hospitalization for heart failure decreased

Table 4.18 Observational studies on smoking cessation and heart failure (incident heart failure and heart failure-related complications)

Study	Design/population	Findings: RR (95% CI)	Comments
Suskin et al. (2001) ^a	<ul style="list-style-type: none"> • Prospective cohorts (observational analyses of two multicenter trials included in the Study of Left Ventricular Dysfunction Prevention and Intervention) • 6,704 participants with left ventricular ejection fraction <35% but no history of overt congestive heart failure, mean 60 years of age, 86% men, predominantly White but also African American and other races/ethnicities, 55% former smokers • Years of data collection: not provided • Belgium, Canada, and United States • Mean follow-up: 41 months (treatment trial) and 37 months (prevention trial) • Main outcome: total mortality 	<ul style="list-style-type: none"> • Total mortality: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (quit ≤2 years): 1.10 (0.94–1.29) – Former smoker (quit >2 years): 0.95 (0.82–1.09) – Current smoker: 1.40 (1.21–1.63) • Similar results for mortality from congestive heart failure, hospitalization for congestive heart failure, hospitalization for MI, and mortality or hospitalization because of congestive heart failure or MI 	—
Shah et al. (2010) ^a	<ul style="list-style-type: none"> • Prospective cohort (observational analyses of Survival and Ventricular Enlargement trial) • 924 patients with left ventricular dysfunction 3–16 days after MI, restricted to smokers at baseline who survived to 6 months without interim event, 82% men, 54 years of age (mean), 63% quit smoking, 85 deaths • Years of data collection: not provided • United States • Median follow-up: 42 months • Main outcome: death 	<ul style="list-style-type: none"> • Total mortality: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (months of consistent cessation^b): <ul style="list-style-type: none"> ○ 6: 0.57 (0.36–0.91) ○ 12: 0.58 (0.33–0.99) ○ 16: 0.60 (0.34–1.07) ○ 24: 0.53 (0.25–1.08) • Similar results for outcomes of death or recurrent MI and death or hospitalization for heart failure • Similar trend of decreased risk at 6 months of cessation for endpoint of death or recurrent MI, hospitalization for heart failure, or stroke 	—

Table 4.18 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Gopal et al. (2012) ^a	<ul style="list-style-type: none"> • Prospective cohort (Health, Aging, and Body Composition Study) • 2,125 participants, 70–79 years of age (mean: 73.6 years), 30% men, Whites and African Americans, 35% former smokers, all Medicare beneficiaries and without prevalent heart failure, 231 cases of heart failure • Recruited in 1997–1998 • United States • Median follow-up: 9.4 years • Outcome: heart failure 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (overall): 1.31 (0.98–1.75) – Current smoker (overall): 1.73 (1.15–2.59) • Smoking intensity (number of pack-years^c): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ 1–11: 1.05 (0.64–1.72) ○ 12–35: 1.23 (0.82–1.83) ○ >35: 1.64 (1.11–2.42) – Current smoker: <ul style="list-style-type: none"> ○ 1–11: 1.92 (0.76–4.88) ○ 12–35: 1.67 (0.89–3.15) ○ >35: 1.71 (0.97–3.01) 	—
Ahmed et al. (2015) ^a	<ul style="list-style-type: none"> • Prospective cohort (Cardiovascular Health Study) • 4,482 participants, ≥65 years of age, 40% men, multiple races/ethnicities (Whites, African Americans, others), 29% former smokers who quit >15 years earlier without prevalent heart failure, 1,204 cases of heart failure • 1989–1993 (baseline) • United States (four counties) • Follow-up: 13 years • Main outcome: heart failure 	<ul style="list-style-type: none"> • Former smokers restricted to those who had quit >15 years • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (overall): 1.07 (0.91–1.25) – Current smoker (overall): 1.19 (0.99–1.44) • Smoking intensity (number of pack-years^c): <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: <ul style="list-style-type: none"> ○ <8: 1.06 (0.83–1.36) ○ 8–15: 0.86 (0.62–1.20) ○ 16–31: 0.99 (0.77–1.28) ○ ≥32: 1.31 (1.03–1.65) • Similar results for outcome of mortality, but stronger association for current smokers: <ul style="list-style-type: none"> – 2.17 (1.91–2.47) 	—

Table 4.18 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015) ^a	<ul style="list-style-type: none"> • Prospective cohort • 1.93 million participants; ≥30 years of age; 49% men, predominantly White (also South Asian and Black), and 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD; 4,097 cases of heart failure in former smokers • 1997–2010 • England • Median follow-up: 6 years 	<ul style="list-style-type: none"> • Heart failure by smoking status (age-adjusted): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <2: 0.87 (0.60–1.26) ○ 2–9: 0.72 (0.52–0.99) ○ >10: 0.60 (0.44–0.81) 	See Table 4.17 for concerns about validity

Notes: **CALIBER** = Clinical research using LInked Bespoke studies and Electronic health Records; **CI** = confidence interval; **CVD** = cardiovascular disease; **MI** = myocardial infarction; **RR** = risk ratio.

^aMeasure(s) of association adjusted for covariate(s).

^bDuration of consistent smoking cessation after MI, compared with continuation of smoking, among those who were stable baseline smokers and survived up to that time without recurrent MI or hospitalization for heart failure.

^cPack-years = number of packs of cigarettes smoked per day multiplied by the number of years smoked cigarettes.

with increased time since quitting; the decrease was substantially different between current and former smokers after 25 or more years of cessation.

In their analyses of data from 4,850 elderly participants free of overt CHD, heart failure, and significant valvular disease in the ARIC study, Nadruz and colleagues (2016) found that, after adjusting for potential confounders, current smokers had a greater left-ventricular mass index and left-ventricular mass/volume ratio, a higher prevalence of left-ventricular hypertrophy, and worse diastolic function than never smokers. In contrast, former smokers showed echocardiographic features similar to those of never smokers.

Other researchers have assessed the relationship between smoking cessation and elevated risk of complications related to heart failure and found associations between cessation and decreased risk of hospitalization for or mortality from heart failure and other adverse events. For example, the prevention and intervention trials of the Study of Left Ventricular Dysfunction studied 6,704 persons with a left ventricular ejection fraction <0.35 with or without symptoms of congestive heart failure. Compared with never smokers (Table 4.18), former smokers had no difference in adjusted risk of overall mortality, mortality from congestive heart failure, hospitalization for congestive heart failure, hospitalization for MI, or risk of mortality or hospitalization due to congestive heart failure or MI (Suskin et al. 2001). Risks were similar in those who had stopped smoking for 2 or fewer years and those who had quit more than 2 years earlier. In contrast, continued smoking was associated with higher risk of overall mortality, hospitalization for congestive heart failure, hospitalization for MI, and mortality or hospitalization due to congestive heart failure or MI. Suskin and colleagues (2001) concluded that smoking cessation was associated with a rapid decrease in risk of morbidity and mortality among these participants. The reduction in mortality was similar in magnitude to the decrease from (a) the appropriate use of an angiotensin-converting enzyme inhibitor or beta-adrenergic blocking agents, or (b) all commonly used treatments of spironolactone among patients with reduced left ventricular systolic function and symptoms of congestive heart failure.

In the Survival and Ventricular Enlargement trial involving patients with left ventricular dysfunction after MI, 924 participants were stable smokers at baseline. Among those who survived to 6 months without a recurrent event, those who had quit for 6 months had a lower risk of death than those who continued to smoke (Table 4.18) (Shah et al. 2010). Similar patterns were observed during follow-up at 12, 16, and 24 months and for composite endpoints (death or hospitalization for heart failure; death or recurrent MI). At 6 months of cessation after an MI, there

was a similar trend toward lower risk for the combined endpoint of death, MI, hospitalization for heart failure, or stroke (adjusted HR = 0.72; 95% CI, 0.52–1.01). Earlier, in a cohort of 4,024 patients receiving dialysis, the rate of new-onset congestive heart failure (based on hospital claims data) was similar in former smokers and never smokers (Foley et al. 2003). These findings indicate the importance of smoking cessation among persons who are at elevated risk for complications related to heart failure (Suskin et al. 2001; Shah et al. 2010).

Summary of the Evidence

There is limited evidence that smoking cessation is associated with a reduced risk of incident heart failure and adverse events related to heart failure.

Smoking Cessation and Venous Thromboembolism

The term “venous thromboembolism” (VTE) refers to a blood clot that forms in a vein; an embolism occurs when the clot breaks free. The incidence of VTE in the United States has been estimated to be approximately 300,000 to 600,000 per year (Silverstein et al. 1998; White et al. 2005; Spencer et al. 2006), but these estimates are based on older data (Benjamin et al. 2017). A systematic review and meta-analysis (covering 1980–2013) found that, compared with never smoking, current smoking (RR = 1.23; 95% CI, 1.14–1.33; 15 studies) and former smoking (RR = 1.10; 95% CI, 1.03–1.17; 14 studies) are associated with an increased risk of incident VTE (Cheng et al. 2013). This study did not evaluate the association between time since smoking cessation and risk of VTE.

Summary of the Evidence

A meta-analysis showed that current and former cigarette smokers have an increased risk of VTE when compared with never smokers, and the RR for former smokers is lower than that for current smokers. There is no evidence available on how the risk of VTE changes with time since cessation.

Smoking Cessation and Lower-Extremity Peripheral Artery Disease

Peripheral artery disease (PAD) results from the narrowing (usually due to atherosclerosis) of the peripheral arteries leading to the legs, abdominal organs, arms, and head. This disorder most commonly affects the arteries

of the legs. The presence of PAD of the lower limbs can be detected by measuring the ABI, which is the ratio of blood pressure in the lower leg to that in the upper arm (as discussed in the earlier section on smoking cessation and subclinical atherosclerosis). Importantly, a low ABI does not indicate which blood vessels are narrowed or blocked. Approximately 8.5 million people in the U.S. have PAD (CDC 2016a). One symptom of PAD is intermittent claudication, or leg cramping induced by exercise (also known as classic claudication). An estimated 10% of persons with PAD have intermittent claudication, approximately 40% have no leg pain, and 50% have other leg symptoms (Hirsch et al. 2001; Benjamin et al. 2017). PAD leads to impaired function and reduces quality of life. Further, PAD is a systemic atherosclerotic disease, and is therefore a risk factor for poor clinical outcomes, including CHD and stroke (Heald et al. 2006; Benjamin et al. 2017).

The 1983 Surgeon General's report concluded that cigarette smoking is the most powerful risk factor predisposing men and women to atherosclerotic peripheral vascular disease (USDHHS 1983). According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and atherosclerosis (USDHHS 2004), as discussed earlier in this section. The 2004 Surgeon General's report concluded that "the new findings on subclinical disease indicate the potential for preventing more advanced and clinically symptomatic disease through quitting smoking and maintained cessation" (USDHHS 2004, p. 379).

The 1990 Surgeon General's report discussed results from two small studies comparing the risk of PAD between smokers and former smokers, finding that former smokers had a 50–58% lower risk of PAD than current smokers (Hughson et al. 1978; Jacobsen et al. 1984). Several studies of persons with PAD found that those who quit smoking had improved performance and overall survival. Since 1990, the literature on this topic has grown substantially, as reviewed in the next two sections.

A meta-analysis conducted by Lu and colleagues (2014) quantified the association between active smoking and PAD. This meta-analysis, which was restricted to studies examining the risk of developing PAD, defined PAD on the basis of an ABI ≤ 0.90 , a claudication questionnaire, or peripheral angiography. Although the risk of PAD was lower for former smokers than for current smokers, the risk of PAD in both groups was still significantly higher than that for never smokers. Compared with nonsmokers, current smokers had 2.71 times the pooled odds of PAD (95% CI, 2.28–3.21). As shown in Figure 4.3, there were 40 estimates in this meta-analysis (Lu et al. 2014) of the risk of PAD gathered from 29 studies of former smokers compared with never smokers. Of the 40 estimates,

29 (72.5%) were statistically significant, and the pooled OR comparing former with never smokers was 1.67 (95% CI, 1.54–1.81). This estimate included studies of the general population, as well as studies of persons with underlying diseases, such as diabetes mellitus.

Lu and colleagues (2014) identified two studies (Törnwall et al. 2000; Cui et al. 2006) that compared risk of PAD between former and current smokers and found a reduced risk of PAD among former smokers. In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, among a cohort of 26,872 male smokers who were 50–69 years of age at entry, the HR of PAD during a median follow-up of 4 years in former smokers was 0.86 (95% CI, 0.75–0.99) compared with the HR among current smokers (Törnwall et al. 2000). As this study did not include never smokers, its results were not included in the pooled estimate reported by Lu and colleagues (2014). In the report by Cui and colleagues (2006) on a cross-sectional study of 1,215 elderly Japanese men, those authors found that, compared with current smokers, there was no significant difference in the odds of PAD (ABI < 0.90) after less than 10 years of smoking cessation (OR = 0.8; 95% CI, 0.4–1.8) or after 10–19 years of cessation (OR = 1.0; 95% CI, 0.4–2.2) (Cui et al. 2006). The risk of PAD was reduced, however, among those who had quit smoking for 20 or more years (OR = 0.3; 95% CI, 0.1–0.9).

The meta-analysis by Lu and colleagues (2014) focused on publications that reported ORs or RRs, and it treated RRs as ORs. Several other key articles on this topic that were not included in the meta-analysis—because of a restriction or publication after the literature search or for another reason—are described below.

Fowkes and colleagues (1992) reported that lifetime cumulative cigarette smoking was strongly related to risk of PAD, with additional risks among current and former smokers abstinent less than 5 years. Elsewhere, in a cohort of Icelandic men, when compared with never smoking, former smoking was associated with having 3.5 times the odds of prevalent intermittent claudication and 2.3 times the odds of incident intermittent claudication during follow-up from 1968 to 1986; neither of these ORs was significant (Ingolfsson et al. 1994). Among smokers, those who smoked 15 or more cigarettes per day had a higher risk of incident intermittent claudication. In a later study, Foley and colleagues (2003) reported that in a cohort of 4,024 patients receiving dialysis, former smokers had an adjusted rate of peripheral vascular disease similar to that of lifelong nonsmokers. In a prospective cohort study of 39,825 initially healthy women from the Women's Health Study, Conen and colleagues (2011) reported that smoking cessation substantially reduced the risk of symptomatic PAD, but former smokers still had an excess risk of PAD compared with never smokers. Compared with

Figure 4.3 Comparison of risk of peripheral arterial disease between former and never smokers

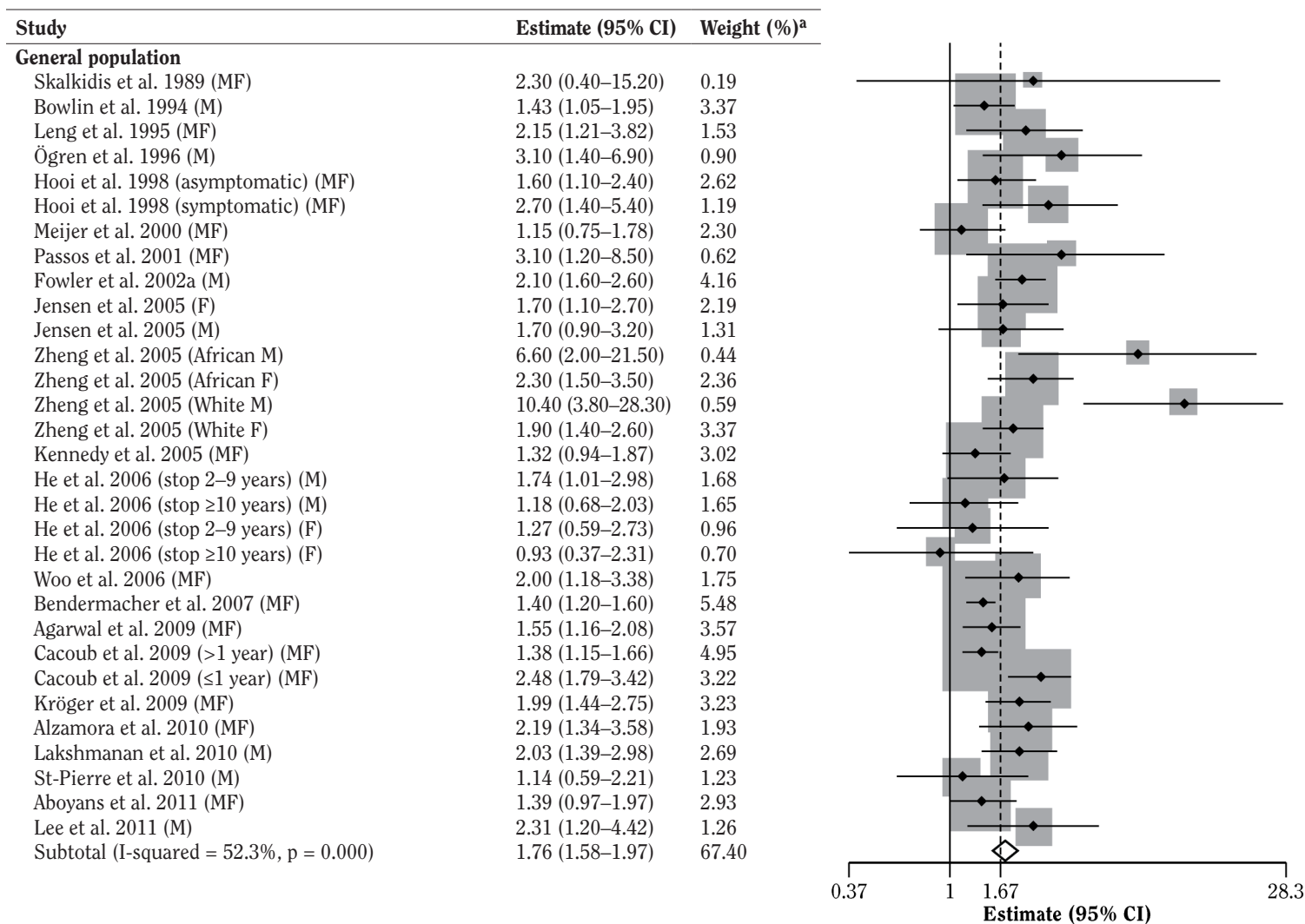
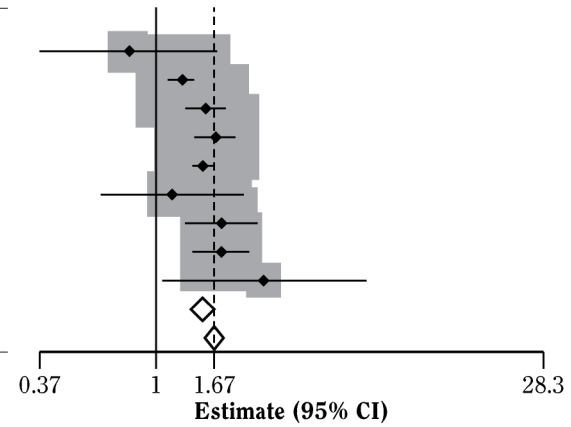


Figure 4.3 Continued

Study	Estimate (95% CI)	Weight (%) ^a
Disease study population		
Adler et al. 2002 (DM) (MF)	0.80 (0.37–1.72)	0.95
O'Hare et al. 2002 (hemodialysis) (wave 3, 4) (MF)	1.27 (1.13–1.42)	5.85
O'Hare et al. 2002 (hemodialysis) (wave 1) (MF)	1.55 (1.31–1.83)	5.17
Rajagopalan et al. 2006 (<1 year) (hemodialysis) (MF)	1.68 (1.41–2.01)	5.03
Rajagopalan et al. 2006 (>1 year) (hemodialysis) (MF)	1.51 (1.38–1.65)	6.13
Norman et al. 2006 (DM) (MF)	1.16 (0.62–2.15)	1.36
Li et al. 2007 (DM) (MF)	1.79 (1.30–2.46)	3.27
Luo et al. 2007 (HT) (MF)	1.79 (1.40–2.29)	4.10
Tavintharan et al. 2009 (DM) (MF)	2.55 (1.05–6.20)	0.74
Subtotal (I-squared = 54.0%, p = 0.026)	1.52 (1.36–1.69)	32.60
Overall (I-squared = 54.7%, p = 0.000)	1.67 (1.54–1.81)	100.00



Source: Lu et al. (2014), with permission.

Note: **CI** = confidence interval; **DM** = diabetes mellitus; **F** = females; **HT** = hypertension; **M** = males; **MF** = males and females.

^aWeights are from random effects analysis.

current smokers, the adjusted HR of symptomatic PAD among former smokers was 0.39 (95% CI, 0.24–0.66) for less than 10 years of cessation, 0.28 (95% CI, 0.17–0.46) for 10–20 years of cessation, and 0.16 (0.10–0.26) for more than 20 years of cessation. Compared with never smokers, the adjusted HR of symptomatic PAD among former smokers was 3.16 (95% CI, 2.04–4.89).

In the CALIBER program, the age-adjusted HR of PAD decreased substantially with increased time since smoking cessation (Pujades-Rodriguez et al. 2015). Compared with current smokers, former smokers who had quit for more than 10 years had an age-adjusted HR for PAD of 0.27 (95% CI, 0.22–0.33). Compared with women who had never smoked, however, the age-adjusted hazard of PAD was still elevated significantly in women who had quit smoking for 10 or more years (HR = 1.36; 95% CI, 1.11–1.67).

Smoking has also been associated with other forms of PAD, such as Raynaud's disease or syndrome, which is a form of functional PAD that begins with severe vasoconstriction followed by dilatation (widening of the blood vessels) not due to blockage. Various studies have associated current smoking with Raynaud's, with a stronger association evident in men than in women. In the Framingham Offspring cohort, former smokers did not have an elevated risk of Raynaud's compared with never smokers (Brand et al. 1997; Suter et al. 2007). Smoking cessation is recommended for persons with Raynaud's, because the vasoconstrictive substances in cigarettes likely make the condition worse (Pope 2007). The IARC's (2007) review on smoking cessation found consistent evidence from a number of small case series that smoking cessation was associated with improved thromboangiitis obliterans (Buerger's disease), which is an inflammatory, obliterative disease that affects small- and medium-sized arteries, is unrelated to atherosclerosis, and is specific to smokers. Later, Klein-Weigel and colleagues (2016) concluded that smoking cessation is the most important intervention among patients with Buerger's disease.

Prognosis of PAD

In addition to its association with the onset of PAD, smoking or the continuation of smoking after a PAD diagnosis is a major risk factor for the progression of PAD and PAD-related outcomes (Jonason and Ringqvist 1985; Ameli et al. 1989; Wiseman et al. 1989; Selvarajah et al. 2014). Correspondingly, current clinical guidelines recommend smoking cessation among patients with PAD (Olin et al. 2010; Rooke et al. 2011; Smith Jr et al. 2011; Tendra et al. 2011; Gerhard-Herman et al. 2017).

A systematic review that assessed the effects of clinical interventions for persons with chronic PAD (based on literature searched through 2005) concluded that

smoking cessation combined with exercise may increase walking distance (Cassar and Bachoo 2006). This conclusion was based on a randomized controlled study that assessed the impact of a “stop smoking and keep walking” intervention compared with usual care among 882 Australian men 65–79 years of age who had early PAD (Fowler et al. 2002b). Specifically, the intervention combined a community-based intervention of smoking cessation (where applicable) with increased physical activity. At 12 months, a higher proportion of men in the intervention group had an improved maximum walking distance compared with those in the usual-care group (23% vs. 15%, $p = 0.008$). In addition, compared with the control group, more men in the intervention group reported walking more than three times per week for recreation (34% vs. 25%, $p = 0.01$). Also, although the finding was not statistically significant, more men in the intervention group had stopped smoking (12% vs. 8%, $p = 0.43$).

A systematic review of smoking cessation and prognosis for PAD based on a 1996 search (Girolami et al. 1999) summarized some of the findings reported in the 1990 Surgeon General's report (USDHHS 1990). Most of the findings showed that smoking cessation was associated with favorable outcomes. A study of 415 smokers with intermittent claudication and an ABI <0.9, however, found no difference in deterioration of the ABI at 1 year between current smokers and former smokers (Smith et al. 1996). Of note, this analysis adjusted only for diabetes status; former smokers were more likely than current smokers to have diabetes.

In a registry of 467 stable outpatients who smoked and had symptomatic PAD, those who quit smoking had, during a mean follow-up of 14 months, a nonadjusted relative risk of death of 1.83 (95% CI, 0.65–5.15) compared with continuing smokers (Álvarez et al. 2013). This study was limited by the small number of events, however, making it challenging to draw conclusions. In an earlier study, among 138 patients with peripheral arterial occlusive disease, a subgroup of 38 patients who had smoked an average of 1.5 packs of cigarettes per day for more than 42 years had more severe claudication pain, lower oxygen uptake at peak exercise, and a higher oximeter electrode power than a subgroup of 100 patients who had quit smoking for an average of 7 years (Gardner 1996). Results were similar after adjusting for baseline ABI. In a later study of 204 patients with claudication or critical limb ischemia who had undergone lower-extremity angiography, smoking cessation was associated with a lower 5-year adjusted HR of mortality (HR = 0.33; 95% CI, 0.13–0.80) and improved amputation-free survival (HR = 0.40; 95% CI, 0.19–0.83) compared with those who continued to smoke (Armstrong et al. 2014). Nonsignificant HRs were observed in this study for MI, stroke, and major

amputation (there were few cases of these outcomes); a nonsignificant HR in the opposite direction was observed for major adverse limb events.

Summary of the Evidence

There is evidence that former cigarette smokers have a lower risk of incident PAD than current smokers and that the risk of PAD decreases with increased time since smoking cessation. Compared with never smokers, former smokers typically have an increased risk of PAD. Despite few large prospective cohort studies assessing these associations, evidence suggests that smoking cessation is associated with improved prognosis among persons with PAD.

Smoking Cessation and Abdominal Aortic Aneurysm

An aortic aneurysm is a ballooning or bulging area on the aorta wall, which can lead to rupture or dissection (a split between the layers of the wall of the aorta, thus trapping blood) (American Heart Association 2017). The prevalence of abdominal aortic aneurysms (AAAs) extending 2.9–4.9 centimeters (cm) among men has been estimated to be 1.3% in those 45–54 years of age and 12.5% in those 75–85 years of age; the prevalence among women has been estimated at 0% (45–54 years of age) and 5.2% (75–85 years of age) (Hirsch et al. 2006). These estimates, however, came predominantly from cohorts of White men and women. Ruptures in patients with AAA are more common in current smokers (a doubling of risk) and among women (almost four times the risk) (Sweeting et al. 2012).

According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and AAA (USDHHS 2004). That report stated that “smoking is one of the few currently avoidable causes of this frequently fatal disease” (p. 397). According to the 1990 Surgeon General's report (USDHHS 1990), former smokers have a reduced risk of death from aortic aneurysm compared with current smokers, but the report noted that more detailed analyses by duration of smoking abstinence are needed. The 1990 report did not provide any formal conclusions about smoking cessation and AAA.

The 1990 report discussed results from five prospective cohort studies that compared risk of death from AAA between former smokers and current smokers. Overall, in men there was a consistent pattern of a reduced risk of death from AAA among former smokers compared with current smokers. At the time, evidence was more limited in women. Since publication of the 1990 report, many

additional studies have been published on this topic, as summarized below and in Table 4.19.

In 1999, a literature review concluded that smoking was strongly associated with AAA (Blanchard 1999). Some of the studies in this review examined associations with this outcome between former smokers and never smokers. For example, during 40 years of follow-up of the British Doctors' Study, the rate of death from non-syphilitic AAA (standardized for age and calendar period) was more than four times as high among current smokers and more than twice as high among former smokers as among never smokers (CIs not provided) (Doll et al. 1994). In the Cardiovascular Health Study of older Americans, the prevalence of AAA was 6.8% for never smokers, 11.5% for former smokers, and 14.4% for current smokers (Alcorn et al. 1996).

Several observational studies published in 1997 or later have assessed the relationship between smoking cessation and the incidence or prevalence of AAA. Overall, the evidence suggests that smoking cessation is associated with a decreased risk of AAA (Lederle et al. 1997, 2000, 2003; Wilmink et al. 1999; Singh et al. 2001; Wong et al. 2007; Forsdahl et al. 2009; Kent et al. 2010; Stackelberg et al. 2014; Tang et al. 2016). Even so, compared with never smokers, former smokers tend to have an increased risk of AAA that can persist for decades after quitting (Wong et al. 2007).

Findings from observational studies on cessation and AAA are summarized in Table 4.19. For example, in two cohorts of veterans undergoing screening in the Aneurysm Detection and Management study, the OR for AAA (diameter ≥ 4.0 cm) among former smokers compared with current smokers was 0.73 (95% CI, 0.66–0.82) for every 10 years of smoking cessation (Lederle et al. 1997, 2000). In addition, after accounting for number of years smoked, risk of AAA was higher in current smokers than in former smokers (Table 4.19). In a later study, in a large cohort of patients who underwent ultrasound screening for AAA, former smokers had a lower prevalence of AAA than current smokers, and risk decreased as duration of cessation increased from less than 5 years to more than 10 years (Kent et al. 2010). Similar patterns of decreasing risk as duration of cessation increased were observed in other studies (Wong et al. 2007; Stackelberg et al. 2014; Tang et al. 2016).

According to data from 2002 from CPS II that was reported in the 2004 Surgeon General's report, mortality attributable to AAA was significantly higher among men and women who were current smokers compared with never smokers (USDHHS 2004). Risk of mortality due to AAA was lower in former smokers than in current smokers but was higher in former smokers than in never smokers. Pujades-Rodriguez and colleagues (2015), in their analysis of data from the CALIBER program, reported that the age-adjusted HR of AAA tended to decrease with increased

Table 4.19 Observational studies on smoking cessation and abdominal aortic aneurysm

Study	Design/population	Findings: RR (95% CI)	Comments
Lederle et al. (1997, 2000) ^a	<ul style="list-style-type: none"> • Cross-sectional analyses (Aneurysm Detection and Management) • Two cohorts of veterans, 50–79 years of age, 97% men, 87% White (also African American and other races/ethnicities), no history of AAA • Sample sizes and number of AAAs (≥ 3.0 cm): <ul style="list-style-type: none"> – Cohort 1: n = 73,451; 3,366 AAAs – Cohort 2: n = 52,745; 1,917 AAAs • Screened in 1992–95 and 1995–97, respectively • United States 	<ul style="list-style-type: none"> • Cohort 1: <ul style="list-style-type: none"> – AAA 3.0–3.9 cm diameter <ul style="list-style-type: none"> ◦ Current smoker: 1.00 (referent) ◦ Former smoker (per 10 years since quitting): 0.81 (0.76–0.86) – AAA ≥ 4.0 cm diameter <ul style="list-style-type: none"> ◦ Current smoker: 1.00 (referent) ◦ Former smoker (per 10 years since quitting): 0.72 (0.65–0.79) • Cohort 2: similar findings 	—
Wilmink et al. (1999) ^a	<ul style="list-style-type: none"> • Nested case-control study • Men, >50 years of age, 210 cases of AAA (>29 cm) from AAA screening study, 237 age-matched controls, 64% of cases and 63% of controls were former smokers • Years of data collection: not provided • Huntingdon, United Kingdom 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 4.0 (1.7–9.5) – Current smoker: 9.0 (3.4–24.0) – Similar results when reclassified based on cotinine level • Years since quitting: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker <ul style="list-style-type: none"> ◦ 1–5: 0.62 (0.2–1.7) ◦ 6–10: 0.47 (0.2–1.3) ◦ 11–20: 0.61 (0.3–1.3) ◦ 21–30: 0.28 (0.1–0.7) ◦ ≥ 30 years: 0.20 (0.1–0.4) – When also adjusted for duration of smoking, results trended toward weaker associations 	Adjusting for duration of smoking in the time-since-quitting analysis might lead to overadjustment (results not shown)
Lederle et al. (2003)	<ul style="list-style-type: none"> • Prospective cohort (Cancer Prevention Study II) • 508,351 participants; >30 years of age; tended to be White, married, and educated; 1,296 deaths from AAA • Participants were screened between October 1992 and March 1995 • United States (all 50 states) • Follow-up: 14 years 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 2.4 – Current smoker: 6.0 	Unpublished data presented in systematic review; 95% CIs not provided; adjusted for age and potentially other factors

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Wong et al. (2007) ^a	<ul style="list-style-type: none"> • Prospective cohort (Health Professionals Follow-Up Study) • 39,352 men, 40–75 years of age at baseline, 10% current smokers at baseline, healthy (no prior CVD), excluded nondrinkers who had quit in prior 10 years, 376 cases of AAA • 1986–2002 • United States 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <10: 6.5 (4.5–9.3) ○ ≥10: 2.5 (1.8–9.3) – Current smoker (number of cigarettes smoked per day): <ul style="list-style-type: none"> ○ 1–4: 1.8 (0.4–7.4) ○ 5–14: 5.9 (3.0–11.4) ○ 15–24: 14.2 (9.4–21.5) ○ ≥25: 15.2 (9.9–23.3) 	—
Forsdahl et al. (2009) ^a	<ul style="list-style-type: none"> • Prospective cohort study (Tromsø) • 4,345 participants, 25–82 years of age at baseline, 59.5 years of age (mean), 37% former smokers, no AAA or unknown AAA status, 119 incident cases of AAA • 1994–2001 • Norway 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <10: 2.88 (1.23–6.75) ○ 10–19: 2.90 (1.25–6.72) ○ ≥20: 1.26 (0.54–2.96) – Current smoker (number of cigarettes smoked per day): <ul style="list-style-type: none"> ○ <10: 6.19 (2.86–13.38) ○ 10–19: 9.78 (4.89–19.58) ○ ≥20: 13.72 (6.12–30.78) 	Logistic regression used; cross-sectional analyses (Singh et al. 2001) found smoking was a risk factor for prevalence of AAA
Kent et al. (2010) ^a	<ul style="list-style-type: none"> • Cross-sectional analysis (prevalence in cohort, Life Line Screening database) • 3.1 million participants without prior repair of AAA, <85 years of age, 63.1 years of age (mean), 35% men, 87% White (also Hispanic, African American, Native American, and Asian), and 23,446 with AAA (≥3 cm) • Screened in 2003–2008 • United States 	<ul style="list-style-type: none"> • Smoking status: <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ○ <5: 0.87 (0.84–0.912) ○ 5–10: 0.68 (0.65–0.71) ○ >10: 0.42 (0.41–0.43) 	—

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015)	<ul style="list-style-type: none"> • Prospective cohort • 1.93 million participants, ≥ 30 years of age, 49% men, predominantly White (also South Asian and Black), 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records), no history of CVD, 1,238 cases of AAA in former smokers • 1997–2010 • England • Median follow-up: 6 years 	<ul style="list-style-type: none"> • AAA by smoking status (age-adjusted): <ul style="list-style-type: none"> – Current smoker: 1.00 (referent) – Former smoker (years since quitting): <ul style="list-style-type: none"> ◦ <2: 0.84 (0.47–1.51) ◦ 2–9: 0.78 (0.52–1.17) ◦ >10: 0.25 (0.20–0.32) 	See Table 4.17 for concerns about validity
Stackelberg et al. (2014) ^a	<ul style="list-style-type: none"> • Two prospective cohorts (Cohort of Swedish Men and Swedish Mammography Cohort) • Participants 46–84 years of age, 37% of men were former smokers, 25% of women were former smokers, no known diagnosis of AAA or cancer (other than nonmelanoma skin cancer) • Sample sizes and number of AAAs by cohort: <ul style="list-style-type: none"> – Cohort of Swedish Men: 42,596, 958 AAA – Swedish Mammography Cohort: 35,550, 199 AAA • 1998–2011 • Sweden • Mean follow-up: 12.7 years 	<ul style="list-style-type: none"> • Men: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (<20 years since quitting): 3.77 (3.08–4.63) – Former smoker (≥ 20 years since quitting): 1.61 (1.27–2.03) – Current smoker (<20 pack-years): 3.06 (2.37–3.95) – Current smoker (≥ 20 pack-years): 6.55 (5.36–7.99) • Women: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker (<20 years since quitting): 4.63 (3.04–7.06) – Former smoker (≥ 20 years since quitting): 0.82 (0.35–1.92) – Current smoker (<20 pack-years): 7.01 (4.63–10.62) – Current smoker (≥ 20 pack-years): 6.55 (5.36–7.99) 	Less power to detect associations in women (199 cases) than in men (958 cases)

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Tang et al. (2016) ^a	<ul style="list-style-type: none"> • Prospective cohort (Atherosclerosis Risk in Communities Study) • 26% former smokers • 15,703 participants, 45–64 years of age at baseline, 45% men, 26% former smokers at baseline, African Americans (27%) and Whites, no prior repair of AAA, excluded uncertain AAA status during follow-up, 590 incident clinical AAAs, 5,578 participants underwent ultrasound screening from 2011 to 2013 (identified 75 asymptomatic AAAs) • 1987–2011 • United States • Median follow-up: 22.5 years 	<ul style="list-style-type: none"> • Incident clinical AAAs: <ul style="list-style-type: none"> – Baseline smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Former smoker: 2.45 (1.85–3.25) ○ Current smoker: 7.59 (5.78–10.0) – Longitudinal smoking status: <ul style="list-style-type: none"> ○ Never smoker: 1.00 (referent) ○ Quit before first visit: 1.83 (1.19–2.81) ○ Recent quitter^b: 3.50 (1.53–8.04) ○ Continuous smoker: 6.41 (3.67–11.2) • Similar pattern of associations with prevalent asymptomatic AAAs detected in 2011–2013 subgroup 	—

Notes: **AAA** = abdominal aortic aneurysm; **CALIBER** = Clinical research using Linked Bespoke studies and Electronic health Records; **CI** = confidence interval; **cm** = centimeter; **RR** = risk ratio.

^aMeasure(s) of association adjusted for covariate(s).

^bRecent quitter defined as someone who had quit for at least 3–8 years after the first visit in 1987.

time since smoking cessation (Table 4.19). Even so, in a comparison restricted to men and using never smokers as the referent, the age-adjusted hazard of AAA was still elevated in those who had quit smoking for 10 or more years (HR = 1.47, 95% CI, 1.10–1.95).

Prognosis of AAA

In the Aneurysm Detection and Management study, Bhak and colleagues (2015) assessed 534 veterans for the clinical risk factors associated with the expansion rate of AAA (i.e., the rate at which the AAA widens). The expansion rate of AAA is important to monitor, because (1) the risk of an AAA rupture is proportional to the maximum diameter of the AAA and (2) the mortality rate for rupture is high in those with aneurysms greater than 4–5 cm in diameter (Hirsch et al. 2006). Current smokers had an aortic expansion rate 0.05 cm/year greater (95% CI, 0.2–0.8) than former smokers—a 19% increase (Bhak et al. 2015).

Bhak and colleagues (2015) performed a pooled analysis of individual-level data from 12 studies. In one of the 12 studies, Sweeting and colleagues (2012) found that, compared with former and never smoking, current smoking increased the growth rate of AAA by 0.35 mm/year, and the rupture rate was twice as high in men and women who were current smokers as it was in nonsmokers. In another of the 12 studies (Brady et al. 2004), among 1,743 patients in the United Kingdom Small Aneurysm Trial, the growth rate of AAA was 0.42 mm/year higher in current smokers than in former smokers (95% CI, 0.17–0.68). There was no difference in the growth rate of AAA between former and never cigarette smokers. Using this same study population, Brown and Powell (1999) found that the adjusted hazard of AAA rupture was lower in former smokers (HR = 0.59; 95% CI, 0.39–0.89) than in current smokers. Other researchers have also found that smoking or a history of smoking is associated with an increased growth rate in AAA (Chang et al. 1997; Lindholt et al. 2001).

Koole and colleagues (2012) assessed the relationships between smoking status and outcomes of endovascular aneurysm repair among 8,638 patients (2,406 former smokers) in the European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair study. Compared with never smokers, former and current smokers were more likely to need percutaneous transluminal angioplasty procedures or stents at the time of surgery (10.5%, 11.8%, and 13.7%, respectively). Regarding late complications, however, current smokers and former smokers had fewer endoleaks than never smokers. Current cigarette smokers (adjusted HR = 1.45; 95% CI, 1.03–2.05) and former smokers (adjusted HR = 1.23; 95% CI, 0.87–1.72) were more likely than never smokers to have migration of the stent graft.

Summary of the Evidence

Substantial evidence suggests that former smokers have a lower risk of incident AAA than current smokers and that risk decreases with increasing time since smoking cessation. Compared with never smokers, former smokers have an increased risk of AAA that can persist for decades. The evidence also suggests that the diameter of AAA expands at a lower rate in former smokers compared with current smokers.

Summary of the Evidence

This section builds on the 1990 (USDHHS 1990) and subsequent Surgeon General's reports (USDHHS 2001, 2004, 2006, 2010, 2014), providing an updated and overarching summary of what is now known about the relationships between smoking cessation and CVD outcomes. Previous Surgeon General's reports concluded that smoking cessation reduces the risk of CHD, PAD, ischemic stroke, SAH, and, more broadly, CVD morbidity and mortality (Table 4.10). These past reports also concluded that smoking cessation reduces risk of recurrent MI or CVD death among persons with CHD and improves exercise tolerance, reduces risk of amputation, and improves overall survival among patients with PAD. In particular, the 2001 Surgeon General's report concluded that smoking cessation appears to slow the rate of progression of carotid atherosclerosis in women and is associated with improvements in symptoms, prognosis, and survival among women with peripheral vascular atherosclerosis (USDHHS 2001). The evidence presented in this report shows that smoking cessation benefits persons at any age, reducing relative risk of CVD for smokers and the burden of disease from cardiovascular causes.

This section summarizes the large body of evidence related to the benefits of smoking cessation for reducing risk of CVD outcomes, considering evidence from mechanistic, epidemiologic, and clinical studies and applying established guidelines for causal inference (consistency; strength of association; temporality; specificity; experiment and biologic gradient; and coherence, plausibility, and analogy). Previous reports (U.S. Department of Health, Education, and Welfare [USDHEW] 1964; USDHHS 2004) have described this approach to causal inference. The approach is used here to systematically develop the basis for causal conclusions. As described in the 2004 Surgeon General's report, rather than serving as a checklist for assessing causal inference, these causal criteria are used to integrate multiple lines of evidence (USDHHS 2004).

Evaluation of the Evidence

Consistency

The relationships between smoking status and cessation with most of the outcomes described here have been extensively studied in well-designed and adequately powered studies (using observational and experimental designs) across different populations and time periods. Multiple studies have found that smoking cessation is associated with reduction in inflammatory markers and hypercoagulability and with rapid improvement in levels of HDL-C. Several, but not all, studies have found an association between smoking cessation and improved endothelial function. Much evidence documents the fact that former cigarette smokers tend to have less extensive subclinical atherosclerosis than current smokers and that smoking cessation is followed by slower progression of atherosclerosis, particularly for the outcomes of carotid IMT and ABI.

Many studies have also found that, compared with current smokers, former smokers have a lower risk of incident CVD, CHD, stroke, and AAA and that the risks decrease with increasing time since cessation. Studies support similar associations between smoking cessation and outcomes related to AF, SCD, heart failure, VTE, and PAD, although the evidence is more limited with regard to reduced risk with increased time since cessation. Additionally, smoking cessation is consistently associated with reduced risk of recurrent infarction and CVD death among patients with CHD (USDHHS 1990). Similarly, for persons who have already had a stroke, cessation reduces risk for recurrent events. Studies have also found that among patients with PAD, morbidity and mortality are lower in former smokers than in current smokers; in addition, the expansion rate of AAA is lower in former smokers than in current smokers.

Strength of Association

For many CVD outcomes, there is consistent evidence of a substantial reduction in risk among former smokers compared with current smokers; after a certain amount of time has elapsed since cessation, the risk for some outcomes among former smokers even approaches that of never smokers. For example, research estimates that the excess risk of CHD decreases by half approximately 4–5 years after cessation, albeit with substantial variation in estimates among studies, and then gradually approaches the risk of never smokers. For stroke, a similar pattern has been observed, although the risk may not reach that of never smokers. Smoking is strongly related to the risk of AAA; former smokers (particularly those who have quit for long periods) tend to have a substantially lower

risk than those who continue to smoke. For example, in adjusted analyses in the ARIC study, compared with never smokers, current smokers had 6.41 times the risk of a clinical AAA (95% CI, 3.67–11.2); recent quitters (who had quit for at least 3–8 years) had 3.50 times the risk (95% CI, 1.53–8.04); and longer term quitters had 1.83 times the risk (95% CI, 1.19–2.81) (Tang et al. 2016).

Temporality

Many of the studies reviewed here are prospective in nature, and thus smoking status or smoking cessation was measured before the incident outcome. For measurements of biomarkers, several studies assessed changes in these biomarkers after cessation; similar analyses have been carried out for markers of subclinical atherosclerosis. Although some studies are cross-sectional in nature, prospective cohort studies have been carried out for each of the main outcomes discussed, thereby ensuring that smoking cessation preceded the occurrence of the health outcomes. The potential for reverse causality has also been accounted for in these studies to diminish the potential for such bias.

Specificity

In line with observations of reduced risk of overall CVD morbidity or mortality among former smokers compared with current smokers, similar reductions were observed for major causes of CVD morbidity and mortality, such as CHD and stroke and many other subtypes of CVD.

Experiment and Biologic Gradient

Both smoking cessation and time since cessation serve as naturally occurring changes in exposure status that can be used to infer the effect of the intervention of stopping smoking. The temporal pattern of declining risk after smoking cessation is strong evidence for a causal benefit of quitting and reflects a waning of the processes of injury caused by smoking. For most of the CVD outcomes reviewed in this report, most cited studies found a reduction in risk after cessation, followed by a pattern of a continued decrease in risk with longer time since cessation. In parallel, studies using biomarkers found greater reductions in inflammatory markers and hypercoagulability with increasing time since cessation. Evidence from observational studies and clinical trials supports a rapid (within weeks) improvement in levels of HDL-C after cessation, with no clear pattern of change after that time (Forey et al. 2013). Complementary evidence comes from studies showing greater reduction in risk with longer time since cessation for outcomes of incident CVD, congestive heart failure, stroke, and AAA. For the outcomes of incident AF, SCD, heart failure, VTE, and PAD, there

is less evidence available on how risk of these outcomes changes with time since cessation, although the available evidence supports a decrease in risk with increased time since cessation for SCD (Sandhu et al. 2012), heart failure (Pujades-Rodriguez et al. 2015), and PAD (Cui et al. 2006; Conen et al. 2011; Pujades-Rodriguez et al. 2015).

The 1990 Surgeon General's report estimated that excess risk of CHD is reduced by about half after 1 year of smoking cessation and that risk of CHD is similar among former and never smokers after 15 years of smoking cessation (USDHHS 1990). Similarly, the 2001 Surgeon General's report concluded that there is a substantial reduction in risk of CHD among women within 1–2 years of cessation; such a reduction in risk gradually continued to reach that of nonsmokers 10–15 or more years after cessation (USDHHS 2001). More recent analyses using an exponential distribution to quantitatively estimate how rapidly CHD risk decreases after smoking cessation indicate that the excess risk of CHD associated with smoking decreases by 50% about 4.4 years after cessation (95% CI, 3.26–5.95) (Lee et al. 2012). The risk then decreases asymptotically toward the risk among never smokers, as was also reported by the IARC (2007). Another model suggests a rapid decline in risk of acute MI soon after cessation, followed by a slower decline to a risk close to that of never smokers (Hurley 2005).

Similarly, the 1990 Surgeon General's report concluded that after smoking cessation, the risk of stroke returns to that of never smokers within 5–15 years (USDHHS 1990). The 2001 Surgeon General's report modified this conclusion slightly, stating that in most studies, including studies of women, the increased risk of stroke associated with smoking is reversible after cessation, with this risk approaching that of never smokers after 5–15 years of cessation. Another modeling study by Lee and colleagues (2014) estimated that the excess risk of stroke associated with smoking decreases by 50% after 4.78 years (95% CI, 2.17–10.50), but there was considerable unexplained heterogeneity. The modeling study by Hurley (2005) reported a rapid decrease in risk of stroke shortly after cessation (within 1–2 years), followed by a slower decline; the decline in risk of stroke was not as rapid as the decline in risk of acute MI following cessation, and the risk of stroke was estimated to remain elevated even among long-time former smokers. Evidence also supports a reduction in risk of mortality and of subsequent CVD events among patients with CHD who quit smoking after an index CHD event compared with those who continue to smoke (Wilson et al. 2000; Critchley and Capewell 2003; Twardella et al. 2004, 2006; Shah et al. 2010; Breitling et al. 2011a) (Table 4.20). Studies of the impact of counseling on smoking cessation have also found reduced risk of all-cause mortality among patients who received or

were randomized to receive such counseling (Mohiuddin et al. 2007; Van Spall et al. 2007; Buchholz et al. 2017).

Coherence, Plausibility, and Analogy

Evidence linking smoking cessation to reduced risk of CVD should be considered within the broader context of mechanistic research on smoking and CVD. Previous reports concluded that smoking initiates several pathogenetic mechanisms that underlie the development of CVD (USDHHS 2004, 2010, 2014). The 1990 and 2001 Surgeon General's reports and the present updated review have provided evidence of how smoking cessation can reverse or slow these pathogenetic processes (USDHHS 1990) and slow the progression of subclinical atherosclerosis (USDHHS 2001).

Previous reports have also concluded that smoking causes CVD, including subclinical atherosclerosis, CHD, stroke, and AAA (USDHHS 2004). Much evidence supports a dose-response relationship between pack-years of smoking and risk of CVD. Evidence from the present report and previous reports supports the benefits of smoking cessation in terms of reducing risk of CVD. Multiple studies have found a larger relative benefit of cessation among those who quit smoking at younger ages (compared with those who quit later in life), which also aligns with research on the dose-response relationship between smoking and risk of CVD (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013; Thun et al. 2013a). However, given the increasing rates of the various CVDs with increasing age, substantial absolute reductions in the number of CVD events and deaths can still be made by quitting smoking at older ages.

Synthesis of the Evidence

The conclusions presented below are based on interpretations of multiple lines of evidence from a framework built around the guidelines for causal inference. Generally, when the evidence (a) is strong and consistent, (b) shows that former smokers have a lower risk of a CVD outcome (clinical or subclinical) compared with current smokers, (c) shows that the risk of a CVD outcome in former smokers decreases with increased time since cessation, and (d) results from well-designed and sufficiently powered studies, then such evidence is deemed sufficient to support the conclusion that smoking cessation causes a reduction in risk of the CVD outcome. When evidence for CVD outcomes is not as strong (e.g., if evidence on how CVD risk changes with time since cessation is not sufficient), then the evidence is deemed to be suggestive but not sufficient that smoking cessation decreases the risk of these outcomes.

Table 4.20 Observational studies (meta-analyses and individual cohorts) on smoking cessation and prognosis of coronary heart disease or cardiovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Critchley and Capewell (2003)	<ul style="list-style-type: none"> • Meta-analysis of 20 prospective cohorts: <ul style="list-style-type: none"> – Total mortality analysis: n = 12,603; 2,928 cases – Nonfatal MI analysis: n = 6,089; 779 cases • Participants with prior CHD: <ul style="list-style-type: none"> – Mean: 55 years of age – 20% of cases were women (6 studies of men only) – 28–77% cessation rates (mean: 45%) • Most studies began in the 1960s or 1970s • Most from United States or Europe; one from Japan; and one from India • Follow-up: 2–26 years; mean: 5 years • Outcomes: total mortality and nonfatal MI 	<ul style="list-style-type: none"> • Total mortality: <ul style="list-style-type: none"> – Continued smokers: 1.00 (referent) – Cessation group: 0.64 (0.58–0.71) • Nonfatal MI: <ul style="list-style-type: none"> – Continued smokers: 1.00 (referent) – Cessation group: 0.68 (0.57–0.82) 	Restriction to high-quality studies yielded similar results; results were also similar across studies, irrespective of age, sex, index cardiac event, country, or year the study began
Dagenais et al. (2005) ^a	<ul style="list-style-type: none"> • Prospective analyses of clinical trial (Heart Outcomes Prevention Evaluation) • 8,905 participants with stable CVD or diabetes and one additional risk factor (approximately 50% had prior MI); 58% were former smokers • Cases (restricted to those who survived for 6 months): <ul style="list-style-type: none"> – CVD death: 641 – MI: 978 – Stroke: 358 – Total mortality: 1,021 • Started in 1993 • Median follow-up: 4.5 years 	<ul style="list-style-type: none"> • Cardiovascular death, MI, or stroke: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 0.91 (0.80–1.03) – Current smoker: 1.37 (1.14–1.64) – Similar findings for individual outcomes of CVD death, MI, and stroke • Mortality: <ul style="list-style-type: none"> – Never smoker: 1.00 (referent) – Former smoker: 0.93 (0.80–1.08) – Current smoker: 1.99 (1.63–2.44) • No consistent pattern for increased risk of heart failure, revascularization, unstable angina, or occurrence of microalbuminuria 	—

Table 4.20 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Breitling et al. (2011a) ^a	<ul style="list-style-type: none"> • Prospective cohort study (Long-Term Success of Cardiologic Rehabilitation Therapy study) • 1,062 participants: <ul style="list-style-type: none"> – Mean: 59 years of age – 85% male with acute MI, coronary syndrome, or coronary artery intervention seen for rehabilitation – 154 cases who had secondary CVD events • Started in 2000 • Germany • Median follow-up: 8.1 years • Outcome: secondary CVD events 	<ul style="list-style-type: none"> • Abstained from smoking according to self-report: <ul style="list-style-type: none"> – Continued smoker: 1.00 (referent) – Quit after event: 0.38 (0.20–0.73) – Quit before event: 0.62 (0.40–0.97) – Never smoker: 0.47 (0.28–0.78) • Restricted to those who did not change status for 1–3 years: <ul style="list-style-type: none"> – Continued smoker: 1.00 (referent) – Quit after event: 0.17 (0.06–0.44) – Quit before event: 0.42 (0.25–0.70) – Never smoker: 0.32 (0.18–0.55) 	Similar findings for 1-year and 3-year follow-ups (Twardella et al. 2004, 2006)

Notes: **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **MI** = myocardial infarction; **RR** = risk ratio.

^aMeasure(s) of association adjusted for covariate(s).

Conclusions

1. The evidence is sufficient to infer that smoking cessation reduces levels of markers of inflammation and hypercoagulability and leads to rapid improvement in the level of high-density lipoprotein cholesterol.
2. The evidence is sufficient to infer that smoking cessation leads to a reduction in the development of subclinical atherosclerosis, and that progression slows as time since cessation lengthens.
3. The evidence is sufficient to infer that smoking cessation reduces the risk of cardiovascular morbidity and mortality and the burden of disease from cardiovascular disease.
4. The evidence is sufficient to infer that the relative risk of coronary heart disease among former smokers compared with never smokers falls rapidly after cessation and then declines more slowly.
5. The evidence is sufficient to infer that smoking cessation reduces the risk of stroke morbidity and mortality.
6. The evidence is sufficient to infer that, after smoking cessation, the risk of stroke approaches that of never smokers.
7. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of atrial fibrillation.
8. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of sudden cardiac death among persons without coronary heart disease.
9. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of heart failure among former smokers compared with persons who continue to smoke.
10. Among patients with left-ventricular dysfunction, the evidence is suggestive but not sufficient to infer that smoking cessation leads to increased survival and reduced risk of hospitalization for heart failure.
11. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of venous thromboembolism.
12. The evidence is suggestive but not sufficient to infer that smoking cessation substantially reduces the risk of peripheral arterial disease among former smokers compared with persons who continue to smoke, and that this reduction appears to increase with time since cessation.
13. The evidence is suggestive but not sufficient to infer that, among patients with peripheral arterial disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival.
14. The evidence is sufficient to infer that smoking cessation substantially reduces the risk of abdominal aortic aneurysm in former smokers compared with persons who continue to smoke, and that this reduction increases with time since cessation.
15. The evidence is suggestive but not sufficient to infer that smoking cessation slows the expansion rate of abdominal aortic aneurysm.

Implications

The evidence is clear and certain that smoking cessation reduces the risk for major CVD outcomes. The decline over time in the prevalence of adult cigarette smoking has contributed to the decline of CVD mortality. Intensified efforts by clinicians, healthcare systems, communities, and states to encourage and help smokers to quit will contribute to reducing the burden of CVD at the patient and population levels.

Smoking Cessation After a Diagnosis of Coronary Heart Disease

Heart disease is the leading cause of death in the United States for both men and women (Xu et al. 2018). The term “heart disease” refers to several types of heart conditions. In the United States the most common type of heart disease is coronary artery disease, which affects the

blood flow to the heart. Smoking is a key risk factor for developing coronary heart disease (CHD) (U.S. Department of Health and Human Services [USDHHS] 2004).

This section reviews the evidence on the benefits of cigarette smoking cessation in people with established

CHD. It focuses on the endpoints of all-cause mortality, cause-specific mortality, and the incidence of new or recurrent cardiac events. As advances in clinical treatment regimens for CHD have improved the prognosis for persons with cardiovascular events, the previously established evidence that smoking represents a causal factor for CHD has led to studies investigating the potential benefit of smoking cessation for reducing risk of mortality after a diagnosis. The body of evidence on this topic, which began to emerge in the 1970s, has grown to the point that substantial scientific evidence now exists on this topic.

Conclusions from Previous Surgeon General's Reports

Previous Surgeon General's reports have not specifically evaluated the evidence concerning the impact of cigarette smoking cessation on mortality after a diagnosis of CHD; in fact, this is the first Surgeon General's report to address the potential health benefits of smoking cessation after such a diagnosis. Previous reports have concluded that sufficient evidence exists to infer that smoking causes premature death, multiple diseases, and other adverse health effects (USDHHS 2014). The 1990 report, which focused on the benefits of smoking cessation, reported conclusions on the decline in risk for CHD and stroke among those who quit smoking compared with those who continued to smoke. In addition, the report concluded that, "Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies this reduction in risk of recurrence or premature death has been 50 percent or more" (USDHHS 1990, p. 260). The report noted a lack of relevant findings for stroke.

Considering the biological processes by which smoking increases risk for multiple diseases and mortality, the adverse health effects of smoking would be expected to apply to persons diagnosed with CHD in the same way as they apply to persons in the general population who are at risk for first events. The 2010 Surgeon General's report, *How Tobacco Smoke Causes Disease*, detailed the many mechanisms leading to these adverse health effects (USDHHS 2010).

Biological Basis

This review emphasizes all-cause mortality, cause-specific mortality, and the incidence of new or recurrent cardiac events. Regarding all-cause mortality, the mortality burden from smoking is largely attributable to its

role in causing multiple types of cancer, various cardiovascular diseases, and chronic obstructive pulmonary disease (COPD). Many aspects of the pathogenesis of these diseases in smokers have been characterized, and these same mechanisms would apply to persons who have been diagnosed with CHD (USDHHS 2010). With regard to the risk for cardiovascular disease following cessation, the risk for several consequences of smoking—including endothelial dysfunction, increased risk for thrombosis, and reduced oxygen delivery—would be expected to lessen in the short term after cessation (USDHHS 2010). As detailed in the 2014 Surgeon General's report, in addition to causally increasing risk for specific disease endpoints, smoking causes systemic inflammation and oxidative stress and has widespread and complex effects on immune function (USDHHS 2014). The 2004 Surgeon General's report concluded that smoking causes overall poorer health that leaves smokers with a diminished health status compared with nonsmokers (USDHHS 2004).

Literature Review Methods and Other Methodologic Considerations

The literature search strategy for this review was designed to have high sensitivity by searching broadly in the MEDLINE database and then manually identifying articles with evidence on the association between smoking cessation in patients with CHD and clinical endpoints. For example, key terms in the initial search included "smoking cessation" and "coronary heart disease" OR "cardiovascular disease." The relevant evidence identified was most abundant on the specific topics of the associations between persistent smoking versus quitting smoking with the outcomes of all-cause mortality, cause-specific mortality (focused on cardiac causes of death and sudden death), and risk of new or recurrent cardiac events. Consequently, the evidence review for this section focuses on these three endpoints.

Because of the methodologic limitations of other designs, the summary tables in this section include data only from original research reports on prospective cohort studies. Relevant systematic reviews and meta-analyses were incorporated into the discussion of the evidence, but they were not included in the evidence tables. The reference lists of all published papers reviewed, including the systematic reviews, were searched to check for potentially eligible studies.

Several points relevant to considerations of methodology were consistent across the range of outcomes addressed. First, because all evidence summarized in the evidence tables was generated from prospective cohort

studies, it benefited from the methodologic strengths of such studies in addressing the question of the effect of smoking cessation in patients with CHD. Specifically, these were studies of cohorts of patients diagnosed with a specific heart disease, most often myocardial infarction (MI), or who had undergone a specific cardiovascular procedure such as percutaneous coronary intervention (PCI) or coronary bypass surgery. In all the studies, smoking status was measured at the time of initial diagnosis. To assess the health effects of smoking cessation, areas of interest included findings only from those who were current smokers at the time of diagnosis; this review did not consider results pertaining to those who were never smokers or former smokers at diagnosis. Further, a follow-up measurement of smoking status after baseline was required to distinguish those who quit smoking (henceforth called “quitters”) from those who remained smokers (henceforth called “persistent smokers”). The timing of the follow-up assessment of smoking status represents a key study design feature because only patients who survived to the follow-up assessment were eligible for inclusion in the cohorts, as explained below. The more remote the follow-up assessment from the start of follow-up, the greater the likelihood for cohort attrition due to mortality; to the extent that persistent smokers experience greater mortality soon after the cardiac diagnosis, there would be an increasing bias toward the null with a lengthening interval from baseline to follow-up.

The definitions of “quitters” and “persistent smokers” varied across studies, ranging from sustained abstinence or continued smoking across several longitudinal follow-up points to self-reported quitting or continued smoking at a single follow-up time point. Alternatively, in some studies smoking status was analyzed as a time-dependent variable to account for the many possible transitions in smoking status that can take place over time. After the baseline assessment, current smokers could be classified as quitters or persistent smokers on the basis of a follow-up assessment; at that point, the prospective follow-up for outcomes began. With these shared features of study design, this body of evidence is focused specifically on those who were current smokers at the time of the cardiac diagnosis, with the analysis targeting the effect of quitting compared with persistent smoking within this population. Of note, several studies were initially randomized treatment trials in which sufficient data had been collected to address smoking cessation within the context of a subsequent observational cohort study of trial participants.

For the endpoint of all-cause mortality, evidence tables (Tables 4.21 and 4.22) present details of 34 reports from 32 studies. The index diagnosis used to define the patient cohorts was MI (or included MI with

other conditions such as angina) in the majority (61%) of studies on this topic. Other index diseases were coronary artery disease (CAD) (15% of studies); CHD (6% of studies); and in one study, cardiac arrest. Among studies that defined the cohort on the basis of an index procedure, the most common procedures were PCI (9% of studies) and coronary artery bypass surgery (6%). The studies included in the evidence tables for cause-specific mortality (Table 4.23) and new/recurrent cardiac events (Table 4.24) numbered 13 and 15, respectively.

Epidemiologic and Clinical Evidence

Smoking Cessation and All-Cause Mortality in Patients with Coronary Heart Disease

Table 4.21 summarizes studies (N = 24) of cohorts of patients who were current smokers at the time of a CHD diagnosis that assessed the association between smoking cessation and all-cause mortality by comparing quitters and persistent smokers (the referent). Although all the studies relied on prospective cohorts, they varied widely in sample size, population composition, duration of follow-up, and consideration of potential confounding variables. Sample sizes ranged from 87 to 8,489 persons, and follow-up ranged from 6 months to 30 years. Some estimates of relative risk (RR) were unadjusted, and others were extensively adjusted for demographic, lifestyle, family history, or clinical characteristics. Despite this variability in design features, the results across studies were consistent, as illustrated by the forest plot in the top portion of Figure 4.4. When quitters were compared with persistent smokers, this forest plot, which illustrates results for the 24 studies that included an RR estimate and 95% confidence interval (CI) for all-cause mortality, shows that the RR estimates in every case were less than 1.0. The estimates ranged from 0.11 to 0.93, with a median RR of 0.55, or a reduction of 45% in the rate of mortality. The study showing the weakest association (Chow et al. 2010) (RR = 0.93; 95% CI, 0.59–1.46) also had the shortest follow-up (6 months); this may be too brief a period to observe the full impact of quitting (versus persistent smoking) on mortality. When the results of this study were presented on the basis of a composite outcome of MI or stroke or death, the results aligned more closely with those of other studies (RR = 0.74; 95% CI, 0.53–1.02) (Chow et al. 2010).

One of the 24 studies (Breitling et al. 2011a) in Table 4.21 measured self-reported smoking and also incorporated a biomarker of smoking (blood concentration of cotinine). This study found that smoking classification based on self-reports alone underestimated the strength of

Table 4.21 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing all-cause mortality in those who quit smoking with persistent cigarette smokers

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Wilhelmsson et al. (1975)	<ul style="list-style-type: none"> • 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months after MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented 	<ul style="list-style-type: none"> • 0.51 (0.27–0.96) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated on basis of data presented in Table 5 in Wilhelmsson and colleagues (1975)</p>
Sparrow and Dawber (1978)	<ul style="list-style-type: none"> • Framingham Study • 195 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as former smokers or persistent smokers based on smoking status after data collection immediately preceding and following MI (indeterminate timing) • 56 quitters, 139 persistent smokers • Cohort established 1949, 22 years of follow-up through 1978 • United States • 6-year follow-up results presented 	<ul style="list-style-type: none"> • 0.62 (0.33–1.15) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated on basis of data presented on page 429 in Sparrow and Dawber (1978)</p>
Baughman et al. (1982)	<ul style="list-style-type: none"> • 87 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after infarct (indeterminate timing) • 45 quitters, 42 persistent smokers • Enrollment period: 1968–1971, with follow-up through 1978 • United States • 99-month mean follow-up (survivors) 	<ul style="list-style-type: none"> • 0.35 (0.18–0.66) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated on basis of data presented at top of right-hand column on page 877 in Baughman and colleagues (1982)</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Mulcahy et al. (1982)	<ul style="list-style-type: none"> • 517 male patients <60 years of age with first diagnosis of unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters if stopped smoking at least 3 months before last follow-up or death (indeterminate timing) • 282 quitters, 235 persistent smokers • Enrollment period: 1961–1975 with follow-up through 1979 • Ireland • 99-month mean follow-up (survivors) 	<ul style="list-style-type: none"> • 0.59 (0.47–0.73) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated on basis of data presented in Table 1 in Mulcahy and colleagues (1982)</p>
Aberg et al. (1983)	<ul style="list-style-type: none"> • 983 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3-month follow-up • 542 quitters, 441 persistent smokers • Enrollment period: 1968–1977 • Sweden • 10.5 years maximum follow-up 	<ul style="list-style-type: none"> • All-cause mortality: <ul style="list-style-type: none"> – All ages: 0.63 (0.50–0.79) – ≤50 years of age: 0.46 (0.25–0.84) – >50 years of age: 0.65 (0.50–0.83) • 5-year survival: <ul style="list-style-type: none"> – Quitters: 84% – Persistent smokers: 78% – p <0.0001 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Presented survival plots and p values only from Cox proportional hazards regression models</p> <p>Risk ratio calculated from data presented in Table 6 in Aberg and colleagues (1983)</p>
Perkins and Dick (1985)	<ul style="list-style-type: none"> • 119 patients with first-time diagnosis of MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI (indeterminate timing) • 52 quitters, 67 persistent smokers • Enrollment period: 1974–1977 • United Kingdom • 5-year follow-up 	<ul style="list-style-type: none"> • 0.39 (0.20–0.74) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table II in Perkins and Dick (1985)</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Rønnevik et al. (1985)	<ul style="list-style-type: none"> • 453 patients with first-time diagnosis of AMI who were current smokers at diagnosis within a randomized controlled trial • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI on basis of continued follow-up (indeterminate timing) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up: 17.3 months 	<ul style="list-style-type: none"> • All-cause mortality (placebo group): 0.74 (0.42–1.30) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Results presented limited to placebo group because of observed interaction of treatment (timolol) with smoking</p> <p>Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985)</p>
Hallstrom et al. (1986)	<ul style="list-style-type: none"> • 310 patients with cardiac arrest who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 2 months or less after cardiac arrest • 91 quitters, 219 persistent smokers • Study period: 1970–1981 • United States • Mean follow-up: 47.5 months 	<ul style="list-style-type: none"> • 0.79 (0.50–1.06) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in bottom right-hand column of page 272 of Hallstrom and colleagues (1986)</p>
Burr et al. (1992)	<ul style="list-style-type: none"> • DART • 1,186 nondiabetic male patients ≤70 years of age with MI who were current smokers at diagnosis and survived at least 6 months • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 665 quitters, 521 persistent smokers • Study period: indeterminate • United Kingdom • 18-month follow-up 	<ul style="list-style-type: none"> • 0.52 (0.32–0.83) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Mortality ratios based on average annual mortality rates</p> <p>Unadjusted risk ratio calculated from Table 2 in Burr and colleagues (1992)</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Cavender et al. (1992)	<ul style="list-style-type: none"> • CASS • 284 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 97 quitters, 187 persistent smokers • Enrollment period: 1974–1979 • United States and Canada (15 clinical sites) • 10-year follow-up 	<ul style="list-style-type: none"> • All-cause mortality: 0.63 (0.40–0.97) • 10-year survival: <ul style="list-style-type: none"> – Quitters: 80% – Persistent smokers: 69% – p = 0.025 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>“Persistent smoker” defined as a person who smoked during the follow-up interval (questionnaires every 6 months)</p> <p>Risk ratio calculated from data presented in the title of Figure 2 in Cavender and colleagues (1992); a Cox proportional hazards model was fit with smoking as a time-dependent covariate to account for quitters who reverted to smoking</p> <p>Cox proportional hazards model showed that smoking during 50% and 100% of the follow-up period increased the RR of death by 1.56 and 1.73, respectively</p> <p>Survival plots and p values presented only from Cox proportional hazards regression models</p>
Gupta et al. (1993)	<ul style="list-style-type: none"> • 225 patients with CHD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status since the time of diagnosis of CAD (indeterminate timing) • 173 quitters, 52 persistent smokers • Study baseline: 1980 • India • Approximately 6-year follow-up 	<ul style="list-style-type: none"> • 0.70 (0.49–1.01) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented on page 127 of Gupta and colleagues (1993)</p> <p>Adjusted hazards ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Gupta and colleagues (1993) underestimated association because of inclusion of nonsmokers in the reference category; hazard ratio was 1.28 (95% CI, 1.01–2.09) after adjusting for sex, age, hypertension, cholesterol, diabetes, and history of MI or congestive heart failure</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Tofler et al. (1993)	<ul style="list-style-type: none"> MILIS study 641 patients with AMI who were current smokers at diagnosis All current smokers at baseline Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up 360 quitters, 281 persistent smokers Enrollment period: 1974–1979 United States 4-year follow-up results presented 	<ul style="list-style-type: none"> All-cause mortality: <ul style="list-style-type: none"> – Total: 0.48 (0.31–0.73) – <12 years of education: 0.63 (0.39–1.03) – ≥12 years of education: 0.39 (0.18–0.89) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table 3 in Tofler and colleagues (1993)</p>
Greenwood et al. (1995)	<ul style="list-style-type: none"> ASSET 532 patients with MI who were current smokers at diagnosis All current smokers at baseline Categorized as quitters or persistent smokers based on smoking status at 1-month follow-up 396 quitters, 136 persistent smokers Study period: 1986–1988 (enrollment) England 6.3-year median follow-up 	<ul style="list-style-type: none"> All-cause mortality: 0.56 (0.33–0.98) 10-year survival: <ul style="list-style-type: none"> – Quitters: 80% – Persistent smokers: 69% – p = 0.025 	<p>Quitters vs. persistent smokers (referent)</p> <p>Logistic regression models</p> <p>Adjusted for age, history of diabetes, history of angina, and treatment with antiarrhythmic drugs at discharge</p>
Herlitz et al. (1995)	<ul style="list-style-type: none"> 217 patients with AMI who were current smokers at diagnosis and survived at least 1 year All current smokers at baseline Categorized as quitters or persistent smokers based on smoking status after 1 year of follow-up 115 quitters, 102 persistent smokers Enrollment period: 1986–1987 Sweden 4-year follow-up results presented 	<ul style="list-style-type: none"> 0.55 (0.34–0.91) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated on basis of data presented in text and mortality rates presented in Figure 2 in Herlitz and colleagues (1995)</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Kinjo et al. (2005)	<ul style="list-style-type: none"> • OACIS study • 1,424 patients with AMI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 3 months after discharge • 1,056 quitters, 368 persistent smokers • Study period: 1998–2003 • Japan • 2.5-year mean follow-up 	<ul style="list-style-type: none"> • Adjusted hazard ratio: 0.39 (0.20–0.77) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for sex, age, BMI, hypertension, dyslipidemia, diabetes, obesity, prior MI, prior angina pectoris, prior cerebrovascular disease, heart rate, Killip class ≥ 2, anterior wall MI, atrial fibrillation, ventricular fibrillation, and revascularization</p>
Gerber et al. (2009)	<ul style="list-style-type: none"> • ISFAMI • 798 patients ≤ 65 years of age with first-time MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 417 quitters, 381 persistent smokers • Study period: 1992–2005 • Israel • 13.2-year median follow-up 	<ul style="list-style-type: none"> • Adjusted odds ratio: 0.63 (0.48–0.82) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Proportional hazards models, with smoking modeled as time-dependent covariate</p> <p>Adjusted for sex, age, ethnicity, education, income, employment, hypertension, dyslipidemia, diabetes, obesity, physical activity, Q-wave AMI, CABG, PTCA, unstable angina pectoris, and heart failure during follow-up</p>
Chow et al. (2010)	<ul style="list-style-type: none"> • OASIS 5 trial • 4,324 patients with unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 30 days of follow-up • 2,802 quitters, 1,522 persistent smokers • Study baseline: 2003–2005 • 41 countries • 6-month follow-up 	<ul style="list-style-type: none"> • Adjusted odds ratio: 0.93 (0.59–1.46) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Logistic regression models</p> <p>Paper presented measures of association as odds ratios, but because they were from a prospective cohort study, these are RR estimates</p> <p>Adjusted for sex, age, hypertension history, diabetes, prior MI, BMI, creatinine, PCI/CABG before 30 days, and medications</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Shah et al. (2010)	<ul style="list-style-type: none"> • SAVE trial • 731 patients with AMI with left ventricular systolic dysfunction who were current smokers at diagnosis • All current smokers at baseline who survived at least 6 months • Categorized as quitters or persistent smokers based on smoking status after 6 months of follow-up • 463 quitters, 268 persistent smokers • Study baseline: 1987–1990 • United States • 42-month median follow-up 	<ul style="list-style-type: none"> • Adjusted hazard ratio for all-cause mortality by follow-up interval: <ul style="list-style-type: none"> – 6 months: 0.57 (0.36–0.91) – 12 months: 0.58 (0.33–0.99) – 16 months: 0.60 (0.34–1.07) – 24 months: 0.53 (0.25–1.08) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Proportional hazards regression models</p> <p>Propensity score (on basis of 24 parameters) adjusted model</p> <p>Reduction in risk started early and was maintained over time</p> <p>Results presented combined mortality with MI or hospitalization for heart failure</p>
Breitling et al. (2011a)	<ul style="list-style-type: none"> • KAROLA study • 1,062 total patients with AMI, coronary syndrome, coronary artery intervention who were current smokers at diagnosis • All results presented in table limited to current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at rehabilitation discharge • Numbers of quitters and persistent smokers vary by classification method • 85% men, mean 59 years of age • Study baseline: 2000 • Germany • 8.1-year median follow-up 	<ul style="list-style-type: none"> • Outcome was fatal or nonfatal secondary cardiovascular disease events (MI, ischemic stroke, deaths with cardiovascular disease as the main cause): <ul style="list-style-type: none"> – Self-report plus cotinine (169 quitters, 154 persistent smokers): adjusted hazard ratio 0.38 (0.20–0.73) – Self-report plus cotinine, limited to those who remained quitters or persistent smokers throughout follow-up (101 quitters, 98 persistent smokers): adjusted hazard ratio 0.17 (0.06–0.44) – Self-report only (204 quitters, 53 persistent smokers): adjusted hazard ratio 0.75 (0.35–1.60) 	<p>Hazard ratio for quitters vs. persistent smokers</p> <p>Results indicate that using a biomarker of smoking results in greater magnitude of risk reduction compared with self-report alone</p> <p>Results indicate that magnitude of risk reduction is greater when maintaining abstinence</p> <p>Taken in combination, these findings indicate that the association with quitting smoking is likely underestimated in most studies because studies of this type typically have not used biomarkers and continuous maintenance of smoking abstinence</p> <p>Earlier results from this same study showing similar findings were included in Twardella and colleagues (2006)</p> <p>Adjusted for sex, age, diabetes, triglycerides, total and LDL cholesterol, and ACE inhibitor at discharge</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Chen et al. (2012)	<ul style="list-style-type: none"> • 8,489 patients undergoing PCI (stent implantation) who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up (indeterminate timing) • 4,440 quitters, 4,049 persistent smokers • Study period: 2004–2010 • China • 3.0-year median follow-up 	<ul style="list-style-type: none"> • Adjusted hazard ratio: 0.11 (0.06–0.22) 	<p>Hazard ratio for quitters vs. persistent smokers</p> <p>Adjusted for sex, age, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, unstable angina, family history of CHD, ejection fraction, lesion type, reference vessel diameter, lesion length, restenotic lesion, calcification, angulated/total occlusion, thrombus, predilation, stent length, and postdilation</p>
Álvarez et al. (2013)	<ul style="list-style-type: none"> • FRENA registry • 1,182 patients who were current smokers at diagnosis • 475 with CAD, 240 with CVD, 467 with PAD • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 512 quitters, 670 persistent smokers • Study period: 2003–2010 • Spain • 14-month mean follow-up 	<ul style="list-style-type: none"> • Adjusted hazard ratio: 0.51 (0.22–1.15) 	<p>Mortality ratio for quitters vs. persistent smokers</p> <p>Adjusted for comorbidity, atrial fibrillation, medications, and creatinine clearance</p>
de Boer et al. (2013)	<ul style="list-style-type: none"> • 497 patients undergoing PCI who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1-year follow-up • 210 quitters, 287 persistent smokers • Study baseline: 1980–1985 • Netherlands • 19.5-year median follow-up, 30 years maximum • 56 years of age average 	<ul style="list-style-type: none"> • All cause-mortality: adjusted hazard ratio 0.57 (0.46–0.71) • 30-year survival: 2.1 times as high in quitters as in persistent smokers (29% vs. 14%) • Life expectancy: 2.1 years longer in quitters vs. persistent smokers (18.5 vs. 16.4 years) 	<p>Adjusted hazard ratio comparing quitters plus nonsmokers vs. persistent smokers</p> <p>Having the baseline age of the cohort combined with a 30-year follow-up period enabled unique evaluation of impact on survival; adjustments not clearly specified, but there appears to have been adjustment for sex, age, indication for PCI, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, multivessel disease, clinical success of PCI, and family history of CHD</p>

Table 4.21 Continued

Study	Design/population	Findings: RR ^a (95% CI)	Comments
Liu et al. (2013)	<ul style="list-style-type: none"> • 430 male CHD patients undergoing PCI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average) 	<ul style="list-style-type: none"> • Risk ratio: 0.17 (0.05–0.63) 	<p>Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013); data represent major clinical outcomes for persistent smokers, quitters, and nonsmokers</p> <p>Adjusted hazard ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Liu and colleagues (2013) will underestimate association because of inclusion of nonsmokers in the reference group; hazard ratio was 2.43 (95% CI, 1.17–5.05) after adjusting for age, hypertension, dyslipidemia, aspirin use, and statin use</p>
Hammal et al. (2014)	<ul style="list-style-type: none"> • APPROACH registry • 2,583 patients undergoing coronary angiography for CAD who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1-year follow-up • 1,519 quitters, 1,064 persistent smokers • Study period: 2003–2010 • Canada • 42.2-month mean follow-up • 56 years of age (mean) 	<ul style="list-style-type: none"> • Outcome all-cause mortality plus comparison of survival: <ul style="list-style-type: none"> – Total cohort (unmatched): 0.54 (0.39–0.73) – Subgroup receiving medical treatment (matched): 0.59 (0.31–1.11) – Subgroup receiving revascularization: 0.46 (0.22–0.96) – Survival in total cohort: 95.7% in quitters vs. 92.0% in persistent smokers – Survival in subgroup receiving medical treatment: 93.0% in quitters vs. 88.0% in persistent smokers – Survival in subgroup receiving revascularization: 94.9% in quitters vs. 88.9% in persistent smokers (p <0.05) 	<p>Quitters vs. persistent smokers</p> <p>Risk ratios calculated from data presented in Table 7 in Hammal and colleagues (2014)</p> <p>No explicit adjustments; matching was on basis of propensity scores</p>

Notes: **ACE** = angiotensin-converting enzyme; **AMI** = acute myocardial infarction; **APPROACH** = Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease; **ASSET** = Anglo-Scandinavian Study of Early Thrombolysis; **BMI** = body mass index; **CABG** = coronary artery bypass grafting; **CAD** = coronary artery disease; **CASS** = Coronary Artery Surgery Study; **CHD** = coronary heart disease; **CI** = confidence interval; **DART** = Diet and Reinfarction Trial; **FRENA** = Factores de Riesgo y Enfermedad Arterial [Registry]; **ISFAMI** = Israel Study of First Acute Myocardial Infarction; **KAROLA** = Langzeiterfolge der Kardiologischen Anschlussheilbehandlung (Long-Term Success of Cardiologic Rehabilitation Therapy); **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **MILIS** = Multicenter Investigation of Limitation of Infarct Size; **OACIS** = Osaka Acute Coronary Insufficiency Study; **OASIS** = Organization to Assess Strategies in Acute Ischemic Syndromes; **PAD** = peripheral artery disease; **PCI** = percutaneous coronary intervention; **PTCA** = percutaneous transluminal coronary angioplasty; **RR** = relative risk; **SAVE** = Sleep Apnea Cardiovascular Endpoints.

^aRR unless specified otherwise.

Table 4.22 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing all-cause mortality in those who remained persistent smokers with those who quit smoking

Study	Design/population	Findings: RR (95% CI)	Comments
Salonen (1980)	<ul style="list-style-type: none"> • 523 male patients ≤65 years of age with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 221 quitters, 302 persistent smokers • Enrollment period: 1968–1977 • Finland • 3-year follow-up 	<ul style="list-style-type: none"> • 1.7 (1.1–2.6) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted rate ratios</p>
Daly et al. (1983)	<ul style="list-style-type: none"> • 374 patients with unstable angina or MI who were current smokers at diagnosis and survived at least 2 years • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 2-year follow-up • 217 quitters, 157 persistent smokers • Enrollment period: 1974–1979 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined 	<ul style="list-style-type: none"> • 2.8 (p <0.01) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Mortality ratios calculated from average annual mortality rates</p> <p>Unadjusted rate ratios</p> <p>Presented survival plots and p values only from Cox proportional hazards regression models</p>
Johansson et al. (1985)	<ul style="list-style-type: none"> • 156 female patients with MI who were current smokers at diagnosis and survived at least 3 months • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months of follow-up • 81 quitters, 75 persistent smokers • Study period: 1968–1977 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined 	<ul style="list-style-type: none"> • Unadjusted: 2.3 (1.2–4.4) • Fully adjusted: 2.7 (CI not presented) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted rate ratios</p> <p>Cox proportional hazards models; fully adjusted model included mean peak SAST, Q waves, and angina pectoris known before the infarction</p> <p>Presented survival plots</p> <p>Example of adjustment resulting in stronger association</p>

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	<ul style="list-style-type: none"> • CASS • 4,165 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented 	<ul style="list-style-type: none"> • 1.55 (1.29–1.85) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Quitters had a worse prognostic profile than persistent smokers at baseline</p> <p>The definition of persistent smoker was self-reported smoking at every follow-up</p> <p>The definition of quitter was someone who quit 1 year before study entry and reported not smoking at every follow-up</p> <p>Cox proportional hazards models using a propensity-score approach to adjust for covariates</p> <p>Propensity-score adjustment approach on basis of the following variables: age, sex congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of $\geq 50\%$</p>
Hermanson et al. (1988)	<ul style="list-style-type: none"> • CASS • 1,893 patients with CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on quitting smoking within 1 year before the baseline angiogram • 807 quitters, 1,086 persistent smokers • Enrollment period: 1974–1979 • United States • Average follow-up: 5.3 years 	<ul style="list-style-type: none"> • All-cause mortality, total: 1.7 (1.4–2.0) • All-cause mortality stratified by age group (years): <ul style="list-style-type: none"> – 55–64: 1.7 (1.4–2.1) – ≥ 70: 1.6 (1.1–2.3) – 55–59: 1.5 (1.1–2.0) – 60–64: 2.0 (1.5–2.6) – 65–69: 1.4 (0.9–2.0) – ≥ 70: 3.3 (1.5–7.1) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Hazard ratios</p> <p>Same CASS as in Vliestra and colleagues (1986)</p> <p>Presented age-specific associations</p>

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Peters et al. (1995)	<ul style="list-style-type: none"> • CAST I and CAST II • 1,026 patients with left ventricular dysfunction after MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 517 quitters, 509 persistent smokers • Enrollment period: 1987–1991 • United States • 15.5-month mean follow-up 	<ul style="list-style-type: none"> • 1.64 (0.97–2.79) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards regression models using smoking as a time-dependent covariate</p> <p>Adjusted for sex, age, angina, heart failure, ejection fraction, history of MI, diabetes, hypertension, history of coronary artery angioplasty or bypass grafts, history of diabetes, history of congestive heart failure, CAST treatment condition, angina, use of thrombolytic agents during qualifying MI, and other study-specific treatment variables</p>
Voors et al. (1996)	<ul style="list-style-type: none"> • 167 patients with coronary bypass surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1 year of follow-up • 72 quitters, 95 persistent smokers • Enrollment period: 1976–1977 • Netherlands • 15 years of follow-up 	<ul style="list-style-type: none"> • 0.9 (0.5–1.6) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards regression models</p> <p>This result is for the complete follow-up period from 1 year to 15 years after surgery</p> <p>In Table 6 in Voors and colleagues (1996), the result for 5 to 15 years after surgery was an RR of 1.7 (95% CI, 0.8–3.5) adjusted for sex, age, plus the following variables if $p < 0.10$ (unclear from text which variables met this criterion): obesity; elevated cholesterol and triglyceride levels; angina; heart failure; ejection fraction; history of MI, diabetes, and/or hypertension; family history of CAD, diabetes, and/or congestive heart failure; and number of vessels diseased and other characteristics of index diagnosis</p>
Hasdai et al. (1997)	<ul style="list-style-type: none"> • 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16-year maximum 	<ul style="list-style-type: none"> • 1.44 (1.02–2.11) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for significant differences in baseline variables</p> <p>Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD</p>

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	<ul style="list-style-type: none"> • 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-years median follow-up (range 13–26 years) 	<ul style="list-style-type: none"> • 1.68 (1.33–2.13) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization</p>
Zhang et al. (2015)	<ul style="list-style-type: none"> • SYNTAX • 1,793 patients with complex CAD who were current smokers at diagnosis • Use of time-dependent covariates may have included all participants (never, former, and current smokers at baseline) • Smoking categorized at 6 months, 1 year, 3 years, and 5 years of follow-up • Indeterminate study period • Multicenter, multinational study • 5 years of follow-up 	<ul style="list-style-type: none"> • 1.80 (1.27–2.54) 	<p>Smoking status analyzed as a time-dependent covariate</p> <p>Cox proportional hazards regression models</p> <p>Composite endpoint of death/MI/stroke</p> <p>Never precisely specified, but this estimate likely included the total study population, including never smokers and former smokers as well as current smokers at baseline</p> <p>Assume adjusted for other independent predictors listed in Table 3 in Zhang and colleagues (2015): PCI vs. CABG, age, COPD, PVD, LVEF <30%, amiodarone therapy on discharge (never specified in text)</p>

Notes: **CABG** = coronary artery bypass grafting; **CAD** = coronary artery disease; **CAGE 50** = number of segments with coronary artery stenosis $\geq 50\%$; **CASS** = Coronary Artery Surgery Study; **CAST** = Cardiac Arrhythmia Suppression Trial; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction; **PVD** = peripheral vascular disease; **PCI** = percutaneous coronary intervention; **RR** = relative risk; **SAST** = serum aspartate amino transferase; **SYNTAX** = SYnergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery Trial.

Table 4.23 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing cause-specific mortality from cardiac endpoints and sudden death in those who remained persistent cigarette smokers with those who quit smoking

Study	Design/population	Findings: RR (95% CI)	Comments
Wilhelmsson et al. (1975)	<ul style="list-style-type: none"> • 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months following MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented 	<ul style="list-style-type: none"> • Cardiovascular death: 2.05 (0.99–4.27) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated using the data presented in Table 5 in Wilhelmsson and colleagues (1975)</p>
Salonen (1980)	<ul style="list-style-type: none"> • 523 male patients ≤65 years of age with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 221 quitters, 302 persistent smokers • Enrollment period: 1968–1977 • Finland • 3-year follow-up 	<ul style="list-style-type: none"> • Ischemic heart disease: 1.6 (1.0–2.7) • Other cardiovascular disease: 1.5 (0.3–8.0) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p>
Mulcahy et al. (1982)	<ul style="list-style-type: none"> • 517 male patients <60 years of age with first diagnosis of unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on stopping smoking at least 3 months before the last follow-up or death (indeterminate timing) • 282 quitters, 235 persistent smokers • Enrollment period: 1961–1975, with follow-up through 1979 • Ireland • 99-month mean follow-up (survivors) 	<ul style="list-style-type: none"> • Cardiac failure: 2.70 (0.84–8.66) • Sudden death: 1.77 (1.23–2.54) • Fatal MI: 1.68 (1.04–2.72) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated using data presented in Table 2 in Mulcahy and colleagues (1982)</p>

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Daly et al. (1983)	<ul style="list-style-type: none"> • 374 patients with unstable angina or MI who were current smokers at diagnosis and survived at least 2 years • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 2-year follow-up • 217 quitters, 157 persistent smokers • Enrollment period: 1974–1979 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined 	<ul style="list-style-type: none"> • Vascular causes: 2.4 ($p < 0.01$) • Fatal reinfarction: 2.6 ($p = 0.02$) • Sudden death: 1.6 ($p = 0.14$) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Mortality ratios based on average annual mortality rates</p> <p>Presented survival plots and p values only from Cox proportional hazards regression models</p>
Rønnevik et al. (1985)	<ul style="list-style-type: none"> • 453 patients with first-time diagnosis of acute MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI with continued follow-up (indeterminate time) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up 17.3 months 	<ul style="list-style-type: none"> • Cardiac causes (placebo group): 1.17 (0.62–2.22) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985)</p> <p>Results presented limited to the placebo group because of an observed interaction of the treatment (timolol) with smoking</p>
Hallstrom et al. (1986)	<ul style="list-style-type: none"> • 310 patients with cardiac arrest who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 2 months or less after cardiac arrest • 91 quitters, 219 persistent smokers • Study period: 1970–1981 • United States • Mean follow-up 47.5 months 	<ul style="list-style-type: none"> • Cardiac arrest: 1.55 (0.98–2.45) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented on page 272 in Hallstrom and colleagues (1986)</p>

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	<ul style="list-style-type: none"> • CASS Trial • 4,165 patients with angiographically confirmed coronary artery disease who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented 	<ul style="list-style-type: none"> • Cardiac contributing: 1.60 (0.89–2.86) • Sudden death: 1.82 (1.14–2.89) • MI: 1.78 (1.36–2.33) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards models using a propensity score approach to adjust for covariates</p> <p>Quitters had a worse prognostic profile than persistent smokers at baseline</p> <p>The definition of persistent smoker was self-reported smoking at every follow-up; the definition of a quitter was someone who had quit 1 year before study entry and reported not smoking at every follow-up</p> <p>Propensity-score adjustment approach based on age, sex, congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of $\geq 50\%$</p>
Hermanson et al. (1988)	<ul style="list-style-type: none"> • CASS • 1,893 patients with CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on quitting smoking within 1 year before the baseline angiogram • 807 quitters, 1,086 persistent smokers • Study period: 1974–1979 (enrollment) • United States • Average follow-up 5.3 years 	<ul style="list-style-type: none"> • Cardiac causes: 1.37 ($p = .001$) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Hazard ratios</p> <p>Overall and stratified by age group</p> <p>Same CASS as in Vliestra et al. (1986)</p> <p>Risk ratio calculated from data presented on page 1,367 of Hermanson and colleagues (1988)</p>

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Gupta et al. (1993)	<ul style="list-style-type: none"> • 225 patients with CHD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status since the time of diagnosis of CAD (indeterminate) • 173 quitters, 52 persistent smokers • Study baseline: 1980 • India • ~ 6-year average follow-up 	<ul style="list-style-type: none"> • Sudden death: 1.48 (0.81–2.71) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented on page 127 of Gupta and colleagues (1993)</p>
Peters et al. (1995)	<ul style="list-style-type: none"> • CAST I and CAST II • 1,026 patients with left ventricular dysfunction after MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 517 quitters, 509 persistent smokers • Enrollment period: 1987–1991 • United States • 15.5-month mean follow-up 	<ul style="list-style-type: none"> • Arrhythmic mortality: 1.80 (0.88–3.67) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards regression models using smoking as a time-dependent covariate</p> <p>Adjusted for sex, age, angina, heart failure, ejection fraction, history of MI, diabetes, hypertension, history of coronary artery angioplasty or bypass grafts, history of diabetes, history of congestive heart failure, CAST treatment condition, angina, use of thrombolytic agents during qualifying MI, and other study-specific treatment variables</p>
Hasdai et al. (1997)	<ul style="list-style-type: none"> • 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16 years maximum 	<ul style="list-style-type: none"> • Cardiac causes: 1.49 (0.89–2.51) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for significant differences in baseline variables</p> <p>Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD</p>

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	<ul style="list-style-type: none"> • 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-year median follow-up (range 13–26 years) 	<ul style="list-style-type: none"> • Cardiac causes: 1.75 (1.30–2.37) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization</p>
Liu et al. (2013)	<ul style="list-style-type: none"> • 430 male CHD patients undergoing percutaneous coronary intervention who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average) 	<ul style="list-style-type: none"> • Cardiac causes: 7.7 (0.9–68.8) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013)</p>

Notes: **CABG** = coronary artery bypass grafting; **CAD** = coronary artery disease; **CAGE 50** = number of segments with coronary artery stenosis ≥50%; **CASS** = Coronary Artery Surgery Study; **CAST** = Cardiac Arrhythmia Suppression Trial; **CHD** = coronary heart disease; **CI** = confidence interval; **MI** = myocardial infarction; **RR** = relative risk.

Table 4.24 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing incidence of cardiac endpoints in those who remained persistent cigarette smokers with those who quit smoking or vice versa

Study	Design/population	Findings: RR (95% CI)	Comments
Wilhelmsson et al. (1975)	<ul style="list-style-type: none"> • 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months following MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented 	<ul style="list-style-type: none"> • Reinfarction: 0.49 (0.29–0.82) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated based on the data presented in Table 5 in Wilhelmsson and colleagues (1975)</p>
Sparrow and Dawber (1978)	<ul style="list-style-type: none"> • Framingham Study • 195 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after data collection immediately preceding and following MI (indeterminate timing) • 56 quitters, 139 persistent smokers • Cohort established 1949: 22 years of follow-up through 1978 • United States • 6-year follow-up results presented 	<ul style="list-style-type: none"> • Reinfarction: 0.76 (0.37–1.58) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated based on data presented on page 430 in Sparrow and Dawber (1978)</p>
Aberg et al. (1983)	<ul style="list-style-type: none"> • 983 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3-month follow-up • 542 quitters, 441 persistent smokers • Enrollment period: 1968–1977 • Sweden • 10.5-year maximum follow-up 	<ul style="list-style-type: none"> • Reinfarction: 0.67 (0.53–0.84) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table 7 in Aberg and colleagues (1983)</p>

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Perkins and Dick (1985)	<ul style="list-style-type: none"> • 119 patients with first-time diagnosis of MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI (indeterminate time) • 52 quitters, 67 persistent smokers • Enrollment period: 1974–1977 • United Kingdom • 5-year follow-up 	<ul style="list-style-type: none"> • Reinfarction: 3.87 (0.81–18.37) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table II in Perkins and Dick (1985)</p>
Rønnevik et al. (1985)	<ul style="list-style-type: none"> • 453 patients with first-time diagnosis of acute MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI based on continued follow-up (indeterminate time) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up 17.3 months 	<ul style="list-style-type: none"> • MI: 0.54 (0.32–0.93) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Results presented limited to the placebo group because of an observed interaction of treatment (timolol) with smoking</p> <p>Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985)</p>

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	<ul style="list-style-type: none"> • CASS • 4,165 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented 	<ul style="list-style-type: none"> • 5-year MI hospitalization: 0.63 (0.51–0.78) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards models using a propensity score approach to adjust for covariates</p> <p>Propensity-score adjustment approach on basis of the following variables: age, sex, congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of $\geq 50\%$</p> <p>Quitters had a worse prognostic profile than persistent smokers at baseline</p> <p>The definition of persistent smoker was self-reported smoking at every follow-up; the definition of a quitter was someone who had quit 1 year before study entry and reported not smoking at every follow-up</p>
Herlitz et al. (1995)	<ul style="list-style-type: none"> • 217 patients with acute MI who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 1 year of follow-up • 115 quitters, 102 persistent smokers • Enrollment period: 1986–1987 • Sweden • 4-year follow-up results presented 	<ul style="list-style-type: none"> • Reinfarction: 0.99 (0.42–2.33) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Unadjusted risk ratios</p> <p>Risk ratio calculated from data presented in Table 4 in Herlitz and colleagues (1995)</p>

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Voors et al. (1996)	<ul style="list-style-type: none"> • 167 patients with coronary bypass surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1 year of follow-up • 72 quitters, 95 persistent smokers • Enrollment period: 1976–1977 • Netherlands • 15 years of follow-up 	<ul style="list-style-type: none"> • MI: 2.3 (1.1–5.1) • Reoperation: 2.5 (1.1–5.9) • Angina: <ul style="list-style-type: none"> – 1–15 years post-surgery: 1.2 (0.8–1.7) – 5–15 years post-surgery: 2.0 (1.1–3.6) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Cox proportional hazards regression models</p> <p>Adjusted for sex, age, plus the following variables if $p < 0.10$ (unclear from text which variables met this criterion): obesity, diabetes, elevated cholesterol and triglyceride levels, hypertension, history of heart failure, preoperative angina pectoris, family history of CAD, number of vessels diseased, completeness of revascularization, number of distal anastomoses, left ventricular function, history of MI, indication for operation, presence of collateral arteries, left main CAD, and proximal left anterior descending artery disease</p>
Hasdai et al. (1997)	<ul style="list-style-type: none"> • 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16 years maximum 	<ul style="list-style-type: none"> • MI: 0.68 (.54–.86) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Proportional hazards model</p> <p>Never smokers were used as the referent for estimating the RRs; 0.68 was the RR of MI for quitters vs. never smokers, and 1.44 (1.02–2.11) was the RR for death for persistent smokers vs. never smokers</p> <p>Adjusted for significant differences in baseline variables</p> <p>Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD</p>

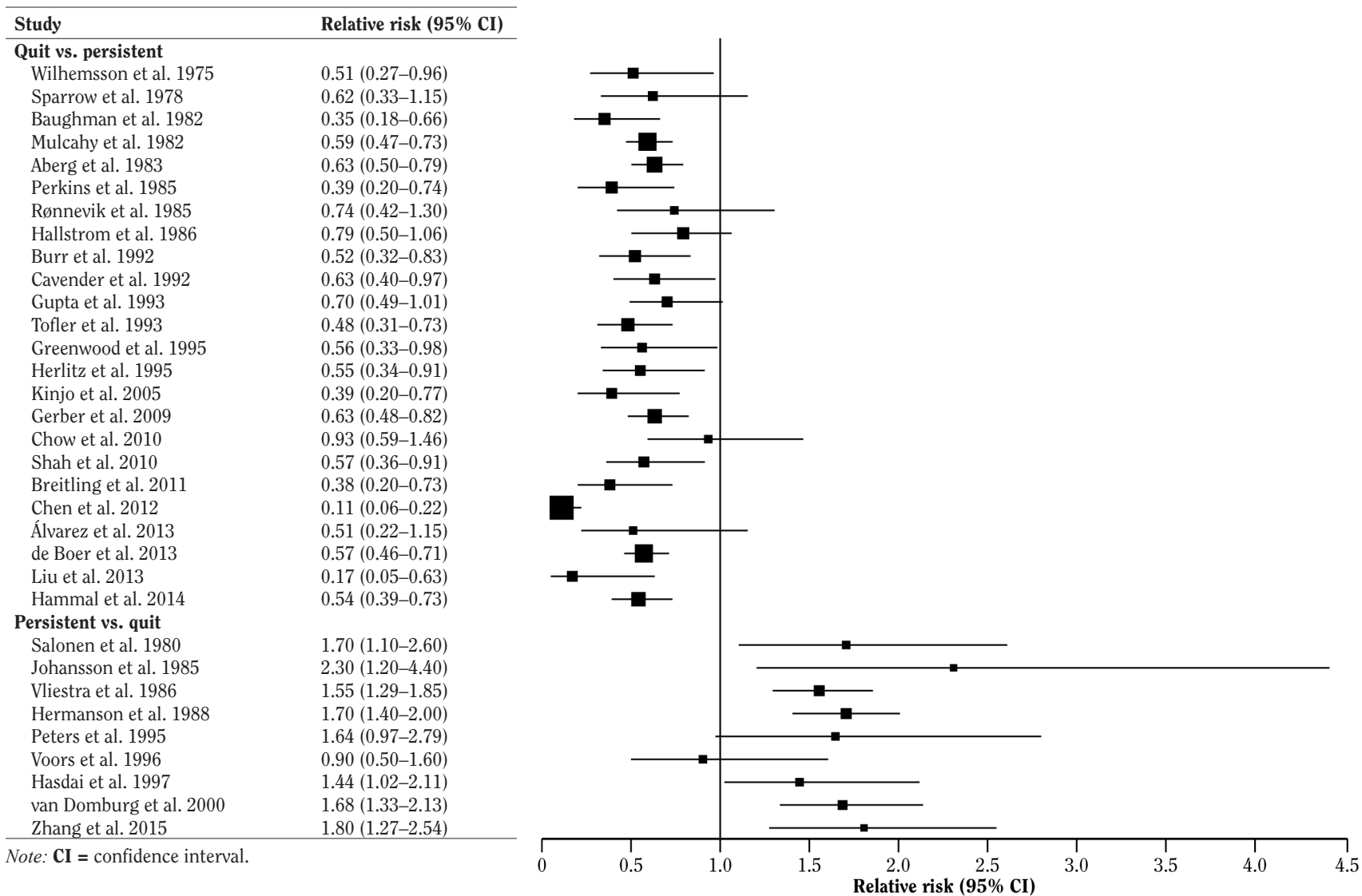
Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	<ul style="list-style-type: none"> • 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-year median follow-up (range 13–26 years) 	<ul style="list-style-type: none"> • Repeat CABG/PTCA: 1.41 (1.02–1.94) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Proportional hazards models</p> <p>Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization</p>
Chow et al. (2010)	<ul style="list-style-type: none"> • OASIS trial • 4,324 patients with unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 30 days of follow-up • 2,802 quitters, 1,522 persistent smokers • Study baseline: 2003–2005 • 41 countries • 6-month follow-up 	<ul style="list-style-type: none"> • MI: 0.57 (0.36–0.89) • Stroke: 0.40 (0.14–1.17) 	<p>Quitters vs. persistent smokers (referent)</p> <p>Logistic regression models</p> <p>Paper presented measures of association as odds ratios, but for this prospective cohort study, these were converted to RR</p> <p>Adjusted for sex, age, hypertension history, diabetes, prior MI, BMI, creatinine, PCI/CABG before 30 days, and medications</p>
Chen et al. (2012)	<ul style="list-style-type: none"> • 8,489 patients undergoing PCI (stent implantation) who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up (indeterminate timing) • 4,440 quitters, 4,049 persistent smokers • Study period: 2004–2010 • China • 3.0-year median follow-up 	<ul style="list-style-type: none"> • Repeat revascularization: 1.59 (1.36–1.85) 	<p>Hazard ratio for quitters vs. persistent smokers</p> <p>Adjusted for sex, age, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, unstable angina, family history of CHD, ejection fraction, lesion type, reference vessel diameter, lesion length, restenotic lesion, calcification, angulated/total occlusion, thrombus, predilation, stent length, and postdilation</p>

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Álvarez et al. (2013)	<ul style="list-style-type: none"> • FRENA registry • 1,182 patients who were current smokers at diagnosis • 475 with CAD, 240 with CVD, 467 with PAD • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 512 quitters, 670 persistent smokers • Study period: 2003–2010 • Spain • 14-month mean follow-up 	<ul style="list-style-type: none"> • MI: 0.70 (0.26–1.88) 	<p>Mortality ratio for quitters vs. persistent smokers</p> <p>Adjusted for comorbidity, atrial fibrillation, medications, and creatinine clearance</p>
Choi et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort • 275 patients who were current smokers at diagnosis of MI • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 144 quitters, 131 persistent smokers • Study period: 1999–2008 • South Korea • Regularly followed for 1 year after MI 	<ul style="list-style-type: none"> • Re-intervention or MI: 2.9 (0.2–33.0) 	<p>Persistent smokers vs. quitters (referent)</p> <p>Risk ratio for re-intervention or MI</p> <p>Not clear that the estimate was adjusted for any factors</p>
Liu et al. (2013)	<ul style="list-style-type: none"> • 430 male CHD patients undergoing PCI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average) 	<ul style="list-style-type: none"> • Revascularization: 2.89 (1.05–8.0) • MI: <ul style="list-style-type: none"> – 1.4% in persistent smokers – 0% in quitters • RR for quitters vs. persistent = 0.0 	<p>Persistent smokers vs. quitters (referent)</p> <p>Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013)</p> <p>Adjusted hazard ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Liu and colleagues (2013) will underestimate association because of inclusion of nonsmokers in the referent</p> <p>Hazard ratio was 2.43 (95% CI, 1.17–5.05) after adjusting for age, hypertension, dyslipidemia, aspirin use, and statin use</p>

Notes: **BMI** = body mass index; **CABG** = coronary artery bypass grafting; **CAD** = coronary artery disease; **CAGE 50** = number of segments with coronary artery stenosis ≥50%; **CASS** = Coronary Artery Surgery Study; **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **FRENA** = Factores de Riesgo y Enfermedad Arterial [Registry]; **MI** = myocardial infarction; **OASIS** = Organization to Assess Strategies in Ischemic Syndromes; **PAD** = peripheral artery disease; **PCI** = percutaneous coronary intervention; **PTCA** = percutaneous transluminal coronary angioplasty; **RR** = relative risk.

Figure 4.4 Relative risk for all-cause mortality after cardiac event among those who were current smokers when diagnosed, by smoking status

the association between cessation and mortality compared with classification of smoking by both self-reported and biomarker data. These results replicated previous findings from this research group (Twardella et al. 2006). Because most findings are based on self-reported smoking status, the pattern of associations in comparisons of self-reported with biomarker-based classification suggests that the associations observed in studies that rely on self-reported smoking may be underestimated because of the misclassification from self-reports.

Table 4.22 summarizes studies in cohorts of patients with CHD that assessed the association between smoking cessation and all-cause mortality by comparing persistent smokers with quitters as the reference group; the lower portion of Figure 4.4 presents a forest plot for the nine reports that included an RR and a 95% CI. Among the 10 reports from the 9 studies detailed in Table 4.22, all but 1 report showed an RR estimate of 1.44 or greater for persistent smokers. As can be seen in the forest plot, seven of the nine RR estimates it contains were statistically significant. The median RR was 1.67, indicative of an increase of two-thirds in the all-cause mortality rate in persistent smokers compared with quitters.

Taken together, the results of the studies summarized in Tables 4.21 and 4.22 and in Figure 4.4 show very clear, consistent, and strong associations. In total, 97% (31/32) of the studies reported associations indicating that smoking cessation was associated with a reduction in all-cause mortality when compared with persistent smoking. These associations were statistically significant in 78% (25/32) of the studies—a high proportion, given that 25% (8/32) of the studies had total samples of fewer than 300 patients and the median follow-up period was only 4.5 years. These results align closely with the results of meta-analyses published in 1999 (van Berkel et al. 1999) and in 2003 (Critchley and Capewell 2003) that reported summary RRs in quitters versus persistent smokers of 0.62 (95% CI, 0.57–0.68) (van Berkel et al. 1999) and 0.64 (95% CI, 0.58–0.71) (Critchley and Capewell 2003), respectively. When these associations are viewed from the reverse perspective of comparing persistent smokers with quitters, they are of a magnitude similar to the association of smoking with all-cause mortality in general cohorts, as reported in the 2014 Surgeon General's report (USDHHS 2014).

A central issue in assessing this body of evidence is that among current cigarette smokers diagnosed with CHD, those who quit may differ from persistent smokers in ways that could generate an apparent benefit of smoking cessation that reflects confounding. Many of the associations presented in the evidence tables in the present report are not adjusted for any potential confounding variables. The results in Table 4.21 that begin with the study

of Kinjo and colleagues (2005) and then go up through a 2014 report were estimated mainly with Cox proportional hazard models that adjusted for a wide range of potential confounding variables. These 10 studies had RR estimates that ranged from 0.11 to 0.93, with a median of 0.52. Only 3 of the 17 RR estimates were 0.63 or higher, and the 3 lowest RRs equaled 0.11 (once) and 0.17 (twice), with those results indicating a very strong protective effect for quitting. Notably, the studies that compared the characteristics of quitters with persistent smokers found that quitters tended to be older and to have a predominance of other characteristics associated with a worse prognosis. This pattern could lead to confounding that would diminish a true association.

The presence of confounding is supported by the increased association observed in some studies that adjusted for potential confounding variables. For example, in the study by Johansson and colleagues (1985), which compared persistent smokers with quitters, the unadjusted RR of death was 2.3 for the persistent smokers, and after adjustment for the key prognostic factors that differed between persistent smokers and quitters, the RR increased to 2.7 (Table 4.22). Thus, confounding appears an unlikely explanation for the finding of reduced all-cause mortality in quitters versus persistent smokers among those who were current smokers at the time of diagnosis with a cardiac condition. In contrast, it could be helpful in explaining the results of studies in which quitters, not persistent smokers, were the referent.

Concerns about confounding can be further addressed by analyzing evidence from studies of smoking cessation interventions that provide evidence to address this issue. For example, in an observational cohort study of 13,815 patients diagnosed with MI who were current smokers discharged alive from the hospital, those who received an inpatient smoking cessation intervention were compared with those who did not receive this intervention (Bucholz et al. 2017). At 30 days of follow-up, those who received the intervention had significantly reduced all-cause mortality (hazard ratio [HR] = 0.77; 95% CI, 0.62–0.96), and this benefit persisted even after 17 years of follow-up (HR = 0.93; 95% CI, 0.89–0.96) after adjustment for a wide range of potential confounding variables.

Elsewhere, in a randomized controlled trial of an intensive smoking cessation intervention (n = 109) compared with usual care (n = 100) in a population of 30- to 75-year-olds diagnosed with acute cardiovascular disease, after 2 years of follow-up the intervention group had 4.3 times the proportion of continuous abstinence from smoking compared with the usual-care group (Mohiuddin et al. 2007). During this same 2-year interval, compared with the usual-care group, the intervention group experienced a 44% reduction in hospitalizations (RR = 0.56;

95% CI, 0.37–0.85) and a reduction of more than three-quarters in all-cause mortality (RR = 0.23; 95% CI, 0.07–0.79) (Mohiuddin et al. 2007). Given the randomized trial design, this study provides experimental evidence of the association between smoking cessation and reduced fatal and nonfatal outcomes. Associations of this magnitude from a high-quality experimental study with relatively short-term follow-up provide strong evidence supporting an immediate and direct benefit of quitting and greatly reduce the likelihood that uncontrolled confounding explains the results of the observational studies.

Smoking Cessation and Cause-Specific Mortality in Cardiac Patients

The indication of a strong inverse association between smoking cessation and all-cause mortality after patients are diagnosed with CHD raises a question as to which causes of death are affected. Table 4.23 presents 20 specific associations comparing persistent smokers to quitters from 13 studies of cohorts of patients with CHD that assessed smoking cessation in relation to cause-specific mortality; these studies focused on either specific cardiac endpoints or sudden death. The 16 RR estimates with CIs are summarized in forest plots in Figure 4.5.

The results shown in Figure 4.5 are stratified by cause-of-death groups, with “cardiac” and “cardiac contributing” comprising the largest group (n = 9 data points), followed by sudden death (n = 3 data points), fatal reinfarction (n = 2 data points), and 1 each for ischemic heart disease and arrhythmic mortality. The visual impression of consistently strong associations shown in Figure 4.5 is reinforced by the complete evidence in Table 4.23, as all 20 associations presented in the table indicate increased risk associated with persistent smoking, with RRs ranging from 1.17 to 7.70, with a median of 1.60. The RRs were statistically significant in 45% (9/20), a smaller proportion than observed for all-cause mortality; because the magnitudes of the RRs were similar for all-cause and cause-specific mortality, the reduced statistical precision due to the smaller numbers of deaths for cause-specific compared with all-cause mortality likely explains the lower proportion of significant estimates. This body of evidence demonstrates that in current smokers diagnosed with CHD, the reduction in all-cause mortality associated with smoking cessation is attributable, at least in part, to a reduction in mortality from cardiac outcomes and sudden death. Cigarette smoking is an established cause of MI and other cardiovascular endpoints, as reviewed in prior Surgeon General’s reports (USDHHS 1983, 2010, 2014); thus, the associations reviewed in Table 4.23 and summarized in a forest plot in Figure 4.5 are consistent with prior evidence on this topic in the general population.

Smoking Cessation and Risk of Recurrence or New Cardiac Events in Cardiac Patients

Studies in cohorts of patients with CHD who were current smokers at the time of diagnosis that assessed the risk of new or recurrent cardiac events in relation to quitting versus persistent smoking are summarized in Table 4.24 and, for those studies with RRs and 95% CIs, in forest plots in Figure 4.6. Thirteen studies provided results for MI, including the outcomes of “reinfarction” and “MI hospitalization”; consistent with Figure 4.6, the associations tended to be either strongly in the protective direction for quitters compared with persistent smokers as the reference category (85% [11/13] RRs \leq 0.76; overall median RR = 0.67) or, alternatively, strongly in the direction of increased risk for persistent smokers relative to quitters as the referent. Of the two studies with results not strongly in the protective direction, the associations were null in one (RR = 0.99; 95% CI, 0.42–2.33) (Herlitz et al. 1995) and positive in the other (RR = 3.87; 95% CI, 0.81–18.37) (Perkins and Dick 1985). As seen in Figure 4.6, these two studies introduce heterogeneity. The overall results of these studies comprise a strong body of evidence indicating that smoking cessation after a diagnosis of a previous MI or other cardiac disease reduces the risk of MI.

The results for the endpoints of stroke, angina, or repeat procedures also indicate benefit from smoking cessation—that is, reduced risk in quitters versus persistent smokers. One study found that quitters had a lower risk of stroke (RR = 0.40; 95% CI, 0.14–1.17) compared with persistent smokers, but the results were not statistically significant (Chow et al. 2010). The one study of angina (Voors et al. 1996) found a weak, nonsignificant association for the entire follow-up period (RR = 1.2; 95% CI, 0.8–1.7), but a significant association for the period from 5 to 15 years after surgery (RR = 2.0; 95% CI, 1.3–3.6). Four studies reported results using repeat procedures as endpoints; these included repeat coronary artery bypass grafting/percutaneous transluminal coronary angioplasty (CABG/PTCA), reoperation, and repeat vascularization. Three studies observed increased risk for repeat procedures—CABG/PTCA, reoperation, or repeat vascularization—in persistent smokers when quitters were the referent (RR \geq 1.4). In the fourth study, authored by Chen and colleagues (2012), the results were strongly in the opposite direction, with an RR of 1.59 (95% CI, 1.36–1.85) for repeat revascularization in quitters compared with persistent smokers as the referent. This discrepant result notwithstanding, the overall evidence summarized in Table 4.24 and Figure 4.6 indicates reduced risk associated with smoking cessation relative to persistent smoking for the occurrence of adverse cardiac events among patients with CHD who were current smokers at diagnosis.

Figure 4.5 Cause-specific mortality from cardiovascular endpoints and sudden death in persistent smokers versus quitters

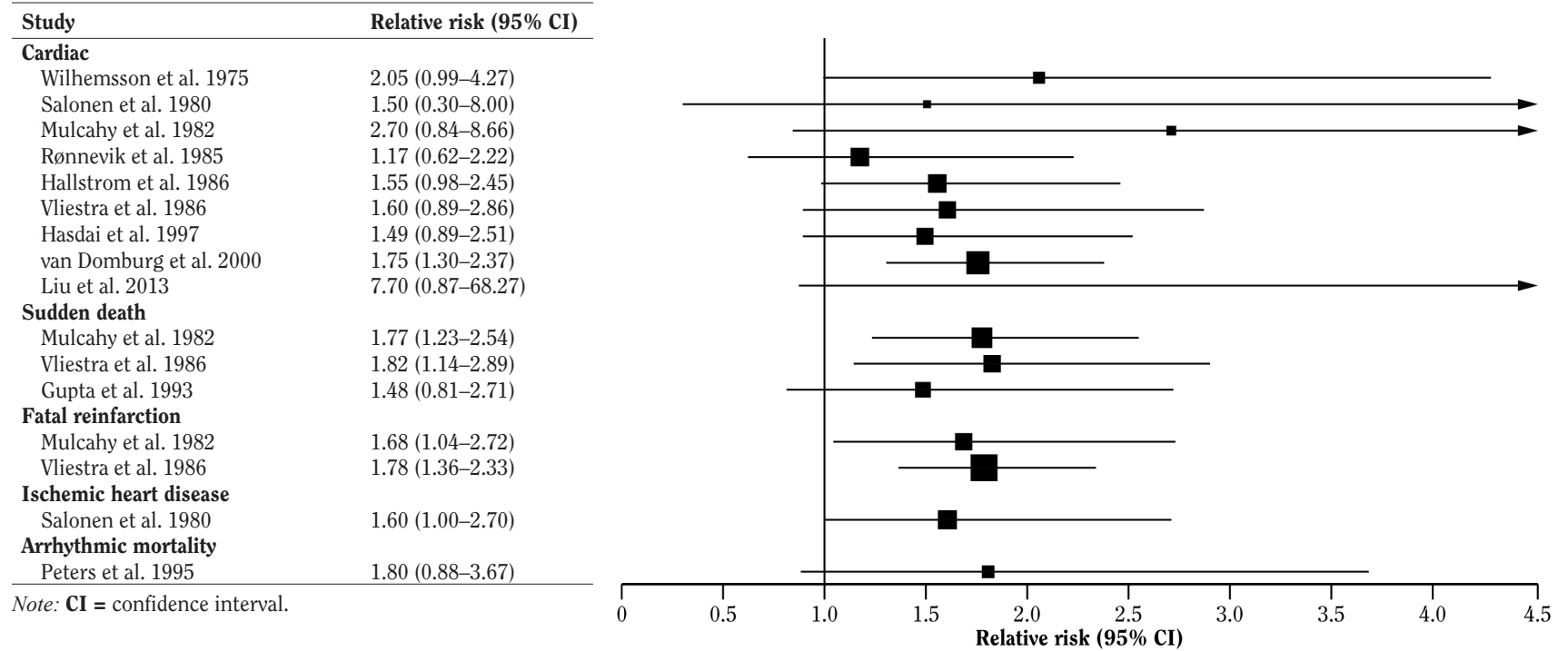
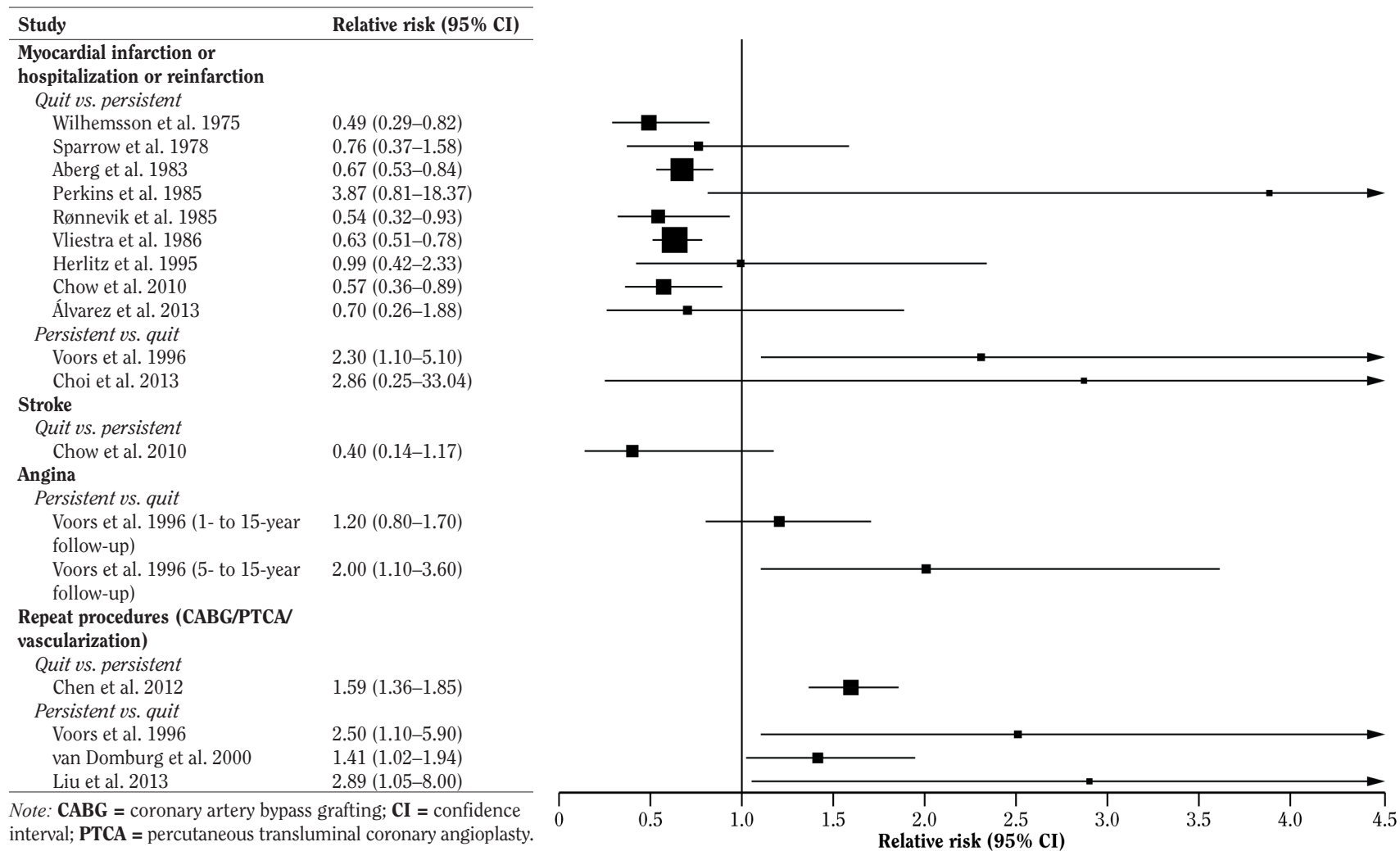


Figure 4.6 Comparison of incidence of new cardiac endpoints among persistent smokers and quitters



Summary of the Evidence

This review is the first Surgeon General's report to address the benefits of smoking cessation specifically in patients diagnosed with CHD. The importance of this topic is amplified by the fact that survival after a diagnosis of CHD has improved markedly during the past several decades (e.g., Savastano et al. 2014). Within this focus on the health benefits of cessation among patients already diagnosed with CHD, evidence was summarized on associations of cessation (versus persistent smoking) with all-cause mortality, deaths from cardiac causes and sudden death, and risk of recurrent or new cardiac events.

Methodologic Considerations

This review focused on direct evidence regarding the potential health benefits of smoking cessation—that is, quitting rather than continuing to smoke—among patients with CHD who were current smokers at the time of the index event. All the studies used in the review involved a prospective cohort, ensuring that the temporal relationship between cessation and outcome was correctly characterized. The evidence was abundant: Among the identified studies included in the evidence tables on the association between smoking cessation and important outcomes, there were 34 reports on all-cause mortality, 13 (yielding 20 distinct associations) on cause-specific mortality, and 15 on the risk of new or recurrent cardiac events. Thus, the strength with which inferences can be made is enhanced by the focus, quality, and scope of the evidence.

However, the potential role of confounding is a concern in drawing inferences from this body of evidence because (1) some associations considered were not adjusted for potential confounding variables and (2) among current cigarette smokers diagnosed with CHD, those who quit may have had a lower risk profile. A comparison of results from a study (Johansson et al. 1985) that used both unadjusted results and those that were adjusted for potential confounders indicated, however, that the adjusted results tended to be equal to or stronger than the unadjusted results. Thus, despite the potential for confounding to threaten the internal validity of the evidence, confounding is unlikely to have affected the validity of the overall evidence.

Compared with cohort studies in the general population, another noteworthy feature of follow-up studies of smoking cessation in patients with CHD is that the duration of follow-up tends to be shorter, sometimes only 6 months, and the median follow-up in this review was just 4.5 years. By contrast, 10 years was the median length

of follow-up in cohort studies of smoking, in relation to all-cause mortality in the general population, that were included in the meta-analysis of Gellert and colleagues (2012). With a shorter duration of follow-up, fewer end-points will be observed, and precision is reduced for estimating differences in outcome rates between quitters and persistent smokers.

Another caveat is that most studies included in this review relied on self-reports to determine smoking status; the results of two studies that compared biochemical assessments of smoking status with self-reported smoking suggest that relying on self-reported smoking alone can underestimate the true association (Twardella et al. 2006; Breitling et al. 2011a).

Evaluation of the Evidence

Causal Criteria

This Surgeon General's report is the first to consider the potential health benefits of smoking cessation in patients after a diagnosis of CHD. The report considers the totality of the evidence and references key criteria for causation established in the 1964 and 2004 Surgeon General's reports (U.S. Department of Health, Education, and Welfare [USDHEW] 1964; USDHHS 2004).

Temporality

The studies included in the evidence tables all had similar design features commonly used in prospective cohort studies. First, they studied patients who were current smokers when diagnosed with CHD. Second, patients were followed and reassessed to determine who quit smoking and who remained a smoker. Third, after quitters were distinguished from persistent smokers, there was subsequent follow-up for mortality and/or new cardiac events. Therefore, appropriate temporality is evident because, in all studies reviewed, smoking cessation preceded the occurrence of health outcomes in patients with CHD.

Consistency

The preponderance of the high-quality, focused bodies of evidence reviewed in this section showed that among patients who were current smokers when diagnosed with CHD, quitting smoking was consistently associated with reduced all-cause mortality compared with continuing to smoke. The studies focused primarily on MI as the index diagnosis, but they also included people with established CHD; the results were consistent regardless of the index condition. The studies were carried out

in a wide range of geographic locations; spanned several decades of research; and varied widely in methodology, such as sample size, timing of the measurement of change in smoking status, definition of quitters and persistent smokers, and control for potential confounding variables. Despite the potential for this variability to introduce inconsistencies across studies, a very clear, consistent set of results accrued over time. The evidence about cause-specific mortality and new or recurrent cardiac events also was highly consistent.

Strength of Association

The strength of the association observed for the outcome of all-cause mortality is best viewed in context of the existing evidence from the general population. The association between smoking and overall mortality was reviewed in the 1979 Surgeon General's report with a finding that the RR for overall mortality in cigarette smokers compared with nonsmokers was 1.7 (USDHEW 1979b), which is quite similar to an estimate arrived at in 2014 based on data in the 1964 Surgeon General's report (Schumacher et al. 2014). Because patients with CHD tend to be older than the general population, evidence specific to elderly populations is relevant. A systematic review of smoking and all-cause mortality in the elderly (defined as ≥ 60 years old) estimated a summary RR across studies of 1.83 (95% CI, 1.65–2.03) for current smoking versus never smoking (Gellert et al. 2012). Against this backdrop, the evidence for the association between smoking cessation and all-cause mortality in patients with CHD is of similar magnitude to findings from studies in the general population. In comparisons with persistent smokers, the median RR for all-cause mortality was 0.545 for those who quit smoking cigarettes; conversely, in reports that compared persistent smokers with quitters, the median RR was 1.67. The comparable magnitude of these associations is notable, considering that results for the general population are based on current versus never smokers, whereas the evidence reviewed here contrasts quitters with persistent smokers within a population made up entirely of current smokers at baseline.

The evidence presented for cause-specific mortality as an endpoint showed that, compared with quitting smoking, persistent smoking was strongly associated with increased mortality from cardiovascular disease endpoints and sudden death, with the median RR of 1.6 being very similar to that observed for all-cause mortality. Among patients with CHD who were current smokers when diagnosed, the risk of new or recurrent cardiac events was also observed to be strongly reduced by smoking cessation compared with persistent smoking; for example, the median RR for MI was 0.67.

When this body of evidence is viewed collectively, a consistent and coherent pattern of findings emerges

showing that among patients with CHD who are smokers when they are diagnosed, compared with those who remain smokers, those who quit smoking have a reduced risk of (1) dying from all causes and, specifically, dying from cardiovascular disease or experiencing sudden death and (2) experiencing new or recurrent cardiac events. The observed associations were strong, and the magnitude of these associations is even more impressive when the methodologic issues discussed above that would tend to bias these associations toward the null are carefully considered.

Experiment

For drawing causal inferences, studies of smoking cessation interventions that include results for clinical endpoints provide very strong evidence. In what can be viewed as quasi-experimental evidence, a large-scale, observational prospective cohort study found a strong all-cause mortality benefit in patients diagnosed with MI who received an inpatient smoking cessation intervention compared with those who did not receive an inpatient smoking cessation intervention (Bucholz et al. 2017). Earlier, in a randomized controlled trial of an intensive smoking cessation intervention compared with usual care among patients diagnosed with acute coronary syndrome or decompensated heart failure, the intervention group experienced marked and statistically significant reductions in all-cause mortality and hospitalizations (Mohiuddin et al. 2007). Strong associations from an experimental study favor the likelihood of an actual direct and causal association and weigh against uncontrolled confounding as an explanation of the results of the observational studies. The studies that provide direct evidence on this question consistently indicate that compared with persistent smoking, smoking cessation leads to substantial decreases in all-cause mortality.

Specificity

The relevance of the criterion of specificity to the evidence considered in this report lies in the comparison of the results for cause-specific mortality with the results for all-cause mortality. These results are similar. A substantial reduction in all-cause mortality associated with smoking cessation that was paralleled by a similar reduction for specific cardiac causes of death provides evidence to support the conclusion that at least a portion of the health benefits of smoking cessation in patients with CHD results from reduced risk of death from cardiac causes. The mortality reduction experienced in quitters would also be expected to be present for other causes of death known to be caused by smoking, but the evidence base ascertained for this review provided little evidence on this question.

Coherence

The causal criterion of coherence weighed heavily in evaluating the overall body of evidence as to whether smoking cessation can be considered a cause of mortality reduction in patients with CHD. The evidence on mortality reduction in patients with CHD following cessation needs to be interpreted in the context of the larger body of evidence on smoking cessation in relation to mortality in the general population. Previous Surgeon General's reports have concluded that smoking causes increased all-cause mortality in the general population. Based on the causal criterion of coherence, smoking cessation would be expected to decrease all-cause mortality in patients with heart disease, as in the general population. Similarly, because active smoking is causally associated with many adverse cardiac endpoints, it would be expected a priori that smoking cessation in patients with CHD would be associated with reduced risk of developing recurrent CHD. The combination of the substantial body of evidence reviewed here, which documents that smoking cessation is associated with reduced risk of death and disease, along with the fact that this evidence is in accord with a priori expectations about the known adverse health effects of smoking in the general population, strengthens the argument inferring a causal association.

Further adding to the coherence of the evidence are the established roles of smoking in causing endothelial dysfunctions and increasing risk for thrombosis, two etiologic pathways that contribute substantially to ischemic heart disease (USDHHS 2010; Barua and Ambrose 2013; Vanhoutte et al. 2017). Increasing endothelial production of adhesion molecules and decreasing production of vasodilators are some known mechanisms through which smoking causes endothelial dysfunction (USDHHS 2010). In addition, through adverse effects on endothelial cells, as well as on platelets, fibrinogen, and coagulation factors, smoking increases the risk of thrombosis, a key mechanism in the pathogenesis of MI and stroke (USDHHS 2010; Barua and Ambrose 2013). McEvoy and colleagues (2015b) examined three sets of markers in participants in the Multi-Ethnic Study of Atherosclerosis (MESA): inflammatory biomarkers, vascular dynamics and function, and subclinical atherosclerosis. Inflammatory markers were lower in former smokers compared with current smokers, and a longer time since quitting was associated with lower inflammatory markers. Results from a few studies provide evidence that in current smokers diagnosed with heart disease, quitting smoking is associated with biomarker profiles of reduced risk compared with persistent smoking. For example, smoking cessation in patients with acute MI was associated with improved coronary endothelial function, an improvement not seen in nonsmokers (Hosokawa

et al. 2008). Further, in patients with CAD, smoking cessation resulted in a reduced risk profile for macrophage cholesterol efflux (Song et al. 2015).

Synthesis of the Evidence

An extensive body of relevant evidence from prospective cohort studies was identified and reviewed. All studies were based on cohorts of patients who were current cigarette smokers when diagnosed with heart disease and who were followed up to first determine if they had quit smoking or continued to smoke and then to determine their vital status and to identify new or recurrent cardiac events. Most of this overall high-quality evidence indicates that in patients who are current smokers when diagnosed with heart disease, smoking cessation after the diagnosis is strongly and causally associated with reduced all-cause mortality. In patients with heart disease who are current smokers when diagnosed, the evidence indicates that smoking cessation reduces the risk of dying by almost one-half, a very strong clinical benefit. Not only is this unequivocally demonstrated in the data from prospective cohort studies, but the corroborating experimental evidence on this topic strongly reinforces this conclusion. Additionally, the evidence reviewed here demonstrates that the health benefits of smoking cessation after a heart disease diagnosis extend to mortality specifically from cardiac causes and sudden death. Third, the evidence indicates that smoking cessation is associated with decreased risk of new or recurrent cardiac events. Based on the causal criterion of coherence, the known causal associations between smoking and these outcomes in the general population support the causal nature of the associations.

Because all the currently available evidence is from prospective studies, the temporal nature of the association is not ambiguous. The evidence for each outcome showed a high degree of consistency across diverse study populations and measurement approaches. These characteristics of the evidence clearly indicate that in current smokers diagnosed with heart disease, smoking cessation is associated with reduced risk of all-cause mortality, cause-specific mortality, and new or recurrent cardiac events.

Conclusions

1. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between

smoking cessation and a reduction in all-cause mortality.

2. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reductions in deaths due to cardiac causes and sudden death.
3. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reduced risk of new and recurrent cardiac events.

Implications

The evidence summarized in this section documents that cigarette smoking cessation has a profoundly positive impact on overall survival in patients who are current cigarette smokers when diagnosed with CHD. The reductions in risk are substantial for total mortality and cardiovascular disease-specific outcomes. Estimates across studies indicate that smoking cessation reduces relative risks for these outcomes by 30–40%. Considered in the context of current knowledge of the health benefits of smoking cessation in the general population,

cessation of smoking would be expected to have major health benefits in patients diagnosed with CHD. This evidence has clear clinical implications. Current cigarette smokers who are diagnosed with CHD can improve their prognosis by quitting smoking. Providing evidence-based smoking cessation services to patients with CHD who smoke would be expected to have a substantial beneficial impact on their prognosis, with the magnitude of the benefits in some instances even equaling or exceeding that of other state-of-the-art therapies. A Cochrane review found evidence for efficacy of smoking cessation interventions in patients hospitalized for cardiovascular disease (Rigotti et al. 2012). The critical role of smoking cessation in cardiac rehabilitation is already recognized in evidence-based medicine guidelines (King et al. 2005; Smith et al. 2006); the new conclusions of this report can be cited in further emphasizing to the public health, clinical, and patient and caregiver communities just how critical it is to provide evidence-based smoking cessation services to cardiac patients. In particular, cardiologists who provide care to patients who have experienced cardiovascular events should (a) clearly communicate to these patients that quitting smoking is the most important action they can take to improve their prognosis and (b) offer patients evidence-based cessation treatments, including counseling, medications, and referral to more intensive assistance, including state quitlines (Fiore et al. 2008; U.S. Preventive Services Task Force 2015).

Chronic Respiratory Disease

Tobacco smoke contains thousands of chemical components that are inhaled and then deposited throughout the large and small airways and alveoli of the lungs (U.S. Department of Health and Human Services [USDHHS] 2010). The toxic components of cigarette smoke injure the lungs through a variety of mechanisms, including oxidative injury and inflammation, carcinogenesis, and effects on the immune system (USDHHS 2010, 2014). For example, acrolein and formaldehyde impair ciliary clearance and nitrogen oxides cause inflammation of the airways, while cadmium and hydrogen cyanide result in direct oxidant injury and impaired oxidative metabolism (USDHHS 2010). Cigarette smoke initiates an inflammatory process that results in direct destruction of lung parenchyma that is mediated through (a) the release of proteinases that damage the extracellular matrix of the lung, (b) apoptosis because of oxidative stress, and (c) loss of matrix–cell attachment and ineffective repair of elastin and other extracellular matrix components that enlarge the airspace (USDHHS 2010, 2014). Although successful

smoking cessation ends daily exposure to innumerable injurious compounds, the prolonged deleterious effects of tobacco smoke result in irreversible impairment in immune responses, changes in the makeup of the lung microbiome, and continued lung injury even after cessation (USDHHS 2014).

This section provides an update on the evidence about smoking cessation and respiratory health among persons with chronic obstructive pulmonary disease (COPD) or asthma.

Conclusions from Previous Surgeon General’s Reports

Associations of cigarette smoking with chronic respiratory diseases, including COPD, asthma, and interstitial lung diseases, have been addressed in numerous Surgeon General’s reports since 1964 (U.S. Department

of Health, Education, and Welfare [USDHEW] 1964). The 1964 report concluded that cigarette smoking is the most important cause of chronic bronchitis (USDHEW 1964). The principal topic of the 1984 report was COPD (USDHHS 1984), and later reports addressed active smoking, exposure to secondhand smoke, and major respiratory diseases (USDHHS 2004, 2006, 2014). The conclusions from these reports addressed the causation and exacerbation of chronic respiratory disease by tobacco smoking; the risks of respiratory infections, a frequent contributor to exacerbation of chronic respiratory diseases; and the benefits of cessation (USDHEW 1964; USDHHS 1984). Several Surgeon General’s reports have addressed the health benefits of smoking cessation for COPD; these conclusions are listed in Table 4.25.

keyword terms was used for each of the following concepts: (1) smoking cessation, (2) respiratory phenomena, (3) asthma, (4) chronic obstructive pulmonary disease, (5) emphysema, and (6) chronic bronchitis. Studies that did not focus on smoking cessation were excluded. To formulate conclusions, evidence cited in the 2014 Surgeon General’s report on smoking was considered along with any newly available evidence. Search results were limited to studies published in English and to original research. The primary search identified 1,977 items. Two independent reviewers identified 45 articles through consensus after reviewing the titles and abstracts. After a full review of the 45 articles, 24 articles (17 on COPD and 7 on asthma) were selected as relevant for this update.

Literature Review Methods

MEDLINE, SCOPUS, and EMBASE were searched for studies that focused on smoking cessation and COPD or asthma and were published between January 1, 2008, and May 26, 2016. A systematic literature search was created for PubMed and translated to the EMBASE and SCOPUS databases. A combination of controlled vocabulary and

Chronic Obstructive Pulmonary Disease

This section addresses advances in the evidence base on COPD and smoking cessation and the implications of the new findings. Our current understanding of the pathogenesis of COPD underscores the importance of smoking cessation in slowing and eventually ending lung damage associated with tobacco smoke. The occurrence of clinical

Table 4.25 Conclusions about smoking cessation and chronic respiratory disease from previous Surgeon General’s reports

Report	Conclusions
USDHHS (2010, p. 10)	<ul style="list-style-type: none"> Smoking cessation remains the only proven strategy for reducing the pathogenetic processes leading to chronic obstructive pulmonary disease.
USDHHS (1990, p. 11)	<ul style="list-style-type: none"> Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking. For persons without overt chronic obstructive pulmonary disease (COPD), smoking cessation improves pulmonary function about 5 percent within a few months after cessation. Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers. With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers.
USDHHS (1984, p. 10)	<ul style="list-style-type: none"> Cessation of smoking leads eventually to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.
USDHEW (1979a, p. 18)	<ul style="list-style-type: none"> Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms. Cessation reduces the chance of premature death from chronic bronchitis and emphysema.

Notes: **COLD** = chronic obstructive lung disease; **COPD** = chronic obstructive pulmonary disease; **USDHEW** = U.S. Department of Health, Education, and Welfare; **USDHHS** = U.S. Department of Health and Human Services.

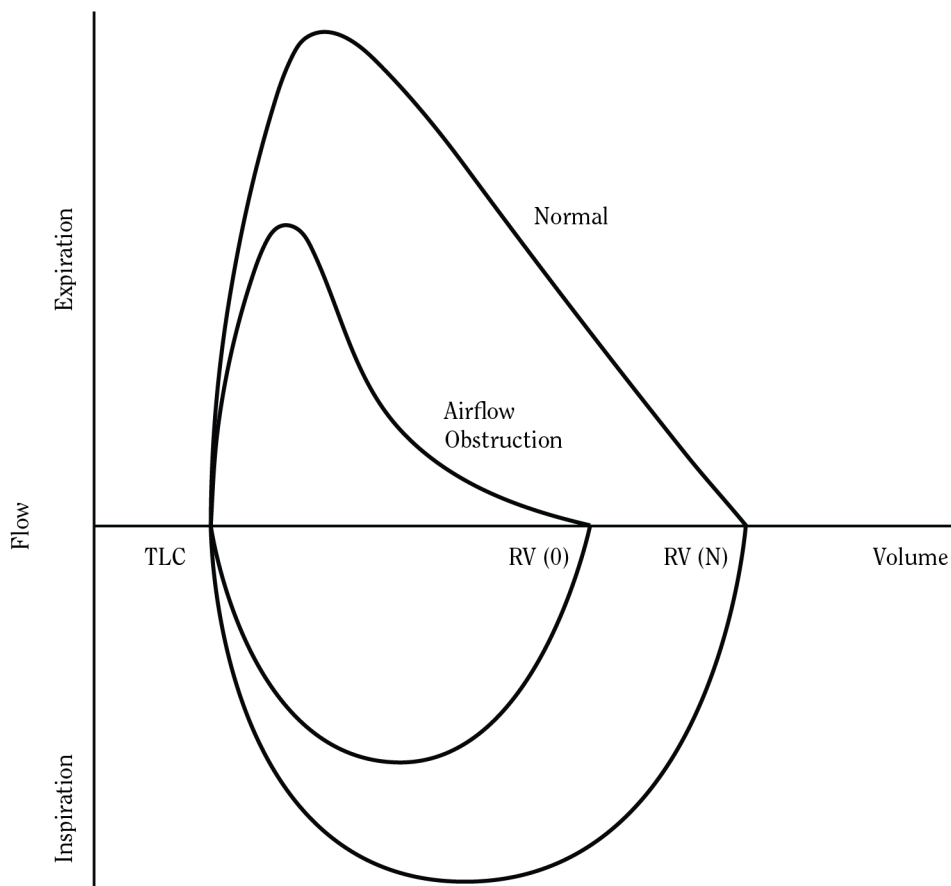
COPD reflects a long course of progressive deterioration of lung function that can begin before conception, as maternal smoking during pregnancy affects the development of lungs in fetuses (Cook et al. 1998; Checkley et al. 2010, 2016).

COPD is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (Celli et al. 2004; USDHHS 2014; Benditt n.d.) (Figure 4.7). The development of airflow limitation among those with COPD is usually progressive and reflects the ongoing processes of lung injury that are initiated and sustained by persistent exposure to tobacco smoke (Rabe et al. 2007). Thus, smoking cessation is critical in preventing COPD, slowing its progression, and treating this disorder. Although previous definitions have focused on phenotypes of COPD, such as chronic

bronchitis and emphysema, the diagnosis of COPD has now been standardized on the basis of spirometry and the presence of airflow obstruction (i.e., a reduced ratio of forced expiratory volume at 1 second [FEV_1] to forced vital capacity [FVC]) that does not fully reverse after bronchodilation (Tashkin and Murray 2009). Previously, COPD was defined by a fixed ratio (post-bronchodilator $FEV_1/FVC < 70\%$) (Rabe et al. 2007). There is debate, however, on using the lower limit of normal for selected reference populations as the best approach to standardizing the interpretation of spirometry results by accounting for age, sex, height, and race (Mannino et al. 2007; Swanney et al. 2008; Miller et al. 2011b; Mannino and Diaz-Guzman 2012; Quaderi and Hurst 2017).

Thus, FEV_1/FVC is generally used to define COPD, but FEV_1 and the rate of decline of FEV_1 have been the two most widely used outcome measures for clinical trials related to COPD. These indicators are also associated

Figure 4.7 Flow-volume loops for a person with (obstruction) and without (normal) chronic obstructive pulmonary disease



Source: Benditt (n.d.). Copyright © University of Washington, 2004.

Note: RV = residual volume; TLC = total lung capacity.

with measures of health-related quality of life and mortality (Wise 2006). Additionally, however, there is evidence to support the presence of considerable smoking-related respiratory disease among persons with normal lung function. For example, in a study by Woodruff and colleagues (2016), half of current or former smokers with preserved pulmonary function exhibited respiratory symptoms, and former smokers with preserved lung function had higher rates of exacerbation events than lifelong non-smokers. Sensitive imaging approaches are now used to quantify changes in the lungs, including emphysema, that have health implications. Oelsner and colleagues (2014) found higher all-cause mortality among former and current smokers with emphysematous changes on computed tomography (CT) and preserved pulmonary function. However, the analysis did not find differences in the risk of having such changes by smoking status.

Smoking Cessation and Chronic Obstructive Pulmonary Disease

Cigarette smoking is the most common cause of COPD in the United States (Xu et al. 1992; Anthonisen et al. 1994; Perret et al. 2014) and is a consistent and strong risk factor for the development of COPD (USDHHS 2014). In the United States, the population-attributable risk for developing COPD caused by smoking has been estimated to be as high as 80–90% (Eisner et al. 2010; USDHHS 2014). Although observational evidence shows that air pollution adversely affects persons with COPD, not starting to smoke and smoking cessation remain the only proven prevention strategies for reducing the risk of developing chronic respiratory diseases caused by cigarette smoking (Xu et al. 1992; Anthonisen et al. 1994; Abramson et al. 2015). Smoking cessation can prevent or delay the development of airflow limitation and slow the progression of chronic respiratory disease; it is the only intervention that has been shown to reduce the rate of FEV₁ decline in both men and women (Thomson et al. 2004) and to reduce all-cause mortality among those with COPD (Anthonisen et al. 2005).

Epidemiology of Mortality from Chronic Obstructive Pulmonary Disease in Relation to Tobacco Cessation

The relationship between temporal trends in the decline of smoking prevalence and trends in COPD morbidity and mortality is complex, as evidenced by data collected in the United States (Mannino and Buist 2007). Prevalence estimates of COPD have limited validity because symptoms related to COPD, such as dyspnea on exertion and limitation in physical activity, are nonspecific (Tashkin and Murray 2009). Nonetheless, some trends

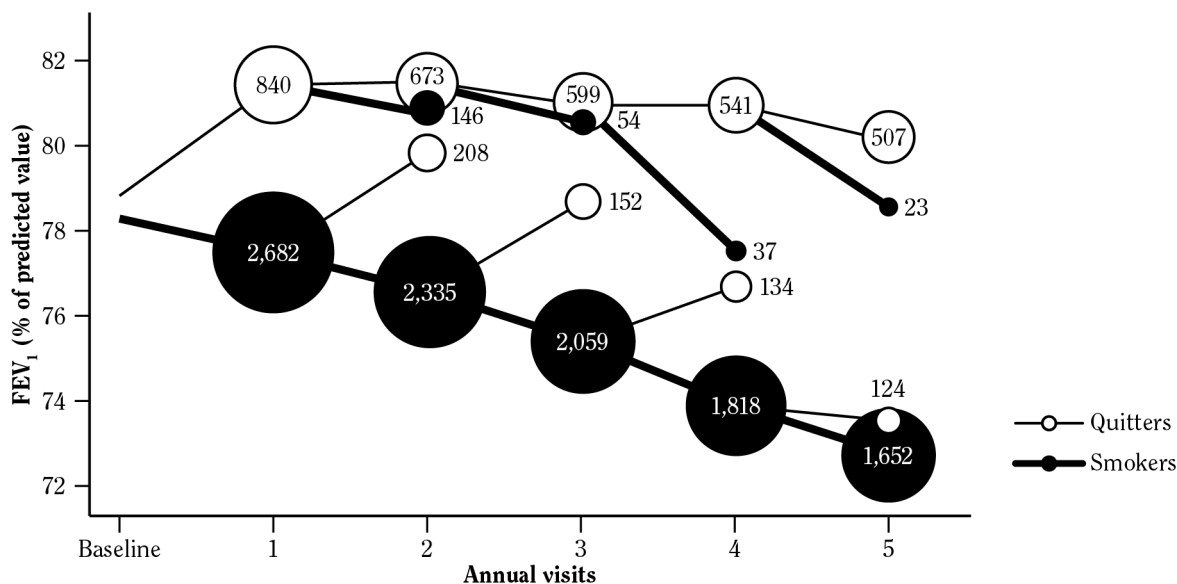
are quickly apparent from surveillance data. Among all U.S. adults, age-adjusted mortality from COPD increased from 29.4 per 100,000 population in 1968 to 67.0 per 100,000 population in 1999 and then declined slightly to 63.7 per 100,000 population in 2011 (Ford 2015). Mortality from COPD among men has declined since 1999, but among women, the age-adjusted mortality continues to increase (Ford 2015). Despite this narrowing of the difference between men and women, mortality rates in men continue to exceed those in women (Ford 2015). Notably, among certain population subgroups (i.e., Black men, White men, adults 55–64 years of age, adults 65–74 years of age), mortality rates have declined during the past decade (Ford 2015).

How Smoking Cessation Affects the Decline of Lung Function in Smokers

The 1990 Surgeon General's report on the health benefits of smoking cessation cited only three studies concerning the effect of smoking cessation on the decline of lung function (USDHHS 1990). The 1990 report did provide a conclusion that "With sustained abstinence from smoking, the rate of decline of pulmonary function in former smokers returns to that of never smokers" (USDHHS 1990, p 349). Since the 1990 report, both clinical and population studies have examined the association between cessation of tobacco smoking and the decline of lung function.

The Lung Health Study, a randomized clinical trial of smoking cessation and respiratory outcomes, evaluated the effect of an intensive smoking cessation intervention (combined randomly with either the inhaled bronchodilator ipratropium bromide or placebo) on the rate of FEV₁ decline among 5,887 cigarette smokers 35–60 years of age with mild-to-moderate airflow limitation from COPD (Anthonisen et al. 1994). Participants who continued to smoke had a greater decline in FEV₁ at the 5-year follow-up (Figure 4.8) compared with those who quit. In a separate analysis of data from the Lung Health Study, a decrease in the number of cigarettes smoked by continued smokers did not reduce the rate of decline of lung function compared with complete cessation, unless the number of cigarettes smoked was reduced by at least 85% (Simmons et al. 2005). The benefit of a lower decline of FEV₁ among participants in the smoking intervention program compared with the control group persisted over 11 years of follow-up (Anthonisen et al. 2002; Murray et al. 2002). Participants in the smoking intervention group had a lower decline of FEV₁ than participants receiving usual care (the control group) (Anthonisen et al. 2002). Men who quit smoking at the beginning of the Lung Health Study had a rate of decline in FEV₁ of 30.2 milliliters (mL)/year, whereas this measure declined at 21.5 mL/year in women

Figure 4.8 Impact of smoking cessation and resumption on FEV₁ decline in the Lung Health Study cohort of patients with chronic obstructive pulmonary disease



Source: Scanlon and colleagues (2000, p. 384). Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

Note: FEV₁ = forced expiratory volume at 1 second.

who quit. Men who continued to smoke throughout the 11 years of follow-up experienced an FEV₁ decline of 66.1 mL/year, and women who continued to smoke experienced a decline of 54.2 mL/year (Anthonisen et al. 1994). At the 14.5-year follow-up, all-cause mortality was lower in the intervention group than in the usual-care group (8.8 per 1,000 person-years vs. 10.4 per 1,000 person-years, $p = 0.03$) (Anthonisen et al. 2005).

Several studies have examined how quickly benefits of smoking cessation are observed. In an analysis of a 6-year follow-up of 4,451 Japanese American men participating in the Honolulu Heart Program, Burchfiel and colleagues (1995) reported that the rate of FEV₁ decline was reduced in participants who quit smoking compared with those who continued smoking. These researchers also found that, after 2 years of successful cessation, the reduced rate of FEV₁ decline among quitters approximated that of participants who never smoked. In contrast, the rate of FEV₁ decline in the first 2 years was similar between quitters and those who continued to smoke. This last finding suggests that the effects of smoking cessation on decline in lung function are not immediate and may take up to 2 years to be manifested.

Table 4.26 summarizes reports published in 2009 or later offering further evidence on smoking cessation

and the natural history of COPD and other respiratory outcomes from long-term studies. Studies and trials have continued to demonstrate immediate improvement in self-reported respiratory symptoms at 1 to 3 months after cessation (Louhelainen et al. 2009; Etter 2010) and an improvement in FEV₁ and in COPD-specific outcomes at 1 year after quitting (Tashkin et al. 2011; Dhariwal et al. 2014). Smoking cessation has a beneficial effect at any age, although the benefit was found to be more pronounced among persons who quit before 30 years of age compared with those who quit after 40 years of age (Kohansal et al. 2009).

Although smoking cessation results in less severe respiratory symptoms, the inflammatory burden may persist. In a prospective cohort, Louhelainen and colleagues (2009) found oxidant and protease burden in airways (using sputum as a proxy to measure airway inflammation) that persisted for months after smoking cessation. Versluis and colleagues (2009) found that adenosine receptor mechanisms may be implicated in the progression of the inflammatory response after cessation in cigarette smokers with COPD. Specifically, the expression of adenosine receptors increased in some sputum cell types and sputum adenosine levels appeared to rise in those with COPD 1 year after smoking cessation (Versluis et al. 2009).

Table 4.26 Studies on smoking cessation and chronic obstructive pulmonary disease, 2009–2017

Study	Design/population	Findings
Lung function		
Kohansal et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort • 4,391 participants 13–71 years of age with two or more valid spirometry measurements during follow-up periods (1971–1997) of the Framingham Offspring Study • Participants divided into three groups: <ul style="list-style-type: none"> – Never smokers (n = 1,578) – Continuous smokers (n = 754) – Other smokers, which included former smokers (n = 2,059) • Never smokers and continuous smokers were further divided into categories of healthy and nonhealthy 	<p>Smoking cessation had a beneficial effect at any age, but it was more pronounced in earlier quitters</p> <p>The rate of FEV₁ decline in both male and female smokers who quit before age 30 was indistinguishable from healthy never smokers</p> <p>In contrast, smokers who quit after 40 years of age showed a significantly enhanced rate of decline of FEV₁ versus healthy never smokers and earlier quitters, but their rate was not significantly different from that of continuous smokers</p> <p>The mean FEV₁ decline value among continuous smokers (with 95% CI) was 38.2 ml (33.9–42.6) for males and 23.9 ml (20.9–27.0) for females, with p = 0.001 for male vs. female (p ≤ 0.05 versus healthy never smokers)</p>
Louhelainen et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort • 61 smokers: <ul style="list-style-type: none"> – 21 with chronic bronchitis or COPD – 15 with asthma – 25 asymptomatic • Followed 3 months after smoking cessation 	Although symptoms improved after smoking cessation, oxidant and protease burden in the airways continued for months after cessation
Takabatake et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort • 82 former smokers with COPD • Followed for 30 months 	<i>CDC6</i> may be one of the susceptibility genes that contributes to rapid decline in lung function despite smoking cessation in patients with COPD
Versluis et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort • 26 smokers who had successfully quit for at least 1 year: <ul style="list-style-type: none"> – 11 with COPD – 15 asymptomatic • Followed at 1 year after cessation 	Adenosine-related effector mechanisms are involved in the persistence and progression of the inflammatory response in COPD after 1 year of smoking cessation
Mazur et al. (2011)	<ul style="list-style-type: none"> • Prospective cohort • 474 current smokers • 155 with COPD symptoms • 319 no symptoms • Followed for 2 years, with 111 succeeding in cessation 	After 2 years of follow-up, levels of surfactant protein A were higher in those who continued smoking compared with those who quit
Tashkin et al. (2011)	<ul style="list-style-type: none"> • Randomized controlled trial • 504 participants (smokers with mild-to-moderate COPD): <ul style="list-style-type: none"> – 250 in the varenicline treatment group – 254 in the placebo treatment group 	In this 1-year cessation trial of smokers with COPD, continuous abstinence compared with continuous smoking significantly improved (p = 0.0069) mean change from baseline in post-bronchodilator FEV ₁ (although the difference subsequently narrowed) and total scores on the Clinical COPD Questionnaire at 12 weeks, with sustained improvement thereafter on that instrument
Dhariwal et al. (2014)	<ul style="list-style-type: none"> • Prospective cohort • 358 heavy smokers screened: <ul style="list-style-type: none"> – 38 with COPD – 55 with normal spirometry • Control group: 19 nonsmokers • Followed for 1 year 	<p>Smoking cessation had differential effects on lung function (FEV₁ and gas transfer) and features revealed on high-resolution CT images (emphysema and micronodules)</p> <p>Smoking cessation in patients with COPD caused transient improvement in FEV₁ and decreased the presence of micronodules</p>

Table 4.26 Continued

Study	Design/population	Findings
Lung function (continued)		
Ito et al. (2015)	<ul style="list-style-type: none"> • Cross-sectional • 93 participants divided into four groups: <ul style="list-style-type: none"> – Former smokers with COPD (n = 23) – Smokers with COPD (n = 17) – Current smokers (n = 27) – Nonsmokers (n = 26) 	One year after smoking cessation, participants with COPD had improved mucociliary clearance
Respiratory symptoms		
Etter (2010)	<ul style="list-style-type: none"> • Prospective cohort • Visitors to Stop-tabac.ch website • 18 years of age or older • 15,916 participants at baseline • 1,831 participants at 1-month follow-up 	<p>Smoking cessation was followed by a rapid and substantial improvement in self-reported respiratory symptoms</p> <p>In the 252 baseline smokers who had quit smoking at 30-day follow-up, there was a substantial decrease in the proportion of participants who declared that they often coughed even without a cold (from 51.6% at baseline to 15.5% at follow-up), expectorated when they coughed in the morning (from 47.6% to 19.4%), were out of breath after climbing stairs or after a quick walk (from 75.0% to 48.4%), and who had a wheezing respiration (from 33.7% to 10.3%) (p = 0.001 for all before/after comparisons)</p>
Josephs et al. (2017)	<ul style="list-style-type: none"> • Retrospective cohort • 16,479 patients with COPD with outcomes over 3 years • 8,941 former smokers 	<p>Former smokers had significantly reduced risk of death, hospitalization, and visits to the emergency department</p> <p>Compared with active smokers, ex-smokers had significantly reduced risk of death, with a hazard ratio (95% CI) of 0.78 (0.70–0.87); hospitalization, 0.82 (0.74–0.89); and emergency department attendance, 0.78 (0.70–0.88)</p>
Imaging		
Ashraf et al. (2011)	<ul style="list-style-type: none"> • Prospective cohort • 726 current and former smokers • Aged 50–70 years • Smoking history of more than 20 pack-years. • Former smokers were only included if they had quit smoking after the age of 50 years and less than 10 years before inclusion. • All subjects had to have an FEV₁ at least 30% of predicted normal. • Followed for more than 2 years 	<p>Current smoking status was associated with lower lung density and a difference in lung density between current and former smokers who were observed at baseline, which corresponded closely to changes in lung density after cessation</p> <p>After smoking cessation (n = 77) 15th percentile density (PD15) decreased by 6.2 g/l (p < 0.001) in the first year, and by a further 3.6 g/l (p < 0.001) in the second year, after which no further change could be detected; moreover, the first year after relapse to smoking (n = 18) PD15 increased by 3.7 g/l (p = 0.02)</p>
Miller et al. (2011a)	<ul style="list-style-type: none"> • Prospective cohort • 10 former smokers with COPD after 4 years of not smoking 	Cessation of tobacco smoking in heavy smokers with moderately severe emphysema was associated with evidence of persistent airway inflammation and progression of emphysema on CT
Shaker et al. (2011)	<ul style="list-style-type: none"> • Prospective cohort • 36 former smokers with COPD • Followed for 2–4 years 	Inflammation partly masked the presence of emphysema on CT, and smoking cessation resulted in a paradoxical fall in lung density, which resembled rapid progression of emphysema; this fall in density likely resulted from an anti-inflammatory effect of smoking cessation

Table 4.26 Continued

Study	Design/population	Findings
Imaging (continued)		
Hoesein et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort • 3,670 male smokers • 1- and 3-year follow-up • Follow-up CT and pulmonary testing 	<p>Current smokers had yearly FEV₁ decline of 69 mL, and participants who had quit smoking more than 5 years earlier had a yearly decline of 57.5 mL</p> <p>Compared with current smokers, participants who had quit smoking more than 5 years earlier showed significantly lower rates of progression of emphysema on CT</p>
Hlaing et al. (2015)	<ul style="list-style-type: none"> • Prospective cohort • 45 persons with COPD who stopped smoking • Followed for 1 year 	On the CT image, significant decreases occurred in mean lung density and the attenuation value separating the least 15% pixels, but there was a significant increase in the percentage of the relative area of the lungs with attenuation values <-950 Hounsfield units
Takayanagi et al. (2017)	<ul style="list-style-type: none"> • Prospective cohort • 58 patients with COPD at the time of their enrollment at the hospital and 2 years later 	Airway disease and vascular remodeling may be reversible to some extent through smoking cessation and appropriate treatment
Immunity		
Roos-Engstrand et al. (2009)	<ul style="list-style-type: none"> • Case-control • 19 persons with stable COPD: <ul style="list-style-type: none"> – 7 smokers – 12 former smokers • Compared with 12 age-matched never smokers and 13 pack-years-matched smokers with normal lung function 	Five years after smoking cessation, former smokers with COPD had significantly higher percentages of CD8+ cells compared with never smokers
DNA methylation		
Tsaprouni et al. (2014)	<ul style="list-style-type: none"> • Cross-sectional • Discovery cohort: 464 participants who were either diagnosed with CAD (n = 238) or were considered healthy (controls, n = 226): <ul style="list-style-type: none"> – Current smokers (n = 22) – Former smokers (n = 263) – Never smokers (n = 179) • Replication cohort: 356 female participants, all twins: <ul style="list-style-type: none"> – Current smokers (n = 41) – Former smokers (n = 104) – Never smokers (n = 211) 	The effect of smoking on DNA methylation was partially reversible following smoking cessation for longer than 3 months
Wan et al. (2012)	<ul style="list-style-type: none"> • Cross-sectional • Discovery cohort: 1,085 participants with ≥5 pack-years of cigarette smoking and reported FEV₁ limitation, as well as one eligible sibling with ≥5 pack-years of cigarette smoking: <ul style="list-style-type: none"> – Current smokers (n = 396) – Former smokers (n = 689) • Replication cohort: 369 participants with FEV₁ limitation: <ul style="list-style-type: none"> – Never smokers (n = 68) – Current smokers (n = 103) – Former smokers (n = 198) 	The existence of dynamic, site-specific methylation changes in response to smoking may contribute to the risks associated with cigarette smoking that persist after cessation

Notes: **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **CT** = computed tomography; **FEV₁** = forced expiratory volume at 1 second; **CAD** = coronary artery disease; **mL** = milliliter.

In a later study, Mazur and colleagues (2011) assessed levels of surfactant protein A (SP-A) among smokers, nonsmokers, and former smokers over a 2-year period. Although plasma SP-A levels tended to decline among those who quit smoking, no significant difference from baseline was evident at the 2-year follow-up. A difference in plasma SP-A levels was evident, however, between those who quit and active smokers, whose SP-A levels continued to increase (Mazur et al. 2011).

Novel Diagnostics for Assessing the Impact of Smoking Cessation on the Progression of Chronic Obstructive Pulmonary Disease

Since the earlier Surgeon General's reports on this topic (USDHHS 1984, 2004), new techniques—such as imaging—have been used to investigate the natural history of COPD. These techniques have provided insights into structural changes and genomics, epigenomics, and other “-omics” approaches that help to better understand the molecular determinants of COPD risk and the persistence of risk after cessation. Furthermore, novel therapeutic options—such as epigenetic regulation—can be reprogrammed, potentially modifying risk and supporting treatment of disease states (Sakao and Tatsumi 2011).

Imaging

Quantitative volumetric CT scanning, a well-established diagnostic modality, can assess pathology *in vivo*, enabling morphologic phenotyping of three critical components of the progression of COPD: emphysema (Bankier et al. 2002; Madani et al. 2008), thickening of the airway wall (Orlandi et al. 2005; Coxson 2008), and trapping of expiratory air (Mets et al. 2012). These measures correlate with pathologic measures of emphysema and small airways disease and predict such clinical outcomes as FEV₁ decline (Mohamed Hoesein et al. 2011) and frequency of exacerbation (Han et al. 2011). Additionally, the growing adoption of annual CT scans to screen for lung cancer makes possible volumetric analysis at a population level over time, providing a powerful tool for assessing changes in lung structure after cessation of exposure to tobacco smoke, at least in this high-risk group. Low-dose CT used in annual screening enables the assessment of airways and lung parenchyma with less radiation compared with conventional CT scanning. Examining the effects of cessation on volumetric CT imaging is complicated, however, by the contradiction between the reported short-term and long-term effects of smoking. Specifically, previous studies have demonstrated that current cigarette smoking increases measurements of lung density and that these changes are most likely a result of accumulation of particulate matter resulting in inflammation (Grydeland

et al. 2009), but over the long term, the emphysematous changes related to inhaling tobacco smoke result in low lung density (Ashraf et al. 2011). It is important that changes in lung density over the short term not be interpreted as either the progression of emphysema or improvement in that condition. Smoking cessation has been shown to reduce lung density, and the rate of reduction increases at 2 years post-cessation (Scanlon et al. 2000; Ashraf et al. 2011). At 2 years post-cessation, lung density stabilizes, suggesting a reversal of the inflammatory sequelae of exposure to tobacco smoke, which is consistent with findings on lung function in the Lung Health Study (Scanlon et al. 2000; Ashraf et al. 2011). A similar study by Takayanagi and colleagues (2017) demonstrated progression of emphysema, particularly in the subgroup of patients with exacerbations, but imaging findings related to airway disease and pulmonary vasculature did not change in proportion to the progression of emphysema.

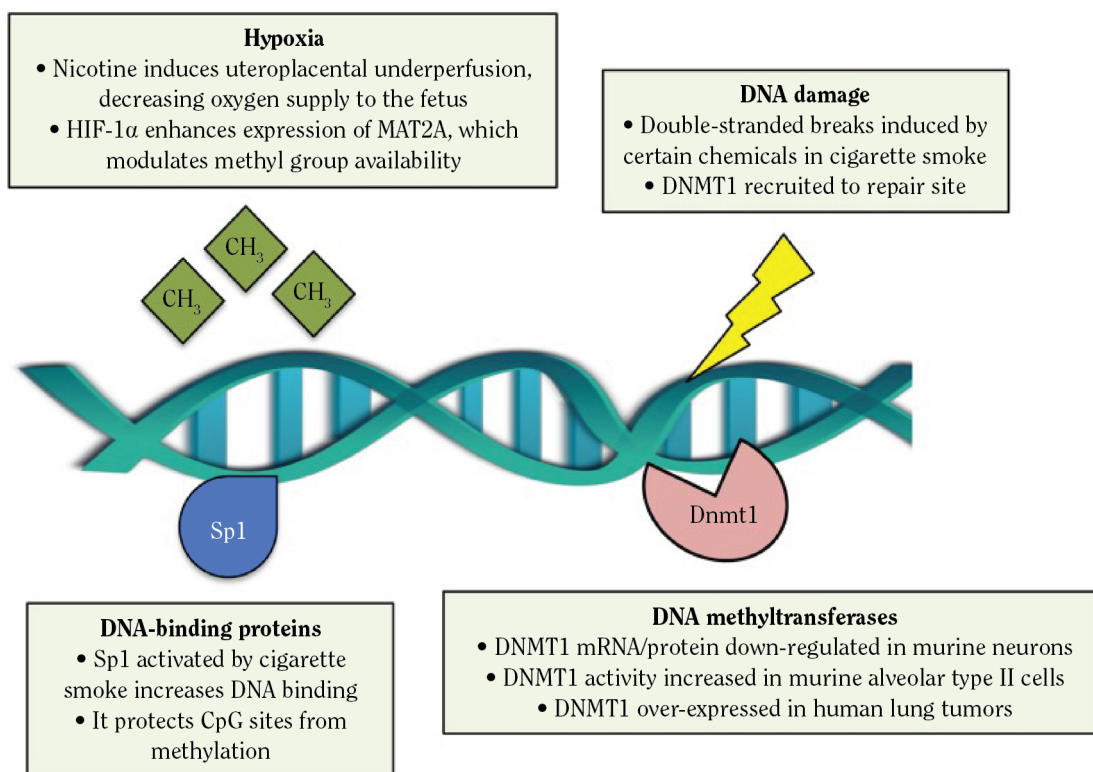
Advances in Epigenetics

Epigenetics is defined as the study of mechanisms that cause heritable changes in gene expression rather than alterations in the underlying sequence of deoxyribonucleic acid (DNA) (Dupont et al. 2009). Epigenetics can help measure the extent to which gene expression is altered in response to environmental exposure. Because epigenetics is a dynamic process, tracking the epigenome over time in relation to smoking cessation becomes relevant. Recent studies have demonstrated a role of DNA methylation, one of the main forms of epigenetic modification, in the pathways of smoking and smoking-induced diseases via the regulation of gene expression and genome stability (Figure 4.9). Methylation may underlie disease-specific gene expression changes, and characterization of these changes is a critical first step toward the identification of epigenetic markers and the possibility of developing novel epigenetic therapeutic interventions for COPD (Vucic et al. 2014).

Smoking alters the bronchial airway epithelial transcriptome and induces expression of genes involved in the regulation of oxidative stress, xenobiotic metabolism, and oncogenesis while suppressing those involved in the regulation of inflammation and tumor suppression (Spira et al. 2004). DNA methylation studies have been performed on a range of samples, including whole-blood homogenates and cells obtained from bronchial brushing and buccal swabbing (Breitling et al. 2011b; Tsaprouni et al. 2014; Guida et al. 2015; Wan et al. 2015).

An increasing number of smoking-related CpG sites (sites with a cytosine nucleotide next to a guanine nucleotide in the linear sequence) in various genes—such as aryl-hydrocarbon receptor repressor (*AHR*), coagulation factor II receptor-like 3 (*F2RL3*), and G protein-coupled

Figure 4.9 Cigarette smoking and DNA methylation



Source: Lee and Pausova (2013). Copyright © 2013 Lee and Pausova.

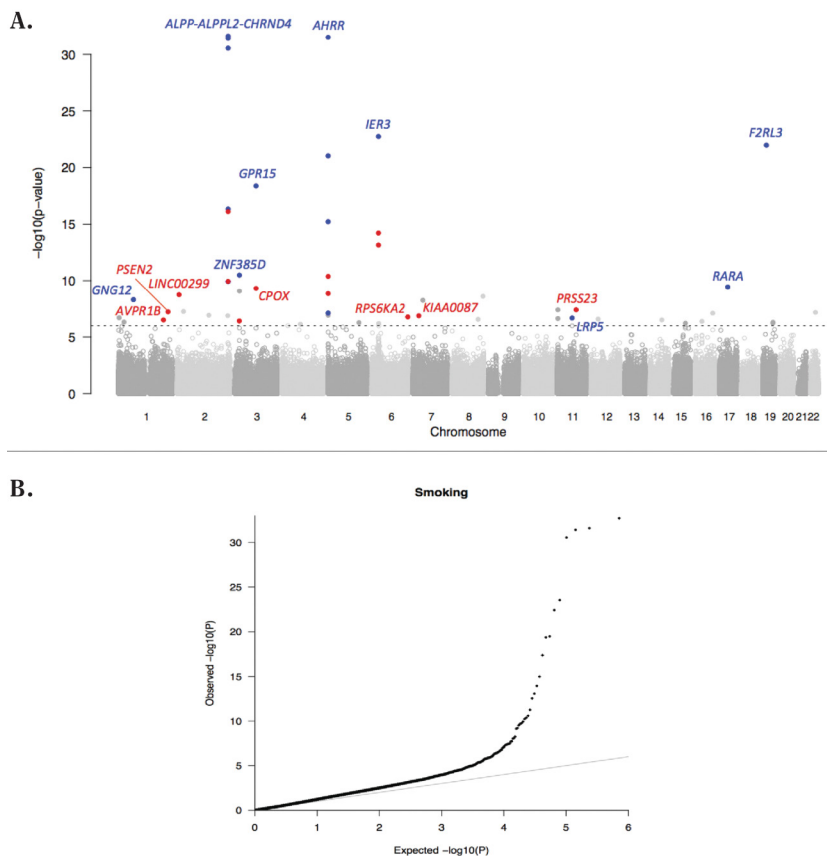
receptor 15 (*GPR15*)—have been discovered by epigenome-wide association studies based on samples of whole blood; these markers have shown utility as quantitative biomarkers of current and past smoking exposure and predictors of smoking-related disease risk (Figure 4.10) (Breitling et al. 2011b; Tsaprouni et al. 2014; Guida et al. 2015). Breitling and colleagues (2011b) found that DNA methylation was significantly lower in smokers than nonsmokers (percent difference in methylation = 12%; $p = 2.7 \times 10^{-31}$) in *F2RL3* and correlated negatively with the number of smoked cigarettes and positively with the duration of smoking abstinence. Similar exposure-related differences in the methylation of this gene were seen in another study, with the intensity of *F2RL3* methylation increasing gradually in long-term (>20 years) quitters to levels similar to that of never smokers (Zhang et al. 2014).

Guida and colleagues (2015) conducted epigenome-wide association studies to capture the dynamics of smoking-induced epigenetic changes after smoking cessation using genome-wide methylation profiles obtained from blood samples in 745 women from two European populations. The authors found that *LRRN3* also was significantly overexpressed in current smokers as compared

with never smokers (fold change = 2.85; $p = 2.1 \times 10^{-24}$). Similar to the findings of Breitling and colleagues (2011b), Guida and colleagues (2015) demonstrated a dose-response relationship between methylation and time since cessation. The expression of only one additional gene, *FOXO3*, was found to be upregulated in current smokers (fold change = 1.27; $p = 4.3 \times 10^{-6}$) (Guida et al. 2015).

Wan and colleagues (2012) assessed the impact of DNA methylation after smoking cessation over time among those in the International COPD Genetics Network ($n = 1,085$), followed by replication in the Boston Severe Early Onset COPD study ($n = 369$). These investigators identified a novel locus (*GPR15*) associated with cigarette smoking and found evidence to suggest that the existence of smoking-related, site-specific methylation changes may contribute to extended risks associated with cigarette smoking after cessation. Among former smokers, participants with the highest cumulative exposure to smoke and shortest duration of smoking cessation had the lowest mean methylation, but participants with the lowest cumulative exposure to smoke and the longest duration of cessation had the highest mean methylation, suggesting a dose-dependent response. Tsaprouni and colleagues

Figure 4.10 Epigenome-wide association study Manhattan plot and Q-Q plot for smoking status in the Cardiogenics Cohort



Source: Tsaprouni and colleagues (2014), with permission.

Note: In Panel A, the vertical axis indicates ($-\log_{10}$ transformed) observed p values, and the dotted horizontal line indicates the threshold of significance ($p = 10^{-6}$) to select markers for replication. Previously reported loci are indicated in blue, and new loci and new signals in known loci are marked in red. Panel B illustrates the distribution of the p values.

(2014) showed that the effect of smoking on DNA methylation was partially reversible following cessation of more than 3 months. That study additionally used whole-blood, ribonucleic acid (RNA) sequencing to demonstrate evidence of the higher expression of *PSEN2*, *PRSS23*, *RARA*, *F2RL3*, *GPR15*, *CPOX*, *AHRR*, and *RPS6KA2* genes among former and current smokers. Only *GPR15* showed a clear trend of higher gene expression in smokers compared with nonsmokers, suggesting that a reduction in methylation levels observed in smokers leads to higher levels of RNA transcription (Tsaprouni et al. 2014).

Advances in Proteomics

Smoking-related inflammation secondary to lung disease has been well described in earlier reports (USDHHS 2014). The 2014 Surgeon General's report concluded that

sufficient evidence exists to infer that components of cigarette smoke affect the immune system and that some of these effects are immune system activating, while others are immunosuppressive (USDHHS 2014). Alterations in innate and adaptive immunity result in both emphysema and airway remodeling, and a range of pathways for inflammatory biomarkers related to smoking have been described (Ito et al. 2006; USDHHS 2014). Profiles of inflammatory biomarkers change after smoking cessation. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (Coxson et al. 2013) found that several circulating biomarkers were associated with both the severity (SP-D, soluble receptor for advanced glycation end products [sRAGE], *CCL18*) and progression (SP-D, sRAGE, fibrinogen, interleukin [IL] 6, and CRP) of emphysema assessed by volumetric

CT imaging. Circulating biomarkers may provide an additional proxy for lung inflammation and emphysematous change. SP-D, one of several surfactant proteins, is thought to be related to pulmonary immunity (Kishore et al. 2006) and is higher in persons with COPD (Lomas et al. 2009). This relative increase is believed to reflect, in part, inflammation in the lung leading to degradation and leakage into the circulation. sRAGE is thought to protect against inflammation, and low levels of sRAGE have been associated with several inflammatory diseases, such as diabetes and cardiovascular disease (Rapoeseiras-Roubín et al. 2010). Although the biomarkers discussed in this chapter thus far were found to be associated with lower baseline lung density and accelerated decline in lung density among smokers, whether the low levels of sRAGE and SP-D are a contributing factor or a consequence of COPD is unclear (Coxson et al. 2013). Circulating sRAGE could be a useful biomarker in monitoring the consequences of novel interventions such as the administration of retinoic acid, stem cell technology, and the use of growth factors targeting the emphysema component of COPD and smoking cessation (Coxson et al. 2013).

Biomarkers in sputum also have been found to change after smoking cessation. In a cross-sectional study of 240 participants, Titz and colleagues (2015) found that the sputum proteome and the transcriptome of former smokers largely approached those in never smokers. Nevertheless, some long-term effects of prior smoking remain evident in the sputum of former smokers, as indicated by the increase in *IFNG* and *NFKB* signaling, which are both associated with an M1 polarization in the sputum of former smokers (Titz et al. 2015). Singh and colleagues (2011) found that IL-18R protein expression was higher on alveolar macrophages in the lung tissue of COPD patients (mean: 23.2%) compared with controls (mean: 2% in former smokers and 2.5% in nonsmokers).

Advances in the Microbiome

The role of the microbiome in COPD pathogenesis has become an active area of research (Martinez et al. 2013; Sze et al. 2014; Mammen and Sethi 2016). Studies have shown that tobacco smoking affects both the oral and intestinal microbiota (Biedermann et al. 2013; Morris et al. 2013), but it is not clear whether the lung microbiota is also affected by tobacco cessation (Morris et al. 2013; Yu et al. 2016). Some researchers postulate that alterations of the gut microbiome may help to explain mechanisms of inflammation in the lung that lead to the development of COPD or its exacerbations (Martinez et al. 2013; Sze et al. 2014; Malhotra and Olsson 2015). Research has revealed that smoking cessation also leads to changes in the microbiome, but it is uncertain whether

smoking cessation leads to higher or lower bacterial diversity and whether specific families of bacteria are consistently affected (Delima et al. 2010; Biedermann et al. 2013; Munck et al. 2016; Yu et al. 2016).

Synthesis of the Evidence

Evidence considered in this report strengthens the foundation for inferring that smoking cessation remains the only intervention that attenuates loss of lung function over time among those with COPD and reduces risk of developing COPD in cigarette smokers (USDHHS 1984, 2004, 2014). The beneficial effect of cessation in slowing the decline of lung function in persons with COPD is well documented and was stated in a conclusion of the 1990 Surgeon General's report; the rate of decline decreases after cessation and is maintained at the new lower level unless smoking is resumed (USDHHS 1990). The available evidence shows an immediate benefit over several years for the rate of decline, but does not show whether further gains occur subsequently. Clinical studies show recovery of lung function and improvement in respiratory symptoms shortly after cessation, but inflammation continues to exist months after cessation.

Unfortunately, COPD is a progressive disease in the face of sustained smoking, and at the time of diagnosis the loss of lung function is irreversible. However, further progression can be prevented by cessation. Support for this conclusion, reinforcing that of the 1990 report, comes from the understanding that smoking leads to inflammation and injury of the lungs and from mounting epidemiological evidence that cessation slows the accelerated loss of lung function in smokers. Turning to the criteria used for causal inference in these reports, temporality is appropriate (i.e., cessation is followed by changes in the progression of COPD), the biological basis for a benefit of cessation has been well established in prior Surgeon General's reports, and the epidemiological evidence is consistent.

Further insights on mechanisms are emerging. Recent imaging studies suggest that there are longer-term benefits of cessation (e.g., research has shown measurable reductions in lung density on CT imaging 2 years after cessation). Accordingly, the mechanisms by which smoking cessation attenuates the decline of lung function and reduces the risk of COPD need to be better understood.

Many studies using new approaches are now underway. Studies using biomarkers and omics can provide insights into the potential mechanisms by which smoking cessation could attenuate declines in lung function. This review did not find any evidence to link genetic makeup to how cessation affects this decline. However, studies that evaluated the emerging areas of epigenetics, proteomics, and the microbiome have yielded promising findings.

Conclusions

1. Smoking cessation remains the only established intervention to reduce loss of lung function over time among persons with chronic obstructive pulmonary disease and to reduce the risk of developing chronic obstructive pulmonary disease in cigarette smokers.
2. The evidence is suggestive but not sufficient to infer that airway inflammation in cigarette smokers persists months to years after smoking cessation.
3. The evidence is suggestive but not sufficient to infer that changes in gene methylation and profiles of proteins occur after smoking cessation.
4. The evidence is inadequate to infer the presence or absence of a relationship between smoking cessation and changes in the lung microbiome.

Asthma

Asthma is characterized by variable airflow obstruction, and its symptoms include wheezing and dyspnea with exertion (Chung et al. 2014). Chronic changes in the airway, referred to as airway remodeling, can lead to irreversible loss of lung function (Pascual and Peters 2005). The 2004 and 2014 Surgeon General's reports (USDHHS 2004, 2014) reviewed the topic of active smoking and asthma in children and adults, a topic updated here to focus on smoking cessation. Smoking has detrimental effects on asthma morbidity. Compared with nonsmokers with asthma, smokers with asthma have more severe symptoms, higher rates of hospitalization, accelerated decline in lung function, a shift from eosinophilia toward neutrophilia, and impaired therapeutic response to inhaled and oral corticosteroids (Thomson et al. 2004; McLeish and Zvolensky 2010).

Smoking as a Risk Factor for Asthma

The 2014 Surgeon General's report concluded that the evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults. With regard to exacerbation of asthma, the report concluded that the evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults. In the United States, cigarette smoking is prevalent among persons with asthma. Data from 2010 from the Behavioral Risk Factor Surveillance System show that nearly 17% of people without asthma smoked, and 21% of people with asthma smoked (CDC n.d.). For example, Silverman and colleagues

(2003) examined nearly 2,000 persons 18–54 years of age who presented at an emergency department with acute asthma. Asthma symptoms and smoking status were assessed via structured interview. Of persons presenting at the emergency department with acute asthma, 35% were current cigarette smokers, and an additional 23% were former smokers. Interestingly, no difference in pulmonary function was seen between smokers and nonsmokers upon their arrival in the emergency department.

Some observational evidence shows an association between incident asthma and smoking, but the evidence is mixed (McLeish and Zvolensky 2010). The association of smoking with asthma is stronger among certain subgroups of the population. Specifically, among women, the prevalence of asthma is higher among cigarette smokers compared with nonsmokers, but findings have not been consistent in showing a similar difference in the prevalence of asthma among men (McLeish and Zvolensky 2010). Additionally, women who quit smoking may have a higher asthma remission rate (Holm et al. 2007). Most studies concerning adolescents have found higher rates of smoking among adolescents with asthma than among those without asthma (McLeish and Zvolensky 2010). Among adults, this trend is less consistent, possibly because of smoking cessation among adults with asthma.

The U.S. Black Women's Health Study, a prospective cohort study with 46,182 participants, found an exposure-response relationship between smoking and the incidence of adult-onset asthma. Adjusted hazard ratios for former active smoking, current active smoking, and exposure to secondhand smoke were, respectively, 1.36 (95% confidence interval [CI], 1.11–1.67), 1.43 (95% CI, 1.15–1.77), and 1.21 (95% CI, 1.00–1.45) compared with never active or never passive smoking (Coogan et al. 2015). Although current evidence suggests a possible causal relationship between active smoking and the incidence of asthma in adults, the evidence is not sufficient to state conclusively whether smoking is a directly causal risk factor, per the conclusion of the 2014 Surgeon General's report (McLeish and Zvolensky 2010; USDHHS 2014).

Smoking Cessation, Asthma Symptoms, and Lung Function

Asthma-related morbidity and mortality are higher in current cigarette smokers compared with never smokers (Thomson et al. 2004). Smokers with asthma have more severe symptoms (Althuis et al. 1999; Siroux et al. 2000), a greater need for rescue medications (Gallefoss and Bakke 2003), and poorer health status compared with never smokers (Gallefoss and Bakke 2003; Jang et al. 2010). In an experimental study of smokers with asthma, the decrement in FEV₁ after smoking cessation was inversely associated with baseline FEV₁. This finding suggests that

smokers with asthma who have worse lung function may be particularly susceptible to the acute effects of tobacco smoke (Jang et al. 2010). Compared with nonsmokers with asthma, smokers with atopic asthma are less responsive to inhaled adenosine and corticosteroids, which may point toward differences in airway inflammation (Oosterhoff et al. 1993; Lazarus et al. 2007). Admission rates to hospital for asthma and hospital-based care are higher in smokers than in those who have never smoked (Prescott et al. 1997; Sippel et al. 1999), although possibly not in younger adult smokers (Rasmussen et al. 2002). The 6-year mortality rate following a near-fatal asthma attack is higher for smokers than nonsmokers (age-adjusted odds ratio [OR] = 3.6; 95% CI, 2.0–6.2) (Marquette et al. 1992).

In combination, cigarette smoking and asthma accelerate the decline of lung function to a greater degree than either factor alone (Lange et al. 1998; Apostol et al. 2002). For example, the Copenhagen City Heart Study, which included longitudinal measurement of FEV₁ over a 15-year period, found that the average decline in FEV₁ among persons with asthma was greater in smokers than nonsmokers (Lange et al. 1998). The average annual decline in FEV₁ in men with asthma who were 40–59 years of age was 33 mL/year in nonsmokers (n = 36) and 58 mL/year in smokers (n = 150; p < 0.001) (Lange et al. 1998). The combination of chronic hypersecretion of mucus and smoking in adults with asthma was associated with a greater decline in FEV₁ than in adults without asthma (Lange et al. 1998). A study of 4,000 adults who were 18–30 years of age at enrollment (Apostol et al. 2002) and who were followed for more than 10 years with serial spirometry measurements found that the decline in FEV₁ was 8.5% in never smokers without asthma (n = 2,393), 10.1% in never smokers with asthma (n = 437), and 11.1% in smokers without asthma (n = 514). The combination of having asthma and smoking ≥15 cigarettes per day (n = 101) had a synergistic effect on the decline in lung function, resulting in a 17.8% decline in FEV₁ over 10 years (Apostol et al. 2002).

Cigarette smoking has been found to decrease the effectiveness of inhaled corticosteroids (Thomson et al. 2004). The mechanisms of corticosteroid resistance in smokers with asthma are not well understood, but this resistance could result from alterations in the phenotypes of airway inflammatory cells (e.g., increased neutrophils, reduced eosinophils); changes in the glucocorticoid receptor α -to- β ratio (e.g., overexpression of glucocorticoid receptor β); and increased activation of proinflammatory transcription factors (e.g., nuclear factor- κ B) or reduced activity of histone deacetylase (Thomson et al. 2004). Chalmers and colleagues (2002), who examined the effect of treatment with inhaled fluticasone propionate on morning and evening peak expiratory flow (PEF) among a cohort of steroid-naïve smokers and nonsmokers, found

that the mean morning PEF increased significantly more in nonsmokers than in smokers (27 liters [L]/minute vs. -5 L/minute). Inhaled corticosteroids that are often prescribed to treat the exacerbations discussed in this chapter thus far appear to be less effective in treating asthma among smokers (Chalmers et al. 2002). Chaudhuri and colleagues (2006) examined the effects of smoking cessation on lung function and airway inflammation among 32 smokers with asthma at 6 weeks and found a decreased proportion of sputum neutrophils (mean percent difference, 29 [51 to -8]; p = 0.013) among those who quit smoking, suggesting a possible mechanism for improved response to inhaled corticosteroids after cessation (Chaudhuri et al. 2006).

Several studies have examined smoking cessation and its association with asthma symptoms and lung function (Table 4.27). For example, Tønnesen and colleagues (2005) examined the effects of smoking cessation and reduction in smoking on asthma symptoms. Participants were divided into three groups: smokers who had reduced their cigarette consumption (to fewer than seven cigarettes per day), former smokers who had achieved complete cessation, and smokers who continued smoking as usual. Participants in both the smoking reduction and smoking cessation groups also used nicotine replacement therapy as an aid to reduce or quit use. Those in the cessation group experienced significant decreases in the use of rescue inhalers, frequency of daytime asthma symptoms, and bronchial hyperreactivity, and they had a 25% reduction in inhaled steroids (Tønnesen et al. 2005). In addition, persons in this group reported significant improvements in both their overall and asthma-related quality of life. Compared with those in the cessation group, improvements were not as great among those who reduced their consumption of cigarettes. Chaudhuri and colleagues (2006) found significant improvements in spirometry (FEV₁ and PEF) among former smokers after 1 week of cessation, and the improvements continued through 6 weeks of cessation. Moreover, asthma control improved, and after 6 weeks of cessation, counts of sputum neutrophils decreased.

Observational studies suggest that cigarette smoking increases the risk for poor asthma control by as much as 175% for such outcomes as asthma attacks, interference with daily activities, and greater severity of wheezing and breathlessness (McLeish and Zvolensky 2010). The wide range of effect sizes appears to be attributable in large measure to differences in methodology across these investigations. Regardless, cigarette smoking among persons with asthma is associated with increased risk of mortality, more frequent asthma attacks, exacerbations of the disease, and symptoms such as wheezing and nighttime awakenings (McLeish and Zvolensky 2010). In persons with asthma, smoking cessation is associated

Table 4.27 Studies on smoking cessation and asthma, 2009–2017

Study	Design/population	Findings
Tønnesen et al. (2005)	<ul style="list-style-type: none"> • Prospective cohort • 220 smokers with asthma: <ul style="list-style-type: none"> – 79 reducers (reduced consumption to <7 cigarettes per day) – 82 quitters – 59 continued smokers • Reduction and cessation groups used NRT as cessation aid 	<p>Quitters reported a significant decrease in use of rescue inhalers, frequency of daytime asthma symptoms and bronchial hyperactivity, and reduction in inhaled steroid use</p> <p>Those in this group also reported significant improvement both in overall and asthma-related quality of life</p>
Chaudhuri et al. (2006)	<ul style="list-style-type: none"> • Prospective cohort • 32 smokers with asthma: <ul style="list-style-type: none"> – 21 quitters – 11 continued smokers • Followed up for 6 weeks • Recorded PEF morning and night 	Lung function in quitters improved significantly within a week of stopping smoking and these improvements continued through 6 weeks of cessation
Broekema et al. (2009)	<ul style="list-style-type: none"> • Cross-sectional • 147 patients with asthma: <ul style="list-style-type: none"> – 66 never smokers – 46 former smokers – 35 current smokers 	Epithelial characteristics in former smokers were similar to those in never smokers, suggesting that smoke-induced changes can be reversed by smoking cessation
Jang et al. (2010)	<ul style="list-style-type: none"> • Prospective cohort • 22 patients with asthma who continued to smoke • 10 patients with asthma who quit smoking at 3 months • Measured FEV₁ 	Patients with asthma who quit smoking showed less airway obstruction
Cerveri et al. (2012)	<ul style="list-style-type: none"> • Prospective cohort • 9,092 with asthma • 1,045 without asthma at 9-year follow-up 	Smoking was significantly less frequent among participants with asthma than in the rest of the population (26 vs. 31%; <i>p</i> <0.001)
Polosa et al. (2014)	<ul style="list-style-type: none"> • Prospective cohort • 18 e-cigarette users with mild-to-moderate asthma • Followed up for 24 months 	E-cigarette use ameliorated both objective and subjective asthma outcomes, and beneficial effects may persist in the long term
Munck et al. (2016)	<ul style="list-style-type: none"> • Prospective cohort • 44 patients with asthma, of whom 25 quit smoking at 12 weeks 	Although tobacco smokers with asthma had a greater bacterial diversity in the induced sputum compared with nonsmoking healthy controls, smoking cessation did not change microbial diversity

Notes: **FEV₁** = forced expiratory volume at 1 second; **PEF** = peak expiratory flow.

with improvements in lung function (specifically PEF), the number of asthma symptoms, treatment outcomes, and asthma-specific quality-of-life scores.

Smoking Cessation Biomarkers and the Microbiome in Asthma

Counts of sputum neutrophils, an indicator of airway inflammation, are reported to be higher in heavy smokers with mild asthma compared with nonsmokers with asthma (Chalmers et al. 2001). Sputum concentrations of cytokines such as IL-8 are also higher in smokers with asthma (Chalmers et al. 2001), but sputum concentrations in other cytokines, such as IL-18, are suppressed in smokers with asthma (McKay et al. 2004). The elevated

sputum neutrophil count found in high-intensity smokers with asthma may be partly responsible for their reduced responsiveness to corticosteroids (Meagher et al. 1996). Unlike eosinophils, which are exquisitely sensitive to corticosteroids, neutrophils are poorly responsive to corticosteroid therapy (Green et al. 2002), and their survival and proliferation are promoted by glucocorticoids. In a study of 32 smokers, smoking cessation resulted in reduction in induced sputum neutrophils by bronchoalveolar lavage among subjects with asthma but no change in mediator levels (Chaudhuri et al. 2006). In contrast, research on the effect of smoking cessation on airway inflammation in COPD has shown that elevated levels of most inflammatory cells, including neutrophils, persist in former smokers

(Turato et al. 1995; Domagala-Kulawik et al. 2003; Willemse et al. 2004) and that inflammation can even increase (Willemse et al. 2005). Only a few studies have specifically assessed the lung microbiome among former smokers with asthma (Charlson et al. 2010; Huang et al. 2011; Morris et al. 2013), with Munck and colleagues (2016) finding that current smokers had greater bacterial diversity in their induced sputum and that smoking cessation did not lead to changes in microbial diversity at 12 weeks.

Synthesis of the Evidence

Cigarette smoking has adverse effects on the respiratory health of people with asthma and has been found to causally contribute to the worsening of asthma. Asthma involves chronic inflammation of the airways, and smoking has been shown to increase inflammation, with clinical consequences. Smoking cessation has been linked to improvement in a variety of clinical indicators, including fewer asthma symptoms; less frequent use of inhalers, including inhaled corticosteroids; and improved outcomes, including an attenuation in the decline of lung function, fewer asthma exacerbations, and lower mortality.

In the 2014 Surgeon General's report, the evidence was considered sufficient to infer a causal relationship between active smoking and asthma exacerbations in adults. The report did not specifically address smoking cessation, while offering the recommendation that people with asthma should not smoke, given the causal association of smoking with exacerbations.

The evidence reviewed in this report documents that smoking cessation improves lung function, reduces symptoms, and improves treatment outcomes among persons with asthma. Cohort studies have documented that cigarette smoking acts synergistically with asthma to accelerate the decline of lung function. With regard to the natural history of asthma, the findings of cohort studies also suggest that smoking cessation can attenuate the decline of lung function among persons with asthma (Apostol et al. 2002).

Because smoking is a powerful cause of inflammation of the respiratory tract, cessation would be expected

to reduce inflammation in people with asthma, thereby improving clinical status. Thus it is biologically plausible that smoking cessation would improve outcomes in people with asthma who smoke. The observational evidence is consistent with this conclusion but limited in scope, and there are few studies that have followed people with asthma over longer periods of time to characterize how outcomes change with increasing duration of cessation.

Conclusions

1. The evidence is suggestive but not sufficient to infer that smoking cessation reduces asthma symptoms and improves treatment outcomes and asthma-specific quality-of-life scores among persons with asthma who smoke.
2. The evidence is suggestive but not sufficient to infer that smoking cessation improves lung function among persons with asthma who smoke.

Implications

While the evidence remains "suggestive" concerning smoking cessation and clinical outcomes in people with asthma who smoke, clinicians should recommend cessation for their patients with asthma who smoke. Smoking worsens the status of those with asthma, and the evidence reviewed in this report shows favorable consequences of quitting. Even the perception of a causal relationship with asthma among smokers may be an impetus for cessation (Godtfredsen et al. 2001).

Further research is needed to address gaps in the evidence related to smoking cessation and asthma. One area that requires further investigation is the relationship between cigarette smoking and the response to corticosteroids among persons with asthma. The mechanisms for this relationship are not well understood, and smoking cessation studies can help to elucidate pathways and potential therapies, including the potential role of neutrophils in corticosteroid resistance in asthma.

Reproductive Health

The first Surgeon General's report addressed the deleterious effects of maternal smoking on fetal growth (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). Subsequent Surgeon General's reports identified causal associations between active smoking and other adverse reproductive health outcomes for women or men, including decreased female fertility, pregnancy

complications, preterm delivery, and erectile dysfunction (U.S. Department of Health and Human Services [USDHHS] 2014). Although the effects of smoking on reproductive health are well established, the benefits of smoking cessation for reproductive health have been studied less extensively. This section provides current information on the potential benefits of smoking cessation

for maternal health during pregnancy, for birth outcomes, and for female and male reproductive health.

Conclusions from Previous Surgeon General's Reports

The 1990 Surgeon General's report on the health benefits of smoking cessation included six conclusions on smoking cessation and reproductive health (Table 4.28) (USDHHS 1990). The report concluded that women who stopped smoking before or during the first trimester of pregnancy had infants with a birth weight similar to that seen among never smoking or nonsmoking women, while smoking cessation later in pregnancy increased infants' birth weights relative to those of infants born to women who continued to smoke throughout pregnancy. In contrast, reductions in smoking intensity during pregnancy did little to reverse the smoking-related reduction of birth weight. The 1990 report also found that women who stopped smoking experienced natural menopause at an age similar to that of nonsmoking women, which was 1 to 2 years later than women who were active smokers.

Four subsequent Surgeon General's reports provided updated conclusions on the reproductive health effects of smoking and the biological mechanisms underlying these effects. However, these reports did not address the effects of smoking cessation (USDHHS 2001, 2004, 2010, 2014).

Literature Review Methods

A systematic literature review was conducted to update the cessation-specific conclusions of the 1990 Surgeon General's report. The search was restricted to English-language articles available on PubMed or EMBASE and published between January 2000 and February 2017. In the PubMed search strategy (Table 4.29), Medical Subject Headings ("MeSH") terms were used to capture relevant articles. Retrieved articles included at least one term related to smoking cessation (e.g., "former smokers") and at least one term related to reproductive health (e.g., "pregnancy"). Citations from retrieved articles and past Surgeon General's reports were used to identify articles not captured by the search, including several articles published between 1997 and 1998.

Sources of Bias in Observational Studies of Smoking and Reproductive Health

Most studies related to prenatal maternal smoking, smoking cessation, and health outcomes rely on self-reports

to characterize maternal smoking, but findings from several studies indicate that the use of self-reports to determine smoking status in pregnant women substantially misclassifies exposure as a result of underreporting. For example, various studies that assessed smoking cessation using both self-reports and biochemical markers, such as salivary or urinary cotinine, have found that pregnant women consistently underreport being smokers and generally overreport cessation (George et al. 2006; England et al. 2007; Andersen et al. 2009; Shipton et al. 2009; Dietz et al. 2011; Rode et al. 2013). Notably, in a study of women participating in a randomized trial for preeclampsia prevention, an analysis that included cotinine-validation of self-reported quit status found that the degree of misclassification was lower among women who reported never smoking or who reported quitting before pregnancy than among women who reported quitting after becoming pregnant (England et al. 2007; Rode et al. 2013). In this study, misclassification from over-reporting of cessation led to a modest overestimation of the magnitude of associations between maternal smoking and such outcomes as birth weight and small-for-gestational age (SGA) (England et al. 2007). Finally, reports on quitting late in pregnancy may be subject to more misclassification than reports on quitting early in pregnancy (Tong et al. 2015).

The degree of misclassification of smoking status varies across studies. Factors that may have contributed to this variation include the type of biomarker and the cut point selected for classification of active smoking, the country where the study was conducted, whether women were aware that biochemical validation would occur, when during the pregnancy the women were asked about smoking, the woman's smoking intensity, and the woman's age and other sociodemographic factors. Estimates of the percentage of true active smokers misclassified as quitters or nonsmokers have ranged from 23% to 25% (England et al. 2007; Shipton et al. 2009; Dietz et al. 2011), while estimates of the percentage of self-reported quitters who had evidence from a biomarker of active smoking have ranged from 0% to 25% (George et al. 2006; Andersen et al. 2009; Rode et al. 2013; Tong et al. 2015). Differential misclassification of smoking status by such factors as intensity of smoking can bias the results of studies examining the effects of smoking or smoking cessation on birth outcomes. For example, England and colleagues (2007) found that women who misreported cessation were more likely to be light smokers (1–9 cigarettes per day) than women who accurately reported their smoking status. This misclassification may bias estimates of associations between smoking status during pregnancy and birth outcomes, such as hypertensive disorders of pregnancy and SGA, for both quitters (e.g., by including continuing smokers in the group classified as quitters) and continuing smokers

Table 4.28 Conclusions from the 1990 Surgeon General’s report on the health benefits of smoking cessation and reproductive health

Conclusions
1. Women who stop smoking before becoming pregnant have infants of the same birth weight as those born to never smokers.
2. Pregnant smokers who stop smoking at any time up to the 30th week of gestation have infants with higher birth weight than do women who smoke throughout pregnancy. Quitting in the first 3 to 4 months of pregnancy and abstaining throughout the remainder of pregnancy protect the fetus from the adverse effects of smoking on birth weight.
3. Evidence from two intervention trials suggests that reducing daily cigarette consumption without quitting has little or no benefit for birth weight.
4. Recent estimates of the prevalence of smoking during pregnancy, combined with an estimate of the relative risk of low birth weight outcome in smokers, suggest that 17 to 26 percent of low birth weight births could be prevented by eliminating smoking during pregnancy: in groups with a high prevalence of smoking (e.g., women with less than a high school education), 29 to 49 percent of low birth weight births might be prevented by elimination of cigarette smoking during pregnancy.
5. Approximately 30 percent of women who are cigarette smokers quit after recognition of pregnancy, with greater proportions quitting among married women and especially among women with higher levels of educational attainment.
6. Smoking causes women to have natural menopause 1 to 2 years early. Former smokers have an age at natural menopause similar to that of never smokers.

Source: USDHHS (1990, p. 410).

Table 4.29 PubMed systematic search strategy

Smoking search terms	Reproductive health search terms ^a
smoking cessation OR “former smoker” OR “former smokers” OR ex-smok* OR exsmok* OR quit* smok* OR stop* smok*	reproduction OR reproductive OR Reproductive Health[mh] OR Reproductive Medicine[mh] OR birth OR Parturition[mh] OR pregnancy OR pregnan* OR gestation* OR fertility OR infertility OR fertile OR infertile OR fecundability OR fecundity OR subfertility OR “sub-fertility” OR Subfertile OR “sub-fertile” OR amenorrhea OR conception OR Fertilization[mh] OR “spontaneous abortion” OR “Abortion, Spontaneous”[mh] OR stillbirth OR Miscarriage* OR Fetal Death[mh] OR preterm OR Premature Birth[mh] OR “Infant, Premature”[mh] OR “Obstetric Labor, Premature”[mh] OR placenta OR Placenta Diseases[mh] OR preeclampsia OR “Pre-Eclampsia”[mh] OR “pre-eclampsia” OR “fetal growth” OR Fetal Development[mh] OR Fetal Growth Retardation[mh] OR birthweight OR “birth weight” OR “Infant, Low Birth Weight”[mh] OR Birth Weight[mh] OR “fetal mortality” OR Fetal Mortality[mh] OR “neonatal mortality” OR “perinatal mortality” OR Perinatal Mortality[mh] OR Perinatal Death[mh] OR “infant mortality” OR Infant Mortality[mh] OR congenital OR Congenital Abnormalities[mh] OR SIDS OR Sudden Infant Death[mh] OR “Sudden Infant Death” OR menopause OR “sexual performance” OR “sexual dysfunction” OR “Sexual Dysfunction, Physiological”[mh] OR erection OR Penile Erection[mh] OR erectile OR Erectile Dysfunction[mh] OR impotence OR “Impotence, Vasculogenic”[mh] OR sperm OR Spermatozoa[mh] OR Spermatogenesis[mh] OR semen OR Semen Analysis[mh] OR Prenatal OR “pre-natal” OR Prenatal Care[mh] OR Prenatal Injuries[mh] OR Prenatal Diagnosis[mh] OR “Embryonic and Fetal Development”[mh]

Notes: **Mh** = to search Medical Subjects Headings (MeSH) in MEDLINE or PubMed.

^aUsed in conjunction with all smoking search terms.

(e.g., by omitting light smokers because they incorrectly reported cessation) (England et al. 2007).

Many studies of the association of tobacco use with pregnancy outcomes have assessed smoking status at a single point during pregnancy, but because women may change their patterns of tobacco use during pregnancy by quitting, cutting back, and/or relapsing, using a

single assessment of exposure can result in misclassification of exposure across a pregnancy (Pickett et al. 2003, 2005). For example, in a prospective cohort of Dutch women, 34% reported cessation during the first trimester, but were later reclassified as continuing smokers after responding to questionnaires in the second and third trimesters (Bakker et al. 2011). Thus the assessment of

smoking status at a single time point rather than multiple time points during pregnancy can result in misclassification of exposure (Pickett et al. 2009).

Overall, women who smoke differ from those who do not in several ways with regard to lifestyle and behaviors, leading to the potential for confounding (Subar et al. 1990; Midgette et al. 1993; Maxson et al. 2012). For example, smokers may be more likely than nonsmokers to use alcohol and/or illicit substances that can affect birth outcomes (Coleman-Cowger et al. 2017). Fully controlling for these differences in estimating the benefits of quitting can be difficult, but failure to do so may result in unrecognized residual confounding, which was illustrated, for example, in a study of Swedish women. There, Juárez and Merlo (2013) compared results of a conventional multivariable linear regression analysis with those of a multilevel analysis that used siblings to estimate woman-specific, smoking-associated changes in birth weight (i.e., comparing the birth weights of infants born to the same woman whose exposure to smoking changed between pregnancies and controlling for birth order). The association between maternal smoking behavior and birth weight remained significant in the sibling analysis, but it was attenuated in comparison with the conventional analysis. Specifically, the babies of women who smoked heavily throughout pregnancy had an adjusted reduction in birth weight of 303 grams (g) relative to those of nonsmokers in the conventional analysis; in the sibling analysis, the reduction was 226 g. Using similar methods in a cohort of Danish births, Obel and colleagues (2016) also found that the association between smoking during pregnancy and low birth weight (<2,500 g) was moderately attenuated in a sibling analysis in comparison with a conventional analysis (adjusted odds ratio [aOR] = 1.68 and 2.60, respectively).

Pregnancy Complications

Ectopic Pregnancy

An ectopic pregnancy, which occurs when implantation of the fertilized ovum takes place outside the uterus, most often in the fallopian tubes, affects an estimated 1% to 2% of pregnancies (CDC 1995; Van Den Eeden et al. 2005). The 1990 Surgeon General's report found only sparse evidence that current or former smokers were at higher risk of ectopic pregnancy (Chow et al. 1988; USDHHS 1990; Kalandidi et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006), but the 2014 Surgeon General's report found sufficient evidence to conclude that active smoking causally increases

the risk of ectopic pregnancy (USDHHS 2014). Potential mechanisms underlying this relationship identified from animal research include damage to a fallopian tube or dysfunction of that structure, damage to the oviduct epithelium, a decrease in the ratio of ciliated to secretory oviductal cells, a decrease in smooth muscle contractions of the oviduct, and decreased oviductal blood flow (USDHHS 2014). A review of studies that included former smokers with an ectopic pregnancy found that the majority of studies reported no significant association between that outcome and past smoking (Chow et al. 1988; Kalandidi et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006).

Summary of the Evidence

The 2014 Surgeon General's report concluded that "the evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy" (USDHHS 2014, p. 487). A systematic review of the literature did not identify additional studies since that report that assessed the risk of ectopic pregnancy among former smokers. Therefore, a new conclusion on smoking cessation and ectopic pregnancy is not provided in this report.

Spontaneous Abortion

Spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks' gestation, although it is sometimes defined as occurring before 28 weeks. Recognized spontaneous abortion occurs in approximately 12% of pregnancies, usually before 12 weeks' gestation (McNair and Altman 2011). Very early losses may go unrecognized, and the true incidence of pregnancy loss may be as high as 30% to 45% (Wilcox et al. 1988; Eskenazi et al. 1995).

The 1990 Surgeon General's report did not provide a conclusion about the association between smoking cessation and spontaneous abortion because of a paucity of research among former smokers. The 2004 Surgeon General's report, however, reviewed the evidence on an association between maternal smoking and spontaneous abortion, finding the evidence suggestive but not sufficient to infer a causal relationship (USDHHS 2004), and cessation was not examined. The 2010 Surgeon General's report updated the 2004 report, but it did not include conclusions on the strength of evidence for causality. Proposed mechanisms underlying a potential association that were set forth in that report included effects of hypoxia due to exposure to CO, vasoconstrictive and antimetabolic effects resulting from placental insufficiency, and the direct toxic effects of constituents in cigarette smoke (USDHHS 2010). The 2014 Surgeon General's report noted that

studies have found associations between active smoking and spontaneous abortion, but it considered the evidence suggestive but not sufficient to reach a causal conclusion, in part because of study limitations, including difficulty controlling for potential confounders and a lack of data on conception karyotype (USDHHS 2014).

Summary of the Evidence

The 2014 Surgeon General's report concluded that "the evidence is suggestive, but not sufficient, to infer a causal relationship between maternal active smoking and spontaneous abortion" (USDHHS 2014, p. 489). However, a systematic review of the literature identified no known studies that have specifically assessed the association between smoking cessation and risk of spontaneous abortion; therefore, this report does not make any new conclusions regarding this outcome.

Placental Abruption

Placental abruption, which affects an estimated 0.3% to 2% of pregnancies (Ananth et al. 2015; Ruitter et al. 2015), is the premature separation of the placenta from the uterine wall (Rasmussen et al. 1996; Ananth et al. 2001, 2005; Kyrklund-Blomberg et al. 2001; Luke et al. 2017; Räisänen et al. 2018). Placental abruption can lead to perinatal mortality (Raymond and Mills 1993; Ananth and Wilcox 2001; Kyrklund-Blomberg et al. 2001; Räisänen et al. 2018), neonatal asphyxia (Heinonen and Saarikoski 2001), preterm delivery, significant maternal blood loss, and disseminated intravascular coagulation (Hladky et al. 2002).

The only study on the risk of placental abruption (Naeye 1980) cited in the 1990 Surgeon General's report (USDHHS 1990) found that smoking for more than 6 years was associated with an increased risk of placental abruption, but that women who quit smoking by their first prenatal visit were not at increased risk of placental abruption relative to never smokers. The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of placental abruption, and it included one study demonstrating increased risk of this event in former smokers (Spinillo et al. 1994; USDHHS 2004). That study, however, was limited by its small sample, and it did not include information about the timing of cessation. The 2010 Surgeon General's report reviewed potential mechanisms underlying the association between smoking and abruption, including smoking-related degenerative and/or inflammatory changes in the placenta, reduced vitamin C levels and impaired collagen synthesis in smokers, microinfarcts, and atheromatous changes in placental vessels (USDHHS 2010). That report identified one study indicating that, when women stop

smoking between pregnancies, their risk of abruption is similar to that of nonsmokers (Ananth and Cnattingius 2007). Because abruption is a rare outcome, large, population-based samples are needed to study risk factors for its occurrence. One study published since the 2010 report (Räisänen et al. 2014) had a sufficient sample to examine smoking cessation and placental abruption. In this population-based cohort of more than 1 million births in Finland, Räisänen and colleagues (2014) found that placental abruption occurred in 0.3% of pregnancies among both nonsmokers and women who quit smoking during the first trimester of pregnancy, but in 0.6% of pregnancies among women who continued to smoke after the first trimester. That study, however, did not include adjustments for covariates, and the results of testing for statistical significance were not presented. A smaller study of births at an Australian hospital found that women who were smokers at the first antenatal visit did not differ significantly in risk of placental abruption from nonsmokers (aOR = 0.82; 95% confidence interval [CI], 0.27–2.44) or from women who quit smoking within a year before their first antenatal visit (aOR = 2.45; 95% CI, 0.20–29.29) (Bickerstaff et al. 2012).

Summary of the Evidence

The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of placental abruption. Since then, only two studies have examined smoking cessation and risk of placental abruption, and both had important methodological limitations. Consequently, the evidence is inadequate to infer that smoking cessation before or during early pregnancy reduces the risk of placental abruption compared with continued smoking.

Placenta Previa

Placenta previa is the complete or partial obstruction of the cervix by the placenta, a problem that affects an estimated 0.4% to 0.7% of births (Comeau et al. 1983; Iyasu et al. 1993; Faiz and Ananth 2003; Luke et al. 2017). Placenta previa can lead to important maternal and infant complications, including preterm delivery, hemorrhage, and even maternal, fetal, or neonatal death (Salihu et al. 2003; Creasy et al. 2004). One mechanism through which smoking could increase risk for this condition is compensatory placental enlargement in response to chronic hypoxia and ischemia resulting from smoking (USDHHS 2010).

The 1990 Surgeon General's report cited only one study examining the risk of placenta previa among former smokers (Naeye 1980); this study found that women who quit smoking before or during early pregnancy were

at increased risk relative to never smokers. The 2004 Surgeon General's report found sufficient evidence to conclude that active smoking increases the risk of placenta previa, but it did not address risk in former smokers (USDHHS 2004). Since the 2004 report, two studies have examined placenta previa in quitters. In a study of Finnish women, Räisänen and colleagues (2014) observed that placenta previa occurred in an estimated 0.2% of pregnancies in each of four exposure groups (nonsmokers, women who quit smoking during the first trimester, women who continued to smoke after the first trimester, and women for whom no information was available on their smoking status). As indicated earlier, however, the study did not adjust for covariates, and the results of testing for significance were not presented. In their study of Australian women, Bickerstaff and colleagues (2012) found that women who had quit smoking in the 12 months before entry into prenatal care had a reduced risk of placenta previa compared with those still smoking when they entered prenatal care, but the difference was not statistically significant (aOR = 0.45; 95% CI, 0.16–1.29).

Summary of the Evidence

Since the 2004 Surgeon General's report, only two studies have examined smoking cessation and risk of placental abruption, and both had important methodological limitations. Consequently, the evidence is inadequate to determine whether smoking cessation before or during pregnancy reduces the risk of placenta previa compared with continued smoking.

Premature Rupture of Membranes

Premature rupture of the membranes (PROM) refers to rupture of the amniotic sac before the onset of labor. When this occurs before 37 weeks' gestation, it is referred to as preterm PROM (PPROM). PPRM complicates 1–2% of pregnancies, and it may contribute to up to 40% of preterm deliveries (Arias and Tomich 1982; Mercer et al. 2000; Lee and Silver 2001; Bond et al. 2017; Mercer 2017). PPRM (Smith et al. 2005) increases perinatal morbidity and mortality through increased rates of preterm delivery and by elevating the risk of intra-amniotic infection, neonatal sepsis, placental abruption, and pulmonary hypoplasia (Bond et al. 2017; Sim et al. 2017). Risk factors for PPRM include nutritional deficiencies in vitamin C (Hadley et al. 1990; Casanueva et al. 1993; Woods Jr et al. 2001; Siega-Riz et al. 2003), copper (Artal et al. 1979; Kiilholma et al. 1984), and zinc (Sikorski et al. 1988; Harger et al. 1990; Ekwo et al. 1992; Scholl et al. 1993); vaginal bleeding (Harger et al. 1990; Ekwo et al. 1992; Committee on Practice Bulletins—Obstetrics 2016); bacterial vaginosis (Kurki et al. 1992; Mercer et al.

2000); and intra-amniotic infections (Naeye and Peters 1980; Ekwo et al. 1993; Heffner et al. 1993; Asrat 2001; Committee on Practice Bulletins—Obstetrics 2016). PROM may result from structural deficiencies of the chorioamniotic membranes (Lee and Silver 2001; Tchirikov et al. 2018), disruptions in collagen metabolism (Draper et al. 1995; Tchirikov et al. 2018), and accelerated senescence of membranes because of high levels of oxidative stress (Menon et al. 2014).

The 1990 Surgeon General's report on smoking cessation did not consider associations between cessation and PROM. The 2004 Surgeon General's report on smoking concluded that active smoking causally increases the risk of PROM (USDHHS 2004). Hypothesized mechanisms included effects of smoking on the immune system, resulting in increased risk of genital tract infections or inflammatory responses or reductions in nutrients, such as vitamin C (USDHHS 2010). One study included in the 2004 report assessed risk in former smokers; the aOR for PPRM among quitters compared with never smokers was less than that for continuing smokers versus never smokers (aOR = 1.58; 95% CI, 0.77–3.27 and aOR = 2.08; 95% CI, 1.37–3.13, respectively), suggesting that smoking cessation may reduce the risk of PPRM compared with continued smoking (Harger et al. 1990).

Four studies published since the 2004 Surgeon General's report have examined the risk of PROM and/or of PPRM in smokers and quitters. Bickerstaff and colleagues (2012) found that the risk of term PROM in women who had quit smoking in the 12 months before entry into prenatal care did not differ significantly from that of women still smoking when they entered prenatal care (aOR = 0.61; 95% CI, 0.33–1.15). Later, Blatt and colleagues (2015) analyzed data from certificates of live births in Ohio and found that women who quit after the second trimester had a higher incidence of PROM (5.3%) than nonsmokers and continuing smokers (2.8% and 3.2%, respectively), but they did not report results of testing for statistical significance or adjustments for confounders. In a subsample of women in this cohort with a previous preterm delivery, Wallace and colleagues (2017) found that second-trimester quitters also experienced the highest prevalence of PROM (14.4%), with rates of 6.2% and 7.3% for nonsmokers and continuing smokers, respectively. Again, potential confounding was not addressed, and it is possible that the findings could be explained by reverse causation (i.e., the occurrence of pregnancy complications could have motivated late-pregnancy cessation). Finally, in a study involving data from three randomized trials of metronidazole for bacterial vaginosis that included more than 4,000 deliveries, Andres and colleagues (2013) found no differences in risk of PPRM between nonsmokers (4.1%), smokers who

quit during pregnancy (4.2%), and continuing smokers (4.5%); the OR for quitters was 1.04 (95% CI, 0.55–1.95) in a comparison with nonsmokers. Adjustment for demographic and obstetrical factors did not change this finding.

Summary of the Evidence

The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of PROM (USDHHS 2004). Since then, studies examining the effect of smoking cessation compared with continuing to smoke on the risk of PROM have not shown significant reductions in risk, and in one sample from Ohio, PROM risk appears to have increased in quitters. Therefore, the evidence is inadequate to determine whether smoking cessation before or during pregnancy reduces the risk of PROM compared with continuing to smoke.

Preeclampsia

Preeclampsia is a syndrome of reduced organ perfusion attributable to vasospasm and endothelial activation that is marked by proteinuria, hypertension, and dysfunction of the endothelial cells lining the uterus, with onset after 20 weeks' gestation. Eclampsia refers to a condition in which preeclampsia is accompanied by generalized seizures not explained by other causes (Cunningham et al. 2013). Preeclampsia affects an estimated 1% to 6% of pregnancies (Abalos et al. 2013). Advances in research during the past 15 years have led to significant progress in our understanding of the etiology of preeclampsia. A process known as pseudo-vascularization enables increased uteroplacental perfusion and adequate oxygen and nutrient transport to the fetus by converting low-capacity uterine spiral arteries into high-capacitance, low-resistance vessels; this requires the upregulation of proangiogenic molecules in processes completed by around 20 weeks' gestation. Evidence indicates that preeclampsia is a manifestation of an imbalance between proangiogenic factors, such as placental growth factor (PlGF), and antiangiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). Elevated levels of sFlt-1 and reduced levels of PlGF have been documented in women with preeclampsia, and evidence of this imbalance can precede the onset of clinical disease (Chaiworapongsa et al. 2004; Levine et al. 2004; Robinson et al. 2006). Importantly, pseudo-vascularization is incomplete in preeclampsia; cytotrophoblasts do not adequately invade the spiral arteries, resulting in placental ischemia, downregulation of proangiogenic vascular endothelial growth factor (VEGF) family molecules, and upregulation of antiangiogenic placental factors, such as sFlt-1 and sEng. The etiology of abnormal placentation that precedes

preeclampsia is uncertain, but it may involve placental hypoxia, oxidative stress, and genetic factors (Jim and Karumanchi 2017).

An inverse association between maternal cigarette smoking and the risk of preeclampsia has been recognized for decades, and now some mechanistic understanding exists of this association. Smoking during pregnancy has been associated with reduced sFlt-1 levels in uncomplicated pregnancies (Levine et al. 2006; Jeyabalan et al. 2008), and a reduction in the ratio of sFlt-1:PlGF has been described in smokers with preeclampsia (Jääskeläinen et al. 2017). Notably, reductions in the risk of preeclampsia have not been observed in users of smokeless tobacco, suggesting that nicotine is not the agent responsible for reduced risk in cigarette smokers. In an sFlt-1 preeclampsia-like mouse model, treatment with low-dose CO prevented late-gestation hypertension, proteinuria, and reduced Bowman's space in the kidneys (Venditti et al. 2014), supporting a role for CO rather than nicotine.

Some investigators have proposed that preeclampsia is a two-stage disease, requiring abnormal placentation, insufficient invasion of extravillous cytotrophoblasts, insufficient remodeling of the maternal spiral arteries, and reduced placental perfusion in the first stage, followed by the clinical stages of the disease that involve the release of damaging endothelial factors into the maternal circulation (Roberts and Hubel 2009; Palei et al. 2013; Gathiram and Moodley 2016). It is unclear whether smoking could affect the risk of preeclampsia in one or both of these stages. Developing a better understanding of the implications of the timing of exposure to cigarette smoking in the risk of preeclampsia could lead to a better understanding of the underlying pathophysiological process and point to potential treatments.

The 1990 Surgeon General's report found that the available data supported the idea that former smokers were at reduced risk of preeclampsia relative to never smokers (although to a lesser extent than active smokers) (Marcoux et al. 1989; USDHHS 1990), but there was inadequate evidence from which to draw causal conclusions (USDHHS 1990). The 2004 Surgeon General's report concluded that maternal active smoking is causally associated with reduced risk of preeclampsia, but it did not review the outcomes with regard to former smokers (USDHHS 2004). The 2010 and 2014 reports reviewed potential underlying mechanisms (summarized above), but they did not review the outcomes for risk relative to smoking cessation.

A 2007 review of preeclampsia and smoking included six studies of the risk of preeclampsia in quitters (England and Zhang 2007); of the three studies that evaluated risk in women who quit before pregnancy, none found a significant protective effect among quitters (Marcoux et al.

1989; England et al. 2002; Parazzini et al. 2003). Four of the six studies examined cessation during pregnancy: one found a significantly reduced risk in quitters (Sibai et al. 1995), and three reported point estimates less than unity but no statistically significant associations (Marcoux et al. 1989; Martin et al. 2000; England et al. 2002). Finally, one study combined women who quit before pregnancy with women who quit during early pregnancy and reported no significant associations for any intensity of smoking (Zhang et al. 1999).

Table 4.30 presents eight studies published in 2007 or later and not included in the above review that assessed the relationship between smoking status (including cessation) and risk of preeclampsia. One of the eight (England et al. 2007) was a reanalysis of an earlier study (England et al. 2002) that was included in the review by England and Zhang (2007), but in the reanalysis, the authors used urine cotinine to validate cessation. Two of the eight studies combined preeclampsia with gestational hypertension and thus did not evaluate preeclampsia separately (England et al. 2007; Blatt et al. 2015); two assessed cessation before pregnancy (Blatt et al. 2015; Kharkova et al. 2017); one combined cessation before pregnancy with cessation during early pregnancy (England et al. 2007); and six assessed cessation during pregnancy (Fasting et al. 2009; Xiong et al. 2009; Wikstrom et al. 2010; Engel et al. 2013; Räisänen et al. 2014; Blatt et al. 2015). Five of the eight studies reported results of statistical testing, and none found a significant reduction in the risk of preeclampsia among quitters. Two of the three studies not reporting results of statistical testing reported prevalence estimates in quitters that were lower than those in non-smokers (Räisänen et al. 2014; Blatt et al. 2015), but in one study, this was only true for women who quit in the second trimester (Blatt et al. 2015), and neither of these studies adjusted for potential confounders (preeclampsia was not a primary outcome in either study). Of the six studies assessing cessation during pregnancy, the timing of cessation varied, including at greater than 28 weeks gestation (Fasting et al. 2009), in the first 20 weeks gestation or the second 20 weeks gestation (Xiong et al. 2009), between 15 and 30 weeks gestation (Wikstrom et al. 2010), in the first trimester or in the second trimester (Engel et al. 2013), and in the first trimester (Räisänen et al. 2014; Blatt et al. 2015).

All eight studies found lower point estimates for risk of preeclampsia among women who continued to smoke during pregnancy compared with women who did not smoke (range of aORs = 0.5–0.8) (England et al. 2007; Fasting et al. 2009; Xiong et al. 2009; Wikstrom et al. 2010; Engel et al. 2013; Räisänen et al. 2014; Blatt et al. 2015; Kharkova et al. 2017). Findings were statistically significant in four studies (England et al. 2007; Wikstrom et al.

2010; Engel et al. 2013; Kharkova et al. 2017) and not significant in one study (Xiong et al. 2009), and the results of statistical testing were not presented in three studies (Fasting et al. 2009; Räisänen et al. 2014; Blatt et al. 2015). Of interest, one of the three studies with a significant finding was a large population-based study in Sweden in which women who did not smoke at the first antenatal visit, but who had resumed by the third trimester, had a significantly reduced risk of preeclampsia compared with women who did not smoke during pregnancy (aOR = 0.65; 95% CI, 0.50–0.85) (Wikstrom et al. 2010).

Summary of the Evidence

The 2004 Surgeon General's report concluded that maternal active smoking is causally associated with reduced risk of preeclampsia (USDHHS 2004). Results of studies published since the 2004 report provide additional support that continued smoking during pregnancy is associated with reduced risk of preeclampsia. However, the review did not find substantial evidence to support an inverse association between smoking before or during early pregnancy and reduced risk of preeclampsia among women who quit smoking before late pregnancy. Therefore, the evidence is insufficient to conclude that smoking during early or mid-pregnancy alone, and not during late pregnancy, is associated with a reduced risk of preeclampsia. Continued smoking may reduce the risk of preeclampsia through its effects on angiogenic factors late in pregnancy rather than through upstream effects on placentation during early pregnancy, but the evidence is currently insufficient to draw conclusions about such mechanisms.

Gestational Weight Gain

Weight gain associated with smoking cessation has been well described in the general population (reviewed by Bush et al. 2016), but it has been less well studied in pregnant and postpartum women. Fear of weight gain and/or weight retention could be a barrier to cessation or sustained abstinence from smoking in pregnant and postpartum women (Lawson 1994; Hotham et al. 2002; Berg et al. 2008). Gaining weight above the recommended levels (Institute of Medicine [IOM] 2009) can result in infants' being born large for gestational age (Goldstein et al. 2017), and weight gain below the recommended levels can result in infants' being born small for gestational age or with low birth weight (Siega-Riz et al. 2009). Smoking cessation during pregnancy could have unintended adverse effects on pregnancy or other health outcomes by increasing the number of pregnancies with excessive weight gain; conversely, smoking cessation-related weight gain could also reduce the number of pregnancies with inadequate weight

Table 4.30 Studies on smoking cessation and preeclampsia

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
England et al. (2002) (original analysis); England et al. (2007) (reanalysis)	<ul style="list-style-type: none"> Randomized trial for preeclampsia prevention (2007 study was a reanalysis of 2002 study) n = 4289 1992–1995 United States (multisite) 	<ul style="list-style-type: none"> Nonsmokers: Never smoked regularly Quit before pregnancy: Quit before last menstrual period, validated with cotinine mid-pregnancy Quit during pregnancy: Quit after last menstrual period, validated with cotinine mid-pregnancy Continued smoking: Smoking at study enrollment Smoking status based on self-reports obtained at study enrollment (13–21 weeks’ gestation) in 2007 study Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks) For 2007 analysis, quit groups were combined 	<p>2002 analysis:</p> <ul style="list-style-type: none"> Preeclampsia: Gestational hypertension plus proteinuria within 7 days or the development of HELLP syndrome or eclampsia in the presence of hypertension <p>2007 analysis:</p> <ul style="list-style-type: none"> Hypertensive disorders of pregnancy: Pregnancy-associated hypertension without proteinuria, preeclampsia, or eclampsia 	<p>2002 analysis—adjusted RR for preeclampsia (95% CI):</p> <ul style="list-style-type: none"> Quit before pregnancy: 1.1 (0.7–1.7) Quit during pregnancy: 0.9 (0.6–1.3) Continued smoking: 0.7 (0.5–1.1) <p>2007 reanalysis—crude and adjusted OR for hypertensive disorders of pregnancy (95% CI):</p> <ul style="list-style-type: none"> Quit preconception or by mid-pregnancy: <ul style="list-style-type: none"> – Unadjusted: 0.9 (0.8–1.2) – Adjusted: 1.1 (0.9–1.3) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 0.6 (0.5–0.7) – Adjusted 0.6 (0.5–0.8) 	<p>Reanalysis of data used in 2002 study after obtaining cotinine validation of smoking status</p> <p>Results adjusted for maternal BMI, study center, and private health insurance</p> <p>Did not account for alcohol or substance use</p>
Fasting et al. (2009)	<ul style="list-style-type: none"> Prospective intervention study to prevent allergies in children n = 711 2000–2002 Norway 	<ul style="list-style-type: none"> Nonsmoker: Not smoking when became pregnant Quit smoking: Smoking when became pregnant, quit by study enrollment Continued smoking: Smoking when became pregnant, still smoking at enrollment Smoking status based on self-reports collected at enrollment (median gestational age: 11 weeks, all <28 weeks) 	Preeclampsia assessed by maternal questionnaire	<p>Number (%) of women with preeclampsia:</p> <ul style="list-style-type: none"> Nonsmoker: 21 (4%) Quit smoking: 11 (10%) Continued smoking: 1 (2%) 	<p>Results not adjusted for potential confounders</p> <p>Results of statistical testing not presented</p> <p>Did not account for alcohol or substance use</p>

Table 4.30 Continued

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
Xiong et al. (2009)	<ul style="list-style-type: none"> • Case-control study • n = 337 • 2003–2006 • Quebec, Canada 	<ul style="list-style-type: none"> • Nonsmokers: Did not smoke before or during pregnancy • Quit smoking early: Smoked during pregnancy but quit in the first 20 weeks • Quit smoking late: Smoked during pregnancy but quit in the second 20 weeks of pregnancy • Continued smoking: Smoked before and during pregnancy • Smoking status based on self-reports ascertained from interviews conducted during postpartum period 	Preeclampsia: Blood pressure at least 140/90 on two occasions at least 4 hours apart after 20 weeks' gestation and with proteinuria	<p>Unadjusted and adjusted OR for preeclampsia (95% CI):</p> <ul style="list-style-type: none"> • Nonsmokers: Reference • Quit smoking early: <ul style="list-style-type: none"> – Unadjusted: 0.91 (0.42–1.96) – Adjusted 1.03 (0.41–2.60) • Quit smoking late: <ul style="list-style-type: none"> – Unadjusted: 0.79 (0.21–2.96) – Adjusted 0.78 (0.12–5.02) • Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 0.63 (0.23–1.73) – Adjusted 0.62 (0.16–2.37) 	<p>Results adjusted for maternal age, race, education, marital status, family income, BMI, gravidity, abortion, alcohol consumption, and cesarean section</p> <p>Did not account for substance use</p>
Wikström et al. (2010)	<ul style="list-style-type: none"> • Population-based cohort study • Swedish Medical Birth Register • Singleton, term births • n = 379,214 • 1999–2006 • Sweden 	<ul style="list-style-type: none"> • Nonuser: Did not smoke or use tobacco at either study visit (early or late) • Quit by late pregnancy: Smoked at the early visit but not the late visit • Continued smoking: Smoked at the time of both visits (early and late) • Started smoking by late pregnancy: Did not smoke at early visit but smoked at late visit • Smoking status obtained by midwives from maternal self-reports at entry into prenatal care (<15 weeks' gestation) and at 30–32 weeks' gestation 	<p>Preeclampsia identified using ICD-10 codes</p> <p>Blood pressure \geq140/90 with proteinuria after 20 weeks' gestation</p>	<p>Adjusted OR for preeclampsia:</p> <ul style="list-style-type: none"> • Nonsmoker: Reference • Quit by late pregnancy: 0.94 (0.83–1.08) • Continued smoking: 0.50 (0.45–0.56) • Started smoking by late pregnancy: 0.65 (0.50–0.85) 	<p>Results adjusted for early-pregnancy BMI, maternal age, parity, and years of education</p> <p>Did not account for alcohol or substance use</p>
Engel et al. (2013)	<ul style="list-style-type: none"> • Population-based prospective cohort • n = 70,729 • 1999–2008 • Norway 	<ul style="list-style-type: none"> • Nonsmoker: Never smoked • Smoked first trimester only • Smoked first and second trimesters • Smoked first and third trimesters • Smoked third trimester only • Smoked all trimesters • Smoking status obtained from maternal interviews conducted in early pregnancy (~18 weeks) and late pregnancy (~30 weeks) 	Preeclampsia obtained from registry, diagnosis obtained by midwife from antenatal medical record	<p>Adjusted OR for preeclampsia (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker: Reference • Smoked first trimester only: 0.99 (0.87–1.11) • Smoked first and second trimesters: 0.89 (0.64–1.23) • Smoked first and third trimesters: 0.62 (0.31–1.27) • Smoked third trimester only: 0.78 (0.20–3.09) • Smoked all trimesters: 0.57 (0.46–0.70) 	<p>Results adjusted for parity, maternal education, BMI, education level, diabetes, and multiple observations per woman</p> <p>Did not account for alcohol or substance use</p>

Table 4.30 Continued

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
Räsänen et al. (2014)	<ul style="list-style-type: none"> Population-based retrospective cohort Finnish Medical Birth Register Singleton deliveries, live or stillborn after 22 weeks' gestation n = 1,164,953 1991–2010 Finland 	<ul style="list-style-type: none"> Nonsmokers Quit smoking: Quit during the first trimester Continued smoking: Still smoking after the first trimester Smoking history based on self-reports ascertained from the Finnish Medical Birth Register Details on when and how data were collected were not reported 	Preeclampsia definition and ascertainment not described	<p>Percentage preeclampsia:</p> <ul style="list-style-type: none"> Nonsmokers: 2.0% Quit smoking: 1.1% Continued smoking: 1.3% 	<p>Results not adjusted for potential confounders</p> <p>Results of statistical testing not presented</p> <p>Did not account for alcohol or substance use</p>
Blatt et al. (2015)	<ul style="list-style-type: none"> Population-based retrospective cohort Ohio certificates of live birth n = 927,424 2006–2012 Ohio 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during the 3 months before pregnancy or during pregnancy Quit preconception: Smoked during the 3 months before pregnancy but not during pregnancy Quit first trimester: Smoked first trimester only Quit second trimester: Smoked first and second trimester, not third Continued smoking: Smoked throughout pregnancy Smoking history ascertained from vital statistics data and certificates of live birth 	Gestational hypertension/preeclampsia combined; obtained from certificate of live birth	<p>Percentage gestational hypertension/preeclampsia:</p> <ul style="list-style-type: none"> Nonsmokers: 4.6% Quit preconception: 5.2% Quit first trimester: 4.9% Quit second trimester: 4.2% Continued smoking: 3.3% 	<p>Findings not adjusted for potential confounders</p> <p>Results of statistical testing not presented</p> <p>Did not account for alcohol or substance use</p>
Kharkova et al. (2017)	<ul style="list-style-type: none"> Population-based study using registry data n = 39,566 2006–2009 Russia 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke before or during pregnancy Quit smoking: Smoked before but not during pregnancy Continued smoking: Smoked before and during pregnancy Smoking status based on self-reports obtained at first antenatal visit 	Preeclampsia or eclampsia classified according to ICD-10 definitions: hypertension $\geq 140/90$ accompanied by edema and proteinuria with onset after 20 weeks' gestation; eclampsia was convulsions or coma in pregnant or puerperal women with hypertension, edema, or proteinuria	<p>OR for eclampsia/preeclampsia:</p> <ul style="list-style-type: none"> Smokers: Reference Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 1.09 (0.91–1.30) – Adjusted: 1.10 (0.91–1.32) Nonsmokers: <ul style="list-style-type: none"> – Unadjusted: 1.32 (1.19–1.47) – Adjusted: 1.37 (1.23–1.54) 	<p>Results adjusted for maternal age, residence, ethnicity, marital status, parity, alcohol abuse, year of delivery, BMI, and excessive weight gain</p> <p>Did not account for substance use</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **kg** = kilogram; **ICD** = International Classification of Diseases; **lbs** = pounds; **HELLP** = hemolysis, elevated liver enzymes, and low platelet count; **OR** = odds ratio; **RR** = risk ratio; **SD** = standard deviation.

gain. In 2015, 48% of U.S. women gained weight in excess of recommended levels, and 21% gained below recommended levels (CDC 2016b).

The 1990 Surgeon General's report noted that, compared with continued smoking, cessation during pregnancy may be associated with increased gestational weight gain (USDHHS 1990). More recent Surgeon General's reports have not addressed gestational weight gain and smoking cessation.

In a 2017 Cochrane Review of psychosocial interventions for supporting women to stop smoking during pregnancy, two of the identified randomized clinical trials addressed weight gain and also included biochemical validation of cessation (Chamberlain et al. 2017). One found a significant increase in weight gain by 8 months' gestation of 1.0 kilogram (kg) (2.2 pounds [lbs]) in the intervention versus the control group (Sexton and Hebel 1984); the other, which had fewer participants, found a 2.8-kg (6.2 lbs) unadjusted increase in weight gain among quitters compared with continuing smokers (Washio et al. 2011). This difference was no longer significant after adjustment for potential confounders (including pre-pregnancy BMI), but those possible confounders did not include gestational age at delivery. A significant increase in mean gestational weight gain per 10% increase in the number of negative smoking tests (during the course of the study) was not significant after adjustment for birth weight, suggesting that at least some of the potential effects of cessation on weight gain were from an increase in fetal growth (Washio et al. 2011).

Various observational studies have also found increased gestational weight gain in quitters compared with continuing smokers. Of six observational studies published since 2000, one examined gestational weight gain among women by smoking status across two consecutive pregnancies (Abrevaya 2008), and five examined this outcome by smoking status in individual pregnancies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015; Hulman et al. 2016) (Table 4.31). Each of the latter five studies examined cessation at different time points in the conception and timing of pregnancy: two examined cessation before pregnancy (Favaretto et al. 2007; Blatt et al. 2015), four examined cessation during pregnancy (Favaretto et al. 2007; Adegboye et al. 2010; Blatt et al. 2015; Hulman et al. 2016), and two examined cessation by combining those who quit before and during pregnancy (Favaretto et al. 2007; Rode et al. 2013). None of the five studies compared gestational weight gain or rate of weight gain before and after smoking cessation. Four of the five studies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) adjusted for at least some potential confounders (including pre-pregnancy BMI) in some of the analyses. Four of the five studies (Favaretto

et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) assessed gestational weight gain using recommendations from the IOM, which are specific for pre-pregnancy BMI (Rasmussen et al. 2009).

In the single study examining weight gain by smoking status across pregnancies, Abrevaya and colleagues (2008) found a significantly greater gain in gestational weight during the second pregnancy among women who quit smoking between pregnancies compared with those who smoked during both pregnancies, even after adjusting for potential confounders. However, a limitation of this study was that smoking patterns were reduced to a few simplified categories. If smoking cessation during pregnancy does increase weight gain, then the effect could have been missed using this approach.

All five of the studies of individual pregnancies found that gestational weight gain in quitters was higher than gestational weight gain in continuing smokers (range: 0.5–2.8 kg). The comparisons were statistically significant in three of the five studies (Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015), and statistical comparisons were not presented in the other two studies (Favaretto et al. 2007; Hulman et al. 2016). Adegboye and colleagues (2010) found that women who quit smoking during the first trimester gained 1.5-kg more weight than women who continued to smoke during pregnancy (unadjusted, $p < 0.001$). Rode and colleagues (who combined women who quit smoking before and during pregnancy) reported weight gains of 15.9 kg in quitters and 13.3 kg in continuing smokers, and the differences were significant after adjustment. Blatt and colleagues found, in unadjusted analyses, that women who quit smoking in the first or second trimester gained 6.2- and 3.3-pounds (2.8 kg and 1.5 kg, respectively) more weight than women who continued to smoke during pregnancy (Blatt et al. 2015). Hulman and colleagues (2016) examined cessation during pregnancy and trajectories of gestational weight gain based on weight gain in the first trimester and rate of weight gain in the second and third trimesters. The authors reported higher projected weight gains of 2.7 kg (adjusted for pre-pregnancy BMI) in quitters compared with continuing smokers, but did not report whether the findings were statistically significant. Favaretto and colleagues (2007) found a modest increase in gestational weight gain in women who quit smoking before or during pregnancy compared with those who continued to smoke during pregnancy: unadjusted estimates extrapolated to delivery were 13.4 kg and 12.9 kg, respectively. However, the authors did not stratify results by the timing of cessation with conception and did not report results of significance testing for this portion of the analysis.

Four of the five studies examining individual pregnancies and comparing quitters with nonsmokers

Table 4.31 Studies on smoking cessation and gestational weight gain

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Sexton and Hebel (1984)	<ul style="list-style-type: none"> • Randomized controlled trial of a behavioral intervention to increase smoking cessation • Enrolled pregnant women <18 weeks' gestation who smoked at least 10 cigarettes/day at or just before pregnancy • n = 935 • Years of data collection not reported • Maryland 	<ul style="list-style-type: none"> • Quit smoking by late pregnancy (8th month) • Continued smoking in late pregnancy (8th month) • Cessation confirmed with salivary thiocyanate collected during 8th month of pregnancy 	Gestational weight gain during the 8th month of pregnancy	<p>Mean gestational weight gain:</p> <ul style="list-style-type: none"> • Control group: 11.9 kg • Intervention group: 12.9 kg • Difference: 1.0 kg • p <0.05 	<p>Results not adjusted for confounders or gestational age at last measurement</p> <p>Did not account for alcohol or substance use</p>

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Favaretto et al. (2007)	<ul style="list-style-type: none"> • Prospective cohort study • n = 4,000 • 1991–1995 • Brazil 	<ul style="list-style-type: none"> • Nonsmoker: Never smoked • Continued smoking: Smoking at least 1 cigarette/day as of study interview • Quit smoking: <ul style="list-style-type: none"> – >6 months before pregnancy – Between 6 months before pregnancy and conception – Between conception and mid-pregnancy • Smoking history ascertained from maternal interviews conducted during the second trimester 	Gestational weight gain calculated using information from chart review; used last measured weight and extrapolated to delivery	<p>Mean gestational weight gain (SD):</p> <ul style="list-style-type: none"> • Measured: <ul style="list-style-type: none"> – Never smoked: 11.2 kg (5.8 kg) – Quit smoking (groups combined): 12.1 kg (6.1 kg) – Continued smoking: 11.7 (6.5 kg) • Extrapolated: <ul style="list-style-type: none"> – Never smoker: 12.4 kg (6.1 kg) – Quit smoking (groups combined): 13.4 kg (6.2 kg) – Continued smoking: 12.9 kg (6.8 kg) <p>Difference in gestational weight gain by timing of cessation (95% CI):</p> <ul style="list-style-type: none"> • Never smoked: Reference • Before conception: <ul style="list-style-type: none"> – Unadjusted: 0.14 kg (-0.54–0.81 kg) – Adjusted: 0.53 kg (-0.12–1.19 kg) • Quit <6 months before conception: <ul style="list-style-type: none"> – Unadjusted: 0.90 (0.19–1.62 kg) – Adjusted: 1.00 (0.32–1.69 kg) • Quit after conception through mid-pregnancy: <ul style="list-style-type: none"> – Unadjusted: 1.78 (0.98–2.57 kg) – Adjusted: 1.54 (0.78–2.31 kg) <p>Adjusted RR for weight gain in excess of IOM standards (95% CI):</p> <ul style="list-style-type: none"> • Never smoked: Reference • Quit overall: 1.2 (1.05–1.37) • Quit <6 months before conception: 1.14 (0.94–1.38) • Quit after conception through mid-pregnancy: 1.34 (1.10–1.63) 	<p>Results adjusted for maternal age, education, race, parity, clinical center, and pre-pregnancy BMI</p> <p>Did not account for alcohol or substance use</p>

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Abrevaya et al. (2008)	<ul style="list-style-type: none"> Population-based, retrospective cohort study Linked Michigan certificates of live birth First and second pregnancies in which women smoked during the first pregnancy n = 14,731 (18–24 years of age) n = 8,044 (25–30 years of age) 1989–2004 Michigan 	<ul style="list-style-type: none"> Smoking status across pregnancies Quit smoking: Smoked during the first pregnancy, not during the second pregnancy Continued smoking in both pregnancies Smoking status based on smoking history collected for certificates of live birth, which used one question on tobacco use during pregnancy (yes/no) 	Gestational weight gain obtained from certificates of live birth	<p>Difference in mean gestational weight gain among women who smoked during the first pregnancy (95% CI):</p> <ul style="list-style-type: none"> Quit smoking: Reference Continued smoking: <ul style="list-style-type: none"> – 18–24 years of age: -1.99 lbs (-2.50– -1.49 lbs) – 25–30 years of age: -2.10 lbs (-2.67– -1.54 lbs) 	<p>Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father’s name on birth certificate, number of prenatal visits, and first-birth value of the outcome</p> <p>Did not account for alcohol or substance use</p>
Adegboye et al. (2010)	<ul style="list-style-type: none"> Retrospective cohort study Risk factors for postpartum weight retention Singleton pregnancies n = 1,753 1984–1985 Sweden 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking: Quit smoking during first trimester and remained abstinent throughout pregnancy Continued smoking: Continued to smoke during pregnancy Smoking status based on self-reports but details not reported 	<p>Gestational weight gain calculated by subtracting maternal weight at the end of gestation from self-reported pre-pregnancy weight</p> <p>Compared with IOM (2009) recommendations</p>	<p>Unadjusted mean gestational weight gain (SD):</p> <ul style="list-style-type: none"> Nonsmoker: 14.1 kg (4.0 kg) Quit smoking: 15.3 kg (4.4 kg) Continued smoking: 13.8 kg (4.3 kg) p <0.001, ANOVA <p>OR (95% CI) for gestational weight gain in excess of IOM recommendations:</p> <ul style="list-style-type: none"> Nonsmoker: Reference Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 1.6 (1.1–2.1) – Adjusted: 2.0 (1.4–3.0) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 1.0 (0.8–1.3) – Adjusted: 1.3 (0.9–1.8) 	<p>Results adjusted for birth weight, gestational age, parity, pre-pregnancy BMI, alcohol consumption, physical activity, and breakfast frequency</p> <p>Did not account for substance use</p>

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Washio et al. (2011)	<ul style="list-style-type: none"> • Randomized controlled trial of a voucher incentive to increase smoking cessation • Pregnant smokers • n = 154 • 2001–2006 • Vermont 	<ul style="list-style-type: none"> • Quit smoking: Past 7-day abstinence confirmed by urine cotinine at the end of pregnancy • Continued smoking: Not abstinent at the end of pregnancy • Not reported when cessation data were collected 	Weight at delivery and pre-pregnancy weight	<p>Mean gestational weight gain (SD):</p> <ul style="list-style-type: none"> • Control group: 15.0 +/- 0.8 kg <ul style="list-style-type: none"> – Intervention group: 15.0 +/- 0.9 kg – Difference = 0.0 kg – p = 0.97 • Quit smoking: 17.2 +/- 1.1 kg <ul style="list-style-type: none"> – Continued smoking: 15.4 +/- 0.6 kg – Difference = 2.8 kg – p = 0.04 <p>Adjusted mean difference in gestational weight gain:</p> <ul style="list-style-type: none"> • Quit smoking vs. continued smoking: <ul style="list-style-type: none"> – 2.4 kg – p = 0.06 • Mean increase in gestational weight gain of 0.34 kg per 10% increase in cessation: <ul style="list-style-type: none"> – p = 0.03 (results adjusted for pre-pregnancy BMI and parity) – p = 0.13 (results adjusted for pre-pregnancy BMI, parity, and birth weight) 	Loss of significance after adjustment for birth weight suggests that the increase in gestational weight gain in quitters compared with continuing smokers was attributable in part to increased fetal growth

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Rode et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort of pregnant women who received an intervention to be smokefree • Singleton, term pregnancies • n = 1,774 • 1996–1999 • Denmark 	<ul style="list-style-type: none"> • Nonsmokers: Not defined • Quit smoking: Quit immediately before or during pregnancy • Continued smoking: Not further defined • Smoking status based on self-reports assessed at 12–18 weeks' and 37 weeks' gestation and 1 year postpartum • Salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation 	Gestational weight gain at 37 weeks' gestation compared with recommendations from IOM (2009)	<p>Mean gestational weight gain at 37 weeks (SD), difference in gestational weight gain (95% CI):</p> <ul style="list-style-type: none"> • Nonsmokers: 13.46 kg (4.71 kg) (reference) • Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 2.44 kg (1.86–3.03 kg) – Adjusted: 2.01 kg (1.51–2.64 kg) • Continued smoking: <ul style="list-style-type: none"> – Unadjusted: -0.14 kg (-7.4–0.47 kg) – Adjusted: -0.10 kg (-0.67–0.48 kg) <p>Adjusted OR (95% CI) for gestational weight gain in excess of IOM recommendations:</p> <ul style="list-style-type: none"> • Nonsmokers: Reference • Quit smoking: 1.9 (1.5–2.4) • Continued smoking: 1.2 (0.9–1.5) 	<p>Weight gain adjusted for pre-pregnancy BMI, gestational age, and parity</p> <p>Salivary cotinine for subgroup reported but report did not describe whether it was integrated into main analysis</p> <p>Did not account for alcohol or substance use</p> <p>OR for gaining in excess of IOM recommendations adjusted for gestational age and preeclampsia</p>
Blatt et al. (2015)	<ul style="list-style-type: none"> • Population-based retrospective cohort study • Ohio certificates of live birth • n = 927,424 • 2006–2012 • Ohio 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke during the 3 months before pregnancy or during pregnancy • Quit smoking before pregnancy: Smoked during the 3 months before pregnancy but not during pregnancy • Quit smoking first trimester: Smoked first trimester only • Quit smoking second trimester: Smoked first and second trimester, not third • Continued smoking: Smoked throughout pregnancy • Smoking history ascertained from vital statistics data and certificates of live birth 	Gestational weight gain calculated from maternal weight at delivery vs. preconception weight	<p>Mean gestational weight gain (SD):</p> <ul style="list-style-type: none"> • Nonsmoker: 31.2 lbs (+/- 16.9 lbs) • Quit smoking before pregnancy: 36.4 lbs (+/- 18.8 lbs) • Quit smoking first trimester: 36.5 lbs (+/- 19.2 lbs) • Quit smoking second trimester: 33.6 lbs (+/- 19.5 lbs) • Continued smoking: 30.3 lbs (+/- 8.9 lbs) • All comparisons: p <0.001 	<p>Findings not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p>

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Hulman et al. (2016)	<ul style="list-style-type: none"> Longitudinal cohort study Singleton pregnancies n = 509 2013 Ontario, Canada 	<ul style="list-style-type: none"> Nonsmokers: Women who never smoked Quit smoking: Smoked previously but quit when they found out they were pregnant Continued smoking: Still smoking at study assessment Smoking status based on maternal self-reports obtained during survey conducted at ~32 weeks' gestation 	<p>Gestational weight gain calculated from pre-pregnancy weight (or first available antenatal visit) and serial weight measurements obtained from medical record review</p> <p>Rate of weight gain (kg/week) in second and third trimesters compared with recommendations from IOM:</p> <ul style="list-style-type: none"> Underweight: 0.44–0.58 Normal: 0.35–0.50 Overweight: 0.23–0.33 Obese: 0.17–0.27 	<p>Mean gestational weight gain (95% CI) based on trajectories for the end of the 39th week:</p> <ul style="list-style-type: none"> Nonsmoker: 14 kg Quit smoking: 16.7 kg (15.1–18.4 kg) Continued smoking: 14 kg <p>Total first trimester gestational weight gain (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker: 1.7 kg (1.4–2.1 kg) Quit smoking: 1.2 kg (0.3–2.1 kg) Continued smoking: 3.5 kg (2.4–4.6 kg) <p>Rate of weight gain in second and third trimesters:</p> <ul style="list-style-type: none"> Quit smoking: 0.60 kg/week (0.54–0.65 kg/week) Vs. nonsmokers: +22% (11–34%) Vs. continued smokers: +53% (32–75%) <p>Rate of weight gain by IOM categories: kg/week (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker: <ul style="list-style-type: none"> Underweight: 0.52 (0.42–0.62) Normal: 0.51 (0.49–0.54) Overweight: 0.52 (0.48–0.55) Obese: 0.38 (0.33–0.42) Quit smoking: <ul style="list-style-type: none"> Underweight: 0.62 (0.50–0.73) Normal: 0.61 (0.56–0.67) Overweight: 0.62 (0.56–0.68) Obese: 0.48 (0.41–0.54) Continued smoking: <ul style="list-style-type: none"> Underweight: 0.44 (0.33–0.56) Normal: 0.44 (0.37–0.50) Overweight: 0.44 (0.37–0.51) Obese: 0.30 (0.23–0.37) 	<p>Results adjusted for maternal age, race, parity, marital status, education, income, and BMI</p> <p>Did not account for alcohol or substance use</p>

Notes: ANOVA = analysis of variance; BMI = body mass index; CI = confidence interval; IOM = Institute of Medicine; kg = kilograms; lbs = pounds; OR = odds ratio; RR = relative risk; SD = standard deviation.

(Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015) found a significant increase in gestational weight gain in quitters (range: 0.5–2.4 kg). One study did not report statistical comparisons (Hulman et al. 2015). The two studies examining cessation before pregnancy both found significant increases in gestational weight gain among women who quit before but close to the time of conception in comparisons with nonsmokers (range: 1.0–2.4 kg) (Favaretto et al. 2007; Blatt et al. 2015). The study by Favaretto and colleagues (2007) also found that weight gain in women who had quit more than 6 months before conception did not differ significantly from that of nonsmokers, even after adjusting for potential confounders. Of the four studies examining cessation during pregnancy, three (Favaretto et al. 2007; Adegboye et al. 2010; Blatt et al. 2015) reported significant increases in weight in quitters compared with nonsmokers. Adegboye and colleagues (2010) and Blatt and colleagues (2015) examined cessation in the first trimester, which was associated with increases in weight gain of 1.2 kg (Adegboye et al. 2010) and 1.1 kg (Blatt et al. 2015), respectively. Blatt and colleagues (2015) also described a significant increase in weight gain (2.4 kg) among women who quit during the second trimester in a comparison with nonsmokers. Favaretto and colleagues (2007) examined cessation between conception and mid-pregnancy (20–28 weeks gestation) and found a 1.54-kg increase in weight gain in quitters compared with nonsmokers after adjusting for pre-pregnancy BMI and other potential confounders. Hulman and colleagues (2016) also examined cessation during pregnancy and reported that projected gestational weight gain, based on weight gain trajectories and adjusted for confounders, was higher by 2.7 kg in quitters than in nonsmokers, but results of testing for statistical significance were not presented. Rode and colleagues reported a 2.0-kg (95% CI, 1.5–2.6 kg) increase in adjusted gestational weight gain in women who quit smoking before or during pregnancy compared with women who were nonsmokers (Rode et al. 2013).

Two of the four studies examining cessation during pregnancy also compared weight gain early and late in pregnancy. Rode and colleagues (2013) found that at 16 weeks' gestation no differences existed in weight gain when nonsmokers, women who quit before or during pregnancy, and continuing smokers were compared after adjustment for pre-pregnancy BMI, gestational age, and parity. By 37 weeks' gestation, however, women who had quit smoking had a significant, adjusted 4.4-lb [2.0 kg] increase in weight gain in comparison with nonsmokers, while continuing smokers and nonsmokers did not experience relative increases in weight gain. In contrast, Hulman and colleagues (2016) found that continuing smokers gained more than twice as much weight during the first

trimester as women who quit smoking upon learning of their pregnancy (adjusted difference = 3.0 kg [6.6 lbs] after controlling for sociodemographic characteristics and pre-pregnancy BMI). The weekly rate of weight gain in the second and third trimesters was highest, however, in women who quit smoking during pregnancy. Quitters had a 22% faster rate of weight gain in the second and third trimesters of pregnancy compared with nonsmokers and a 53% faster rate of weight gain compared with continuing smokers (Hulman et al. 2016).

Four studies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) examined gestational weight gain with respect to IOM recommendations (IOM 1990). Two studies (Favaretto et al. 2007; Adegboye et al. 2010) found that women who quit smoking during pregnancy were significantly more likely to gain weight in excess of IOM recommendations compared with nonsmokers, even after controlling for pre-pregnancy BMI and other factors (adjusted RR: 1.34 [95% CI, 1.10–1.63]; and adjusted OR: 2.0 [95% CI, 1.4–3.0], respectively). Rode and colleagues (2013) found that the percentage of women who gained in excess of IOM guidelines differed significantly by smoking status (45.9%, 34.6%, and 31.3% for women who quit before or during pregnancy, continuing smokers, and nonsmokers, respectively, $P < 0.001$), and after adjustment for gestational age and preeclampsia, quitters were significantly more likely to gain in excess of IOM recommendations than nonsmokers (OR 1.9 95% CI 1.5–2.4). Adjusted models comparing quitters with continuing smokers were not reported (Rode et al. 2013). Hulman and colleagues (2016) examined IOM recommendations for rate of weight gain and found that women who quit smoking during pregnancy on average gained above the rate recommended by the IOM in the second and third trimesters for all pre-pregnancy BMI categories, and weight gain by women who continued to smoke varied by pre-pregnancy BMI category (under- and normal-weight women on average gained within the recommended rate range while overweight and obese women gained faster than the recommended rate). Among nonsmokers, only those who were underweight gained at a rate within IOM recommendations; all other groups gained at a rate exceeding IOM recommendations (Hulman et al. 2016).

Summary of the Evidence

The evidence describing the associations between smoking status, quitting, and gestational weight gain has expanded considerably since the 1990 Surgeon General's report, but there has been some variation in the covariates included in the analytic models and in the time points used to define smoking cessation (e.g., preconception, in early gestation, by mid-pregnancy, during gestation).

Nonetheless, the evidence is sufficient to infer that women who quit smoking shortly before or during pregnancy gain more weight during gestation than women who continue to smoke, and the findings are consistent, including data from two randomized clinical trials. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than nonsmokers. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy are at increased risk of excess weight gain, per IOM guidelines, compared with nonsmokers. However, very little evidence could be used to compare the risk of excess gestational weight gain in quitters with that in continuing smokers.

Prenatal smoking cessation has substantial health benefits for mothers and offspring, and providing assistance with weight management while promoting smoking cessation could help to optimize outcomes.

Gestational Diabetes

Gestational diabetes mellitus (GDM), which is defined as carbohydrate intolerance leading to hyperglycemia with onset or first recognition during pregnancy, affects 4% to 9% of pregnancies in the United States (DeSisto et al. 2014). Although this complication usually resolves after delivery, up to one-third of affected women have diabetes or impaired glucose metabolism at postpartum screening. Women with GDM are at increased risk for cesarean delivery, and their infants are at increased risk for macrosomia (i.e., being large for gestational age), neonatal hypoglycemia, and fetal hyperinsulinemia (Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group 2008). Most women who develop GDM have preexisting impaired beta cell function and chronic insulin resistance that is characteristic of type 2 diabetes, and women with a history of GDM are at substantially increased risk for the future development of type 2 diabetes, providing evidence of a common underlying mechanism (Mack and Tomich 2017). Furthermore, GDM is consistently associated with both higher pre-pregnancy BMI and excessive gestational weight gain (Brunner et al. 2015; Najafi et al. 2019).

The 1990 Surgeon General's report did not examine smoking and GDM, but the 2001 Surgeon General's report on women and smoking described inconsistent evidence of an association between smoking and GDM (USDHHS 2001). The 2014 Surgeon General's report did not examine smoking and GDM, but did conclude that smoking is causally associated with type 2 diabetes and did address smoking cessation and risk of type 2 diabetes (USDHHS 2014). In one large study, the risk of incident type 2 diabetes for short-term quitters was higher than that of current smokers but decreased to the level for never smokers

by 12 years (Yeh et al. 2010; USDHHS 2014). In another large study, the risk of type 2 diabetes decreased to that of nonsmokers 5 years after quitting in women and 10 years after quitting in men (Will et al. 2001; Wendland et al. 2008; USDHHS 2014). The transient increase in risk for quitters may be the result of short-term effects on weight gain. The 2014 report did not address GDM specifically.

In light of the potential for increased short-term morbidity associated with weight gain following smoking cessation, an increase in gestational weight gain associated with smoking cessation could be associated with adverse pregnancy outcomes, such as GDM or macrosomia, regardless of whether smoking itself is directly causally associated with GDM (Rasmussen et al. 2009). Therefore, smoking cessation and GDM were reviewed in this section absent an established causal relationship between active smoking and GDM in these reports.

Five studies on smoking and GDM published since the 2001 report included prevalence estimates for GDM among nonsmokers, former smokers, and continuing smokers (England et al. 2004; Fasting et al. 2009; Erickson and Arbour 2012; Räisänen et al. 2014; Blatt et al. 2015). Three of these were large, population-based studies (Erickson and Arbour 2012; Räisänen et al. 2014; Blatt et al. 2015), and two were small, clinic-based studies (England et al. 2004; Fasting et al. 2009). Räisänen and colleagues (2014) reported a greater prevalence of GDM among women who quit smoking in the third trimester (9.8%) compared with never smokers (7.6%) and with continuing smokers (7.6%); Erickson and Arbour (2012) reported the lowest GDM prevalence in continuing smokers (3.8% to 4.9%), with prevalence equaling 5.4% in quitters and 6.7% in nonsmokers; and Blatt and colleagues (2015) reported the lowest prevalence in nonsmokers (5.4%) and a slightly higher prevalence in preconception quitters (5.8%) and in first- and second-trimester quitters (5.6% and 5.5%, respectively). In none of these three studies was GDM the primary outcome of interest, and none reported results of testing for statistical significance in direct comparisons or the results of adjusted analyses. The study populations in these analyses were very large, however.

In one of the two smaller studies, England and colleagues (2004) reported a significant increase in mean adjusted plasma glucose concentration after a 1-hour, 50-g glucose challenge in continuing smokers compared with never smokers (112.6 milligrams per deciliter [mg/dL] vs. 108.3 mg/dL, $p < 0.01$), but no differences were seen when never smokers were compared with women who had quit before pregnancy (108.5 mg/dL) or during pregnancy (109.5 mg/dL). Compared with nonsmokers, continued smoking was significantly associated with GDM (aOR = 1.9; 95% CI, 1.0–3.6), but no significant associations were

observed for smoking with cessation before (aOR = 0.8; 95% CI, 0.3–2.1) or during pregnancy (aOR = 1.4; 95% CI, 0.5–2.9) (England et al. 2004). In the other of the smaller studies, Fasting and colleagues (2009) reported identical estimates of GDM prevalence (3%) for never smokers and smokers who quit early in pregnancy and an estimate of 5% for women who continued to smoke. GDM was not the primary outcome of interest, however, and the number of GDM cases was small (only three each in the groups of quitters and continuing smokers), and an adjusted analysis was not performed.

Summary of the Evidence

Only a limited number of studies on the relationship between smoking cessation and GDM were identified, and in the majority of those studies, GDM was not the main outcome of interest, potentially limiting assessment for relevant covariates and confounders. Thus, the evidence is inadequate to determine whether smoking cessation during pregnancy increases the risk of gestational diabetes.

Birth Outcomes

Birth Defects

The 2014 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between maternal smoking in early pregnancy and increased risk for orofacial clefts (USDHHS 2014). However, the evidence was suggestive but not sufficient to infer an increased risk for other birth defects—including clubfoot, gastroschisis, and atrial septal heart defects—for women who smoke in early pregnancy (USDHHS 2014). Based on the available scientific evidence, the 2014 report recommended providing information on the risk of orofacial clefts as part of efforts to reduce smoking prior to conception and in early pregnancy (USDHHS 2014); however, few studies have specifically assessed the risk for orofacial clefts among women who are former smokers. One study has assessed the risk for any major anomaly among women who quit smoking during the first trimester compared with women who did not smoke during pregnancy (Räsänen et al. 2014). However, due to the limited number of studies published to date specifically related to cessation and risk for specific birth defect categories, including orofacial clefts, this report does not reach any new conclusions regarding these outcomes.

Fetal Growth and Birth Weight

The effects of maternal smoking on birth weight have been recognized since the 1964 Surgeon General's

report, which found that infants of smokers were more likely than those of nonsmokers to weigh less than 2,500 g at birth (USDHEW 1964). Birth weight is determined by both gestational age at delivery and the rate of fetal growth, and subsequent Surgeon General's reports have addressed these factors separately when examining birth weight as an outcome. The 1990 Surgeon General's report noted that the risk of being small for gestational age (typically defined as weight \leq 10th percentile for gestational age) was 3.5- to 4-fold higher in infants of smokers than in infants of nonsmokers (USDHHS 1990). The report concluded that babies of women who quit smoking before conception did not experience smoking-related reductions in fetal growth, while cessation before the third trimester significantly attenuated the deleterious effects of maternal smoking on fetal growth (USDHHS 1990). The 2004 Surgeon General's report found sufficient evidence to infer a causal relationship between smoking and both fetal growth restriction and reduced gestational age/increased preterm delivery (USDHHS 2004). It confirmed the 1990 Surgeon General's report's finding that cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004). The 2014 Surgeon General's report explored in depth the relationships between smoking and fetal growth. The report concluded that nicotine is unlikely to be the main contributor in tobacco smoke to fetal growth restriction, with products of combustion likely playing a major role in this regard (USDHHS 2014). This report did not address the benefits of smoking cessation, however.

Several subsequent studies have supported the conclusions of the 1990 and 2004 Surgeon General's reports that smoking cessation attenuates the adverse effects of smoking on fetal growth and birth weight. There are several methodologic challenges, however, in studies of fetal growth and birth weight. First, fetal growth is not linear, and the most rapid rate of growth occurs in the third trimester (Kiserud et al. 2017). As a consequence, assessing the timing of tobacco exposure with respect to position on the fetal growth curve is essential to characterizing the mechanisms through which tobacco use exerts adverse effects and cessation benefits fetal growth. Many of the studies identified in the literature review, however, did not assess tobacco use and cessation across the entire pregnancy. Second, as previously described, smokers typically differ from nonsmokers in numerous behavioral, obstetrical, and other health-related factors, and a failure to control for potential confounders may result in residual confounding. High-quality data on many potentially important exposures for fetal growth, such as use of alcohol and/or illicit drugs, are often lacking in registries and other commonly used sources of data.

Birth Weight

Table 4.32 presents 40 studies that examined birth weight and smoking cessation during pregnancy. Studies varied in the use of biochemical validation of reported cessation, in descriptions about the timing of cessation, and in adjustments for potential confounders. Twenty of the studies addressed gestational age by restricting the analysis to term infants and/or adjusting for gestational age (Hrubá and Kachlik 2000; Lindley et al. 2000; England et al. 2001a,b, 2007; Mendez et al. 2008; Nijati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; Kabir et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Juarez and Merlo 2013; Miyake et al. 2013; Rode et al. 2013; Slatter et al. 2014; Suzuki et al. 2014, 2016; Hayes et al. 2016); 25 included adjustment for at least some additional confounders (Lindley et al. 2000; England et al. 2001a,b, 2007; Dejmek et al. 2002; Wen et al. 2005; Abrevaya 2008; Nijati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; McCowan et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Himes et al. 2013; Juarez and Merlo 2013; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Meghea et al. 2014; Suzuki et al. 2014, 2016; Bailey 2015; Yan and Groothuis 2015; Hayes et al. 2016); and 9 included biochemical validation of smoking cessation (England et al. 2001a,b; Secker-Walker and Vacek 2002; Malchodi et al. 2003; England et al. 2007; Andersen et al. 2009; Benjamin-Garner and Stotts 2013; Rode et al. 2013; Bailey 2015; Hayes et al. 2016). Five studies did not differentiate between either quitting before pregnancy and quitting during early pregnancy or a combination of both and, thus, could not isolate the effects of quitting during pregnancy (Hrubá and Kachlik 2000; England et al. 2007; Vardavas et al. 2010; Murphy et al. 2013; Rode et al. 2013). Nineteen studies used smoking status in late pregnancy to categorize exposure groups, thus those studies did not combine late quitters with continuing smokers, or women who relapsed with women who remained abstinent (Lindley et al. 2000; England et al. 2001a,b, 2007; Dejmek et al. 2002; Secker-Walker and Vacek 2002; Malchodi et al. 2003; Andersen et al. 2009; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Himes et al. 2013; Juarez and Merlo 2013; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Slatter et al. 2014; Bailey 2015; Blatt et al. 2015; Yan and Groothuis 2015; Wallace et al. 2017). Only two studies adjusted for or otherwise addressed alcohol and other substance use (Murphy et al. 2013; Bailey 2015), and seven adjusted for alcohol use but not other substance use (Dejmek et al. 2002; Wen et al. 2005; Sasaki et al. 2008; McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Yan and Groothuis 2015), and one excluded women who used illicit drugs

(Himes et al. 2013). Five studies accounted for gestational age and also adjusted for confounders, included biochemical validation of quit status, and incorporated well-defined exposure groups that included smoking status in late pregnancy (England et al. 2001a,b, 2007; Andersen et al. 2009; Benjamin-Garner and Stotts 2013; Rode et al. 2013). None of these five adjusted for alcohol or illicit drug use.

Despite these methodologic differences, most of the 40 studies found that (a) women who continued to smoke past early pregnancy delivered infants of lower birth weight than those of nonsmokers and (b) cessation before or during pregnancy attenuated or eliminated this effect. These findings were consistent in studies controlling for gestational age at birth and/or excluding preterm deliveries (Lindley et al. 2000; England et al. 2001b, 2007; Mendez et al. 2008; Nijati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; Kabir et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Juarez and Merlo 2013; Miyake et al. 2013; Rode et al. 2013; Slatter et al. 2014; Suzuki et al. 2014, 2016) and in studies that addressed illicit drug and/or alcohol use (Dejmek et al. 2002; Wen et al. 2005; Sasaki et al. 2008; McCowan et al. 2009; Bakker et al. 2011; Himes et al. 2013; Miyake et al. 2013; Murphy et al. 2013; Bailey 2015; Yan and Groothuis 2015).

Four of the 40 studies validated smoking status while also adjusting for gestational age or restricting the study to term births, adjusting for potential confounders, and assessing smoking status in late pregnancy. Results from the two studies comparing quitters with nonsmokers found no difference in mean adjusted birth weight (England et al. 2007; Andersen et al. 2009), and the other two studies were randomized clinical trials of cessation interventions and thus compared quitters with continuing smokers (England et al. 2001b; Benjamin-Garner and Stotts 2013). In these two studies, the adjusted mean difference in birth weight between infants of quitters and those of continuing smokers was an excess of 100 and 300 g, respectively. However, England and colleagues (2007) combined women who quit before pregnancy with women who quit during pregnancy and, thus, could not address the effect of cessation during pregnancy.

One large study (previously described) used a sibling-comparison analysis to address the problem of potential uncontrolled confounding in the relationship between smoking during pregnancy and the birth weight of offspring (Juarez and Merlo 2013). Compared with the conventional analysis performed with all singleton births in the dataset, the sibling analysis revealed a reduced effect of smoking on gestational age-adjusted birth weight. In the sibling analysis, continuous smoking through pregnancy reduced birth weight by 162 g for light smokers (≤ 10 cigarettes per day) and by 226 g for heavy smokers (> 10 cigarettes per day), versus reductions of

Table 4.32 Studies on smoking cessation and birth weight

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Hrubá and Kachlik (2000)	<ul style="list-style-type: none"> Retrospective, clinic-based study Term, singleton deliveries n = 1,147 Years of data collection not reported Czech Republic 	<ul style="list-style-type: none"> Nonsmokers: Never smoked Quit smoking: Smoked but quit before pregnancy or during the first trimester Continued smoking: Smoked throughout pregnancy, either daily or occasionally Smoking status based on self-report from interview conducted shortly after delivery 	<p>Mean birth weight (SD) and difference in mean birth weight (among women without exposure to secondhand smoke):</p> <ul style="list-style-type: none"> Nonsmokers: 3,383 g (456) (reference) Quit smoking: 3,414 g (459), +31 g Continued smoking: 3,298 g (484), -85 g 	<p>Analysis restricted to term births</p> <p>Results not adjusted for potential confounders</p> <p>Analysis stratified by exposure to secondhand smoke</p> <p>Did not account for alcohol or illicit drug use</p>
Lindley et al. (2000)	<ul style="list-style-type: none"> Population-based, retrospective cohort study Analysis of births from the Swedish Birth Registry ≥32 weeks' gestation at delivery, excluded pregnancies with complication or congenital malformations n = 15,185 1991–1992 Sweden 	<ul style="list-style-type: none"> Nonsmoker: Not a smoker or less than daily smoker at first prenatal visit Quit smoking: Smoked daily at first prenatal visit but did not smoke at late visit Continued smoking: Smoked at first and late prenatal visits: <ul style="list-style-type: none"> Light smoker: 1–9 cigarettes/day Heavy smoker: ≥10 cigarettes/day Smoking status based on self-reports at first and late (~32 weeks) prenatal visits 	<p>Mean adjusted birth weight and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3,459 g, p <0.001 Quit smoking: -26 g (not significant) Continued smoking <ul style="list-style-type: none"> Light smokers: -136 g, p <0.001 Heavy smokers: -175 g, p <0.001 	<p>Results adjusted for sex of the infant, gestational age, parity, maternal age, height, and BMI</p> <p>Did not account for alcohol or illicit drug use</p>
England et al. (2001b)	<ul style="list-style-type: none"> Randomized clinical trial of a smoking cessation intervention Singleton, term pregnancies n = 926 1987–1991 Multiple centers in the United States 	<ul style="list-style-type: none"> Quit smoking before enrollment: Smoked within 1 week of learning they were pregnant but quit by enrollment Quit smoking after enrollment: Smoked within 1 week of learning they were pregnant and at enrollment but quit after enrollment Continued to smoke: <ul style="list-style-type: none"> Did not change: Cotinine, cigarettes/day changed by <50% Reduced: Reduced cotinine, cigarettes/day by >50% Increased: Increased cotinine, cigarettes/day by >50% Smoking status based on self-report obtained at enrollment and in the third trimester, validated using urine cotinine collected concurrently 	<p>Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight (95% CI)</p> <ul style="list-style-type: none"> Self-report: <ul style="list-style-type: none"> Continued to smoke/did not change: 3,205 g (reference) Quit smoking after enrollment: +286 g (196–376 g) Cotinine validated: <ul style="list-style-type: none"> Continued to smoke/did not change: 3,216 g (reference) Quit smoking after enrollment: +197 g (94–301 g) Mean adjusted birth weight of those who reduced or increased cotinine or cigarettes/day did not differ from that of women who did not change 	<p>Only smokers enrolled; no nonsmoker comparison group</p> <p>Analysis restricted to term births</p> <p>Results adjusted for maternal age, parity, race, BMI, state of clinic's location, sex of the infant, and gestational age</p> <p>Did not account for alcohol or illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
MacArthur et al. (2001)	<ul style="list-style-type: none"> • Randomized clinical trial of a behavioral intervention of antismoking education with long-term follow-up • n = 1,853 • 1981–1982 • Alabama 	<ul style="list-style-type: none"> • Nonsmokers: Not smoking at enrollment • Quit smoking by 6 weeks • Quit smoking 7–16 weeks • Quit smoking ≥17 weeks • Continued smoking • Smoking status based on self-reports at enrollment into prenatal care 	<p>Unadjusted mean birth weight and difference in mean birth weight:</p> <ul style="list-style-type: none"> • Nonsmokers: 3,445 g (reference) • Quit by 6 weeks: 3,433 g, -12 g • Quit 7–16 weeks: 3,389 g, -56 g • Quit ≥17 weeks: 3,327 g, -118 g • Continued smoking: 3,149 g, -296 g 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p> <p>Direct statistical comparisons between groups not shown</p>
Dejmek et al. (2002)	<ul style="list-style-type: none"> • Population-based retrospective cohort • n = 6,866 • 1994–1999 • Czech Republic 	<ul style="list-style-type: none"> • Nonsmoker: Not smoking when pregnancy recognized • Quit after pregnancy recognized: <ul style="list-style-type: none"> – Moderate smokers: 1–10 cigarettes/day – Heavy smokers: >10 cigarettes/day • Continued smoking: <ul style="list-style-type: none"> – Moderate smokers: 1–10 cigarettes/day – Heavy smokers: >10 cigarettes/day • Smoking status based on self-reports obtained at delivery 	<p>Difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker (reference) • Quit after pregnancy recognized: <ul style="list-style-type: none"> – Moderate smoker: -22 g (-64–19 g) – Heavy smoker: -66 g (-146–14 g) • Continued smoking: <ul style="list-style-type: none"> – 1–10 cigarettes/day: -152 g (-185– -117 g) – >10 cigarettes/day: -259 g (-342– -175 g) 	<p>Results adjusted for maternal age, district, ethnicity, education, parity, sex, height, pre-pregnancy weight, alcohol consumption, and season</p> <p>Did not account for illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Secker-Walker and Vacek (2002)	<ul style="list-style-type: none"> • Randomized clinical trial of a smoking cessation intervention • Singleton births • n = 240 • 1988–1992 • Vermont 	<ul style="list-style-type: none"> • Quit smoking: Smoked at enrollment but quit in late pregnancy (~35 weeks' gestation) • Continued smoking: Smoked at enrollment and in late pregnancy: <ul style="list-style-type: none"> – Reduced by <50% – Reduced by ≥50% • Smoking status based on self-reports and urine cotinine obtained at enrollment into prenatal care [14.6 (7.0) weeks] and near the end of pregnancy [35.0 (1.2) weeks] 	<p>Mean infant birth weight (95% CI):</p> <ul style="list-style-type: none"> • Self-report (adjusted results were adjusted for number of cigarettes smoked/day at first visit): <ul style="list-style-type: none"> – Reduced <50%: <ul style="list-style-type: none"> ○ Unadjusted: 3,203 g (3,127–3,278 g) ○ Adjusted: 3,203 g (3,128–3,278 g) – Reduced ≥50%: <ul style="list-style-type: none"> ○ Unadjusted: 3,239 g (3,096–3,382 g) ○ Adjusted: 3,267 g (3,124–3,410 g) – Quit: <ul style="list-style-type: none"> ○ Unadjusted: 3,446 (3,298–3,594 g) ○ Adjusted: 3,413 g (3,270–3,556 g) • With biochemical validation (adjusted results were adjusted for cotinine concentration at first visit): <ul style="list-style-type: none"> – Reduced <50%: <ul style="list-style-type: none"> ○ Unadjusted: 3,205 g (3,124–3,286 g) ○ Adjusted: 3,214 g (3,133–3,295 g) – Reduced ≥50%: <ul style="list-style-type: none"> ○ Unadjusted: 3,184 g (3,069–3,298 g) ○ Adjusted: Reduced 3,226 g (3,114–3,338 g) – Quit (based on self-reports): <ul style="list-style-type: none"> ○ Unadjusted: 3,465 g (3,306–3,624 g) ○ Adjusted: 3,447 g (3,291–3,604 g) <p>Difference in mean adjusted infant birth weight:</p> <ul style="list-style-type: none"> • Quit vs. reduced <50%: <ul style="list-style-type: none"> – Self-report: 210 g – Cotinine validated: 233 g 	<p>All study participants were smokers at the time of recruitment; no nonsmoker comparison group</p> <p>Did not account for alcohol or illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Malchodi et al. (2003)	<ul style="list-style-type: none"> • Randomized clinical trial of a smoking cessation intervention • n = 142 • 1998–2000 • Connecticut 	<ul style="list-style-type: none"> • Quit smoking: Smoked daily in the week before learning they were pregnant but quit by 36 weeks' gestation • Continued smoking: Smoked daily in the week before learning they were pregnant and were still smoking at 36 weeks' gestation: <ul style="list-style-type: none"> – 1–6 cigarettes/day – >6 cigarettes/day • Smoking status based on self-reports • Quit status confirmed with both expired CO and urine cotinine collected at 36 weeks 	<p>Mean birth weight (SD):</p> <ul style="list-style-type: none"> • Continued smoking, 1–6 cigarettes/day: 3,071 g (525) • Continued smoking, >6 cigarettes/day: 2,841 g (447) • Quit smoking: 3,289 g (592) <p>Difference in mean birth weight:</p> <ul style="list-style-type: none"> • Quit smoking vs. continued smoking >6 cigarettes/day: +448 g, p <0.01 	<p>All study participants were smokers; no nonsmoker comparison group</p> <p>Results not adjusted for potential confounders</p> <p>Authors reported that no baseline variables were associated with infant birth weight</p> <p>Did not account for alcohol or illicit drug use</p>
Vogazianos et al. (2005)	<ul style="list-style-type: none"> • Population-based retrospective cohort • n = 59,014 • 1990–1996 • Cyprus 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke before or during pregnancy • Quit smoking: Smoked before but not during pregnancy; not clear how many women quit smoking during pregnancy and how they were categorized • Continued smoking: Smoked before and during pregnancy • Smoking status based on retrospective self-reports; exact timing of data collection not reported 	<p>Mean birth weight:</p> <ul style="list-style-type: none"> • Nonsmoker: 3,254 g • Quit smoking: 3,258 g • Continued smoking: 3,162 g <p>Difference in mean birth weight (95% CI):</p> <ul style="list-style-type: none"> • Quit smoking vs. nonsmoker: +4 g (-29–37 g) • Continued smoking vs. nonsmoker: -92 g (-125– -59 g) 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or illicit drug use</p>
Wen et al. (2005)	<ul style="list-style-type: none"> • Wen et al. (2005) • Pregnancy Risk Assessment Monitoring System • Singleton, live births • n = 9,499 • 1989–1992 • Taipei City, Taiwan 	<ul style="list-style-type: none"> • Nonsmokers: Details not provided • Quit smoking: Quit by the time of the first prenatal visit in the first trimester; not clear if this included those who quit before pregnancy • Continued smoking: Smoked after the first visit in the first trimester • Smoking status based on self-reports 	<p>Mean adjusted birth weight (SD) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> • Continuing smokers: 3,027 g (450) (reference) • Nonsmokers: 3,184 g (430 g), +157 g, p <0.05 • Quit smoking: 3,195 g (447 g), +168 g, p <0.05 	<p>Results adjusted for maternal age, parity, alcohol use, and sex of the infant</p> <p>Did not account for illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
England et al. (2007)	<ul style="list-style-type: none"> • Randomized trial for preeclampsia prevention • Nulliparous women • n = 4,289 • 1992–1995 • Multiple centers in the United States 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked regularly • Quit before pregnancy: Quit before last menstrual period and validated with cotinine mid-pregnancy • Quit during pregnancy: Quit after last menstrual period and validated with cotinine mid-pregnancy • Quit before/during pregnancy: Women from two previous categories combined • Continued smoking: Smoking at study enrollment • Smoking status based on self-reports obtained at study enrollment (13–21 weeks' gestation) • Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks' gestation) 	<p>Mean adjusted birth weight (SE) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> • Nonsmokers: 3,232 g (12.3 g) (reference) • Quit before or during pregnancy, self-report: 3,233 g (17.7 g), +1 g • Quit before or during pregnancy, cotinine validated: 3,253 g (19.3 g), +21 g • Continued smoking: 3,071 g (19.1g), -161 g, p <0.05 	<p>Results adjusted for maternal BMI, race, study center, sex of the infant, and gestational age</p> <p>Did not account for alcohol or illicit drug use</p>
Abrevaya et al. (2008)	<ul style="list-style-type: none"> • Analysis of linked certificates of live births • First and second singleton pregnancies in which women smoked during the first pregnancy • n = 22,775 • 1989–2004 • Michigan 	<ul style="list-style-type: none"> • Quit smoking between pregnancies: Smoked during the first pregnancy but not during the second pregnancy • Continued smoking during both pregnancies: Smoked during first and second pregnancies • Smoking status based on smoking history collected from certificates of live births, which used one question on tobacco use during pregnancy (yes/no) 	<p>Mean adjusted birth weight (SD) and difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> • 18–24 years of age: <ul style="list-style-type: none"> – Quit: 3,258 g (545 g) (reference) – Continued smoking: -134 g (-152– -115 g) • 25–30 years of age: <ul style="list-style-type: none"> – Quit: 3,317 g (536 g) (reference) – Continued smoking: -115 g (-138– -92 g) 	<p>Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father's name on birth certificate, number of prenatal visits, and first-birth value of the outcome</p> <p>Did not account for alcohol or illicit substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Mendez et al. (2008)	<ul style="list-style-type: none"> Prospective cohort study of childhood overweight Term births n = 482 1997–1998 Spain 	<ul style="list-style-type: none"> Nonsmokers: Never smoked Quit smoking before pregnancy Quit smoking during the first trimester Continued smoking: Still smoking during the second trimester Smoking status based on self-reports ascertained at recruitment 	<p>Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Nonsmokers/quit smoking before pregnancy: 3,282 g (442 g) Quit smoking during the first trimester: 3,259 g (417 g), +23 g Continued smoking: 3,085 g (430 g), -197 g, p < 0.05 compared with nonsmokers/women who quit smoking before pregnancy 	<p>Analysis restricted to term births</p> <p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or illicit drug use</p>
Nijati et al. (2008)	<ul style="list-style-type: none"> Prospective cohort study Singleton births n = 939 2006 Hiroshima, Japan 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke before or during pregnancy Quit smoking: Quit during pregnancy Continued smoking: Smoked before and continued smoking during pregnancy Smoking status based on self-reports ascertained by questionnaire Did not describe when questionnaire was administered, when women quit smoking, and procedures for follow-up and outcomes ascertainment 	<p>Mean birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: <ul style="list-style-type: none"> – Unadjusted: 3,075 g (368 g) (reference) – Adjusted 3,241 g (377 g) (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 3,043 g (421 g), -32 g – Adjusted: 3,197 g (377 g), -44 g Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 2,897 g (348 g), -178 g – Adjusted: 3,099 g (462 g), -142 g, p = 0.0004 	<p>Results adjusted for sex of the infant, parity, maternal age, mother's BMI and height, gestational age, and exposure to secondhand smoke during pregnancy</p> <p>Did not account for alcohol or illicit drug use</p>
Sasaki (2008)	<ul style="list-style-type: none"> Prospective cohort study of gene–environment interactions in women Singleton pregnancies Excluded women with pregnancy complications (hypertension, diabetes) n = 460 2002–2005 Sapporo, Japan 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking: Quit in the first trimester Continuing smokers: Smoked after the first trimester Smoking status based on self-reports ascertained from a questionnaire administered at study enrollment 	<p>Mean unadjusted birth weight (SD) (Kruskal-Wallis test, p = 0.003) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3,078 g (347 g) (reference) Quit smoking: 3,138 g (384 g), -60 g Continued smoking: 2,961 g (386 g), -117 g <p>Difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: -31 g Continued smoking: -148 g 	<p>Results adjusted for maternal age, height, weight, gestational weight gain, alcohol use, parity, sex of the infant, gestational age, and income</p> <p>Did not account for illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Andersen et al. (2009)	<ul style="list-style-type: none"> • Clinic-based study of endothelial function by smoking status • Term pregnancies without complications (diabetes, hypertension) • n = 266 • 2003–2004 • Denmark 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke before pregnancy • Quit smoking: Smoked during pregnancy but quit by 18 weeks' gestation • Continued smoking: Smoked throughout pregnancy • Smoking status based on self-reports ascertained from questionnaire and validated with serum cotinine 	<p>Mean unadjusted birth weight (95% CI) and difference in mean birth weight</p> <ul style="list-style-type: none"> • Nonsmoker: 3.65 kg (3.01–4.50 kg) (reference) • Quit smoking: 3.60 kg (3.06–4.55 kg), -0.05 kg • Continued smoking: 3.30 kg (2.54–4.14): – Unadjusted: -364 g – Adjusted: -242 g, p = 0.002 	<p>Analysis restricted to term births</p> <p>Birth weight difference for continued smoking vs. nonsmokers adjusted for endothelial nitric oxide synthase, pre-pregnancy BMI, parity, gestational age, and sex of the infant</p> <p>Did not account for alcohol or illicit drug use</p>
Fasting et al. (2009)	<ul style="list-style-type: none"> • Prospective intervention of allergy prevention in children • n = 711 • 2000–2002 • Norway 	<ul style="list-style-type: none"> • Nonsmoker: Not smoking when became pregnant • Quit smoking: Smoking when became pregnant but quit by enrollment • Continued smoking: Smoking when became pregnant and still smoking at enrollment • Smoking status based on self-reports collected at study enrollment (median gestational age 11 weeks, all <28 weeks) 	<p>Mean birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> • Nonsmoker: 3,646 g (518 g) (reference) • Quit smoking: 3,628 g (497 g), -14 g • Continued smoking: 3,449 g (486 g), -197 g 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or illicit drug use</p> <p>Did not show direct statistical comparisons between groups</p>
Johansson et al. (2009)	<ul style="list-style-type: none"> • Births from the Swedish Birth Registry • First and second consecutive, singleton pregnancies • n = 555,046 • 1983–2002 • Sweden 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke during either pregnancy • Quit smoking: Smoked during first but not during second pregnancy • Started smoking: Smoked during second but not during first pregnancy • Continued smoking: Smoked during both pregnancies • Smoking status ascertained from Swedish Birth Registry, as derived from first antenatal visit, typically <15 weeks' gestation; no information on cessation during pregnancy 	<p>Mean birth weight second pregnancy (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> • First pregnancy for each exposure group (reference) • Nonsmoker: 3,658 g (535 g), +173 g • Quit smoking: 3,643 g (539 g), +233 g • Started smoking: 3,520 g (545 g), +80 g • Continued smoking: 3,430 g (539 g), +119 g 	<p>Quit status defined across pregnancies but not within pregnancies</p> <p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p> <p>Did not show direct statistical comparisons between groups</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Kabir et al. (2009)	<ul style="list-style-type: none"> • Cross-sectional study of changes in smoking status after a workplace smoking ban • Singleton, live births • n = 15,241 • 2003 and 2005 • Ireland 	<ul style="list-style-type: none"> • Nonsmokers: Never smokers • Quit smoking: Former smokers • Continued smoking: Current smokers • Smoking status based on self-reports • No details of how and when smoking status was ascertained • Authors reported that smoking status across different periods of gestation was not available 	<p>Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> • 2003: <ul style="list-style-type: none"> – Nonsmoker: 3,527 g (3,450–3,604 g) (reference) – Quit smoking: 3,549 g (3,435–3,663 g), +22 g – Continued smoking: 3,250 g (3,157–3,343 g), -370 g • 2005: <ul style="list-style-type: none"> – Nonsmoker: 3,503 g (3,426–3,580 g) (reference) – Former smoker: 3,547 g (3,433–3,661 g), +44 g – Current smoker: 3,220 g (3,127–3,313 g), -283 g 	<p>Results adjusted for gestational age</p> <p>Results not adjusted for other potential confounders</p> <p>Did not account for alcohol or substance use</p>
McCowan et al. (2009)	<ul style="list-style-type: none"> • Prospective cohort study designed to develop screening tests for pregnancy complications • n = 2,504 • 2004–2007 • New Zealand and Australia 	<ul style="list-style-type: none"> • Nonsmokers: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but quit before being interviewed at 15 weeks' gestation • Continued smoking: Smoked at 15 weeks' gestation • Smoking status based on self-reports ascertained at 15 weeks' gestation 	<p>Mean adjusted birth weight (SD) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> • Nonsmoker: 3,409 (592 g) (reference) • Quit smoking: 3,479 g (560 g) +70 g (-6–146 g), p = 0.09 • Continued smoking: 3,139 (751g) -270 g (-350– -190 g), p <0.001 	<p>Results adjusted for maternal age; ethnicity; marital status; employment; BMI; bleeding during pregnancy; folic acid use; multivitamin use; alcohol consumption at 15 weeks' gestation; and scores for depression, stress, or anxiety</p> <p>Did not account for illicit drug use</p>
Adegboye et al. (2010)	<ul style="list-style-type: none"> • Retrospective cohort study of risk factors for postpartum weight retention • Singleton pregnancies • n = 1,753 • 1984–1985 • Sweden 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked • Quit smoking: Quit smoking during first trimester and remained abstinent throughout pregnancy • Continued smoking: Continued to smoke during pregnancy • Smoking status based on self-reports collected after delivery; details not reported 	<p>Mean unadjusted birth weight (SD):</p> <ul style="list-style-type: none"> • Nonsmoker: 3.5 kg (0.5 kg) • Quit smoking: 3.4 kg (0.5 kg) • Continued smoking 3.3 kg (0.5 kg) • p <0.001 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Prabhu et al. (2010)	<ul style="list-style-type: none"> Prospective cohort study of risk factors for childhood asthma and allergy n = 1,924 1997–1999 Scotland 	<ul style="list-style-type: none"> Nonsmoker: Never smoked or quit smoking before pregnancy (additional details related to timing of cessation not reported) Quit smoking: Quit in first trimester Continued smoking in first trimester: <ul style="list-style-type: none"> No change in number of cigarettes/day Reduced number of cigarettes/day Smoking status based on self-reports obtained at enrollment in the first trimester and at 32 weeks' gestation 	<p>Difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> Continued smoking, no change in number of cigarettes/day (reference) Nonsmoker: +290 g (115–463 g) Reduced number of cigarettes/day: +104 g (-73–282 g) Quit smoking: +246 g (46–445 g) 	<p>Results adjusted for sex of the infant, maternal height, plasma alpha-tocopherol and cholesterol, paternal smoking, and gestational age</p> <p>Did not account for alcohol or substance use</p>
Vardavas et al. (2010)	<ul style="list-style-type: none"> Population-based cohort study n = 1,400 2007–2008 Crete, Greece 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke from 3 months before and throughout pregnancy Quit smoking: Stopped smoking between 3 months before pregnancy and 12 weeks' gestation Continued smoking: Smoked at 12 weeks' gestation Smoking status based on self-reports obtained at enrollment, second, and third trimesters 	<p>Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker: 3,171 g (473 g) (reference) Quit smoking: 3,207 g (465 g), +39 g (-18–96 g) Continued smoking: 3,059 g (498 g), -119 g (-177– -62 g) 	<p>Results adjusted for gestational age, parity, origin (Greek/non-Greek), maternal education, age, and sex of the infant</p> <p>Did not account for alcohol or illicit drug use</p>
Bakker et al. (2011)	<ul style="list-style-type: none"> Population-based, prospective cohort study n = 5,389 2001–2005 Netherlands 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking: Smoked during pregnancy but only during first trimester Continued smoking (categories collapsed for analysis): <ul style="list-style-type: none"> Second trimester: Smoked during pregnancy and during second trimester Third trimester: Smoked during pregnancy and during third trimester Smoking status based on self-reports obtained in each trimester of pregnancy 	<p>Mean birth weight (SD) and difference in mean birth weight (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers: 3,473 g (547 g) (reference) Quit smoking: <ul style="list-style-type: none"> Unadjusted: 3,418 g (555 g), -55 g, p <0.05 Adjusted, single assessment: -14 g (-49–20 g) Adjusted, repeated assessment of smoking status: +38 g (-3–79 g) Continued smoking: <ul style="list-style-type: none"> Unadjusted: 3,274 g (500 g), -199 g, p <0.01 Adjusted, single assessment: -157 g (-194– -120 g) Adjusted, repeated assessment of smoking status: -143 g (-175– -111 g) 	<p>Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, maternal stress, gestational age at birth, and sex of the fetus</p> <p>Did not account for illicit drug use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Benjamin-Garner and Stotts (2013)	<ul style="list-style-type: none"> • Randomized trial of a behavioral intervention for smoking cessation • Term, singleton pregnancies • 2001–2004 • n = 260 • 2001–2004 • Texas 	<ul style="list-style-type: none"> • Quit smoking: Salivary cotinine <15 ng/mL in late pregnancy (36 weeks' gestation) • Light smoker: Salivary cotinine <150 ng/mL at enrollment, continued smoking (stayed light or increased to heavy) • Heavy smoker: Salivary cotinine ≥150 ng/mL at enrollment, continued smoking (stayed heavy or decreased to light) • Smoking status based on self-report and salivary cotinine obtained at enrollment (16–26 weeks' gestation), 36 weeks' gestation, and 6 weeks postpartum 	<p>Mean unadjusted birth weight (SD) and difference in mean unadjusted birth weight:</p> <ul style="list-style-type: none"> • Quit smoking: 3,415 g (521g) (reference) • Light smoker, stayed light: 3,252 g (504 g), -163 g • Light smoker, increased to heavy: 3,212 g (447 g), -203 g • Heavy smoker, decreased to light: 3,315 g (368 g), -100 g • Heavy smoker, stayed heavy: 3,116 g (447 g), 299 g • Pairwise comparison found that the only significant difference was between heavy smokers who stayed heavy smokers and quitters (p = 0.02). Findings did not change after adjustment for potential confounders (p = 0.05). 	<p>Randomized cessation trial, and thus no comparison group of nonsmokers</p> <p>Results adjusted for maternal age, race/ethnicity, parity, education, income, sex of the infant, gestational age at delivery, pre-pregnancy BMI, and gestational weight gain (education and parity removed from final models)</p> <p>Restricted to term births</p> <p>Did not account for alcohol or substance use</p>
Himes et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort study • Date not provided • n = 119 • Rhode Island 	<ul style="list-style-type: none"> • Nonsmokers: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but quit before delivery • Smoked throughout pregnancy • Smoking status throughout pregnancy based on self-reports obtained in third trimester of pregnancy, >28 weeks' gestation 	<p>Mean unadjusted birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> • Smokers: 3,162 g (434 g) (reference) • Nonsmokers: 3,464 g (444 g), +302 g • Quit smoking: 3,557 g (504 g), +395 g 	<p>Differences between continuing smokers and nonsmokers and quitters were statistically significant, even after adjusting for socioeconomic status, maternal age, income, and education (data not shown)</p> <p>Excluded women who used illicit drugs</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Juarez and Merlo (2013)	<ul style="list-style-type: none"> • Births from the Swedish Medical Birth Register • Singleton, term births • n = 677,922 births for conventional analysis • n = 62,941 siblings for sibling analysis • 2002–2010 • Sweden 	<ul style="list-style-type: none"> • Nonsmokers: Not smoking at either early or late antenatal visit • Continued smoking: Smoking at early and late antenatal visits: <ul style="list-style-type: none"> – Light, light smoker – Light, heavy smoker – Heavy, light smoker – Heavy, heavy smoker • Quit smoking: Smoked at first but not second antenatal visit: <ul style="list-style-type: none"> – Light, quit smoking – Heavy, quit smoking • Started smoking: Did not smoke at first antenatal visit but smoked at second antenatal visit: <ul style="list-style-type: none"> – Nonsmoker, light smoker – Nonsmoker, heavy smoker • Light smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day • Smoking status obtained from the Swedish Medical Birth Register which relies on self-reported data collected during early (10–12 weeks’ gestation) and late (30–32 weeks’ gestation) antenatal visits 	<p>Difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> • Conventional analysis: <ul style="list-style-type: none"> – Nonsmokers (reference) – Quit smoking: <ul style="list-style-type: none"> ○ Light, quit: -47 g (-55– -40 g) ○ Heavy, quit: -79 g (-100– -58 g) – Continued smoking: <ul style="list-style-type: none"> ○ Heavy, heavy: -303 g (-313– -292 g) ○ Light, heavy: -265 g (-279– -250 g) ○ Heavy, light: -254 g (-266– -242 g) ○ Light, light: -221 g (-227– -214 g) – Started smoking: <ul style="list-style-type: none"> ○ Nonsmoker, light: -129 g (-142– -117 g) ○ Nonsmoker, heavy: -142 g (-177– -108 g) • Sibling analysis: <ul style="list-style-type: none"> – Nonsmokers (reference) – Quit smoking: <ul style="list-style-type: none"> ○ Light, quit: -29 g (-42– -16 g) ○ Heavy, quit: -1 g (-46– -44 g) – Continued smoking: <ul style="list-style-type: none"> ○ Heavy, heavy: -226 g (-274– -179 g) ○ Light, heavy: -259 g (-309– -209 g) ○ Heavy, light: -194 g (-238– -151 g) ○ Light, light: -162 g (-178– -147 g) – Started smoking: <ul style="list-style-type: none"> ○ Nonsmoker, light: -77 g (-97– -57 g) ○ Nonsmoker, heavy: -83 g (-140– -25 g) – Effects of smoking on birth weight were attenuated by 6–78 g using sibling analysis compared with traditional analysis 	<p>Results adjusted for gestational age, marital status, maternal age, birth order, sex of the newborn, pregnancy complications (diabetes, hypertension, urinary problems). and use of snus</p> <p>Did not account for alcohol or substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Miyake et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort study • n = 1,565 • 2007–2008 • Japan 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke during pregnancy • Quit smoking: <ul style="list-style-type: none"> – First trimester: Smoked during first trimester only – Second or third trimester: Smoked during second or third trimester but not throughout pregnancy • Continued smoking: Smoked throughout pregnancy • Smoking status for each trimester of pregnancy based on self-reports obtained after delivery 	<p>Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> • Nonsmoker: 3,011 g (2,994, 3,027) (reference) • Quit smoking first trimester: 3,028 g (2,951–3,104 g), +17 g • Quit smoking second or third trimester: 2,958 g (2,838–3,079 g), -53 g • Continued smoking: 2,841 g (2,738–2,944 g), -170 g • p for trend = 0.005 	<p>Results adjusted for maternal age, residence, education, employment, alcohol consumption, and BMI; family structure; gestational age at birth; and sex of the infant</p> <p>Did not address illicit drug use</p>
Murphy et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort study • Singleton pregnancies • n = 1,216 • 2010–2011 • Dublin, Ireland 	<ul style="list-style-type: none"> • Nonsmoker: Not defined • Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit • Continued smoking: Smoked during 6 months before pregnancy, at first prenatal visit, and during third trimester • Smoking status based on self-reports obtained at enrollment and third trimester 	<p>Mean birth weight (SD) and difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker: 3,496 g (509 g) (reference) • Quit smoking: 3,503 (491 g), +7 g (-81–95 g) • Continued smoking: 3,305 g (491 g), -191 g (-194– -88 g) 	<p>Results adjusted for maternal age, BMI, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use</p>
Rode et al. (2013)	<ul style="list-style-type: none"> • Prospective cohort study • Singleton, term pregnancies • n = 1,774 • 1996–1999 • Copenhagen, Denmark 	<ul style="list-style-type: none"> • Nonsmokers: Not defined • Quit smoking: Quit smoking immediately before or during pregnancy • Continued smoking: Not defined • Smoking status based on self-reports and on salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation • Smoking status assessed at 12–18 weeks' gestation, 37 weeks' gestation, and 1 year postpartum 	<p>Mean birth weight (SD) and difference in mean birth weight (95% CI):</p> <ul style="list-style-type: none"> • Nonsmokers: 3,675 g (482 g) (reference) • Quit: 3,670 g (510 g) <ul style="list-style-type: none"> – Unadjusted difference: +4 g (-66–64 g) – Adjusted difference: +26 g (-29–81 g) • Continued smoking: 3,405 g (487 g) <ul style="list-style-type: none"> – Unadjusted difference: -270 g (-333– -208 g) – Adjusted difference: -260 g (-318– -204 g) 	<p>Results adjusted for pre-pregnancy BMI, gestational age, and parity</p> <p>Restricted to term births</p> <p>Did not account for alcohol or substance use</p> <p>Salivary cotinine for subgroup reported but not integrated into main analysis</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Meghea et al. (2014)	<ul style="list-style-type: none"> Prospective cohort study n = 474 2008–2009 Romania 	<ul style="list-style-type: none"> Nonsmokers: Not smoking when learned of pregnancy Quit smoking: Quit upon learning of pregnancy Continued smoking: Smoking at time of study interview (gestational age not reported) Smoking history based on self-reports obtained at study enrollment (gestational age not reported) 	<p>Mean unadjusted birth weight and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmoker: 3382 g (reference) Quit smoking: 3340 g <ul style="list-style-type: none"> – Unadjusted: -42 g – Adjusted: -48 g Continued smoking: 3176 g <ul style="list-style-type: none"> – Unadjusted: -206 g, p <0.05 – Adjusted: -165 g 	<p>Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity</p> <p>Did not account for alcohol or substance use</p>
Räisänen et al. (2014)	<ul style="list-style-type: none"> Finnish Medical Birth Register Singleton deliveries, live or stillborn n = 1,164,953 1991–2010 Finland 	<ul style="list-style-type: none"> Nonsmokers: Not defined Quitters: Quit smoking during first trimester Continuing smokers: Smoked after first trimester Smoking history ascertained from the Finnish Medical Birth Register 	<p>Mean unadjusted birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3,575 g (547 g) (reference) Quitters: 3,531 g (546 g), -44 g Continuing smokers: 3,383 g (586 g), -192 g 	<p>Results not adjusted for potential confounders</p> <p>Results of statistical testing not provided.</p> <p>Did not account for alcohol or substance use</p>
Slatter et al. (2014)	<ul style="list-style-type: none"> Study of smoking and placental pathology Singleton, term births Excluded women with diabetes or hypertension n = 236 2009–2011 New Zealand 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking: Stopped smoking at least 4 weeks before delivery Continued smoking: Smoked during pregnancy and up to delivery Smoking history based on self-reports obtained at the time placentas were collected 	<p>Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3.56 kg (0.36 kg) Quit smoking: 3.64 kg (0.59 kg), +0.08 kg Continuing smokers: 3.29 kg (0.49 kg), -0.27 kg 	<p>Results not adjusted for potential confounders, but restricted to term births</p> <p>Did not account for alcohol or substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Suzuki et al. (2014)	<ul style="list-style-type: none"> Prospective cohort study Singleton deliveries 1991–2006 n = 2,663 Japan 	<ul style="list-style-type: none"> Nonsmokers: Never smoked Quit smoking before pregnancy Quit smoking during early pregnancy Continued smoking: Smoking at study enrollment Smoking exposure categories not further defined Smoking history based on self-reports obtained during early pregnancy (usually first trimester) 	<p>Mean unadjusted birth weight (SD):</p> <ul style="list-style-type: none"> Nonsmokers: 3,069 g (387 g) Quit before pregnancy: 3,052 g (393 g) Quit during early pregnancy: 3,046 g (409 g) Continued smoking: 2,902 g (409 g) <p>Mean adjusted birth weight and difference in mean adjusted birth weight, by sex:</p> <ul style="list-style-type: none"> Boys: <ul style="list-style-type: none"> Nonsmokers: 3,084 g (reference) Quit smoking before pregnancy: 3,015 g, -69 g, p = 0.2 Quit smoking during early pregnancy: 3,065 g, -19 g, p = 0.9 Continued smoking: 2,960 g, -124 g, p = 0.002 Girls: <ul style="list-style-type: none"> Nonsmokers: 3,039 g (reference) Quit smoking before pregnancy: 3,029 g, -10 g, p = 0.99 Quit smoking during early pregnancy: 3,063 g, +24 g, p = 0.8 Continued smoking: 2,888 g, -151 g, p = 0.002 	<p>Results adjusted for maternal age, parity, BMI, and gestational age</p> <p>Did not account for alcohol or substance use</p>
Bailey (2015)	<ul style="list-style-type: none"> Randomized clinical trial of smoking cessation intervention n = 1,486 2008–2012 Tennessee 	<ul style="list-style-type: none"> Quit smoking: Smoked at first prenatal visit but quit by third trimester Continued smoking: Smoked at first prenatal visit and still smoking in the third trimester Smoking history based on self-reports obtained at first prenatal visit Quit status ascertained in third trimester by exhaled CO, urine cotinine, and self-report at delivery 	<p>Mean adjusted birth weight and difference in mean adjusted birth weight:</p> <ul style="list-style-type: none"> Quit smoking: 3,216 g, +204 g Continued smoking: 3,012 g (reference) p < 0.001 	<p>Randomized cessation trial and thus no comparison group of nonsmokers</p> <p>Results adjusted for maternal age, education, marital status, insurance status, and marijuana use</p> <p>Examined alcohol use, but it was not significant in the model</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Blatt et al. (2015)	<ul style="list-style-type: none"> Population-based retrospective cohort study using Ohio certificates of live birth n = 927,424 2006–2012 Ohio 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy Quit smoking before pregnancy: Smoked during 3 months before pregnancy but not during pregnancy Quit smoking, first trimester: Smoked during first trimester only Quit smoking, second trimester: Smoked during first and second trimesters, but not third trimester Continued smoking: Smoked throughout pregnancy Smoking history ascertained from vital statistics data and certificates of live birth 	<p>Mean birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3,340 g (558 g) (reference) Quit smoking before pregnancy: 3,339 g (557 g), -1 g Quit smoking, first trimester: 3,280 g (590 g), -60 g Quit smoking, second trimester: 3,072 g (763 g), -268 g Continued smoking: 3,090 g (542), -250 g 	<p>Results not adjusted for potential confounders</p> <p>Statistical testing not reported</p> <p>Did not account for alcohol or substance use</p>
Grzeskowiak et al. (2015)	<ul style="list-style-type: none"> Retrospective cohort study n = 7,658 2000–2005 South Australia 	<ul style="list-style-type: none"> Nonsmokers Quit smoking during pregnancy Continued smoking: Smoked during pregnancy Smoking status not further defined Smoking history based on self-reports ascertained at first prenatal care visit 	<p>Mean birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmokers: 3,410 g (610 g) (reference) Quit smoking: 3,408 g (608 g) (-2 g) Continuing smokers 3,155 g (628 g), -255 g, p <0.001 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p>
Yan and Groothuis (2015)	<ul style="list-style-type: none"> Population-based cohort study Singleton pregnancies Excluded women with chronic diseases n = 11,131 2000–2001 United Kingdom 	<ul style="list-style-type: none"> Nonsmokers: Not defined Quit smoking before pregnancy (timing of cessation not specified) Quit smoking during pregnancy (month of cessation noted) Continued smoking: Smoked beyond 7 months' gestation Smoking history based on self-reports ascertained when infants were 9 months old 	<p>Mean unadjusted birth weight (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> Nonsmokers 3,452 g (551 g) Quit smoking before pregnancy: -8 g Quit smoking month 1: -5 g Quit smoking month 2: -5 g Quit smoking month 3: -9 g Quit smoking month 4: -143 g, p <0.05 Quit smoking month 5: -170 g, p <0.05 Quit smoking month 6: -184 g Quit smoking month 7: -215 g, p <0.05 Continued smoking: -245 g, p <0.05 Quit smoking trimester 1: -5 g Quit smoking trimester 2: -159 g, p <0.05 Continued smoking: -245 g, p <0.05 	<p>Results adjusted for birth year/quarter of infant, maternal weight, height, income, prenatal care initiation, alcohol use, maternal employment status, home satisfaction, religion affiliation, and racist or religion-based insults in living area</p> <p>Did not account for substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Hayes et al. (2016)	<ul style="list-style-type: none"> • Quasi-experimental, historical cohort of smoking cessation intervention trial • Excluded deliveries of infants <1,500 g • n = 652 • 2004–2005 • Ireland 	<ul style="list-style-type: none"> • Quit smoking before enrollment: Smoked when became pregnant, quit before first study visit, and did not resume smoking • Quit smoking after enrollment: Smoked at time of first study visit but quit by third study visit (combined with “attempted to quit” for adjusted analysis) • Attempted to quit: Attempted to quit at first or second study visit but resumed at one or more visits (combined with “quit smoking after enrollment” for adjusted analysis) • Continued smoking: Smoked at the time of all three study visits • Smoking status based on self-reports and validated with urine cotinine levels at second study visit (did not describe how cotinine levels were used in the analysis), and ascertained at three visits (12–18 weeks’ gestation, 28–32 weeks’ gestation, and within 1 week of delivery) 	<p>Median birth weight and difference in mean birth weight (95% CI):</p> <ul style="list-style-type: none"> • Quit smoking before enrollment: 3,600 g, 3,595 g (reference) • Quit smoking after enrollment: 3,340 g, p = 0.07 • Attempted to quit: 3,450 g, p = 0.13 • Continued smoking: 3,260 g, 3,269 g, -326 g (-483– -17), p < 0.01 <p>Difference in mean adjusted birth weight (95% CI):</p> <ul style="list-style-type: none"> • All: <ul style="list-style-type: none"> – Continued smoking (reference) – Quit smoking before enrollment: +288 g (153–423 g) – Quit smoking after enrollment or attempted to quit: +147 g (50–244 g) • Preterm: <ul style="list-style-type: none"> – Continued smoking (reference) – Quit smoking before enrollment: +67 g (-272–407 g) – Quit smoking after enrollment or attempted to quit: +181 g (-236–600 g) • Term: <ul style="list-style-type: none"> – Continued smoking (reference) – Quit smoking before enrollment: +327 g (183–472 g) – Quit smoking after enrollment or attempted to quit: +146 g (46–246 g) 	<p>Randomized cessation trial and thus no comparison group of never smokers</p> <p>Results adjusted for other smokers in the household, gestational age at delivery, and sex of infant</p> <p>Did not account for alcohol or substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Suzuki et al. (2016) (continues on next page)	<ul style="list-style-type: none"> • Population-based cohort study • Singleton pregnancies • n = 7,734 • 2011–2014 • Japan 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked • Quit smoking before pregnancy: Not further defined • Quit smoking during early pregnancy: Not further defined • Continued smoking: Currently smoking at time in which study questionnaire was administered • Smoking status based on self-reports collected in second trimester 	<p>Mean birth weights (SD) and difference in mean birth weight:</p> <ul style="list-style-type: none"> • Nonsmokers: 3,015 g (427 g) (reference) • Quit smoking before pregnancy: 3,029 g (408 g), +14 g • Quit smoking during early pregnancy: 3,011 g (444 g), -4 g • Continued smoking: 2,873 g (423 g), -142 g <p>Mean adjusted birth weights (SE) and difference in mean adjusted birth weight by sex of newborn:</p> <ul style="list-style-type: none"> • Female: <ul style="list-style-type: none"> – Nonsmokers: 3,018 g (16 g) (reference) – Quit smoking before pregnancy: 3,030 g (18 g), +12 g, p = 0.7 – Quit smoking during early pregnancy: 2,979 g (21 g), -39 g, p = 0.06 – Continued smoking: 2,894 (28 g), -124 g, p <0.001 • Male: <ul style="list-style-type: none"> – Nonsmokers: 3,096 g (17 g) (reference) – Quit before pregnancy: 3,089 g (18 g), -7 g, p = 0.9 – Quit during early pregnancy: 3,068 g (20 g), -28 g, p = 0.2 – Continued smoking: 2,960 g (27 g), -136 g, p <0.001 • Term births—Female: <ul style="list-style-type: none"> – Nonsmokers: 3,056 g (16 g) (reference) – Quit before pregnancy: 3,069 g (19 g), +13, p = 0.6 – Quit during early pregnancy: 3,021 g (21 g), -35 g, p = 0.1 – Continued smoking: 2,928 g (28 g), -128 g, p <0.001 	<p>Results adjusted for partner’s smoking status, income, birth order, pregnancy complications (hypertension, diabetes), pre-pregnancy weight, gestational weight gain, maternal age, and gestational age</p> <p>Results stratified by term/preterm delivery</p> <p>Did not account for alcohol or substance use</p>

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
(continued from previous page) Suzuki et al. (2016)	—	—	<ul style="list-style-type: none"> • Term births—Male: <ul style="list-style-type: none"> – Nonsmokers 3,142 g (18 g) (reference) – Quit before pregnancy: 3,134 g (19 g), +8 g, p = 0.9 – Quit during early pregnancy: 3,110 g (21 g), -32 g, p = 0.2 – Continued smoking: 3,005 g (28 g), -137 g, p <0.001 	—
Wallace et al. (2017) (reanalysis of Blatt et al. [2015])	<ul style="list-style-type: none"> • Population-based retrospective cohort study using Ohio certificates of live birth • Singleton pregnancies • Excluded congenital malformations • All participants had at least one previous preterm delivery • n = 36,432 • 2006–2012 • Ohio 	<ul style="list-style-type: none"> • Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy • Quit smoking by first trimester: Smoked during 3 months before pregnancy but not during pregnancy • Quit by second trimester: Smoked during first trimester but not during second and third trimesters • Quit by third trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Smoking status obtained from U.S. certificates of live birth 	<p>Mean birth weight (SD) and difference in birth weight:</p> <ul style="list-style-type: none"> • Nonsmokers: 2,964 g (764 g) (reference) • Quit smoking by first trimester: 2,951 g (745 g), -13 g • Quit smoking by second trimester: 2,841 g (819 g), -123 g • Quit smoking by third trimester: 2,343 g (1,061 g), -621 g • Continued smoking: 2,743 g (667 g), -221 g • All comparisons significant at p <0.01 	<p>Results not adjusted for confounders</p> <p>Did not account for alcohol or substance use</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **CO** = carbon monoxide; **g** = grams; **kg** = kilograms; **ng/mL** = nanograms per milliliter; **SD** = standard deviation; **SE** = standard error.

221 and 303 g in the conventional analysis for light and heavy smokers, respectively. Also, in the sibling analysis, cessation was associated with a reduction in birth weight of 29 g (95% CI, -42 to -16) for light smokers compared with nonsmokers, but it was not associated with a significant reduction in birth weight in heavy smokers (-1 g; 95% CI, -46–44). By comparison, using nonsibling controls, babies of light smokers who quit had a reduction in birth weight of 47 g (95% CI, -55 to -40), while heavy smokers who quit had a reduction of 79 g (95% CI, -100 to -58) compared with nonsmokers during pregnancy.

Several of the studies published since the 1990 and 2004 Surgeon General's reports examined the specific timing of tobacco smoke exposure and fetal growth. Yan and Groothuis (2015), who examined birth outcomes in more than 11,000 women and 2,000 smokers by gestational month of cessation through month 7, found little effect of smoking on birth weight in the first 3 months of pregnancy but increasing effects for every month women smoked after that. Estimates of the effect of smoking on birth weight were adjusted for several socioeconomic factors and alcohol use but not for gestational age, and they were statistically significant for months 4, 5, and 7. However, cessation status was not biochemically validated. Elsewhere, Blatt and colleagues (2015) examined cessation in a cohort of more than 900,000 births by trimester in a study using Ohio birth certificate data. Those researchers found a greater reduction in birth weight in quitters compared with nonsmokers over time (-60 g for smoking in the first trimester only, -268 g for smoking in the second trimester) but no further reduction for smoking through the third trimester (-250 g). The results were not adjusted for potential confounders or for gestational age, however, and there was no biochemical validation of cessation. All comparisons were statistically significant.

Two studies examined smoking patterns across pregnancies and, thus, focused on cessation between pregnancies rather than on cessation during pregnancies. Abrevaya (2008) found that, after stratifying results by age, both the younger (18–24 years of age) and older (25–30 years of age) groups of continuing smokers had babies with lower mean birth weights compared with quitters, even after adjusting for multiple potential confounders (-134 g and -115 g, respectively) (Abrevaya 2008). In Sweden, Johansson and colleagues (2009) assessed smoking status during antenatal care for mothers having two live births, comparing the outcomes of the second pregnancy within exposure groups with those for the first pregnancy, and found increases in birth weight of the babies of quitters (233 g) and nonsmokers (173 g) that exceeded the increase in continuing smokers (119 g). An important limitation of study designs that examine outcomes across consecutive pregnancies is that the smoking exposure categories

are often simplified (e.g., assessing smoking at only one time point for each pregnancy). If the timing of cessation (such as during pregnancy rather than before pregnancy, or during a specific trimester of pregnancy) affects infant birth weight, the effect may not be detected in studies with limited assessment of smoking exposure.

Summary of the Evidence. Since the 2004 Surgeon General's report confirmed that smoking cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004), numerous studies have assessed the relationships between smoking and smoking cessation and fetal growth. Many studies adjusted for multiple confounders, and some included biochemical validation of quit status. The evidence is sufficient to infer that smoking cessation during pregnancy reduces the effects of smoking on birth weight and gestational-age adjusted birth weight. Depending on the timing of cessation, the birth weight of infants of women who quit smoking before or in early pregnancy approached or met that of nonsmokers in many studies. The evidence is inadequate to infer the exact gestational age before which cessation should occur to eliminate the effects of smoking on birth weight or gestational-age adjusted birth weight.

Small for Gestational Age

In addition to gestational age-adjusted birth weight or birth weight in term infants, the designation of SGA (a birth weight \leq 10th percentile for gestational age) or the infant's SGA status can be used as an indicator of fetal growth. SGA is a less sensitive measure of fetal growth than gestational age-adjusted birth weight, but it is strongly associated with increased morbidity and mortality (Pallotto and Kilbride 2006; Katz et al. 2013). The association between smoking-related reduction in birth weight and infant mortality has been studied in detail, as reviewed in the 2014 Surgeon General's report (USDHHS 2014).

Table 4.33 presents studies published after the year 2000 that addressed smoking cessation and SGA infants. Twenty-two studies were identified. Definitions for SGA included, by percentile of birth weight, less than the 2.5th, 3rd, 5th, and 10th percentiles; they also included greater than 2 standard deviations (SD) below the mean. All of the studies but one (Grzeskowiak et al. 2015) included adjustments for potential confounders; three also adjusted for alcohol consumption but not substance use (McCowan et al. 2009; Bakker et al. 2011; Tong et al. 2017); and two addressed both alcohol consumption and substance use (Erickson and Arbour 2012; Murphy et al. 2013). Two studies examined smoking status across two consecutive pregnancies (Okah et al. 2007; Kvalvik et al. 2017), and 20 examined cessation with respect to single pregnancies. Of those 20 studies, 19 compared infants of women who quit smoking with those of nonsmokers

Table 4.33 Studies on smoking cessation and small for gestational age infants

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Mitchell et al. (2002)	<ul style="list-style-type: none"> • Case-control • Term births without congenital anomalies • n = 1,714 • 1995–1997 • New Zealand 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked cigarettes regularly, or did not smoke during 12 months before pregnancy or during pregnancy • Quit smoking before pregnancy: Smoked during 12 months before pregnancy but not during pregnancy • Quit smoking during pregnancy • Continued smoking during pregnancy, increased amount • Continued smoking during pregnancy, decreased amount • Continued smoking during pregnancy, amount did not change • Smoking status based on self-reports obtained from a postpartum interview 	<10th percentile for sex	<p>Unadjusted and adjusted ORs for SGA (95% CI):</p> <ul style="list-style-type: none"> • Nonsmokers (reference) • Quit smoking before pregnancy: <ul style="list-style-type: none"> – Unadjusted: 0.83 (0.55–1.27) – Adjusted: 1.03 (0.64–1.64) • Quit smoking during pregnancy: <ul style="list-style-type: none"> – Unadjusted: 1.13 (0.73–1.75) – Adjusted: 1.14 (0.68–1.91) • Continued smoking during pregnancy, increased amount: <ul style="list-style-type: none"> – Unadjusted: 1.94 (1.02–3.67) – Adjusted: 2.07 (0.97–4.42) • Continued smoking during pregnancy, decreased amount: <ul style="list-style-type: none"> – Unadjusted: 2.56 (1.86–3.52) – Adjusted: 3.23 (2.14–4.86) • Continued smoking during pregnancy, amount did not change: <ul style="list-style-type: none"> – Unadjusted: 3.35 (1.98–5.66) – Adjusted: 4.88 (2.66–8.94) 	Results adjusted for maternal education, occupation, marital status, ethnicity, parity, age, age at first pregnancy, height, pre-pregnancy weight, hypertension, and marijuana use
England et al. (2007)	<ul style="list-style-type: none"> • Randomized trial for preeclampsia prevention • n = 4,289 • 1992–1995 • United States 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked regularly • Quit before pregnancy: Quit before last menstrual period and validated with cotinine mid-pregnancy • Quit during pregnancy: Quit after last menstrual period and validated with cotinine mid-pregnancy • Quit before or during pregnancy: Quit groups from two previous categories combined • Continued smoking: Smoking at study enrollment • Smoking status based on self-reports obtained at study enrollment (13–21 weeks' gestation) in 2007 study • Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks' gestation) 	≤10th percentile for race, sex, and parity	<p>Unadjusted and adjusted OR (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker (reference) • Quit before or during pregnancy: <ul style="list-style-type: none"> – Unadjusted: 1.0 (0.7–1.4) – Adjusted: 1.0 (0.7–1.5) • Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 1.9 (1.5–2.4) – Adjusted: 2.0 (1.6, 2.7) 	Results adjusted for maternal BMI and study center Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Okah et al. (2007)	<ul style="list-style-type: none"> Population-based retrospective cohort study using certificates of live births in Missouri First and second singleton live births n = 5,107 1994–2003 Missouri 	<ul style="list-style-type: none"> Nonsmokers: Smoked during neither pregnancy Smoked during first but not during second pregnancy Smoked during second but not during first pregnancy Smoked during both pregnancies Smoking history ascertained from vital statistics data and certificates of live births, which used one question on tobacco use during pregnancy (yes/no) 	<10th percentile for gestational age	<p>Adjusted OR for SGA in second pregnancy (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Smoked during first but not during second pregnancy: 1.31 (0.65–2.65) Smoked during second but not during first pregnancy: 1.83 (1.19–2.82) Smoked during both pregnancies: 2.80 (2.00–3.93) 	<p>Results adjusted for maternal age, race, and medical risk for SGA</p> <p>Did not account for alcohol or substance use</p>
Pipkin (2008)	<ul style="list-style-type: none"> Prospective cohort study of the genetics of preeclampsia Singleton pregnancies with moderate to severe preeclampsia n = 1,001 Years: Not reported United Kingdom 	<ul style="list-style-type: none"> Nonsmoker: Never smoked Quit smoking: Quit before first antenatal visit but quit time not reported Continued smoking: Smoking at the time of antenatal booking Smoking status based on self-reports obtained at antenatal booking 	<3rd percentile for gestational age	<p>Percentage SGA and adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker: 27.9% (reference) Quit smoking: 37.5% Continued smoking: 46.1%; 2.20 (1.41–3.44) 	Results adjusted for maternal parity and BMI and sex of the infant
McCowan et al. (2009)	<ul style="list-style-type: none"> Prospective cohort study n = 2,504 2004–2007 New Zealand and Australia 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during pregnancy Quit smoking: Smoked during pregnancy but quit before being interviewed at 15 weeks' gestation Continued smoking: Smoking at 15 weeks' gestation Smoking status based on self-reports ascertained at 15 weeks' gestation 	SGA birth weight <10th customized centile	<p>Adjusted OR (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: 1.06 (0.67–1.68) Continued smoking: 1.76 (1.03–3.02) 	<p>Results adjusted for maternal age; ethnicity; marital status; employment status; BMI; bleeding during pregnancy; folic acid use; multivitamin use; alcohol use at 15 weeks' gestation; and scores for depression, stress, or anxiety</p> <p>Did not account for substance use</p>

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Polakowski et al. (2009)	<ul style="list-style-type: none"> Population-based retrospective cohort study using certificates of live births Singleton pregnancies >28 weeks' gestation n = 915,441 2005 Multiple sites in the United States 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during any trimester of pregnancy Quit smoking, first trimester: Smoked during first trimester but not during second and third trimesters Quit smoking, second trimester: Smoked during second trimester but not during third trimester Continued smoking: Smoked during all three trimesters Excluded women who did not fit any of the categories above Smoking history ascertained from vital statistics data and certificates of live births 	Birth weight <10th percentile weight for gestational age	<p>Adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Term (≥37 completed weeks): <ul style="list-style-type: none"> Continued smoking (reference) Nonsmokers: 0.41 (0.40–0.42) Quit smoking, first trimester: 0.45 (0.42–0.48) Quit smoking, second trimester: 0.59 (0.54–0.64) Preterm (28–36 completed weeks): <ul style="list-style-type: none"> Continued smoking (reference) Nonsmokers: 0.45 (0.42–0.47) Quit smoking, first trimester: 0.47 (0.40–0.55) Quit smoking, second trimester: 0.88 (0.72–1.08) 	<p>Results adjusted for maternal age, race/ethnicity, marital status, education, late entry into prenatal care, and history of preterm delivery</p> <p>Did not account for alcohol or substance use</p>
Vardavas et al. (2010)	<ul style="list-style-type: none"> Population-based, prospective cohort study Singleton pregnancies n = 1,400 2007–2008 Crete, Greece 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke from 3 months before pregnancy through pregnancy Quit smoking: Stopped smoking sometime between 3 months before pregnancy and 12 weeks' gestation. Continued smoking: Smoking at 12 weeks' gestation Smoking status based on self-reports obtained at enrollment and during second and third trimesters 	Birthweight <10th percentile for gestational age	<p>Unadjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: 0.73 (0.34–1.59) Continued smoker: 2.36 (1.42–3.93) <p>Adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: 0.74 (0.34–1.62) Continued smoker: 2.63 (1.55–4.49) 	<p>Results adjusted for origin, parity, maternal education, and age and sex of the infant</p> <p>Did not account for alcohol or substance use</p>
Bakker et al. (2011)	<ul style="list-style-type: none"> Population-based, prospective cohort study n = 5389 2001–2005 Netherlands 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking, first trimester: Smoked only during first trimester Quit smoking, second trimester: Smoked during second trimester (combined with “continued smoking” for this analysis) Continued smoking: smoked during third trimester (combined with “quit smoking, second trimester” for this analysis) Smoking status based on self-reports obtained in each trimester of pregnancy 	Birth weight <5th percentile for gestational age	<p>Adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 1.17 (0.73–1.88) Continued smoking 2.11 (1.55–2.88) 	<p>Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, maternal stress, gestational age at birth; and sex of the fetus</p> <p>Did not account for substance use</p>

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Baba et al. (2012)	<ul style="list-style-type: none"> Population-based cohort study based on Swedish Medical Birth Register Singleton pregnancies n = 846,411 1999–2010 Sweden 	<ul style="list-style-type: none"> Nonusers: Did not use snuff or smoke cigarettes before pregnancy or during early pregnancy (≤15 weeks' gestation) Quit smoking, early: Smoked before pregnancy but quit during early pregnancy Continued smoking, early: Smoked before and during early pregnancy (based on first assessment of smoking status at ≤15 weeks' gestation) Quit smoking, late: Smoked during early pregnancy but not during late pregnancy (based on assessment of smoking status at ≤15 weeks' gestation and 30–32 weeks' gestation) Continued smoking: Smoked during early and late pregnancy Smoking status based on self-reports assessed at first antenatal visit (typically ≤15 weeks' gestation) and again in late pregnancy (typically 30–32 weeks' gestation) 	Birth weight >2 SD below the mean for gestational age using sex-specific growth curves	<p>Unadjusted and adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Based on early assessment: <ul style="list-style-type: none"> Nonuser (reference) Quit smoking, early: <ul style="list-style-type: none"> Unadjusted: 1.17 (1.11–1.24) Adjusted: 1.03 (0.98–1.09) Continued smoking, early: <ul style="list-style-type: none"> Unadjusted: 2.69 (2.58–2.80) Adjusted: 2.55 (2.43–2.67) Based on late assessment: <ul style="list-style-type: none"> Nonuser (reference) Quit smoking, late: <ul style="list-style-type: none"> Unadjusted: 2.01 (1.83–2.21) Adjusted: 1.82 (1.65–2.01) Continued smoking, late: <ul style="list-style-type: none"> Unadjusted: 3.18 (3.01–3.36) Adjusted: 3.21 (3.02–3.40) <p>Adjusted OR for preterm SGA and term SGA (95% CI):</p> <ul style="list-style-type: none"> Nonuser (reference) Quit smoking, early: <ul style="list-style-type: none"> Preterm SGA: 0.86 (0.76–0.98) Term SGA: 1.07 (1.01–1.14) Continued smoking, early: <ul style="list-style-type: none"> Preterm SGA: 1.85 (1.67–2.06) Term SGA: 2.76 (2.62–2.91) 	<p>Results adjusted for maternal age, parity, education, early pregnancy BMI, cohabitation, height, pregestational diabetes, and essential hypertension</p> <p>Did not account for alcohol or substance use</p>
Bickerstaff et al. (2012)	<ul style="list-style-type: none"> Retrospective cohort n = 30,524 1997–2006 Australia 	<ul style="list-style-type: none"> Nonsmokers: Never smoked or quit >12 months before booking Quit smoking: Smoked during 12 months before booking but quit before booking Continuing smokers: Currently smoking at booking Smoking status based on routinely collected clinical data 	<10th and <3rd percentiles using customized centiles for Australian ethnicities	<p>Adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> 10th percentile: <ul style="list-style-type: none"> Continuing smokers vs. nonsmokers: 2.26 (2.08–2.47) Quit smoking vs. continuing smokers: 0.43 (0.33–0.57) 3rd percentile: <ul style="list-style-type: none"> Continuing smokers vs. nonsmokers: 2.41 (2.14–2.73) Quit smoking vs. continuing smokers: 0.46 (0.31–0.68) 	<p>Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity</p> <p>Did not account for alcohol or substance use</p>

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Erickson and Arbour (2012)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using the British Columbia Perinatal Registry Singleton pregnancies n = 233,891 2001–2006 British Columbia, Canada 	<ul style="list-style-type: none"> Nonsmokers: Never smoked Quit smoking: Not further defined, timing not specified Continued smoking: Smoking at first prenatal visit, subgrouped by smoking intensity: <ul style="list-style-type: none"> Light: 1–4 cigarettes/day Moderate: 5–9 cigarettes/day Heavy: ≥10 cigarettes/day Smoking history based on self-reports typically ascertained at the first prenatal visit (12–18 weeks' gestation) 	Birth weight <3rd and <10th percentiles for gestational age	Adjusted OR for SGA (95% CI): <ul style="list-style-type: none"> 3rd percentile: <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 0.86 (0.72–1.03) Continued smoking: <ul style="list-style-type: none"> Light: 1.33 (1.11–1.60) Moderate: 1.82 (1.51–2.20) Heavy: 2.37 (2.06–2.72) 10th percentile: <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 0.84 (0.76–0.92) Continued smoking: <ul style="list-style-type: none"> Light: 1.24 (1.12–2.72) Moderate: 1.74 (1.57–1.93) Heavy: 2.14 (1.98–2.32) 	Results adjusted for maternal age, parity, prenatal care visits, diabetes, hypertension, pre-pregnancy weight, presence of a partner, alcohol and drug use, and sex of the infant
Miyake et al. (2013)	<ul style="list-style-type: none"> Retrospective cohort study n = 1,565 2007–2008 Japan 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during pregnancy Quit smoking, first trimester: Smoked only during first trimester Quit smoking, second or third trimester: Smoked during the second or third trimester but not throughout pregnancy Continued smoking: Smoked throughout pregnancy Smoking status for each trimester of pregnancy based on self-reports obtained after delivery 	Birth weight <10th percentile for gestational age	Adjusted OR for SGA (95% CI): <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking, first trimester: <ul style="list-style-type: none"> Overall: 0.53 (0.13–1.49) Male infants: 1.02 (0.16–3.81) Female infants: 0.24 (0.01–1.22) Quit smoking, second or third trimester: <ul style="list-style-type: none"> Overall: 1.93 (0.55–5.27) Male infants: 1.67 (0.08–11.08) Female infants: 2.14 (0.48–6.92) Continued smoking: <ul style="list-style-type: none"> Overall: 2.87 (1.11–6.56) Male infants: 4.21 (1.26–12.14) Female infants: 1.51 (0.23–5.96) 	Results adjusted for region of residence; number of children; family structure; maternal age, education, employment, alcohol consumption, and BMI; gestational age at birth; and sex of the infant Did not account for substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Murphy et al. (2013)	<ul style="list-style-type: none"> Prospective cohort study Singleton pregnancies n = 1,216 2010–2011 Ireland 	<ul style="list-style-type: none"> Nonsmoker: Not defined Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit Continued smoking: Smoked during 6 months before pregnancy, at first prenatal visit, and during third trimester Smoking status based on self-reports obtained at enrollment and in third trimester 	Birth weight <10th percentile, corrected for maternal height and weight, parity, infant sex, ethnicity, and gestation	<p>OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 0.81 (0.46–1.40) – Adjusted: 1.05 (0.58–1.89) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 2.09 (1.27–3.44), – Adjusted: 1.39 (1.06–1.84) 	Birth weight adjusted for maternal age, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use
Rode et al. (2013)	<ul style="list-style-type: none"> Prospective cohort study Singleton, term pregnancies n = 1,774 1996–1999 Denmark 	<ul style="list-style-type: none"> Nonsmokers: Not defined Quit smoking: Quit immediately before or during pregnancy Continued smoking: Not defined. Smoking status based on self-reports assessed at 12–18 weeks' and 37 weeks' gestation and 1 year postpartum Salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation 	Birth weight <10th percentile for gestational age	<p>OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 1.1 (0.7–1.7) – Adjusted: 1.0 (0.6–1.6) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 3.5 (2.4–4.9) – Adjusted: 3.6 (2.5–5.2) 	<p>Birth weight adjusted for pre-pregnancy BMI, preeclampsia, and parity</p> <p>Salivary cotinine for subgroup reported but not integrated into main analysis</p> <p>Did not account for alcohol or substance use</p>
Meghea et al. (2014)	<ul style="list-style-type: none"> Prospective cohort study n = 474 2008–2009 Romania 	<ul style="list-style-type: none"> Nonsmokers: Not smoking when learned they were pregnant Quit smoking: Quit upon learning of pregnancy Continued smoking: Smoking at time of study interview (gestational age not reported) Smoking history based on self-reports obtained at study enrollment (gestational age not reported) 	Birth weight <10th percentile for gestational age	<p>Adjusted OR for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 2.16 (1.05–4.43) Continued smoking: 1.79 (0.74–4.32) 	<p>Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity</p> <p>Did not account for alcohol or substance use</p>

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Räisänen et al. (2014)	<ul style="list-style-type: none"> Population-based study based on Finnish Medical Birth Register Singleton pregnancies, live or stillborn after 22 weeks' gestation n = 1,164,953 1991–2010 Finland 	<ul style="list-style-type: none"> Nonsmokers: Not further defined Quit smoking: Quit smoking during first trimester Continued smoking: Smoked after first trimester Smoking history ascertained from the Finnish Medical Birth Register 	Birth weight >2 SD below sex- and parity-specific means for gestational age	OR for SGA (95% CI): <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> Unadjusted: 1.33 (1.26–1.41) Adjusted: 1.16 (1.09–1.23) Continued smoking: <ul style="list-style-type: none"> Unadjusted: 2.38 (2.33–2.44) Adjusted: 2.47 (2.41–2.53) 	<ul style="list-style-type: none"> Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant Did not account for alcohol or substance use
Suzuki et al. (2014)	<ul style="list-style-type: none"> Prospective cohort study Singleton pregnancies n = 2,663 1991–2006 Japan 	<ul style="list-style-type: none"> Nonsmoker: Never smoked Quit smoking before pregnancy: Not further defined Quit smoking, first trimester Continued smoking: Smoked after first trimester Smoking history based on self-reports obtained in early pregnancy (usually first trimester) 	Birth weight <10th percentile using sex-specific growth curves for infants in Japan	Adjusted OR for SGA (95% CI): <ul style="list-style-type: none"> Boys: <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking before pregnancy: 1.2 (0.5–3.2) Quit smoking, first trimester: 1.0 (0.5–2.1) Continued smoking: 3.2 (1.7–6.2) Girls: <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking before pregnancy: 0.5 (0.1–1.5) Quit smoking, first trimester: 1.1 (0.6–2.0) Continued smoking: 2.5 (1.3–5.2) 	<ul style="list-style-type: none"> Results adjusted for maternal age and BMI Did not account for alcohol or substance use
Blatt et al. (2015)	<ul style="list-style-type: none"> Population-based retrospective cohort study using certificates of live births in Ohio n = 927,424 2006–2012 Ohio 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy Quit before pregnancy: Smoked during 3 months before pregnancy but not during pregnancy Quit first trimester: Smoked only during first trimester Quit second trimester: Smoked during first and second trimesters but not third trimester Continued smoking: Smoked throughout pregnancy Smoking history ascertained from vital statistics data and certificates of live births 	Birthweight <10th and <5th percentiles for gestational age	Adjusted OR for SGA (95% CI): <ul style="list-style-type: none"> <10th percentile: <ul style="list-style-type: none"> Nonsmoker (reference) Quit first trimester: 1.19 (1.13–1.24) Quit second trimester: 1.67 (1.57–1.78) Continued smoking: 2.26 (2.22–2.31) <5th percentile: <ul style="list-style-type: none"> Nonsmoker (reference) Quit first trimester: 1.25 (1.17–1.33) Quit second trimester: 1.83 (1.68–1.99) Continued smoking: 2.44 (2.37–2.51) 	<ul style="list-style-type: none"> Results adjusted for maternal age, race, education, marital status, hypertension, diabetes, and BMI Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Grzeskowiak et al. (2015)	<ul style="list-style-type: none"> Retrospective cohort study n = 7,658 2000–2005 South Australia 	<ul style="list-style-type: none"> Nonsmokers Quit smoking Continued smoking Smoking status not further defined Smoking history based on self-reports ascertained at antenatal booking 	Birth weight <10th percentile for gestational age by sex of the infant and maternal height and parity	<p>Percentage SGA:</p> <ul style="list-style-type: none"> Nonsmokers: 7.1% (reference) Quit smoking: 8.1%, p = 0.81 Continued smoking: 15.3%, p <0.001 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p>
Kvalvik et al. (2017)	<ul style="list-style-type: none"> Population-based retrospective cohort study using the Medical Birth Registry of Norway First and second births n = 118,355 1999–2014 Norway 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke at the end of either pregnancy Daily smoker/quit smoking: Smoked daily at end of first pregnancy but not smoking at end of second pregnancy Nonsmoker/daily smoker: Not smoking at end of first pregnancy but smoked daily at end of second pregnancy Daily smoker/daily smoker: Smoked daily at end of both pregnancies Did not describe how smoking status was ascertained 	Birth weight <10th and <2.5th percentile for gestational age by sex	<p>RR for SGA at second pregnancy (95% CI):</p> <ul style="list-style-type: none"> <10th percentile: <ul style="list-style-type: none"> Nonsmoker (reference) Daily smoker/quit smoking: <ul style="list-style-type: none"> Unadjusted: 1.5 (1.3–1.6) Adjusted: 1.5 (1.3–1.7) Nonsmoker/daily smoker: <ul style="list-style-type: none"> Unadjusted: 2.1 (1.8–2.5) Adjusted: 2.1 (1.8–2.5) Daily smoker/daily smoker: <ul style="list-style-type: none"> Unadjusted: 2.9 (2.7–3.1) Adjusted: 2.9 (2.7–3.1) <2.5th percentile: <ul style="list-style-type: none"> Nonsmoker (reference) Daily smoker/quit smoking: <ul style="list-style-type: none"> Unadjusted: 1.5 (1.1–2.0) Adjusted: 1.5 (1.1–2.0) Nonsmoker/daily smoker: <ul style="list-style-type: none"> Unadjusted: 3.2 (2.4–4.3) Adjusted: 3.1 (2.3–4.2) Daily smoker/daily smoker: <ul style="list-style-type: none"> Unadjusted: 4.0 (3.4–4.7) Adjusted: 3.9 (3.3–4.6) 	<p>Results adjusted for maternal age, marital status, and year of first birth</p> <p>Did not account for alcohol or substance use</p>

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Tong et al. (2017)	<ul style="list-style-type: none"> Population-based retrospective cohort study n = 88,933 2009–2011 United States 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy or during last 3 months of pregnancy Quit smoking: Smoked during 3 months before pregnancy but not during last 3 months of pregnancy Continued smoking, nondaily: Smoked during 3 months before pregnancy and <1 cigarette/day during last 3 months of pregnancy Continued smoking, daily: Smoked during 3 months before pregnancy and smoked ≥1 cigarette/day during last 3 months of pregnancy Smoking status based on survey administered postpartum 	≤10th percentile birth weight for gestational age by sex and race	<p>Prevalence ratio for SGA (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 1.0 (0.9–1.1) – Adjusted: 0.9 (0.9–1.0) Continued smoking: <ul style="list-style-type: none"> – Nondaily: <ul style="list-style-type: none"> ○ Unadjusted: 1.6 (1.3–1.9) ○ Adjusted: 1.4 (1.1–1.8) – Daily: <ul style="list-style-type: none"> ○ Unadjusted: 2.2 (2.0–2.4) ○ Adjusted: 2.0 (1.9–2.2) 	<p>Results adjusted for maternal age, parity, education, marital status, BMI, trimester of entry into prenatal care, and alcohol use during pregnancy</p> <p>Did not account for substance use</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **OR** = odds ratio; **RR** = risk ratio; **SD** = standard deviation; **SGA** = small for gestational age.

(Mitchell et al. 2002; England et al. 2007; Pipkin 2008; Andersen et al. 2009; McCowan et al. 2009; Polakowski et al. 2009; Vardavas et al. 2010; Bakker et al. 2011; Baba et al. 2012; Erickson and Arbour 2012; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Suzuki et al. 2014; Blatt et al. 2015; Grzeskowiak et al. 2015; Tong et al. 2017), and 1 study compared them with the infants of continuing smokers (Bickerstaff et al. 2012). In general, these 20 studies found that women who continued to smoke past early pregnancy had an elevated risk of SGA delivery and that cessation attenuated or eliminated this excess risk.

Seven of the 20 studies examined a combined-exposure variable of cessation before pregnancy with cessation during early pregnancy, and thus could not isolate the effects of cessation by timeframe (before and after conception) (England et al. 2007; Andersen et al. 2009; Vardavas et al. 2010; Bickerstaff et al. 2012; Murphy et al. 2013; Rode et al. 2013; Tong et al. 2017). Six of these seven studies found no difference in SGA risk in quitters compared with nonsmokers (England et al. 2007; Andersen et al. 2009; Vardavas et al. 2010; Murphy et al. 2013; Rode et al. 2013; Tong et al. 2017), while one (Bickerstaff et al. 2012) found a significant decrease in risk among quitters compared with continuing smokers (aOR = 0.43; 95% CI, 0.33–0.57). In 2 of the 20 studies, the timing of cessation with respect to conception was not described (Pipkin 2008; Erickson and Arbour 2012). Pipkin and colleagues (2008) did not perform any testing for statistical significance; and Erickson and Arbour (2012) found no increased risk of SGA among infants of quitters. Six of the 20 studies included assessment of smoking status in late pregnancy (typically in the third trimester) (Mitchell et al. 2002; Bakker et al. 2011; Baba et al. 2012; Rode et al. 2013; Blatt et al. 2015; Tong et al. 2017), thus reducing any potential contribution of unidentified relapse. Of these studies, five found no significant increase in risk of SGA infants among quitters whose status was verified in late pregnancy, and one (Baba et al. 2013) found an increased risk for late, but not early, quitters. One of the six studies assessed timing by trimester (Blatt et al. 2015) and found significant increases in risk in both early quitters (smoked in first trimester only) and later quitters (smoked in first and second trimesters only) (aOR = 1.19; 95% CI, 1.13–1.24, and 1.67; 95% CI, 1.57–1.78, respectively) when compared with nonsmokers. One study included biochemical validation of smoking cessation (Rode et al. 2013) and combined preconception and early-pregnancy quitters. The study found no increase for SGA risk in quitters when compared with nonsmokers.

Of the two studies that examined smoking cessation across consecutive pregnancies, one found no increased risk of SGA in babies of women who quit by the second pregnancy compared with women who did not smoke in

either pregnancy (Okah et al. 2007), and the other found a significant increase for SGA in quitters compared with women who did not smoke during either pregnancy (Kvalvik et al. 2017). However, the basis for the different findings is not clear. Both studies were population based, used an SGA definition of less than 10th percentile, and relied on self-reported smoking status, and both adjusted for several potential confounders (for maternal age, race, and medical risk factors for SGA, and for maternal age, marital status, and year of first birth, respectively). The two studies were conducted in different countries (United States and Norway, respectively), however, and although Okah and colleagues (2007) categorized smoking status as positive or negative for each pregnancy, Kvalvik and colleagues (2017) specifically assessed smoking status at the end of each pregnancy.

Summary of the Evidence. Since the 2004 Surgeon General's report confirmed that smoking cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004), numerous studies have assessed the relationships between smoking and smoking cessation and SGA, and most have adjusted for multiple confounders. The evidence is sufficient to infer that smoking cessation before or during early pregnancy reduces the risk of SGA birth compared with continued smoking. The evidence is suggestive but not sufficient to infer that the risk of an SGA birth in women who quit smoking before or during early pregnancy does not differ from that for nonsmokers. The evidence is inadequate to determine the gestational age before which smoking cessation should occur to eliminate the effects of smoking on risk of SGA.

Preterm Delivery

Delivery before 37 completed weeks' gestation is a leading cause of neonatal morbidity and mortality (March of Dimes et al. 2012; Menon 2012; Blencowe et al. 2013; Katz et al. 2013), and this problem affects approximately 15 million births per year globally (World Health Organization 2017) and nearly 10% of births in the United States (Martin et al. 2017). Preterm delivery can be medically indicated (about two-thirds of all preterm deliveries) or spontaneous (about one-third of preterm deliveries). Spontaneous preterm delivery encompasses preterm labor, premature rupture of membranes, and spontaneous fetal loss. Medically indicated preterm delivery can be the outcome of numerous maternal and fetal conditions, including maternal chronic diseases, such as hypertension or diabetes, and pregnancy complications, such as preeclampsia, GDM, or abnormal placentation (Purisch and Gyamfi-Bannerman 2017). Numerous risk factors for spontaneous preterm delivery have been identified, including prior spontaneous preterm delivery, intrauterine

infections, shortened cervix, multifetal pregnancy, fetal abnormalities, uterine anomalies, Black race, interpregnancy interval less than 18 months, low socioeconomic status, low gestational weight gain, poor nutrition status, and advanced maternal age (Conde-Agudelo et al. 2006; USDHHS 2010; Purisch and Gyamfi-Bannerman 2017).

The 1990 Surgeon General's report identified a reduced risk of preterm delivery among women who quit smoking before or during pregnancy relative to continuing smokers, but the report found insufficient evidence to draw conclusions about the effects of smoking cessation on both preterm delivery and gestational duration (USDHHS 1990). The 2004 Surgeon General's report found a causal relationship between maternal smoking and preterm delivery (gestational age <37 weeks) and shorter gestational duration (number of days or weeks of pregnancy) (USDHHS 2004). The 2010 Surgeon General's report reviewed mechanisms hypothesized to explain the increased risk of preterm delivery among smokers, including increased risk of genitourinary tract infections, alterations in vaginal flora and localized immunosuppression, alterations in cervical cytokine profiles, reductions in maternal zinc levels, dysregulation of the fetal immune system, and alterations in myometrial contractility (USDHHS 2010).

Twenty-five studies published in 2000 or later that examined smoking cessation and preterm delivery were identified (Table 4.34). Two studies (Abrevaya 2008; Mohsin and Jalaludin 2008) examined cessation across two consecutive pregnancies, and 23 examined cessation in single pregnancies (Hrubá and Kachlik 2000; Vogazianos et al. 2005; McCowan et al. 2009; Polakowski et al. 2009; Anderka et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Baba et al. 2012; Bickerstaff et al. 2012; Erickson and Arbour 2012; Batech et al. 2013; Miyake et al. 2013; Murphy et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Bailey 2015; Smith et al. 2015; Yan and Groothuis 2015; Dahlin et al. 2016; Moore et al. 2016; Suzuki et al. 2016; Tong et al. 2017; Wallace et al. 2017). All but three studies (Hrubá and Kachlik 2000; Vogazianos et al. 2005; Suzuki et al. 2016) adjusted for at least some potential confounders, and five addressed alcohol consumption (McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Yan and Groothuis 2015; Tong et al. 2017), while three addressed both alcohol and substance use (Erickson and Arbour 2012; Bailey 2015; Smith et al. 2015).

Of the 23 studies examining individual pregnancies, 8 classified exposure combining cessation before pregnancy with cessation during early pregnancy and, thus, could not estimate the effect of cessation after conception (Hrubá and Kachlik 2000; Anderka et al. 2010; Vardavas et al. 2010; Baba et al. 2012; Bickerstaff et al. 2012; Murphy et al. 2013; Dahlin et al. 2016; Tong et al. 2017). Of these

eight studies, five compared quitters with nonsmokers and found no statistically significant difference in risk between the two groups (Vardavas et al. 2010; Baba et al. 2012; Murphy et al. 2013; Dahlin et al. 2016; Tong et al. 2017). Bickerstaff and colleagues (2012) compared quitters with continuing smokers and found no difference in risk. Six of the 23 studies examined cessation before conception; 4 compared quitters with nonsmokers (Vogazianos et al. 2005; Smith et al. 2015; Yan and Groothuis 2015; Moore et al. 2016). Three of the four found no significant differences in preterm deliveries (Vogazianos et al. 2005; Smith et al. 2015; Yan and Groothuis 2015), and one found a slightly reduced risk in quitters (Moore et al. 2016). One study compared women who quit before pregnancy with continuing smokers and found a significantly reduced risk of preterm delivery (Batech et al. 2013); and one study reported percentages of preterm infants for nonsmokers and women who quit before pregnancy (5.0% and 5.8%, respectively), as well as for other cessation groups, but adjustment for confounding was not performed, and only an overall chi-square test result was reported (Suzuki et al. 2016).

Twelve of the 23 studies examined cessation during pregnancy (McCowan et al. 2009; Polakowski et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Bailey 2015; Smith et al. 2015; Yan and Groothuis 2015; Moore et al. 2016; Suzuki et al. 2016; Wallace et al. 2017); of those, 7 found no statistically significant increase in the risk of preterm delivery in quitters compared with nonsmokers (McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Smith et al. 2015; Yan and Groothuis 2015). Moore and colleagues (2016) and Wallace and colleagues (2017) used data from state certificates of live birth in Ohio, and both found an increased risk of preterm delivery in those who quit late in pregnancy, but not in those who quit early in the pregnancy compared with nonsmokers. Using a large sample of more than 900,000 births, Moore and colleagues (2016) found an increase in risk among second-trimester quitters (aOR = 1.70; 95% CI, 1.60–1.80) but not in earlier quitters (first trimester) compared with those who were nonsmokers. Wallace and colleagues (2017) found an increased risk in third-trimester quitters (aOR = 1.81; 95% CI, 1.48–2.21) but not in second- or first-trimester quitters compared with nonsmokers. One study found a significant difference across smoking categories overall, but women who quit during pregnancy were not compared directly with other groups (Suzuki et al. 2016). In another study using a large sample of 900,000 births, significant reductions in the risk of preterm delivery were found among first- and second-trimester quitters compared with continuing smokers (aOR = 0.69; 95% CI, 0.65–0.74 and aOR = 0.87; 95% CI, 0.79–0.96, respectively)

Table 4.34 Studies on smoking cessation and preterm delivery

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Hrubá and Kachlik (2000)	<ul style="list-style-type: none"> Retrospective, clinic-based study Term, singleton deliveries n = 1,147 Years of data collection not reported Czech Republic 	<ul style="list-style-type: none"> Nonsmoker: Never smoked Quit smoking: Smoked but quit before pregnancy or during first trimester Continued smoking: Smoked throughout pregnancy either daily or occasionally Smoking status based on self-reports from interviews conducted shortly after delivery Findings stratified by exposure to environmental tobacco smoke 	≤36 weeks' gestation	<p>Percentage preterm delivery:</p> <ul style="list-style-type: none"> Continued smoking: 10.0% No exposure to environmental tobacco smoke: <ul style="list-style-type: none"> Nonsmoker: 6.5% Quit smoking: 6.3% Continued smoking: 10.0% Exposure to environmental tobacco smoke: <ul style="list-style-type: none"> Nonsmoker: 9.4% Quit smoking: 4.8% 	<p>Results not adjusted for potential confounders</p> <p>No statistical testing reported</p> <p>Did not account for alcohol or substance use</p>
Vogazianos et al. (2005)	<ul style="list-style-type: none"> Population-based, retrospective cohort study n = 59,014 1990–1996 Cyprus 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke before or during pregnancy Quit smoking: Smoked before but not during pregnancy Continued smoking: Smoked before and during pregnancy Not clear how many women quit smoking during pregnancy and how they were categorized Smoking status based on maternal self-reports obtained during physician interviews 	<38 weeks' gestation	<p>OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 1.02 (0.73–1.43) Continued smoking: 2.58 (2.05–3.25) 	<p>Results not adjusted for potential confounders</p> <p>Did not account for alcohol or substance use</p>
Abrevaya et al. (2008)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using linked certificates of live births in Michigan First and second pregnancies in which women smoked during the first pregnancy n = 14,731 n = 8,044 1989–2004 Michigan 	<ul style="list-style-type: none"> Quit smoking between pregnancies: Smoked during first pregnancy but not during second pregnancy Continued smoking: Smoked during first and second pregnancies Smoking status based on smoking history collected from certificates of live births, which used one question on tobacco use during pregnancy (yes/no) 	<37 weeks' gestation	<p>Adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Quit smoking between pregnancies (reference) Continued smoking: <ul style="list-style-type: none"> 18–24 years of age: 1.04 (0.89–1.22) 25–30 years of age: 1.12 (0.89–1.40) 	<p>Results adjusted for maternal race, education, income, population, interpregnancy interval, and year of birth; trimester of first prenatal visit; number of prenatal visits; presence of father's name on birth certificate; and first-birth value of the outcome</p> <p>Did not account for alcohol or substance use</p>

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Mohsin and Jalaludin (2008)	<ul style="list-style-type: none"> Population-based retrospective cohort study Consecutive singleton births n = 244,480 1994–2004 Australia 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during either pregnancy Quit smoking between pregnancies: Smoked during first pregnancy but not during second pregnancy Resumed smoking between pregnancies: Smoked during second pregnancy but not during first pregnancy Continued smoking: Smoked during first and second pregnancies Smoking status based on self-reports 	<37 weeks' gestation	Adjusted OR for preterm delivery at second pregnancy (95% CI): <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking between pregnancies: 1.41 (1.29–1.55) Resumed smoking between pregnancies: 1.43 (1.37–1.60) Continued smoking: 1.89 (1.8–1.99) 	Results adjusted for interpregnancy interval and other factors not explicitly reported
McCowan et al. (2009)	<ul style="list-style-type: none"> Prospective cohort study designed to develop screening tests for pregnancy complications 2004–2007 n = 2,504 New Zealand and Australia 	<ul style="list-style-type: none"> Nonsmokers (did not smoke during pregnancy) Quit smoking: Smoked during pregnancy but quit before the study interview (~15 weeks' gestation) Continued smoking: Smoking at time of study interview (~15 weeks' gestation) Smoking status based on self-reports ascertained at 15 weeks' gestation 	Spontaneous preterm labor or preterm, premature rupture of membranes resulting in a preterm delivery at <37 weeks' gestation	Adjusted OR for spontaneous preterm delivery (95% CI): <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 1.03 (0.49–2.18) Continued smoking: 3.21 (1.42–7.23) 	Results adjusted for demographic factors (maternal age, ethnicity, marital status, employment status, and BMI) and clinical risk factors (bleeding during pregnancy; folic acid use; multivitamin use; alcohol use at 15 weeks' gestation; and scores for depression, stress, or anxiety) Did not account for substance use
Polakowski et al. (2009)	<ul style="list-style-type: none"> Population-based retrospective cohort study Singleton deliveries, ≥28 weeks' gestation n = 915,441 2005 United States (11 states) 	<ul style="list-style-type: none"> Nonsmoker: Smoked zero cigarettes in all trimesters of pregnancy Quit first trimester: Smoked during first trimester but not during second and third trimesters Quit second trimester: Smoked during second trimester but not during third trimester Continued smoking: Smoked during all three trimesters Excluded women who did not fit in any of these categories Smoking status based on certificates of live births 	Preterm delivery 28–≤37 weeks' gestation based on last menstrual period, unless implausible (then based on clinical estimate)	Adjusted OR for preterm delivery (95% CI): <ul style="list-style-type: none"> Preterm, non-SGA: <ul style="list-style-type: none"> Continued smoking (reference) Nonsmokers: 0.72 (0.70–0.74) Quit first trimester: 0.69 (0.65–0.74) Quit second trimester 0.87 (0.79–0.96) Preterm, SGA: <ul style="list-style-type: none"> Continued smoking (reference) Nonsmokers: 0.45 (0.42–0.47) Quit first trimester: 0.47 (0.40–0.55) Quit second trimester: 0.88 (0.72–1.08) 	Results adjusted for maternal age, race/ethnicity, marital status, education, late entry into prenatal care, and history of preterm delivery Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Anderka et al. (2010)	<ul style="list-style-type: none"> Population-based, case-control study n = 4,667 1997–2003 United States 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before conception or during any trimester of pregnancy Quit smoking: Smoked preconception but not during any trimester of pregnancy, smoked in first trimester but not in second or third trimesters, or smoked in second trimester but not in third trimester Continued smoking: Smoked during all three trimesters Smoking status based on maternal self-reports obtained during interviews conducted 6 weeks–24 months postpartum 	<37 weeks' gestation	<p>Percentage and adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker 7.6% (reference) Quit smoking: 8.0%, adjusted OR not reported Continued smoking: 11.5%, 1.59 (1.13–2.25) 	<p>Results adjusted for maternal age, race/ethnicity, education, and birthplace</p> <p>Did not account for alcohol or substance use</p>
Vardavas et al. (2010)	<ul style="list-style-type: none"> Population-based, prospective cohort study Singleton pregnancies 2007–2008 n = 1,400 Greece 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during 3 months before pregnancy Quit smoking: Smoked within 3 months before pregnancy and/or during the first 12 weeks of pregnancy but quit by the time of study interview (~12 weeks' gestation) Continued smoking: Smoked during 3 months before pregnancy, during first 12 weeks of pregnancy, and at the time of the study interview (~12 weeks' gestation) Smoking status based on self-reports ascertained at approximately 12 weeks' gestation 	<37 weeks' gestation	<p>OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 0.86 (0.54–1.38) – Adjusted: 0.90 (0.56–1.46) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 1.22 (0.82–1.83) – Adjusted: 1.28 (0.84–1.94) 	<p>Results adjusted for origin, parity, maternal education and age, and sex of the infant</p> <p>Did not account for alcohol or substance use</p>

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bakker et al. (2011)	<ul style="list-style-type: none"> Population-based cohort study 2001–2005 n = 5,389 Netherlands 	<ul style="list-style-type: none"> Nonsmokers: Did not smoke during pregnancy Quit smoking, first trimester: Smoked only during first trimester (combined with “quit smoking, second and third trimesters” for analysis) Quit smoking, second trimester: Smoked during second trimester (combined with “quit smoking, first and third trimesters” for analysis) Continued smoking: Smoked during third trimester (combined with “quit smoking, first and second trimesters” for analysis) Smoking status based on self-reports obtained during each trimester 	<37 weeks' gestation	Adjusted OR for preterm delivery (95% CI): <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking, first trimester: 0.66 (0.37–1.17) Continued smoking: 1.25 (0.88–1.78) 	Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, and stress; gestational age at birth; and sex of the fetus Did not account for substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Baba et al. (2012)	<ul style="list-style-type: none"> Population-based retrospective cohort study using the Swedish Medical Birth Register n = 776,836 1999–2009 Sweden 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy or before registration for antenatal care Quit smoking: Smoked during 3 months before pregnancy but quit by registration for antenatal care Continued smoking: Smoking at registration for antenatal care Smoking status based on self-reports assessed at first antenatal visit (typically ≤15 weeks' gestation) 	<ul style="list-style-type: none"> Overall preterm delivery: <37 weeks' gestation Very preterm delivery: <32 weeks' gestation Moderate preterm delivery: 32–36 weeks' gestation Spontaneous preterm delivery: Spontaneous onset of labor and preterm premature rupture of the membranes Induced preterm delivery: Vaginally induced onset of labor and cesarean delivery before the onset of labor 	<p>OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: <ul style="list-style-type: none"> <37 weeks: 1.02 (0.99–1.06) <32 weeks: 1.04 (0.94–1.15) 32–36 weeks: 1.02 (0.98–1.06) – Adjusted: <ul style="list-style-type: none"> <37 weeks: 0.90 (0.87–0.94) <32 weeks: 0.91 (0.82–1.01) 32–36 weeks: 0.90 (0.86–0.94) Spontaneous preterm delivery: 0.92 (0.88–0.96) Induced preterm delivery: 0.86 (0.79–0.92) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: <ul style="list-style-type: none"> <37 weeks: 1.43 (1.38–1.48) <32 weeks: 1.84 (1.69–2.00) 32–36 weeks: 1.37 (1.32–1.41) – Adjusted: <ul style="list-style-type: none"> <37 weeks: 1.30 (1.25–1.36) <32 weeks: 1.68 (1.52–1.84) 32–36 weeks: 1.25 (1.20–1.30) Spontaneous preterm delivery: 1.32 (1.26–1.38) Induced preterm delivery: 1.20 (1.12–1.29) 	<p>Results adjusted for BMI in early pregnancy, maternal age, parity, education, and cohabitation</p> <p>Did not account for alcohol or substance use</p>
Bickerstaff et al. (2012)	<ul style="list-style-type: none"> Retrospective cohort study 1997–2006 n = 30,524 Australia 	<ul style="list-style-type: none"> Nonsmoker: Never smoked or quit >12 months before booking Quit smoking: Smoked during 12 months before booking but quit before booking Continued smoking: Currently smoking at booking Smoking status based on routinely collected clinical data 	<37 weeks' gestation	<p>Percentage with preterm delivery:</p> <ul style="list-style-type: none"> Nonsmoker: 9.7% Quit smoking: 12.7% Continued smoking: 12.9% <p>Adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Continued smoking vs. nonsmoker: 1.42 (1.28–1.59) Quit smoking vs. continued smoking: 0.92 (0.69–1.23) 	<p>Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity</p> <p>Did not account for alcohol or substance use</p>

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Erickson and Arbour (2012)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using the British Columbia Perinatal Database Registry Singleton deliveries n = 233,891 2001–2006 British Columbia, Canada 	<ul style="list-style-type: none"> Nonsmoker: Never smoked Quit smoking: Former smoker (time of cessation in former smokers with respect to pregnancy was not available) Continued smoking: Current smoker at time of smoking status assessment: <ul style="list-style-type: none"> – Light: 1–4 cigarettes/day – Moderate: 5–9 cigarettes/day – Heavy: ≥10 cigarettes/day Smoking history based on self-reports typically ascertained at first prenatal visit 	20–36 completed weeks' gestation	Adjusted OR for preterm delivery (95% CI): <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: 1.18 (1.08–1.28) Continued smoking: <ul style="list-style-type: none"> – 1–4 cigarettes/day: 1.25 (1.13–1.38) – 5–9 cigarettes/day: 1.24 (1.10–1.39) – ≥10 cigarettes/day: 1.39 (1.28–1.52) 	Results adjusted for maternal age, parity, prenatal care visits, diabetes, hypertension, pre-pregnancy weight, presence of a partner, alcohol and drug use, and sex of the infant
Batech et al. (2013)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using certificates of live births in California n = 65,228 2007–2008 California 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy Quit smoking: Smoked during 3 months before pregnancy but not during any trimester of pregnancy Continued smoking: Smoked during any trimester of pregnancy Smoking history obtained from the state's certificate of live births 	<37 weeks' gestation	Adjusted OR for preterm delivery (95% CI): <ul style="list-style-type: none"> Continued smoking (reference) Nonsmokers: <ul style="list-style-type: none"> – 2007: 0.68 (0.58–0.79) – 2008: 0.68 (0.58–0.80) Quit smoking: <ul style="list-style-type: none"> – 2007: 0.69 (0.51–0.92) – 2008: 0.69 (0.51–0.93) 	Results adjusted for age and various other factors in multiple models, including ethnicity; education; enrollment in the Women, Infants, and Children program; trimester of entry into prenatal care; and primary source of payment
Miyake et al. (2013)	<ul style="list-style-type: none"> Retrospective cohort study n = 1,565 2007–2008 Japan 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during pregnancy Quit smoking, first trimester: Smoked during first trimester only Quit smoking, second or third trimester: Smoked during second or third trimester but not throughout pregnancy Continued smoking: Smoked throughout pregnancy Smoking status for each trimester based on self-reports obtained after delivery 	<37 weeks' gestation	Adjusted OR for preterm delivery (95% CI): <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking, first trimester: 2.51 (0.90–5.98) Quit smoking, second or third trimester: 3.14 (0.71–9.80) Continued smoking: 2.06 (0.47–6.34) 	Results adjusted for maternal age, residence, education, employment, alcohol consumption, and BMI; family structure; gestational age at birth; and sex of the infant

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Murphy et al. (2013)	<ul style="list-style-type: none"> Prospective cohort study Singleton pregnancies n = 1,216 2010–2011 Dublin, Ireland 	<ul style="list-style-type: none"> Nonsmoker: Not defined Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit Continued smoking: Smoked during 6 months before pregnancy, and smoking at first prenatal visit and during third trimester Smoking status based on self-reports obtained at enrollment and during third trimester 	<37 weeks' gestation	<p>Crude and adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> Crude: 1.14 (0.51–2.56) Adjusted: 1.68 (0.51–5.63) Continued smoking: <ul style="list-style-type: none"> Crude: 1.25 (0.51–3.10) Adjusted: 1.09 (0.86–1.75) 	Birth weight adjusted for maternal age, BMI, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use
Meghea et al. (2014)	<ul style="list-style-type: none"> Prospective cohort study n = 474 2008–2009 Romania 	<ul style="list-style-type: none"> Nonsmokers: Not smoking when learned of pregnancy Quit smoking: Quit upon learning of pregnancy Continued smoking: Smoking at time of study interview (gestational age not reported) Smoking history based on self-reports obtained at study enrollment (gestational age not reported) 	<37 weeks' gestation	<p>Adjusted OR (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: 1.41 (0.59–3.37) Continued smoking: 1.29 (0.46–3.67) 	<p>Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity</p> <p>Did not account for alcohol or substance use</p>
Räsänen et al. (2014)	<ul style="list-style-type: none"> Population-based retrospective cohort using Finnish Medical Birth Register Singleton deliveries, live or stillborn after 22 weeks' gestation n = 1,164,953 1991–2010 Finland 	<ul style="list-style-type: none"> Nonsmokers: Not further defined Quit smoking: Quit smoking during first trimester Continued smoking: Smoked after first trimester Smoking history based on self-reports ascertained from the Finnish Medical Birth Register 	<37 weeks' gestation	<p>Odds ratio for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> Unadjusted: 1.04 (0.98–1.10) Adjusted: 1.01 (0.95–1.07) Continuing smokers: <ul style="list-style-type: none"> Unadjusted: 1.35 (1.31–1.38) Adjusted: 1.39 (1.36–1.43) 	<p>Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant</p> <p>Did not account for alcohol or substance use</p>

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bailey (2015)	<ul style="list-style-type: none"> Randomized clinical trial of smoking cessation intervention 2008–2012 n = 1,486 Tennessee 	<ul style="list-style-type: none"> Quit smoking: Smoked at first prenatal visit but quit by third trimester Continued smoking: Smoked at first prenatal visit and still smoking during third trimester Smoking history based on self-reports obtained at first prenatal visit Quit status ascertained during third trimester by exhaled CO and urine cotinine and by self-report at delivery 	Preterm delivery not defined	<p>Percentage preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Quit smoking: 9.8% Continued smoking: 13.8% p = 0.089 	<p>Randomized cessation trial and thus no comparison group of never smokers</p> <p>Results adjusted for maternal age, education, marital status, insurance status, and marijuana use</p> <p>Examined maternal race, previous pregnancies, live deliveries, and alcohol use, but they were not significant in the model</p>
Smith et al. (2015)	<ul style="list-style-type: none"> Population-based case-cohort study n = 1,887 2009–2010 United Kingdom 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during preconception or early (1–13 weeks) or late (14–32 weeks) during pregnancy Quit smoking before pregnancy: Smoked preconception but not during early or late pregnancy Quit smoking, first trimester: Smoked during early pregnancy but not during late pregnancy Continued smoking: Smoked during late pregnancy Smoking status based on self-reports obtained from maternal interview conducted shortly after delivery 	32–36 weeks' gestation	<p>Adjusted RR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking before pregnancy: 0.93 (0.72–1.20) Quit smoking, first trimester: 1.12 (0.76–1.66) Continued smoking: 1.38 (1.04–1.84) 	Results adjusted for maternal age, ethnicity, BMI, education level, and lifestyle factors (recreational drug and alcohol use, dietary practices, and folic acid supplements)

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Yan and Groothuis (2015)	<ul style="list-style-type: none"> Population-based cohort study Singleton pregnancies Excluded women with chronic diseases n = 11,131 2000–2001 United Kingdom 	<ul style="list-style-type: none"> Nonsmokers: Not defined Quit smoking before pregnancy: Timing of cessation not specified Quit smoking during pregnancy (month of cessation noted) Continued smoking: Quit during third trimester or did not quit Smoking history based on self-reports ascertained when infants were 9 months old 	<37 weeks' gestation, based on gestational age estimated by research team	<ul style="list-style-type: none"> Difference in percentage of preterm delivery: Nonsmokers (reference) Quit smoking before pregnancy: +0.8% Quit smoking, first trimester: +0.1%, p = 0.8 Quit smoking, second trimester: +2.8%, p = 0.08 Continued smoking: +2.9%, p <0.01 	<p>Adjusted for birth year/quarter of infant and maternal weight, height, income, initiation of prenatal care, alcohol use, employment status, home satisfaction, religion affiliation, and racist or religion-based insults in living area</p> <p>Did not account for substance use</p>
Dahlin et al. (2016)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using the Swedish Medical Birth Register n = 1,371,274 1999–2012 Sweden 	<ul style="list-style-type: none"> Nonsmokers: No antenatal tobacco use Quit smoking: Smoked during 3 months before pregnancy but quit by the first antenatal visit Continued smoking: Smoked ≥1 cigarette/day at the time of the first antenatal visit Smoking status based on self-reports derived from the Swedish Medical Birth Register 	<ul style="list-style-type: none"> Extreme preterm delivery: <28 weeks' gestation Very preterm delivery: 28–31 weeks' gestation Moderate preterm delivery: 32–36 weeks' gestation 	<p>OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> – Unadjusted preterm delivery: <ul style="list-style-type: none"> ○ Extreme: 1.12 (0.97–1.29) ○ Very: 1.03 (0.93–1.13) ○ Moderate: 1.05 (1.02–1.08) – Adjusted preterm delivery: <ul style="list-style-type: none"> ○ Extreme: 1.02 (0.88–1.18) ○ Very: 0.92 (0.83–1.02) ○ Moderate: 0.94 (0.91–1.01) Continued smoking: <ul style="list-style-type: none"> – Unadjusted preterm delivery: <ul style="list-style-type: none"> ○ Extreme: 1.87 (1.64–2.12) ○ Very: 1.68 (1.54–1.83) ○ Moderate: 1.39 (1.34–1.43) – Adjusted preterm delivery: <ul style="list-style-type: none"> ○ Extreme: 1.74 (1.51–1.99) ○ Very: 1.52 (1.38–1.67) ○ Moderate: 1.27 (1.23–1.31) 	<p>Results adjusted for maternal age, parity, cohabitation with father, country of birth, education, and BMI</p> <p>Did not account for alcohol or substance use</p>

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Moore et al. (2016) (continues on next page)	<ul style="list-style-type: none"> Population-based, retrospective cohort using certificates of live births in Ohio Singleton births without congenital anomalies n = 913,757 2006–2012 Ohio 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy Quit smoking before pregnancy: Smoked during 3 months before pregnancy but not during first trimester Quit smoking, first trimester: Smoked during first trimester but not during second and third trimesters Quit smoking, second trimester: Smoked during second trimester but not during third trimester Continued smoking: Smoked during all three trimesters Smoking status obtained from Ohio certificates of live birth 	<ul style="list-style-type: none"> Overall preterm delivery: <37 weeks' gestation based on clinician's best estimate of gestational age Extreme preterm delivery: 20–27 weeks' gestation Preterm delivery: 28–36 weeks' gestation Spontaneous preterm delivery: Not medically indicated Indicated preterm delivery: Births complicated by intrauterine growth restriction, preeclampsia, or eclampsia following induction of labor 	<p>Adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Overall: <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking before pregnancy: 0.91 (0.88–0.94) Quit smoking, first trimester: 1.02 (0.98–1.07) Quit smoking, second trimester: 1.70 (1.60–1.80) Continued smoking: 1.21 (1.19–1.24) Extreme preterm: <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking before pregnancy: 0.87 (0.77–0.98) Quit smoking, first trimester: 1.20 (1.03–1.40) Quit smoking, second trimester: Not applicable Continued smoking: 0.90 (0.83–0.97) Preterm: <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking before pregnancy: 0.91 (0.88–0.94) Quit smoking, first trimester: 1.01 (0.96–1.05) Quit smoking, second trimester: 1.46 (1.37–1.55) Continued smoking: 1.24 (1.21–1.26) 	Results adjusted for maternal race, education, age, Medicaid, marital status, and parity

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
(continued from previous page) Moore et al. (2016) (continues on next page)	—	—	—	<p>Indicated preterm delivery (95% CI):</p> <ul style="list-style-type: none"> • Overall: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.92 (0.87–0.97) – Quit smoking, first trimester: 1.01 (0.94–1.09) – Quit smoking, second trimester: 1.78 (1.62–1.96) – Continued smoking: 1.22 (1.18–1.26) • Extreme preterm: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.85 (0.78–0.93) – Quit smoking, first trimester: 0.93 (0.82–1.05) – Quit smoking, second trimester: Not applicable – Continued smoking: 0.73 (0.69–0.78) • Preterm: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.91 (0.87–0.96) – Quit smoking, first trimester: 0.99 (0.92–1.07) – Quit smoking, second trimester: 1.66 (1.51–1.83) – Continued smoking: 1.18 (1.14–1.22) 	—

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
(continued from previous page) Moore et al. (2016)	—	—	—	Spontaneous preterm delivery (95% CI): <ul style="list-style-type: none"> • Overall: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.90 (0.87–0.93) – Quit smoking, first trimester: 1.03 (0.97–1.08) – Quit smoking, second trimester: 1.65 (1.54–1.77) – Continued smoking: 1.20 (1.17–1.22) • Extreme preterm: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.88 (0.77–1.02) – Quit smoking, first trimester: 1.20 (1.00–1.43) – Quit smoking, second trimester: Not applicable – Continued smoking: 0.93 (0.84–1.02) • Preterm: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking before pregnancy: 0.90 (0.87–0.94) – Quit smoking, first trimester: 1.02 (0.96–1.08) – Quit smoking, second trimester: 1.37 (1.26–1.48) – Continued smoking: 1.25 (1.22–1.28) 	—
Suzuki et al. (2016)	<ul style="list-style-type: none"> • Population-based, cohort study • Singleton pregnancies • n = 7734 • 2011–2014 • Japan 	<ul style="list-style-type: none"> • Nonsmokers: Never smoked • Quit smoking before pregnancy: Not further defined • Quit smoking during early pregnancy: Not further defined • Continued smoking: Currently smoking at time study questionnaire was administered • Smoking status based on self-reports collected during second trimester 	Preterm delivery not defined	Percentage preterm delivery: <ul style="list-style-type: none"> • Nonsmoker: 5.0% • Quit smoking before pregnancy: 5.8% • Quit smoking during early pregnancy: 5.6% • Continued smoking: 8.9% • Chi-square test p = 0.008 	<ul style="list-style-type: none"> • Results not adjusted for potential confounders • Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wallace et al. (2017)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using certificates of live births in Ohio Singleton pregnancies Excluded congenital malformations All participants had at least one previous preterm delivery 2006–2012 n = 36,432 Ohio 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during 3 months before pregnancy Quit smoking by first trimester: Smoked during 3 months before pregnancy but not during first trimester Quit by second trimester: Smoked during first trimester but not during second or third trimesters Quit by third trimester: Smoked during second trimester but not during third trimester Continued smoking: Smoked during all three trimesters Smoking status obtained from Ohio certificates of live birth 	<37 weeks' gestation	<p>Adjusted OR for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking by first trimester: 0.97 (0.86–1.09) Quit smoking by second trimester: 1.10 (0.93–1.29) Quit smoking by third trimester: 1.81 (1.48–2.21) Continued smoking: 1.14 (1.07–1.22) 	<p>Results adjusted for maternal race, marital status, and Medicaid enrollment</p> <p>Did not account for alcohol or substance use</p>
Tong et al. (2017)	<ul style="list-style-type: none"> Population-based, retrospective cohort study n = 88,933 2009–2011 United States 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during past 2 years and did not smoke during 3 months before pregnancy Quit smoking: Smoked during 3 months before pregnancy but not during last 3 months of pregnancy Continued smoking, nondaily: Smoked during 3 months before pregnancy and smoked <1 cigarette/day in last 3 months of pregnancy Continued smoking, daily: Smoked during 3 months before pregnancy and smoked ≥1 cigarette/day during last 3 months of pregnancy 	<37 weeks' gestation based on clinical estimate of gestation from birth certificates	<p>Crude and adjusted prevalence ratio for preterm delivery (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: <ul style="list-style-type: none"> Crude: 1.0 (0.9–1.1) Adjusted: 1.0 (0.9–1.1) Continued smoking, nondaily: <ul style="list-style-type: none"> Crude: 1.0 (0.8–1.3) Adjusted: 1.0 (0.8–1.2) Continued smoking, daily: <ul style="list-style-type: none"> Crude 1.3: (1.2–1.4) Adjusted: 1.3 (1.2–1.4) 	<p>Prevalence ratios adjusted for maternal age, parity, education, marital status, BMI, trimester of entry into prenatal care, and alcohol use during pregnancy</p> <p>Did not account for substance use</p>

Notes: **BMI** = body mass index; **CI** = confidence interval; **CO** = carbon monoxide; **OR** = odds ratio; **RR** = risk ratio; **SGA** = small for gestational age.

(Polakowski et al. 2009), and in a smaller study, no significant difference was found between quitters and continuing smokers (Bailey 2015). Three studies were not sufficiently large to examine cessation during pregnancy, and the CIs were wide (McCowan et al. 2009; Miyake et al. 2013; Meghea et al. 2014).

In one of the 23 studies examining individual pregnancies, the timing of cessation was not described (Erickson and Arbour 2012); in that study, a modest but significant increase in risk was found among quitters compared with nonsmokers (aOR = 1.18; 95% CI, 1.08–1.28). Only 1 of the 23 studies included biochemical validation of smoking status (Bailey 2015); that study was a randomized clinical trial of a smoking cessation intervention (n = 1,486 who received the intervention vs. 461 who received usual care) in which no statistically significant difference was found in the risk of preterm delivery among women in the intervention group between women who quit smoking during pregnancy and continuing smokers (13.8% among continuing smokers and 9.8% among quitters [p = 0.09]).

Of the two studies that examined cessation across pregnancies, one found an increased risk of preterm delivery in the second pregnancy in women who quit between pregnancies versus those who did not smoke in either (aOR = 1.41; 95% CI, 1.29–1.55) (Mohsin and Jalaludin 2008), and the other found no difference in the risk of preterm delivery during the second pregnancy for women who quit between pregnancies compared with those who smoked during both pregnancies (Abrevaya 2008). As was previously discussed, examining outcomes across pregnancies can be limited by an oversimplification of exposure categories, but this design can reduce the contributions of confounding from environmental and genetic factors. If smoking cessation during pregnancy affects the risk of preterm delivery, then the effect could be missed using this method.

Summary of the Evidence. Since the 2004 Surgeon General's report found a causal relationship between maternal smoking and preterm delivery (gestational age <37 weeks) and shorter gestational duration (USDHHS 2004), numerous studies have assessed the relationships between smoking cessation before and/or during pregnancy and preterm delivery, and most have adjusted for multiple confounders. Most of these studies compared the risk of preterm delivery in quitters to that in nonsmokers, while fewer studies directly compared the risk in quitters to that in continuing smokers. The majority of studies that compared quitters and nonsmokers found no difference in risk of preterm delivery, and studies that compared quitters and continuing smokers reported mixed results (all reported lower risk in quitters compared with continuing smokers overall, but not all findings were significant). There were limited data with which to assess the role

of timing of cessation for risk of preterm delivery, but the largest studies that examined trimester-specific cessation reported that earlier cessation produces greater benefits for risk of preterm delivery than later cessation. The evidence is suggestive but not sufficient to infer that the risk of preterm delivery in women who quit smoking before or during early pregnancy does not differ from that of nonsmokers. The evidence is suggestive but not sufficient to infer that women who quit smoking before conception or during early pregnancy have a reduced risk of preterm delivery compared with women who continue to smoke.

Stillbirth, Perinatal Mortality, and Infant Mortality

Stillbirth (typically defined as a fetal death after 28 weeks' gestation), perinatal mortality (stillbirths and deaths in the first week of life), and infant mortality (neonatal [death in the first month of life] and postnatal [death from 1 month to 1 year of life]) have all been associated with prenatal exposure to tobacco in previous Surgeon General's reports. The 1990 Surgeon General's report on smoking cessation presented evidence that women who quit smoking are at lower risk of perinatal mortality relative to continuing smokers, although the studies were too few to be conclusive (USDHHS 1990). No conclusions were drawn about the relationship between smoking cessation and infant mortality. The 2004 and 2014 Surgeon General's reports concluded that infants of smokers are at higher risk of stillbirth, perinatal mortality, and neonatal mortality than infants of nonsmokers (USDHHS 2004, 2014). Overall, these reports did not review the effects of cessation on these risks. The 2004 Surgeon General's report also found that smoking during or after pregnancy increases the risk of sudden infant death syndrome, but this outcome was not reviewed in this report due to the lack of studies directly assessing the consequences of smoking cessation on sudden infant death syndrome (USDHHS 2004).

Stillbirth, perinatal, and infant mortality are multifactorial in etiology, and many of their causal factors are also causally associated with smoking. For example, smoking is causally associated with preterm delivery, PPRM, placenta previa, and placental abruption—all of which contribute to perinatal and neonatal mortality; and preterm delivery accounts for more than one-third of infant deaths (Matthews et al. 2015). Therefore, the effects of cessation on those pathways would likely translate into beneficial effects on more distal outcomes. In addition, approximately half of perinatal deaths in the United States are stillbirths, and half are deaths in the first week

of life. Therefore, effects of smoking cessation on stillbirth or deaths in the first week of life likely also affect rates of perinatal mortality. The relationship between smoking and fetal growth was explored in depth in the 2014 Surgeon General's report (USDHHS 2014). Briefly, when the distributions of birth weight for the infants of smokers and their corresponding mortality rates are examined, infants of smokers have higher mortality than those of nonsmokers at every birth weight when each population is adjusted to its own z-scale for birth weight (Wilcox 2001). Thus, maternal smoking affects infant mortality independently of its effects on birth weight. Infants of nonsmokers are less likely to be born with low birth weight than those of smokers, but when they are, the underlying etiologies are associated with higher mortality (Wilcox 2001).

Stillbirth

Five studies published after 2000 were identified that examined smoking cessation and stillbirth; four examined cessation with respect to individual pregnancies (Wisborg et al. 2001; Erickson and Arbour 2012; Räisänen et al. 2014; Bjørnholt et al. 2016), and one examined cessation across two consecutive pregnancies (Högberg and Cnattingius 2007) (Table 4.35). All four studies examining cessation with respect to individual pregnancies included adjustment for at least some confounders, and two included adjustment for alcohol use or for alcohol and other substance use (Wisborg et al. 2001; Erickson and Arbour 2012). Three studies relied on data from registries (Erickson and Arbour 2012; Räisänen et al. 2014; Bjørnholt et al. 2016), and none included biochemical validation of cessation status. Two studies examined women who quit smoking during early pregnancy (Räisänen et al. 2014; Bjørnholt et al. 2016), and one (Wisborg et al. 2001) assessed smoking status in late pregnancy (30 weeks). No studies examined both the effects of quitting early versus quitting late in pregnancy. Three studies found no increased risk of stillbirth among women who quit smoking during early pregnancy compared with nonsmokers (Wisborg et al. 2001; Räisänen et al. 2014; Bjørnholt et al. 2016), and one found increased risk in quitters but not in continuing smokers (Erickson and Arbour 2012). This last study, however, did not address the timing of cessation in quitters with respect to pregnancy, and smoking status was ascertained only at the first prenatal visit, making it possible that some former smokers had relapsed by the end of pregnancy compared with women who smoked in neither pregnancy. However, the risk of stillbirth in the second pregnancy was significantly elevated among women who smoked during both pregnancies.

In the study that examined cessation across consecutive pregnancies (Högberg and Cnattingius 2007),

a large, population-based study using data from the Swedish Medical Birth Register, women who smoked during the first pregnancy but not during the second pregnancy did not have an increased risk of stillbirth in the second pregnancy.

Summary of the Evidence

Since the 2004 and 2014 Surgeon General's reports found that infants of smokers are at higher risk of stillbirth than infants of nonsmokers (USDHHS 2004, 2014), several studies have examined the effects of smoking cessation on the risk of stillbirth, and findings have been mixed. These studies were limited by a lack of biochemical validation and inconsistent assessment of the timing of cessation during preconception and gestation. Consequently, the evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of stillbirth compared with continued smoking.

Perinatal Mortality

Two studies published after 2000 were identified that examined smoking cessation and perinatal mortality (Bickerstaff et al. 2012; Bailey 2015) (Table 4.36). Bickerstaff and colleagues (2012) examined risk in a retrospective cohort study of Australian women who had quit smoking in the year before pregnancy or after becoming pregnant but before the first antenatal visit, while Bailey (2015) examined risk in women participating in a randomized smoking cessation trial in the state of Tennessee who smoked during the first trimester of pregnancy but had quit by the third trimester. These two studies relied on self-reported tobacco use and adjusted for several potential confounders. Both studies found a reduction in the risk of perinatal mortality in quitters compared with continuing smokers, with findings from Bailey (2015) reaching statistical significance. Neither study compared quitters with nonsmokers.

Summary of the Evidence

Since the 2004 and 2014 Surgeon General's reports concluded that children of smokers are at higher risk of perinatal mortality than children of nonsmokers (USDHHS 2004, 2014), few studies have addressed smoking cessation and perinatal mortality. The evidence is inadequate to determine whether cessation before or during pregnancy reduces the risk of perinatal mortality compared with continued smoking.

Infant Mortality

Three studies published later than 2000 were identified that examined smoking cessation and infant death

Table 4.35 Studies on smoking cessation and stillbirth

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wisborg et al. (2001)	<ul style="list-style-type: none"> • Prospective cohort study • Singleton pregnancies • n = 25,102 • 1989–1996 • Denmark 	<ul style="list-style-type: none"> • Nonsmokers: Not smoking at time of either antenatal interview • Quit smoking: Stopped smoking by second antenatal interview • Continued smoking: Smoking ≥ 1 cigarette/day at both antenatal interviews • Smoking status ascertained from maternal interviews conducted before first antenatal visit (typically 16 weeks' gestation) and before the 30-week antenatal visit 	Death of a fetus at or after 28 weeks' gestation	<p>Crude and adjusted OR for stillbirth (95% CI):</p> <ul style="list-style-type: none"> • Nonsmokers (reference) • Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 0.9 (0.5–1.9) – Adjusted: 0.9 (0.5–1.9) • Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 2.0 (1.4–2.9) – Adjusted: 1.9 (1.3–2.9) 	<p>Results adjusted for parity; maternal age, education, employment, caffeine and alcohol intake, weight, and height; and sex of the infant</p> <p>Did not account for substance use</p>
Högberg and Cnattingius (2007)	<ul style="list-style-type: none"> • Population-based cohort study • First and second singleton births • n = 526,691 • 1983–2001 • Sweden 	<ul style="list-style-type: none"> • Nonsmokers: Not smoking daily at time of first antenatal visit • Moderate smoker: Smoking 1–9 cigarettes/day at time of first antenatal visit • Heavy smoker: Smoking ≥ 10 cigarettes/day at time of first antenatal visit • Quit smoking: Not smoking in second pregnancy • Smoking history ascertained from medical birth registry, which included smoking status collected at first antenatal visit (typically <15 weeks' gestation) 	Fetal death after at least 28 completed weeks' gestation	<p>Crude and adjusted OR for stillbirth in second pregnancy (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker both pregnancies (reference) • Nonsmoker/moderate smoker: <ul style="list-style-type: none"> – Unadjusted: 0.85 (0.54–1.32) – Adjusted: 0.82 (0.52–1.30) • Nonsmoker/heavy smoker: <ul style="list-style-type: none"> – Unadjusted: 1.09 (0.49–2.45) – Adjusted: 0.92 (0.38–2.22) • Moderate smoker/nonsmoker (quit smoking): <ul style="list-style-type: none"> – Unadjusted: 1.17 (0.91–1.50) – Adjusted: 1.11 (0.85–1.44) • Moderate smoker/moderate smoker: <ul style="list-style-type: none"> – Unadjusted: 1.15 (0.92–1.43) – Adjusted: 1.16 (0.92–1.46) • Moderate smoker/heavy smoker: <ul style="list-style-type: none"> – Unadjusted: 1.64 (1.21–2.23) – Adjusted: 1.56 (1.13–2.16) • Heavy smoker/nonsmoker (quit smoking): <ul style="list-style-type: none"> – Unadjusted: 0.88 (0.51–1.51) – Adjusted: 0.67 (0.36–1.26) • Heavy smoker/moderate smoker: <ul style="list-style-type: none"> – Unadjusted: 1.50 (1.09–2.06) – Adjusted: 1.41 (1.01–1.96) • Heavy smoker/heavy smoker: <ul style="list-style-type: none"> – Unadjusted: 1.70 (1.32–2.19) – Adjusted: 1.55 (1.17–2.04) 	<p>Results adjusted for maternal age, education, cohabitation with the father, mother's country of birth, interpregnancy interval, stillbirth in first pregnancy, and year of second delivery</p> <p>Did not account for alcohol or substance use</p>

Table 4.35 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Erickson and Arbour (2012)	<ul style="list-style-type: none"> Population-based retrospective cohort study using the British Columbia Perinatal Database Registry Singleton deliveries n = 233,891 2001–2006 British Columbia, Canada 	<ul style="list-style-type: none"> Nonsmoker: Never smoked Quit smoking: Former smoker (time of cessation in former smokers with respect to pregnancy was not available) Continued smoking: Current smoker at time of smoking status assessment Light: 1–4 cigarettes/day Moderate: 5–9 cigarettes/day Heavy: ≥10 cigarettes/day Smoking history based on self-reports typically ascertained at first prenatal visit 	Fetal death ≥20 weeks' gestation or >500 g	<p>Adjusted OR for stillbirth (95% CI):</p> <ul style="list-style-type: none"> Nonsmoker (reference) Quit smoking: 1.43 (1.03–2.00) Continued smoking <ul style="list-style-type: none"> – Light: 1.08 (0.67–1.72) – Moderate: 1.19 (0.71–1.97) – Heavy: 1.40 (0.97–2.03) 	Results adjusted for parity; prenatal care visits; maternal age, diabetes, hypertension, pre-pregnancy weight, and alcohol and drug use; presence of a partner; and sex of the infant
Räisänen et al. (2014)	<ul style="list-style-type: none"> Population-based retrospective cohort using Finnish Medical Birth Register Singleton deliveries, live or stillborn after 22 weeks' gestation 1991–2010 n = 1,164,953 Finland 	<ul style="list-style-type: none"> Nonsmokers: Not further defined Quit smoking: Quit smoking during first trimester Continued smoking: Smoked after first trimester Smoking history based on self-reports ascertained from the Finnish Medical Birth Register Details on when and how data were collected were not reported 	Stillbirth definition not provided	<p>OR for stillbirth (95% CI):</p> <ul style="list-style-type: none"> Reference (nonsmokers) Quit smoking: <ul style="list-style-type: none"> – Unadjusted: 0.70 (0.60–0.81) – Adjusted: 1.07 (0.92–1.26) Continued smoking: <ul style="list-style-type: none"> – Unadjusted: 1.03 (0.97–1.10) – Adjusted: 1.13 (1.06–1.20) 	<p>Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant</p> <p>Did not account for alcohol or substance use</p>
Bjørnholt et al. (2016)	<ul style="list-style-type: none"> Population-based cohort study using the Danish Medical Birth Register Singleton births n = 841,228 1997–2010 Denmark 	<ul style="list-style-type: none"> Nonsmoker: Did not smoke during pregnancy Quit smoking: Quit during first trimester or early in second trimester Continued smoking: Still smoking at time of first antenatal visit Smoking status ascertained from maternal interviews at first antenatal visit (13–15 weeks' gestation) 	<ul style="list-style-type: none"> 1997–2004: Fetal death after 28 completed weeks' gestation 2004–2010: Fetal death after 22 completed weeks' gestation Stillbirth further categorized as antepartum (before delivery) or intrapartum (during delivery) 	<p>Adjusted OR for stillbirth (95% CI):</p> <ul style="list-style-type: none"> All: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking: 1.03 (0.80–1.32) – Continued smoking: 1.47 (1.35–1.62) Antepartum: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking: 0.83 (0.61–1.13) – Continued smoking: 1.45 (1.31–1.61) Intrapartum: <ul style="list-style-type: none"> – Nonsmoker (reference) – Quit smoking: 1.94 (1.10–3.41) – Continued smoking: 1.47 (1.12–1.92) 	Results adjusted for year of delivery, maternal age, and marital or partner status

Notes: **CI** = confidence interval; **OR** = odds ratio.

Table 4.36 Studies on smoking cessation and perinatal mortality

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bickerstaff et al. (2012)	<ul style="list-style-type: none"> Retrospective cohort study 1997–2006 n = 30,524 Australia 	<ul style="list-style-type: none"> Nonsmoker: Never smoked or quit >12 months before booking Quit smoking: Smoked during 12 months before booking but quit before booking Continued smoking: Currently smoking at booking Smoking status based on routinely collected clinical data at antenatal booking 	Stillbirths and neonatal deaths during delivery hospitalization	<p>Adjusted OR for perinatal mortality (95% CI):</p> <ul style="list-style-type: none"> Continued smoking vs. nonsmoker: 1.36 (0.99–1.87) Quit smoking vs. continued smoking: 0.78 (0.28–2.16) 	<p>Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity</p> <p>Did not account for alcohol or substance use</p>
Bailey (2015)	<ul style="list-style-type: none"> Randomized clinical trial of smoking cessation intervention n = 1,486 2008–2012 Tennessee 	<ul style="list-style-type: none"> Quit smoking: Smoked at first prenatal visit but quit by third trimester Continued smoking: Smoked at first prenatal visit and still smoking during third trimester Smoking history based on self-reports obtained at first prenatal visit Quit status ascertained during third trimester by exhaled CO and urine cotinine and by self-reports at delivery 	Fetal or neonatal demise not defined	<p>Percentage perinatal deaths:</p> <ul style="list-style-type: none"> Quit smoking: 0.2% Continued smoking: 1.0% p = 0.046 	<p>Randomized cessation trial and thus no comparison group of never smokers</p> <p>Results adjusted for maternal age, education, marital status, insurance status, and marijuana use</p> <p>Examined alcohol use, but not significant in the model</p>

Notes: **CI** = confidence interval; **CO** = carbon monoxide; **OR** = odds ratio.

(Table 4.37). One study examined cessation with respect to individual pregnancies (Wisborg et al. 2001), and two examined cessation across two consecutive pregnancies (Abrevaya 2008; Johansson et al. 2009). All three studies relied on self-reported smoking status and adjusted for multiple potential confounders, with one also adjusting for alcohol use (Wisborg et al. 2001), but none adjusted for substance use. In a prospective cohort study of Danish women, Wisborg and colleagues (2001) found that, compared with women who did not smoke at all during pregnancy, women who smoked during pregnancy but quit by the time of the first antenatal interview (around 16 weeks' gestation) had no significant increase in the risk of infant death (aOR = 1.0; 95% CI, 0.5–1.9). Johansson and colleagues, who examined smoking status at the first antenatal visit in two consecutive pregnancies, found no increase in infant mortality for the second pregnancy among women who were light smokers in the first pregnancy but had quit by the second pregnancy compared with women who did not smoke in either pregnancy (aOR = 1.0; 95% CI, 0.8–1.5). This study, however, found increased risk in women who were heavy smokers in the first pregnancy and quit by the second pregnancy (aOR = 1.4; 95% CI, 1.0–2.0). Similarly, heavy smokers who smoked only in the second pregnancy had a significantly increased risk of infant mortality for that pregnancy (aOR = 1.8; 95% CI, 1.0–2.9). In the third study, Abrevaya and colleagues (2008) found no significant difference in the risk of infant mortality during the second pregnancy in women who smoked during the first but not the second pregnancy compared with women who smoked during both pregnancies. Comparisons between women who quit smoking by the second pregnancy and women who did not smoke in either pregnancy were not reported.

Summary of the Evidence

Since the 2004 Surgeon General's report (USDHHS 2004), few studies have addressed smoking cessation and infant mortality, and findings have been mixed. The evidence is inadequate to infer that women who quit smoking before or during early pregnancy have reduced risk for infant mortality compared with continuing smokers.

Female Reproductive Health

Fertility

“Infertility” is defined as the inability to achieve pregnancy following 12 months of regular, unprotected sexual intercourse (Practice Committee of American Society for Reproductive Medicine [PCASRM] 2013), while “fecundity” refers to the biologic ability to conceive. Subfertility

is any form of reduced fertility in couples trying to conceive. Up to 15% of couples have some form of infertility (Thoma et al. 2013), approximately half of which is related to female causes, 30% to male causes, and 20% to both male and female causes (Kovac et al. 2015). Women can have primary infertility (inability to conceive and no previous pregnancies), or secondary infertility (inability to conceive following a previous pregnancy). The PCASRM (2012) has estimated that 13% of infertility may be attributable to smoking.

Several pathways involved in reproduction could be targets of toxicants in cigarette smoke that adversely affect fertility (Dechanet et al. 2011; Marom-Haham and Shulman 2016). Cigarette smoking could affect folliculogenesis by inhibiting the growth of follicles or the maturation of oocytes. Possible mechanisms include abnormal oxidative stress, increased apoptosis, abnormal cross talk between oocytes and granulosa cells by inhibition of gap-junction formation between cells, or impairment of oocyte nuclear function by damaging DNA or interfering with meiosis. In addition, compounds in cigarette smoke could disrupt steroidogenesis, leading to alterations of estrogens and/or androgens in the follicular environment. Cigarette smoke, through its proangiogenic or antiangiogenic properties, could affect the early development of the embryo. Additionally, cigarette smoke could target the oviduct (by acting on its adhesive properties, ciliary activity, or muscular contractions) or the endometrium (by impairing endometrial proliferation or maturation, or by causing aberrant regulation of angiogenesis). Finally, tobacco smoke could cause vascular impairment in the uterine arteries or could affect myometrial contractility, which could adversely affect implantation (Dechanet et al. 2011; Marom-Haham and Shulman 2016).

The 1990 Surgeon General's report found evidence that cessation before attempted conception restored the fertility of former smokers to that of never smokers (Baird and Wilcox 1985; Daling et al. 1985; Howe et al. 1985; USDHHS 1990). The 2001 Surgeon General's report reviewed conception delay and infertility and found that although active smoking was associated with conception delay, the effect appeared to be reversible, as several studies observed similar conception rates for former and never smokers (USDHHS 2001). The report noted that smoking was consistently associated with impaired fertility in both case-control and cohort studies, and some studies found evidence of a dose-response relationship. Former smokers appeared to have little excess risk of impaired fertility. The report also concluded that smokers are at increased risk of primary and secondary infertility, but it did not draw conclusions about smoking cessation (USDHHS 2001).

The 2004 Surgeon General's report reviewed studies of smoking and fertility in women and found consistent

Table 4.37 Studies on smoking cessation and infant mortality

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wisborg et al. (2001)	<ul style="list-style-type: none"> Prospective cohort study Singleton pregnancies n = 25,102 1989–1996 Denmark 	<ul style="list-style-type: none"> Nonsmokers: Not smoking at time of either antenatal interview Quit smoking: Smoked during pregnancy but quit by first antenatal interview Continued smoking: Smoked ≥ 1 cigarette/day at first antenatal interview Smoking status ascertained from maternal interviews conducted before first antenatal visit (typically 16 weeks' gestation) and before the 30-week antenatal visit 	Death of a liveborn infant before 1 year of age	<p>Crude and adjusted OR for infant mortality (95% CI):</p> <ul style="list-style-type: none"> Nonsmokers (reference) Quit smoking: <ul style="list-style-type: none"> Unadjusted: 1.0 (0.5–1.9) Adjusted: 0.9 (0.5–1.9) 	<p>Results adjusted for parity; maternal age, education, employment, caffeine and alcohol intake, weight, and height; and sex of the infant</p> <p>Did not account for substance use</p>
Abrevaya et al. (2008)	<ul style="list-style-type: none"> Population-based, retrospective cohort study using Michigan-linked certificates of live births First and second pregnancies in which women smoked during the first pregnancy n = 14,731 (18–24 years of age) n = 8,044 (25–30 years of age) 1989–2004 Michigan 	<ul style="list-style-type: none"> Quit smoking: Smoked during first pregnancy but not during second pregnancy Continued smoking during both pregnancies: Smoked during first and second pregnancies Smoking status based on smoking history collected from certificates of live birth, which used one question on tobacco use during pregnancy (yes/no) 	Death of a liveborn infant within 1 year of birth	<p>Adjusted OR for infant mortality (95% CI):</p> <ul style="list-style-type: none"> Quit smoking (reference) Continued smoking during both pregnancies: <ul style="list-style-type: none"> 18–24 years of age: 1.07 (0.71–1.61) 25–30 years of age: 0.67 (0.28–1.62) 	<p>Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father's name on birth certificate, number of prenatal visits, and first-birth value of the outcome</p> <p>Did not account for alcohol or substance use</p>

Table 4.37 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Johansson et al. (2009)	<ul style="list-style-type: none"> • Births from the Swedish Birth Register • First and second singleton pregnancies • n = 555,046 • Sweden 	<ul style="list-style-type: none"> • Nonsmokers: Not smoking at first antenatal visit in either pregnancy • Quit smoking: Smoked at first antenatal visit of first pregnancy but not at first antenatal visit of second pregnancy • Relapsed: Did not smoke at first antenatal visit of first pregnancy but smoked at first antenatal visit of second pregnancy • Continued smoking: Smoked at first antenatal visit of both pregnancies: <ul style="list-style-type: none"> – Light smoker: 1–9 cigarettes/day – Heavy smoker: ≥10 cigarettes/day • Smoking status based on maternal self-reports obtained at first antenatal visit and on Swedish Birth Register 	Death during the first year of life in a liveborn infant from second pregnancy, born ≥22 weeks' gestation	<p>Adjusted OR for infant mortality after second pregnancy (95% CI):</p> <ul style="list-style-type: none"> • Nonsmoker (reference) • Quit smoking: <ul style="list-style-type: none"> – Light smoker, first pregnancy: 1.0 (0.8–1.5) – Heavy smoker, first pregnancy: 1.4 (1.0–2.0) • Relapsed: <ul style="list-style-type: none"> – Light smoker, second pregnancy: 1.1 (0.8–1.5) – Heavy smoker, second pregnancy: 1.8 (1.0–2.9) • Continued smoking (results attenuated when also adjusted for gestational age and placental abruption; remained significant for all but light/light smokers): <ul style="list-style-type: none"> – Light/light: 1.3 (1.1–1.6) – Heavy/light: 1.5 (1.1–1.9) – Light/heavy: 1.7 (1.3–2.2) – Heavy/heavy: 2.0 (1.7–2.4) 	<p>Results adjusted for maternal age, education, country of birth, interpregnancy interval, and year of delivery</p> <p>Did not account for alcohol or substance use</p>

Notes: **CI** = confidence interval; **OR** = odds ratio.

evidence that smoking reduces fecundity and increases the risk of primary infertility, with some evidence presented of a dose-response relationship with the number of cigarettes smoked. The report concluded that a causal relationship exists between smoking and reduced fertility in women, but it did not draw conclusions related to cessation (USDHHS 2004). The 2010 Surgeon General's report provided an updated review of smoking and fertility in women, including a meta-analysis of 12 studies that calculated an overall OR of 1.6 (95% CI, 1.3–1.9) for infertility versus nonsmokers (Augood et al. 1998). Earlier, a meta-analysis of data from seven studies of in vitro fertilization (IVF) patients indicated a significant reduction in conceptions per cycle in smokers compared with nonsmokers (OR = 0.57; 95% CI, 0.42–0.78) (Hughes and Brennan 1996). A subsequent review of 22 studies reported that 19 found evidence of adverse effects of smoking on female reproduction (Wilks and Hay 2004).

Since 2000, two papers have examined smoking cessation and fertility in women. In a study of 569 women who became pregnant without infertility treatment, Munafò and colleagues (2002) found that women who smoked in the year before conception took approximately 2 months longer to conceive than women who quit at least a year before conception. In multivariable models that adjusted for age, weight, lifetime use of oral contraceptives, alcohol consumption, and vigorous exercise, the number of pack-years of smoking was not associated with time to conception among former smokers ($p = 0.093$), but the number of cigarettes smoked per day was associated with increased time to conception among women who smoked during the period in which they were trying to conceive.

Radin and colleagues (2014) examined the association between fecundability (the probability of becoming pregnant in a single menstrual cycle), duration of active smoking, and smoking cessation in a prospective cohort of women in Denmark who were 18–40 years of age. The women were followed for up to 12 cycles after beginning to attempt conception. Overall, former smokers, occasional smokers, and regular smokers did not differ in fecundability from never smokers in models that adjusted for age, partner smoking, passive smoking, and the number of cycles at risk (adjusted fecundability ratios [aFRs] = 0.99, 1.11, and 0.89, respectively). Former smokers with at least 10 pack-years of smoking, however, had significantly reduced fecundability (aFR = 0.74).

Summary of the Evidence

The current review confirms findings of previous Surgeon General's reports that support a causal association between smoking and reduced fertility (USDHHS 2001, 2004). Although past reports of the Surgeon General found a causal association between smoking and reduced

fertility and suggestive evidence of restored fertility after smoking cessation, studies published since 2000 do not provide sufficient evidence to build upon the findings of the previous reports. Recent evidence is inadequate to further elucidate the association between smoking cessation or the timing of cessation and attempted conception and improved fecundability. The evidence is inadequate to elucidate the association between smoking cessation or the timing of cessation and fertility or fecundity.

Age at Menopause

The age of natural menopause is defined as the age menses cease for 12 consecutive months with no obvious cause, such as pregnancy or lactation, and it may be an important predictor of subsequent morbidity and mortality. The risks of cardiovascular disease and osteoporosis are higher for women with earlier menopause, but their risk of breast cancer is reduced (Gold 2011). Age at menopause was found to be associated with increased all-cause mortality when women with natural menopause before 40 years of age were compared with those who experienced menopause at 50 years of age or older (Gold 2011). Earlier, a large international study of women from 11 countries found the median age at menopause to be 50 years (range: 49–52 years across the countries) (Morabia and Costanza 1998). Factors associated with earlier menopause in epidemiologic studies include non-White race, low socioeconomic status, nulliparity, never using oral contraceptives, and lower weight (Gold 2011). Mechanisms contributing to an effect of smoking on age at menopause could involve genetics, environmental exposures, hormonal pathways, and health status (Gold et al. 2001, 2011; He and Murabito 2014; Sapre and Thakur 2014; Schoenaker et al. 2014).

The 1990 Surgeon General's report noted that cigarette smoking has consistently been associated with earlier menopause in epidemiologic studies (USDHHS 1990). The report found that smokers experience menopause 1 to 2 years earlier than nonsmokers and that the consistency of study findings and evidence for a dose-response relationship supported a causal association. The report also noted that the age of menopause in former smokers appeared to be closer to that in never smokers than in current smokers, suggesting that the effects of smoking on age at menopause may be at least partially reversible (USDHHS 1990). The data at that time were found to be limited, however, with few studies examining the duration of cessation or lifetime tobacco exposure.

The 2001 Surgeon General's report found that smoking was consistently associated with a 1- to 2-year decrease in age at natural menopause and concluded that smokers have a younger age at natural menopause than nonsmokers (USDHHS 2001). Possible mechanisms addressed in that report included exposure of the

ovaries to toxic components in tobacco smoke (animal studies suggest that tobacco smoke may cause follicular atresia) and the effects of nicotine on the metabolism of sex hormones. Although the report did not draw conclusions on smoking cessation, it did summarize studies that included former smokers (USDHHS 2001); those studies had mixed results.

Just over a decade after the 2001 Surgeon General's report, a meta-analysis of 11 papers published between 1997 and 2009 (comprising about 50,000 women) found that smoking was significantly associated in all the studies with earlier age at natural menopause (Sun et al. 2012). After adjustment for heterogeneity, the OR for onset of earlier menopause was 0.67 (95% CI, 0.61–0.73), and menopause was estimated to take place an average of approximately 1 year earlier in smokers compared with nonsmokers. Results from some of the studies supported the notion that the timing of menopause may be dependent on the amount of cigarettes smoked and/or the duration of smoking. Kinney and colleagues (2006) analyzed longitudinal data from almost 500 women and found that a change in age of menopause was observed only among active smokers who smoked more than 14 cigarettes per day or who had accumulated at least 20 pack-years. Those authors found no association between menopause and previous smoking, even among women who had smoked more than 14 cigarettes per day, smoked more than 10 pack-years, or who had quit smoking within the past decade (Kinney et al. 2006). Similarly, Blanck and colleagues (2004) found that in a study of 874 women, menopause came earliest among current smokers who started smoking in their teens, smoked at least 20 cigarettes per day, smoked for 10 to 19 years, or had at least 10 pack-years. Former smokers and never smokers did not differ in time to menopause, however, even after adjusting for number of term pregnancies and education (Blanck et al. 2004).

In a study of more than 5,500 women, Van Asselt and colleagues (2004) found that although there was a significant association between current smoking and earlier age of menopause (rate ratio = 1.41; 95% CI, 1.32–1.50), there was no association with former smoking (rate ratio = 0.95; 95% CI, 0.89–1.02). The latter was true regardless of the number of years since cessation. In a more recent study of more than 2,000 women, Mikkelsen and colleagues (2007) found that—after adjusting for marital status, education level, social participation, health status, and coffee consumption—women who stopped smoking more than 10 years before menopause were significantly less likely to have an early menopause (<45 years of age) (aOR = 0.13; 95% CI, 0.05–0.36) than women who were current smokers (aOR = 1.59; 95% CI, 1.11–2.28). Finally, in one of the few longitudinal studies of smoking status and

menopause, Hayatbakhsh and colleagues (2012) followed more than 3,500 Australian women and found that women smoking at the 21-year follow-up were 61% more likely to experience menopause before 45 years of age than women who had never smoked (adjusted hazard ratio [HR] = 1.61; 95% CI, 1.27–2.04), even after adjusting for education, ethnicity, BMI, use of oral contraceptives, and gravidity. Those who quit smoking before the 14-year follow-up assessment had a risk of early menopause that was the same as that of never smokers, while those who quit later (between 14 and 21 years of follow-up) may have been at increased risk (HR = 1.36; 95% CI, 0.89–2.07). Among those smoking at the 14-year follow-up, only smoking more than 20 cigarettes per day was significantly associated with early menopause.

Menopause is associated with the exhaustion of the ovarian follicular pool (Vermeulen 1993; Hacker et al. 2015), and it has been hypothesized that smoking could alter the timing of menopause by hastening the decline of ovarian reserves. Evidence for this pathway (Richardson et al. 2014) includes studies demonstrating an increased concentration of follicular-stimulating hormone (FSH) in smokers compared with nonsmokers (Cooper et al. 1995) and a reduced number of oocytes retrieved in IVF cycles in smokers compared with nonsmokers (Zenzes et al. 1997; El-Nemr et al. 1998; Fuentes et al. 2010). The mechanisms underlying the potential effects of tobacco smoke on ovarian reserves are not well understood, but they could include direct effects on gametes or effects on ovarian vascularization (Richardson et al. 2014). A mechanism involving depletion of ovarian reserves would likely result in an irreversible effect on age at menopause.

It has also been hypothesized that antiestrogenic effects of environmental toxicants, such as those found in tobacco smoke, could contribute to earlier age at menopause (Gu et al. 2013). Potential pathways include inhibition of estrogen biosynthesis, induction of the 2-hydroxylation pathway, and competitive binding of estrogen receptors or sex hormone-binding globulin (Baron et al. 1990). Gu and colleagues (2013), who used luteal phase urine samples from 603 premenopausal women in the Nurses' Health Study II to study specific pathways, found lower total estrogen and estrogen metabolites and parent estrogens in current smokers compared with never smokers (with statistically significant differences for estradiol), suggesting that cigarette smoking reduces the biosynthesis of estrogen and induces estrogen metabolism. No differences were seen in levels of individual estrogen metabolites, metabolic pathway groups, or pathway ratios between never and former smokers (most of whom had quit more than 5 years earlier), suggesting that the effects of smoking on estrogen biosynthesis may be reversible. The authors were unable to

examine whether components of tobacco smoke bind estrogen receptors or sex hormone-binding globulin.

Summary of the Evidence

The 2001 Surgeon General's report found that "[w]omen smokers have a younger age at natural menopause than do nonsmokers and may experience more menopausal symptoms" (USDHHS 2001, p. 14). Several papers published since the 2001 report provide additional evidence that active smoking results in earlier age at menopause. Several of these recent papers also examined risk in former smokers and found no evidence of earlier age at menopause, suggesting that the mechanisms through which smoking affects age at menopause are at least partially reversible. However, uncertainty remains regarding the role of the duration and amount of smoking in former smokers, and these variables were categorized differently across studies. Therefore, the evidence is suggestive but not sufficient to conclude that cessation reduces the risk of earlier menopause compared with continued smoking, and uncertainty remains regarding the contributions to the risk of earlier menopause of age at cessation, the number of years smoked, the number of cigarettes smoked per day, and the number of pack-years smoked in former smokers.

Male Reproductive Health

Fertility and Sperm Quality

The 1990 Surgeon General's report found few studies about sperm quality after smoking cessation, and those studies had serious limitations (USDHHS 1990). The 2004 Surgeon General's report concluded that the evidence was inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality, but the evidence did suggest that smokers have decreased semen volume and increased abnormal morphologic forms (USDHHS 2004). The clinical relevance of these findings, however, was uncertain. The 2010 Surgeon General's report, which also reviewed sperm quality and male fertility, noted that studies conducted after the 2004 report strengthened the evidence that smoking affects semen quality and fertility (USDHHS 2010). The 2010 report reviewed potential mechanisms, including alterations in the hormonal milieu, effects on the sperm plasma membrane, and damage to DNA and/or chromosomes in sperm. The report also noted that (a) studies designed to address the timing of exposure in relation to the maturation of sperm cells had not been conducted and (b) the effects of tobacco smoke on spermatogonial stem cells could cause long-term effects that could persist after

smoking cessation, while effects on both epididymal sperm and mature sperm could be reversible (USDHHS 2010). The report also noted that studies examining hormone levels in male smokers and nonsmokers found inconsistent results and variation in how obesity was considered (obesity is associated with the conversion of androgens to estrogen) and in the type of circulating hormones studied (free or bioavailable levels). The report found consistent evidence linking smoking in men to chromosomal changes and DNA damage in sperm, which affects male fertility, pregnancy viability, and anomalies in offspring.

Among the studies published after the 2010 Surgeon General's report was a meta-analysis of 20 studies comprising more than 5,800 men, with the authors' finding that cigarette smoking was associated with reduced sperm count, lower motility, and changes in morphology (Sharma et al. 2016). Elsewhere, in a small study of 136 men that excluded those with known infertility, levels of testosterone, luteinizing hormone, and prolactin were higher in smokers (≥ 5 cigarettes/day) than never smokers, but there were no differences in these measures between former smokers and never smokers (Blanco-Munoz et al. 2012). In another study, Santos and colleagues (2011) evaluated sperm quality after participation in a 3-month smoking cessation program. A man in the study had smoked about 30 cigarettes per day for about 13 years and had secondary infertility. The monitoring found an improvement in his sperm count (from 28.6 to 72.2 million/ejaculate) and motility (32.7% to 78.8%) but no changes in sperm DNA fragmentation, number of germinal cells, or morphology. In addition, the percentage of sperm tails increased with tyrosine-phosphorylated proteins and the number of rapid spermatozoa recuperated after an enrichment technique, suggesting that the transduction signals necessary for proper motility and capacitation were improved. Finally, a study of rats found that both the motility and amount of sperm decreased significantly with exposure to nicotine, and that this was accompanied by reduced fertility; declines were ameliorated by the cessation of nicotine exposure in the male rats (Oyeyipo et al. 2011).

Summary of the Evidence

Little new evidence published since the 2010 Surgeon General's report has addressed whether the effects of smoking on male fertility and sperm quality are reversible with cessation. Therefore, the evidence is inadequate to determine whether smoking cessation reduces the effects of smoking on male fertility and sperm quality.

Erectile Dysfunction

"Erectile dysfunction" (ED) is defined as the persistent inability of a male to attain and maintain an erection

adequate for satisfactory sexual performance (National Institutes of Health Consensus Development Panel on Impotence 1993). Using data from the National Health and Nutrition Examination Survey of 2001–2002, Selvin and colleagues (2007) estimated that 18.4% of U.S. men 20 years of age or older had ED, or 18 million nationwide. Globally, 322 million men may be affected by the year 2025.

The 1990 Surgeon General's report found that smoking may be associated with impaired male sexual performance, but because the data were limited, no conclusions could be drawn regarding the relationships between smoking cessation and sexual performance or the surrogate penile brachial index, which is calculated as the systolic blood pressure in the penis divided by the systolic blood pressure in the arm (USDHHS 1990). The 2014 Surgeon General's report found the evidence sufficient to infer a causal relationship between smoking and ED. This conclusion was on the basis of consistent findings of smoking as a risk factor for ED across both cross-sectional and prospective population-based cohort studies. These studies confirmed the appropriate temporality of the association and evidence of a dose-response relationship between the magnitude of the risk and the level of exposure. Potential mechanisms were also reviewed in the 2014 Surgeon General's report and included the effects of nicotine on the dynamics of blood flow required for erection (nicotine induces vasospasm in the penile arteries); formation of atherosclerotic lesions in the penile arteries; degenerative changes in the penile tissue, such as decreases in smooth muscle, sinusoidal endothelium, nerve fibers and capillaries, and increased collagen density; reduced endothelium-derived production of nitric oxide in the vasculature of the penis; adverse effects on vascular medial elastic fibers; and oxidative injury due to the production of superoxide radicals in the cavernosal smooth muscle cells (USDHHS 2014).

The 2014 Surgeon General's report also addressed smoking cessation, although that report did not draw related conclusions. The report reviewed selected results from two population-based studies (the Vietnam Experience Study of 1985–1986 and the prospective Massachusetts Male Aging Study) against findings that smoking cessation leads to recovery of erectile function (Mannino et al. 1994; Feldman et al. 2000; USDHHS 2014). However, the Massachusetts Male Aging Study, which followed quitters for nearly 9 years, did not show evidence that the incidence of ED was reduced after cessation (Feldman et al. 2000). In that study, however, participants had started smoking at an early age (mean age: 16.6 years) and had a substantial lifetime exposure (mean pack-years: 39.4), so that results could not be generalized to populations with lower levels of tobacco exposure (Feldman et al. 2000). Notably, a separate analysis of the Massachusetts Male Aging Study found that cessation

appeared to protect against the progression of ED but had little effect on remission (Travison et al. 2007).

Experimental studies of the acute effects of short-term smoking cessation reviewed in the 2014 Surgeon General's report show that cessation may result in improvements in erectile function. For example, Glina and colleagues (1988), who monitored intracavernous pressure after pharmacologic stimulation in 12 smokers on a day of abstinence and after smoking two cigarettes, found that all participants obtained an erection on days of abstinence, but only four smokers did so on days of smoking cigarettes (Glina et al. 1988). Later, Sighinolfi and colleagues (2007), who studied 20 chronic smokers with ED using penile color Doppler ultrasonography after pharmacostimulation at baseline and after 24 to 36 hours of abstinence from smoking, also achieved positive results. At baseline, 50% of these smokers had abnormal peak systolic velocity and 75% had abnormal end diastolic velocity, but at 24 to 36 hours, none had abnormal peak systolic velocity and just 15% had abnormal end diastolic velocity. Finally, in a sample of 10 current, long-term smokers, cessation for 24 hours significantly improved nocturnal penile tumescence and rigidity (Guay et al. 1998).

Table 4.38 presents seven cross-sectional studies of risk of ED in former smokers that were not reviewed in the 2014 Surgeon General's report. Six of the seven studies found a higher prevalence of ED among both former and continuing smokers (range in aOR for former smokers relative to never smokers: 1.3–2.15) (Bortolotti et al. 2001; Mirone et al. 2002; Safarinejad 2003; Austoni et al. 2005; Chew et al. 2009), but the associations for both former and current smokers did not reach significance in one study (Shiri et al. 2005). One study reported an aOR of less than 1.0 for former smokers (Lam et al. 2006), but this result was not statistically significant.

In a study of 1,580 men, Chew and colleagues (2009) found that both former and current smokers were at higher risk of ED compared with never smokers (overall aOR = 1.3 and 1.6, respectively, adjusted for age and symptomatic cardiovascular disease, including hypertension, ischemic heart disease, peripheral arterial disease, and stroke), but by age group, associations between former or current smoking and ED were significant only among men 50 years of age and older. Similarly, in a study of 2,010 men, Mirone and colleagues (2002) found that current smokers and former smokers had similar aORs for ED (1.7 and 1.6, respectively, adjusted for age and education); those researchers also found that smoking for more than 20 years increased the odds of ED compared with smoking for 20 years or less (aOR = 1.6 and 1.2, respectively). The increased risk was limited to current and former smokers without chronic medical conditions (aOR = 1.7–2.4 for current smokers without medical conditions, 0.4–1.2 for

Table 4.38 Studies on smoking cessation and erectile dysfunction

Study ^a	Design/population	Reference	Results: Adjusted OR (95% CI)	Comments
Bortolotti et al. (2001)	<ul style="list-style-type: none"> • Cross-sectional • Men with diabetes • n = 9,670 • 1996 • Italy 	Never smokers	<ul style="list-style-type: none"> • Former smokers: 1.5 (1.3–1.6)^b • Current smokers: 1.4 (1.3–1.6)^b 	Former smoker if quit more than 1 year before survey; adjusted for age
Mirone et al. (2002)	<ul style="list-style-type: none"> • Cross-sectional • n = 2,010 • 1996–1997 • Italy 	Never smokers	<ul style="list-style-type: none"> • Former smokers: 1.6 (1.1–2.3)^b • Current smokers: 1.7 (1.2–2.4)^b 	Former smoker if quit more than 1 year before survey; adjusted for age and education
Safarinejad (2003)	<ul style="list-style-type: none"> • Population-based, cross-sectional • Men 20–70 years of age • n = 2,444 • Year: Not reported • Iran 	Never smokers	<ul style="list-style-type: none"> • Former smokers: 2.15 (1.38–3.1)^b • Current smokers: 2.41 (1.52–3.30)^b 	Adjusted for age
Austoni et al. (2005)	<ul style="list-style-type: none"> • Cross-sectional • Men attending free andrologic consultations • n = 16,724 • 2001–2002 • Italy 	Never smokers	<ul style="list-style-type: none"> • Former smokers: <ul style="list-style-type: none"> – Overall: 1.3 (1.2–1.5)^b – Smoked <10 years: 1.0 (0.6–1.7) – Smoked 10–20 years: 1.2 (0.8–1.8) – Smoked >20 years: 2.0 (1.3–2.0)^b • Current smokers: <ul style="list-style-type: none"> – <10 cigarettes/day: 1.0 (0.9–1.2) – ≥10 cigarettes/day: 1.4 (1.2–1.5)^b – Smoked <10 years: 1.1 (0.7–1.6) – Smoked 10–20 years: 1.7 (1.2–2.3)^b – Smoked >20 years: 1.6 (1.3–2.0)^b 	Former smoker if quit more than 1 year before survey; adjusted for age, marital status, education, BMI, physical activity, and chronic diseases
Shiri et al. (2005)	<ul style="list-style-type: none"> • Population-based, cross-sectional analysis within prospective cohort • Men 50, 60, or 70 years of age in 1994 • n = 1,442 • 1994 • Finland 	Never smokers	<ul style="list-style-type: none"> • Former smokers: 1.3 (0.9–1.8) • Current smokers: 1.4 (0.9–2.2) 	Adjusted for age, education, marital status, and alcohol consumption
Lam et al. (2006)	<ul style="list-style-type: none"> • Population-based, cross-sectional • Men 31–60 years of age • n = 819 • 2001 • Hong Kong 	Never smokers	<ul style="list-style-type: none"> • Former smokers: 0.93 (0.60–1.45) • Current smokers: <ul style="list-style-type: none"> – <20 cigarettes/day: 1.02 (0.69–1.51) – ≥20 cigarettes/day: 1.47 (1.00–2.16)^b 	Erectile dysfunction defined as sexual dissatisfaction and/or erectile difficulty; adjusted for age

Table 4.38 Continued

Study ^a	Design/population	Reference	Results: Adjusted OR (95% CI)	Comments
Chew et al. (2009)	<ul style="list-style-type: none"> • Population-based, cross-sectional • n = 1,580 • 2001–2002 • Australia 	Never smokers	<ul style="list-style-type: none"> • Former smokers: <ul style="list-style-type: none"> – Overall: 1.33 (0.95–1.87) – Quit ≤5 years: 1.22 (0.67–2.22) – Quit 6–10 years: 2.26 (1.09–4.70)^b – Quit >10 years: 1.32 (0.92–1.89) – <50 years of age: 1.18 (0.61–2.31) – ≥50 years of age: 2.56 (1.42–4.58)^b • Current smokers: <ul style="list-style-type: none"> – Overall: 1.57 (1.02–2.42)^b – 1–10 cigarettes/day: 1.30 (0.69–2.44) – 11–20 cigarettes/day: 1.69 (0.79–3.64) – >20 cigarettes/day: 1.57 (0.74–3.34) – <50 years of age: 0.82 (0.40–1.69) – ≥50 years of age: 1.47 (0.99–2.18) 	Adjusted for age and symptomatic cardiovascular disease, including hypertension, ischemic heart disease, peripheral arterial disease, and stroke

Notes: **BMI** = body mass index; **CI** = confidence interval; **OR** = odds ratio.

^aMeasure of association adjusted for covariate(s).

^bp <0.05.

current smokers with medical conditions; and aOR = 1.4–1.7 for former smokers without medical conditions, 0.4–1.2 for former smokers with medical conditions). Among former smokers, the risk of ED was not clearly associated with the number of years since cessation.

In a large study with more than 16,000 participants, Austoni and colleagues (2005) found associations between smoking and ED that were similar for current smokers smoking more than 10 cigarettes per day and former smokers compared with never smokers (aOR = 1.4; 95% CI, 1.2–1.5, and aOR = 1.3; 95% CI, 1.2–1.5, respectively, adjusted for age, marital status, education, BMI, physical activity, and chronic diseases). There was no increased risk for men who smoked 10 or fewer cigarettes per day, but the risk of ED increased with duration of smoking for both current and former smokers. When stratified by the presence or absence of medical conditions (hypertension, cardiovascular disease, diabetes, and hypercholesterolemia), aORs were similar for those with and without each condition in former smokers, and all associations were significant except for former smokers with hypercholesterolemia (aOR = 1.2; 95% CI, 0.9–1.6). Earlier, in a sample of nearly 10,000 men with diabetes, Bortolotti and colleagues (2001) found that both former smokers and current smokers had a higher risk of ED relative to never smokers (aOR = 1.5; 95% CI, 1.3–1.6 and aOR = 1.4; 95% CI, 1.3–1.6, respectively, results adjusted for age). Increased time since cessation was not clearly associated with reduced risk of ED among former smokers.

In a prospective study of more than 1,400 men 50–75 years of age, Shiri and colleagues (2005) observed elevated but nonsignificant aORs for ED among former and current smokers at baseline (1.3; 95% CI, 0.9–1.8, and 1.4; 95% CI, 0.9–2.2, respectively, adjusted for age, education, marital status, and alcohol consumption) but did not find a dose-response relationship in current smokers with duration of smoking or in former smokers with the number of years of smoking (not shown in table). In a follow-up survey conducted 5 years later, spontaneous recovery was not significantly associated with being a former smoker (aOR = 0.7; 95% CI, 0.3–1.3). When the sample was limited to men without ED at baseline in 1994, smokers who developed vascular disease by 1999 had a 3-fold greater risk of developing ED by 2004 (adjusted incidence density ratio = 3.1; 95% CI, 1.3–7.5; covariates included age, education, marital status, diabetes, depression, BMI, and alcohol consumption) compared with men who never smoked and did not develop vascular disease (men included in the final model were not specified) (Shiri et al. 2006). In contrast, smokers who did not develop vascular disease did not have an increased risk of ED. Former smokers were not at increased risk for ED, independent of vascular disease. Finally, in a prospective study of almost

300 smokers seeking smoking cessation services who reported having symptoms of ED with onset more than 5 years after initiating smoking, Pourmand and colleagues (2004) found that at 1-year follow-up, ED status improved by at least one grade in 25% of former smokers but such improvement was not observed among continuing smokers (results of statistical testing not presented).

Summary of the Evidence

Cross-sectional studies consistently found that former smokers had an increased prevalence of ED relative to never smokers, and in some instances, prevalence was similar to that of current smokers. In contrast, results of prospective studies were mixed, with some showing no increased risk of ED in former smokers compared with never smokers, and others showing increased risk. Experimental studies of short-term cessation suggest that such cessation is associated with acute improvements in erectile function. Limited data suggest that smoking contributes to ED at least in part through its effects on the risk of vascular disease. Smoking likely has both reversible (such as nicotine-induced vasospasm of penile arteries) and irreversible (such as degenerative tissue changes) effects on erectile function, complicating interpretation of data across different study designs. Changes in risk of ED by duration or intensity of smoking could further complicate the interpretation of data. Therefore, the evidence is inadequate to determine whether smoking cessation reduces the risk of ED compared with continued smoking. The evidence is suggestive but not sufficient to conclude that former smokers are at increased risk of ED compared with never smokers.

Synthesis of the Evidence

Smoking has diverse adverse effects on the reproductive health of females and males. This review has found numerous health benefits of cessation for women and their fetuses and newborns. For males, evidence of the reproductive health benefits (e.g., enhancing sperm quality and functionality, avoiding erectile dysfunction) of cessation is more limited.

Conclusions

1. The evidence is sufficient to infer that smoking cessation by pregnant women benefits their health and that of their fetuses and newborns.
2. The evidence is inadequate to infer that smoking cessation before or during early pregnancy reduces

the risk of placental abruption compared with continued smoking.

3. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of placenta previa compared with continued smoking.
4. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of premature rupture of the membranes compared with continued smoking.
5. The evidence is inadequate to infer that smoking during early or mid-pregnancy alone, and not during late pregnancy, is associated with a reduced risk of preeclampsia.
6. The evidence is sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than those who continue to smoke.
7. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than nonsmokers.
8. The evidence is inadequate to infer that smoking cessation during pregnancy increases the risk of gestational diabetes.
9. The evidence is sufficient to infer that smoking cessation during pregnancy reduces the effects of smoking on fetal growth and that quitting smoking early in pregnancy eliminates the adverse effects of smoking on fetal growth.
10. The evidence is inadequate to determine the gestational age before which smoking cessation should occur to eliminate the effects of smoking on fetal growth.
11. The evidence is sufficient to infer that smoking cessation before or during early pregnancy reduces the risk for a small-for-gestational-age birth compared with continued smoking.
12. The evidence is suggestive but not sufficient to infer that women who quit smoking before conception or during early pregnancy have a reduced risk of preterm delivery compared with women who continue to smoke.
13. The evidence is suggestive but not sufficient to infer that the risk of preterm delivery in women who quit smoking before or during early pregnancy does not differ from that of nonsmokers.
14. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of stillbirth.
15. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of perinatal mortality among smokers.
16. The evidence is inadequate to infer that women who quit smoking before or during early pregnancy have a reduced risk for infant mortality compared with continued smokers.
17. The evidence is inadequate to infer an association between smoking cessation, the timing of cessation, and female fertility or fecundity.
18. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of earlier age at menopause compared with continued smoking.
19. The evidence is inadequate to infer that smoking cessation reduces the effects of smoking on male fertility and sperm quality.
20. The evidence is suggestive but not sufficient to infer that former smokers are at increased risk of erectile dysfunction compared with never smokers.
21. The evidence is inadequate to infer that smoking cessation reduces the risk of erectile dysfunction compared with continued smoking.

Implications

As with previous reports, the evidence presented in this section reaffirms that cigarette smoking cessation before and during pregnancy reduces the adverse effects of smoking on fetal growth, including risk for being small for gestational age and low birth weight. The timing of the cessation and its beneficial effects are consistent with fetal growth patterns, which accelerate during the third trimester; thus, quitting early in pregnancy obviates the birth weight reduction that results from smoking throughout pregnancy. The evidence also suggests that smoking cessation may reduce the risk of other adverse outcomes, including placental abruption, preterm delivery, stillbirth, and early menopause. If smoking cessation reduces the

risk of such pregnancy complications as placental abruption and preterm delivery, then reductions in such downstream outcomes as stillbirths and perinatal and neonatal mortality would also be expected. More research on the timing of cessation with respect to pregnancy onset is needed to determine how to maximize improvements in pregnancy outcomes for women and infants.

Prenatal smoking cessation has substantial health benefits for mothers and offspring, but the evidence summarized in this section also provides some support that selected adverse outcomes might also be increased with smoking cessation. For example, increased gestational weight gain associated with cessation could potentially increase the percentage of women who exceed recommended gestational weight gain and experience associated complications, while simultaneously reducing the

percentage of women with inadequate weight gain. Potential unintended consequences, such as excess weight gain, should be considered when implementing smoking cessation interventions for pregnant women. Such interventions could, for example, incorporate weight management programs for at-risk women.

The evidence related to cessation and reduced fertility in men and women remains mixed and inconclusive, and our understanding of the mechanism(s) underlying these effects is limited, especially for women. Further research is needed to determine whether and when in the life course cessation of smoking needs to occur to benefit female and male fertility. Such evidence is needed so that the appropriate information can be communicated to patients and providers so that interventions can be tailored accordingly.

References¹

- Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2013;170(1):1–7.
- Aberg A, Bergstrand R, Johansson S, Ulvenstam G, Vedin A, Wedel H, Wilhelmsson C, Wilhelmsen L. Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. *British Heart Journal* 1983;49(5):416–22.
- Aboyans V, McClelland RL, Allison MA, McDermott MM, Blumenthal RS, Macura K, Criqui MH. Lower extremity peripheral artery disease in the absence of traditional risk factors. The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 2011;214(1):169–73.
- Abramson MJ, Koplin J, Hoy R, Dharmage SC. Population-wide preventive interventions for reducing the burden of chronic respiratory disease. *International Journal of Tuberculosis and Lung Disease* 2015;19(9):1007–18.
- Abrevaya J. Trends and determinants of second-pregnancy smoking among young-adult mothers who smoked during their first pregnancy. *Nicotine and Tobacco Research* 2008;10(6):951–7.
- Adegboye AR, Rossner S, Neovius M, Lourenco PM, Linde Y. Relationships between prenatal smoking cessation, gestational weight gain and maternal lifestyle characteristics. *Women Birth* 2010;23(1):29–35.
- Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care* 2002;25(5):894–9.
- Agarwal S. The association of active and passive smoking with peripheral arterial disease: results from NHANES 1999–2004. *Angiology* 2009;60(3):335–45.
- Ahmed AA, Patel K, Nyaku MA, Kheirbek RE, Bittner V, Fonarow GC, Filippatos GS, Morgan CJ, Aban IB, Mujib M, et al. Risk of heart failure and death after prolonged smoking cessation: role of amount and duration of prior smoking. *Circulation: Heart Failure* 2015;8(4):694–701.
- Al-Mamgani A, van Rooij PH, Mehilal R, Verduijn GM, Tans L, Kwa SL. Radiotherapy for T1a glottic cancer: the influence of smoking cessation and fractionation schedule of radiotherapy. *European Archives of Otorhinolaryngology* 2014;271(1):125–32.
- Alberg AJ, Worley ML, Tooze JA, Hatcher JL, Carpenter MJ, Day TA, Sullivan CA, Warren GW, Sterba KR, Weaver KE. The validity of self-reported recent smoking in head and neck cancer surgical patients. *Otolaryngology and Head and Neck Surgery* 2015;153(6):990–5.
- Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjoth F, Overvad K, Lip GY, Larsen TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health study. *Chest* 2014;145(3):559–66.
- Alcorn HG, Wolfson SK Jr, Sutton-Tyrrell K, Kuller LH, O’Leary D. Risk factors for abdominal aortic aneurysms in older adults enrolled in The Cardiovascular Health Study. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1996;16(8):963–70.
- Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, Totoki Y, Fujimoto A, Nakagawa H, Shibata T, et al. Mutational signatures associated with tobacco smoking in human cancer. *Science* 2016;354(6312):618–22.
- Althuis MD, Sexton M, Prybylski D. Cigarette smoking and asthma symptom severity among adult asthmatics. *Journal of Asthma* 1999;36(3):257–64.
- Álvarez LR, Balibrea JM, Surinach JM, Coll R, Pascual MT, Toril J, Lopez-Jimenez L, Monreal M. Smoking cessation and outcome in stable outpatients with coronary, cerebrovascular, or peripheral artery disease. *European Journal of Preventive Cardiology* 2013;20(3):486–95.
- Alzamora MT, Fores R, Baena-Diez JM, Pera G, Toran P, Sorribes M, Vicheto M, Reina MD, Sancho A, Albaladejo C, et al. The Peripheral Arterial Disease Study (PERART/ARTPER): prevalence and risk factors in the general population. *BMC Public Health* 2010;10:38.
- Amato M, Frigerio B, Castelnuovo S, Ravani A, Sansaro D, Tremoli E, Squellerio I, Cavalca V, Veglia F, Sirtori CR, et al. Effects of smoking regular or light cigarettes on brachial artery flow-mediated dilation. *Atherosclerosis* 2013;228(1):153–60.
- Ameli FM, Stein M, Provan JL, Prosser R. The effect of postoperative smoking on femoropopliteal bypass grafts. *Annals of Vascular Surgery* 1989;3(1):20–5.
- American Association for Cancer Research. Tobacco and cancer: AACR Tobacco and Cancer Subcommittee, n.d.; <http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/tobacco-and-cancer___F3F578.aspx#.WvWYgn8pCUk>; accessed: May 15, 2018.
- American Cancer Society. What is cervical cancer, December 5, 2016; <<https://www.cancer.org/cancer/cervical-cancer/about/what-is-cervical-cancer.html>>; accessed: October 3, 2017.

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- American Heart Association. Your aorta: the pulse of life, July 31, 2017; <https://www.heart.org/HEARTORG/Conditions/VascularHealth/AorticAneurysm/Your-Aorta-The-Pulse-of-Life_UCM_475411_Article.jsp>; accessed: September 9, 2017.
- American Society of Clinical Oncology. Tobacco cessation tools and resources, n.d.; <<https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control/tobacco-cessation-tools-resources>>; accessed: May 15, 2018.
- Ananth CV, Cnattingius S. Influence of maternal smoking on placental abruption in successive pregnancies: a population-based prospective cohort study in Sweden. *American Journal of Epidemiology* 2007;166(3):289–95.
- Ananth CV, Keyes KM, Hamilton A, Gissler M, Wu C, Liu S, Luque-Fernandez MA, Skjaerven R, Williams MA, Tikkanen M, et al. An international contrast of rates of placental abruption: an age-period-cohort analysis. *PLoS One* 2015;10(5):e0125246.
- Ananth CV, Oyelese Y, Yeo L, Pradhan A, Vintzileos AM. Placental abruption in the United States, 1979 through 2001: temporal trends and potential determinants. *American Journal of Obstetrics and Gynecology* 2005;192(1):191–8.
- Ananth CV, Smulian JC, Demissie K, Vintzileos AM, Knuppel RA. Placental abruption among singleton and twin births in the United States: risk factor profiles. *American Journal of Epidemiology* 2001;153(8):771–8.
- Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. *American Journal of Epidemiology* 2001;153(4):332–7.
- Anderka M, Romitti PA, Sun L, Druschel C, Carmichael S, Shaw G. Patterns of tobacco exposure before and during pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2010;89(4):505–14.
- Andersen MR, Simonsen U, Uldbjerg N, Aalkjaer C, Stender S. Smoking cessation early in pregnancy and birth weight, length, head circumference, and endothelial nitric oxide synthase activity in umbilical and chorionic vessels: an observational study of healthy singleton pregnancies. *Circulation* 2009;119(6):857–64.
- Andres RL, Zhao Y, Klebanoff MA, Hauth JC, Caritis SN, Carey JC, Wapner RJ, Iams JD, Leveno KJ, Miodovnik M, et al. The impact of tobacco use on preterm premature rupture of the membranes. *American Journal of Perinatology* 2013;30(3):185–90.
- Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. The Lung Health Study. *JAMA: the Journal of the American Medical Association* 1994;272(19):1497–505.
- Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *American Journal of Respiratory and Critical Care Medicine* 2002;166(5):675–9.
- Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Annals of Internal Medicine* 2005;142(4):233–9.
- Apostol GG, Jacobs DR Jr, Tsai AW, Crow RS, Williams OD, Townsend MC, Beckett WS. Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. *American Journal of Respiratory and Critical Care Medicine* 2002;166(2):166–72.
- Arias F, Tomich P. Etiology and outcome of low birth weight and preterm infants. *Obstetrics and Gynecology* 1982;60(3):277–81.
- Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *Journal of Vascular Surgery* 2014;60(6):1565–71.
- Artal R, Burgeson R, Fernandez FJ, Hobel CJ. Fetal and maternal copper levels in patients at term with and without premature rupture of membranes. *Obstetrics and Gynecology* 1979;53(5):608–10.
- Ashraf H, Lo P, Shaker SB, de Bruijne M, Dirksen A, Tønnesen P, Dahlbäck M, Pedersen JH. Short-term effect of changes in smoking behaviour on emphysema quantification by CT. *Thorax* 2011;66(1):55–60.
- Asrat T. Intra-amniotic infection in patients with preterm prelabor rupture of membranes. Pathophysiology, detection, and management. *Clinics in Perinatology* 2001;28(4):735–51.
- Asthana A, Johnson HM, Piper ME, Fiore MC, Baker TB, Stein JH. Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. *American Heart Journal* 2010;160(3):458–63.
- Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. *Human Reproduction* 1998;13(6):1532–9.
- Austoni E, Mirone V, Parazzini F, Fasolo CB, Turchi P, Pescatori ES, Ricci E, Gentile V. Smoking as a risk factor for erectile dysfunction: data from the Andrology Prevention Weeks 2001–2002 a study of the Italian Society of Andrology (s.I.a.). *European Urology* 2005;48(5):810–7; discussion 7–8.
- Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. *European Journal of Epidemiology* 2012;27(4):297–304.

- Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. *BJOG* 2013;120(4):456–62.
- Bailey BA. Effectiveness of a pregnancy smoking intervention: the Tennessee Intervention for Pregnant Smokers program. *Health Education and Behavior* 2015;42(6):824–31.
- Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *JAMA: the Journal of the American Medical Association* 1985;253(20):2979–83.
- Bak S, Sindrup SH, Alslev T, Kristensen O, Christensen K, Gaist D. Cessation of smoking after first-ever stroke: a follow-up study. *Stroke* 2002;33(9):2263–9.
- Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Medicine* 2005;2(6):e160.
- Bakker R, Kruithof C, Steegers EA, Tiemeier H, Mackenbach JP, Hofman A, Jaddoe VW. Assessment of maternal smoking status during pregnancy and the associations with neonatal outcomes. *Nicotine and Tobacco Research* 2011;13(12):1250–6.
- Baldassarre D, Castelnuovo S, Frigerio B, Amato M, Werba JP, De Jong A, Ravani AL, Tremoli E, Sirtori CR. Effects of timing and extent of smoking, type of cigarettes, and concomitant risk factors on the association between smoking and subclinical atherosclerosis. *Stroke* 2009;40(6):1991–8.
- Bankier AA, Madani A, Gevenois PA. CT quantification of pulmonary emphysema: assessment of lung structure and function. *Critical Reviews in Computed Tomography* 2002;43(6):399–417.
- Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. *American Journal of Obstetrics and Gynecology* 1990;162(2):502–14.
- Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2013;33(7):1460–7.
- Batech M, Tonstad S, Job JS, Chinnock R, Oshiro B, Allen Merritt T, Page G, Singh PN. Estimating the impact of smoking cessation during pregnancy: the San Bernardino County experience. *Journal of Community Health* 2013;38(5):838–46.
- Batty GD, Kivimaki M, Gray L, Smith GD, Marmot MG, Shipley MJ. Cigarette smoking and site-specific cancer mortality: testing uncertain associations using extended follow-up of the original Whitehall study. *Annals of Oncology* 2008;19(5):996–1002.
- Baughman KL, Hutter AM Jr, DeSanctis RW, Kallman CH. Early discharge following acute myocardial infarction. Long-term follow-up of randomized patients. *Archives of Internal Medicine* 1982;142(5):875–8.
- Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Annals of Internal Medicine* 2003;138(11):891–7.
- Bendermacher BL, Teijink JA, Willigendael EM, Bartelink ML, Peters RJ, de Bie RA, Buller HR, Boiten J, Langenberg M, Prins MH. A clinical prediction model for the presence of peripheral arterial disease—the benefit of screening individuals before initiation of measurement of the ankle-brachial index: an observational study. *Vascular Medicine* 2007;12(1):5–11.
- Benditt J. A primer on reading pulmonary function tests, n.d.; <https://courses.washington.edu/med610/pft/pft_primer.html>; accessed: August 27, 2018.
- Benjamin-Garner R, Stotts A. Impact of smoking exposure change on infant birth weight among a cohort of women in a prenatal smoking cessation study. *Nicotine and Tobacco Research* 2013;15(3):685–92.
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation* 2017;135(10):e146–e603.
- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019;139(10):e56–e528.
- Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tobacco Control* 2013;22(Suppl 1):i14–i17.
- Berg CJ, Park ER, Chang Y, Rigotti NA. Is concern about post-cessation weight gain a barrier to smoking cessation among pregnant women? *Nicotine and Tobacco Research* 2008;10(7):1159–63.
- Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2002;22(10):1668–73.
- Berrick AJ. The tobacco-free generation proposal. *Tobacco Control* 2013;22(Suppl 1):i22–i26.
- Bhak RH, Wininger M, Johnson GR, Lederle FA, Messina LM, Ballard DJ, Wilson SE. Factors associated with small abdominal aortic aneurysm expansion rate. *JAMA Surgery* 2015;150(1):44–50.
- Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke* 2008;39(9):2439–43.
- Bickerstaff M, Beckmann M, Gibbons K, Flenady V. Recent cessation of smoking and its effect on pregnancy

- outcomes. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2012;52(1):54–8.
- Biedermann L, Zeitz J, Mwinyi J, Sutter-Minder E, Rehman A, Ott SJ, Steurer-Stey C, Frei A, Frei P, Scharl M, et al. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 2013;8(3):e59260.
- Bjørnholt SM, Leite M, Albieri V, Kjaer SK, Jensen A. Maternal smoking during pregnancy and risk of stillbirth: results from a nationwide Danish register-based cohort study. *Acta Obstetrica et Gynecologica Scandinavica* 2016;95(11):1305–12.
- Blakely T, Barendregt JJ, Foster RH, Hill S, Atkinson J, Sarfati D, Edwards R. The association of active smoking with multiple cancers: national census-cancer registry cohorts with quantitative bias analysis. *Cancer Causes and Control* 2013;24(6):1243–55.
- Blanchard JF. Epidemiology of abdominal aortic aneurysms. *Epidemiologic Reviews* 1999;21(2):207–21.
- Blanck HM, Marcus M, Tolbert PE, Schuch C, Rubin C, Henderson AK, Zhang RH, Hertzberg VS. Time to menopause in relation to PBBs, PCBs, and smoking. *Maturitas* 2004;49(2):97–106.
- Blanco-Munoz J, Lacasana M, Aguilar-Garduno C. Effect of current tobacco consumption on the male reproductive hormone profile. *Science of the Total Environment* 2012;426:100–5.
- Blann AD, Steele C, McCollum CN. The influence of smoking on soluble adhesion molecules and endothelial cell markers. *Thrombosis Research* 1997;85(5):433–8.
- Blatt K, Moore E, Chen A, Van Hook J, DeFranco EA. Association of reported trimester-specific smoking cessation with fetal growth restriction. *Obstetrics and Gynecology* 2015;125(6):1452–9.
- Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, Kinney M, Lawn J. Born too soon: the global epidemiology of 15 million preterm births. *Reproductive Health* 2013;10(Suppl 1):S2.
- Bond DM, Middleton P, Levett KM, van der Ham DP, Crowther CA, Buchanan SL, Morris J. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD004735. DOI: 10.1002/14651858.CD004735.pub4.
- Borland R. A strategy for controlling the marketing of tobacco products: a regulated market model. *Tobacco Control* 2003;12(4):374–82.
- Borland R. Minimising the harm from nicotine use: finding the right regulatory framework. *Tobacco Control* 2013;22(Suppl 1):i6–i9.
- Bortolotti A, Fedele D, Chatenoud L, Colli E, Coscelli C, Landoni M, Lavezzari M, Santeusano F, Parazzini F. Cigarette smoking: a risk factor for erectile dysfunction in diabetics. *European Urology* 2001;40(4):392–6; discussion 7.
- Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Annals of Oncology* 2012;23(7):1880–8.
- Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA: the Journal of the American Medical Association* 2008;300(23):2765–78.
- Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *American Journal of Epidemiology* 2003;157(3):185–94.
- Bowlin SJ, Medalie JH, Flocke SA, Zyzanski SJ, Goldbourt U. Epidemiology of intermittent claudication in middle-aged men. *American Journal of Epidemiology* 1994;140(5):418–30.
- Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation* 2004;110(1):16–21.
- Brand FN, Larson MG, Kannel WB, McGuirk JM. The occurrence of Raynaud's phenomenon in a general population: the Framingham Study. *Vascular Medicine* 1997;2(4):296–301.
- Breitling LP, Rothenbacher D, Vossen CY, Hahmann H, Wusten B, Brenner H. Validated smoking cessation and prognosis in patients with stable coronary heart disease. *Journal of the American College of Cardiology* 2011a;58(2):196–7.
- Breitling LP, Yang R, Korn B, Burwinkel B, Brenner H. Tobacco-smoking-related differential DNA methylation: 27K discovery and replication. *American Journal of Human Genetics* 2011b;88(4):450–7.
- Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, Lopez-Abente G, Tzonou A, Chang-Claude J, Bolm-Audorff U, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *International Journal of Cancer* 2000;86(2):289–94.
- Brenner H, Gefeller O, Greenland S. Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. *Epidemiology* 1993;4(3):229–36.
- Broekema M, ten Hacken NH, Volbeda F, Lodewijk ME, Hylkema MN, Postma DS, Timens W. Airway epithelial changes in smokers but not in ex-smokers with asthma. *American Journal of Respiratory and Critical Care Medicine* 2009;180(12):1170–8.

- Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. U.K. Small Aneurysm Trial participants. *Annals of Surgery* 1999;230(3):289–96.
- Brunner S, Stecher L, Ziebarth S, Nehring I, Rifas-Shiman SL, Sommer C, Hauner H, von Kries R. Excessive gestational weight gain prior to glucose screening and the risk of gestational diabetes: a meta-analysis. *Diabetologia* 2015;58(10):2229–37.
- Buchholz EM, Beckman AL, Kiefe CI, Krumholz HM. Life years gained from smoking-cessation counseling after myocardial infarction. *American Journal of Preventive Medicine* 2017;52(1):38–46.
- Buckland G, Travier N, Huerta JM, Bueno-de-Mesquita HB, Siersema PD, Skeie G, Weiderpass E, Engeset D, Ericson U, Ohlsson B, et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. *International Journal of Cancer* 2015;137(3):598–606.
- Burchfiel CM, Marcus EB, Curb JD, Maclean CJ, Vollmer WM, Johnson LR, Fong KO, Rodriguez BL, Masaki KH, Buist AS. Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. *American Journal of Respiratory and Critical Care Medicine* 1995;151(6):1778–85.
- Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Haematological prognostic indices after myocardial infarction: evidence from the Diet and Reinfarction Trial (DART). *European Heart Journal* 1992;13(2):166–70.
- Bush T, Lovejoy JC, Deprey M, Carpenter KM. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity* 2016;24(9):1834–41.
- Cacoub P, Cambou JP, Kownator S, Belliard JP, Beregi JP, Branchereau A, Carpentier P, Leger P, Luizy F, Maiza D, et al. Prevalence of peripheral arterial disease in high-risk patients using ankle-brachial index in general practice: a cross-sectional study. *International Journal of Clinical Practice* 2009;63(1):63–70.
- Callard C, Thompson D, Collishaw N. Transforming the tobacco market: why the supply of cigarettes should be transferred from for-profit corporations to non-profit enterprises with a public health mandate. *Tobacco Control* 2005a;14(4):278–83.
- Callard CD, Collishaw NE. Supply-side options for an end-game for the tobacco industry. *Tobacco Control* 2013; 22(Suppl 1):i10–i13.
- Callard CD, Thompson D, Collishaw N. *Curing the addiction to profits: a supply-side approach to phasing out tobacco*. Ottawa (Ontario, Canada): Canadian Centre for Policy Alternatives, 2005b.
- Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, Feigelson HS, Thun MJ. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. *Cancer* 2002;94(9):2490–501.
- Campbell PT, Rebbeck TR, Nishihara R, Beck AH, Begg CB, Bogdanov AA, Cao Y, Coleman HG, Freeman GJ, Heng YJ, et al. Proceedings of the Third International Molecular Pathological Epidemiology (MPE) Meeting. *Cancer Causes and Control* 2017;28(2):167–76.
- Camplain R, Meyer ML, Tanaka H, Palta P, Agarwal SK, Aguilar D, Butler KR, Heiss G. Smoking behaviors and arterial stiffness measured by pulse wave velocity in older adults: the Atherosclerosis Risk in Communities (ARIC) study. *American Journal of Hypertension* 2016;29(11):1268–75.
- Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, Dligach D, Finan S, Gainer V, Shadick NA, Murphy S, et al. Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. *Neurology* 2017;89(13):1408–15.
- Caponnetto P, Russo C, Di Maria A, Morjaria JB, Barton S, Guarino F, Basile E, Proiti M, Bertino G, Cacciola RR, et al. Circulating endothelial-coagulative activation markers after smoking cessation: a 12-month observational study. *European Journal of Clinical Investigation* 2011;41(6):616–26.
- Casanueva E, Polo E, Tejero E, Meza C. Premature rupture of amniotic membranes as functional assessment of vitamin C status during pregnancy. *Annals of the New York Academy of Sciences* 1993;678:369–70.
- Cassar K, Bachoo P. Peripheral arterial disease. *Clinical Evidence* 2006;(15):164–76.
- Cavender JB, Rogers WJ, Fisher LD, Gersh BJ, Coggin CJ, Myers WO. Effects of smoking on survival and morbidity in patients randomized to medical or surgical therapy in the Coronary Artery Surgery Study (CASS): 10-year follow-up. CASS Investigators. *Journal of the American College of Cardiology* 1992;20(2):287–94.
- Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88(5 Pt 1):2149–55.
- Celli BR, MacNee W, Agusti AA, Anzueto A, Berg B, Buist AS, Calverley PM, Chavannes N, Dillard T, Fahy B, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal* 2004;23(6):932–46.
- Centers for Disease and Control Prevention. Ectopic pregnancy—United States, 1990–1992. *Morbidity and Mortality Weekly Report* 1995;44(3):46–8.
- Centers for Disease Control and Prevention. Peripheral arterial disease (PAD) fact sheet, June 16, 2016a;

- <https://www.cdc.gov/dhdsdp/data_statistics/fact_sheets/fs_pad.htm>; accessed: March 18, 2019.
- Centers for Disease Control and Prevention. QuickStats: gestational weight gain among women with full-term, singleton births, compared with recommendations—48 states and the District of Columbia. *Morbidity and Mortality Weekly Report* 2016b;65(40):1121.
- Centers for Disease Control and Prevention. Heart attack, 2017; <https://www.cdc.gov/heartdisease/heart_attack.htm>; accessed: September 9, 2017.
- Centers for Disease Control and Prevention. Coronary artery disease (CAD), August 10, 2015; <https://www.cdc.gov/heartdisease/coronary_ad.htm>; accessed: October 29, 2018.
- Centers for Disease Control and Prevention. *Asthma Stats*, n.d.; <https://www.cdc.gov/asthma/asthma_stats/asthma_stats_factsheet.pdf>; accessed: May 7, 2019.
- Cerveri I, Cazzoletti L, Corsico AG, Marcon A, Niniano R, Grosso A, Ronzoni V, Accordini S, Janson C, Pin I, et al. The impact of cigarette smoking on asthma: a population-based international cohort study. *International Archives of Allergy and Immunology* 2012;158(2):175–83.
- Chaikriangkrai K, Jhun HY, Palamaner Subash Shantha G, Bin Abdulhak A, Sigurdsson G, Nabi F, Mahmarian JJ, Chang SM. Coronary artery calcium score as a predictor for incident stroke: systematic review and meta-analysis. *International Journal of Cardiology* 2017;236:473–7.
- Chaiworapongsa T, Romero R, Espinoza J, Bujold E, Mee Kim Y, Goncalves LF, Gomez R, Edwin S. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of pre-eclampsia. Young Investigator Award. *American Journal of Obstetrics and Gynecology* 2004;190(6):1541–7; discussion 7–50.
- Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;57(3):226–30.
- Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest* 2001;120(6):1917–22.
- Chamberlain C, O'Mara-Eves A, Porter J, Coleman T, Perlen SM, Thomas J, McKenzie JE. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub5.
- Chang JB, Stein TA, Liu JP, Dunn ME. Risk factors associated with rapid growth of small abdominal aortic aneurysms. *Surgery* 1997;121(2):117–22.
- Chao A, Thun MJ, Henley SJ, Jacobs EJ, McCullough ML, Calle EE. Cigarette smoking, use of other tobacco products and stomach cancer mortality in U.S. adults: the Cancer Prevention Study II. *International Journal of Cancer* 2002;101(4):380–9.
- Chao A, Thun MJ, Jacobs EJ, Henley SJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the Cancer Prevention Study II. *Journal of the National Cancer Institute* 2000;92(23):1888–96.
- Charlson ES, Chen J, Custers-Allen R, Bittinger K, Li H, Sinha R, Hwang J, Bushman FD, Collman RG. Disordered microbial communities in the upper respiratory tract of cigarette smokers. *PLoS One* 2010;5(12):e15216.
- Charvat H, Sasazuki S, Inoue M, Iwasaki M, Sawada N, Shimazu T, Yamaji T, Tsugane S, Group JS. Prediction of the 10-year probability of gastric cancer occurrence in the Japanese population: the JPHC Study Cohort II. *International Journal of Cancer* 2016;138(2):320–31.
- Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, McSharry CP, Thomson NC. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *American Journal of Respiratory and Critical Care Medicine* 2006;174(2):127–33.
- Checkley W, Pollard SL, Siddharthan T, Babu GR, Thakur M, Miele CH, Van Schayck OC. Managing threats to respiratory health in urban slums. *Lancet Respiratory Medicine* 2016;4(11):852–4.
- Checkley W, West KP Jr, Wise RA, Baldwin MR, Wu L, LeClerq SC, Christian P, Katz J, Tielsch JM, Khatry S, et al. Maternal vitamin A supplementation and lung function in offspring. *New England Journal of Medicine* 2010;362(19):1784–94.
- Chelland Campbell S, Moffatt RJ, Stamford BA. Smoking and smoking cessation—the relationship between cardiovascular disease and lipoprotein metabolism: a review. *Atherosclerosis* 2008;201(2):225–35.
- Chen J, Jiang R, Garces YI, Jatoi A, Stoddard SM, Sun Z, Marks RS, Liu Y, Yang P. Prognostic factors for limited-stage small cell lung cancer: a study of 284 patients. *Lung Cancer* 2010;67(2):221–6.
- Chen LS, Baker T, Hung RJ, Horton A, Culverhouse R, Hartz S, Saccone N, Cheng I, Deng B, Han Y, et al. Genetic risk can be decreased: quitting smoking decreases and delays lung cancer for smokers with high and low CHRNA5 risk genotypes—a meta-analysis. *EBioMedicine* 2016;11:219–26.
- Chen T, Li W, Wang Y, Xu B, Guo J. Smoking status on outcomes after percutaneous coronary intervention. *Clinical Cardiology* 2012;35(9):570–4.
- Chen ZM, Peto R, Iona A, Guo Y, Chen YP, Bian Z, Yang L, Zhang WY, Lu F, Chen JS, et al. Emerging tobacco-related cancer risks in China: a nationwide, prospective study of 0.5 million adults. *Cancer* 2015;121(Suppl 17):3097–3106.

- Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG, Wu SH. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Medicine* 2013;10(9):e1001515.
- Chew KK, Bremner A, Stuckey B, Earle C, Jamrozik K. Is the relationship between cigarette smoking and male erectile dysfunction independent of cardiovascular disease? Findings from a population-based cross-sectional study. *Journal of Sexual Medicine* 2009;6(1):222–31.
- Chiang CH, Lu CW, Han HC, Hung SH, Lee YH, Yang KC, Huang KC. The relationship of diabetes and smoking status to hepatocellular carcinoma mortality. *Medicine (Baltimore)* 2016;95(6):e2699.
- Choi SH, Terrell JE, Bradford CR, Ghanem T, Spector ME, Wolf GT, Lipkus IM, Duffy SA. Does quitting smoking make a difference among newly diagnosed head and neck cancer patients? *Nicotine and Tobacco Research* 2016;18(12):2216–24.
- Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the etiology of cancers of the digestive tract. *International Journal of Cancer* 1991;49(3):381–6.
- Choi YJ, Park JS, Kim U, Lee SH, Son JW, Shin DG, Kim YJ, Jeong MH, Ahn YK, Cho MC, et al. Changes in smoking behavior and adherence to preventive guidelines among smokers after a heart attack. *Journal of Geriatric Cardiology* 2013;10(2):146–50.
- Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation* 2010;121(6):750–8.
- Chow WH, Daling JR, Weiss NS, Voigt LF. Maternal cigarette smoking and tubal pregnancy. *Obstetrics and Gynecology* 1988;71(2):167–70.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal* 2014;43(2):343–73.
- Clague J, Shao L, Lin J, Chang S, Zhu Y, Wang W, Wood CG, Wu X. Sensitivity to NNKOAc is associated with renal cancer risk. *Carcinogenesis* 2009;30(4):706–10.
- Clair C, Rigotti NA, Porneala B, Fox CS, D’Agostino RB, Pencina MJ, Meigs JB. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA: the Journal of the American Medical Association* 2013;309(10):1014–21.
- Colamesta V, D’Aguanno S, Breccia M, Bruffa S, Cartoni C, La Torre G. Do the smoking intensity and duration, the years since quitting, the methodological quality and the year of publication of the studies affect the results of the meta-analysis on cigarette smoking and acute myeloid leukemia (AML) in adults? *Critical Reviews in Oncology/Hematology* 2016;99:376–88.
- Coleman-Cowger VH, Schauer GL, Peters EN. Marijuana and tobacco co-use among a nationally representative sample of U.S. pregnant and non-pregnant women: 2005–2014 National Survey on Drug Use and Health findings. *Drug and Alcohol Dependence* 2017;177:130–5.
- Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *American Journal of Cardiology* 2013;112(8):1142–7.
- Comeau J, Shaw L, Marcell CC, Lavery JP. Early placenta previa and delivery outcome. *Obstetrics and Gynecology* 1983;61(5):577–80.
- Committee on Practice Bulletins—Obstetrics. *Premature Rupture of Membranes*. Practice Bulletin No. 172. Washington (DC): The American College of Obstetricians and Gynecologists, October 2016.
- Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA: the Journal of the American Medical Association* 2006;295(15):1809–23.
- Conen D, Everett BM, Kurth T, Creager MA, Buring JE, Ridker PM, Pradhan AD. Smoking, smoking cessation, [corrected] and risk for symptomatic peripheral artery disease in women: a cohort study. *Annals of Internal Medicine* 2011;154(11):719–26.
- Coogan PF, Castro-Webb N, Yu J, O’Connor GT, Palmer JR, Rosenberg L. Active and passive smoking and the incidence of asthma in the black women’s health study. *American Journal of Respiratory and Critical Care Medicine* 2015;191(2):168–76.
- Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. *Thorax* 1998;53(10):884–93.
- Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the International BEACON Consortium. *Journal of the National Cancer Institute* 2010;102(17):1344–53.
- Cooper GS, Baird DD, Hulka BS, Weinberg CR, Savitz DA, Hughes CL Jr. Follicle-stimulating hormone concentrations in relation to active and passive smoking. *Obstetrics and Gynecology* 1995;85(3):407–11.
- Cote ML, Colt JS, Schwartz KL, Wacholder S, Ruterbusch JJ, Davis F, Purdue M, Graubard BI, Chow WH. Cigarette smoking and renal cell carcinoma risk among black and white Americans: effect modification by hypertension and obesity. *Cancer Epidemiology, Biomarkers and Prevention* 2012;21(5):770–9.

- Coxson HO. Quantitative computed tomography assessment of airway wall dimensions: current status and potential applications for phenotyping chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society* 2008;5(9):940–5.
- Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A, et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. *Lancet Respiratory Medicine* 2013;1(2):129–36.
- Creasy RK, Resnik R, Iams JD, editors. Placenta previa and abruptio placentae. In: *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia (PA): W.B. Saunders Company, 2004.
- Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA: the Journal of the American Medical Association* 2003;290(1):86–97.
- Croyle RT, Morgan GD, Fiore MC. Addressing a core gap in cancer care—The NCI Moonshot Program to help oncology patients stop smoking. *New England Journal of Medicine* 2019;380(6):512–5.
- Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. *Nature Reviews: Cardiology* 2013;10(4):219–30.
- Cui R, Iso H, Yamagishi K, Tanigawa T, Imano H, Ohira T, Kitamura A, Sato S, Shimamoto T. Relationship of smoking and smoking cessation with ankle-to-arm blood pressure index in elderly Japanese men. *European Journal of Cardiovascular Prevention and Rehabilitation* 2006;13(2):243–8.
- Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *European Urology* 2016;70(3):458–66.
- Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS, editors. Chapter 40: hypertensive disorders. In: *Williams Obstetrics*. 24th ed. New York (NY): McGraw-Hill, 2013:728–79.
- Czernin J, Waldherr C. Cigarette smoking and coronary blood flow. *Progress in Cardiovascular Diseases* 2003;45(5):395–404.
- Dagenais GR, Yi Q, Lonn E, Sleight P, Ostergren J, Yusuf S. Impact of cigarette smoking in high-risk patients participating in a clinical trial. A substudy from the Heart Outcomes Prevention Evaluation (HOPE) trial. *European Journal of Cardiovascular Prevention and Rehabilitation* 2005;12(1):75–81.
- Dahlin S, Gunnerbeck A, Wikstrom AK, Cnattingius S, Edstedt Bonamy AK. Maternal tobacco use and extremely premature birth—a population-based cohort study. *BJOG* 2016;123(12):1938–46.
- Daling JR, Weiss NS, Voigt L, Spadoni LR, Soderstrom R, Moore DE, Stadel BV. Tubal infertility in relation to prior induced abortion. *Fertility and Sterility* 1985;43(3):389–94.
- Daly LE, Mulcahy R, Graham IM, Hickey N. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *British Medical Journal (Clinical Research Ed.)* 1983;287(6388):324–6.
- Daynard RA. Doing the unthinkable (and saving millions of lives). *Tobacco Control* 2009;18(1):2–3.
- de Boer SP, Serruys PW, Valstar G, Lenzen MJ, de Jaegere PJ, Zijlstra F, Boersma E, van Domburg RT. Life-years gained by smoking cessation after percutaneous coronary intervention. *American Journal of Cardiology* 2013;112(9):1311–4.
- Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S, Hedon B, Dechaud H. Effects of cigarette smoking on reproduction. *Human Reproduction Update* 2011;17(1):76–95.
- Dejmek J, Solansky I, Podrazilova K, Sram RJ. The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. *Environmental Health Perspectives* 2002;110(6):601–6.
- Delima SL, McBride RK, Preshaw PM, Heasman PA, Kumar PS. Response of subgingival bacteria to smoking cessation. *Journal of Clinical Microbiology* 2010;48(7):2344–9.
- Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA: the Journal of the American Medical Association* 2012;308(8):796–803.
- DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. *Preventing Chronic Disease* 2014;11:E104.
- Dhariwal J, Tennant RC, Hansell DM, Westwick J, Walker C, Ward SP, Pride N, Barnes PJ, Kon OM, Hansel TT. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. *Chest* 2014;145(5):1006–15.
- Dietz PM, Homa D, England LJ, Burley K, Tong VT, Dube SR, Bernert JT. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. *American Journal of Epidemiology* 2011;173(3):355–9.
- Dobson Amato KA, Hyland A, Reed R, Mahoney MC, Marshall J, Giovino G, Bansal-Travers M, Ochs-Balcom HM, Zevon MA, Cummings KM, et al. Tobacco cessation

- may improve lung cancer patient survival. *Journal of Thoracic Oncology* 2015;10(7):1014–9.
- Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328(7455):1519.
- Doll R, Peto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. *British Journal of Cancer* 2005;92(3):426–9.
- Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;309(6959):901–11.
- Domagala-Kulawik J, Maskey-Warzechowska M, Kraszewska I, Chazan R. The cellular composition and macrophage phenotype in induced sputum in smokers and ex-smokers with COPD. *Chest* 2003;123(4):1054–9.
- Doonan RJ, Hausvater A, Scallan C, Mikhailidis DP, Pilote L, Daskalopoulou SS. The effect of smoking on arterial stiffness. *Hypertension Research* 2010;33(5):398–410.
- Draper D, McGregor J, Hall J, Jones W, Beutz M, Heine RP, Porreco R. Elevated protease activities in human amnion and chorion correlate with preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1995;173(5):1506–12.
- Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. *Seminars in Reproductive Medicine* 2009;27(5):351–7.
- Edjoc RK, Reid RD, Sharma M. The effectiveness of smoking cessation interventions in smokers with cerebrovascular disease: a systematic review. *BMJ Open* 2012;2(6).
- Edjoc RK, Reid RD, Sharma M, Fang J. The prognostic effect of cigarette smoking on stroke severity, disability, length of stay in hospital, and mortality in a cohort with cerebrovascular disease. *Journal of Stroke and Cerebrovascular Diseases* 2013;22(8):e446–e454.
- Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2010;182(5):693–718.
- Ekwo EE, Gosselink CA, Moawad A. Unfavorable outcome in penultimate pregnancy and premature rupture of membranes in successive pregnancy. *Obstetrics and Gynecology* 1992;80(2):166–72.
- Ekwo EE, Gosselink CA, Woolson R, Moawad A. Risks for premature rupture of amniotic membranes. *International Journal of Epidemiology* 1993;22(3):495–503.
- El-Nemr A, Al-Shawaf T, Sabatini L, Wilson C, Lower AM, Grudzinskas JG. Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer. *Human Reproduction* 1998;13(8):2192–8.
- Engel SM, Scher E, Wallenstein S, Savitz DA, Alsaker ER, Trogstad L, Magnus P. Maternal active and passive smoking and hypertensive disorders of pregnancy: risk with trimester-specific exposures. *Epidemiology* 2013;24(3):379–86.
- England L, Zhang J. Smoking and risk of preeclampsia: a systematic review. *Frontiers in Bioscience* 2007;12:2471–83.
- England LJ, Grauman A, Qian C, Wilkins DG, Schisterman EF, Yu KF, Levine RJ. Misclassification of maternal smoking status and its effects on an epidemiologic study of pregnancy outcomes. *Nicotine and Tobacco Research* 2007;9(10):1005–13.
- England LJ, Kendrick JS, Gargiullo PM, Zahniser SC, Hannon WH. Measures of maternal tobacco exposure and infant birth weight at term. *American Journal of Epidemiology* 2001a;153(10):954–60.
- England LJ, Kendrick JS, Wilson HG, Merritt RK, Gargiullo PM, Zahniser SC. Effects of smoking reduction during pregnancy on the birth weight of term infants. *American Journal of Epidemiology* 2001b;154(8):694–701.
- England LJ, Levine RJ, Qian C, Morris CD, Sibai BM, Catalano PM, Curet LB, Klebanoff MA. Smoking before pregnancy and risk of gestational hypertension and preeclampsia. *American Journal of Obstetrics and Gynecology* 2002;186(5):1035–40.
- England LJ, Levine RJ, Qian C, Soule LM, Schisterman EF, Yu KF, Catalano PM. Glucose tolerance and risk of gestational diabetes mellitus in nulliparous women who smoke during pregnancy. *American Journal of Epidemiology* 2004;160(12):1205–13.
- Eom BW, Joo J, Kim S, Shin A, Yang HR, Park J, Choi IJ, Kim YW, Kim J, Nam BH. Prediction model for gastric cancer incidence in Korean population. *PLoS One* 2015;10(7):e0132613.
- Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. *BMC Public Health* 2012;12:102.
- Eskenazi B, Gold EB, Lasley BL, Samuels SJ, Hammond SK, Wight S, O'Neill Rasor M, Hines CJ, Schenker MB. Prospective monitoring of early fetal loss and clinical spontaneous abortion among female semiconductor workers. *American Journal of Industrial Medicine* 1995;28(6):833–46.
- Etter JF. Short-term change in self-reported COPD symptoms after smoking cessation in an internet sample. *European Respiratory Journal* 2010;35(6):1249–55.
- Everatt R, Kuzmickiene I, Virviciute D, Tamosiunas A. Cigarette smoking, educational level and total and site-specific cancer: a cohort study in men in Lithuania. *European Journal of Cancer Prevention* 2014;23(6):579–86.

- Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. *Journal of Maternal-Fetal & Neonatal Medicine* 2003;13(3):175–90.
- Fasting MH, Oien T, Storro O, Nilsen TI, Johnsen R, Vik T. Maternal smoking cessation in early pregnancy and offspring weight status at four years of age. A prospective birth cohort study. *Early Human Development* 2009;85(1):19–24.
- Favaretto AL, Duncan BB, Mengue SS, Nucci LB, Barros EF, Kroeff LR, Vigo A, Schmidt MI. Prenatal weight gain following smoking cessation. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2007;135(2):149–53.
- Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke* 2005;36(12):2773–80.
- Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, McKinlay JB. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Preventive Medicine* 2000;30(4):328–38.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Foley RN, Herzog CA, Collins AJ. Smoking and cardiovascular outcomes in dialysis patients: the United States Renal Data System Wave 2 study. *Kidney International* 2003;63(4):1462–7.
- Fonseca-Moutinho JA. Smoking and cervical cancer. *ISRN Obstetrics and Gynecology* 2011;2011:847684.
- Ford ES. Trends in mortality from COPD among adults in the United States. *Chest* 2015;148(4):962–70.
- Forey BA, Fry JS, Lee PN, Thornton AJ, Coombs KJ. The effect of quitting smoking on HDL-cholesterol—a review based on within-subject changes. *Biomark Research* 2013;1(1):26.
- Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromsø Study, 1994–2001. *Circulation* 2009;119(16):2202–8.
- Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *American Journal of Epidemiology* 1992;135(4):331–40.
- Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382(9901):1329–40.
- Fowler B, Jamrozik K, Norman P, Allen Y. Prevalence of peripheral arterial disease: persistence of excess risk in former smokers. *Australian and New Zealand Journal of Public Health* 2002a;26(3):219–24.
- Fowler B, Jamrozik K, Norman P, Allen Y, Wilkinson E. Improving maximum walking distance in early peripheral arterial disease: randomised controlled trial. *Australian Journal of Physiotherapy* 2002b;48(4):269–75.
- Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *American Journal of Epidemiology* 2007;165(12):1424–33.
- Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA: the Journal of the American Medical Association* 2011;306(7):737–45.
- Fuentes A, Munoz A, Barnhart K, Arguello B, Diaz M, Pommer R. Recent cigarette smoking and assisted reproductive technologies outcome. *Fertility and Sterility* 2010;93(1):89–95.
- Fujino Y, Mizoue T, Tokui N, Kikuchi S, Hoshiyama Y, Toyoshima H, Yatsuya H, Sakata K, Tamakoshi A, Ide R, et al. Cigarette smoking and mortality due to stomach cancer: findings from the JACC Study. *Journal of Epidemiology* 2005;15(Suppl 2):S113–S119.
- Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A. Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature. *Gynecological Endocrinology* 2011;27(8):597–604.
- Galloway MS, Tai E, Rohan EA. Smoking cessation treatment programs offered at hospitals providing oncology services. *Journal of Smoking Cessation* 2019;14(1):65–71.
- Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management in asthmatics? *Patient Education and Counseling* 2003;49(1):91–7.
- Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P. Tobacco smoking and cancer: a meta-analysis. *International Journal of Cancer* 2008;122(1):155–64.
- Gardner AW. The effect of cigarette smoking on exercise capacity in patients with intermittent claudication. *Vascular Medicine* 1996;1(3):181–6.
- Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiology. *Cardiovascular Journal of Africa* 2016;27(2):71–8.

- GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* 2017;389(10082):1885–906.
- Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Archives of Internal Medicine* 2012;172(11):837–44.
- George L, Granath F, Johansson AL, Cnattingius S. Self-reported nicotine exposure and plasma levels of cotinine in early and late pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2006;85(11):1331–7.
- Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. *American Heart Journal* 2011;161(1):145–51.
- Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y. Smoking status and long-term survival after first acute myocardial infarction: a population-based cohort study. *Journal of the American College of Cardiology* 2009;54(25):2382–7.
- Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135(12):e726–e779.
- Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P, Girolami A, Buller HR. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Archives of Internal Medicine* 1999;159(4):337–45.
- Glina S, Reichelt AC, Leao PP, Dos Reis JM. Impact of cigarette smoking on papaverine-induced erection. *Journal of Urology* 1988;140(3):523–4.
- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA: the Journal of the American Medical Association* 2001;285(18):2370–5.
- Godtfredsen NS, Lange P, Prescott E, Osler M, Vestbo J. Changes in smoking habits and risk of asthma: a longitudinal population based study. *European Respiratory Journal* 2001;18(3):549–54.
- Gold EB. The timing of the age at which natural menopause occurs. *Obstetrics and Gynecology Clinics of North America* 2011;38(3):425–40.
- Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology* 2001;153(9):865–74.
- Goldenberg I, Jonas M, Tenenbaum A, Boyko V, Matetzky S, Shotan A, Behar S, Reicher-Reiss H. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Archives of Internal Medicine* 2003;163(19):2301–5.
- Goldstein AO, Ripley-Moffitt CE, Pathman DE, Patsakham KM. Tobacco use treatment at the U.S. National Cancer Institute’s designated cancer centers. *Nicotine and Tobacco Research* 2013;15(1):52–8.
- Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, et al. Association of gestational weight gain with maternal and infant outcomes. *JAMA: the Journal of the American Medical Association* 2017;317(21):2207–25.
- Golzarand M, Toolabi K, Ebrahimi-Mameghani M, Aliasgarzadeh A, Arefhosseini S. Association between modifiable lifestyle factors and inflammatory markers in patients with metabolic syndrome. *Eastern Mediterranean Health Journal* 2012;18(7):735–41.
- Gong J, Hutter C, Baron JA, Berndt S, Caan B, Campbell PT, Casey G, Chan AT, Cotterchio M, Fuchs CS, et al. A pooled analysis of smoking and colorectal cancer: timing of exposure and interactions with environmental factors. *Cancer Epidemiology, Biomarkers and Prevention* 2012;21(11):1974–85.
- Gonzalez CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Simán H, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *International Journal of Cancer* 2003;107(4):629–34.
- Goodman MT, Moriwaki H, Vaeth M, Akiba S, Hayabuchi H, Mabuchi K. Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan. *Epidemiology* 1995;6(1):36–41.
- Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, Kim L, Bibbins-Domingo K, Tindle H, Harris TB, et al. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *American Heart Journal* 2012;164(2):236–42.
- Gotto AM Jr. The Multiple Risk Factor Intervention Trial (MRFIT). A return to a landmark trial. *JAMA: the Journal of the American Medical Association* 1997;277(7):595–7.
- Gram IT, Braaten T, Lund E, Le Marchand L, Weiderpass E. Cigarette smoking and risk of colorectal cancer among Norwegian women. *Cancer Causes and Control* 2009;20(6):895–903.

- Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;57(10):875–9.
- Greenwood DC, Muir KR, Packham CJ, Madeley RJ. Stress, social support, and stopping smoking after myocardial infarction in England. *Journal of Epidemiology and Community Health* 1995;49(6):583–7.
- Gritz ER, Toll BA, Warren GW. Tobacco use in the oncology setting: advancing clinical practice and research. *Cancer Epidemiology, Biomarkers and Prevention* 2014;23(1):3–9.
- Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, Gulsvik A, Bakke PS. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. *European Respiratory Journal* 2009;34(4):858–65.
- Grzeskowiak LE, Hodyl NA, Stark MJ, Morrison JL, Clifton VL. Association of early and late maternal smoking during pregnancy with offspring body mass index at 4 to 5 years of age. *Journal of Developmental Origins of Health and Disease* 2015;6(6):485–92.
- Gu F, Caporaso NE, Schairer C, Fortner RT, Xu X, Hankinson SE, Eliassen AH, Ziegler RG. Urinary concentrations of estrogens and estrogen metabolites and smoking in Caucasian women. *Cancer Epidemiology, Biomarkers and Prevention* 2013;22(1):58–68.
- Guay AT, Perez JB, Heatley GJ. Cessation of smoking rapidly decreases erectile dysfunction. *Endocrine Practice* 1998;4(1):23–6.
- Guida F, Sandanger TM, Castagné R, Campanella G, Polidoro S, Palli D, Krogh V, Tumino R, Sacerdote C, Panico S, et al. Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. *Human Molecular Genetics* 2015;24(8):2349–59.
- Guo W, Blot WJ, Li JY, Taylor PR, Liu BQ, Wang W, Wu YP, Zheng W, Dawsey SM, Li B, et al. A nested case-control study of oesophageal and stomach cancers in the Linxian Nutrition Intervention Trial. *International Journal of Epidemiology* 1994;23(3):444–50.
- Gupta R, Gupta KD, Sharma S, Gupta VP. Influence of cessation of smoking on long term mortality in patients with coronary heart disease. *Indian Heart Journal* 1993;45(2):125–9.
- Hacker NF, Gambone JC, Hobel CJ. *Hacker & Moore's Essentials of Obstetrics and Gynecology*. 6th ed. Philadelphia (PA): Elsevier, 2015.
- Hadley CB, Main DM, Gabbe SG. Risk factors for preterm premature rupture of the fetal membranes. *American Journal of Perinatology* 1990;7(4):374–9.
- Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac arrest. *New England Journal of Medicine* 1986;314(5):271–5.
- Halvorsen B, Lund Sagen E, Ueland T, Aukrust P, Tonstad S. Effect of smoking cessation on markers of inflammation and endothelial cell activation among individuals with high risk for cardiovascular disease. *Scandinavian Journal of Clinical and Laboratory Investigation* 2007;67(6):604–11.
- Hammal F, Ezekowitz JA, Norris CM, Wild TC, Finegan BA. Smoking status and survival: impact on mortality of continuing to smoke one year after the angiographic diagnosis of coronary artery disease, a prospective cohort study. *BMC Cardiovascular Disorders* 2014;14:133.
- Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, Criner GJ, Kim V, Bowler RP, Hanania NA, et al. Chronic obstructive pulmonary disease exacerbations in the COPD Gene study: associated radiologic phenotypes. *Radiology* 2011;261(1):274–82.
- Hannan LM, Jacobs EJ, Thun MJ. The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. *Cancer Epidemiology, Biomarkers and Prevention* 2009;18(12):3362–7.
- Hansen K, Ostling G, Persson M, Nilsson PM, Melander O, Engstrom G, Hedblad B, Rosvall M. The effect of smoking on carotid intima-media thickness progression rate and rate of lumen diameter reduction. *European Journal of Internal Medicine* 2016;28:74–9.
- Harger JH, Hsing AW, Tuomala RE, Gibbs RS, Mead PB, Eschenbach DA, Knox GE, Polk BF. Risk factors for preterm premature rupture of fetal membranes: a multicenter case-control study. *American Journal of Obstetrics and Gynecology* 1990;163(1 Pt 1):130–7.
- Hartge P, Silverman D, Hoover R, Schairer C, Altman R, Austin D, Cantor K, Child M, Key C, Marrett LD, et al. Changing cigarette habits and bladder cancer risk: a case-control study. *Journal of the National Cancer Institute* 1987;78(6):1119–25.
- Hasdai D, Garratt KN, Grill DE, Lerman A, Holmes DR Jr. Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularization. *New England Journal of Medicine* 1997;336(11):755–61.
- Hassan MM, Spitz MR, Thomas MB, El-Deeb AS, Glover KY, Nguyen NT, Chan W, Kaseb A, Curley SA, Vauthey JN, et al. Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *International Journal of Cancer* 2008;123(8):1883–91.
- Hastie CE, Haw S, Pell JP. Impact of smoking cessation and lifetime exposure on C-reactive protein. *Nicotine and Tobacco Research* 2008;10(4):637–42.

- Hatsukami DK. Ending tobacco-caused mortality and morbidity: the case for performance standards for tobacco products. *Tobacco Control* 2013;22(Suppl 1):i36–i37.
- Hatsukami DK, Benowitz NL, Donny E, Henningfield J, Zeller M. Nicotine reduction: strategic research plan. *Nicotine and Tobacco Research* 2013;15(6):1003–13.
- Hatsukami DK, Perkins KA, Lesage MG, Ashley DL, Henningfield JE, Benowitz NL, Backinger CL, Zeller M. Nicotine reduction revisited: science and future directions. *Tobacco Control* 2010;19(5):e1–e10.
- Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorrhology. *Journal of Internal Medicine* 2002;252(2):130–9.
- Hayatbakhsh MR, Clavarino A, Williams GM, Sina M, Najman JM. Cigarette smoking and age of menopause: a large prospective study. *Maturitas* 2012;72(4):346–52.
- Hayes C, Kearney M, O'Carroll H, Zgaga L, Geary M, Kelleher C. Patterns smoking behaviour in low-income pregnant women: a cohort study of differential effects on infant birth weight. *International Journal of Environmental Research and Public Health* 2016;13(11).
- He C, Murabito JM. Genome-wide association studies of age at menarche and age at natural menopause. *Molecular and Cellular Endocrinology* 2014;382(1):767–79.
- He Y, Jiang B, Li LS, Li LS, Sun DL, Wu L, Liu M, He SF, Liang BQ, Hu FB, et al. Changes in smoking behavior and subsequent mortality risk during a 35-year follow-up of a cohort in Xi'an, China. *American Journal of Epidemiology* 2014;179(9):1060–70.
- He Y, Jiang Y, Wang J, Fan L, Li X, Hu FB. Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China. *Journal of Vascular Surgery* 2006;44(2):333–8.
- Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis* 2006;189(1):61–9.
- Hecht SS. Lung carcinogenesis by tobacco smoke. *International Journal of Cancer* 2012;131(12):2724–32.
- Heffner LJ, Sherman CB, Speizer FE, Weiss ST. Clinical and environmental predictors of preterm labor. *Obstetrics and Gynecology* 1993;81(5 Pt 1):750–7.
- Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circulation: Heart Failure* 2013;6(3):606–19.
- Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;123(8):933–44.
- Heinonen S, Saarikoski S. Reproductive risk factors of fetal asphyxia at delivery: a population based analysis. *Journal of Clinical Epidemiology* 2001;54(4):407–10.
- Helmerson J, Larsson A, Vessby B, Basu S. Active smoking and a history of smoking are associated with enhanced prostaglandin F₂(alpha), interleukin-6 and F₂-isoprostane formation in elderly men. *Atherosclerosis* 2005;181(1):201–7.
- Herlitz J, Bengtson A, Hjalmarson A, Karlson BW. Smoking habits in consecutive patients with acute myocardial infarction: prognosis in relation to other risk indicators and to whether or not they quit smoking. *Cardiology* 1995;86(6):496–502.
- Hermanson B, Omenn GS, Kronmal RA, Gersh BJ. Beneficial six-year outcome of smoking cessation in older men and women with coronary artery disease. Results from the CASS registry. *New England Journal of Medicine* 1988;319(21):1365–9.
- Himes SK, Stroud LR, Scheidweiler KB, Niaura RS, Huestis MA. Prenatal tobacco exposure, biomarkers for tobacco in meconium, and neonatal growth outcomes. *Journal of Pediatrics* 2013;162(5):970–5.
- Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA: the Journal of the American Medical Association* 2001;286(11):1317–24.
- Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, et al. Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery. *Journal of the American College of Cardiology* 2006;47(6):1239–312.
- Hisamatsu T, Miura K, Arima H, Kadota A, Kadowaki S, Torii S, Suzuki S, Miyagawa N, Sato A, Yamazoe M, et al. Smoking, smoking cessation, and measures of subclinical atherosclerosis in multiple vascular beds in Japanese men. *Journal of the American Heart Association* 2016;5(9).
- Hjermann I, Holme I, Leren P. Oslo Study Diet and Antismoking Trial. Results after 102 months. *American Journal of Medicine* 1986;80(2A):7–11.
- Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *Lancet* 1981;2(8259):1303–10.

- Hladky K, Yankowitz J, Hansen WF. Placental abruption. *Obstetrical and Gynecological Survey* 2002;57(5):299–305.
- Hlaing TM, Wang YS, Chen S-M, Wang J-S. The high resolution computed tomography in assessment of patients with emphysema following smoking cessation. *Journal of Internal Medicine of Taiwan* 2015;26:107–14.
- Hoesein FAAM, Zanen P, de Jong PA, van Ginneken B, Boezen HM, Groen HJ, Oudkerk M, de Koning HJ, Postma DS, Lammers JW. Rate of progression of CT-quantified emphysema in male current and ex-smokers: a follow-up study. *Respiratory Research* 2013;14:55.
- Högberg L, Cnattingius S. The influence of maternal smoking habits on the risk of subsequent stillbirth: is there a causal relation? *BJOG* 2007;114(6):699–704.
- Holm M, Omenaas E, Gíslason T, Svanes C, Jögi R, Norrman E, Janson C, Torén K. Remission of asthma: a prospective longitudinal study from northern Europe (RHINE study). *European Respiratory Journal* 2007;30(1):62–5.
- Holme I, Retterstol K, Norum KR, Hjermann I. Lifelong benefits on myocardial infarction mortality: 40-year follow-up of the randomized Oslo diet and antismoking study. *Journal of Internal Medicine* 2016;280(2):221–7.
- Hooi JD, Stoffers HE, Kester AD, Rinkens PE, Kaiser V, van Ree JW, Knottnerus JA. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. *Scandinavian Journal of Primary Health Care* 1998;16(3):177–82.
- Hosokawa S, Hiasa Y, Miyazaki S, Ogura R, Miyajima H, Ohara Y, Yuba K, Suzuki N, Takahashi T, Kishi K, et al. Effects of smoking cessation on coronary endothelial function in patients with recent myocardial infarction. *International Journal of Cardiology* 2008;128(1):48–52.
- Hotham ED, Atkinson ER, Gilbert AL. Focus groups with pregnant smokers: barriers to cessation, attitudes to nicotine patch use and perceptions of cessation counselling by care providers. *Drug and Alcohol Review* 2002;21(2):163–8.
- Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *British Medical Journal (Clinical Research Ed.)* 1985;290(6483):1697–700.
- Hrubá D, Kachlik P. Influence of maternal active and passive smoking during pregnancy on birthweight in newborns. *Central European Journal of Public Health* 2000;8(4):249–52.
- Hu FB, Stampfer MJ, Manson JE, Grodstein F, Colditz GA, Speizer FE, Willett WC. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *New England Journal of Medicine* 2000;343(8):530–7.
- Hu J, Ugnat AM, Canadian Cancer Registries Epidemiology Research Group. Active and passive smoking and risk of renal cell carcinoma in Canada. *European Journal of Cancer* 2005;41(5):770–8.
- Huang B, Svensson P, Arnlov J, Sundstrom J, Lind L, Ingelsson E. Effects of cigarette smoking on cardiovascular-related protein profiles in two community-based cohort studies. *Atherosclerosis* 2016;254:52–8.
- Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, Woyke T, Allgaier M, Bristow J, Wiener-Kronish JP, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *Journal of Allergy and Clinical Immunology* 2011;127(2):372–81, e1–e3.
- Hughes EG, Brennan BG. Does cigarette smoking impair natural or assisted fecundity? *Fertility and Sterility* 1996;66(5):679–89.
- Hughson WG, Mann JI, Tibbs DJ, Woods HF, Walton I. Intermittent claudication: factors determining outcome. *British Medical Journal* 1978;1(6124):1377–9.
- Hulman A, Lutsiv O, Park CK, Krebs L, Beyene J, McDonald SD. Are women who quit smoking at high risk of excess weight gain throughout pregnancy? *BMC Pregnancy and Childbirth* 2016;16:263.
- Hunter KA, Garlick PJ, Broom I, Anderson SE, McNurlan MA. Effects of smoking and abstention from smoking on fibrinogen synthesis in humans. *Clinical Science* 2001;100(4):459–65.
- Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, Feuer EJ. Trends in esophageal adenocarcinoma incidence and mortality. *Cancer* 2013;119(6):1149–58.
- Hurley SF. Short-term impact of smoking cessation on myocardial infarction and stroke hospitalisations and costs in Australia. *Medical Journal of Australia* 2005;183(1):13–7.
- Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;378(9799):1297–305.
- Huxley RR, Yatsuya H, Lutsey PL, Woodward M, Alonso A, Folsom AR. Impact of age at smoking initiation, dosage, and time since quitting on cardiovascular disease in African Americans and Whites: the atherosclerosis risk in communities study. *American Journal of Epidemiology* 2012;175(8):816–26.
- Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine* 2008;358(19):1991–2002.
- Ingolfsson IO, Sigurdsson G, Sigvaldason H, Thorgeirsson G, Sigfusson N. A marked decline in the prevalence and incidence of intermittent claudication in Icelandic men 1968–1986: a strong relationship to smoking and

- serum cholesterol—the Reykjavik Study. *Journal of Clinical Epidemiology* 1994;47(11):1237–43.
- Institute of Medicine. *Nutrition During Pregnancy: Part I Weight Gain and Part II Nutrient Supplements*. Washington (DC): National Academy Press, 1990.
- Institute of Medicine and the National Research Council. *Weight Gain During Pregnancy: Re-Examining the Guidelines*. Washington (DC): National Academies Press, 2009.
- International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking*. Vol. 83. Lyon (France): International Agency for Research on Cancer, 2004.
- International Agency for Research on Cancer. *Tobacco Control: Reversal of Risk After Quitting Smoking*. IARC Handbooks of Cancer Prevention, Volume 11. Lyon (France): IARC Press, 2007.
- International Agency for Research on Cancer. *Personal Habits and Indoor Combustions*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100E. Lyon (France): IARC Press, 2012.
- International Association for the Study of Lung Cancer. Patient resources: tobacco cessation, n.d.; <<https://www.iaslc.org/patient-resources/tobacco-cessation-0>>; accessed: May 15, 2018.
- International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodill A, Green J, Peto J, Plummer M, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *International Journal of Cancer* 2006;118(6):1481–95.
- Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbeck's Archives of Surgery* 2008;393(4):535–45.
- Ito JT, Ramos D, Lima FF, Rodrigues FM, Gomes PR, Moreira GL, Macchione M, Toledo AC, Ramos EM. Nasal mucociliary clearance in subjects with COPD after smoking cessation. *Respiratory Care* 2015;60(3):399–405.
- Ito K, Yamamura S, Essilfie-Quaye S, Cosio B, Ito M, Barnes PJ, Adcock IM. Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-kappaB suppression. *Journal of Experimental Medicine* 2006;203(1):7–13.
- Iyasu S, Saftlas AK, Rowley DL, Koonin LM, Lawson HW, Atrash HK. The epidemiology of placenta previa in the United States, 1979 through 1987. *American Journal of Obstetrics and Gynecology* 1993;168(5):1424–9.
- Jääskeläinen T, Suomalainen-König S, Hämäläinen E, Pulkki K, Romppanen J, Heinonen S, Laivuori H. Angiogenic profile and smoking in the Finnish Genetics of Pre-Eclampsia Consortium (FINNPEC) cohort. *Annals of Medicine* 2017;49(7):593–602.
- Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. *Resuscitation* 2004;63(3):233–49.
- Jacobsen UK, Dige-Pedersen H, Gyntelberg F, Svendsen UG. “Risk factors” and manifestations of arteriosclerosis in patients with intermittent claudication compared to normal persons. *Danish Medical Bulletin* 1984;31(2):145–8.
- Jang AS, Park SW, Kim DJ, Uh S, Kim YH, Whang HG, Lim GI, Park CS. Effects of smoking cessation on airflow obstruction and quality of life in asthmatic smokers. *Allergy, Asthma & Immunology Research* 2010;2(4):254–9.
- Jayalekshmi PA, Hassani S, Nandakumar A, Koriyama C, Sebastian P, Akiba S. Gastric cancer risk in relation to tobacco use and alcohol drinking in Kerala, India—Karunagappally cohort study. *World Journal of Gastroenterology* 2015;21(44):12676–85.
- Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS. Smoking and cancer risk in Korean men and women. *Cancer Causes and Control* 2004;15(4):341–8.
- Jensen SA, Vatten LJ, Nilsen TI, Romundstad PR, Myhre HO. The association between smoking and the prevalence of intermittent claudication. *Vascular Medicine* 2005;10(4):257–63.
- Jeyabalan A, Powers RW, Durica AR, Harger GF, Roberts JM, Ness RB. Cigarette smoke exposure and angiogenic factors in pregnancy and preeclampsia. *American Journal of Hypertension* 2008;21(8):943–7.
- Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *New England Journal of Medicine* 2013;368(4):341–50.
- Jiang CQ, Xu L, Lam TH, Lin JM, Cheng KK, Thomas GN. Smoking cessation and carotid atherosclerosis: the Guangzhou Biobank Cohort Study—CVD. *Journal of Epidemiology and Community Health* 2010;64(11):1004–9.
- Jiang X, Castela JE, Yuan JM, Stern MC, Conti DV, Cortessis VK, Pike MC, Gago-Dominguez M. Cigarette smoking and subtypes of bladder cancer. *International Journal of Cancer* 2012;130(4):896–901.
- Jim B, Karumanchi SA. Preeclampsia: pathogenesis, prevention, and long-term complications. *Seminars in Nephrology* 2017;37(4):386–97.

- Jöckel KH, Lehmann N, Jaeger BR, Moebus S, Möhlenkamp S, Schermund A, Dragano N, Stang A, Gronemeyer D, Seibel R, et al. Smoking cessation and subclinical atherosclerosis—results from the Heinz Nixdorf Recall Study. *Atherosclerosis* 2009;203(1):221–7.
- Johansson AL, Dickman PW, Kramer MS, Cnattingius S. Maternal smoking and infant mortality: does quitting smoking reduce the risk of infant death? *Epidemiology* 2009;20(4):590–7.
- Johansson S, Bergstrand R, Pennert K, Ulvenstam G, Vedin A, Wedel H, Wilhelmsson C, Wilhelmsen L, Aberg A. Cessation of smoking after myocardial infarction in women. Effects on mortality and reinfarctions. *American Journal of Epidemiology* 1985;121(6):823–31.
- Johnson HM, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, Baker TB, Fiore MC, Stein JH. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *Journal of the American College of Cardiology* 2010;55(18):1988–95.
- Jonason T, Ringqvist I. Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication. *Acta Medica Scandinavica* 1985;218(1):27–33.
- Josephs L, Culliford D, Johnson M, Thomas M. Improved outcomes in ex-smokers with COPD: a UK primary care observational cohort study. *European Respiratory Journal* 2017;49(5).
- Juarez SP, Merlo J. Revisiting the effect of maternal smoking during pregnancy on offspring birthweight: a quasi-experimental sibling analysis in Sweden. *PLoS One* 2013;8(4):e61734.
- Kabir Z, Clarke V, Conroy R, McNamee E, Daly S, Clancy L. Low birthweight and preterm birth rates 1 year before and after the Irish workplace smoking ban. *BJOG* 2009;116(13):1782–7.
- Kalandidi A, Doulgerakis M, Tzonou A, Hsieh CC, Aravandinos D, Trichopoulos D. Induced abortions, contraceptive practices, and tobacco smoking as risk factors for ectopic pregnancy in Athens, Greece. *British Journal of Obstetrics and Gynaecology* 1991;98(2):207–13.
- Kane EV, Roman E, Cartwright R, Parker J, Morgan G. Tobacco and the risk of acute leukaemia in adults. *British Journal of Cancer* 1999;81(7):1228–33.
- Karaer A, Avsar FA, Batioglu S. Risk factors for ectopic pregnancy: a case-control study. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2006;46(6):521–7.
- Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, Ezzati M, Bhutta ZA, Marchant T, Willey BA, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *Lancet* 2013;382(9890):417–25.
- Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *JAMA: the Journal of the American Medical Association* 1993;269(2):232–6.
- Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. *JAMA: the Journal of the American Medical Association* 2008;299(17):2037–47.
- Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, Burke GL, Enright P, Cushman M. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Archives of Internal Medicine* 2005;165(16):1896–902.
- Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC, Greco G. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *Journal of Vascular Surgery* 2010;52(3):539–48.
- Kharkova OA, Grjibovski AM, Krettek A, Nieboer E, Odland JO. First-trimester smoking cessation in pregnancy did not increase the risk of preeclampsia/eclampsia: A Murmansk County Birth Registry study. *PLoS One* 2017;12(8):e0179354.
- Khoo D, Chiam Y, Ng P, Berrick AJ, Koong HN. Phasing-out tobacco: proposal to deny access to tobacco for those born from 2000. *Tobacco Control* 2010;19(5):355–60.
- Khuri FR, Kim ES, Lee JJ, Winn RJ, Benner SE, Lippman SM, Fu KK, Cooper JS, Vokes EE, Chamberlain RM, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. *Cancer Epidemiology, Biomarkers and Prevention* 2001;10(8):823–9.
- Kianoush S, Yakoob MY, Al-Rifai M, DeFilippis AP, Bittencourt MS, Duncan BB, Bensenor IM, Bhatnagar A, Lotufo PA, Blaha MJ. Associations of cigarette smoking with subclinical inflammation and atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health). *JAMA: the Journal of the American Medical Association* 2017;6(6).
- Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, Poewe W, Willeit J. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke* 2002;33(9):2170–6.
- Kiilholma P, Gronroos M, Erkkola R, Pakarinen P, Nanto V. The role of calcium, copper, iron and zinc in preterm delivery and premature rupture of fetal membranes. *Gynecologic and Obstetric Investigation* 1984;17(4):194–201.
- Kim CK, Kim BJ, Ryu WS, Lee SH, Yoon BW. Impact of smoking cessation on the risk of subarachnoid

- haemorrhage: a nationwide multicentre case control study. *Journal of Neurology, Neurosurgery and Psychiatry* 2012a;83(11):1100–3.
- Kim J, Gall SL, Dewey HM, Macdonell RA, Sturm JW, Thrift AG. Baseline smoking status and the long-term risk of death or nonfatal vascular event in people with stroke: a 10-year survival analysis. *Stroke* 2012b;43(12):3173–8.
- Kim Y, Shin A, Gwack J, Jun JK, Park SK, Kang D, Shin HR, Chang SH, Yoo KY. [Cigarette smoking and gastric cancer risk in a community-based cohort study in Korea]. *Journal of Preventive Medicine and Public Health. Yebang Uihakhoe Chi* 2007;40(6):467–74.
- King CC, Piper ME, Gepner AD, Fiore MC, Baker TB, Stein JH. Longitudinal impact of smoking and smoking cessation on inflammatory markers of cardiovascular disease risk. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2017;37(2):374–9.
- King ML, Williams MA, Fletcher GF, Gordon NF, Gulanick M, King CN, Leon AS, Levine BD, Costa F, Wenger NK. Medical director responsibilities for outpatient cardiac rehabilitation/secondary prevention programs: a scientific statement from the American Heart Association/American Association for Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2005;112(21):3354–60.
- Kinjo K, Sato H, Sakata Y, Nakatani D, Mizuno H, Shimizu M, Sasaki T, Kijima Y, Nishino M, Uematsu M, et al. Impact of smoking status on long-term mortality in patients with acute myocardial infarction. *Circulation Journal* 2005;69(1):7–12.
- Kinney A, Kline J, Levin B. Alcohol, caffeine and smoking in relation to age at menopause. *Maturitas* 2006;54(1):27–38.
- Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, Giordano D, Cecatti JG, Abdel Aleem H, Talegawkar SA, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Medicine* 2017;14(1):e1002220.
- Kishore U, Greenhough TJ, Waters P, Shrive AK, Ghai R, Kamran MF, Bernal AL, Reid KB, Madan T, Chakraborty T. Surfactant proteins SP-A and SP-D: structure, function and receptors. *Molecular Immunology* 2006;43(9):1293–315.
- Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, Jauch E, Moomaw CJ, Shukla R, Gebel J, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke* 2002;33(5):1321–6.
- Klein-Weigel P, Volz TS, Zange L, Richter J. Buerger's disease: providing integrated care. *Journal of Multidisciplinary Healthcare* 2016;9:511–8.
- Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: final data for 2014. *National Vital Statistics Reports* 2016;65(4):1–122.
- Kohansal R, Martinez-Cambor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *American Journal of Respiratory and Critical Care Medicine* 2009;180(1):3–10.
- Koizumi Y, Tsubono Y, Nakaya N, Kuriyama S, Shibuya D, Matsuoka H, Tsuji I. Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan. *International Journal of Cancer* 2004;112(6):1049–55.
- Kondo T, Hayashi M, Takeshita K, Numaguchi Y, Kobayashi K, Iino S, Inden Y, Murohara T. Smoking cessation rapidly increases circulating progenitor cells in peripheral blood in chronic smokers. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2004;24(8):1442–7.
- Kondo T, Osugi S, Shimokata K, Honjo H, Morita Y, Maeda K, Yamashita K, Muramatsu T, Shintani S, Matsushita K, et al. Smoking and smoking cessation in relation to all-cause mortality and cardiovascular events in 25,464 healthy male Japanese workers. *Circulation Journal* 2011;75(12):2885–92.
- Koole D, Moll FL, Buth J, Hobo R, Zandvoort H, Pasterkamp G, van Herwaarden JA. The influence of smoking on endovascular abdominal aortic aneurysm repair. *Journal of Vascular Surgery* 2012;55(6):1581–6.
- Kovac JR, Khanna A, Lipshultz LI. The effects of cigarette smoking on male fertility. *Postgraduate Medicine* 2015;127(3):338–41.
- Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes and Control* 1993;4(2):101–10.
- Kröger K, Dragano N, Stang A, Moebus S, Möhlenkamp S, Mann K, Siegrist J, Jöckel KH, Erbel R. An unequal social distribution of peripheral arterial disease and the possible explanations: results from a population-based study. *Vascular Medicine* 2009;14(4):289–96.
- Kurki T, Sivonen A, Renkonen OV, Savia E, Ylikorkala O. Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstetrics and Gynecology* 1992;80(2):173–7.
- Kurosawa M, Kikuchi S, Xu J, Inaba Y. Highly salted food and mountain herbs elevate the risk for stomach cancer death in a rural area of Japan. *Journal of Gastroenterology and Hepatology* 2006;21(11):1681–6.
- Kurth T, Kase CS, Berger K, Gaziano JM, Cook NR, Buring JE. Smoking and risk of hemorrhagic stroke in women. *Stroke* 2003a;34(12):2792–5.
- Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. *Stroke* 2003b;34(5):1151–5.
- Kvalvik LG, Haug K, Klungsoy K, Morken NH, DeRoo LA, Skjaerven R. Maternal smoking status in successive pregnancies and risk of having a small for gestational

- age infant. *Paediatric and Perinatal Epidemiology* 2017;31(1):21–8.
- Kweon SS, Lee YH, Shin MH, Choi JS, Rhee JA, Choi SW, Ryu SY, Kim BH, Nam HS, Jeong SK, et al. Effects of cumulative smoking exposure and duration of smoking cessation on carotid artery structure. *Circulation Journal* 2012;76(8):2041–7.
- Kwon Y, Norby FL, Jensen PN, Agarwal SK, Soliman EZ, Lip GY, Longstreth WT Jr, Alonso A, Heckbert SR, Chen LY. Association of smoking, alcohol, and obesity with cardiovascular death and ischemic stroke in atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS). *PLoS One* 2016;11(1):e0147065.
- Kyrklund-Blomberg NB, Gennser G, Cnattingius S. Placental abruption and perinatal death. *Paediatric and Perinatal Epidemiology* 2001;15(3):290–7.
- La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Smoking and renal cell carcinoma. *Cancer Research* 1990;50(17):5231–3.
- Lakshmanan R, Hyde Z, Jamrozik K, Hankey GJ, Norman PE. Population-based observational study of claudication in older men: the Health in Men Study. *Medical Journal of Australia* 2010;192(11):641–5.
- Lam TH, Abdullah AS, Ho LM, Yip AW, Fan S. Smoking and sexual dysfunction in Chinese males: findings from men's health survey. *International Journal of Impotence Research* 2006;18(4):364–9.
- Land SR, Toll BA, Moinpour CM, Mitchell SA, Ostroff JS, Hatsukami DK, Duffy SA, Gritz ER, Rigotti NA, Brandon TH, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. *Clinical Cancer Research* 2016;22(8):1907–13.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *New England Journal of Medicine* 1998;339(17):1194–200.
- Lao XQ, Jiang CQ, Zhang WS, Adab P, Lam TH, Cheng KK, Thomas GN. Smoking, smoking cessation and inflammatory markers in older Chinese men: the Guangzhou Biobank Cohort Study. *Atherosclerosis* 2009;203(1):304–10.
- Lawson EJ. The role of smoking in the lives of low-income pregnant adolescents: a field study. *Adolescence* 1994;29(113):61–79.
- Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, Deykin A, DiMango E, Fish JE, Ford JG, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *American Journal of Respiratory and Critical Care Medicine* 2007;175(8):783–90.
- Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, Barone GW, Bandyk D, Moneta GL, Makhoul RG. The aneurysm detection and management study screening program: validation cohort and final results. *Archives of Internal Medicine* 2000;160(10):1425–30.
- Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, Krupski WC, Barone GW, Acher CW, Ballard DJ. Prevalence and associations of abdominal aortic aneurysm detected through screening. *Annals of Internal Medicine* 1997;126(6):441–9.
- Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. *Journal of Vascular Surgery* 2003;38(2):329–34.
- Lee KW, Pausova Z. Cigarette smoking and DNA methylation. *Frontiers in Genetics* 2013;4:132.
- Lee PN, Fry JS, Hamling JS. Using the negative exponential distribution to quantitatively review the evidence on how rapidly the excess risk of ischaemic heart disease declines following quitting smoking. *Regulatory Toxicology and Pharmacology* 2012;64(1):51–67.
- Lee PN, Fry JS, Thornton AJ. Estimating the decline in excess risk of cerebrovascular disease following quitting smoking—a systematic review based on the negative exponential model. *Regulatory Toxicology and Pharmacology* 2014;68(1):85–95.
- Lee T, Silver H. Etiology and epidemiology of preterm premature rupture of the membranes. *Clinics in Perinatology* 2001;28(4):721–34.
- Lee YH, Shin MH, Kweon SS, Choi JS, Rhee JA, Ahn HR, Yun WJ, Ryu SY, Kim BH, Nam HS, et al. Cumulative smoking exposure, duration of smoking cessation, and peripheral arterial disease in middle-aged and older Korean men. *BMC Public Health* 2011;11:94.
- Lehmann N, Mohlenkamp S, Mahabadi AA, Schmermund A, Roggenbuck U, Seibel R, Gronemeyer D, Budde T, Dragano N, Stang A, et al. Effect of smoking and other traditional risk factors on the onset of coronary artery calcification: results of the Heinz Nixdorf Recall Study. *Atherosclerosis* 2014;232(2):339–45.
- Leng GC, Lee AJ, Fowkes FG, Lowe GD, Housley E. The relationship between cigarette smoking and cardiovascular risk factors in peripheral arterial disease compared with ischaemic heart disease. The Edinburgh Artery Study. *European Heart Journal* 1995;16(11):1542–8.
- Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005;111(3):363–8.
- Leufkens AM, Van Duijnhoven FJ, Siersema PD, Boshuizen HC, Vrieling A, Agudo A, Gram IT, Weiderpass E, Dahm C, Overvad K, et al. Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition Study. *Clinical Gastroenterology and Hepatology* 2011;9(2):137–44.

- Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, Sibai BM, Epstein FH, Romero R, Thadhani R, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *New England Journal of Medicine* 2006;355(10):992–1005.
- Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, et al. Circulating angiogenic factors and the risk of preeclampsia. *New England Journal of Medicine* 2004;350(7):672–83.
- Levitzky YS, Cupples LA, Murabito JM, Kannel WB, Kiel DP, Wilson PW, Wolf PA, O'Donnell CJ. Prediction of intermittent claudication, ischemic stroke, and other cardiovascular disease by detection of abdominal aortic calcific deposits by plain lumbar radiographs. *American Journal of Cardiology* 2008;101(3):326–31.
- Li H, Srinivasan SR, Berenson GS. Comparison of the measures of pulsatile arterial function between asymptomatic younger adult smokers and former smokers: the Bogalusa Heart Study. *American Journal of Hypertension* 2006;19(9):897–901.
- Li J, Luo Y, Xu Y, Yang J, Zheng L, Hasimu B, Yu J, Hu D. Risk factors of peripheral arterial disease and relationship between low ankle-brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with type 2 diabetes. *Circulation Journal* 2007;71(3):377–81.
- Li LF, Chan RL, Lu L, Shen J, Zhang L, Wu WK, Wang L, Hu T, Li MX, Cho CH. Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms (review). *International Journal of Molecular Medicine* 2014;34(2):372–80.
- Liang LR, Wong ND, Shi P, Zhao LC, Wu LX, Xie GQ, Wu YF. Cross-sectional and longitudinal association of cigarette smoking with carotid atherosclerosis in Chinese adults. *Preventive Medicine* 2009;49(1):62–7.
- Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105(9):1135–43.
- Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. *Leukemia* 2007;21(6):1137–40.
- Limburg PJ, Vierkant RA, Cerhan JR, Yang P, Lazovich D, Potter JD, Sellers TA. Cigarette smoking and colorectal cancer: long-term, subsite-specific risks in a cohort study of postmenopausal women. *Clinical Gastroenterology and Hepatology* 2003;1(3):202–10.
- Limsui D, Vierkant RA, Tillmans LS, Wang AH, Weisenberger DJ, Laird PW, Lynch CF, Anderson KE, French AJ, Haile RW, et al. Cigarette smoking and colorectal cancer risk by molecularly defined subtypes. *Journal of the National Cancer Institute* 2010;102(14):1012–22.
- Lin JS, Olson CM, Johnson ES, Senger CA, Soh CB, Whitlock EP. *The Ankle Brachial Index for Peripheral Artery Disease Screening and Cardiovascular Disease Prediction in Asymptomatic Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force*. Evidence Synthesis No. 100. AHRQ Publication No. 12-05162-EF-1. Rockville (MD): Agency for Healthcare Research and Quality, 2013.
- Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes and Control* 2005;16(3):285–94.
- Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke* 2016;47(8):1975–81.
- Lindholt JS, Heegaard NH, Vammen S, Fasting H, Henneberg EW, Heickendorff L. Smoking, but not lipids, lipoprotein(a) and antibodies against oxidised LDL, is correlated to the expansion of abdominal aortic aneurysms. *European Journal of Vascular and Endovascular Surgery* 2001;21(1):51–6.
- Lindley AA, Becker S, Gray RH, Herman AA. Effect of continuing or stopping smoking during pregnancy on infant birth weight, crown-heel length, head circumference, ponderal index, and brain:body weight ratio. *American Journal of Epidemiology* 2000;152(3):219–25.
- Lindstrom D. Comments regarding 'Measuring effects of smoking and smoking cessation in patients with vascular disease'. *European Journal of Vascular and Endovascular Surgery* 2010;40(3):363–4.
- Liu C, Cui H, Gu D, Zhang M, Fang Y, Chen S, Tang M, Zhang B, Chen H. Genetic polymorphisms and lung cancer risk: evidence from meta-analyses and genome-wide association studies. *Lung Cancer* 2017;113:18–29.
- Liu J, Zhu ZY, Gao CY, Wang XP, Zhang Y, Jin WD, Qi DT, Li MW. Long-term effect of persistent smoking on the prognosis of Chinese male patients after percutaneous coronary intervention with drug-eluting stent implantation. *Journal of Cardiology* 2013;62(5):283–8.
- Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelsler C, Gulati M, Masoudi FA, Goff DC Jr. Estimating longitudinal risks and benefits from cardiovascular preventive therapies among Medicare patients: the Million Hearts Longitudinal ASCVD Risk Assessment Tool: a special report From the American Heart Association and American College of Cardiology. *Journal of the American College of Cardiology* 2017;69(12):1617–36.
- Lomas DA, Silverman EK, Edwards LD, Locantore NW, Miller BE, Horstman DH, Tal-Singer R. Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. *European Respiratory Journal* 2009;34(1):95–102.

- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007;115(4):459–67.
- Louhelainen N, Ryttilä P, Haahtela T, Kinnula VL, Djukanovic R. Persistence of oxidant and protease burden in the airways after smoking cessation. *BMC Pulmonary Medicine* 2009;9:25.
- Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. *Heart* 2014;100(5):414–23.
- Lúdvíksdóttir D, Blöndal T, Franzon M, Gudmundsson TV, Säwe U. Effects of nicotine nasal spray on atherogenic and thrombogenic factors during smoking cessation. *Journal of Internal Medicine* 1999;246(1):61–6.
- Luke B, Gopal D, Cabral H, Stern JE, Diop H. Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology. *American Journal of Obstetrics and Gynecology* 2017;217(3):327e1–327e14.
- Luo YY, Li J, Xin Y, Zheng LQ, Yu JM, Hu DY. Risk factors of peripheral arterial disease and relationship between low ankle brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with hypertension. *Journal of Human Hypertension* 2007;21(6):461–6.
- Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, Canzian F, Stepilowski E, Arslan AA, Gross M, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *American Journal of Epidemiology* 2009;170(4):403–13.
- MacArthur C, Knox EG, Lancashire RJ. Effects at age nine of maternal smoking in pregnancy: experimental and observational findings. *BJOG* 2001;108(1):67–73.
- Mack LR, Tomich PG. Gestational diabetes: diagnosis, classification, and clinical care. *Obstetrics and Gynecology Clinics of North America* 2017;44(2):207–17.
- Madani A, Van Muylem A, de Maertelaer V, Zanen J, Gevenois PA. Pulmonary emphysema: size distribution of emphysematous spaces on multidetector CT images—comparison with macroscopic and microscopic morphometry. *Radiology* 2008;248(3):1036–41.
- Madsen BS, Jensen HL, van den Brule AJ, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina—population-based case-control study in Denmark. *International Journal of Cancer* 2008;122(12):2827–34.
- Madsen C, Nafstad P, Eikvar L, Schwarze PE, Rønningen KS, Haaheim LL. Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. *European Journal of Epidemiology* 2007;22(5):311–7.
- Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. *Preventive Medicine* 2003;37(4):283–90.
- Malchodi CS, Oncken C, Dornelas EA, Caramanica L, Gregonis E, Curry SL. The effects of peer counseling on smoking cessation and reduction. *Obstetrics and Gynecology* 2003;101(3):504–10.
- Malhotra R, Olsson H. Immunology, genetics and microbiota in the COPD pathophysiology: potential scope for patient stratification. *Expert Review of Respiratory Medicine* 2015;9(2):153–9.
- Mammen MJ, Sethi S. COPD and the microbiome. *Respirology* 2016;21(4):590–9.
- Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;370(9589):765–73.
- Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007;62(3):237–41.
- Mannino DM, Diaz-Guzman E. Interpreting lung function data using 80% predicted and fixed thresholds identifies patients at increased risk of mortality. *Chest* 2012;141(1):73–80.
- Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *American Journal of Epidemiology* 1994;140(11):1003–8.
- Marano KM, Kathman SJ, Jones BA, Nordskog BK, Brown BG, Borgerding MF. Study of cardiovascular disease biomarkers among tobacco consumers. Part 3: evaluation and comparison with the U.S. National Health and Nutrition Examination Survey. *Inhalation Toxicology* 2015;27(3):167–73.
- March of Dimes; The Partnership for Maternal, Newborn, and Child Health; Save the Children; World Health Organization. *Born Too Soon: The Global Action Report on Preterm Birth*. Geneva (Switzerland): World Health Organization, 2012.
- Marcoux S, Brisson J, Fabia J. The effect of cigarette smoking on the risk of preeclampsia and gestational hypertension. *American Journal of Epidemiology* 1989;130(5):950–7.
- Marom-Haham L, Shulman A. Cigarette smoking and hormones. *Current Opinion in Obstetrics and Gynecology* 2016;28(4):230–5.
- Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, Durocher A, Tonnel AB. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. *American Review of Respiratory Disease* 1992;146(1):76–81.
- Marron M, Boffetta P, Zhang ZF, Zaridze D, Wunsch-Filho V, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International Journal of Epidemiology* 2010;39(1):182–96.

- Martin CL, Hall MH, Campbell DM. The effect of smoking on pre-eclampsia in twin pregnancy. *BJOG* 2000;107(6):745–9.
- Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2016. *NCHS Data Brief* 2017;(287):1–8.
- Martinez FJ, Erb-Downward JR, Huffnagle GB. Significance of the microbiome in chronic obstructive pulmonary disease. *Annals of the American Thoracic Society* 2013;10(Suppl):S170–S179.
- Matthews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. *National Vital Statistics Reports* 2015;64(9):1–30.
- Maxson PJ, Edwards SE, Ingram A, Miranda ML. Psychosocial differences between smokers and non-smokers during pregnancy. *Addictive Behaviors* 2012;37(2):153–9.
- Mazur W, Toljamo T, Ohlmeier S, Vuopala K, Nieminen P, Kobayashi H, Kinnula VL. Elevation of surfactant protein A in plasma and sputum in cigarette smokers. *European Respiratory Journal* 2011;38(2):277–84.
- McCowan LM, Dekker GA, Chan E, Stewart A, Chappell LC, Hunter M, Moss-Morris R, North RA. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. *BMJ* 2009;338:b1081.
- McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales—I. cigarette smoking. *European Journal of Cancer* 1992;28A(12):2050–4.
- McEvoy JW, Blaha MJ, DeFilippis AP, Lima JA, Bluemke DA, Hundley WG, Min JK, Shaw LJ, Lloyd-Jones DM, Barr RG, et al. Cigarette smoking and cardiovascular events: role of inflammation and subclinical atherosclerosis from the MultiEthnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2015a;35(3):700–9.
- McEvoy JW, Nasir K, DeFilippis AP, Lima JA, Bluemke DA, Hundley WG, Barr RG, Budoff MJ, Szklo M, Navas-Acien A, et al. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2015b;35(4):1002–10.
- McKay A, Komai-Koma M, MacLeod KJ, Campbell CC, Kitson SM, Chaudhuri R, Thomson L, McSharry C, Liew FY, Thomson NC. Interleukin-18 levels in induced sputum are reduced in asthmatic and normal smokers. *Clinical and Experimental Allergy* 2004;34(6):904–10.
- McLaughlin JK, Lindblad P, Mellemegaard A, McCredie M, Mandel JS, Schlehofer B, Pommer W, Adami HO. International renal-cell cancer study. I. Tobacco use. *International Journal of Cancer* 1995;60(2):194–8.
- McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JF, Jr. A population-based case-control study of renal cell carcinoma. *Journal of the National Cancer Institute* 1984;72(2):275–84.
- McLeish AC, Zvolensky MJ. Asthma and cigarette smoking: a review of the empirical literature. *Journal of Asthma* 2010;47(4):345–61.
- McNair T, Altman K. Miscarriage and recurrent pregnancy loss. In: Hurt KJ, Guile MW, Bienstock JL, Fox HE, Wallach EE, editors. *The Johns Hopkins Manual of Gynecology and Obstetrics*. 4th ed. Baltimore (MD): Lippincott Williams & Wilkins, 2011:438–9.
- Meagher LC, Cousin JM, Seckl JR, Haslett C. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. *Journal of Immunology* 1996;156(11):4422–8.
- Meghea CI, Rus IA, Chereches RM, Costin N, Caracostea G, Brinzaniuc A. Maternal smoking during pregnancy and birth outcomes in a sample of Romanian women. *Central European Journal of Public Health* 2014;22(3):153–8.
- Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam Study. *Archives of Internal Medicine* 2000;160(19):2934–8.
- Mendez MA, Torrent M, Ferrer C, Ribas-Fito N, Sunyer J. Maternal smoking very early in pregnancy is related to child overweight at age 5–7 y. *American Journal of Clinical Nutrition* 2008;87(6):1906–13.
- Menon R. Preterm birth: a global burden on maternal and child health. *Pathogens and Global Health* 2012;106(3):139–40.
- Menon R, Boldogh I, Hawkins HK, Woodson M, Polettini J, Syed TA, Fortunato SJ, Saade GR, Papaconstantinou J, Taylor RN. Histological evidence of oxidative stress and premature senescence in preterm premature rupture of the human fetal membranes recapitulated in vitro. *American Journal of Pathology* 2014;184(6):1740–51.
- Mercer BM. Brief latency after premature rupture of the membranes at term: correction of a propagated error. *American Journal of Obstetrics and Gynecology* 2017;217(6):663–4.
- Mercer BM, Goldenberg RL, Meis PJ, Moawad AH, Shellhaas C, Das A, Menard MK, Caritis SN, Thurnau GR, Dombrowski MP, et al. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. *American Journal of Obstetrics and Gynecology* 2000;183(3):738–45.
- Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2014;34(3):509–15.
- Mets OM, de Jong PA, van Ginneken B, Gietema HA, Lammers JW. Quantitative computed tomography in COPD: possibilities and limitations. *Lung* 2012;190(2):133–45.

- Meyer J, Rohrmann S, Bopp M, Faeh D, Swiss National Cohort Study Group. Impact of smoking and excess body weight on overall and site-specific cancer mortality risk. *Cancer Epidemiology, Biomarkers and Prevention* 2015;24(10):1516–22.
- Midgette AS, Baron JA, Rohan TE. Do cigarette smokers have diets that increase their risks of coronary heart disease and cancer? *American Journal of Epidemiology* 1993;137(5):521–9.
- Mikkelsen TF, Graff-Iversen S, Sundby J, Bjertness E. Early menopause, association with tobacco smoking, coffee consumption and other lifestyle factors: a cross-sectional study. *BMC Public Health* 2007;7:149.
- Miller M, Cho JY, Pham A, Friedman PJ, Ramsdell J, Broide DH. Persistent airway inflammation and emphysema progression on CT scan in ex-smokers observed for 4 years. *Chest* 2011a;139(6):1380–7.
- Miller MR, Quanjer PH, Swanney MP, Ruppel G, Enright PL. Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. *Chest* 2011b;139(1):52–9.
- Mirone V, Imbimbo C, Bortolotti A, Di Cintio E, Colli E, Landoni M, Lavezzari M, Parazzini F. Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. *European Urology* 2002;41(3):294–7.
- Mitchell EA, Thompson JM, Robinson E, Wild CJ, Becroft DM, Clark PM, Glavish N, Pattison NS, Pryor JE. Smoking, nicotine and tar and risk of small for gestational age babies. *Acta Paediatrica* 2002;91(3):323–8.
- Miyake Y, Tanaka K, Arakawa M. Active and passive maternal smoking during pregnancy and birth outcomes: the Kyushu Okinawa maternal and child health study. *BMC Pregnancy and Childbirth* 2013;13:157.
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114(2):119–25.
- Moffatt RJ, Biggerstaff KD, Stamford BA. Effects of the transdermal nicotine patch on normalization of HDL-C and its subfractions. *Preventive Medicine* 2000;31(2 Pt 1):148–52.
- Mohamed Hoesein FA, de Hoop B, Zanen P, Gietema H, Kruitwagen CL, van Ginneken B, Isgum I, Mol C, van Klaveren RJ, Dijkstra AE, et al. CT-quantified emphysema in male heavy smokers: association with lung function decline. *Thorax* 2011;66(9):782–7.
- Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. *Chest* 2007;131(2):446–52.
- Mohsin M, Jalaludin B. Influence of previous pregnancy outcomes and continued smoking on subsequent pregnancy outcomes: an exploratory study in Australia. *BJOG* 2008;115(11):1428–35.
- Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ* 2015;350:h1551.
- Moore E, Blatt K, Chen A, Van Hook J, DeFranco EA. Relationship of trimester-specific smoking patterns and risk of preterm birth. *American Journal of Obstetrics and Gynecology* 2016;215(1):109.e101–e106(1).
- Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. *American Journal of Epidemiology* 1998;148(12):1195–205.
- Morales NA, Romano MA, Cummings KM, Marshall JR, Hyland AJ, Hutson A, Warren GW. Accuracy of self-reported tobacco use in newly diagnosed cancer patients. *Cancer Causes and Control* 2013;24(6):1223–30.
- Moreno H Jr, Chalon S, Urae A, Tangphao O, Abiose AK, Hoffman BB, Blaschke TF. Endothelial dysfunction in human hand veins is rapidly reversible after smoking cessation. *American Journal of Physiology* 1998;275(3 Pt 2):H1040–H1045.
- Morita K, Tsukamoto T, Naya M, Noriyasu K, Inubushi M, Shiga T, Katoh C, Kuge Y, Tsutsui H, Tamaki N. Smoking cessation normalizes coronary endothelial vasomotor response assessed with 15O-water and PET in healthy young smokers. *Journal of Nuclear Medicine* 2006;47(12):1914–20.
- Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, Flores SC, Fontenot AP, Ghedin E, Huang L, et al. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. *American Journal of Respiratory and Critical Care Medicine* 2013;187(10):1067–75.
- Moura MA, Bergmann A, Aguiar SS, Thuler LC. The magnitude of the association between smoking and the risk of developing cancer in Brazil: a multicenter study. *BMJ Open* 2014;4(2):e003736.
- Moy KA, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. *Cancer Epidemiology, Biomarkers and Prevention* 2010;19(9):2287–97.
- Müezzinler A, Mons U, Gellert C, Schöttker B, Jansen E, Kee F, O'Doherty MG, Kuulasmaa K, Freedman ND, Abnet CC, et al. Smoking and all-cause mortality in older adults: results from the CHANCES Consortium. *American Journal of Preventive Medicine* 2015;49(5):e53–e63.

- Mulcahy R, Hickey N, Graham I, Daly L. The influence of subsequent cigarette smoking habits on causes and mode of death in survivors of unstable angina or myocardial infarction. *European Heart Journal* 1982;3(2):142–5.
- Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA: the Journal of the American Medical Association* 1982;248(12):1465–77.
- Munafò M, Murphy M, Whiteman D, Hey K. Does cigarette smoking increase time to conception? *Journal of Biosocial Science* 2002;34(1):65–73.
- Munck C, Helby J, Westergaard CG, Porsbjerg C, Backer V, Hansen LH. Smoking cessation and the microbiome in induced sputum samples from cigarette smoking asthma patients. *PLoS One* 2016;11(7):e0158622.
- Murphy DJ, Dunney C, Mullally A, Adnan N, Deane R. Population-based study of smoking behaviour throughout pregnancy and adverse perinatal outcomes. *International Journal of Environmental Research and Public Health* 2013;10(9):3855–67.
- Murray RP, Connett JE, Rand CS, Pan W, Anthonisen NR. Persistence of the effect of the Lung Health Study (LHS) smoking intervention over eleven years. *Preventive Medicine* 2002;35(4):314–9.
- Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma. A second look. *Cancer* 1995;75(10):2552–7.
- Musselman JR, Blair CK, Cerhan JR, Nguyen P, Hirsch B, Ross JA. Risk of adult acute and chronic myeloid leukemia with cigarette smoking and cessation. *Cancer Epidemiology* 2013;37(4):410–6.
- Myint PK, Welch AA, Bingham SA, Luben RN, Wareham NJ, Day NE, Khaw KT. Smoking predicts long-term mortality in stroke: The European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study. *Preventive Medicine* 2006;42(2):128–31.
- Nadrusz W Jr, Claggett B, Goncalves A, Querejeta-Roca G, Fernandes-Silva MM, Shah AM, Cheng S, Tanaka H, Heiss G, Kitzman DW, et al. Smoking and cardiac structure and function in the elderly: the ARIC Study (Atherosclerosis Risk in Communities). *Circulation: Cardiovascular Imaging* 2016;9(9):e004950.
- Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. *Obstetrics and Gynecology* 1980;55(6):701–4.
- Naeye RL, Peters EC. Causes and consequences of premature rupture of fetal membranes. *Lancet* 1980;1(8161):192–4.
- Nagareddy P, Smyth SS. Inflammation and thrombosis in cardiovascular disease. *Current Opinion in Hematology* 2013;20(5):457–63.
- Najafi F, Hasani J, Izadi N, Hashemi-Nazari SS, Namvar Z, Mohammadi S, Sadeghi M. The effect of prepregnancy body mass index on the risk of gestational diabetes mellitus: a systematic review and dose-response meta-analysis. *Obesity Reviews* 2019;20(3):472–86.
- Nance R, Delaney J, McEvoy JW, Blaha MJ, Burke GL, Navas-Acien A, Kaufman JD, Oelsner EC, McClelland RL. Smoking intensity (pack/day) is a better measure than pack-years or smoking status for modeling cardiovascular disease outcomes. *Journal of Clinical Epidemiology* 2017;81:111–9.
- National Cancer Institute. Cancer Center Cessation Initiative, April 25 April 25, 2018; <<https://cancercontrol.cancer.gov/brp/tcrb/cessation-initiative.html>>; accessed: May 15, 2018.
- National Center for Health Statistics. Mortality multiple cause micro-data files, 2014: public-use data file and documentation: NHLBI tabulations, 2017; <http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm#Mortality_Multiple>; accessed: September 9, 2017.
- National Comprehensive Cancer Network. About NCCN, n.d.; <<https://www.nccn.org/about/>>; accessed: October 5, 2018.
- National Institutes of Health Consensus Development Panel on Impotence. NIH Consensus Conference. Impotence. *JAMA: the Journal of the American Medical Association* 1993;270(1):83–90.
- Nijati K, Satoh K, Otani K, Kimata Y, Ohtaki M. Regression analysis of maternal smoking effect on birth weight. *Hiroshima Journal of Medical Sciences* 2008;57(2):61–7.
- Nishihara R, Morikawa T, Kuchiba A, Lochhead P, Yamauchi M, Liao X, Imamura Y, Nosho K, Shima K, Kawachi I, et al. A prospective study of duration of smoking cessation and colorectal cancer risk by epigenetics-related tumor classification. *American Journal of Epidemiology* 2013;178(1):84–100.
- Niu J, Lin Y, Guo Z, Niu M, Su C. The epidemiological investigation on the risk factors of hepatocellular carcinoma: a case-control study in southeast China. *Medicine (Baltimore)* 2016;95(6):e2758.
- Nomura AM, Wilkens LR, Henderson BE, Epplein M, Kolonel LN. The association of cigarette smoking with gastric cancer: the multiethnic cohort study. *Cancer Causes and Control* 2012;23(1):51–8.
- Norman PE, Davis WA, Bruce DG, Davis TM. Peripheral arterial disease and risk of cardiac death in type 2 diabetes—the Fremantle Diabetes Study. *Diabetes Care* 2006;29(3):575–80.
- O’Hare AM, Hsu CY, Bacchetti P, Johansen KL. Peripheral vascular disease risk factors among patients undergoing hemodialysis. *Journal of the American Society of Nephrology* 2002;13(2):497–503.
- Obel C, Zhu JL, Olsen J, Breining S, Li J, Gronborg TK, Gissler M, Rutter M. The risk of attention deficit hyperactivity disorder in children exposed to maternal

- smoking during pregnancy—a re-examination using a sibling design. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 2016;57(4):532–7.
- Odongua N, Chae YM, Kim MR, Yun JE, Jee SH. Associations between smoking, screening, and death caused by cervical cancer in Korean women. *Yonsei Medical Journal* 2007;48(2):192–200.
- Oelsner EC, Hoffman EA, Folsom AR, Carr JJ, Enright PL, Kawut SM, Kronmal R, Lederer D, Lima JA, Lovasi GS, et al. Association between emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. *Annals of Internal Medicine* 2014;161(12):863–73.
- Ögren M, Hedblad B, Janzon L. Biased risk factor assessment in prospective studies of peripheral arterial disease due to change in exposure and selective mortality of high-risk individuals. *Journal of Cardiovascular Risk* 1996;3(6):523–8.
- Ohsawa M, Okayama A, Nakamura M, Onoda T, Kato K, Itai K, Yoshida Y, Ogawa A, Kawamura K, Hiramori K. CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Preventive Medicine* 2005;41(2):651–6.
- Okah FA, Hoff GL, Dew P, Cai J. Cumulative and residual risks of small for gestational age neonates after changing pregnancy-smoking behaviors. *American Journal of Perinatology* 2007;24(3):191–6.
- Olin JW, Allie DE, Belkin M, Bonow RO, Casey DE Jr, Creager MA, Gerber TC, Hirsch AT, Jaff MR, Kaufman JA, et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease. *Journal of Vascular Surgery* 2010;52(6):1616–52.
- Oosterhoff Y, Jansen MA, Postma DS, Koeter GH. Airway responsiveness to adenosine 5'-monophosphate in smokers and nonsmokers with atopic asthma. *Journal of Allergy and Clinical Immunology* 1993;92(5):773–6.
- Ordonez-Mena JM, Schottker B, Mons U, Jenab M, Freisling H, Bueno-de-Mesquita B, O'Doherty MG, Scott A, Kee F, Stricker BH, et al. Quantification of the smoking-associated cancer risk with rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium. *BMC Medicine* 2016;14:62.
- Orlandi I, Moroni C, Camiciottoli G, Bartolucci M, Pistolesi M, Villari N, Mascalchi M. Chronic obstructive pulmonary disease: thin-section CT measurement of airway wall thickness and lung attenuation. *Radiology* 2005;234(2):604–10.
- Oyeyipo IP, Raji Y, Emikpe BO, Bolarinwa AF. Effects of nicotine on sperm characteristics and fertility profile in adult male rats: a possible role of cessation. *Journal of Reproduction and Infertility* 2011;12(3):201–7.
- Ozasa K. Smoking and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pacific Journal of Cancer Prevention* 2007;8(Suppl):89–96.
- Pacheco AG, Grinsztejn B, da Fonseca Mde J, Griep RH, Lotufo P, Bensenor I, Mill JG, Moreira Rde C, Moreira RI, Friedman RK, et al. HIV infection is not associated with carotid intima-media thickness in Brazil: a cross-sectional analysis from the INI/ELSA-Brasil Study. *PLoS One* 2016;11(7):e0158999.
- Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. *Acta Physiologica* (Oxford, England) 2013;208(3):224–33.
- Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clinical Obstetrics and Gynecology* 2006;49(2):257–69.
- Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. *Circulation* 2015;132(19):1795–804.
- Pang Q, Qu K, Zhang J, Xu X, Liu S, Song S, Wang R, Zhang L, Wang Z, Liu C. Cigarette smoking increases the risk of mortality from liver cancer: a clinical-based cohort and meta-analysis. *Journal of Gastroenterology and Hepatology* 2015;30(10):1450–60.
- Parajuli R, Bjerkaas E, Tverdal A, Le Marchand L, Weiderpass E, Gram IT. Cigarette smoking and colorectal cancer mortality among 602,242 Norwegian males and females. *Clinical Epidemiology* 2014;6:137–45.
- Parazzini F, Ricci E, Chatenoud L, Tozzi L, Rosa C, Nicolosi AE, Surace M, Benzi G, La Vecchia C. Maternal and paternal smoking and pregnancy-induced hypertension. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2003;109(2):141–4.
- Parazzini F, Tozzi L, Ferraroni M, Bocciolone L, La Vecchia C, Fedele L. Risk factors for ectopic pregnancy: an Italian case-control study. *Obstetrics and Gynecology* 1992;80(5):821–6.
- Parker AS, Cerhan JR, Janney CA, Lynch CF, Cantor KP. Smoking cessation and renal cell carcinoma. *Annals of Epidemiology* 2003;13(4):245–51.
- Pascual RM, Peters SP. Airway remodeling contributes to the progressive loss of lung function in asthma: an overview. *Journal of Allergy and Clinical Immunology* 2005;116(3):477–86; quiz 87.
- Passarelli MN, Newcomb PA, Hampton JM, Trentham-Dietz A, Titus LJ, Egan KM, Baron JA, Willett WC. Cigarette smoking before and after breast cancer diagnosis: mortality from breast cancer and smoking-related diseases. *Journal of Clinical Oncology* 2016;34(12):1315–22.
- Passos VM, Barreto SM, Guerra HL, Firmo JO, Vidigal PG, Lima-Costa MF. The Bambui Health and Aging Study

- (BHAS). Prevalence of intermittent claudication in the aged population of the community of Bambui and its associated factors [English and Portuguese]. *Arquivos Brasileiros de Cardiologia* 2001;77(5):453–62.
- Patel NH, Attwood KM, Hanzly M, Creighton TT, Mehedint DC, Schwaab T, Kauffman EC. Comparative analysis of smoking as a risk factor among renal cell carcinoma histological subtypes. *Journal of Urology* 2015;194(3):640–6.
- Perkins J, Dick TB. Smoking and myocardial infarction: secondary prevention. *Postgraduate Medical Journal* 1985;61(714):295–300.
- Perret JL, Walters EH, Abramson MJ, McDonald CF, Dharmage SC. The independent and combined effects of lifetime smoke exposures and asthma as they relate to COPD. *Expert Review of Respiratory Medicine* 2014;8(4):503–14.
- Peters RW, Brooks MM, Todd L, Liebson PR, Wilhelmsen L. Smoking cessation and arrhythmic death: the CAST experience. *Journal of the American College of Cardiology* 1995;26(5):1287–92.
- Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke* 2013;44(10):2821–8.
- Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 2000;321(7257):323–9.
- Phillips RS, Tuomala RE, Feldblum PJ, Schachter J, Rosenberg MJ, Aronson MD. The effect of cigarette smoking, chlamydia trachomatis infection, and vaginal douching on ectopic pregnancy. *Obstetrics and Gynecology* 1992;79(1):85–90.
- Pickett KE, Kasza K, Biesecker G, Wright RJ, Wakschlag LS. Women who remember, women who do not: a methodological study of maternal recall of smoking in pregnancy. *Nicotine and Tobacco Research* 2009;11(10):1166–74.
- Pickett KE, Rathouz PJ, Kasza K, Wakschlag LS, Wright R. Self-reported smoking, cotinine levels, and patterns of smoking in pregnancy. *Paediatric and Perinatal Epidemiology* 2005;19(5):368–76.
- Pickett KE, Wakschlag LS, Dai L, Leventhal BL. Fluctuations of maternal smoking during pregnancy. *Obstetrics and Gynecology* 2003;101(1):140–7.
- Pinsky PF, Zhu CS, Kramer BS. Lung cancer risk by years since quitting in 30+ pack year smokers. *Journal of Medical Screening* 2015;22(3):151–7.
- Pipkin FB. Smoking in moderate/severe preeclampsia worsens pregnancy outcome, but smoking cessation limits the damage. *Hypertension* 2008;51(4):1042–6.
- Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* 2013;381(9861):133–41.
- Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Archives of Internal Medicine* 2004;164(12):1285–92.
- Polakowski LL, Akinbami LJ, Mendola P. Prenatal smoking cessation and the risk of delivering preterm and small-for-gestational-age newborns. *Obstetrics and Gynecology* 2009;114(2 Pt 1):318–25.
- Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, Russo C. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *International Journal of Environmental Research and Public Health* 2014;11(5):4965–77.
- Pope JE. The diagnosis and treatment of Raynaud's phenomenon: a practical approach. *Drugs* 2007;67(4):517–25.
- Pourmand G, Alidaee MR, Rasuli S, Maleki A, Mehrsai A. Do cigarette smokers with erectile dysfunction benefit from stopping?: a prospective study. *BJU International* 2004;94(9):1310–3.
- Prabhu N, Smith N, Campbell D, Craig LC, Seaton A, Helms PJ, Devereux G, Turner SW. First trimester maternal tobacco smoking habits and fetal growth. *Thorax* 2010;65(3):235–40.
- Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility: a committee opinion. *Fertility and Sterility* 2012;98(6):1400–6.
- Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertility and Sterility* 2013;99(1):63.
- Prescott E, Lange P, Vestbo J. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. Copenhagen City Heart Study Group. *Thorax* 1997;52(3):287–9.
- Proctor RN. *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition*. Berkeley (CA): University of California Press, 2011.
- Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, Smeeth L, Timmis A, Hemingway H. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1,937,360 people in England: lifetime risks and implications for risk prediction. *International Journal of Epidemiology* 2015;44(1):129–41.
- Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. *Seminars in Perinatology* 2017;41(7):387–91.

- Quaderi S, Hurst JR. One-off spirometry is insufficient to rule in or rule out mild to moderate chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2017;196(3):254–6.
- Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine* 2007;176(6):532–55.
- Radin RG, Hatch EE, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis AH, Wise LA. Active and passive smoking and fecundability in Danish pregnancy planners. *Fertility and Sterility* 2014;102(1):183–91.e2.
- Räisänen S, Hogue CJR, Laine K, Kramer MR, Gissler M, Heinonen S. A population-based study of the effect of pregnancy history on risk of stillbirth. *International Journal of Gynaecology and Obstetrics* 2018;140(1):73–80.
- Räisänen S, Sankilampi U, Gissler M, Kramer MR, Hakulinen-Viitanen T, Saari J, Heinonen S. Smoking cessation in the first trimester reduces most obstetric risks, but not the risks of major congenital anomalies and admission to neonatal care: a population-based cohort study of 1,164,953 singleton pregnancies in Finland. *Journal of Epidemiology and Community Health* 2014;68(2):159–64.
- Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Celermajer DS. Arterial endothelial dysfunction related to passive smoking is potentially reversible in healthy young adults. *Annals of Internal Medicine* 1999;130(7):578–81.
- Rajagopalan S, Dellegrottaglie S, Furniss AL, Gillespie BW, Satayathum S, Lameire N, Saito A, Akiba T, Jadoul M, Ginsberg N, et al. Peripheral arterial disease in patients with end-stage renal disease: observations from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Circulation* 2006;114(18):1914–22.
- Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, Moure-González M, Seoane-Blanco A, Varela-Román A, Alvarez E, González-Juanatey JR. Soluble receptor of advanced glycation end products levels are related to ischaemic aetiology and extent of coronary disease in chronic heart failure patients, independent of advanced glycation end products levels: new roles for soluble RAGE. *European Journal of Heart Failure* 2010;12(10):1092–100.
- Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, Sears MR. Risk factors for hospital admission for asthma from childhood to young adulthood: a longitudinal population study. *Journal of Allergy and Clinical Immunology* 2002;110(2):220–7.
- Rasmussen KM, Catalano PM, Yaktine AL. New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. *Current Opinion in Obstetrics and Gynecology* 2009;21(6):521–6.
- Rasmussen S, Irgens LM, Bergsjø P, Dalaker K. Perinatal mortality and case fatality after placental abruption in Norway 1967–1991. *Acta Obstetrica et Gynecologica Scandinavica* 1996;75(3):229–34.
- Raymond EG, Mills JL. Placental abruption. Maternal risk factors and associated fetal conditions. *Acta Obstetrica et Gynecologica Scandinavica* 1993;72(8):633–9.
- Reichert V, Xue X, Bartscherer D, Jacobsen D, Fardellone C, Folan P, Kohn N, Talwar A, Metz CN. A pilot study to examine the effects of smoking cessation on serum markers of inflammation in women at risk for cardiovascular disease. *Chest* 2009;136(1):212–9.
- Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. *Human Reproduction Update* 2014;20(3):353–69.
- Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD001837. DOI: 10.1002/14651858.CD001837.pub3.
- Roach MC, Rehman S, DeWees TA, Abraham CD, Bradley JD, Robinson CG. It's never too late: smoking cessation after stereotactic body radiation therapy for non-small cell lung carcinoma improves overall survival. *Practical Radiation Oncology* 2016;6(1):12–8.
- Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta* 2009;30(Suppl A):S32–S37.
- Robinson CJ, Johnson DD, Chang EY, Armstrong DM, Wang W. Evaluation of placenta growth factor and soluble Fms-like tyrosine kinase 1 receptor levels in mild and severe preeclampsia. *American Journal of Obstetrics and Gynecology* 2006;195(1):255–9.
- Rode L, Kjaergaard H, Damm P, Ottesen B, Hegaard H. Effect of smoking cessation on gestational and postpartum weight gain and neonatal birth weight. *Obstetrics and Gynecology* 2013;122(3):618–25.
- Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA: the Journal of the American Medical Association* 2004;292(3):344–50.
- Rohan TE, Jain M, Rehm JT, Ashley MJ, Bondy SJ, Ferrence RG, Cohen J, Miller AB. Cigarette smoking and risk of death from colorectal cancer in women. *Colorectal Disease* 2000;2(5):298–303.
- Rønnevik PK, Gundersen T, Abrahamsen AM. Effect of smoking habits and timolol treatment on mortality and reinfarction in patients surviving acute myocardial infarction. *British Heart Journal* 1985;54(2):134–9.

- Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Halperin JL, Jaff MR, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline). *Journal of Vascular Surgery* 2011;54(5):e32–e58.
- Roos-Engstrand E, Ekstrand-Hammarstrom B, Pourazar J, Behndig AF, Bucht A, Blomberg A. Influence of smoking cessation on airway T lymphocyte subsets in COPD. *COPD* 2009;6(2):112–20.
- Roura E, Castellsague X, Pawlita M, Travier N, Waterboer T, Margall N, Bosch FX, de Sanjose S, Dillner J, Gram IT, et al. Smoking as a major risk factor for cervical cancer and pre-cancer: results from the EPIC cohort. *International Journal of Cancer* 2014;135(2):453–66.
- Ruiter L, Ravelli AC, de Graaf IM, Mol BW, Pajkrt E. Incidence and recurrence rate of placental abruption: a longitudinal linked national cohort study in the Netherlands. *American Journal of Obstetrics and Gynecology* 2015;213(4):573 e1–8.
- Safarinejad MR. Prevalence and risk factors for erectile dysfunction in a population-based study in Iran. *International Journal of Impotence Research* 2003;15(4):246–52.
- Sakao S, Tatsumi K. The importance of epigenetics in the development of chronic obstructive pulmonary disease. *Respirology* 2011;16(7):1056–63.
- Salihu HM, Li Q, Rouse DJ, Alexander GR. Placenta previa: neonatal death after live births in the United States. *American Journal of Obstetrics and Gynecology* 2003;188(5):1305–9.
- Salonen JT. Stopping smoking and long-term mortality after acute myocardial infarction. *British Heart Journal* 1980;43(4):463–9.
- Sandhu RK, Jimenez MC, Chiuve SE, Fitzgerald KC, Kenfield SA, Tedrow UB, Albert CM. Smoking, smoking cessation, and risk of sudden cardiac death in women. *Circulation: Arrhythmia and Electrophysiology* 2012;5(6):1091–7.
- Sandoval M, Font R, Manos M, Dicenta M, Quintana MJ, Bosch FX, Castellsague X. The role of vegetable and fruit consumption and other habits on survival following the diagnosis of oral cancer: a prospective study in Spain. *International Journal of Oral and Maxillofacial Surgery* 2009;38(1):31–9.
- Santos EP, Lopez-Costa S, Chenlo P, Pugliese MN, Curi S, Ariagno J, Repetto H, Sardi M, Palaoro L, Mendeluk G. Impact of spontaneous smoking cessation on sperm quality: case report. *Andrologia* 2011;43(6):431–5.
- Sapre S, Thakur R. Lifestyle and dietary factors determine age at natural menopause. *Journal of Midlife Health* 2014;5(1):3–5.
- Saraiya M, Berg CJ, Kendrick JS, Strauss LT, Atrash HK, Ahn YW. Cigarette smoking as a risk factor for ectopic pregnancy. *American Journal of Obstetrics and Gynecology* 1998;178(3):493–8.
- Sardari Nia P, Weyler J, Colpaert C, Vermeulen P, Van Marck E, Van Schil P. Prognostic value of smoking status in operated non-small cell lung cancer. *Lung Cancer* 2005;47(3):351–9.
- Sasaki S, Sata F, Katoh S, Saijo Y, Nakajima S, Washino N, Konishi K, Ban S, Ishizuka M, Kishi R. Adverse birth outcomes associated with maternal smoking and polymorphisms in the N-Nitrosamine-metabolizing enzyme genes NQO1 and CYP2E1. *American Journal of Epidemiology* 2008;167(6):719–26.
- Sauvaet C, Lagarde F, Nagano J, Soda M, Koyama K, Kodama K. Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). *Cancer Causes and Control* 2005;16(7):773–80.
- Savastano S, Klersy C, Raimondi M, Langord K, Vanni V, Rordorf R, Vicentini A, Petracci B, Landolina M, Visconti LO. Positive trend in survival to hospital discharge after out-of-hospital cardiac arrest: a quantitative review of the literature. *Journal of Cardiovascular Medicine* 2014;15(8):609–15.
- Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, Tashkin DP. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *American Journal of Respiratory and Critical Care Medicine* 2000;161(2 Pt 1):381–90.
- Schaal C, Chellappan SP. Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. *Molecular Cancer Research* 2014;12(1):14–23.
- Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International Journal of Epidemiology* 2014;43(5):1542–62.
- Scholl TO, Hediger ML, Schall JI, Fischer RL, Khoo CS. Low zinc intake during pregnancy: its association with preterm and very preterm delivery. *American Journal of Epidemiology* 1993;137(10):1115–24.
- Schumacher M, Rücker G, Schwarzer G. Meta-analysis and the Surgeon General's report on smoking and health. *New England Journal of Medicine* 2014;370(2):186–8.
- Secker-Walker RH, Vacek PM. Infant birth weight as a measure of harm reduction during smoking cessation trials in pregnancy. *Health Education and Behavior* 2002;29(5):557–69.
- Selvarajah S, Black JH 3rd, Malas MB, Lum YW, Propper BW, Abularrage CJ. Preoperative smoking is associated with early graft failure after infrainguinal bypass surgery. *Journal of Vascular Surgery* 2014;59(5):1308–14.

- Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the U.S. *American Journal of Medicine* 2007;120(2):151–7.
- Severson RK, Davis S, Heuser L, Daling JR, Thomas DB. Cigarette smoking and acute nonlymphocytic leukemia. *American Journal of Epidemiology* 1990;132(3):418–22.
- Sexton M, Hebel JR. A clinical trial of change in maternal smoking and its effect on birth weight. *JAMA: the Journal of the American Medical Association* 1984;251(7):911–5.
- Shah AM, Pfeffer MA, Hartley LH, Moye LA, Gersh BJ, Rutherford JD, Lamas GA, Rouleau JL, Braunwald E, Solomon SD. Risk of all-cause mortality, recurrent myocardial infarction, and heart failure hospitalization associated with smoking status following myocardial infarction with left ventricular dysfunction. *American Journal of Cardiology* 2010;106(7):911–6.
- Shaker SB, Stavngaard T, Laursen LC, Stoel BC, Dirksen A. Rapid fall in lung density following smoking cessation in COPD. *COPD* 2011;8(1):2–7.
- Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. *European Urology* 2016;70(4):635–45.
- Shields TS, Brinton LA, Burk RD, Wang SS, Weinstein SJ, Ziegler RG, Studentsov YY, McAdams M, Schiffman M. A case-control study of risk factors for invasive cervical cancer among U.S. women exposed to oncogenic types of human papillomavirus. *Cancer Epidemiology, Biomarkers and Prevention* 2004;13(10):1574–82.
- Shikata K, Doi Y, Yonemoto K, Arima H, Ninomiya T, Kubo M, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Population-based prospective study of the combined influence of cigarette smoking and *Helicobacter pylori* infection on gastric cancer incidence: the Hisayama Study. *American Journal of Epidemiology* 2008;168(12):1409–15.
- Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA, Chalmers J. Reliability of self-reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. *BMJ* 2009;339:b4347.
- Shiri R, Hakama M, Hakkinen J, Tammela TL, Auvinen A, Koskimaki J. Relationship between smoking and erectile dysfunction. *International Journal of Impotence Research* 2005;17(2):164–9.
- Shiri R, Hakkinen J, Koskimaki J, Tammela TL, Auvinen A, Hakama M. Smoking causes erectile dysfunction through vascular disease. *Urology* 2006;68(6):1318–22.
- Siega-Riz AM, Promislow JH, Savitz DA, Thorp JM Jr, McDonald T. Vitamin C intake and the risk of preterm delivery. *American Journal of Obstetrics and Gynecology* 2003;189(2):519–25.
- Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, Thieda P, Lux LJ, Lohr KN. A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. *American Journal of Obstetrics and Gynecology* 2009;201(4):339.e1–339.e14.
- Sighinolfi MC, Mofferdin A, De Stefani S, Micali S, Cicero AF, Bianchi G. Immediate improvement in penile hemodynamics after cessation of smoking: previous results. *Urology* 2007;69(1):163–5.
- Sikorski R, Radomanski T, Paszkowski T, Skoda J. Smoking during pregnancy and the perinatal cadmium burden. *Journal of Perinatal Medicine* 1988;16(3):225–31.
- Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest* 2003;123(5):1472–9.
- Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Archives of Internal Medicine* 1998;158(6):585–93.
- Sim WH, Araujo Júnior E, Da Silva Costa F, Sheehan PM. Maternal and neonatal outcomes following expectant management of preterm prelabour rupture of membranes before viability. *Journal of Perinatal Medicine* 2017;45(1):29–44.
- Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RP, Bjornson WM, Tashkin DP. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. *European Respiratory Journal* 2005;25(6):1011–7.
- Singh D, Fox SM, Tal-Singer R, Plumb J, Bates S, Broad P, Riley JH, Celli B. Induced sputum genes associated with spirometric and radiological disease severity in COPD ex-smokers. *Thorax* 2011;66(6):489–95.
- Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø Study. *American Journal of Epidemiology* 2001;154(3):236–44.
- Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. *Chest* 1999;115(3):691–6.
- Sioux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *European Respiratory Journal* 2000;15(3):470–7.
- Sjodahl K, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, Lagergren J. Smoking and alcohol drinking in relation

- to risk of gastric cancer: a population-based, prospective cohort study. *International Journal of Cancer* 2007;120(1):128–32.
- Skalkidis Y, Katsouyanni K, Petridou E, Sehas M, Trichopoulos D. Risk factors of peripheral arterial occlusive disease: a case-control study in Greece. *International Journal of Epidemiology* 1989;18(3):614–8.
- Slatter TL, Park L, Anderson K, Lailai-Tasmania V, Herbison P, Clow W, Royds JA, Devenish C, Hung NA. Smoking during pregnancy causes double-strand DNA break damage to the placenta. *Human Pathology* 2014;45(1):17–26.
- Smith G, Rafuse C, Anand N, Brennan B, Connors G, Crane J, Fraser W, Gratton R, Moutquin JM, Scott H, et al. Prevalence, management, and outcomes of preterm prelabour rupture of the membranes of women in Canada. *Journal of Obstetrics and Gynaecology Canada* 2005;27(6):547–53.
- Smith I, Franks PJ, Greenhalgh RM, Poulter NR, Powell JT. The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. *European Journal of Vascular and Endovascular Surgery* 1996;11(4):402–8.
- Smith LK, Draper ES, Evans TA, Field DJ, Johnson SJ, Manktelow BN, Seaton SE, Marlow N, Petrou S, Boyle EM. Associations between late and moderately preterm birth and smoking, alcohol, drug use and diet: a population-based case-cohort study. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2015;100(6):F486–F491.
- Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113(19):2363–72.
- Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;124(22):2458–73.
- Sobus SL, Warren GW. The biologic effects of cigarette smoke on cancer cells. *Cancer* 2014;120(23):3617–26.
- Song W, Wang W, Dou LY, Wang Y, Xu Y, Chen LF, Yan XW. The implication of cigarette smoking and cessation on macrophage cholesterol efflux in coronary artery disease patients. *Journal of Lipid Research* 2015;56(3):682–91.
- Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. *Stroke* 2008;39(9):2432–8.
- Sparrow D, Dawber TR. The influence of cigarette smoking on prognosis after a first myocardial infarction. A report from the Framingham Study. *Journal of Chronic Diseases* 1978;31(6-7):425–32.
- Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, Becker RC, Goldberg RJ. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *Journal of General Internal Medicine* 2006;21(7):722–7.
- Spinillo A, Capuzzo E, Colonna L, Solerte L, Nicola S, Guaschino S. Factors associated with abruptio placentae in preterm deliveries. *Acta Obstetrica et Gynecologica Scandinavica* 1994;73(4):307–12.
- Spira A, Beane J, Shah V, Liu G, Schembri F, Yang X, Palma J, Brody JS. Effects of cigarette smoke on the human airway epithelial cell transcriptome. *Proceedings of the National Academy of Sciences of the United States of America* 2004;101(27):10143–8.
- St-Pierre A, Cantin B, Lamarche B, Auger D, Després J, Dagenais GR. Intermittent claudication: from its risk factors to its long-term prognosis in men. The Quebec Cardiovascular Study. *Canadian Journal of Cardiology* 2010;26(1):17–21.
- Stackelberg O, Björck M, Larsson SC, Orsini N, Wolk A. Sex differences in the association between smoking and abdominal aortic aneurysm. *British Journal of Surgery* 2014;101(10):1230–7.
- Stamler J, Neaton JD, Cohen JD, Cutler J, Eberly L, Grandits G, Kuller LH, Ockene J, Prineas R. Multiple risk factor intervention trial revisited: a new perspective based on nonfatal and fatal composite endpoints, coronary and cardiovascular, during the trial. *Journal of the American Heart Association* 2012;1(5):e003640.
- Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *New England Journal of Medicine* 2000;343(1):16–22.
- Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. *Gut* 2010;59(1):39–48.
- Stergachis A, Scholes D, Daling JR, Weiss NS, Chu J. Maternal cigarette smoking and the risk of tubal pregnancy. *American Journal of Epidemiology* 1991;133(4):332–7.
- Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA: the Journal of the American Medical Association* 2002;288(11):1388–95.

- Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke* 2007;38(10):2718–25.
- Subar AF, Harlan LC, Mattson ME. Food and nutrient intake differences between smokers and non-smokers in the U.S. *American Journal of Public Health* 1990;80(11):1323–9.
- Sun L, Tan L, Yang F, Luo Y, Li X, Deng HW, Dvornyk V. Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. *Menopause* 2012;19(2):126–32.
- Suner-Soler R, Grau A, Gras ME, Font-Mayolas S, Silva Y, Davalos A, Cruz V, Rodrigo J, Serena J. Smoking cessation 1 year poststroke and damage to the insular cortex. *Stroke* 2012;43(1):131–6.
- Sung NY, Choi KS, Park EC, Park K, Lee SY, Lee AK, Choi IJ, Jung KW, Won YJ, Shin HR. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *British Journal of Cancer* 2007;97(5):700–4.
- Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *Journal of the American College of Cardiology* 2001;37(6):1677–82.
- Suter LG, Murabito JM, Felson DT, Fraenkel L. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *American Journal of Medicine* 2007;120(3):264–71.
- Suzuki K, Sato M, Zheng W, Shinohara R, Yokomichi H, Yamagata Z. Effect of maternal smoking cessation before and during early pregnancy on fetal and childhood growth. *Journal of Epidemiology* 2014;24(1):60–6.
- Suzuki K, Shinohara R, Sato M, Ottawa S, Yamagata Z. Association between maternal smoking during pregnancy and birth weight: an appropriately adjusted model from the Japan Environment and Children's Study. *Journal of Epidemiology* 2016;26(7):371–7.
- Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL, et al. Using the lower limit of normal for the FEV₁/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63(12):1046–51.
- Sweeting MJ, Thompson SG, Brown LC, Powell JT. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *British Journal of Surgery* 2012;99(5):655–65.
- Sze MA, Hogg JC, Sin DD. Bacterial microbiome of lungs in COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;9:229–38.
- Tabuchi T, Ito Y, Ioka A, Nakayama T, Miyashiro I, Tsukuma H. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. *Annals of Oncology* 2013;24(10):2699–704.
- Takabatake N, Toriyama S, Igarashi A, Tokairin Y, Takeishi Y, Konta T, Inoue S, Abe S, Shibata Y, Kubota I. A novel polymorphism in CDC6 is associated with the decline in lung function of ex-smokers in COPD. *Biochemical and Biophysical Research Communications* 2009;381(4):554–9.
- Takayanagi S, Kawata N, Tada Y, Ikari J, Matsuura Y, Matsuoka S, Matsushita S, Yanagawa N, Kasahara Y, Tatsumi K. Longitudinal changes in structural abnormalities using MDCT in COPD: do the CT measurements of airway wall thickness and small pulmonary vessels change in parallel with emphysematous progression? *International Journal of Chronic Obstructive Pulmonary Disease* 2017;12:551–60.
- Tang W, Yao L, Roetker NS, Alonso A, Lutsey PL, Steenson CC, Lederle FA, Hunter DW, Bengtson LG, Guan W, et al. Lifetime risk and risk factors for abdominal aortic aneurysm in a 24-year prospective study highlights: the ARIC study (Atherosclerosis Risk in Communities). *Arteriosclerosis, Thrombosis, and Vascular Biology* 2016;36(12):2468–77.
- Tao L, Wang R, Gao YT, Yuan JM. Impact of postdiagnosis smoking on long-term survival of cancer patients: the Shanghai cohort study. *Cancer Epidemiology, Biomarkers and Prevention* 2013;22(12):2404–11.
- Tashkin DP, Murray RP. Smoking cessation in chronic obstructive pulmonary disease. *Respiratory Medicine* 2009;103(7):963–74.
- Tashkin DP, Rennard S, Taylor Hays J, Lawrence D, Marton JP, Lee TC. Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients. *Respiratory Medicine* 2011;105(11):1682–90.
- Tavintharan S, Ning C, Su Chi L, Tay W, Shankar A, Shyong Tai E, Wong TY. Prevalence and risk factors for peripheral artery disease in an Asian population with diabetes mellitus. *Diabetes & Vascular Disease Research* 2009;6(2):80–6.
- Tchirikov M, Schlabritz-Loutsevitch N, Maher J, Buchmann J, Naberezhnev Y, Winarno AS, Seliger G. Mid-trimester preterm premature rupture of membranes (PPROM): etiology, diagnosis, classification, international recommendations of treatment options and outcome. *Journal of Perinatal Medicine* 2018;46(5):465–88.
- Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, et al. ESC guidelines on the diagnosis and treatment of peripheral artery diseases. *European Heart Journal* 2011;32(22):2851–906.
- Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Buck Louis GM. Prevalence of infertility

- in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertility and Sterility* 2013;99(5):1324–31e1.
- Thomas X, Chelghoum Y. Cigarette smoking and acute leukemia. *Leukemia and Lymphoma* 2004;45(6):1103–9.
- Thomson G, Wilson N, Blakely T, Edwards R. Ending appreciable tobacco use in a nation: using a sinking lid on supply. *Tobacco Control* 2010;19(5):431–5.
- Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *European Respiratory Journal* 2004;24(5):822–33.
- Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-year trends in smoking-related mortality in the United States. *New England Journal of Medicine* 2013a;368(4):351–64.
- Thun MJ, Lopez AD, Hartge P. Smoking-related mortality in the United States. *New England Journal of Medicine* 2013b;368(18):1753.
- Titz B, Sewer A, Schneider T, Elamin A, Martin F, Dijon S, Luettich K, Guedj E, Vuillaume G, Ivanov NV, et al. Alterations in the sputum proteome and transcriptome in smokers and early-stage COPD subjects. *Journal of Proteomics* 2015;128:306–20.
- Tofler GH, Muller JE, Stone PH, Davies G, Davis VG, Braunwald E. Comparison of long-term outcome after acute myocardial infarction in patients never graduated from high school with that in more educated patients. Multicenter Investigation of the Limitation of Infarct Size (MILIS). *American Journal of Cardiology* 1993;71(12):1031–5.
- Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. *Clinical Cancer Research* 2013;19(8):1941–8.
- Tong VT, Althabe F, Aleman A, Johnson CC, Dietz PM, Berrueta M, Morello P, Colomar M, Buekens P, Sosnoff CS, et al. Accuracy of self-reported smoking cessation during pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2015;94(1):106–11.
- Tong VT, England LJ, Rockhill KM, D'Angelo DV. Risks of preterm delivery and small for gestational age infants: effects of nondaily and low-intensity daily smoking during pregnancy. *Paediatric and Perinatal Epidemiology* 2017;31(2):144–8.
- Tønnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, Thomsen C, Nilsson F. Effects of smoking cessation and reduction in asthmatics. *Nicotine and Tobacco Research* 2005;7(1):139–48.
- Tonstad S, Sundfjør T, Seljeflot I. Effect of lifestyle changes on atherogenic lipids and endothelial cell adhesion molecules in young adults with familial premature coronary heart disease. *American Journal of Cardiology* 2005;95(10):1187–91.
- Törnwall ME, Virtamo J, Haukka JK, Aro A, Albanes D, Huttunen JK. Prospective study of diet, lifestyle, and intermittent claudication in male smokers. *American Journal of Epidemiology* 2000;151(9):892–901.
- Tran B, Falster MO, Douglas K, Blyth F, Jorm LR. Smoking and potentially preventable hospitalisation: the benefit of smoking cessation in older ages. *Drug and Alcohol Dependence* 2015;150:85–91.
- Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR. Prospective study of risk factors for esophageal and gastric cancers in the Linxian General Population Trial cohort in China. *International Journal of Cancer* 2005;113(3):456–63.
- Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The natural progression and remission of erectile dysfunction: results from the Massachusetts Male Aging Study. *Journal of Urology* 2007;177(1):241–6; discussion 6.
- Tsaprouni LG, Yang TP, Bell J, Dick KJ, Kanoni S, Nisbet J, Vinuela A, Grundberg E, Nelson CP, Meduri E, et al. Cigarette smoking reduces DNA methylation levels at multiple genomic loci but the effect is partially reversible upon cessation. *Epigenetics* 2014;9(10):1382–96.
- Tse LA, Fang XH, Wang WZ, Qiu H, Yu IT. Incidence of ischaemic and haemorrhagic stroke and the association with smoking and smoking cessation: a 10-year multicentre prospective study in China. *Public Health* 2012;126(11):960–6.
- Turato G, Di Stefano A, Maestrelli P, Mapp CE, Ruggieri MP, Roggeri A, Fabbri LM, Saetta M. Effect of smoking cessation on airway inflammation in chronic bronchitis. *American Journal of Respiratory and Critical Care Medicine* 1995;152(4 Pt 1):1262–7.
- Twardella D, Kupper-Nybelen J, Rothenbacher D, Hahmann H, Wusten B, Brenner H. Short-term benefit of smoking cessation in patients with coronary heart disease: estimates based on self-reported smoking data and serum cotinine measurements. *European Heart Journal* 2004;25(23):2101–8.
- Twardella D, Rothenbacher D, Hahmann H, Wusten B, Brenner H. The underestimated impact of smoking and smoking cessation on the risk of secondary cardiovascular disease events in patients with stable coronary heart disease: prospective cohort study. *Journal of the American College of Cardiology* 2006;47(4):887–9.
- U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999–2016), June 2019; <<http://www.cdc.gov/cancer/dataviz>>; accessed: July 24, 2019.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee*

- to the Surgeon General of the Public Health Service. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.
- U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. A Report of the Surgeon General, 1977–1978*. Washington: U.S. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979a. DHEW Publication No. (CDC) 79-50065.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General*. Washington: U.S. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979b. DHEW Publication No. (PHS) 79-50066.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1982. DHHS Publication No. (PHS) 82-50179.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1983. DHHS Publication No. (PHS) 84-50204.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984. DHHS Publication No. (PHS) 84-50205.
- U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Publication No. (CDC) 89-8411.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.
- U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
- U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
- U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions, September 2015; <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>>; accessed: May 24, 2017.
- University College London, Institute of Digital Health. ClinicAI research using LInked Bespoke studies and Electronic health Records (CALIBER), n.d.; <<http://www.ucl.ac.uk/digital-health/Research/research-projects/Caliber>>; accessed: August 3, 2018.
- van Asselt KM, Kok HS, van Der Schouw YT, Grobbee DE, te Velde ER, Pearson PL, Peeters PH. Current smoking at menopause rather than duration determines the onset of natural menopause. *Epidemiology* 2004;15(5):634–9.
- van Berkel TF, Boersma H, Roos-Hesselink JW, Erdman RA, Simoons ML. Impact of smoking cessation and smoking interventions in patients with coronary heart disease. *European Heart Journal* 1999;20(24):1773–82.

- van den Berkmortel FW, Wollersheim H, van Langen H, Smilde TJ, den Arend J, Thien T. Two years of smoking cessation does not reduce arterial wall thickness and stiffness. *Netherlands Journal of Medicine* 2004;62(7):235–41.
- Van Den Eeden SK, Shan J, Bruce C, Glasser M. Ectopic pregnancy rate and treatment utilization in a large managed care organization. *Obstetrics and Gynecology* 2005;105(5 Pt 1):1052–7.
- van Domburg RT, Meeter K, van Berkel DF, Veldkamp RF, van Herwerden LA, Bogers AJ. Smoking cessation reduces mortality after coronary artery bypass surgery: a 20-year follow-up study. *Journal of the American College of Cardiology* 2000;36(3):878–83.
- Van Spall HG, Chong A, Tu JV. Inpatient smoking-cessation counseling and all-cause mortality in patients with acute myocardial infarction. *American Heart Journal* 2007;154(2):213–20.
- Vanhoutte PM, Shimokawa H, Feletou M, Tang EH. Endothelial dysfunction and vascular disease—a 30th anniversary update. *Acta Physiologica* 2017;219(1):22–96.
- Vardavas CI, Chatzi L, Patelarou E, Plana E, Sarri K, Kafatos A, Koutis AD, Kogevinas M. Smoking and smoking cessation during early pregnancy and its effect on adverse pregnancy outcomes and fetal growth. *European Journal of Pediatrics* 2010;169(6):741–8.
- Venditti CC, Casselman R, Young I, Karumanchi SA, Smith GN. Carbon monoxide prevents hypertension and proteinuria in an adenovirus sFlt-1 preeclampsia-like mouse model. *PLoS One* 2014;9(9):e106502.
- Vermeulen A. Environment, human reproduction, menopause, and andropause. *Environmental Health Perspectives* 1993;101(Suppl 2):91–100.
- Versluis M, ten Hacken N, Postma D, Barroso B, Rutgers B, Geerlings M, Willemse B, Timens W, Hylkema M. Adenosine receptors in COPD and asymptomatic smokers: effects of smoking cessation. *Virchows Archiv* 2009;454(3):273–81.
- Vlietstra RE, Kronmal RA, Oberman A, Frye RL, Killip T 3rd. Effect of cigarette smoking on survival of patients with angiographically documented coronary artery disease. Report from the CASS registry. *JAMA: the Journal of the American Medical Association* 1986;255(8):1023–7.
- Vogazianos P, Fiala J, Vogazianos M. The influence of active maternal smoking during pregnancy on birth weights in Cyprus. *Central European Journal of Public Health* 2005;13(2):78–84.
- Voors AA, van Brussel BL, Plokker HW, Ernst SM, Ernst NM, Koomen EM, Tijssen JG, Vermeulen FE. Smoking and cardiac events after venous coronary bypass surgery. A 15-year follow-up study. *Circulation* 1996;93(1):42–7.
- Vucic EA, Chari R, Thu KL, Wilson IM, Cotton AM, Kennett JY, Zhang M, Lonergan KM, Steiling K, Brown CJ, et al. DNA methylation is globally disrupted and associated with expression changes in chronic obstructive pulmonary disease small airways. *American Journal of Respiratory Cell and Molecular Biology* 2014;50(5):912–22.
- Wallace JL, Aland KL, Blatt K, Moore E, DeFranco EA. Modifying the risk of recurrent preterm birth: influence of trimester-specific changes in smoking behaviors. *American Journal of Obstetrics and Gynecology* 2017;216(3):310.e1–310.e8.
- Wan ES, Qiu W, Baccarelli A, Carey VJ, Bacherman H, Rennard SI, Agusti A, Anderson W, Lomas DA, Demeo DL. Cigarette smoking behaviors and time since quitting are associated with differential DNA methylation across the human genome. *Human Molecular Genetics* 2012;21(13):3073–82.
- Wan ES, Qiu W, Carey VJ, Morrow J, Bacherman H, Foreman MG, Hokanson JE, Bowler RP, Crapo JD, DeMeo DL. Smoking-associated site-specific differential methylation in buccal mucosa in the COPD Gene Study. *American Journal of Respiratory Cell and Molecular Biology* 2015;53(2):246–54.
- Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. *JAMA: the Journal of the American Medical Association* 1995;274(2):155–60.
- Warren GW, Arnold SM, Valentino JP, Gal TJ, Hyland AJ, Singh AK, Rangnekar VM, Cummings KM, Marshall JR, Kudrimoti MR. Accuracy of self-reported tobacco assessments in a head and neck cancer treatment population. *Radiotherapy and Oncology* 2012;103(1):45–8.
- Warren GW, Cartmell KB, Garrett-Mayer E, Salloum RG, Cummings KM. Attributable failure of first-line cancer treatment and incremental costs associated with smoking by patients with cancer. *JAMA Network Open* 2019;2(4):e191703.
- Warren GW, Simmons VN. Tobacco use and the cancer patient. In: Devita VT, Rosenberg SA, Lawrence TS, editors. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Philadelphia (PA): Lippincott Williams & Wilkins, 2018.
- Warren GW, Sobus S, Gritz ER. The biological and clinical effects of smoking by patients with cancer and strategies to implement evidence-based tobacco cessation support. *Lancet Oncology* 2014;15(12):e568–e80.
- Washio Y, Higgins ST, Heil SH, Badger GJ, Skelly J, Bernstein IM, Solomon LJ, Higgins TM, Lynch ME, Hanson JD. Examining maternal weight gain during contingency-management treatment for smoking cessation among pregnant women. *Drug and Alcohol Dependence* 2011;114(1):73–6.
- Weijnenberg MP, Aardening PW, de Kok TM, de Goeij AF, van den Brandt PA. Cigarette smoking and KRAS oncogene mutations in sporadic colorectal cancer: results

- from the Netherlands Cohort Study. *Mutation Research* 2008;652(1):54–64.
- Wen CP, Cheng TY, Lin CL, Wu HN, Levy DT, Chen LK, Hsu CC, Eriksen MP, Yang HJ, Tsai SP. The health benefits of smoking cessation for adult smokers and for pregnant women in Taiwan. *Tobacco Control* 2005;14(Suppl 1):i56–i61.
- Wen CP, Tsai SP, Chen CJ, Cheng TY. The mortality risks of smokers in Taiwan: Part I: cause-specific mortality. *Preventive Medicine* 2004;39(3):528–35.
- Wendland EM, Pinto ME, Duncan BB, Belizán JM, Schmidt MI. Cigarette smoking and risk of gestational diabetes: a systematic review of observational studies. *BMC Pregnancy and Childbirth* 2008;8:53.
- White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Thrombosis and Haemostasis* 2005;93(2):298–305.
- Wikstrom AK, Stephansson O, Cnattingius S. Tobacco use during pregnancy and preeclampsia risk: effects of cigarette smoking and snuff. *Hypertension* 2010;55(5):1254–9.
- Wilcox AJ. On the importance—and the unimportance—of birthweight. *International Journal of Epidemiology* 2001;30(6):1233–41.
- Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *New England Journal of Medicine* 1988;319(4):189–94.
- Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. *Lancet* 1975;1(7904):415–20.
- Wilks DJ, Hay AW. Smoking and female fecundity: the effect and importance of study design. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2004;112(2):127–35.
- Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *International Journal of Epidemiology* 2001;30(3):540–6.
- Willemsse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *European Respiratory Journal* 2004;23(3):464–76.
- Willemsse BW, ten Hacken NH, Rutgers B, Lesman-Leegte IG, Postma DS, Timens W. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *European Respiratory Journal* 2005;26(5):835–45.
- Wilmink TB, Quick CR, Day NE. The association between cigarette smoking and abdominal aortic aneurysms. *Journal of Vascular Surgery* 1999;30(6):1099–105.
- Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Archives of Internal Medicine* 2000;160(7):939–44.
- Wilson N, Thomson GW, Edwards R, Blakely T. Potential advantages and disadvantages of an endgame strategy: a 'sinking lid' on tobacco supply. *Tobacco Control* 2013;22(Suppl 1):i18–i21.
- Wisborg K, Kesmodel U, Henriksen TB, Olsen SF, Secher NJ. Exposure to tobacco smoke in utero and the risk of stillbirth and death in the first year of life. *American Journal of Epidemiology* 2001;154(4):322–7.
- Wise RA. The value of forced expiratory volume in 1 second decline in the assessment of chronic obstructive pulmonary disease progression. *American Journal of Medicine* 2006;119(10 Suppl 1):4–11.
- Wiseman S, Kenchington G, Dain R, Marshall CE, McCollum CN, Greenhalgh RM, Powell JT. Influence of smoking and plasma factors on patency of femoropopliteal vein grafts. *BMJ* 1989;299(6700):643–6.
- Wong DR, Willett WC, Rimm EB. Smoking, hypertension, alcohol consumption, and risk of abdominal aortic aneurysm in men. *American Journal of Epidemiology* 2007;165(7):838–45.
- Woo J, Lynn H, Wong SY, Hong A, Tang YN, Lau WY, Lau E, Orwoll E, Kwok TC. Correlates for a low ankle-brachial index in elderly Chinese. *Atherosclerosis* 2006;186(2):360–6.
- Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *New England Journal of Medicine* 2016;374(19):1811–21.
- Woods JR Jr, Plessinger MA, Miller RK. Vitamins C and E: missing links in preventing preterm premature rupture of membranes? *American Journal of Obstetrics and Gynecology* 2001;185(1):5–10.
- World Health Organization. Preterm birth (fact sheet), November 2017; <<http://www.who.int/mediacentre/factsheets/fs363/en/>>; accessed: April 18, 2018.
- Xie SH, Rabbani S, Petrick JL, Cook MB, Lagergren J. Racial and ethnic disparities in the incidence of esophageal cancer in the United States, 1992–2013. *American Journal of Epidemiology* 2017;186(12):1341–51.
- Xiong X, Zhang J, Fraser WD. Quitting smoking during early versus late pregnancy: the risk of preeclampsia and adverse birth outcomes. *Journal of Obstetrics and Gynaecology Canada. Journal d'Obstétrique et Gynécologie du Canada* 2009;31(8):702–7.
- Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E. Deaths: final data for 2016. *National Vital Statistics Reports* 2018;67(5):1–76.

- Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BG Jr. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *American Review of Respiratory Disease* 1992;146(5 Pt 1):1345–8.
- Yan J, Groothuis PA. Timing of prenatal smoking cessation or reduction and infant birth weight: evidence from the United Kingdom Millennium Cohort Study. *Maternal and Child Health Journal* 2015;19(3):447–58.
- Yang B, Jacobs EJ, Gapstur SM, Stevens V, Campbell PT. Active smoking and mortality among colorectal cancer survivors: the Cancer Prevention Study II nutrition cohort. *Journal of Clinical Oncology* 2015a;33(8):885–93.
- Yang D, Iyer S, Gardener H, Della-Morte D, Crisby M, Dong C, Cheung K, Mora-McLaughlin C, Wright CB, Elkind MS, et al. Cigarette smoking and carotid plaque echodensity in the Northern Manhattan Study. *Cerebrovascular Diseases* 2015b;40(3-4):136–43.
- Yang Q, Tong X, Schieb L, Vaughan A, Gillespie C, Wiltz JL, King SC, Odom E, Merritt R, Hong Y, et al. Vital Signs: Recent Trends in Stroke Death Rates—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;66(35):933–9.
- Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Annals of Internal Medicine* 2010;152(1):10–7.
- Yi M, Chun EJ, Lee MS, Lee J, Choi SI. Coronary CT angiography findings based on smoking status: do ex-smokers and never-smokers share a low probability of developing coronary atherosclerosis? *International Journal of Cardiovascular Imaging* 2015;31(Suppl 2):169–76.
- Yu G, Gail MH, Consonni D, Carugno M, Humphrys M, Pesatori AC, Caporaso NE, Goedert JJ, Ravel J, Landi MT. Characterizing human lung tissue microbiota and its relationship to epidemiological and clinical features. *Genome Biology* 2016;17(1):163.
- Yuan JM, Castelao JE, Gago-Dominguez M, Yu MC, Ross RK. Tobacco use in relation to renal cell carcinoma. *Cancer Epidemiology, Biomarkers and Prevention* 1998;7(5):429–33.
- Zatu MC, Van Rooyen JM, Schutte AE. Smoking and vascular dysfunction in Africans and Caucasians from South Africa. *Cardiovascular Journal of Africa* 2011;22(1):18–24.
- Zendejdel K, Nyren O, Luo J, Dickman PW, Boffetta P, Englund A, Ye W. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *International Journal of Cancer* 2008;122(5):1095–9.
- Zenzes MT, Reed TE, Casper RF. Effects of cigarette smoking and age on the maturation of human oocytes. *Human Reproduction* 1997;12(8):1736–41.
- Zhang J, Klebanoff MA, Levine RJ, Puri M, Moyer P. The puzzling association between smoking and hypertension during pregnancy. *American Journal of Obstetrics and Gynecology* 1999;181(6):1407–13.
- Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, et al. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation* 2008;118(15):1577–84.
- Zhang Y, Yang R, Burwinkel B, Breitling LP, Brenner H. F2RL3 methylation as a biomarker of current and lifetime smoking exposures. *Environmental Health Perspectives* 2014;122(2):131–7.
- Zhang YJ, Iqbal J, van Klaveren D, Campos CM, Holmes DR, Kappetein AP, Morice MC, Banning AP, Grech ED, Bourantas CV, et al. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. *Journal of the American College of Cardiology* 2015;65(11):1107–15.
- Zheng ZJ, Rosamond WD, Chambless LE, Nieto FJ, Barnes RW, Hutchinson RG, Tyroler HA, Heiss G. Lower extremity arterial disease assessed by ankle-brachial index in a middle-aged population of African Americans and Whites: the Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Preventive Medicine* 2005;29(5 Suppl 1):42–9.
- Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: a meta-analysis of prospective studies. *International Journal of Cardiology* 2016;218:259–66.

Chapter 5

The Benefits of Smoking Cessation on Overall Morbidity, Mortality, and Economic Costs

Introduction 439

Benefits of Smoking Cessation on Overall Morbidity 439

Conclusions from Previous Surgeon General's Reports 439

Description of the Literature Review 440

Assessment of Morbidity 440

Assessment of Smoking Status 440

Epidemiologic Evidence 457

Cross-Sectional Studies 457

Longitudinal Studies 458

Synthesis of the Evidence 460

Summary of the Evidence 460

Benefits of Smoking Cessation on All-Cause Mortality 461

Conclusions from Previous Surgeon General's Reports 461

Summary of the Evidence 464

Benefits of Smoking Cessation on Economic Costs 465

Economic Costs of Smoking 465

Economics of Smoking Cessation 466

Principles of Cost-Benefit and Cost-Effectiveness Analysis 467

Cost-Effectiveness of Clinical Smoking Cessation Interventions 467

Cost-Effectiveness of Nonclinical Smoking Cessation Interventions 482

Cost-Effectiveness of Tobacco Price Increases Through Taxation 482

Synthesis of the Evidence 482

Summary of the Evidence 485

Conclusions 485

References 486

Introduction

Cigarette smoking causes multiple diseases and reduces the general level of health of smokers (U.S. Department of Health and Human Services [USDHHS] 2004, 2014). These health consequences have been well documented in previous Surgeon General's reports. The 1964 report first summarized results on smoking and all-cause mortality, finding that smoking causes a 70% increase in risk of adverse health consequences (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). The 2004 report found smoking generally diminishes health (USDHHS 2004). General measures of health can be informative because they provide an integrative indicator of the health burden placed on smokers and on society overall. In addition to the direct human costs that smoking places on persons and society, one general measure with acknowledged implications for public health policy and practice is the economic cost of smoking.

This chapter considers broad indicators of burden in relation to smoking cessation, including morbidity,

mortality, and economic costs. Initially, it considers how general indicators of health can change after smoking cessation. This type of information is critical to informing smokers about the potential benefits of cessation and serves as a strong rationale to provide interventions that can help increase the success of quitting smoking. Such programs may be offered through healthcare organizations, communities, states, and other organizations. Smoking is known to generate healthcare and other economic costs and to affect the economics of the households of smokers (USDHHS 2014). Previous Surgeon General's reports on tobacco have periodically reviewed the economic costs of smoking, as tracked by the Centers for Disease Control and Prevention's (CDC's) Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) model. This chapter expands on this work by focusing on the most recently available scientific literature on the economic benefits of smoking cessation, while also complementing the kinds of cost estimates previously provided by SAMMEC.

Benefits of Smoking Cessation on Overall Morbidity

Chapter 4 of this report (The Health Benefits of Smoking Cessation) describes the associations between smoking cessation and changes in risk for specific disease outcomes. It also addresses how cessation affects the natural history of various disease outcomes, such as by slowing the progression of underlying pathophysiological processes. In addition to the beneficial impacts on specific disease outcomes, previous reviews of smoking cessation and morbidity (Goldenberg et al. 2014) have concluded that cessation is associated with improvement in health-related quality of life (HRQoL), a broad construct defined by *Healthy People 2020* as “a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning” (Office of Disease Prevention and Health Promotion 2018). In a complementary conclusion, after evaluating a broad range of general evidence, the 2004 Surgeon General's report concluded that active smoking is causally associated with diminished health status (USDHHS 2004).

This chapter addresses the evidence on smoking cessation and its relationship to more general measures of health outcomes, particularly whether cessation improves general QoL compared with continued smoking. This review aligns with and complements the approach

used in previous Surgeon General's reports on smoking, including the 2014 Surgeon General's report (USDHHS 2014). However, to limit the scope of this review, some of the many correlates of well-being (e.g., absenteeism from work) are not specifically considered.

Conclusions from Previous Surgeon General's Reports

Previous Surgeon General's reports (USDHHS 1990, 2004) have comprehensively covered the relationship between smoking and general morbidity. The 1990 Surgeon General's report on the health benefits of smoking cessation synthesized scientific evidence about cessation and its effects on general morbidity, concluding that “former smokers have better health status than current smokers as measured in a variety of ways, including days of illness, number of health complaints, and self-reported health status” (USDHHS 1990, p. 9). However, that report also found that the reviewed studies were “extremely heterogeneous, with some methodologic shortcomings” (USDHHS 1990, p. 89) and that the “variety of measures used makes direct comparison across studies problematic” (USDHHS

1990, p. 87). The 2004 Surgeon General's report on the health consequences of active smoking subsequently reviewed studies that included various indicators of general health, concluding that "the evidence is sufficient to infer a causal relationship between smoking and diminished health status that may be manifest as increased absenteeism from work and increased use of medical care services" (USDHHS 2004, p. 676). In addition, a major conclusion of the 2004 report was that "quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general" (USDHHS 2004, p. 25). The present chapter updates these findings on the basis of more recent studies of smoking cessation and indicators of general morbidity.

Description of the Literature Review

Scientific literature from 1990 to 2017 was systematically reviewed, and reference lists from the identified articles were searched for additional studies. Search terms included "smoking cessation," "epidemiology," "morbidity," "health status," and "quality of life." Studies were included if they measured the benefit of smoking cessation for general morbidity in former cigarette smokers; thus, the appropriate comparison group was continuing cigarette smokers but not never smokers. Accordingly, only studies that specifically and directly compared outcomes between former cigarette smokers (defined in multiple ways) and current cigarette smokers were considered. Studies that included former cigarette smokers but used only never smokers as the reference group were not included because such studies were not informative for the purpose of this chapter. However, when informative comparisons were made in eligible studies that met the criterion of comparisons with current smokers, some findings for never smokers were included.

Following the systematic review of literature, 24 studies published from 1995 to 2016 were identified that assessed smoking cessation and general morbidity, including 7 cross-sectional studies (Table 5.1) (Tillmann and Silcock 1997; Olufade et al. 1999; Mulder et al. 2001; Bolliger et al. 2002; Mody and Smith 2006; Heikkinen et al. 2008; McClave et al. 2009) and 16 prospective cohort studies (Tables 5.2–5.4) (Stewart et al. 1995; Taira et al. 2000; Bolliger et al. 2002; Zillich et al. 2002; Erickson et al. 2004; Mitra et al. 2004; Croghan et al. 2005; Wiggers et al. 2006; Jensen et al. 2007; Rungruanghiranya et al. 2008; Gutiérrez-Bedmar et al. 2009; Balduyck et al. 2011; Papadopoulos et al. 2011; Hays et al. 2012; Piper et al. 2012; Tian et al. 2016).

Assessment of Morbidity

The general measures of morbidity used in the 24 identified studies varied but cover three main categories: general, smoking specific, or disease specific:

1. **General.** Many studies used general measures of HRQoL, most frequently the Short Form (SF)-36 (SF-36) and SF-12 surveys, both the Medical Outcomes Study (Ware Jr and Sherbourne 1992) and RAND versions (Hays and Morales 2001). One study (Mitra et al. 2004) adapted the SF-36 for use in a population with mobility impairments. The other generic measures of HRQoL included the 15-D (dimensional) (Sintonen 1995), the EuroQoL (The EuroQol Group 1990), the QoL Inventory (Frisch et al. 1992), the World Health Organization's QOL-BREF (Skevington et al. 2004), CDC's HRQOL-4 and its Healthy Days Symptoms Module (Moriarty et al. 2003), and the Functional Status Questionnaire (Jette et al. 1986). The studies identified in the literature review also assessed dissatisfaction with life and general health status.
2. **Smoking specific.** One study (Olufade et al. 1999) used the Smoking Cessation Quality of Life (SCQoL) questionnaire.
3. **Disease specific.** Some studies used disease-specific measures of HRQoL. These measures assess the impact of specific diseases on relevant components of QoL. The European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire QLQ-C30 (Aaronson et al. 1993) was used, along with the LC13 module for lung cancer (Bergman et al. 1994) and the H&N35 module for head and neck cancer (Bjordal et al. 1994). Other disease-specific instruments included the Aquarel questionnaire for patients with pacemakers (Stofmeel et al. 2001), the Clinical COPD Questionnaire (van der Molen et al. 2003), and the VasuQoL questionnaire for patients with peripheral arterial disease (Morgan et al. 2001).

Assessment of Smoking Status

Most of the 24 identified studies assessed cigarette smoking status by self-report. Self-reported smoking status continues to be sufficiently valid and reliable for studying the general population but may be less accurate for assessing smoking in high-risk or medical patients (Velicer et al. 1992; USDHHS 2004, 2014).

Table 5.1 Cross-sectional studies about smoking status and quality of life

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Tillmann and Silcock (1997)	<ul style="list-style-type: none"> • Cross-sectional study • Current smokers and ex-smokers randomly selected from records of nine general practices • n = 3,000 • 1995 • Scotland 	<ul style="list-style-type: none"> • Current smokers (n = 1,500) • Ex-smokers of 5 years or more (n = 1,500) 	<ul style="list-style-type: none"> • SF-36 • EuroQoL tariff scores 	<ul style="list-style-type: none"> • HRQoL, as measured by SF-36 and EuroQoL tariff scores, was significantly higher for ex-smokers than for current smokers. • Mean difference by measure and QoL dimension: <ul style="list-style-type: none"> – EuroQoL tariff: 0.03 (95% CI, 0.011–0.058), p = 0.004 – Physical functioning: 3.93 (95% CI, 1.267–6.585), p = 0.004 – Role-physical: 4.52 (95% CI, 0.519–8.516), p = 0.027 – Bodily pain: 3.10 (95% CI, 0.508–5.698), p = 0.019 – General health: 5.32 (95% CI, 3.027–7.611), p = 0.000 – Vitality: 5.41 (95% CI, 3.348–7.469), p = 0.000 – Social functioning: 4.36 (95% CI, 1.015–6.810), p = 0.000 – Role-emotional: 4.77 (95% CI, 0.960–8.588), p = 0.014 – Mental health: 5.13 (95% CI, 3.401–6.907), p = 0.000 	—

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Olufade et al. (1999)	<ul style="list-style-type: none"> • Cross-sectional study conducted as a pilot test of SCQoL questionnaire • Convenience sample of smokers and former smokers, 18 years of age and older at health clinics • n = 101 • 1997–1998 • United States 	<ul style="list-style-type: none"> • Current smokers (n = 75) • Former smokers, smokefree for ≥2 weeks (n = 23) 	<ul style="list-style-type: none"> • SF-36 • SCQoL 	<ul style="list-style-type: none"> • Compared with current smokers, former smokers had significantly higher scores on physical functioning, vitality, general health, and PCS-36, but they showed no significant differences on other SF-36 measures • Compared with current smokers, former smokers had significantly higher scores on SCQoL measures of self-control, sleep, and anxiety, but they did not differ on social interactions or cognitive functioning • SF-36, mean difference (former smoker vs. current smoker) by QoL dimension: <ul style="list-style-type: none"> – Physical functioning: 15.7, p <0.05 – Role-physical: 13.5, p >0.05 – Role-emotional: 11.3, p >0.05 – Vitality: 15.1, p <0.05 – Mental health: 7.4, p >0.05 – Social functioning: 5.4, p >0.05 – Bodily pain: 2.9, p >0.05 – General health: 21.5, p <0.01 – PCS-36: 6.1, p <0.05 – MCS-36: 3.4, p >0.05 • SCQoL, mean difference (former smoker vs. current smoker) by QoL dimension: <ul style="list-style-type: none"> – Social interactions: 7.9, p >0.05 – Self-control: 45.2, p <0.01 – Sleep: 15.1, p <0.01 – Cognitive functioning: 9.7, p >0.05 – Anxiety: 15.2, p <0.05 	—

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Mulder et al. (2001)	<ul style="list-style-type: none"> • Cross-sectional study • Random sample of the general population, 20–59 years of age without a history of smoking-related chronic diseases • n = 9,660 • 1995–1997 • The Netherlands 	<ul style="list-style-type: none"> • Never smokers • Ex-smokers • Current smokers 	<ul style="list-style-type: none"> • RAND-36 (adapted from SF-36) 	<ul style="list-style-type: none"> • Ex-smokers reported significantly higher QoL scores than current smokers for all QoL dimensions ($p < .05$), except for bodily pain • Adjusted mean scores on QoL measures did not differ significantly between never smokers and ex-smokers, except for bodily pain ($p < 0.0001$) • A higher number of years since quitting was associated with higher scores on general health, vitality, mental health, and the MCS • Differences in QoL scores between ex-smokers and current smokers were more pronounced for QoL dimensions reflecting mental health than physical health • No significant trend was observed for time since quitting 	—

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Bellido-Casado et al. (2004)	<ul style="list-style-type: none"> • Cross-sectional study • Representative sample of the general population older than 14 years of age • n = 265 • 1997–2000 • Spain 	<ul style="list-style-type: none"> • Smokers • Nonsmokers • Former smokers 	<ul style="list-style-type: none"> • SF-36 	<ul style="list-style-type: none"> • No statistically significant differences by smoking status in measures of physical health (p = 0.682) or emotional health (p = 0.430) • Physical QoL dimensions—mean scores (95% CI): <ul style="list-style-type: none"> – Physical function: <ul style="list-style-type: none"> ○ Smokers: 86.92 (83.14–90.71) ○ Former smokers: 89.09 (84.74–93.44) – Role-emotional: <ul style="list-style-type: none"> ○ Smokers: 86.81 (78.79–94.83) ○ Former smokers: 89.57 (80.35–98.79) – Bodily pain: <ul style="list-style-type: none"> ○ Smokers: 68.24 (62.36–74.13) ○ Former smokers: 67.22 (60.46–73.99) – General health: <ul style="list-style-type: none"> ○ Smokers: 59.54 (54.72–64.36) ○ Former smokers: 61.24 (55.71–66.78) • Emotional QoL dimensions—mean scores (95% CI): <ul style="list-style-type: none"> – Vitality: <ul style="list-style-type: none"> ○ Smokers: 59.07 (53.32–64.83) ○ Former smokers: 63.55 (56.94–70.17) – Social function: <ul style="list-style-type: none"> ○ Smokers: 83.66 (78.10–89.22) ○ Former smokers: 88.00 (81.60–94.39) – Role-emotional: <ul style="list-style-type: none"> ○ Smokers: 79.44 (69.01–89.87) ○ Former smokers: 84.67 (72.68–96.66) – Mental health: <ul style="list-style-type: none"> ○ Smokers: 71.99 (66.90–77.08) ○ Former smokers: 74.33 (68.48–80.18) 	Adjusted for age, sex, social class, alcohol consumption, accumulated exposure to tobacco, diurnal sleepiness, number of known risk factors, and BMI

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Mody and Smith (2006)	<ul style="list-style-type: none"> • Cross-sectional study • Representative sample of noninstitutionalized adults from the 2001 Behavioral Risk Factor Surveillance System • n = 209,031 • 2001 • United States 	<ul style="list-style-type: none"> • Nonsmokers (n = 108,072) • Current smokers (n = 48,096) • Ex-smokers (n = 52,863) 	<ul style="list-style-type: none"> • HRQoL measured by self-rated health status, number of days of poor physical health, number of days of poor mental health, and number of days of activity limitations 	<ul style="list-style-type: none"> • Compared with ex-smokers, current smokers were (reported as ORs): <ul style="list-style-type: none"> – 1.48 (95% CI, 1.32–1.65) times as likely to experience ≥14 days of activity limitations in the past 30 days – 1.29 (no CI provided) times as likely to report poor general health – 1.30 (95% CI, 1.19–1.42) times as likely to report ≥14 days of poor physical health – 1.65 (95% CI, 1.50–1.81) times as likely to report ≥14 days of poor mental health 	Adjusted for age, sex, race, education level, marital status, annual household income, BMI, and presence of at least one comorbid disease
Heikkinen et al. (2008)	<ul style="list-style-type: none"> • Cross-sectional study • Nationally representative sample of adults, 30 years of age and older • n = 8,028 • 2000–2001 • Finland 	<ul style="list-style-type: none"> • Never smokers • Daily smokers • Occasional smokers • Ex-smokers (reported not smoking for at least the past month) 	<ul style="list-style-type: none"> • 15-D • Overall QoL was assessed by a single-question measure that captured the respondent's perception and estimation of his or her QoL 	<ul style="list-style-type: none"> • Ex-smokers reported higher scores than daily smokers on most dimensions of QoL • Compared with men who smoked daily, men who were ex-smokers scored significantly higher in mobility, seeing, breathing, usual activities, discomfort and symptoms, depression, distress, and vitality (p <.05) and significantly lower in excreting (p <0.05) • Compared with women who smoked daily, women who were ex-smokers scored significantly higher on breathing, eating, depression, distress, and vitality (p <0.05) 	Adjusted for age

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
McClave et al. (2009) (continues on next page)	<ul style="list-style-type: none"> • Cross-sectional study • Representative sample of noninstitutionalized adults from the 2006 Behavioral Risk Factor Surveillance System surveys in Delaware, Hawaii, Rhode Island, and New York • n = 17,800 • United States 	<ul style="list-style-type: none"> • Never smokers (n = 9,149) • Former smokers (n = 5,522) • Nonquitters (n = 1,363) • Unsuccessful quitters (n = 1,766) 	<ul style="list-style-type: none"> • CDC HRQoL-14 Healthy Days Symptoms Module • Self-rated general health status • Life dissatisfaction 	<ul style="list-style-type: none"> • Former smokers were less likely than nonquitters to report life dissatisfaction and frequent depressive symptoms • No significant differences were found in general health status, frequent anxiety symptoms, frequent mental distress, frequent physical distress, frequent activity limitations, frequent pain, infrequent vitality, and frequent sleep impairment • Among men, no significant differences in HRQoL were found between former smokers and nonquitters • Among women, unsuccessful quitters were more likely than current smokers to report the frequent occurrence of mental distress, physical distress, and pain (p <.05) • OR (95% CI) by QoL dimension and smoking status: <ul style="list-style-type: none"> – Fair/poor general health: <ul style="list-style-type: none"> ◦ Former smoker: 1.1 (0.7–1.7) ◦ Never smoker: 1.1 (0.7–1.7) – Life dissatisfaction: <ul style="list-style-type: none"> ◦ Former smoker: 0.5 (0.3–0.9) ◦ Never smoker: 0.4 (0.2–0.7) – Frequent anxiety symptoms: <ul style="list-style-type: none"> ◦ Former smoker: 0.7 (0.5–1.1) ◦ Never smoker: 0.5 (0.4–0.7) – Frequent depressive symptoms: <ul style="list-style-type: none"> ◦ Former smoker: 0.7 (0.4–1.0) ◦ Never smoker: 0.6 (0.4–1.0) – Frequent mental distress: <ul style="list-style-type: none"> ◦ Former smoker: 1.3 (0.8–2.0) ◦ Never smoker: 0.8 (0.5–1.3) – Frequent physical distress: <ul style="list-style-type: none"> ◦ Former smoker: 1.3 (0.8–2.0) ◦ Never smoker: 1.0 (0.6–1.5) 	Adjusted for age, race/ethnicity, sex, education, marital status, employment status, chronic disease, and healthcare coverage; unsuccessful quitters were respondents who had smoked at least 100 cigarettes in their lifetime, currently smoked every day or some days, and had abstained from smoking for 1 day or longer during the previous year in an unsuccessful attempt to quit smoking; and nonquitters were current smokers who made no attempt to quit

Table 5.1 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
(continued from previous page) McClave et al. (2009)	—	—	—	<ul style="list-style-type: none"> – Frequent activity limitations: <ul style="list-style-type: none"> ○ Former smoker: 1.2 (0.7–2.1) ○ Never smoker: 0.8 (0.5–1.4) – Frequent pain: <ul style="list-style-type: none"> ○ Former smoker: 1.3 (0.8–1.9) ○ Never smoker: 1.0 (0.7–1.4) – Infrequent vitality: <ul style="list-style-type: none"> ○ Former smoker: 1.1 (0.8–1.5) ○ Never smoker: 1.1 (0.8–1.4) – Frequent sleep impairment: <ul style="list-style-type: none"> ○ Former smoker: 0.8 (0.6–1.1) ○ Never smoker: 0.6 (0.4–0.8) 	—

Notes: **15-D** = 15 dimensions (generic, self-administered measure of HRQoL); **BMI** = body mass index; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **EuroQoL** = European quality of life; **HRQoL** = health-related quality of life; **MCS** = Mental Component Summary; **OR** = odds ratio; **PCS** = Physical Component Summary; **QoL** = quality of life; **SCQoL** = Smoking Cessation Quality of Life; **SF** = Short Form (survey).

Table 5.2 Prospective studies about smoking status and quality of life

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Stewart et al. (1995)	<ul style="list-style-type: none"> • Cohort study from RCT of smoking cessation • Current smokers, 18–65 years of age at the time of enrollment into RCT, randomly selected in California and abstinent for 24 hours at baseline • n = 323 • United States • HRQoL follow-up at 6 months; smoking status assessed at 3 and 6 months 	<ul style="list-style-type: none"> • Smokers: Had smoked within the last 7 days (n = 220) • Nonsmokers: Had not smoked within the past 7 days; confirmed with cotinine test (n = 103) 	<ul style="list-style-type: none"> • Mental health: <ul style="list-style-type: none"> – Psychological well-being/distress – Depression/behavioral–emotional control – Anxiety – Positive affect – Cognitive functioning – Energy/fatigue – Sleep adequacy – Self-esteem – Sense of mastery • Physical health: <ul style="list-style-type: none"> – Physical functioning – Role functioning – Social functioning – Pain – Current health perceptions 	<ul style="list-style-type: none"> • Compared with smokers at 6 months, nonsmokers had: • Significantly higher scores on mental health dimensions • Significantly lower scores on physical and role functioning • No difference in scores on physical functioning, social functioning, pain, and current health perceptions • Mean difference (smokers vs. nonsmokers) at 6 months by QoL component and dimension: <ul style="list-style-type: none"> – Mental health: <ul style="list-style-type: none"> ○ Psychological well-being/distress: 4.4, p <.05 ○ Depression/behavioral–emotional control: 4.9, p <.01 ○ Anxiety: 7.7, p <.001 ○ Positive affect: 4.2, p <.05 ○ Cognitive functioning: 3.4, p <.05 ○ Energy/fatigue: 6.6, p <.01 ○ Sleep adequacy: 6.5, p <.05 ○ Self-esteem: 3.6, p <.05 ○ Sense of mastery: 9.3, p <.001 – Physical health: <ul style="list-style-type: none"> ○ Physical functioning: 0.8, p >.05 ○ Role functioning: -6.0, p <.05 ○ Social functioning: -0.7, p >.05 ○ Pain: 3.4, p >.05 ○ Current health perceptions: 3.2, p >.05 	<p>For all QoL dimensions, except sleep adequacy, self-esteem, and sense of mastery, adjusted for age, sex, ethnicity, education, employment status, marital status, number of chronic conditions, number of cigarettes smoked at enrollment, nicotine dependence at enrollment, nicotine gum intervention, and initial assessment of HRQoL; and for sleep adequacy, self-esteem, and sense of mastery dimensions, adjusted for all except initial assessment of HRQoL; excluded those who had relapsed at 3 months but quit again by 6 months and those who were not smoking at 3 months but were smoking at 6 months</p>

Table 5.2 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Erickson et al. (2004)	<ul style="list-style-type: none"> • Short-term longitudinal cohort study • Adults actively attempting to quit smoking • n = 34 • 1999–2002 • United States • Follow-up at 1 week after quitting 	<ul style="list-style-type: none"> • Low addiction: FTND ≤ 6 (n = 22) • High addiction: FTND > 6 (n = 12) 	<ul style="list-style-type: none"> • SCQoL questionnaire: <ul style="list-style-type: none"> – HRQoL – SF-36 • WPS 	<ul style="list-style-type: none"> • Anxiety and cognitive functioning dimensions were significantly worse 1 week after quitting • Self-control dimension improved significantly 1 week after quitting • SF-36 measure of general health showed a significant improvement 1 week after quitting. • WPS score was lower 1 week after quitting but was not significant • Low-addiction group had higher HRQoL at baseline • Compared with the high-addiction group, the low-addiction group showed a significant improvement in more HRQoL domain scores after quitting • SCQoL results by domain: <ul style="list-style-type: none"> – Anxiety: p = 0.04 – Cognitive function: p = 0.02 – Self-control: p = 0.001 – Sleep: p = 0.15 – Social interaction: p = 0.34 • SF-36 results by domain: <ul style="list-style-type: none"> – Bodily pain: p = 0.12 – General health: p = 0.01 – Mental health: p = 0.14 – Physical function: p = 0.27 – Role-emotional: p = 0.65 – Role-physical: p = 0.25 – Social function: p = 0.26 – Vitality: p = 0.53 • WPS: p = 0.17 	—

Table 5.2 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Gutiérrez-Bedmar et al. (2009)	<ul style="list-style-type: none"> • Cohort study • University graduates • n = 5,234 • 1999–2006 • Spain • Follow-up at 4 years 	<ul style="list-style-type: none"> • Baseline: <ul style="list-style-type: none"> – Nonsmokers (n = 2,639) – Ex-smokers (n = 1,419) – Smokers (n = 1,048) • Follow-up: <ul style="list-style-type: none"> – Nonsmokers (n = 3,594) – Smokers (n = 818) – Recent quitters (n = 435) – Starters (n = 205) 	<ul style="list-style-type: none"> • SF-36 (validated Spanish version) 	<ul style="list-style-type: none"> • Ex-smokers had significantly lower mean scores on the SF-36 than nonsmokers in two QoL dimensions: role-physical and bodily pain • Ex-smokers had significantly higher scores than smokers of 15–24 cigarettes per day in two QoL dimensions: general health and role-emotional • Ex-smokers had significantly higher scores than smokers of ≥25 cigarettes per day in four QoL dimensions: general health, social functioning, role-emotional, and mental health • At follow-up, the recent quitters group had significantly better mean scores than smokers in two QoL dimensions: general health and role-emotional 	Adjusted for age and sex
Tian et al. (2016)	<ul style="list-style-type: none"> • Cohort study • 25-year follow-up of participants in a previous cohort, 23–34 years of age at enrollment • n = 2,080 • 2001–2011 • Australia • Follow-up at 2 and 5 years 	<ul style="list-style-type: none"> • Baseline smoking status: <ul style="list-style-type: none"> – Never smoker – Former smoker – Current smoker • Change in smoking status: <ul style="list-style-type: none"> – Stable, never smokers – Stable, former smokers – Resumed – Continuing – Quitter 	<ul style="list-style-type: none"> • SF-12 PCS and MCS 	<ul style="list-style-type: none"> • No significant differences in HRQoL dimensions at baseline between never and former smokers. • Continuing smokers had larger reductions than quitters • The risk of clinically significant improvement in physical HRQoL was higher for quitters than for continuing smokers • Clinically meaningful improvement in PCS (quitters vs. continuing): RR = 1.43 (95% CI, 1.03–1.98) • Mean difference, baseline PCS (former smokers vs. never smokers): -0.49 (95% CI, -1.32–0.34) • Mean difference, baseline MCS (former smokers vs. never smokers): -0.36 (95% CI, -1.31–0.60) 	Adjusted for age, sex, marital status, follow-up duration, baseline PCS, residing in a major city, education level, BMI, IPAQ level, total alcoholic drinks per day, and diagnosis of current severe psychological distress

Notes: **BMI** = body mass index; **CI** = confidence interval; **FTND** = Fagerström Test for Nicotine Dependence; **HRQoL** = health-related quality of life; **IPAQ** = International Physical Activity Questionnaire; **MCS** = Mental Component Summary; **PCS** = Physical Component Summary; **QoL** = quality of life; **RCT** = randomized controlled trial; **RR** = relative risk; **SCQoL** = Smoking Cessation Quality of Life; **SF** = Short Form (survey); **WPS** = Work Performance Scale.

Table 5.3 Prospective studies of populations undergoing cessation treatment

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Bolliger et al. (2002)	<ul style="list-style-type: none"> • Cohort study from RCT of oral nicotine inhaler for smoking reduction • Healthy adult volunteers, unable or unwilling to stop smoking immediately, randomized to active or placebo inhalers for 18 months and encouraged to reduce smoking as much as possible • n = 400 • Switzerland • Follow-up for 24 months 	<ul style="list-style-type: none"> • Successful reducers: Reduction of daily cigarettes of at least 50% from week 6 to month 24 (n = 25) • Control group: Failed to reduce smoking or carbon monoxide output, or failed to attend one or more of seven follow-up visits (n = 285) 	<ul style="list-style-type: none"> • SF-36: General health, physical functioning, energy, and emotional well-being 	<ul style="list-style-type: none"> • Significantly greater improvement in general health was seen in successful reducers compared with those in the control group • Among successful reducers, physical functioning showed nonsignificant <i>t</i> trend toward greater improvement • Emotional well-being and energy improved more in the successful reducers than among those in the control group, but the difference was not significant • Mean change from baseline by QoL dimension and smoking status: <ul style="list-style-type: none"> – General health: <ul style="list-style-type: none"> ○ Successful reducer: 9.4 ○ Control group: 2.3 ○ p = 0.049 – Physical functioning: <ul style="list-style-type: none"> ○ Successful reducer: 7.4 ○ Control group: 4.9 ○ p = 0.073 – Energy: <ul style="list-style-type: none"> ○ Successful reducer: 6.8 ○ Control group: 5.3 ○ p = 0.23 – Emotional well-being: <ul style="list-style-type: none"> ○ Successful reducer: 6.2 ○ Control group: 4.2 ○ p = 0.50 	—

Table 5.3 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Zillich et al. (2002)	<ul style="list-style-type: none"> • Cohort study • Adult smokers interested in quitting and enrolled in a pharmacist-based smoking cessation program • n = 31 • 2000–2001 • United States • Follow-up at 6 months 	<ul style="list-style-type: none"> • Smoker • Abstinents: Self-reported abstinence during the previous 7 days confirmed with exhaled carbon monoxide test 	<ul style="list-style-type: none"> • SCQoL questionnaire 	<ul style="list-style-type: none"> • Among those who reported abstinence, there were statistically significant improvements for vitality, mental health, and self-control at 3 months (p <.05) 	SCQoL missing for those who did not report abstinence
Croghan et al. (2005)	<ul style="list-style-type: none"> • Cohort study • Patients undergoing treatment for nicotine independence • n = 206 • 1998 • United States • Follow-up for 1 year 	<ul style="list-style-type: none"> • Abstinent ≤6 days (n = 60) • Continuously abstinent for entire year (n = 146) 	<ul style="list-style-type: none"> • SF-36 	<ul style="list-style-type: none"> • Compared with those who were not continuously abstinent for a year, those who were continuously abstinent for a year reported significantly improved MCS, role limitations-emotional, role limitations-physical, and general health 	Controlled for scores at baseline; mean scores not reported
Rungruanghiranya et al. (2008)	<ul style="list-style-type: none"> • Placebo-controlled RCT for effectiveness of nicotine gum • n = 43 • Thailand • Follow-up at 3 months 	<ul style="list-style-type: none"> • Abstinence failure (n = 31) • Abstinence successful: Complete and continuous abstinence for 3 months (n = 12) 	<ul style="list-style-type: none"> • WHOQoL-BREF 	<ul style="list-style-type: none"> • No significant differences in QoL scores were observed between those who successfully quit and those who failed 	—

Table 5.3 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Hays et al. (2012)	<ul style="list-style-type: none"> • Placebo-controlled RCT of varenicline and bupropion sustained release • Adults who had smoked ≥10 cigarettes per day for the past year • n = 2,052 • 2003–2005 • United States • Follow-up for 1 year 	<ul style="list-style-type: none"> • Adults who had smoked ≥10 cigarettes per day for the past year 	<ul style="list-style-type: none"> • SCQoL 	<ul style="list-style-type: none"> • Both treatment groups showed clinically relevant differences in health transition and self-control at 1 year • Those with longer periods of abstinence reported better health transition, self-control, vitality, smoking-related anxiety, and MCS than those with shorter periods of abstinence 	—
Piper et al. (2012)	<ul style="list-style-type: none"> • Cohort study from RCT of smoking cessation treatments • n = 1,504 • 2005–2007 • United States • Follow-up for 3 years 	<ul style="list-style-type: none"> • Non-quitter • Quitter: 7-day point prevalence confirmed with carbon monoxide test 	<ul style="list-style-type: none"> • QoL Inventory 	<ul style="list-style-type: none"> • Compared with nonquitters, quitters reported significantly lower QoL scores at years 1 and 3 • Compared with continuing smokers, quitters showed improved global QoL, HRQoL, and affect at years 1 and 3 and fewer stressors by year 3 	—

Notes: **MCS** = Mental Component Summary; **QoL** = quality of life; **RCT** = randomized controlled trial; **SCQoL** = Smoking Cessation Quality of Life; **SF** = Short Form (survey); **WHOQoL-BREF** = World Health Organization Quality of Life-BREF.

Table 5.4 Prospective studies of special populations

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Taira et al. (2000)	<ul style="list-style-type: none"> • Cohort study of RCT of atherectomy techniques • Patients who underwent percutaneous coronary revascularization for coronary artery disease • n = 1,432 • United States • Follow-up for 1 year 	<ul style="list-style-type: none"> • Nonsmokers • Persistent smokers • Quitters 	<ul style="list-style-type: none"> • SF-36 	<ul style="list-style-type: none"> • All groups showed improvement on dimensions of the SF-36, but persistent smokers showed a smaller improvement than nonsmokers across all dimensions • Quitters showed improvement equal to or better than nonsmokers across all dimensions • Persistent smokers showed significantly less improvement than quitters in three QoL dimensions: physical functioning, social functioning, and mental health • Mean difference by QoL dimension and follow-up period: <ul style="list-style-type: none"> – Physical functioning: <ul style="list-style-type: none"> ○ 6 months: 8.4 (p <0.001) ○ 1 year: 5.8 (p = 0.01) – Role-physical: <ul style="list-style-type: none"> ○ 6 months: 10.3 (p <0.001) ○ 1 year: 6.2 (p = 0.14) – Bodily pain: <ul style="list-style-type: none"> ○ 6 months: 4.2 (p <0.001) ○ 1 year: 2.9 (p = 0.25) – General health: <ul style="list-style-type: none"> ○ 6 months: 5.5 (p = 0.001) ○ 1 year: 4.0 (p = 0.07) – Vitality: <ul style="list-style-type: none"> ○ 6 months: 5.2 (p <0.001) ○ 1 year: 2.7 (p = 0.25) – Social functioning: <ul style="list-style-type: none"> ○ 6 months: 7.5 (p <0.001) ○ 1 year: 6.0 (p = 0.01) – Role-emotional: <ul style="list-style-type: none"> ○ 6 months: 3.7 (p = 0.039) ○ 1 year: 0.1 (p = 0.92) – Mental health: <ul style="list-style-type: none"> ○ 6 months: 3.7 (p <0.001) ○ 1 year: 3.8 (p = 0.05) 	Adjusted for demographic and clinical characteristics, comorbid conditions, and baseline health status

Table 5.4 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Mitra et al. (2004)	<ul style="list-style-type: none"> • Longitudinal survey of adults with disabilities (Massachusetts Survey of Secondary Conditions) • n = 355 • 1996–2000 • Massachusetts 	<ul style="list-style-type: none"> • Nonsmokers • Smokers • Quitters • Starters 	<ul style="list-style-type: none"> • SF-36 (enabled version) 	<ul style="list-style-type: none"> • Compared with smokers, quitters experienced significantly more improvement in mental health, energy and vitality, and general health perception 	Adjusted for sex, race/ethnicity, years of education, age at baseline, number of QoL dimensions on which respondents were dependent on activities of daily living
Wiggers et al. (2006)	<ul style="list-style-type: none"> • RCT of nicotine replacement therapy and behavioral intervention • Patients with symptomatic atherosclerotic disease • n = 344 • The Netherlands • Follow-up for 1 year 	<ul style="list-style-type: none"> • Smokers with a failed quit attempt • Smokers without a failed quit attempt • Quitters 	<ul style="list-style-type: none"> • SF-36 • Aquarel • VascuQoL 	<ul style="list-style-type: none"> • Study found no effects of smoking status on QoL 	—
Jensen et al. (2007)	<ul style="list-style-type: none"> • Longitudinal cohort study • Patients after radical radiotherapy or surgery for head and neck cancer • n = 114 • Denmark 	<ul style="list-style-type: none"> • Never smokers • Smokers • Quitters 	<ul style="list-style-type: none"> • EORTC-C30 • EORTC-H&N35 	<ul style="list-style-type: none"> • Compared with smokers, those who had quit smoking at follow-up showed higher physical and mental functioning • The QoL scores of quitters fell between those of never smokers and smokers 	—

Table 5.4 Continued

Study	Design/population	Smoking status	Health status measure	Outcomes/findings	Comments
Balduyck et al. (2011)	<ul style="list-style-type: none"> • Cohort study • Patients undergoing non-small-cell lung cancer surgery • n = 70 • Belgium • Follow-up for 12 months 	<ul style="list-style-type: none"> • Nonsmokers • Former smokers (stopped smoking before diagnosis of lung cancer) • Recent quitters (patients who stopped smoking between diagnosis and surgery) 	<ul style="list-style-type: none"> • EORTC-C30 • EORTC-LC13 	<ul style="list-style-type: none"> • All groups had a reduction in QoL after surgery, but those who were former smokers at baseline and those who quit smoking after diagnosis showed improved QoL scores at follow-up compared with those who continued smoking 	—
Papadopoulos et al. (2011)	<ul style="list-style-type: none"> • Longitudinal cohort study • Patients with COPD who smoked and were recommended to quit smoking • Greece • n = 26 • Follow-up for 2 months 	<ul style="list-style-type: none"> • Smokers • Quitters 	<ul style="list-style-type: none"> • SF-12 • CCQ 	<ul style="list-style-type: none"> • Those who successfully quit smoking for 2 months showed significant differences in all domains of the SF-12 and in total CCQ score from baseline • CCQ total score: <ul style="list-style-type: none"> – Before: 1.08 ± 0.82 – Follow-up: 0.72 ± 0.69 – p < 0.001 	—

Notes: **CCQ** = Clinical COPD Questionnaire; **COPD** = chronic obstructive pulmonary disease; **EORTC-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module; **EORTC-H&N35** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module; **EORTC-LC13** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer Module; **QoL** = quality of life; **RCT** = randomized controlled trial; **SF** = Short Form (survey); **VascuQoL** = Vascular Quality of Life (questionnaire).

All of the studies determined whether participants were former smokers, but the period of abstinence from smoking required for classification as a former smoker was not uniform across studies, and some studies did not specify a minimum time period of abstinence (McClave et al. 2009; Tian et al. 2016). Some studies confirmed smoking status by a biomarker, such as cotinine (Stewart et al. 1995) or carbon monoxide (Zillich et al. 2002; Rungruanghiranya et al. 2008; Hays et al. 2012; Piper et al. 2012). Several studies (Stewart et al. 1995; Croghan et al. 2005; Wiggers et al. 2006; Piper et al. 2012) defined abstinence as a period of 7 days without smoking, but others used different standards, including 2 weeks (Olufade et al. 1999), 1 month (Mitra et al. 2004; Heikkinen et al. 2008), 3 months (Rungruanghiranya et al. 2008), and 5 years (Tillmann and Silcock 1997). One study, Erickson and colleagues (2004), considered level of addiction and divided former smokers into subgroups of low and high addiction, as assessed by the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991).

Some variation was also observed with regard to comparison groups used across studies. For example, as the reference group for comparing outcomes among those who had quit successfully, McClave and colleagues (2009) used unsuccessful quitters, defined as those who had attempted to quit at least once in the past year but were currently smoking. In a clinical trial of nicotine replacement therapy (NRT), Bolliger and colleagues (2002) compared successful reducers, who were ongoing smokers who had achieved at least a 50% reduction in the number of cigarettes smoked daily from week 6 to month 24 of the trial, with unsuccessful reducers.

Epidemiologic Evidence

Cross-Sectional Studies

Table 5.1 summarizes cross-sectional studies of smoking cessation and morbidity. Seven cross-sectional studies assessed smoking cessation and morbidity by asking participants to self-report smoking status and a measure of morbidity at the time of survey. Several studies that used the SF-36 to assess HRQoL observed that having quit smoking was associated with higher scores on some measures. Tillmann and Silcock (1997), in a study of 3,000 participants, reported significantly higher HRQoL, as measured by SF-36 and EuroQoL tariff scores, among former smokers who had smoked 5 years or more compared with current smokers in Scotland. Olufade and colleagues (1999), in a sample of 101 adults, reported that former smokers (smokefree for 2 or more weeks) had significantly higher scores on physical functioning, vitality, general health, and the Physical Component Summary

compared with current smokers; however, they found no significant differences for other measures on the SF-36. In the Netherlands, Mulder and colleagues (2001) reported significantly higher HRQoL scores for former smokers on all measures of the SF-36, except bodily pain compared with current smokers. In their sample, the HRQoL of former smokers approached that of never smokers, and adjusted mean scores on measures of the SF-36 did not differ significantly between never smokers and former smokers, except for bodily pain. Mulder and colleagues (2001) also found that increasing years since quitting was associated with higher scores on general health, vitality, mental health, and the Mental Component Summary. These researchers noted that overall differences in QoL between former smokers and current smokers were more pronounced for measures of mental health than for physical health. Although the first three studies found various differences by smoking status using the SF-36, in a representative sample of adults older than 14 years of age in Spain, Bellido-Casado and colleagues (2004) found no differences by smoking status in measures of physical, emotional, or mental health in the SF-36.

Two studies used data from the Behavioral Risk Factor Surveillance System (BRFSS), a telephone-based survey of U.S. adults 18 years of age and older. In an analysis of data from 2001 from a representative sample of 209,031 adults, Mody and Smith (2006) found that, compared with nonsmokers and former smokers, current cigarette smokers were more likely to experience (in the past 30 days) 14 or more days of activity limitation, 14 or more days of poor physical health, and 14 or more days of poor mental health. In addition, in their comparisons with former smokers, they found that current smokers were more likely to report poor general health. McClave and colleagues (2009), who used BRFSS data from 2006 in four states, found that former smokers and nonsmokers were less likely than current smokers (nonquitters) to report life dissatisfaction and frequent depressive symptoms; however, there were no significant differences between current and former smokers in reported general health status, frequent anxiety symptoms, frequent mental distress, frequent physical distress, frequent activity limitations, frequent pain, infrequent vitality, or frequent sleep impairment. Among men, there were no significant differences in HRQoL between former and current smokers. Among women, reported frequent mental and physical distress did not differ significantly between former and never smokers and current smokers, but among current smokers, women who tried to quit smoking and failed were more likely to report frequent mental stress and physical distress than were women who did not try to quit.

Heikkinen and colleagues (2008) used the 15-D instrument to assess HRQoL in a nationally representative sample

of about 8,000 adults 30 years of age and older in Finland. Compared with daily smokers, former smokers (defined as those who had not smoked for at least the past month) reported higher scores on most measures of the instrument.

Longitudinal Studies

Tables 5.2–5.4 summarize findings from 16 longitudinal studies of smoking cessation and general morbidity. These studies fall into three categories: (1) prospective cohort studies, (2) randomized controlled trials (RCTs), and (3) observational studies embedded within RCTs in which the data from the RCTs were analyzed as though the studies were observational without preservation of the randomization. With these types of longitudinal designs, smoking status is assessed before the outcome occurs. In contrast, cross-sectional studies assess smoking status and the outcome at the same point in time. Prospective studies were considered for quality of life (Table 5.2), populations receiving cessation treatment (Table 5.3), and populations with specific medical conditions (Table 5.4). Studies included in Table 5.2 were all designed as prospective cohorts (Stewart et al. 1995; Erickson et al. 2004; Gutiérrez-Bedmar et al. 2009; Tian et al. 2016). Table 5.3 includes studies with different longitudinal designs: prospective cohort (Zillich et al. 2002; Croghan et al. 2005), RCT (Rungruanghiranya et al. 2008; Hays et al. 2012), and observational study within an RCT (Bolliger et al. 2002; Piper et al. 2012). Table 5.4 includes longitudinal studies designed as prospective cohorts (Taira et al. 2000; Mitra et al. 2004; Jensen et al. 2007; Balduyck et al. 2011; Papadopoulos et al. 2011) or observational studies within an RCT (Wiggers et al. 2006).

Longitudinal Studies of General Populations

At the 4-year follow-up of 5,234 participants of a study based in Spain, Gutiérrez-Bedmar and colleagues (2009) found that compared with current smokers, mean scores for general, emotional, and mental health were significantly better among recent former smokers who had quit after the baseline assessment and before the 4-year follow-up. Tian and colleagues (2016) assessed HRQoL, using the SF-12, in relation to smoking status at baseline (never, former, and current smokers) and after 5 years of follow-up in about 2,000 Australian adults 31–41 years of age at follow-up. There were no significant differences in measures comparing never and former smokers at baseline, but at the 5-year follow-up, those who had continued to smoke had larger reductions in QoL scores than those who reported being former smokers at follow-up and were smokers at baseline. For these quitters, the estimated relative risk for a clinically significant improvement in physical HRQoL scores was higher compared with continuing

smokers. Additionally, former smokers had a higher likelihood of a clinically significant improvement in emotional and mental health HRQoL scores compared with continuing smokers.

Longitudinal Studies of Populations Undergoing Cessation Treatment

Eight trials considered participants engaged in cessation treatment. In one, Stewart and colleagues (1995) assessed the smoking status of 323 adults enrolled in a community-based RCT of smoking cessation. At baseline, all participants were smokers. At 6 months, quitters had a significantly higher score on all assessed measures of mental health compared with continuing smokers, including psychological well-being, anxiety, positive affect, cognitive functioning, energy, sleep adequacy, self-esteem, and sense of mastery. In contrast, for the five measures of physical health, there were no statistically significant differences between the groups on four measures: physical functioning, social functioning, pain, and current health perceptions.

Zillich and colleagues (2002) used the SCQoL questionnaire to evaluate changes in HRQoL among 31 participants in a nonrandomized, unblinded trial to evaluate the effectiveness of a pharmacist-based smoking cessation program. Vitality, mental health, and self-control improved significantly among those who successfully quit over the 6 months of follow-up compared with baseline. However, data were missing for participants who did not successfully quit and did not return for follow-up. In Switzerland, Bolliger and colleagues (2002) enrolled a cohort of 400 participants from an earlier RCT of an oral nicotine inhaler for smoking reduction and examined QoL in relation to smoking reduction. Healthy adult volunteers were randomized to active or placebo inhalers and encouraged to reduce their smoking as much as possible; the cohort was followed for 24 months. The comparison group of nonreducers (less than a 50% reduction in the number of cigarettes smoked daily from week 6 to month 24) was used for comparison with successful reducers (at least a 50% reduction). Compared with the control group, successful reducers had significantly greater improvement in general health, as measured by the SF-36.

Among those who quit in a study of 34 smokers, Erickson and colleagues (2004) considered whether low (FTND score ≤ 6) or high (FTND score > 6) levels of addiction affected QoL 1 week after the quit date. The lower addiction group showed a significant improvement in more of the HRQoL domain scores after the quit date compared with the higher addiction group.

Croghan and colleagues (2005) evaluated 206 patients treated for nicotine dependence for changes in their health status, as measured by the SF-36, 1 year after consultation

at the Mayo Clinic. Patients who stopped smoking for 1 year or more had significantly higher QoL measures at baseline compared with a demographically similar group who had not stopped smoking. After controlling for baseline scores, patients who stopped smoking for 1 year or more had significantly improved scores on the Mental Component Summary and for role limitations, both emotional and physical, and significantly improved general health compared with those who were not abstinent for a year.

Rungruanghiranya and colleagues (2008) performed a placebo-controlled RCT in Thailand that considered the effectiveness of nicotine gum for cessation and examined changes in QoL after 3 months. Forty-six subjects underwent screening for the study; two were excluded because of NRT use, and one was excluded due to a recent diagnosis of diabetes. Among the 43 participants, the study revealed no significant differences in improved QoL between those who had successfully quit smoking and those who had not.

Piper and colleagues (2012) assessed QoL in 1,504 participants making a quit attempt as part of an RCT of smoking cessation. Both former smokers (i.e., quitters) and current smokers (nonquitters) experienced a reduction in global QoL at the 1- and 3-year follow-ups, but former smokers had a significantly smaller decrease in global QoL. Former smokers showed slight improvement in HRQoL at years 1 and 3, an outcome significantly different from the decreases in HRQoL reported by continuing smokers. Former smokers also reported a decrease in negative affect at 1 year, which differed significantly from the slight increase in continuing smokers.

Hays and colleagues (2012) implemented a placebo-controlled RCT in which 2,052 participants were treated with varenicline, bupropion SR (sustained release), or placebo and followed for 52 weeks. Participants in both treatment groups showed clinically relevant differences in health transition (perceived health compared with baseline) and self-control at follow-up compared with participants in the placebo group at follow-up. In terms of abstinence, those who had a longer period of abstinence reported better health transition and self-control at follow-up compared with those who were abstinent for a shorter period. Among those with a longer period of abstinence, findings were similar to those abstinent for a shorter period of time for vitality, smoking-related anxiety, and improvement in scores on the Mental Component Summary.

Longitudinal Studies of Special Populations

Table 5.4 summarizes six longitudinal studies that considered smoking cessation in special populations defined by disease status. Taira and colleagues (2000) assessed QoL after percutaneous coronary revascularization in 1,432 patients with coronary artery disease within two RCTs (Baim et al. 1998, 2001). All groups (nonsmokers,

former smokers [quitters], and persistent smokers) showed improvements on measures of the SF-36, but the extent of improvement differed by smoking status. At 6 months, after controlling for baseline scores on the SF-36, improvement among former smokers was comparable to that of nonsmokers. At 1 year, persistent smokers continued to show significantly less improvement than former smokers in physical functioning, social functioning, and mental health. Compared with continuing smokers, former smokers made significantly greater gains in both Physical Component Summary and Mental Component Summary scores at 6 months and 1 year.

Using data from Wilber and colleagues (2002), Mitra and colleagues (2004) performed a longitudinal study of 355 adults with disabilities and found that changes in smoking status were associated with future changes in QoL scores—with former smokers experiencing significantly more improvement in mental health, energy and vitality, and perceived general health compared with current smokers. In the Netherlands, Wiggers and colleagues (2006) studied 344 smokers with atherosclerotic vascular disease who were participating in an RCT of NRT combined with a behavioral intervention, and considered both general (SF-36) and disease-specific QoL (Aquarel and VascuQoL). Overall, participants showed improved physical and mental QoL, as measured by SF-36 at follow-up (2, 6, and 12 months), but there were no differences by smoking status. In a study based in Denmark, Jensen and colleagues (2007) considered smoking status and QoL in 114 patients surveyed after treatment for head and neck cancer. Those who had quit smoking at postsurgical follow-up showed higher physical and mental functioning compared with continuing smokers.

In Greece, Papadopoulos and colleagues (2011) investigated smoking cessation and QoL using a disease-specific score (the Clinical COPD Questionnaire [CCQ]) in a cohort of 26 participants with chronic obstructive pulmonary disease who had successfully quit smoking for 2 months. QoL, as measured by both the CCQ and a generic scale (SF-12), improved after 2 months of cessation. Finally, Balduyck and colleagues (2011), in a study based in Belgium, considered 70 patients' return-to-baseline QoL after surgery for lung cancer using a disease-specific score (EORTC-C30 and EORTC-LC13) that was administered after a reduction in smoking following surgery in all three smoking status groups (current smoker, former smokers, and recent quitters). Those who were former smokers at baseline (i.e., before their diagnosis) and those who quit smoking after diagnosis both showed improved QoL at follow-up compared with those who continued to smoke, although those who were former smokers at baseline had a faster return to baseline QoL than recent quitters.

Synthesis of the Evidence

Studies of morbidity and smoking cessation vary in their definitions of cessation, length of follow-up, and morbidity measures, including QoL. Nonetheless, despite these variations, the overall findings indicate that smoking cessation lessens general morbidity, specifically as measured by HRQoL and assessments of health status. Although the level of HRQoL for former cigarette smokers is between that of current smokers and never smokers, the HRQoL of former smokers approaches that of never smokers for many measures. This pattern is found in samples of the general population, in study participants undergoing cessation treatment, and in persons with specific diseases. Moreover, greater benefits have been found for measures of mental health than for measures of physical health. Some evidence suggests that persons with lower levels of addiction before cessation appear to experience greater gains in mental health, and those who are abstinent for a longer period show higher levels of improvement in mental health.

One critical factor to consider in interpreting the evidence on smoking cessation and health is the potential for reverse causation—that is, the presence of symptoms or a disease leading to a decision to quit. If that is the case, the rates of symptoms in cross-sectional data might be higher in former smokers than in current smokers. Even in prospective cohort studies, when changes in indicators of health are tracked over time, the causal direction may be difficult to ascertain, particularly if participants quit as symptoms develop or as their well-being declines. Randomized trials of cessation interventions are not subject to such temporal limitations; however, generalizability may be limited because the populations in these studies may not reflect smokers in general.

Temporal ambiguity is a particular concern in cross-sectional studies that assess smoking status and morbidity at the same time. In these cases, a better HRQoL in former smokers than in current smokers may result from smoking cessation or be a contributing factor to successful smoking cessation. Additionally, lower HRQoL may reduce the ability to successfully quit smoking. One further complication in interpreting cross-sectional data is related to the motivation of smokers to quit because of the development of smoking-related symptoms of disease. This type of reverse causation generally tends to reduce associations of cessation with beneficial outcomes.

Longitudinal studies—including prospective cohort studies, RCTs, and observational studies within an RCT—provide higher quality evidence with less opportunity for temporal ambiguity, and they can measure QoL at baseline before differences across groups classified by smoking status are assessed. However, smokers who do not quit may be less likely to remain in longitudinal studies during

follow-up (Zillich et al. 2002). Regardless, as with the evidence considered in the 1990 Surgeon General's report on the health benefits of smoking cessation (USDHHS 1990), the variety of measures used in studies of cessation can limit comparability and summarization across studies.

Summary of the Evidence

This section reviews evidence on smoking cessation and general morbidity using a variety of broad, nonspecific but validated measures, such as QoL indicators and health status and disease-specific measures. For the measures that are broad and nonspecific, the determinants of responses are multifactorial. Thus, some studies reviewed in this chapter attempted to address potential confounding. Based on consistent evidence across the studies reviewed (Tables 5.1 and 5.2), former smokers have less general morbidity than current smokers, as reflected in higher QoL scores and in multiple measures of health status. Confounding may have affected the results of some of the studies reviewed; however, confounding alone does not adequately explain the consistent finding of lower morbidity and higher QoL among former smokers compared with current smokers. Selection bias is also a potential concern if persistent smokers, particularly those who are ill, are less likely than quitters to remain in follow-up during longitudinal studies.

Despite such limitations, the evidence for lower morbidity and higher QoL among former smokers than among current smokers is strengthened by the higher levels of improvement in QoL seen among those who had abstained from smoking longer; such a finding supports a conclusion of causality. Former smokers tend to have higher morbidity than never smokers; and in some subgroups, the morbidity of former smokers can approach that of never smokers, such as among those with lower levels of addiction before cessation.

A causal link between smoking cessation and a decrease in general morbidity is supported by the biologic plausibility of the relationship. Active smoking drives various nonspecific processes of injury (e.g., inflammation), which lessen with the end of exposure to the toxins in tobacco smoke (USDHHS 2010). Because the morbidity measures addressed in the studies reviewed in this chapter are broad and nonspecific, a single mechanism cannot be invoked to explain the association between smoking cessation and reduction of general morbidity. However, many well-supported mechanisms link smoking cessation to improvements in more specific measures of health, such as disease-specific outcomes, thus underscoring the likelihood that those who quit smoking will have lower rates of morbidity.

Benefits of Smoking Cessation on All-Cause Mortality

Increased all-cause mortality is a well-established causal consequence of smoking (USDHHS 2004, 2014). Chapter 4 of this report (The Health Benefits of Smoking Cessation) summarizes disease risks from smoking and the changes in risk that follow smoking cessation for the major types of chronic diseases. This section briefly summarizes the well-documented and extensive scientific evidence on the health benefits of smoking cessation on all-cause mortality. The review is limited in scope because the topic has been extensively covered in prior reports.

Conclusions from Previous Surgeon General's Reports

The 1964 Surgeon General's report included a table on all-cause mortality with the findings of seven cohort studies. In a pioneering quantitative synthesis of the data from the seven studies, the ratio of deaths observed to deaths expected was 1.68:1 (USDHEW 1964). A contemporary analysis of the data from the 1964 Surgeon General's report showed statistically significant increases in all-cause mortality in all of the studies (Figures 5.1a and 5.1b) (Schumacher et al. 2014). The 1964 Surgeon General's report concluded that, "Cigarette smoking is associated with a 70 percent increase in the age-specific death rates of males, and to a lesser extent with increased death rates of females. The total number of excess deaths causally related to cigarette smoking in the U.S. population cannot be accurately estimated. In view of the continuing and mounting evidence from many sources, it is the judgment of the [Surgeon General's Advisory Committee on Smoking and Health] that cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate" (USDHEW 1964, p. 31).

By the time of the 1964 report, evidence from five cohort studies showed lower risk for all-cause mortality in former smokers compared with current smokers, and data from several cohorts showed declining risk for death in former smokers, compared with current smokers, as the interval since cessation lengthened.

Subsequent Surgeon Generals' reports (USDHEW 1969, 1979; USDHHS 1989, 1990, 2004, 2014) have comprehensively covered this topic and published findings comparable to those in the 1964 Surgeon General's report. In brief, using data from the American Cancer Society's Cancer Prevention Study II, the 1990 Surgeon General's

report included lifetable analyses on the health benefits of smoking cessation, offering the following conclusions on all-cause mortality:

- "Former smokers live longer than continuing smokers, and the benefits of quitting extend to those who quit at older ages. For example, persons who quit smoking before age 50 have one-half the risk of dying in the next 15 years compared with continuing smokers.
- Smoking cessation at all ages reduces the risk of premature death.
- Among former smokers, the decline in risk of death compared with continuing smokers begins shortly after quitting and continues for at least 10 to 15 years. After 10 to 15 years of abstinence, risk of all-cause mortality returns nearly to that of persons who never smoked" (USDHHS 1990, p. 92).

The 2004 Surgeon General's report extended these findings by comprehensively documenting and updating the evidence on active smoking and disease, noting that "fortunately for former smokers, studies show that substantial risks of smoking can be reduced by successfully quitting at any age" (USDHHS 2004, p. 25). Furthermore, the report concluded that "quitting smoking has immediate as well as long-term benefits, reducing risks for disease caused by smoking and improving health in general" (USDHHS 2004, p. 25).

The 2014 Surgeon General's report provided the most recent extensive review of the consequences of smoking on health and confirmed findings from previous reports in the series:

- "The evidence is sufficient to infer that cigarette smoking increases risk for all-cause mortality in men and women.
- The evidence is sufficient to infer that the relative risk of dying from cigarette smoking has increased over the last 50 years in men and women in the United States" (USDHHS 2014, p. 641).

The 2014 Surgeon General's report also compared the relative risks for all-cause mortality in the American Cancer Society's Cancer Prevention Studies I (1959–1965) and II (1982–1988) with those in a pooled analysis of five contemporary cohorts with follow-up through 2010. The

Figure 5.1a Incidence rate ratios for death from any cause, by smoking status

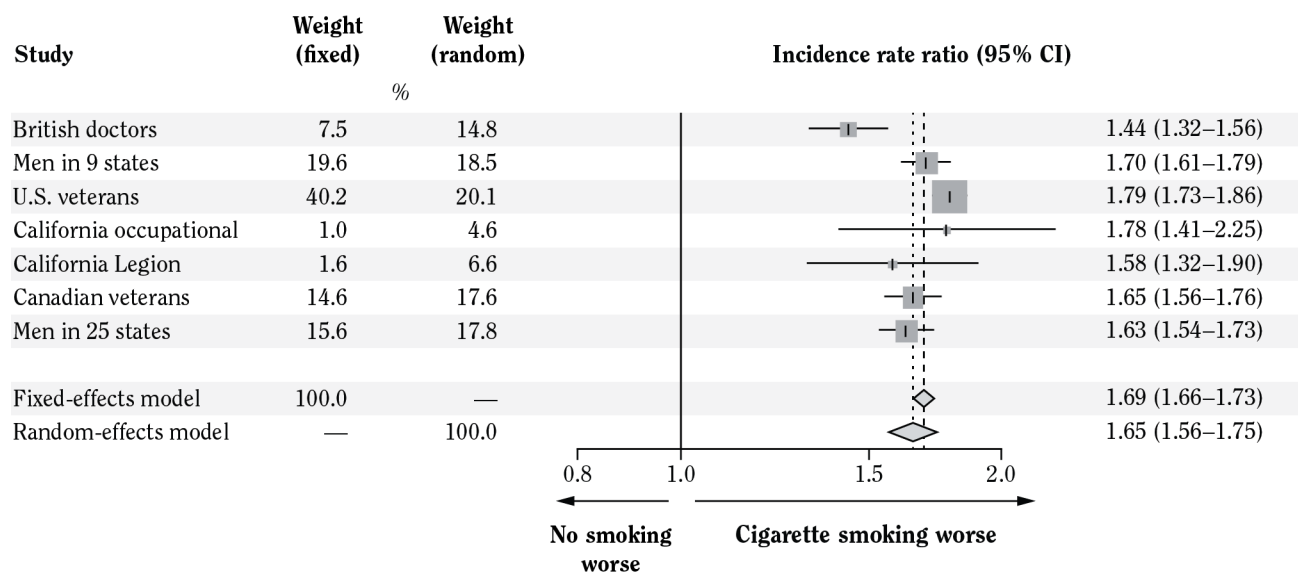
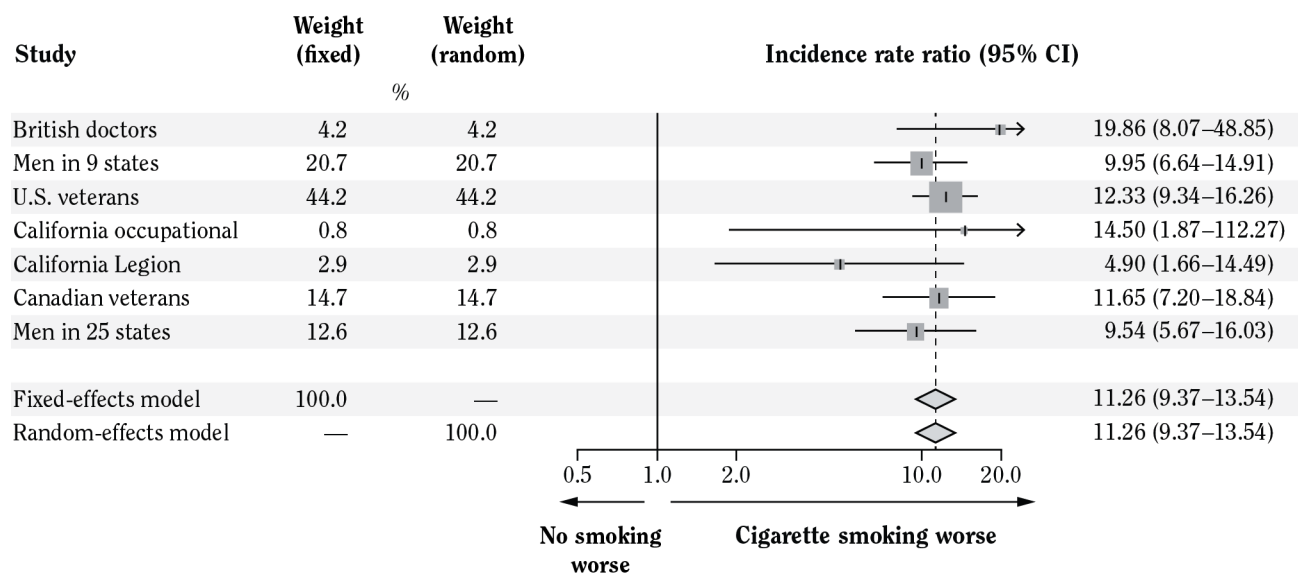


Figure 5.1b Incidence rate ratios for death from lung cancer, by smoking status



Source: Schumacher and colleagues (2014). Copyright © 2014, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Note: **CI** = confidence interval. “Panel A shows incidence-rate ratios for death from any cause, and Panel B shows incidence-rate ratios for death from lung cancer. The incidence rate is the number of events per 100 person-years. Person-years were attributed such that the incidence-rate ratios were equal to the reported mortality ratios implicitly, assuming that data were based on a homogeneous age group. Standard errors were not affected, since they depend only on the number of observed deaths. Since no study-specific detailed tables of data on persons who did not smoke were available, the group of nonsmokers in this forest plot is larger than the one used by Cochran and hence contains more observed deaths; to correct for this, standard errors were inflated accordingly. The horizontal lines represent confidence intervals, with arrows indicating extensions of the intervals. Boxes represent estimated incidence-rate ratios, with the sizes of the boxes indicating the inverse variance of the respective studies. Diamonds represent the pooled incidence-rate ratio. The width of the diamonds represents the width of the 95% confidence interval of the pooled incidence-rate ratio” (Schumacher et al. 2014, p. 187).

comparison revealed rising relative risks for all-cause mortality among current smokers, both men and women, in the contemporary cohorts. Among former smokers, the relative risks were substantially lower in the contemporary cohorts compared with those in the earlier American Cancer Society cohorts. However, compared with never smokers, the relative risks for former smokers were higher in the contemporary cohorts compared with the earlier cohorts (Tables 5.5a and 5.5b).

The 2014 Surgeon General's report also found that despite advancement in disease prevention and treatment over the past 50 years, current cigarette smokers had not experienced as much improvement in life expectancy

compared with former and never smokers. Former smokers had progressively lower relative risk of all-cause mortality the younger they quit smoking (USDHHS 2014). For example, the Million Women Study found that women who quit smoking before 30 years of age and before 40 years of age avoided more than 97% and 90% of excess mortality risk, respectively, compared with those who continued smoking (Pirie et al. 2013). In an analysis of more than 216,000 adults from 1997 to 2004, Jha and colleagues (2013) found a similar relationship between smoking and survival: Smoking cessation before 40 years of age reduced the risk of death associated with continued smoking by approximately 90%. Additionally, adults who

Table 5.5a Relative risks by smoking status and age group among adult men 35 years of age and older, United States

	Current smokers (years of age)				Former smokers (years of age)			
	35–54 ^a	55–64 ^b	65–74 ^b	≥75 ^b	35–54 ^a	55–64 ^b	65–74 ^b	≥75 ^b
Lung cancer	14.33	19.03	28.29	22.51	4.40	4.57	7.79	6.46
Other cancers ^c	1.74	1.86	2.35	2.18	1.36	1.31	1.49	1.46
Coronary heart disease	3.88	2.99	2.76	1.98	1.83	1.52	1.58	1.32
Other heart disease ^d	—	—	2.22	1.66	—	—	1.32	1.15
Cerebrovascular disease	—	—	2.17	1.48	—	—	1.23	1.12
Other vascular diseases ^e	—	—	7.25	4.93	—	—	2.20	1.72
Diabetes mellitus	—	—	1.50	1.00	—	—	1.53	1.06
Other cardiovascular diseases ^f	2.40	2.51	—	—	1.07	1.51	—	—
Influenza, pneumonia, tuberculosis	—	—	2.58	1.62	—	—	1.62	1.42
Chronic obstructive pulmonary disease ^g	—	—	29.69	23.01	—	—	8.13	6.55
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease ^h	4.47	15.17	—	—	2.22	3.98	—	—
All causes	2.55	2.97	3.02	2.40	1.33	1.47	1.57	1.41

Source: Analyses of Cancer Prevention Study II and updated analyses of the pooled contemporary cohort population described in Thun and colleagues (2013) provided to the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

^aRelative risks for 35–54 years of age were obtained from Cancer Prevention Study.

^bRelative risks for 55–64 years of age, 65–74 years of age, and 75 years of age and older were obtained from merged contemporary cohorts (Thun et al. 2013).

^cOther cancers consist of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia.

^dOther heart disease is composed of rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

^eOther vascular diseases are composed of atherosclerosis, aortic aneurysm, and other arterial diseases.

^fFor 35–54 years of age and ages 55–64 years of age, other cardiovascular diseases are composed of other heart disease, cerebrovascular disease, other vascular diseases, and diabetes mellitus and were analyzed and reported as one category. A single relative risk based on combined conditions was used to compute smoking-attributable mortality. Relative risk based on combined conditions was used to compute smoking-attributable mortality in these age strata.

^gChronic obstructive pulmonary disease is composed of bronchitis, emphysema, and chronic airways obstruction.

^hFor 35–54 years of age and 55–64 years of age, influenza, pneumonia, tuberculosis, and chronic obstructive pulmonary disease were analyzed and reported as one category. A single relative risk based on combined conditions was used to compute smoking-attributable mortality.

Table 5.5b Relative risks by smoking status and age group among adult women 35 years of age and older, United States

	Current smokers (years of age)				Former smokers (years of age)			
	35–54 ^a	55–64 ^b	65–74 ^b	≥75 ^b	35–54 ^a	55–64 ^b	65–74 ^b	≥75 ^b
Lung cancer	13.30	18.95	23.65	23.08	2.64	5.00	6.80	6.38
Other cancers ^c	1.28	2.08	2.06	1.93	1.24	1.28	1.26	1.27
Coronary heart disease	4.98	3.25	3.29	2.25	2.23	1.21	1.56	1.42
Other heart disease ^d	—	—	1.85	1.75	—	—	1.29	1.32
Cerebrovascular disease	—	—	2.27	1.70	—	—	1.24	1.10
Other vascular diseases ^e	—	—	6.81	5.77	—	—	2.26	2.02
Diabetes mellitus	—	—	1.54	1.10	—	—	1.29	1.06
Other cardiovascular diseases ^f	2.44	1.98	—	—	1.00	1.10	—	—
Influenza, pneumonia, tuberculosis	—	—	1.75	2.06	—	—	1.28	1.21
Chronic obstructive pulmonary disease ^g	—	—	38.89	20.96	—	—	15.72	7.06
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease ^h	6.43	9.00	—	—	1.85	4.84	—	—
All causes	1.79	2.63	2.87	2.47	1.22	1.34	1.53	1.43

Source: Analyses of Cancer Prevention Study II and updated analyses of the pooled contemporary cohort population described in Thun and colleagues (2013) provided to the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

^aRelative risks for 35–54 years of age were obtained from Cancer Prevention Study.

^bRelative risks for 55–64 years of age, 65–74 years of age, and 75 years of age and older were obtained from merged contemporary cohorts (Thun et al. 2013). Relative risks for other vascular diseases among women 55 years of age and older do not include data from the Women's Health Initiative of the National Heart, Lung, and Blood Institute.

^cOther cancers consist of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia.

^dOther heart disease is composed of rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

^eOther vascular diseases are composed of atherosclerosis, aortic aneurysm, and other arterial diseases.

^fFor 35–54 years of age and ages 55–64 years of age, other cardiovascular diseases are composed of other heart disease, cerebrovascular disease, other vascular diseases, and diabetes mellitus and were analyzed and reported as one category. A single relative risk based on combined conditions was used to compute smoking-attributable mortality. Relative risk based on combined conditions was used to compute smoking-attributable mortality in these age strata.

^gChronic obstructive pulmonary disease is composed of bronchitis, emphysema, and chronic airways obstruction.

^hFor 35–54 years of age and 55–64 years of age, influenza, pneumonia, tuberculosis, and chronic obstructive pulmonary disease were analyzed and reported as one category. A single relative risk based on combined conditions was used to compute smoking-attributable mortality.

had quit smoking at 25–34, 35–44, or 45–54 years of age gained about 10, 9, and 6 years of life, respectively, compared with those who continued smoking. These findings are consistent with those reported in the 2004 and 2014 Surgeon General's reports. Although smokers lose an estimated decade of life on average, smoking cessation by 40 years of age avoided more than 90% of the excess mortality caused by continued smoking (USDHHS 2004, 2010; Pirie et al. 2013). Even quitting smoking by about 60 years of age could reduce premature mortality by 40% (USDHHS 2004, 2010).

Summary of the Evidence

The health benefits of smoking cessation on all-cause mortality have been systematically reviewed in previous Surgeon General's reports (USDHHS 2004, 2014). The evidence published since the 1990 Surgeon General's report continues to affirm that smoking cessation at any age reduces the risk of premature death (Jha et al. 2013; Pirie et al. 2013; USDHHS 2014). The relative risk for dying from smoking has increased over time, but the benefit of quitting persists.

Benefits of Smoking Cessation on Economic Costs

Cigarette smoking causes both substantial morbidity and premature mortality, resulting in significant economic costs for smokers and their families and very large costs for society in general (USDHHS 2004). Because smoking cessation reduces these costs, the comparative costs and benefits of treatments for smoking cessation will help to inform tobacco control strategies for different settings. In evaluating the economic dimensions of smoking cessation, consideration needs to be given to the specific costs and benefits generated by programs or policies that increase successful cessation. These costs and benefits, which extend into numerous sectors beyond healthcare, include the consequences for employment, such as lost productivity from active smoking, as well as for retirement benefits and pensions that may be transferred to never smokers and former smokers from early tobacco-related death among sustained smokers who do not quit (National Cancer Institute and World Health Organization 2016). This section focuses on the economic dimensions of smoking cessation, including the critical comparator: the costs of smoking.

Economic Costs of Smoking

The economic costs of an intervention or managing a health outcome represent the opportunity cost of resources used, which includes direct costs, productivity losses, and intangible costs. Direct costs include direct medical and nonmedical costs; productivity losses—often referred as indirect costs—include the costs associated with morbidity and premature mortality; and intangible costs include such difficult-to-monetize consequences as pain and suffering and emotional well-being (Haddix et al. 2003). As with smoking-attributable increases in morbidity and premature mortality, the economic costs of smoking have been estimated for decades. Since 1991, for example, CDC has used the SAMMEC model to estimate the economic costs associated with lost productivity due to premature death from tobacco use (Shultz et al. 1991; USDHHS 2014). These estimates are produced by first estimating the total number of years of productive life lost from early mortality attributable to smoking and then converting that loss into financial terms to indicate monetary loss because of lost work productivity. Using the SAMMEC model, CDC estimated, for example, that the average annual smoking-attributable economic cost of lost productivity for 2000–2004 was \$96.8 billion when premature mortality alone was considered (CDC 2008). Combining the

costs of lost productivity with the direct healthcare expenditures attributable to smoking of \$96 billion during the same period, the total annual smoking-attributable economic cost was \$193 billion (CDC 2008). Using data linked between the 2006–2010 Medical Expenditure Panel Survey and the 2004–2009 National Health Interview Survey, the estimated annual healthcare expenditure attributable to smoking was as much as \$170 billion in 2010 dollars; public programs—including Medicare, Medicaid, and other federally sponsored programs—accounted for more than 60% of this estimate (Xu et al. 2015b). However, these estimates underestimate the economic impact of smoking, because they do not account for smoking-related disability, smoking-related absenteeism from work, smoking-attributable loss of earnings, and morbidity and mortality attributable to exposure to secondhand smoke.

Regardless, national estimates that are similar to those presented above can be developed for states using the methodology underlying inclusive state-specific estimates, such as those for the state of California made by Max and colleagues (2016). The authors estimated smoking-attributable healthcare costs in California in 2009 using a series of econometric models, which estimated expenditures for such healthcare categories as hospital care, ambulatory care, prescriptions, and home health and nursing home care. An econometric model was also used to predict lost productivity because of illness, particularly how smoking status influenced the number of days absent from work. Premature mortality because of smoking was estimated using an epidemiologic approach. Using these approaches, Max and colleagues (2016) calculated \$1.4 billion in lost productivity from illness and \$6.8 million in lost productivity from premature mortality among smokers in California in 2009.

The 2014 Surgeon General's report used three different approaches, all based on the SAMMEC methodology, to derive updated estimates of smoking-attributable direct healthcare expenditures (USDHHS 2014):

1. Using medical service costs from 2009, the estimated aggregated annual healthcare expenditure attributable to cigarette smoking was \$132.5 billion in 2009 dollars. Using the Medical Care part of the Consumer Price Index to account for inflation (available from the U.S. Bureau of Labor Statistics [2017]), the expenditure in 2017 dollars was \$167.7 billion.
2. Using age- and sex-specific relative risks, the estimated smoking-attributable direct healthcare spending was

\$175.9 billion (in 2013 dollars) and \$196.7 billion in 2017 dollars.

3. Using a two-part regression analysis of Medical Expenditure Panel Survey (MEPS) data, the estimated smoking-attributable direct healthcare spending was \$169.3 billion (in 2010 dollars) and \$207.2 in 2017 dollars (Xu et al. 2015b).
4. The 2014 Surgeon General's report also used updated lifetables and estimates of the present value of future earnings to estimate the smoking-attributable economic cost of lost productivity; the estimate was \$150.7 billion in 2009 dollars (\$190.7 billion in 2017 dollars) (USDHHS 2014). Moreover, the report estimated the economic cost of lost productivity because of exposure to secondhand smoke to be an additional \$5.7 billion in 2009 dollars (\$7.2 billion in 2017 dollars), a figure that did not account for direct healthcare expenditures attributable to exposure to secondhand smoke (USDHHS 2014). The value of lost productivity attributable to premature death from smoking was \$172.2 billion in 2009 (\$217.9 billion in 2017 dollars), and the cost attributable to exposure to secondhand smoke was \$6.5 billion in 2009 (\$8.2 billion in 2017 dollars).

On the basis of these updated estimates, the 2014 Surgeon General's report concluded that the costs of cigarette smoking represented a significant portion (7.6–8.7%) of healthcare expenditures in the United States (USDHHS 2014).

The SAMMEC model uses a cross-sectional approach to determine the economic expenditures of smoking; it estimates the burden of smoking-related disease and death of smokers compared with having a population of all non-smokers and calculates the disease-attributable smoking expenditures within a specific period. Another method for evaluating the overall economic costs of smoking is the life-cycle approach, which estimates the present value of the cost of adding a smoker to society and also considers that benefits from longer lives because of smoking cessation or prevention will be mitigated because of other costs later in life. The life-cycle approach has been implemented using various datasets from national panels in the United States.

Sloan and colleagues (2004) used a life-cycle approach to estimate the overall cost of smoking. They incorporated private costs to smokers, including disability and absenteeism; external costs to society, including Social Security benefits, pensions, and life insurance; and quasi-external costs to family members because of

their exposure to secondhand smoke. The authors estimated that each new cohort of U.S. smokers, beginning at 24 years of age, added \$203.8 billion of new lifetime costs (in year 2000 dollars). Most of the lifetime costs to society were private (\$168.5 billion), but external and quasi-external costs (costs imposed by smoking on the spouse and children of a smoker) (total of \$35.3 billion) were substantial, even after accounting for federal and state tobacco excise taxes at the time of estimation. These external and quasi-external costs are much higher than previous estimates of externalities from cigarette smoking, primarily because of a better understanding of health effects from exposure to secondhand smoke (Chaloupka and Warner 2000; Sloan et al. 2004). Although these estimates suggest that a rational decision maker would never choose to initiate tobacco use, individual decision making may highly discount future negative events for perceived current effects and may be further affected by the limited information on risk considered by potential smokers (Gruber and Koszegi 2001; Gruber 2002).

Regardless of underlying methodology, these estimates document the substantial costs associated with smoking. However, these macro-level costs hide the significant costs incurred by the households of smokers, which include not only the costs of purchasing tobacco products but also economic losses because of absenteeism from work—because of smoking-related morbidity—and of the direct costs of healthcare. Such household costs are differentially distributed in the United States, given the strong gradient of less smoking with increasing income (CDC 2011). Furthermore, the estimated total costs include only direct costs and productivity losses; these estimates do not consider harder-to-quantify and intangible costs, such as those from the grief and suffering of family members and friends of ill smokers. Those costs can be measured through surveys using a “willingness-to-pay” approach, which asks how much a person would pay to avoid such a scenario. Costs estimated through willingness-to-pay approaches are often much larger than costs that are measured directly (Gold et al. 1996).

Economics of Smoking Cessation

An economic analysis of smoking cessation must consider a variety of costs, including costs accrued by smokers before successful cessation. Although many persons can quit smoking without any assistance, others need assistance from public health programs that encourage smoking cessation, or from healthcare services that provide psychological or pharmacologic assistance to help them stop smoking. These interventions, which increase smoking cessation, also have associated costs.

Principles of Cost-Benefit and Cost-Effectiveness Analysis

Policies to encourage beneficial behaviors are often evaluated by cost-benefit analysis, which compares outcomes in terms of dollar value and prioritizes different policies, particularly when resources are scarce or funds are limited (Russell 2015). The simplest method for comparison is to derive a single estimate for each policy by converting all costs and benefits into financial measures. In healthcare, however, the full benefits associated with improved health are not easily converted into financial benefits because of challenges in the financial valuations of extending life or avoiding morbidity (Gold et al. 1996). As a result, cost-effectiveness analysis is often used in healthcare, but the measurements of effect may not always be comparable across studies. One type of cost-effectiveness analysis is cost-utility analysis, in which health benefits are based on a common metric, such as quality-adjusted life-years (QALYs) gained (Gold et al. 1996). Recommendations on cost-effectiveness in health and medicine were published in 1996 (Gold et al. 1996; Russell et al. 1996; Siegel et al. 1996; Weinstein et al. 1996) and updated in 2016 (Sanders et al. 2016).

The particular analytic perspective to choose and the evaluation of ratios are two key considerations for both cost-benefit and cost-effectiveness analyses. The analytic perspective taken can change the costs and benefits of an evaluation, because evaluations using one perspective (e.g., that of a payer) may not include the same costs or benefits as those using another perspective (e.g., that of society in general). For example, if an insurance plan accrues the costs of paying for a smoking cessation program but does not reap the benefits from cessation because persons frequently switch insurance plans, such switching may result in a less cost-effective scenario for the plan. From a societal perspective, however, benefits are accrued from all persons who quit successfully, regardless of switches in insurance plans. Gold and colleagues (1996) recommended the societal perspective as the appropriate analytic perspective to provide a full accounting of costs and benefits, but other perspectives, such as that of the payer when a program to promote smoking cessation is implemented, may be the focus of an analysis. Sanders and colleagues (2016) recommended considering components of cost from an analytical perspective (e.g., from health sector and societal perspectives).

To assess the cost-effectiveness of an intervention, the incremental cost-effectiveness ratio is calculated and evaluated. The ratio estimates how much extra cost is needed for an intervention compared with alternatives (control or next best alternative in terms of effectiveness) to derive an extra unit of benefit (e.g., QALY). To compare the relative value of multiple policy interventions, both absolute cost-effectiveness ratio (the ratio of the cost of intervention

minus costs averted by the intervention, divided by QALYs gained, where the comparison is between an intervention and a “do nothing” or control) and incremental cost-effectiveness ratio (the ratio of costs of interventions minus costs averted by the intervention, divided by QALYs gained, where the comparison is between an intervention and the next best intervention) can be estimated (Cohen and Reynolds 2008). When evaluating one intervention versus a control, the absolute cost-effectiveness and incremental cost-effectiveness are the same. However, an evaluation of multiple interventions should be based on incremental cost-effectiveness ratios. Relying only on absolute cost-effectiveness ratios can distort estimates and result in invalid conclusions. The absolute cost-effectiveness ratios of alternative interventions can be similar and cost-effective when compared with an acceptable threshold. However, when the incremental cost-effectiveness ratio for an alternative is evaluated and compared with the next best alternative, the alternative may not necessarily be cost-effective—even if it is cost-effective when compared with the control.

An international consortium that evaluated the relative costs and benefits of a range of smoking cessation interventions found that in a high-income country, such as the United States, such interventions as automated text messaging, self-help materials, and brief advice from a physician have a low cost but only small effects on smoking cessation. Conversely, pharmacological and psychological interventions (either by telephone or provided in person) are higher in cost but have greater effects on increasing smoking cessation (West et al. 2015). In another examination of relative costs and benefits that used a much different framework to gauge benefit, disability-adjusted life-years gained, Jha and colleagues (2006) found that NRT may be more cost-effective than other interventions—its higher price notwithstanding. A systematic review on the economic impact of a conservative 20% price increase of tobacco products through taxation found evidence of per capita cost savings over the short- and medium terms (Contreary et al. 2015).

Because of their relatively high cost, pharmacologic and psychologic smoking cessation interventions have been more closely evaluated than inexpensive interventions. This report summarizes the cost-effectiveness ratios gleaned from the review of literature on the cost-effectiveness of clinical cessation interventions and compares the estimates to a threshold of cost-effectiveness for clinical interventions used in healthcare (Neumann et al. 2014; Sanders et al. 2016).

Cost-Effectiveness of Clinical Smoking Cessation Interventions

In a systematic review of the literature, Ruger and Lazar (2012) summarized the evidence on the cost-effectiveness of smoking cessation through 2009. This

review covered literature indexed in PubMed and the British National Health Service's Economic Evaluation Database as containing an economic evaluation (cost-benefit, cost-effectiveness, cost-utility, or cost-minimization analysis) of pharmacotherapy or counseling for smoking cessation. The review examined 36 economic evaluations in detail, including 14 studies of NRT, 12 studies of non-nicotine-based pharmacotherapy, and 10 studies of brief counseling for smoking cessation. The review found that cost-effectiveness and other types of economic evaluation studies do not routinely use standard metrics to evaluate benefits and often use the payer's perspective, not the societal perspective as recommended (Tables 5.6–5.8). To standardize dollar value of costs to the same base year, estimates in this section were converted to 2017 U.S. dollars from the base case year (or publication year if the base case year was not known) using the Medical Care part of the Consumer Price Index (all urban consumers). When performing benefit-cost analyses, USDHHS typically values QALY gains at about \$500,000 or \$850,000, depending on the discount rate applied (USDHHS 2016). This is substantially larger than the recently recommended values of \$100,000 or \$150,000 per QALY gained (Neumann et al. 2014).

Table 5.6 summarizes studies on nicotine-based pharmacotherapies. For NRT, RCTs in the United Kingdom estimated that when NRT was added to brief counseling in primary care settings, incremental cost per life-year saved ranged from \$1,115 to \$2,541 depending on the age groups from the national health system perspective (Stapleton et al. 1999). According to two more recent studies, the cost of NRT per additional quitter was \$171 compared with usual care from the health insurance perspective (Salize et al. 2009) and was \$3,781 compared with brief counseling from the state program perspective (Hollis et al. 2007). In an examination of observational data, adding free NRT to quitline counseling in the United States resulted in incremental costs of \$132 per life-year saved and \$267 per quit attempt in Oregon from the program perspective (Fellows et al. 2007) and of \$808 per quit attempt in Minnesota from the funding agency perspective (An et al. 2006). Three studies that used decision-analytic modeling found incremental cost-effectiveness ratios ranging from \$9,463 to \$23,589 per QALY gained for physician-based cessation counseling with nicotine patch compared with counseling alone from the payer perspective (Fiscella and Franks 1996), \$2,388 to \$9,791 per QALY gained from the societal perspective (Cromwell et al. 1997), and \$2,511 to \$6,020 per life-year saved for NRT compared with counseling or advice alone from the national health services perspective (Song et al. 2002).

Five studies that modeled populations of smokers estimated incremental cost-effectiveness ratios for counseling

and NRT compared with brief physician counseling alone ranged from \$1,267 to \$42,160 per life-year saved from the payer perspective (Oster et al. 1986; Wasley et al. 1997; Gilbert et al. 2004; Cornuz et al. 2006) and from \$2,021 to \$9,002 per QALY gained from the societal perspective (Feenstra et al. 2005). Among two studies on pharmacist-directed smoking cessation programs, one involving only the receipt of advice and motivation compared with usual advice from a pharmacist found cost-effectiveness ratios ranging from \$628 to \$2,678 per life-year saved from the payer perspective (Crealey et al. 1998), and the other incorporating four methods under pharmacist direction (quitting cold turkey, two kinds of NRT, and bupropion) compared with self-directed quit attempts found cost-effectiveness ratios ranging from \$478 to \$2,496 per successful quit from the payer perspective (Tran et al. 2002).

Table 5.7 summarizes cost-effectiveness studies of non-nicotine-based pharmacotherapies. Five studies evaluated varenicline and compared it with different comparators (nortryptiline; bupropion, NRT, and unaided cessation; brief counseling alone and unaided cessation; counseling; or NRT). Incremental cost-effectiveness ratios ranged from \$1,409 to \$5,838 per quit attempt from the healthcare system perspective (Hoogendoorn et al. 2008) and from dominates (i.e., less costly and more effective) to \$4,981 per QALY gained from the healthcare payer/system perspective (Hoogendoorn et al. 2008; Howard et al. 2008; Annemans et al. 2009; Bolin et al. 2009b; Igarashi et al. 2009). In some trials, varenicline was more efficacious than the comparison strategy (whether unaided cessation or cessation with NRT or bupropion) and more cost-effective from various perspectives (healthcare payer/system) (Howard et al. 2008; Annemans et al. 2009; Bolin et al. 2009b; Igarashi et al. 2009). Two other studies also showed that an extended period of varenicline treatment compared with placebo or 12 weeks of varenicline, bupropion, or NRT was less costly and more effective per QALY gained from the healthcare perspective (Knight et al. 2010) and was more effective than placebo, with incremental cost-effectiveness ratios as high as \$41,053 per QALY gained from the societal perspective (Bolin et al. 2009a). Studies comparing bupropion with NRT found incremental cost-effectiveness ratios as high as \$1,223 per QALY gained from the societal perspective (Bolin et al. 2006). One study compared bupropion with counseling or advice alone and found that the incremental cost per life-year saved ranged from \$1,603 to \$3,746 from a national health system perspective (Song et al. 2002).

Table 5.8 summarizes 10 studies that evaluated brief counseling therapies conducted with a variety of methods, in diverse settings, and with diverse populations. Using data from RCTs, an evaluation of care that included 20 minutes of bedside counseling, 12 minutes of videos, self-help materials, and follow-up calls found

Table 5.6 Summary of economic evaluations of nicotine-based pharmacotherapies for smoking cessation

Study	Design/population	Effects	Costs	Outcomes/findings
Oster et al. (1986)	<ul style="list-style-type: none"> • Meta-analysis • Cost-effectiveness analysis • Hypothetical group of smokers seen in routine office visits • Intervention/comparison: <ul style="list-style-type: none"> – Physician advice and counseling alone – Nicotine gum and physician advice • Perspective: Payer • Lifetime 	<ul style="list-style-type: none"> • Life-years saved 	<ul style="list-style-type: none"> • Physician time and gum • Base year: 1984 • Source: Retail prices, salary rates 	<ul style="list-style-type: none"> • Range of cost per life-year saved, by sex: <ul style="list-style-type: none"> – Men: \$4,113–\$6,465 (\$18,305–\$28,773 in 2017 \$) – Women: \$6,880–\$9,473 (\$30,620–\$42,160 in 2017 \$)
Fiscella and Franks (1996)	<ul style="list-style-type: none"> • Decision analytic model • Cost-effectiveness and cost-utility analyses • Male and female smokers, 25–69 years of age receiving primary care • Intervention/comparison: <ul style="list-style-type: none"> – Physician-based smoking cessation counseling with nicotine patch – Physician-based smoking cessation counseling alone • Perspective: Payer • Lifetime 	<ul style="list-style-type: none"> • QALYs saved 	<ul style="list-style-type: none"> • Physician time and retail price of nicotine patch • Base year: 1995 • Source: Published average wholesale price 	<ul style="list-style-type: none"> • The nicotine patch produced one additional lifetime quitter at a cost of \$7,332 (\$15,805 in 2017 \$) • Range of incremental cost-effectiveness of the nicotine patch, by sex: <ul style="list-style-type: none"> – Men: \$4,390–\$10,943 per QALY (\$9,463–\$23,589 per QALY in 2017 \$) – Women: \$4,955–\$6,983 per QALY (\$10,681–\$15,053 per QALY in 2017 \$)
Cromwell et al. (1997)	<ul style="list-style-type: none"> • Decision probabilities model • Cost-effectiveness analysis of clinical practice guidelines and cost-utility analysis • Simulated model of U.S. smokers, 18 years of age or older who were willing to make a quit attempt within 1 year • Intervention/comparison: Model of five counseling interventions for primary care physicians (minimal, brief, and full) and specialists (individual intensive and group intensive) with and without transdermal nicotine and nicotine gum • Perspective: Societal • 1 year 	<ul style="list-style-type: none"> • QALYs and life-years saved • Quit rates 	<ul style="list-style-type: none"> • Implementation of guidelines (screening, advice, motivational sessions, and interventions) • Base year: 1995 • Source: Published literature, guideline reports, and Medicare charges 	<ul style="list-style-type: none"> • Implementing the guidelines cost \$3,779 (\$8,146 in 2017 \$) per quitter, \$2,587 (\$5,577 in 2017 \$) per life-year saved, and \$1,915 (\$4,128 in 2017 \$) per QALY saved • Costs per QALY ranged from \$1,108 to \$4,542 (\$2,388 to \$9,791 in 2017 \$) • More intensive interventions were more cost-effective than those with less intensity

Table 5.6 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Wasley et al. (1997)	<ul style="list-style-type: none"> • Meta-analysis • Cost-effectiveness analysis • Hypothetical samples of 400 smokers who smoke ≥ 20 cigarettes per day • Intervention/comparison: <ul style="list-style-type: none"> – Nicotine patch with brief counseling – Brief physician counseling alone • Perspective: Payer • Lifetime 	<ul style="list-style-type: none"> • Life-years saved • Quit rates 	<ul style="list-style-type: none"> • Physician time and nicotine patch • Base year: 1995 • Source: Average retail cost and physicians' medical fee schedules 	<ul style="list-style-type: none"> • Range of average cost per life-year saved, by sex: <ul style="list-style-type: none"> – Men: \$965–\$1,585 (\$2,080–\$3,417 in 2017 \$) – Women: \$1,634–\$2,360 (\$3,522–\$5,087 in 2017 \$) • Range of incremental cost per life-year saved, by sex: <ul style="list-style-type: none"> – Men: \$1,796–\$2,949 (\$3,872–\$6,357 in 2017 \$) – Women: \$3,040–\$4,391 (\$5,553–\$9,379 in 2017 \$)
Crealey et al. (1998)	<ul style="list-style-type: none"> • Case control • Cost-effectiveness analysis • Matched cases (52) and controls (60) in PAS model program in Northern Ireland • Intervention/comparison: <ul style="list-style-type: none"> – Cases received advice and motivation to quit from pharmacist – Matched controls received usual advice from pharmacists • Perspective: Payer • Lifetime 	<ul style="list-style-type: none"> • Life-years saved 	<ul style="list-style-type: none"> • Direct intervention (PAS materials, training for pharmacists, and time spent counseling) • Base year: 1997 • Source: Estimates of program costs and salary rates 	<ul style="list-style-type: none"> • Range of cost for PAS program per life-year saved, by sex: <ul style="list-style-type: none"> – Men: \$337–\$603 (\$683–\$1,222 in 2017 \$) – Women: \$310–\$1,322 (\$628–\$2,678 in 2017 \$)
Stapleton et al. (1999)	<ul style="list-style-type: none"> • Randomized controlled trial and survey • Cost-effectiveness analysis • 1,200 patients who smoked ≥ 15 cigarettes per day in 15 English counties • Intervention/comparison: <ul style="list-style-type: none"> – Brief counseling with general practitioner plus 16-hour nicotine patch treatment and booklet – Brief counseling with general practitioner plus placebo and booklet • Perspective: National Health Service • 12 weeks 	<ul style="list-style-type: none"> • Life-years saved 	<ul style="list-style-type: none"> • Treatment (counseling time, nicotine patches, patient booklets, and biochemical validation of abstinence) • Base year: 1998 • Source: National survey data and resource use survey 	<ul style="list-style-type: none"> • Incremental cost per life-year saved among patients if practitioners could prescribe nicotine patch, by age group: <ul style="list-style-type: none"> – <35 years: \$656 (\$1,288 in 2017 \$) – 35–44 years: \$568 (\$1,115 in 2017 \$) – 45–54 years: \$712 (\$1,398 in 2017 \$) – 55–65 years: \$1,294 (\$2,541 in 2017 \$)

Table 5.6 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Tran et al. (2002)	<ul style="list-style-type: none"> • Observations • Cost-effectiveness and cost-utility analyses • 48 patients 21–70 years of age who had tried at least once to quit smoking • Intervention/comparison: <ul style="list-style-type: none"> – Pharmacist-directed smoking cessation program using four methods (cold turkey, nicotine patch, nicotine gum, bupropion) – Self-directed quit attempt • Perspective: Payer and societal • 1 year, lifetime 	<ul style="list-style-type: none"> • Quit rate • Life-years saved • QALYs saved 	<ul style="list-style-type: none"> • Materials and pharmacist time • Selected cessation methods (retail cost) • Base year: 1997 • Source: Salary data and retail costs 	<ul style="list-style-type: none"> • Incremental costs (in 2017 \$) using pharmacist-directed program, by method of smoking cessation per successful quit from the payer perspective: <ul style="list-style-type: none"> – \$236 (\$478 in 2017 \$) for cold turkey – \$936 (\$1,896 in 2017 \$) for nicotine patch – \$1,232 (\$2,496 in 2017 \$) for nicotine gum – \$1,150 (\$2,370 in 2017 \$) for bupropion
Gilbert et al. (2004)	<ul style="list-style-type: none"> • Markov chain cohort simulation • Cost-effectiveness analysis • Two simulated cohorts of smokers in Seychelles (Africa) • Intervention/comparison: <ul style="list-style-type: none"> – Physician counseling alone – Counseling plus one of five cessation therapies (nicotine gum, patch, spray, inhaler, or bupropion) • Perspective: Third-party payer • Lifetime 	<ul style="list-style-type: none"> • Life-years saved 	<ul style="list-style-type: none"> • Additional physician time required • Treatment (retail prices for generic treatment medications) • Base year: 2002–2003 • Source: Retail prices and wage data 	<ul style="list-style-type: none"> • Incremental cost per life-year saved, by type of therapy (U.S. prices): <ul style="list-style-type: none"> – \$3,712 (\$5,939 in 2017 \$) for nicotine gum – \$1,982 (\$3,171 in 2017 \$) for nicotine patch – \$4,597 (\$7,355 in 2017 \$) for nicotine spray – \$4,291 (\$6,865 in 2017 \$) for nicotine inhaler – \$1,324 (\$2,118 in 2017 \$) for bupropion
Feenstra et al. (2005)	<ul style="list-style-type: none"> • RIVM chronic disease • Cost-effectiveness and cost-utility analyses • Smokers in the Netherlands • Intervention/comparison: <ul style="list-style-type: none"> – Minimal counseling by a general practitioner with or without NRT – Intensive counseling by a general practitioner with NRT or bupropion – Telephone counseling • Perspective: Societal • 1, 10, or 75 years 	<ul style="list-style-type: none"> • Quit rate • Life-years gained • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Healthcare for 11 smoking-related diseases (direct costs only) • Base year: 2000 • Source: Estimated retail costs, standard costing manual, and salary data 	<ul style="list-style-type: none"> • Cost per QALY gained ranged from \$1,109 (\$2,021 in 2017 \$) for telephone counseling to \$4,939 (\$9,002 in 2017 \$) for intensive counseling with nicotine patches or gum

Table 5.6 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
An et al. (2006)	<ul style="list-style-type: none"> • Before and after initiative • Cost-effectiveness analysis • 373 callers to the Minnesota QUITPLAN helpline • Intervention/comparison: <ul style="list-style-type: none"> – Quitline callers before initiative – Quitline callers enrolled in multisession counseling received NRT (patch or gum) by mail • Perspective: Funding agency • 6 months 	<ul style="list-style-type: none"> • Quit rate 	<ul style="list-style-type: none"> • Counseling and provision of free NRT • Base year: Not available • Source: Estimated program costs 	<ul style="list-style-type: none"> • Average number of ex-smokers per month increased from 16 to 124 • Average cost per quit increased from \$1,362 (\$1,926 in 2017 \$) to \$1,934 (\$2,734 in 2017 \$)
Cornuz et al. (2006)	<ul style="list-style-type: none"> • Markov-chain cohort simulation • Cost-effectiveness analysis • Simulated cohorts of smokers in six countries (Canada, France, Spain, Switzerland, United States, and United Kingdom) • Intervention/comparison: <ul style="list-style-type: none"> – Brief cessation counseling by general practitioner – Counseling plus NRT • Perspective: Third-party payer • Lifetime 	<ul style="list-style-type: none"> • Life-years saved 	<ul style="list-style-type: none"> • Additional physician time required plus medications (retail price) • Base year: 2002–2003 • Source: Pharmacy prices and published price data from each country 	<ul style="list-style-type: none"> • Range of cost per life-year saved, by type of therapy and sex: <ul style="list-style-type: none"> – Gum: <ul style="list-style-type: none"> ◦ \$2,230 for men (\$3,568 in 2017 \$) ◦ \$7,643 for women (\$12,228 in 2017 \$) – Patch: <ul style="list-style-type: none"> ◦ \$1,758 for men (\$2,813 in 2017 \$) ◦ \$5,131 for women (\$8,209 in 2017 \$) – Spray: <ul style="list-style-type: none"> ◦ \$1,935 for men (\$3,096 in 2017 \$) ◦ \$7,969 for women (\$12,749 in 2017 \$) – Inhaler: <ul style="list-style-type: none"> ◦ \$3,480 for men (\$5,568 in 2017 \$) ◦ \$8,700 for women (\$13,919 in 2017 \$) – Bupropion: <ul style="list-style-type: none"> ◦ \$792 for men (\$1,267 in 2017 \$) ◦ \$2,922 for women (\$4,675 in 2017 \$)
Fellows et al. (2007)	<ul style="list-style-type: none"> • Before and after free-patch initiative • Cost-effectiveness analysis • 959 smokers who registered for quitline service in Oregon • Intervention/comparison: <ul style="list-style-type: none"> – Pre-initiative program – Free-patch initiative from the Oregon tobacco quitline • Perspective: Program • 1 year 	<ul style="list-style-type: none"> • Quit rate • Life-years saved 	<ul style="list-style-type: none"> • Media and intervention (before and after the initiative) • Base year: 2004 • Source: Quitline utilization and cost data from state, intervention providers, and patients 	<ul style="list-style-type: none"> • Compared with the program before the free-patch initiative, the new initiative increased quitting fourfold and reduced total costs per quit by \$2,688 (\$4,120 in 2017 \$) • Free-patch initiative cost \$86 (\$22–\$353) (\$132 [\$34–\$541] in 2017 \$) per life-year saved and \$174 (\$267 in 2017 \$) per additional quit attempt

Table 5.6 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Hollis et al. (2007)	<ul style="list-style-type: none"> • Randomized trial • Cost-effectiveness analysis • 4,614 callers to the Oregon tobacco quitline who smoked ≥ 5 cigarettes per day • Intervention/comparison: Brief, moderate, and intensive telephone counseling with or without offers of free nicotine patches • Perspective: State program • 1 year 	<ul style="list-style-type: none"> • Abstinence rate 	<ul style="list-style-type: none"> • Interventions • Base year: 2004 • Source: Program records of resources consumed 	<ul style="list-style-type: none"> • Compared with brief counseling with no NRT, the added costs for each additional quit were: <ul style="list-style-type: none"> – \$2,467 (\$3,781 in 2017 \$) for brief counseling plus NRT – \$1,912 (\$2,931 in 2017 \$) for moderate counseling and no NRT – \$2,109 (\$3,233 in 2017 \$) for moderate counseling plus NRT – \$2,640 (\$4,047 in 2017 \$) for intensive counseling and no NRT – \$2,112 (\$3,237 in 2017 \$) for intensive counseling plus NRT
Salize et al. (2009)	<ul style="list-style-type: none"> • Cluster randomized trial • Cost-effectiveness analysis • 577 patients who smoked ≥ 10 cigarettes per day in Germany • Intervention/comparison: <ul style="list-style-type: none"> – Training of general practitioners plus remuneration for each abstinent patient – Training of general practitioners plus cost-free NRT and/or bupropion hydrochloride – A combination of both strategies • Perspective: Health insurance • 1 year 	<ul style="list-style-type: none"> • Abstinence rate 	<ul style="list-style-type: none"> • Interventions • Base year: 2003 • Source: Unit costs per each element of treatment in the trial 	<ul style="list-style-type: none"> • Compared with usual care, both training of general practitioners plus drugs and training of general practitioners plus drugs and remuneration were cost-effective • The cost per additional quitter was \$107 (\$171 in 2017 \$) per patient for training of general practitioners plus drugs and \$97 (\$155 in 2017 \$) per patient for training of general practitioners plus drugs and remuneration

Source: Table 4 in Ruger and Lazar (2012).

Notes: **NRT** = nicotine replacement therapy; **PAS** = pharmacists action on smoking; **QALYs** = quality-adjusted life-years; **RIVM** = chronic disease model developed at the National Institute of Public Health and the Environment in The Netherlands. Estimates converted to 2017 U.S. dollars from the base case year (or publication year if no base case year) using the Medical Care part of the Consumer Price Index (all urban consumers).

Table 5.7 Summary of economic evaluations of non-nicotine-based pharmacotherapies for smoking cessation

Study	Design/population	Effects	Costs	Outcomes/findings
Song et al. (2002)	<ul style="list-style-type: none"> • Decision analytic model • Cost-effectiveness analysis • Simulation based on results from published studies • Intervention/comparison: <ul style="list-style-type: none"> – Advice or counseling alone – Advice or counseling plus NRT or bupropion sustained release – Advice or counseling plus NRT and bupropion sustained release • Perspective: United Kingdom National Health Services • 1 year 	<ul style="list-style-type: none"> • Quit rates • Life-years saved 	<ul style="list-style-type: none"> • Intervention • Base year: 2001 • Source: Published studies 	<ul style="list-style-type: none"> • Range of incremental cost per life-year saved compared with counseling or advice alone, by type of intervention: <ul style="list-style-type: none"> – \$1,441–\$3,455 (\$2,511–\$6,020 in 2017 \$) for NRT – \$920–\$2,150 (\$1,603–\$3,746 in 2017 \$) for bupropion sustained release – \$1,282–\$2,836 (\$2,234–\$4,941 in 2017 \$) for NRT plus bupropion sustained release
Antoñanzas and Portillo (2003)	<ul style="list-style-type: none"> • Adaptation of health and economic consequences of smoking interactive simulation • Cost-effectiveness analysis • Smokers in Spain • Intervention/comparison: <ul style="list-style-type: none"> – Bupropion – NRT (nicotine patch or gum) • Perspective: National health system • 20 years 	<ul style="list-style-type: none"> • Deaths prevented • Life-years saved 	<ul style="list-style-type: none"> • Intervention • Healthcare costs for tobacco-related diseases or conditions (cancers, CHD, stroke, COPD, and low birth weight) • Base year: 1999 • Source: National Health Survey and National Institute of Statistics 	<ul style="list-style-type: none"> • At 20 years, for bupropion and the nicotine patch, respectively, there was a net savings of \$32,920 (\$62,441 in 2017 \$) and \$15,993 (\$30,334 in 2017 \$) per death prevented and a net savings of \$3,852 (\$7,306 in 2017 \$) and \$1,867 (\$3,541 in 2017 \$) per life-year saved • At 20 years, nicotine gum had a cost-effectiveness ratio of \$41,325 (\$78,402 in 2017 \$) per death prevented and \$4,786 (\$9,078 in 2017 \$) per life-year saved
Bolin et al. (2006)	<ul style="list-style-type: none"> • Global health outcomes simulation model • Cost-effectiveness analysis • Model cohort of male and female smokers in Sweden • Intervention/comparison: <ul style="list-style-type: none"> – Bupropion – NRT (nicotine patches and gum) • Perspective: Societal • 20 years 	<ul style="list-style-type: none"> • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Direct costs of smoking (COPD, asthma, CHD, stroke, and lung cancer) • Reduced production and consumption (indirect costs of smoking) • Base year: 2001 • Source: Swedish unit costs, hospital records, and physician records 	<ul style="list-style-type: none"> • When direct and indirect costs on production and consumption were included, bupropion was cost-saving compared with both types of NRT • When only direct costs were included, incremental cost per QALY gained for bupropion compared with nicotine patches was \$702 (\$1,223 in 2017 \$) for men and \$521 (\$908 in 2017 \$) for women

Table 5.7 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Halpern et al. (2007)	<ul style="list-style-type: none"> • Decision analytic model • Cost-effectiveness analysis • Simulation in cohort of 1,000 smokers in the United States • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline (12 weeks) – Nicotine patch (9 weeks) – Bupropion (12 weeks) – No intervention • Perspective: Private health plans, state Medicaid program, and employer • 10 years 	<ul style="list-style-type: none"> • Abstinence rates 	<ul style="list-style-type: none"> • Intervention • Medical care for smoking-related diseases (CHD, COPD, and lung cancer) and pregnancy complications • Productivity losses and absenteeism • Base year: 2005 • Source: Literature 	<ul style="list-style-type: none"> • Compared with unaided cessation, cost-effectiveness of varenicline per additional cessation at 2 years ranged from \$648 (\$953 in 2017 \$) in the private health plan model to \$1,229 (\$1,049 in 2017 \$) in the Medicaid model
Hoogendoorn et al. (2008)	<ul style="list-style-type: none"> • BENESCO model • Cost-effectiveness and cost-utility analyses • Hypothetical cohort of Dutch smokers making a one-time quit attempt • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline – Untreated or treated with bupropion, nortriptyline, or NRT • Perspective: Dutch healthcare system • Lifetime 	<ul style="list-style-type: none"> • Quit rate • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Direct medical costs of smoking-related diseases (COPD, lung cancer, CHD, and stroke) • Base year: 2004 • Source: Estimates from Dutch source data 	<ul style="list-style-type: none"> • Varenicline estimated to cost \$1,472 (\$2,256 in 2017 \$) per QALY gained compared with nortriptyline and \$285 (\$437 in 2017 \$) per QALY gained compared with unaided cessation • Cost of varenicline per additional quitter ranged from \$919 (\$1,409 in 2017 \$) compared with NRT to \$3,809 (\$5,838 in 2017 \$) compared with nortriptyline
Jackson et al. (2007)	<ul style="list-style-type: none"> • Decision tree model • Cost-benefit analysis • Simulation based on published results of clinical trial • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline – Bupropion (brand and generic) – Placebo • Perspective: Employer • 1 year 	<ul style="list-style-type: none"> • Quit rates 	<ul style="list-style-type: none"> • Intervention • Cost of smoking for employer (absenteeism, medical care, time lost, and insurance) • Base year: 2006 • Source: Study detailing direct and indirect costs of smoker to an employer, and pricing related to wholesale acquisition costs 	<ul style="list-style-type: none"> • Cost savings per nonsmoking employee at 1 year, by type of intervention: <ul style="list-style-type: none"> – \$541 (\$765 in 2017 \$) for varenicline – \$270 (\$382 in 2017 \$) for bupropion sustained release (generic) – \$151 (\$213 in 2017 \$) for bupropion sustained release (brand) – \$82 (\$116 in 2017 \$) for placebo

Table 5.7 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Howard et al. (2008)	<ul style="list-style-type: none"> • BENESCO Markov simulation • Cost-utility analysis • Hypothetical cohort of U.S. adult smokers who make a one-time quit attempt • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline – Bupropion – NRT – Unaided quitting • Perspective: U.S. healthcare system • 20 years and lifetime 	<ul style="list-style-type: none"> • QALYs 	<ul style="list-style-type: none"> • Intervention • Direct lifetime costs of smoking-related diseases (lung cancer, COPD, CHD, stroke, and asthma) • Base year: 2005 	<ul style="list-style-type: none"> • Varenicline was less costly and more effective (dominates) than other cessation strategies (bupropion, NRT, and unaided cessation) over either time period studied (20 years and lifetime)
Annemans et al. (2009)	<ul style="list-style-type: none"> • BENESCO Markov simulation • Cost-effectiveness and cost-utility analyses • Cohort of Belgian adult smokers making a one-time quit attempt • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline, bupropion, or NRT with brief counseling – Brief counseling alone – Unaided cessation • Perspective: Healthcare payer (public and private) • Lifetime 	<ul style="list-style-type: none"> • Life-years gained • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Direct medical costs related to smoking comorbidities (COPD, lung cancer, CHD, stroke, and asthma) • Base year: 2007 • Source: Literature and public health databases 	<ul style="list-style-type: none"> • Compared with brief counseling alone and unaided cessation, varenicline cost \$337 (\$456 in 2017 \$) per life-year gained and \$2,325 (\$3,148 in 2017 \$) per QALY gained • Varenicline is cost-saving compared with bupropion and NRT
Bolin et al. (2009a)	<ul style="list-style-type: none"> • BENESCO Markov simulation • Cost-utility analysis • Simulated cohort of adult smokers in Sweden who successfully abstained after an initial 12-week treatment of varenicline • Intervention/comparison: <ul style="list-style-type: none"> – Additional 12 weeks of varenicline – Placebo • Perspective: Societal • 50 years 	<ul style="list-style-type: none"> • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Average direct medical costs from smoking-related diseases (COPD, CHD, stroke, and lung cancer) • Average value of indirect effects (reduced consumption and production) • Base year: 2003 • Source: Healthcare cost data from Skåne, Sweden; estimated prescription prices; and published literature 	<ul style="list-style-type: none"> • Incremental costs per QALY for additional 12 weeks of varenicline compared with placebo were \$7,420 (\$11,871 in 2017 \$) for men and \$7,464 (\$11,941 in 2017 \$) for women • Incremental costs per QALY, including indirect effects, were \$25,359 (\$40,571 in 2017 \$) for men and \$25,660 (\$41,053 in 2017 \$) for women

Table 5.7 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Bolin et al. (2009b)	<ul style="list-style-type: none"> • BENESCO Markov simulation • Cost-effectiveness and cost-utility analyses • Simulated model in four European countries (Belgium, France, Sweden, and United Kingdom) • Intervention/comparison: <ul style="list-style-type: none"> – Varenicline – NRT • Perspective: National healthcare system • Lifetime 	<ul style="list-style-type: none"> • Life-years gained • QALYs gained 	<ul style="list-style-type: none"> • Intervention • Morbidity-related healthcare costs from four smoking-related morbidities (lung cancer, COPD, CHD, and stroke) • Base year: Not available • Source: Country-specific databases 	<ul style="list-style-type: none"> • In a typical smoking cessation intervention, using varenicline instead of NRT was cost-saving in all countries except France, which had a cost-effectiveness ratio of \$3,936 (\$4,981 in 2017 \$) per QALY gained
Igarashi et al. (2009)	<ul style="list-style-type: none"> • Markov model • Cost-utility analysis • Simulated cohort of smokers in Japan who started smoking at 20 years of age • Intervention/comparison: <ul style="list-style-type: none"> – Counseling on smoking cessation by a physician – Counseling plus varenicline therapy • Perspective: Healthcare payer • Lifetime 	<ul style="list-style-type: none"> • QALYs gained 	<ul style="list-style-type: none"> • Treatment • Direct lifetime medical costs for tobacco-associated disease • Base year: 2007 • Source: Survey of public health insurance, National Health Insurance, and drug tariff 	<ul style="list-style-type: none"> • Adding varenicline to counseling increased QALYs and saved medical costs among men • Adding varenicline to counseling had an incremental cost-effectiveness ratio of \$3,010 (\$4,075 in 2017 \$) per QALY gained in women
Knights et al. (2010)	<ul style="list-style-type: none"> • BENESCO Markov simulation • Cost-effectiveness and cost-utility analyses • Hypothetical population of adult American smokers who made a single quit attempt • Intervention/comparison: <ul style="list-style-type: none"> – Initial 12 weeks plus additional 12 weeks of varenicline – 12 weeks of varenicline, bupropion, NRT, or unaided cessation • Perspective: Healthcare system • 5, 10, and 20 years and lifetime 	<ul style="list-style-type: none"> • QALYs gained 	<ul style="list-style-type: none"> • Direct treatment • Morbidity-related healthcare costs of smoking-related diseases (lung cancer, stroke, CHD, COPD, and asthma) • Base year: 2005 • Source: Literature, prices in 2005 U.S. Red Book 	<ul style="list-style-type: none"> • An additional 12 weeks of varenicline increased 1-year abstinence rates from 23% to 28% (compared with initial 12 weeks of varenicline) • During the lifetime of all participants, an additional 12 weeks of varenicline was cost-effective compared with the initial 12 weeks of varenicline (an incremental cost per QALY gained of \$972 (\$1,429 in 2017 \$)) and was less costly and more effective (dominates) than other alternatives (bupropion, NRT, and unaided cessation)

Source: Table 5 in Ruger and Lazar (2012).

Notes: **BENESCO** = benefits of smoking cessation on outcomes; **CHD** = coronary heart disease; **COPD** = chronic obstructive pulmonary disease; **NRT** = nicotine replacement therapy; **QALYs** = quality-adjusted life-years. Estimates converted to 2017 dollars from the base case year (or publication year if no base case year) using the Medical Care part of the Consumer Price Index (all urban consumers).

Table 5.8 Summary of economic evaluations of brief counseling for smoking cessation

Study	Design/population	Effects	Costs	Outcomes/findings
Cummings et al. (1989)	<ul style="list-style-type: none"> • Model: Not available • Cost-effectiveness analysis • Hypothetical group of patients who were smokers and were seen during a routine office visit • Intervention/comparison: Physician counseling patients for 4 minutes during a routine office visit to quit smoking • Perspective: Societal • Time: Not available 	<ul style="list-style-type: none"> • Quit rates • Life-years saved 	<ul style="list-style-type: none"> • Physician time spent counseling • Self-help materials • Base year: 1984 • Source: Average cost of physician visit (\$30) and cost of materials (\$2) 	<ul style="list-style-type: none"> • Brief advice cost \$705–\$988 (\$3,138–\$4,397 in 2017 \$) per life-year saved for men and \$1,204–\$2,058 (\$5,358–\$9,159 in 2017 \$) per life-year saved for women
Meenan et al. (1998)	<ul style="list-style-type: none"> • Randomized controlled trial • Cost-effectiveness analysis • Hospitalized adult smokers in two acute-care hospitals in a large group model HMO in Oregon and Washington • Intervention/comparison: <ul style="list-style-type: none"> – 20-minute bedside counseling session with health counselor, 12-minute video, self-help materials, and one or two follow-up phone calls – Usual care • Perspective: Implementing hospital • 1 year 	<ul style="list-style-type: none"> • Quit rates • Life-years saved 	<ul style="list-style-type: none"> • Intervention (identify patients, deliver counseling, and follow-up) • Base year: 1994 • Source: Project surveys, expense reports, retrospective labor estimates, financial staff of HMO, and estimates from literature 	<ul style="list-style-type: none"> • Cost of intervention was \$159 (\$358 in 2017 \$) per smoker • Incremental cost per incremental quit was \$3,697 (\$8,382 in 2017 \$) • Incremental cost per incremental discounted life-year saved was \$1,691–\$7,444 (\$3,809–\$16,769 in 2017 \$)
Haile et al. (2002)	<ul style="list-style-type: none"> • Cohort • Cost-effectiveness analysis • All smokers attending a noncardiac surgical preadmission clinic in Australia • Intervention/comparison: Structured, interactive computerized smoking cessation program • Perspective: Hospital/payer • 2 months, 1 year 	<ul style="list-style-type: none"> • Quit rates • Acceptability of computerized smoking cessation intervention 	<ul style="list-style-type: none"> • Intervention (developing program, computer hardware, and software) • Base year: Not available (study conducted in 1999) • Source: Invoice 	<ul style="list-style-type: none"> • Costs of intervention at 1 year, by smoking status: <ul style="list-style-type: none"> – \$5.80 (\$11.0 in 2017 \$) per patient – \$24.19 (\$45.9 in 2017 \$) per smoker – \$271.47 (\$514.9 in 2017 \$) per quitter

Table 5.8 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Solberg et al. (2006)	<ul style="list-style-type: none"> • Model: Not available • Cost-utility analysis • Hypothetical group of patients in primary care clinics in the United States • Intervention/comparison: <ul style="list-style-type: none"> – Model 1: One-time counseling – Model 2: Model 1 plus costs of smoking-attributable illness – Model 3: Annual counseling – Model 4: Model 3 plus costs of smoking-attributable illness • Perspective: Societal • Lifetime 	<ul style="list-style-type: none"> • QALYs 	<ul style="list-style-type: none"> • Intervention (clinician time, medication, and patient time and travel) • Preventable smoking-attributed illness • Base year: 2000 • Source: Medicare reimbursement rates, wholesale costs, and healthcare charges 	<ul style="list-style-type: none"> • Cost-effectiveness per QALY saved was \$1,100 (\$2,005 in 2017 \$) for Model 1 and 2,266 (\$4,130 in 2017 \$) for Model 3 • Models 2 and 4 were cost-saving, with net cost savings of \$65 (\$118 in 2017 \$) and \$542 (\$988 in 2017 \$), respectively, per smoker counseled
Akers et al. (2007)	<ul style="list-style-type: none"> • Randomized trial • Cost-effectiveness analysis • Persons in five northern states (Alaska, Idaho, Montana, Oregon, and Washington) who were interested in quitting smokeless tobacco • Intervention/comparison: <ul style="list-style-type: none"> – Self-help manual only – Assisted self-help (manual plus videotape and two supportive phone calls from a tobacco cessation counselor) • Perspective: Societal and provider/agency • 18 months 	<ul style="list-style-type: none"> • Quit rates 	<ul style="list-style-type: none"> • Program (materials, postage, phone services, and counselor and staff time) • Participants' and supporters' time • Base year: 2000 • Source: Cost of materials in bulk and minimum wage in Oregon 	<ul style="list-style-type: none"> • Total cost per participant by perspective and type of treatment: <ul style="list-style-type: none"> – No treatment: <ul style="list-style-type: none"> ◦ Societal: \$0 (\$0 in 2017 \$) ◦ Provider/agency: \$0 (\$0 in 2017 \$) – Manual only: <ul style="list-style-type: none"> ◦ Societal: \$20 (\$36 in 2017 \$) ◦ Provider/agency: \$8 (\$15 in 2017 \$) – Assisted self-help: <ul style="list-style-type: none"> ◦ Societal: \$56 (\$102 in 2017 \$) ◦ Provider/agency: \$39 (\$71 in 2017 \$) • Incremental cost per quit by perspective and type of treatment: <ul style="list-style-type: none"> – Manual only: <ul style="list-style-type: none"> ◦ Societal: \$691 (\$1,259 in 2017 \$) ◦ Provider/agency: \$481 (\$376 in 2017 \$) – Assisted self-help: <ul style="list-style-type: none"> ◦ Societal: \$1,131 (\$2,061 in 2017 \$) ◦ Provider/agency: \$973 (\$1,773 in 2017 \$)

Table 5.8 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Barnett et al. (2008)	<ul style="list-style-type: none"> • Randomized trial • Cost-effectiveness analysis • Mental health outpatients who were smokers and being treated for depression • Intervention/comparison: <ul style="list-style-type: none"> – Brief contact (stop-smoking guide and referral list) – Stepped smoking cessation program • Perspective: Healthcare payer • 18 months 	<ul style="list-style-type: none"> • Abstinence rates • Life-years gained 	<ul style="list-style-type: none"> • All smoking cessation services used by participants, including intervention and referral • Mental healthcare • Base year: 2003 • Source: Retail cost, Medicare reimbursement rates, hospital charge data, and Red Book prices 	<ul style="list-style-type: none"> • Smoking cessation services cost \$6,204 (\$9,926 in 2017 \$) per successful quit or \$5,170 (\$8,271 in 2017 \$) per life-year gained • Cessation services plus mental healthcare cost \$11,496 (\$18,392 in 2017 \$) per successful quit or \$9,580 (\$15,327 in 2017 \$) per life-year gained
Dino et al. (2008)	<ul style="list-style-type: none"> • Markov transition model • Cost-effectiveness analysis • Students 17–25 years of age who smoked ≥5 cigarettes per day and attended selected schools in Florida • Intervention/comparison: <ul style="list-style-type: none"> – Not On Tobacco (or N-O-T) smoking cessation program – Brief, 20-minute intervention • Perspective: School • 25 years of age 	<ul style="list-style-type: none"> • Quit rates • Life-years saved 	<ul style="list-style-type: none"> • Intervention (training, room and board for trainer, brochures, and gifts) • Base year: 2000 • Source: Program and school records 	<ul style="list-style-type: none"> • Incremental cost-effectiveness ratio for N-O-T program was \$443 (\$807 in 2017 \$) per discounted life-year saved in base model: <ul style="list-style-type: none"> – \$1,029 (\$1,875 in 2017 \$) in worst-case scenario – \$274 (\$499 in 2017 \$) in best-case scenario
Ruger et al. (2008)	<ul style="list-style-type: none"> • Randomized controlled trial • Cost-effectiveness and cost-utility analyses • Low-income pregnant women in Boston, Massachusetts • Intervention/comparison: <ul style="list-style-type: none"> – Motivational interviewing with nurse tailored to patient’s stage of readiness for cessation – Brief counseling • Perspective: Societal • Lifetime 	<ul style="list-style-type: none"> • QALYs saved • Life-years saved 	<ul style="list-style-type: none"> • Program (intervention, travel, and training) • Neonatal intensive care • Maternal healthcare (cardiovascular and lung diseases) • Base year: 1997 • Source: Program records and published estimates 	<ul style="list-style-type: none"> • For smoking cessation, intervention was costlier and less effective than usual care • For relapse prevention, cost-effectiveness of the intervention was \$851 (\$1,724 in 2017 \$) per life-year saved and \$628 (\$1,272 in 2017 \$) per QALY saved

Table 5.8 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Thavorn and Chaiyakunapruk et al. (2008)	<ul style="list-style-type: none"> • Markov model • Cost-effectiveness analysis • Two simulated cohorts of Thai smokers—40, 50, and 60 years of age—who regularly smoked 10–20 cigarettes per day • Intervention/comparison: <ul style="list-style-type: none"> – Structured community pharmacist-based smoking cessation program (personalized and supportive advice, assessment, therapy, self-help material, and follow-up visits) – Usual care (assessment, brief advice and support, and therapy without follow-up care) • Perspective: Healthcare system • Lifetime 	<ul style="list-style-type: none"> • Life-years gained 	<ul style="list-style-type: none"> • Intervention (pharmacist training, fees, and medications) • Direct medical costs of smoking-related diseases (COPD, lung cancer, stroke, and cardiovascular disease) • Base year: 2005 • Source: Published studies, information centers, and price index 	<ul style="list-style-type: none"> • In the cohort of those 40 years of age, program resulted in cost savings to the health system of \$500 (\$735 in 2017 \$) for men and \$614 (\$903 in 2017 \$) for women, and 0.18 life-years gained for men and 0.24 life-years gained for women
Boyd and Briggs (2009)	<ul style="list-style-type: none"> • Observational study • Cost-effectiveness and cost-utility analyses • Smokers who accessed either of two cessation services between March and May 2007 in Glasgow, Scotland • Intervention/comparison: <ul style="list-style-type: none"> – One-to-one cessation support in pharmacies – Group counseling in the community – Self-quit attempt • Perspective: National health system • 4 weeks and 1 year 	<ul style="list-style-type: none"> • Quit rates • QALYs 	<ul style="list-style-type: none"> • Intervention costs incurred by National Health Service (NRT, professional time, overhead, and materials used) • Base year: 2007 • Source: Resource use and records from the National Health Service 	<ul style="list-style-type: none"> • Incremental cost per additional 4-week quitter was \$1,512 (\$2,047 in 2017 \$) for pharmacy support and \$2,158 (\$2,922 in 2017 \$) for group counseling in the community compared with self-quit cessation attempts • Incremental cost per QALY gained was \$8,620 (\$11,671 in 2017 \$) for pharmacy services and \$10,579 (\$14,324 in 2017 \$) for group counseling in the community compared with self-quit cessation attempts

Source: Table 6 in Ruger and Lazar (2012).

Notes: **COPD** = chronic obstructive pulmonary disease; **HMO** = health maintenance organization; **NRT** = nicotine replacement therapy; **QALYs** = quality-adjusted life-years. Estimates converted to 2017 dollars from the base case year (or publication year if no base case year) using the Medical Care part of the Consumer Price Index (all urban consumers).

that incremental cost-effectiveness ratios ranged from \$3,809 to \$16,769 per life-year saved compared with usual care from the implementing hospital perspective (Meenan et al. 1998), and another evaluation of stepped cessation services found that ratios per life-year gained ranged from \$8,271 to \$15,327 compared with brief contact from the healthcare perspective (Barnett et al. 2008). Three evaluations of counseling therapies per additional quit found that the incremental cost-effectiveness ratio was \$8,382 from the implementing hospital perspective (Meenan et al. 1998) and that cost-effectiveness ratios ranged from \$9,926 to \$18,392 from the healthcare perspective (Barnett et al. 2008) and from \$1,259 to \$2,061 from the societal perspective (Akers et al. 2007). Using an observational design, Boyd and Briggs (2009) found incremental cost-effectiveness ratios per QALY gained of \$11,671 for one-to-one support (by a pharmacist) and \$14,324 for group counseling, and found incremental cost-effectiveness ratios per quit of \$2,047 and \$2,922 for one-to-one support and for group counseling, respectively, compared with self-quit cessation attempts from the national health system perspective. In other studies that compared brief counseling or smoking cessation programs with usual care, estimated incremental cost-effectiveness ratios ranged from \$499 to \$1,875 per life-year saved from the school perspective (Dino et al. 2008), from \$735 to \$903 from the healthcare perspective (Thavorn and Chaiyakunapruk 2008), and from \$3,138 to \$9,159 per life-year saved from the societal perspective (Cummings et al. 1989). Additionally, the incremental cost-effectiveness ratio was \$4,130 per QALY gained from the societal perspective (Solberg et al. 2006).

Cost-Effectiveness of Nonclinical Smoking Cessation Interventions

Table 5.9 summarizes studies on the cost-effectiveness of various policy interventions that promote smoking cessation. To standardize the dollar value of costs to the same base year, estimates in this section were converted to 2017 U.S. dollars from the base case year (or publication year if no base case year) using the Medical Care part of the Consumer Price Index (all urban consumers). Although these studies share this focus, the evaluations were highly heterogeneous (Ekpu and Brown 2015). Regardless, some of these evaluations estimated cost-effectiveness ratios similar to or greater than those for clinical smoking cessation interventions. The estimated incremental cost-effectiveness ratios for an NRT program and for a smoke-free workplace policy compared with the clinical standard were \$7,736 and \$882 per QALY gained, respectively (Ong and Glantz 2005). Villanti and colleagues (2012) evaluated the American Legacy Foundation's national EX campaign, which was a radio and television campaign from 2008 designed to promote smoking cessation among adult

smokers. The estimated incremental cost-effectiveness ratios ranged from \$47,271 to \$102,883 per QALY gained from the societal perspective when compared with a hypothetical status quo of no program or change in cessation behavior. School-based antitobacco education programs compared with status quo have a much wider range of estimated incremental cost-effectiveness ratios per QALY gained over 50 years, ranging from \$9,294 when considering a 56% reduction in smoking that dissipates in 4 years to \$644,890 when considering a 5% reduction in smoking that dissipates in 1 year from the societal perspective. For the most plausible scenario of 30% effectiveness in preventing smoking, which dissipates in 4 years, the estimated cost-effectiveness ratio was \$37,935 per QALY gained (Tengs et al. 2001). In a study evaluating CDC's *Tips From Former Smokers (Tips) Campaign* among adults, Xu and colleagues (2015a) estimated an incremental cost-effectiveness ratio of \$450 per life-year saved and \$307 per QALY gained in the short run from the funding agency's perspective compared with not having the campaign.

Cost-Effectiveness of Tobacco Price Increases Through Taxation

Contreary and colleagues (2015) conducted a systematic review of the cost-effectiveness of a tobacco price increase through taxation and found only one study that evaluated the cost-effectiveness per QALY gained. The study found that the cost-effectiveness ratio for a 10% increase in per unit price of tobacco through a 15% increase in excise tax was \$3,839 (2017 dollars) per QALY gained over 100 years from the healthcare perspective (van Baal et al. 2007).

Synthesis of the Evidence

The evidence on cost-effectiveness of smoking cessation and the resulting reduction in healthcare expenditures as a result of cessation strongly indicate that smoking cessation interventions should be implemented throughout the healthcare system and supported more broadly by population-level tobacco control measures (e.g., quitlines). The selection of the intervention depends on the feasibility of the intervention and on the context of an organization and its ability to fund the intervention.

Current estimates of the cost-effectiveness of smoking cessation are limited by the variation in methodologies, including heterogeneity in comparators and perspectives. Despite specific recommendations made two decades ago to enhance the comparability of economic evaluations (Gold et al. 1996), compliance with the full set of recommendations on a standard approach to conducting cost-effective analysis remains incomplete (Ronckers et al. 2005; Ruger and Lazar 2012; Ekpu and

Table 5.9 Summary of economic evaluations of nonclinical interventions for smoking cessation

Study	Design/population	Effects	Costs	Outcomes/findings
Tengs et al. (2001)	<ul style="list-style-type: none"> • Tobacco Policy Model (a dynamic simulation model) • Intervention/comparison: <ul style="list-style-type: none"> – School-based antitobacco education to seventh- and eighth-grade students, with 5–56% smoking reductions that dissipate in 1–4 years – Status quo • Students 8 years of age and older • Perspective: Societal • 25–50 years 	<ul style="list-style-type: none"> • QALYs 	<ul style="list-style-type: none"> • Costs of school-based antitobacco education program and annual medical costs • Base year: 1999 • Source: Salaries of educators for public middle school teachers, average class size, and census data 	<ul style="list-style-type: none"> • Cost-effectiveness ratios per QALY gained over the 50 years ranged from \$4,900 (\$9,294 in 2017 \$), when considering a 56% reduction in smoking that dissipates in 4 years, to \$340,000 (\$644,890 in 2017 \$), when considering a 5% reduction in smoking that dissipates in 1 year • For most plausible scenario of 30% reduction in smoking that dissipates in 4 years, the cost-effectiveness ratio per QALY gained over the 50 years was \$20,000 (\$37,935 in 2017 \$)
Ong and Glantz (2005)	<ul style="list-style-type: none"> • Monte Carlo simulation model • Cost-effectiveness and cost-utility analyses • 18 years of age and older • Interventions/comparison: <ul style="list-style-type: none"> – A free NRT program and statewide smokefree workplace campaign – Common clinical standard • Perspective: Not stated • 1 year 	<ul style="list-style-type: none"> • Quit rates • QALYs 	<ul style="list-style-type: none"> • Free NRT program: Average wholesale price for NRT, cost of quit attempt, cost of therapy, and cost of total medication; did not include cost of administration • Source: Wholesale prices for the most inexpensive NRTs • Smokefree workplace policy: Costs for enactment and reinforcement • Source: Occupational Employment Statistics Survey and published studies • Base year: 2001 	<ul style="list-style-type: none"> • Free NRT program: Generated 18,500 quitters, and the cost-effectiveness ratios were \$7,020 (\$12,223 in 2017 \$) per quitter and \$4,440 (\$7,736 in 2017 \$) per QALY gained • Smokefree workplace policy: Generated 10,400 quitters, and the cost-effectiveness ratios were \$799 (\$1,392 in 2017 \$) per quitter and \$506 (\$882 in 2017 \$) per QALY gained

Table 5.9 Continued

Study	Design/population	Effects	Costs	Outcomes/findings
Villanti et al. (2012)	<ul style="list-style-type: none"> • Cost-utility analysis • 18- to 49-year-olds in eight designated markets • Interventions/comparison: <ul style="list-style-type: none"> – National EX campaign to promote smoking cessation – Status quo • Perspective: Societal • 6 months 	<ul style="list-style-type: none"> • QALYs 	<ul style="list-style-type: none"> • EX campaign costs (media, public relations, salaries, and recruitment) and other societal costs (consumer time and treatment costs) • Base year: 2009 • Source: Consumer time lost during exposure to intervention and costs of treatment 	<ul style="list-style-type: none"> • The EX campaign achieved 52,979 additional quit attempts and 4,238 additional quits, and saved 4,450 QALYs • Incremental cost-utility ratios per QALY gained ranged from \$37,355 (\$47,271 in 2017 \$) to \$81,301 (\$102,883 in 2017 \$)
Xu et al. (2015a)	<ul style="list-style-type: none"> • Monte Carlo simulation model • Cost-effectiveness and cost-utility analyses • Quitters, 18 years of age and older • Interventions/comparisons: <ul style="list-style-type: none"> – Tips Campaign – Without Tips Campaign • Perspective: CDC (funding agency) • 6 months 	<ul style="list-style-type: none"> • Quit rates, premature death, life-years, and QALYs 	<ul style="list-style-type: none"> • Cost of Tips Campaign (development, media placement, and evaluation) • Base year: 2012 • Source: CDC Office on Smoking and Health's budget for Tips Campaign 	<ul style="list-style-type: none"> • Prevented 17,109 premature deaths, and saved approximately 179,099 QALYs • Cost-effectiveness ratio was \$480 (\$550 in 2017 \$) per quitter, \$2,819 (\$3,229 in 2017 \$) per premature death averted; \$393 (\$450 in 2017 \$) per life-year saved, and \$268 (\$307 in 2007 \$) per QALY gained

Notes: **NRT** = nicotine replacement therapy; **QALYs** = quality-adjusted life-years; **Tips** = *Tips From Former Smokers Campaign*. Estimates converted to 2017 dollars from the base case year (or publication year if no base case year) using the Medical Care part of the Consumer Price Index (all urban consumers).

Brown 2015). The new recommendations from the second Panel on Cost-Effectiveness in Health and Medicine, which were published after the publication of many of the studies reviewed in this chapter, emphasize the need for compliance with the recommendations for consistency and comparability of studies (Sanders et al. 2016). Additionally, current trends in cigarette smoking and other forms of tobacco product use affect estimates of economic expenditures from smoking and smoking cessation.

Nonetheless, the scientific evidence clearly documents that smoking cessation interventions reduce smoking-attributable expenditures. Evidence on the cost-effectiveness of smoking cessation interventions is consistent across numerous studies—even when considering different methodologies and outcomes.

The evidence from studies of economic burden has shown that cigarette smoking generates substantial

smoking-attributable healthcare expenditures and lost productivity, a conclusion reached in previous reports of the Surgeon General (USDHHS 2014). These expenditures affect the smoker specifically and society generally. Using the values per QALY discussed previously (USDHHS 2016), the evidence from economic evaluations that focus on the cost-effectiveness of smoking cessation interventions demonstrates that such interventions are cost-effective from various perspectives and that the cost-effectiveness ratio from the societal perspective will always be higher than from other perspectives. Taken together, the scientific evidence on the health and cost benefits of smoking cessation interventions indicates that these interventions should be implemented as widely as possible throughout the healthcare system and supported more broadly by population-level tobacco control measures.

Summary of the Evidence

This chapter examines morbidity, mortality, and economic costs in relation to smoking cessation. For general measures of health outcomes, particularly general QoL, there is evidence of higher levels of improvement in QoL among former smokers than among those who continue to smoke. Morbidity is higher in former smokers than in never smokers, but in some subgroups, morbidity among former smokers can approach that of never smokers, such as among those with lower levels of addiction at the time of cessation.

A causal link between smoking cessation and a decrease in general morbidity is supported by the biologic plausibility of the relationship. Many well-supported mechanisms link smoking cessation to improvements in more specific measures of health, such as disease-specific outcomes, thus underscoring the certainty that those who quit smoking will have lower rates of morbidity.

The health benefits of smoking cessation on all-cause mortality have been covered extensively in previous Surgeon General's reports. The evidence that has accumulated since the 1990 Surgeon General's report affirms that smoking cessation at any age reduces the risk of premature death from a smoking-caused illness.

Cigarette smoking generates substantial smoking-attributable healthcare expenditures and lost productivity. These expenditures affect the smoker specifically and society generally. The evidence from economic evaluations that focus on the cost-effectiveness of smoking cessation interventions demonstrates that such interventions are cost-effective from various perspectives. Taken together, the scientific evidence on the health and cost benefits of smoking cessation interventions indicates that these interventions should be implemented as widely as possible throughout the healthcare system and supported more broadly by population-level tobacco control measures.

Conclusions

1. The evidence is sufficient to infer that smoking cessation improves well-being, including higher quality of life and improved health status.
2. The evidence is sufficient to infer that smoking cessation reduces mortality and increases the lifespan.
3. The evidence is sufficient to infer that smoking exacts a high cost for smokers, healthcare systems, and society.
4. The evidence is sufficient to infer that smoking cessation interventions are cost-effective.

References¹

- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;85(5):365–76.
- Akers L, Severson HH, Andrews JA, Lichtenstein E. Cost-effectiveness of self-help smokeless tobacco cessation programs. *Nicotine and Tobacco Research* 2007;9(9):907–14.
- An LC, Schillo BA, Kavanaugh AM, Lachter RB, Luxenberg MG, Wendling AH, Joseph AM. Increased reach and effectiveness of a statewide tobacco quitline after the addition of access to free nicotine replacement therapy. *Tobacco Control* 2006;15(4):286–93.
- Annemans L, Nackaerts K, Bartsch P, Prignot J, Marbaix S. Cost effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation: a BENESCO Markov cost-effectiveness analysis. *Clinical Drug Investigation* 2009;29(10):655–65.
- Antoñanzas F, Portillo F. [Economic evaluation of pharmacotherapies for smoking cessation]. *Gaceta Sanitaria* 2003;17(5):393–403.
- Baim DS, Cutlip DE, Midei M, Linnemeier TJ, Schreiber T, Cox D, Kereiakes D, Popma JJ, Robertson L, Prince R, et al. Final results of a randomized trial comparing the MULTI-LINK stent with the Palmaz-Schatz stent for narrowings in native coronary arteries. *American Journal of Cardiology* 2001;87(2):157–62.
- Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, et al. Final results of the Balloon vs. Optimal Atherectomy Trial (BOAT). *Circulation* 1998;97(4):322–31.
- Balduyck B, Sardari Nia P, Cogen A, Dockx Y, Lauwers P, Hendriks J, Van Schil P. The effect of smoking cessation on quality of life after lung cancer surgery. *European Journal of Cardio-Thoracic Surgery* 2011;40(6):1432–7; discussion 7–8.
- Barnett PG, Wong W, Hall S. The cost-effectiveness of a smoking cessation program for out-patients in treatment for depression. *Addiction* 2008;103(5):834–40.
- Bellido-Casado J, Martin-Escudero J, Duenas-Laita A, Mena-Martin FJ, Arzua-Mouronte D, Simal-Blanco F. The SF-36 Questionnaire as a measurement of health-related quality of life: assessing short- and medium-term effects of exposure to tobacco versus the known long-term effects. *European Journal of Internal Medicine* 2004;15(8):511–7.
- Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *European Journal of Cancer* 1994;30A(5):635–42.
- Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, Kaasa S. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. *Acta Oncologica* 1994;33(8):879–85.
- Bolin K, Lindgren B, Willers S. The cost utility of bupropion in smoking cessation health programs: simulation model results for Sweden. *Chest* 2006;129(3):651–60.
- Bolin K, Mork AC, Wilson K. Smoking-cessation therapy using varenicline: the cost-utility of an additional 12-week course of varenicline for the maintenance of smoking abstinence. *Journal of Evaluation in Clinical Practice* 2009a;15(3):478–85.
- Bolin K, Wilson K, Benhaddi H, de Nigris E, Marbaix S, Mork AC, Aubin HJ. Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation—results from four European countries. *European Journal of Public Health* 2009b;19(6):650–4.
- Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin Å, Perruchoud AP, Säwe U. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ* 2000;321(7257):329–33.
- Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin Å, Perruchoud AP, Säwe U. Influence of long-term smoking reduction on health risk markers and quality of life. *Nicotine and Tobacco Research* 2002;4(4):433–9.
- Boyd KA, Briggs AH. Cost-effectiveness of pharmacy and group behavioural support smoking cessation services in Glasgow. *Addiction* 2009;104(2):317–25.
- Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. *Morbidity and Mortality Weekly Report* 2008;57(45):1226–8.
- Centers for Disease Control and Prevention. Cigarette smoking—United States, 1965–2008. *Morbidity*

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- and *Mortality Weekly Report Supplements* 2011;60(01):109–13.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/comprehensive.pdf>; accessed: July 26, 2017.
- Chaloupka FJ, Warner KE. The Economics of Smoking. In: Culyer AJ, Newhouse JP, editors. *Handbook of Health Economics*, 1B. Amsterdam: Elsevier North Holland, 2000.
- Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. *Journal of the American College of Cardiology* 2008;52(25):2119–26.
- Contreary KA, Chattopadhyay SK, Hopkins DP, Chaloupka FJ, Forster JL, Grimshaw V, Holmes CB, Goetzel RZ, Fielding JE. Economic impact of tobacco price increases through taxation: a Community Guide systematic review. *American Journal of Preventive Medicine* 2015;49(5):800–8.
- Cornuz J, Gilbert A, Pinget C, McDonald P, Slama K, Salto E, Paccaud F. Cost-effectiveness of pharmacotherapies for nicotine dependence in primary care settings: a multinational comparison. *Tobacco Control* 2006;15(3):152–9.
- Crealey GE, McElnay JC, Maguire TA, O'Neill C. Costs and effects associated with a community pharmacy-based smoking-cessation programme. *Pharmacoeconomics* 1998;14(3):323–33.
- Croghan IT, Schroeder DR, Hays JT, Eberman KM, Patten CA, Berg EJ, Hurt RD. Nicotine dependence treatment: perceived health status improvement with 1-year continuous smoking abstinence. *European Journal of Public Health* 2005;15(3):251–5.
- Cromwell J, Bartosch WJ, Fiore MC, Hasselblad V, Baker T. Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *JAMA: the Journal of the American Medical Association* 1997;278(21):1759–66.
- Cummings SR, Rubin SM, Oster G. The cost-effectiveness of counseling smokers to quit. *JAMA: the Journal of the American Medical Association* 1989;261(1):75–9.
- Dino G, Horn K, Abdulkadri A, Kalsekar I, Branstetter S. Cost-effectiveness analysis of the Not On Tobacco program for adolescent smoking cessation. *Prevention Science* 2008;9(1):38–46.
- Ekpu VU, Brown AK. The economic impact of smoking and of reducing smoking prevalence: review of evidence. *Tobacco Use Insights* 2015;8:1–35.
- Erickson SR, Thomas LA, Blitz SG, Pontius LR. Smoking cessation: a pilot study of the effects on health-related quality of life and perceived work performance one week into the attempt. *Annals of Pharmacotherapy* 2004;38(11):1805–10.
- Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Mölken MP. Cost-effectiveness of face-to-face smoking cessation interventions: a dynamic modeling study. *Value in Health* 2005;8(3):178–90.
- Fellows JL, Bush T, McAfee T, Dickerson J. Cost effectiveness of the Oregon quitline “free patch initiative”. *Tobacco Control* 2007;16(Suppl 1):i47–i52.
- Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians’ smoking cessation counseling. *JAMA: the Journal of the American Medical Association* 1996;275(16):1247–51.
- Frisch MB, Cornell J, Villanueva M, Retzlaff PJ. Clinical validation of the Quality of Life Inventory: a measure of life satisfaction for use in treatment planning and outcome assessment. *Psychological Assessment* 1992;4:92–101.
- Gilbert AR, Pinget C, Bovet P, Cornuz J, Shamlaye C, Paccaud F. The cost effectiveness of pharmacological smoking cessation therapies in developing countries: a case study in the Seychelles. *Tobacco Control* 2004;13(2):190–5.
- Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996.
- Goldenberg M, Danovitch I, IsHak WW. Quality of life and smoking. *American Journal on Addictions* 2014;23(6):540–62.
- Gruber J. Smoking’s internalities. *Regulation* 2002–2003;Winter:52–7.
- Gruber J, Koszegi B. Is addiction “rational”? Theory and evidence. *Quarterly Journal of Economics* 2001;116:1261–1303.
- Gutiérrez-Bedmar M, Seguí-Gómez M, Gómez-Gracia E, Bes-Rastrollo M, Martínez-González MA. Smoking status, changes in smoking status and health-related quality of life: findings from the SUN (“Seguimiento Universidad de Navarra”) cohort. *International Journal of Environmental Research and Public Health* 2009;6(1):310–20.
- Haddix AC, Teutsch SM, Corso PS, editors. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation*. 2nd ed. New York (NY): Oxford University Press, 2003.
- Haile MJ, Wiggers JH, Spigelman AD, Knight J, Considine RJ, Moore K. Novel strategy to stop cigarette smoking by surgical patients: pilot study in a preadmission clinic. *ANZ Journal of Surgery* 2002;72(9):618–22.

- Halpern MT, Dirani R, Schmier JK. The cost effectiveness of varenicline for smoking cessation. *Managed Care Interface* 2007;20(10):18–25.
- Hays JT, Croghan IT, Baker CL, Cappelleri JC, Bushmakin AG. Changes in health-related quality of life with smoking cessation treatment. *European Journal of Public Health* 2012;22(2):224–9.
- Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Annals of Medicine* 2001;33(5):350–7.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction* 1991;86(9):1119–27.
- Heikkinen H, Jallinoja P, Saarni SI, Patja K. The impact of smoking on health-related and overall quality of life: a general population survey in Finland. *Nicotine and Tobacco Research* 2008;10(7):1199–207.
- Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tobacco Control* 2007;16(Suppl 1):i53–i59.
- Hoogendoorn M, Welsing P, Rutten-van Mülken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. *Current Medical Research and Opinion* 2008;24(1):51–61.
- Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model: application to a population of U.S. adult smokers. *Pharmacoeconomics* 2008;26(6):497–511.
- Igarashi A, Takuma H, Fukuda T, Tsutani K. Cost-utility analysis of varenicline, an oral smoking-cessation drug, in Japan. *Pharmacoeconomics* 2009;27(3):247–61.
- Jackson KC 2nd, Nahoopii R, Said Q, Dirani R, Brixner D. An employer-based cost-benefit analysis of a novel pharmacotherapy agent for smoking cessation. *Journal of Occupational and Environmental Medicine* 2007;49(4):453–60.
- Jensen K, Jensen AB, Grau C. Smoking has a negative impact upon health related quality of life after treatment for head and neck cancer. *Oral Oncology* 2007;43(2):187–92.
- Jette AM, Davies AR, Cleary PD, Calkins DR, Rubenstein LV, Fink A, Kosecoff J, Young RT, Brook RH, Delbanco TL. The Functional Status Questionnaire: reliability and validity when used in primary care. *Journal of General Internal Medicine* 1986;1(3):143–9.
- Jha P, Chaloupka FJ, Moore J, Gajalakshmi V, Gupta PC, Peck R, Asma S, Zatonski W. Chapter 46: tobacco addiction. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al., editors. *Disease Control Priorities in Developing Countries*. 2nd ed. Washington (DC): The International Bank for Reconstruction and Development/The World Bank Group, 2006.
- Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *New England Journal of Medicine* 2013;368(4):341–50.
- Knight C, Howard P, Baker CL, Marton JP. The cost-effectiveness of an extended course (12+12 weeks) of varenicline compared with other available smoking cessation strategies in the United States: an extension and update to the BENESCO model. *Value in Health* 2010;13(2):209–14.
- Max W, Sung HY, Shi Y, Stark B. The cost of smoking in California. *Nicotine and Tobacco Research* 2016;18(5):1222–9.
- McClave AK, Dube SR, Strine TW, Mokdad AH. Associations between health-related quality of life and smoking status among a large sample of U.S. adults. *Preventive Medicine* 2009;48(2):173–9.
- Meenan RT, Stevens VJ, Hornbrook MC, La Chance PA, Glasgow RE, Hollis JF, Lichtenstein E, Vogt TM. Cost-effectiveness of a hospital-based smoking cessation intervention. *Medical Care* 1998;36(5):670–8.
- Mitra M, Chung MC, Wilber N, Klein Walker D. Smoking status and quality of life: a longitudinal study among adults with disabilities. *American Journal of Preventive Medicine* 2004;27(3):258–60.
- Mody RR, Smith MJ. Smoking status and health-related quality of life: as findings from the 2001 Behavioral Risk Factor Surveillance System data. *American Journal of Health Promotion* 2006;20(4):251–8.
- Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *Journal of Vascular Surgery* 2001;33(4):679–87.
- Moriarty DG, Zack MM, Kobau R. The Centers for Disease Control and Prevention's Healthy Days Measures—population tracking of perceived physical and mental health over time. *Health and Quality of Life Outcomes* 2003;1:37.
- Mulder I, Tjhuis M, Smit HA, Kromhout D. Smoking cessation and quality of life: the effect of amount of smoking and time since quitting. *Preventive Medicine* 2001;33(6):653–60.
- National Cancer Institute, World Health Organization. *The Economics of Tobacco and Tobacco Control*. National Cancer Institute Tobacco Control Monograph 21. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer

- Institute; and World Health Organization, 2016. NIH Publication No. 16-CA-8029A.
- Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *New England Journal of Medicine* 2014;371(9):796–7.
- Office of Disease Prevention and Health Promotion. Health-related quality of life and well-being, April 13, 2018; <<https://www.healthypeople.gov/2020/about/foundation-health-measures/Health-Related-Quality-of-Life-and-Well-Being>>; accessed: April 16, 2018.
- Olufade AO, Shaw JW, Foster SA, Leischow SJ, Hays RD, Coons SJ. Development of the Smoking Cessation Quality of Life questionnaire. *Clinical Therapeutics* 1999;21(12):2113–30.
- Ong MK, Glantz SA. Free nicotine replacement therapy programs vs implementing smoke-free workplaces: a cost-effectiveness comparison. *American Journal of Public Health* 2005;95(6):969–75.
- Oster G, Huse DM, Delea TE, Colditz GA. Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. *JAMA: the Journal of the American Medical Association* 1986;256(10):1315–8.
- Papadopoulos G, Vardavas CI, Limperi M, Linardis A, Georgoudis G, Behrakis P. Smoking cessation can improve quality of life among COPD patients: validation of the clinical COPD questionnaire into Greek. *BMC Pulmonary Medicine* 2011;11:13.
- Piper ME, Kenford S, Fiore MC, Baker TB. Smoking cessation and quality of life: changes in life satisfaction over 3 years following a quit attempt. *Annals of Behavioral Medicine* 2012;43(2):262–70.
- Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* 2013;381(9861):133–41.
- Ronckers ET, Groot W, Ament AJ. Systematic review of economic evaluations of smoking cessation: standardizing the cost-effectiveness. *Medical Decision Making* 2005;25(4):437–48.
- Ruger JP, Lazar CM. Economic evaluation of pharmacological and behavioral therapies for smoking cessation: a critical and systematic review of empirical research. *Annual Review of Public Health* 2012;33:279–305.
- Ruger JP, Weinstein MC, Hammond SK, Kearney MH, Emmons KM. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: a randomized controlled trial. *Value in Health* 2008;11(2):191–8.
- Rungruanghiranya S, Ekpanyaskul C, Hattapornsawan Y, Tundulawessa Y. Effect of nicotine polyestex gum on smoking cessation and quality of life. *Journal of the Medical Association of Thailand* 2008;91(11):1656–62.
- Russell LB. The science of making better decisions about health. In: *Population Health: Behavioral and Social Science Insights*. Rockville (MD): Agency for Healthcare Research and Quality, 2015; <<http://www.ahrq.gov/professionals/education/curriculum-tools/population-health/russell.html>>; accessed: March 15, 2019.
- Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *JAMA: the Journal of the American Medical Association* 1996;276(14):1172–7.
- Salize HJ, Merkel S, Reinhard I, Twardella D, Mann K, Brenner H. Cost-effective primary care-based strategies to improve smoking cessation: more value for money. *Archives of Internal Medicine* 2009;169(3):230–5.
- Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA: the Journal of the American Medical Association* 2016;316(10):1093–103.
- Schumacher M, Rücker G, Schwarzer G. Meta-analysis and the Surgeon General's report on smoking and health. *New England Journal of Medicine* 2014;370(2):186–8.
- Shultz JM, Novotny TE, Rice DP. Quantifying the disease impact of cigarette smoking with SAMMEC II software. *Public Health Reports* 1991;106(3):326–33.
- Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA: the Journal of the American Medical Association* 1996;276(16):1339–41.
- Sintonen H. *The 15D-measure of health-related quality of life. II. Feasibility, reliability and validity of its valuation system*. Working Paper 42. Melbourne (Australia): National Centre for Health Program Evaluation, 1995.
- Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of Life Research* 2004;13(2):299–310.
- Sloan FA, Ostermann J, Picone G, Conover C, Taylor DH Jr. *The Price of Smoking*. Cambridge (MA): The MIT Press, 2004.
- Solberg LI, Maciosek MV, Edwards NM, Khanchandani HS, Goodman MJ. Repeated tobacco-use screening and intervention in clinical practice: health impact and cost effectiveness. *American Journal of Preventive Medicine* 2006;31(1):62–71.
- Song F, Raftery J, Aveyard P, Hyde C, Barton P, Woolacott N. Cost-effectiveness of pharmacological interventions for smoking cessation: a literature review and a decision

- analytic analysis. *Medical Decision Making* 2002;22(5 Suppl):S26–S37.
- Stapleton JA, Lowin A, Russell MA. Prescription of transdermal nicotine patches for smoking cessation in general practice: evaluation of cost-effectiveness. *Lancet* 1999;354(9174):210–5.
- Stewart AL, King AC, Killen JD, Ritter PL. Does smoking cessation improve health-related quality-of-life? *Annals of Behavioral Medicine* 1995;17(4):331–8.
- Stofmeel MA, Post MW, Kelder JC, Grobbee DE, van Hemel NM. Psychometric properties of Aquarel, a disease-specific quality of life questionnaire for pacemaker patients. *Journal of Clinical Epidemiology* 2001;54(2):157–65.
- Taira DA, Seto TB, Ho KK, Krumholz HM, Cutlip DE, Berezin R, Kuntz RE, Cohen DJ. Impact of smoking on health-related quality of life after percutaneous coronary revascularization. *Circulation* 2000;102(12):1369–74.
- Tengs TO, Osgood ND, Chen LL. The cost-effectiveness of intensive national school-based anti-tobacco education: results from the tobacco policy model. *Preventive Medicine* 2001;33(6):558–70.
- Thavorn K, Chaiyakunapruk N. A cost-effectiveness analysis of a community pharmacist-based smoking cessation programme in Thailand. *Tobacco Control* 2008;17(3):177–82.
- The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199–208.
- Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. 50-year trends in smoking-related mortality in the United States. *New England Journal of Medicine* 2013;368(4):351–64.
- Tian J, Venn AJ, Blizzard L, Patton GC, Dwyer T, Gall SL. Smoking status and health-related quality of life: a longitudinal study in young adults. *Quality of Life Research* 2016;25(3):669–85.
- Tillmann M, Silcock J. A comparison of smokers' and ex-smokers' health-related quality of life. *Journal of Public Health Medicine* 1997;19(3):268–73.
- Tran MT, Holdford DA, Kennedy DT, Small RE. Modeling the cost-effectiveness of a smoking-cessation program in a community pharmacy practice. *Pharmacotherapy* 2002;22(12):1623–31.
- U.S. Bureau of Labor Statistics. Consumer Price Index, 2017; <<https://www.bls.gov/cpi/tables/home.htm>>; accessed: July 16, 2019.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.
- U.S. Department of Health, Education, and Welfare. *The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, 1969. DHEW Publication No. 1696-2.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General*. Washington: U.S. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979. DHEW Publication No. (PHS) 79-50066.
- U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS Publication No. (CDC) 89-8411.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
- U.S. Department of Health and Human Services. *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services*. Washington (DC): Office of the Assistant Secretary for Health, 2010.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Department of Health and Human Services. *Guidelines for Regulatory Impact Analysis*, 2016; <https://aspe.hhs.gov/system/files/pdf/242926/HHS_RIAGuidance.pdf>; accessed: December 10, 2019.
- van Baal PH, Brouwer WB, Hoogenveen RT, Feenstra TL. Increasing tobacco taxes: a cheap tool to increase public health. *Health Policy* 2007;82(2):142–52.

- van der Molen T, Willemsse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes* 2003;1:13.
- Velicer WF, Prochaska JO, Rossi JS, Snow MG. Assessing outcome in smoking cessation studies. *Psychological Bulletin* 1992;111(1):23–41.
- Villanti AC, Curry LE, Richardson A, Vallone DM, Holtgrave DR. Analysis of media campaign promoting smoking cessation suggests it was cost-effective in prompting quit attempts. *Health Affairs* 2012;31(12):2708–16.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;30(6):473–83.
- Wasley MA, McNagny SE, Phillips VL, Ahluwalia JS. The cost-effectiveness of the nicotine transdermal patch for smoking cessation. *Preventive Medicine* 1997;26(2):264–70.
- Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA: the Journal of the American Medical Association* 1996;276(15):1253–8.
- West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, Stapleton J, McRobbie H, Pokhrel S, Lester-George A, et al. Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. *Addiction* 2015;110(9):1388–403.
- Wiggers LC, Oort FJ, Peters RJ, Legemate DA, de Haes HC, Smets EM. Smoking cessation may not improve quality of life in atherosclerotic patients. *Nicotine and Tobacco Research* 2006;8(4):581–9.
- Wilber N, Mitra M, Walker DK, Allen D, Meyers AR, Tupper P. Disability as a public health issue: findings and reflections from the Massachusetts Survey of Secondary Conditions. *Milbank Quarterly* 2002;80(2):393–421.
- Xu X, Alexander RL Jr, Simpson SA, Goates S, Nonnemaker JM, Davis KC, McAfee T. A cost-effectiveness analysis of the first federally funded antismoking campaign. *American Journal of Preventive Medicine* 2015a;48(3):318–25.
- Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *American Journal of Preventive Medicine* 2015b;48(3):326–33.
- Zillich AJ, Ryan M, Adams A, Yeager B, Farris K. Effectiveness of a pharmacist-based smoking-cessation program and its impact on quality of life. *Pharmacotherapy* 2002;22(6):759–65.

Chapter 6

Interventions for Smoking Cessation and Treatments for Nicotine Dependence

Introduction 495

Literature Review Methods 496

Behavioral and Psychological Treatments 496

Treatment Strategies 497

Behavioral Therapy 497

Cognitive Therapy 497

Motivational Interviewing 498

Acceptance and Commitment Therapy 499

Contingency Management and Monetary Incentives 499

Relapse Prevention and Recovery 500

Intervention Delivery Modalities 501

Self-Help Materials 501

Face-to-Face Counseling 501

Technology-Mediated Delivery Approaches 504

Pharmacologic Treatments 509

Nicotine Replacement Therapy 515

Bupropion 516

Varenicline 516

Additional Approaches to Medication Therapy 517

Combination Pharmacotherapy 517

Pre-Loading Medication 518

Gradual Reduction 518

Extended Treatment 519

Precision Medicine 519

Real-World Effectiveness of Cessation Medications 520

Combination Treatment—Behavioral Therapy and Pharmacotherapy 522

Modified and Alternative Tobacco Products 522

Very-Low-Nicotine-Content Cigarettes 522

E-Cigarettes 524

Teachable Moments 532

Hospitalization 532

Surgery 534

Lung Cancer Screening 535

Readiness to Quit and Approaches for Quitting Ambivalence 536

Considerations for Subpopulations 537

Pregnant Women 537

Lesbian, Gay, Bisexual, and Transgender Populations 538

Populations with Mental Health Conditions and Co-Occurring Substance Use Disorders	539
Adolescents	540
Dual Tobacco Product Users	541
Light and Nondaily Tobacco Users	543
Emerging Intervention Approaches	544
Emerging Behavioral Treatments	544
Expanding Behavioral Treatment Targets	544
Use of Emerging Technology	544
Emerging Pharmacologic Approaches	545
Summary of the Evidence	546
Conclusions	547
References	549

Introduction

There are now more former cigarette smokers than current smokers in the United States (U.S. Department of Health and Human Services [USDHHS] 2014). For more than a decade, national surveillance data on smoking cessation have revealed a similar pattern, with modest improvement—two-thirds of adult cigarette smokers indicate a desire to quit, and just over half try to quit each year; however, less than 10% of smokers who try to quit succeed in quitting for 6 months or longer (Babb et al. 2017). A large body of evidence highlights the efficacy of multiple treatments that can double or triple the rate of success in quitting smoking (Fiore et al. 2008; Prochaska and Benowitz 2016). This chapter reviews both evidence-based and emerging potential treatments for smoking cessation.

Current evidence-based treatment approaches to smoking cessation include several behavioral treatments—such as individual, group, and telephone counseling—and seven pharmacotherapies approved by the U.S. Food and Drug Administration (FDA). These treatments have been shown to be effective when delivered across a wide variety of settings, via several platforms, and to a diversity of populations—including groups that have been disproportionately impacted by tobacco use, such as low-income populations, and populations with other comorbid medical conditions, including behavioral health conditions (U.S. Preventive Services Task Force [USPSTF] 2015). Evidence indicates that the combined use of both behavioral interventions and pharmacotherapies produces the largest cessation effects (Fiore et al. 2008; Stead and Lancaster 2012a; Stead et al. 2015), but the evidence also indicates that several of these treatments are effective when used alone (Fiore et al. 2008; Cahill et al. 2013; USPSTF 2015; Lancaster and Stead 2017).

The cost-effectiveness of smoking cessation has been documented extensively (Jha et al. 2015) (see Chapter 5. The Benefits of Smoking Cessation on Overall Morbidity and Economic Costs). For example, Maciosek and colleagues (2017a,b) assessed the potential impact of 28 evidence-based clinical preventive services in terms of their cost-effectiveness and clinically preventable burden (measured by quality-adjusted life-years [QALYs] saved). The assessment, which included clinical preventive services for a variety of different risk factors, found that two of the three highest ranking preventive services were related to tobacco, including (a) tobacco use screening and a brief counseling intervention to encourage cessation among adults and (b) counseling to prevent initiation of tobacco use among youth.

Data indicate that despite the availability of evidence-based treatments to achieve smoking cessation, less than one-third of adult cigarette smokers who attempt to quit use any type of cessation counseling and/or FDA-approved cessation medication (Babb et al. 2017). Furthermore, undertreatment is common among smokers who use cessation treatments; rates of relapse are high (above 50%) (García-Rodríguez et al. 2013); and most smokers attempt to quit without using treatment (i.e., they try to quit unassisted or “cold turkey”), with success rates of approximately 7–8% (Fiore and Jaen 2008; Prochaska and Benowitz 2016; Babb et al. 2017; Caraballo et al. 2017). Unaided quitting likely remains common for a number of reasons, including the frequent lack of health insurance among tobacco users (nearly 30% of adult cigarette smokers are uninsured [Jamal et al. 2018]); inadequate public and private insurance coverage of cessation treatments (DiGiulio et al. 2018); inadequate and cumbersome reimbursement for cessation treatments offered by clinicians and hospitals (Fiore et al. 2008); inadequate promotion of cessation treatments to smokers and healthcare providers, which can contribute to low use of these treatments (Fiore et al. 2008); the widespread perception that quitting cold turkey is at least as effective as quitting with the help of counseling and/or medication (Fiore et al. 2008); underfunding of state tobacco quitlines and other cessation services (USDHHS 2014; Campaign for Tobacco-Free Kids 2018); and inadequate integration of tobacco use screening and cessation interventions into routine clinical care (Babb et al. 2017). In addition, because of a lack of specialized training about nicotine dependence and treatment, many clinicians report being hesitant to engage patients in conversations about cessation because they feel they lack the requisite knowledge to do so effectively (Zapka et al. 1999; Simoyan et al. 2002; Blumenthal 2007).

In the past, the tobacco industry has spread the misconceptions that smoking is a personal choice or simply a bad habit, that quitting is a matter of willpower, and that addiction to nicotine is akin to being addicted to caffeine (Henningfield et al. 2006). These messages have contributed to most smokers trying to quit through sheer determination instead of combining a strong motivation to quit with the use of evidence-based cessation treatments. The reality is that nicotine is addictive, and smoking is not merely a habit (USDHHS 1988). Although habitual components of smoking reinforce use, nicotine is a highly addictive drug, like heroin and cocaine (USDHHS 1988, 2014), and nicotine addiction is a chronic, relapsing

condition. Although a majority of smokers in the United States who quit successfully do so without assistance, smokers who use medication and/or behavioral support as part of a quit attempt substantially increase their chances of quitting (Fiore et al. 2008). The conceptualization of nicotine dependence as a chronic, relapsing condition is

not new (Fiore et al. 2008), but it has led to reframing the delivery of smoking cessation treatment as “chronic disease management,” which in turn has given rise to more systematic approaches to delivering nicotine dependence treatment in healthcare settings (Steinberg et al. 2008; Foulds et al. 2010).

Literature Review Methods

This chapter reviews the evidence base for current and potential emerging treatments for smoking cessation, adding to research from the U.S. Public Health Service’s Clinical Practice Guideline on *Treating Tobacco Use and Dependence: 2008 Update* (hereafter referred to as the *Clinical Practice Guideline*) (Fiore et al. 2008). It also explores approaches to increase the impact of smoking cessation treatments through improved efficacy and increased reach. The impact of a smoking cessation intervention is a function of effectiveness (i.e., success as measured in sustained quit rates of, for example, greater than 6 months) multiplied by reach (i.e., the proportion of the population of smokers engaged in treatment). Importantly, interventions that increase reach (i.e., those that are more broadly available and accessible to people, have greater appeal, and are therefore more widely used) may sacrifice efficacy or intensity, while interventions that are more intensive and more effective may have limited reach (Glasgow et al. 2011; Zhu et al. 2012). Given the reality of funding constraints, most states, healthcare systems, and other stakeholders do not have the option of maximizing both the effectiveness and reach of cessation treatments; in practice, they have to balance these approaches.

For this chapter, 38 Cochrane reviews were examined in early 2017. Additional literature searches of English-language articles in PubMed were used to identify new

literature published since the original Cochrane reviews. Searches were primarily restricted to randomized controlled trials (RCTs) of smoking cessation interventions using the terms *smoking cessation* and *randomized controlled trial*. In areas where RCTs were not available, the chapter discusses the available science and identifies areas that lacked depth of evidence from RCTs. Consistent with previous Surgeon General’s reports on tobacco, the content in this report was revised throughout the review process to include studies and information not available at the time the chapters were initially drafted, most notably for topics in which the available science is rapidly emerging (e.g., electronic cigarettes [e-cigarettes]) (King et al. 2018a).

Data reviewed in this chapter are overwhelmingly drawn from studies of adult cigarette smoking cessation, as opposed to cessation of other forms of tobacco products (e.g., cigars, cigarillos, smokeless tobacco, hookah, and e-cigarettes). The paucity of research on cessation treatments for noncigarette tobacco products does not allow for a separate and comprehensive scientific evaluation of such treatments.

This chapter is divided into seven sections: behavioral and psychological treatments, pharmacologic treatments, teachable moments, considerations for subpopulations, emerging intervention approaches, summary of the evidence, and conclusions.

Behavioral and Psychological Treatments

Notable discoveries in the behavioral and social sciences have broadened and deepened understanding of psychosocial influences on the nature and treatment of nicotine dependence, which has given rise to new approaches to behavioral treatment. It has become clear that, as acute nicotine withdrawal dissipates as the length of the quit attempt increases, several factors—including intermittent negative emotional states, repeated urges to smoke, diminished motivation, and decreased self-efficacy about quitting—can persist throughout the cessation process

and undermine quitting (Liu et al. 2013; Ussher et al. 2013). Furthermore, encountering environments and situations previously associated with smoking, such as going to establishments that serve alcohol or interacting with friends who smoke, has been shown to increase risk of relapse (Conklin et al. 2013). Intensive behavioral cessation treatment models for smokers with mental health conditions and substance use disorders that have been adapted to address these factors have been shown to improve quit rates (Das and Prochaska 2017).

Behavioral and psychological strategies that have been shown to be effective in treating tobacco use and nicotine dependence include behavioral therapy and cognitive behavioral therapy (CBT) (Sykes and Marks 2001; Fiore et al. 2008; Perkins et al. 2008), motivational interviewing (Lindson-Hawley et al. 2015), acceptance and commitment therapy (Bricker et al. 2013), and contingency management or incentive-based interventions (which have been found to be effective while incentives are in place) (Cahill et al. 2015). These strategies can be individual- or group-based and can vary in intensity (from brief to more intensive) and in the mode of delivery (e.g., delivery by a clinician, counselor, telephone, or computer). Most research on behavioral treatments has considered packages of multiple treatment elements instead of comparing one element with another (e.g., studies of treatment optimization), making a review of each treatment approach challenging (Piper et al. 2016). In general, the data show a robust dose-response curve, with more intensive behavioral and psychological treatments (e.g., higher amounts of contact time, more sessions) yielding greater odds of sustained cessation (Fiore et al. 2008; USPSTF 2015).

Treatment Strategies

Behavioral Therapy

A large body of scientific literature supports the use of behavioral therapy to help people quit smoking (Fiore et al. 2008; Stead et al. 2016; Lancaster and Stead 2017). Such approaches can be delivered by various types of healthcare providers or counselors to individual persons or groups. Behavioral therapy, which is commonly used with smokers who are contemplating quitting or preparing to quit, seeks to address the historical learning processes directly relevant to smoking and the current contextual factors that make it difficult to quit (e.g., social, behavioral, and environmental factors) (Webb et al. 2010b).

Available evidence supports the effectiveness of both brief cessation interventions and longer, more intensive interventions. USPSTF (2015) and the *Clinical Practice Guideline* (Fiore et al. 2008) each concluded that both minimal (<20 minutes in a single visit) and intensive (≥20 minutes plus one or more follow-up visits) interventions delivered by clinicians are effective in increasing the proportion of adults who successfully quit smoking and remain abstinent for at least 6 months, which is commonly referred to as recent successful cessation. USPSTF (2015) and the *Clinical Practice Guideline* (Fiore et al. 2008) each also concluded that there is a dose-response relationship between the intensity of counseling and

quitting success—that is, the greater the intensity of counseling, the higher the likelihood an individual will quit. Accordingly, behavioral therapy approaches for smoking cessation are delivered over several weeks and focus on the physiological, psychological, social, and environmental aspects of smoking and nicotine dependence (Fiore et al. 2008; USDHHS 2010, 2014). Group treatment typically occurs weekly for several weeks in a series of 60- to 90-minute sessions (Foulds et al. 2006; Kotsen et al. 2017). For example, Public Health England (2017) recommended weekly visits for 6–12 weeks for individuals (30–45 minutes per visit) and groups (60 minutes per visit).

Behavioral treatment approaches equip smokers with practical strategies to avoid and/or cope with triggers, manage cravings, and reduce withdrawal symptoms (Center for Substance Abuse Treatment 2006). These interventions often cover a wide variety of topics—including advice on quitting smoking; assessment of prior quit attempts and lessons that can be drawn from them; assessment of current motivation to quit; identification of cues and triggers for smoking and ways to avoid or manage them; tips on ways to manage mood; and promotion of adherence to treatment engagement (such as using medications correctly) and continued treatment engagement. Adherence to treatment engagement and continued treatment engagement can be promoted by addressing skill building; self-managing withdrawal symptoms; accepting social support; and managing such associated health issues as stress, moodiness, and other substance use (Fiore et al. 2008).

Cognitive Therapy

Cognitive therapy, which includes CBT, is a psychotherapeutic approach rooted in the idea that behavioral problems can be maintained by cognitive factors, including beliefs that lead to automatic thoughts about particular situations. The model uses specific therapeutic strategies to target maladaptive cognitions and help change problematic behaviors (Ellis 1962; Beck 1970; Butler et al. 2006). Contemporary applications of CBT typically emphasize cognitive factors and emotional, physiological, and behavioral components that can reinforce behavior (Butler et al. 2006; Hofmann et al. 2013). CBT is among the most researched psychotherapeutic approaches (Hofmann et al. 2012), with studies addressing a wide variety of behavioral and cognitive disorders, including smoking cessation.

Treatments based on CBT techniques have been found to be highly effective in smoking cessation (Sykes and Marks 2001; Fiore et al. 2008; Perkins et al. 2008). In a systematic review of cognitive therapies from 21 RCTs

that were conducted with 4,946 participants since 2009, the Norwegian Institute of Public Health concluded that:

- Cognitive therapies have similar effects to usual care or minimal interventions in terms of rates of smoking abstinence (up to 6–12 months; $n = 3$ studies);
- Cognitive therapies combined with nicotine replacement therapy (NRT) result in higher abstinence rates (up to 12 months) compared with other interventions that are combined with NRT ($n = 8$ studies);
- Cognitive therapies result in a higher smoking abstinence rate (up to 12 months) compared with other interventions (e.g., advice to quit, exercise, health education) ($n = 6$ studies); and
- Cognitive therapies plus medications improve smoking abstinence rates (up to 12 months) compared with medication only ($n = 5$ studies) (Denison et al. 2017).

CBT has also been studied in relation to other cessation treatments and was found in a meta-analysis by Garcia-Vera and Sanz (2006) to be superior, both alone and in combination with NRT, compared with NRT alone.

Studies have also shown CBT to be effective for smoking cessation in specific populations. For example, in a sample of African Americans, Webb and colleagues (2010a) found that CBT at least doubled the likelihood of cessation through the 6-month follow-up compared with a control group that received only health education. In a separate study, Webb Hooper and colleagues (2017) found that culturally specific CBT resulted in double the 7-day point-prevalence cessation rate compared with nonculturally specific CBT and was significantly more effective at 3-month follow up. CBT has been shown to increase cessation when combined with NRT or other cessation medication in populations who use tobacco and have comorbid substance use or mental health conditions (Haas et al. 2004; Ziedonis et al. 2008; Magill and Ray 2009). However, studies assessing the use of CBT in smokers with schizophrenia, either with or without other intervention components, have yielded more mixed findings (Gelkopf et al. 2012; Tsoi et al. 2013; R  ther et al. 2014; Brody et al. 2017).

Recent research has focused on improving smoking cessation outcomes from previous CBT trials. For example, in a 2017 two-arm, parallel group RCT of a community-based adult sample ($n = 219$), extended CBT treatment of 48 weeks did not yield better cessation outcomes compared with 26 weeks of treatment (Laude et al. 2017). Research has also focused on adapting CBT interventions

to mobile health (mHealth) and web-based platforms and adding technology-based components to further enhance CBT, including testing the effectiveness of CBT in an app-based format (vs. a non-CBT app) (Tudor-Sfetea et al. 2018) and adding virtual reality to CBT to create an immersive and interactive cue exposure paradigm (e.g., exposure to smoking cues without reinforcement, with the goal of disassociating those cues) to standard treatment (Culbertson et al. 2012).

Motivational Interviewing

Both motivational interviewing and adaptations of this approach make use of a distinct style of counseling that is directive, patient-centered, nonconfrontational, nonjudgmental, and highly collaborative (Miller and Rollnick 2002). Motivational interviewing—which can be delivered by healthcare providers, counselors, or quitline coaches—aims to help people explore and resolve any ambivalence about making a behavior change, such as quitting smoking (Miller and Rollnick 2002; Lindson-Hawley et al. 2015). This technique is typically used with persons who are not yet ready to quit tobacco (Miller and Rollnick 2002; Fiore et al. 2008). Counseling techniques—such as expressing empathy, actively listening, reflecting back on what one heard, and building self-efficacy—are at the core of motivational interviewing (Miller and Rollnick 2002).

Motivational interviewing was initially developed to treat alcohol addiction (Miller 1983) and was subsequently adapted for use in tobacco cessation. Lindson-Hawley and colleagues (2015) reviewed 28 studies that compared motivational interviewing to brief advice or usual care for the treatment of tobacco use. Motivational interviewing was used in one to six sessions lasting from 10 to 60 minutes and was delivered by clinicians in primary care settings, emergency departments, or hospitals; in the community; via telephone quitlines; and in military settings. Motivational interviewing was found to significantly increase successful quitting compared to those not receiving the intervention (relative risk [RR] = 1.26; 95% confidence interval [CI], 1.16–1.36; 28 studies; $N = 16,803$). Short motivational interviewing interventions (<20 minutes per session) had an RR of 1.69 (95% CI, 1.34–2.12; 9 trials; $N = 3,651$). Both single-session (RR = 1.26; 95% CI, 1.15–1.40; 16 trials; $N = 12,103$) and multiple-session (RR = 1.20; 95% CI, 1.02–1.42; 11 trials; $N = 3,928$) treatments increased the likelihood of quitting compared with controls. In summary, motivational interviewing is an evidence-based approach that has been shown, when delivered by clinicians or trained counselors, to be more effective in increasing readiness to quit and in helping people quit smoking than brief advice or usual care (e.g., self-help materials) (Lindson-Hawley et al. 2015).

Acceptance and Commitment Therapy

Acceptance-based therapies (ACTs) draw on cognitive therapies but focus on changing psychological events directly. Specifically, ACTs seek to change the function of those events and the relationship an individual has to them (Hayes 2004; Hayes et al. 2006). ACTs focus on the context and functions of psychological phenomena, emphasizing contextual and experiential change strategies to help individuals become more willing to experience their physical sensations, emotions, and thoughts (Hayes et al. 1999; Hayes et al. 2006). In ACTs, “acceptance” is rooted in accepting intense physical sensations (e.g., nicotine withdrawal or urges to smoke) and the emotions and thoughts that accompany those sensations (e.g., anger or sadness, thoughts about wanting a cigarette, etc.). In contrast, “commitment” focuses on articulating what is particularly important to or valued by an individual and leveraging those values to motivate and guide specific actions, like quitting smoking (Hayes et al. 2001, 2006, 2013; Bricker et al. 2010). Clinical treatment research supports ACTs for general behavior change and condition management, including in populations diagnosed with such disorders as major depression, anxiety disorders, borderline personality disorder, chronic pain, and substance abuse (including tobacco use) (Khoury et al. 2013; Kelly et al. 2015; Linehan et al. 2015; Cristea et al. 2017; Meyers et al. 2017). With regard to smoking cessation, a quasi-experimental study ($n = 81$ adult smokers) by Hernández-López and colleagues (2009) compared ACT with CBT using seven weekly 90-minute sessions in a group format. The 30-day point-prevalence quit rate at 12-month follow-up was 30.2% in the ACT condition and 13.2% in the CBT condition (odds ratio [OR] = 5.13, $p < .02$). A randomized trial of 302 adult smokers compared individual and group ACT therapy with bupropion to bupropion only (Bricker et al. 2014a). In this study, intent-to-treat quit rates at 12-month follow-up were 32% in the ACT arm versus 18% in the bupropion-only arm ($p < .05$). ACT has also been studied as part of a telephone-based intervention. For example, in a pilot randomized trial on telephone-delivered ACT versus telephone-delivered CBT in 121 uninsured callers to the South Carolina state quitline, Bricker and colleagues (2014a) found no significant difference in 30-day point-prevalence quit rates at 6-month follow-up.

In recent years, ACT has also been adapted and pilot tested as (a) a smartphone application to reduce smoking (Singh et al. 2017) and to motivate smoking cessation (Bricker et al. 2014b; Bricker et al. 2017) and (b) a web-based intervention (Bricker et al. 2013; Bricker et al. 2018). For example, in a single-arm pilot trial of a smartphone application of ACT (SmartQuit® 2.0) among smokers, Bricker and colleagues (2017) found that at 2-month follow-up, quit rates were 21% for 7-day point

prevalence (vs. 23% for SmartQuit®) and 11% for 30-day point prevalence (vs. 13% for SmartQuit®), and 75% of participants reduced their smoking frequency (vs. 57% for SmartQuit®). Among program completers (24% of the total sample), quit rates were 33% for 7-day point prevalence and 28% for 30-day point prevalence, and 88% of participants reduced their smoking frequency. ACT has also been explored in specific populations, including smokers with depressive symptoms (Jones et al. 2015), smokers with bipolar disorder (Heffner et al. 2015, 2018), veterans with posttraumatic stress disorder (Kelly et al. 2015), and female smokers with cessation-related weight concerns (Bloom et al. 2017). More research is needed to better understand populations and delivery modalities for which ACT is particularly promising as a smoking cessation approach compared with existing cognitive therapies.

Contingency Management and Monetary Incentives

A large body of evidence (Ainscough et al. 2017) supports contingency management, which involves the use of incentives (including money, gift cards, or other tangible goods) to motivate people to change health behaviors, including motivating them to maintain abstinence from substance use over an extended period of time (Lussier et al. 2006). Monetary incentives for quitting or not initiating smoking or tobacco use, such as paying persons for engaging in cessation services and for achieving cessation-related outcomes (e.g., abstinence or participation in treatment), have been tested alone and in combination with cessation medication or counseling as an approach to increase compliance with nicotine dependence treatment and sustained abstinence from tobacco use. In a meta-analysis of the use of incentives for smoking cessation, Cahill and colleagues (2015) analyzed 21 trials of incentive programs that were implemented in a variety of settings for mixed populations and special groups (e.g., pregnant women). The OR for quitting with incentives (compared with controls) at the longest period of follow-up (at least 6 months) was 1.42 (95% CI, 1.19–1.69). Additionally, incentive-based programs increased rates of smoking cessation among pregnant women at both end-of-pregnancy and postpartum assessments. In an analysis by Cahill and Perera (2011), the primary benefit of incentive-based interventions was often seen only while the incentive was still in place. Only one of the reviewed studies (Volpp et al. 2009) in the analysis showed a statistically significant effect of the incentive program after the active incentive phase ended.

A key factor in the success of incentives in motivating smokers to quit may be the behavior that is being incentivized (quitting vs. engaging in treatment) and how the incentive is framed (reward vs. punishment). For example, in the study by Cahill and Perera (2011),

the participating employer opted to charge employees who smoked more for their insurance, rather than paying them for quitting, because nonsmoking employees viewed the latter approach as unacceptable. However, charging employees who smoke higher insurance premiums could have potential unintended consequences, such as leading them to forgo health insurance because it is too expensive or to conceal their smoking status to avoid the surcharges, making it harder to provide these employees with quitting support (Friedman et al. 2016; also see Chapter 7). As this example shows, contingency management could have unintended effects if improperly designed.

In 2011, the Centers for Medicare & Medicaid Services (CMS) launched the Medicaid Incentives for Prevention of Chronic Disease program in 10 states to assess the effectiveness of incentives in increasing certain preventive health behaviors, such as weight management and smoking cessation, among Medicaid beneficiaries as a strategy to improve the management of noncommunicable disease (CMS 2011, 2018). The results described in the final report on the project generally support the incentive approach (Hoerger et al. 2017). Five states (California, Connecticut, New Hampshire, New York, and Wisconsin) implemented incentive programs for smoking cessation. In the three states that tested impacts on program utilization (Connecticut, New Hampshire, and Wisconsin), incentives significantly increased the use of program services. Four of the states (California, Connecticut, New Hampshire, and Wisconsin) assessed the impact of incentives on rates of smoking cessation (which were biochemically verified in Connecticut, New Hampshire, and Wisconsin and self-reported in California); in all four states, rates of smoking cessation increased among those in the incentive group relative to those in the control group (Witman et al. 2018).

In general, motivation to quit and rates of cessation may increase while monetary incentives are in place, but these outcomes are rarely sustained after such incentives are removed. It is unclear whether a monetary incentive-based strategy is practical outside a research setting, given the reluctance of employers and insurers to pay smokers to quit and the potential unintended consequences of charging smokers more for health insurance. More research is needed to (a) explore whether any approaches to incentivizing smoking cessation sustain their effects over time and do not lead to counterproductive outcomes and (b) identify what types of approaches meet these criteria.

Relapse Prevention and Recovery

Most smokers make multiple quit attempts before finally succeeding in quitting for good. Indeed, one study

estimated that smokers may make an average of 30 or more quit attempts (i.e., serious attempts to quit smoking) before eventually succeeding (Chaiton et al. 2016). This means that most quit attempts end in relapse. Most relapses occur during the first few hours, days, or weeks of a quit attempt (Fiore et al. 2008). Although the risk of relapse declines over time, even former smokers who have quit for months or years can relapse (Hawkins et al. 2010).

Several treatment strategies include components designed to prevent relapse or to help smokers recover from relapses. Examples include relapse prevention therapy, which equips smokers with skills for avoiding or coping with high-risk environments and situations (Collins et al. 2010); acceptance and commitment therapy, which teaches smokers coping strategies to help them avoid lapsing into states of distress or giving in to strong urges to smoke (Bricker et al. 2014b); and motivation-enhancing interventions, which have been used to encourage smokers to make a quit attempt even if they are not ready to quit (Fiore et al. 2008; Lindson-Hawley et al. 2015). Each of these treatment models has demonstrated efficacy that is greater than brief advice (Lindson-Hawley et al. 2015) but not substantially greater than an equal-intensity intervention based on the *Clinical Practice Guideline* that addresses relevant risks of smoking, rewards of quitting, roadblocks to cessation, and repetition at each visit (Catley et al. 2016).

Despite the availability of relapse prevention and recovery interventions, scientific literature reviews on the topic highlight the difficulty of preventing and addressing relapse (Agboola et al. 2010; Hajek et al. 2013c). For example, in a Cochrane Review meta-analysis of relapse prevention interventions among smokers during the first 6 months of a quit attempt, Hajek and colleagues (2013c) found no evidence of benefit for additional post-cessation behavioral interventions or combined behavioral and pharmacologic interventions, either overall or for any subgroup. Many of the studies included in the Cochrane Review used small sample sizes and had limited statistical power to detect modest but potentially clinically significant effects, and the interventions may have been insufficient to achieve the desired effect. In addition, some studies focused on long-term abstinence. Therefore, these studies may have overlooked potentially beneficial recycling or recovery effects that result in increased frequency of secondary quit attempts. In a more recent review, Livingstone-Banks and colleagues (2019) found that the evidence does not support the use of behavioral treatments to help prevent relapse following smoking cessation among assisted abstainers. Instead, the most promising treatments involved extending treatment with certain pharmacotherapy, namely varenicline; extending treatment with bupropion was not shown to prevent relapse.

Furthermore, the review found insufficient evidence on extending treatment with NRT in preventing relapse in assisted abstainers. However, evidence for extending NRT in unassisted abstainers suggested a benefit. At present, more research is needed on specific behavioral interventions that can be delivered during the early stages of cessation to help smokers avoid short-term relapse.

Intervention Delivery Modalities

Research demonstrates that behavioral therapy approaches for smoking cessation can be delivered effectively through face-to-face counseling (individually or in groups) and brief clinical interventions (Fiore et al. 2008); and technology-mediated approaches, including telephone-based tobacco quitlines, mHealth, short message service (SMS) texts, web-based interventions, and smartphone applications; and, under certain circumstances, tailored self-help materials (The Community Guide 2011b, 2012b; Whittaker et al. 2012; Stead et al. 2013b, 2017; Lancaster and Stead 2017).

Self-Help Materials

In general, self-help materials for smoking cessation that are not tailored to a particular person or group have limited effectiveness when they are not coupled with in-person or technology-based interventions (Fiore et al. 2008). In a review of behavioral counseling interventions for tobacco cessation among adults, Patnode and colleagues (2015) did not find evidence of increased cessation in a comparison between nontailored self-help materials and no self-help materials. However, tailored self-help materials that are based on specific characteristics or concerns of smokers have been shown to be effective (Fiore et al. 2008; Patnode et al. 2013). Additionally, a Cochrane Review found some efficacy for tailored self-help materials in print, audio, and video forms compared with nontailored materials, but the absolute size of the effect was small (RR = 1.28; 95% CI, 1.18–1.37), and the review did not examine Internet-based materials (Hartmann-Boyce et al. 2014). Still, an effect size of 1.28 can be consequential given how inexpensive tailored self-help materials are relative to cessation medications or multisession counseling. The Cochrane Review also concluded that, although tailored self-help materials may offer some benefit, smokers trying to quit should also seek out more intensive cessation treatments.

Face-to-Face Counseling

Face-to-face counseling—whether delivered in traditional healthcare settings, behavioral healthcare

settings, or community settings—has traditionally been the gold standard for behavioral treatment of nicotine dependence, and its effectiveness is well-established in the scientific literature (Fiore et al. 2008). Noting substantial variability in the specific content of counseling delivered and in the skills of those delivering the counseling, the *Clinical Practice Guideline* concluded that individual in-person counseling achieved an average abstinence rate for cigarette smoking of 16.8%, compared with 10.8% for the control conditions (OR = 1.7; 95% CI, 1.4–2.0) (Fiore et al. 2008). In contrast, in-person group counseling achieved a 13.9% abstinence rate (OR = 1.3; 95% CI, 1.1–1.6).

In a Cochrane Review, Lancaster and Stead (2017) assessed the effectiveness of intensive counseling delivered by a cessation counselor on a one-on-one basis. All 49 RCTs they reviewed, which included approximately 19,000 participants combined, contained a face-to-face intervention component; however, some trials also included the use of other behavioral intervention modalities. The review concluded that individual counseling was more effective than minimal contact (brief advice, usual care, or self-help materials) when pharmacotherapy was not systematically offered to any participants (RR = 1.57; 95% CI, 1.40–1.77). Additionally, there was moderate evidence of a benefit for (a) the addition of intensive counseling (vs. usual care) when cessation pharmacotherapy was offered to all participants (RR = 1.24; 95% CI, 1.01–1.51) and (b) more intensive counseling compared with brief counseling (with or without the addition of cessation pharmacotherapy) (RR = 1.29; 95% CI, 1.09–1.53).

Brief Clinician-Delivered Advice

Clinical and other healthcare settings are a natural channel for delivering brief cessation interventions because at least 70% of tobacco users visit a physician each year (Fiore et al. 2008), almost one-third visit a dentist (Fiore et al. 2008; Carson et al. 2012), and millions see a specialist or are hospitalized (National Center for Health Statistics 2018). Encounters with clinicians represent a key opportunity to engage smokers in cessation treatments because clinical visits can provide teachable moments for patients who are experiencing or at risk for tobacco-related diseases (Fiore et al. 2008). Clinicians can take advantage of this opportunity and enhance the impact of their advice to quit by delivering this advice in a personalized manner that places it in the context of the patient's specific diagnosis and health history (Fiore et al. 2008). Furthermore, smokers respect and trust physicians and expect them to address their tobacco use (Quinn et al. 2005) and are more satisfied with healthcare providers when the providers discuss cessation with them (Bernstein and Boudreaux 2010; Winpenny et al. 2017; Holla et al. 2018).

Evidence increasingly suggests that healthcare providers other than physicians can also be effective in advising smokers to quit. For example, in a Cochrane Review of 11 studies, Rice and colleagues (2017) found moderate evidence that behavioral support provided by nurses can motivate and sustain smoking cessation. In another Cochrane Review of 14 studies totaling more than 10,500 participants, Carr and Ebbert (2012) found evidence suggesting that behavioral interventions conducted by oral health professionals (e.g., dentists and dental hygienists) as part of an oral examination in a dental office or other community setting could increase cessation rates in cigarette smokers and users of smokeless tobacco (pooled OR = 1.71; 95% CI, 1.44–2.03). Research is also emerging about the role that pharmacists and community pharmacies can play in helping to promote tobacco cessation (Augustine et al. 2016; Greenhalgh et al. 2016).

Based on the strong evidence base for brief tobacco cessation interventions, USPSTF (2015) recommends, as a “Grade A” recommendation, that clinicians deliver such interventions to all adult smokers. Even brief (<3 minutes) advice from a physician improves cessation rates (OR = 1.66; 95% CI, 1.42–1.94) (Stead et al. 2013a) and is highly cost-effective (Maciosek et al. 2017a).

As a framework, the 5 A’s method is considered the gold standard for delivering a brief tobacco cessation intervention. The 5 A’s method consists of the following steps:

1. Ask all patients about tobacco use;
2. Advise tobacco users to quit (e.g., “quitting is the best thing you can do for your health”);
3. Assess the patient’s willingness to make a quit attempt (e.g., “have you thought about quitting or are you interested in trying?”);

4. Assist in the quit attempt with medications, counseling, and referrals to behavioral treatment programs; and
5. Arrange follow-up (Table 6.1) (Fiore et al. 2008, p. 39).

Implementation of the 5 A’s by physicians is effective in increasing tobacco cessation and quit attempts among patients and in increasing engagement among patients in other empirically validated cessation treatments (Quinn et al. 2009). Compared with patients who received only one or none of the 5 A’s, delivering all of the 5 A’s increased patients’ receipt of counseling (OR = 11.2; 95% CI, 7.1–17.5), use of FDA-approved cessation medications (OR = 6.2; 95% CI, 4.3–9.0), and combined use of counseling and medication (OR = 14.6; 95% CI, 9.3–23.0) (Kruger et al. 2016).

In practice, however, despite the robust evidence for the effectiveness of brief tobacco interventions, many clinicians do not consistently address tobacco use and nicotine dependence. For example, in nationally representative data from 2000 to 2015, Babb and colleagues (2017) found that 57% of smokers who had seen a health professional in the past year reported receiving advice to quit. In an earlier study, King and colleagues (2013) found that patient reports of their physicians providing each of the 5 A’s typically decreased as the steps progressed, with “Asking” about tobacco use (87.9%) being more prevalent than “Assisting” with a quit attempt (78.2% of those who wanted to quit) and the prevalence of “Assisting” being far more prevalent than “Arranging for follow-up” (17.5% overall). Thus, in practice, clinicians are rarely performing all five actions in the 5 A’s approach. One way to address this problem is by delegating some of the steps of the 5 A’s (e.g., Ask, Assist, Arrange) in whole or in part to other members of the healthcare team (e.g., nurses, physician assistants, roomers, etc.) (Fiore et al. 2008). This approach

Table 6.1 The 5 A’s model for treating tobacco use and dependence

Ask about tobacco use	• Identify and document tobacco use status for every patient at every visit.
Advise to quit	• In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess readiness to make a quit attempt	• Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempts	<ul style="list-style-type: none"> • For the patient willing to make a quit attempt, offer medication and provide or refer for counseling or additional treatment to help the patient quit. • For patients unwilling to quit at the time, provide interventions designed to increase future quit attempts.
Arrange follow-up	<ul style="list-style-type: none"> • For the patient willing to make a quit attempt, arrange for follow-up contacts, beginning within the first week after the quit date. • For patients unwilling to make a quit attempt at the time, address tobacco dependence and willingness to quit at next clinic visit.

Source: Fiore and colleagues (2008, p. 39).

lessens the burden on physicians and emphasizes the importance of quitting to patients (Fiore et al. 2008).

A diagnosis of a tobacco-related disease has been associated with an increase in quit attempts, use of cessation resources (Patel et al. 2009; Schauer et al. 2014b; Gallaway et al. 2019), and cessation and can provide a teachable moment for patients, especially because quitting can often improve a patient's prognosis or symptoms. Studies indicate that healthcare providers may be leveraging this opportunity. For example, in a study of patient-reported receipt of the 5 A's in a nationally representative population of past-year cigarette smokers with and without chronic obstructive pulmonary disease (COPD), Schauer and colleagues (2016c) found that patients with COPD were more likely than those without COPD to receive each step in the 5 A's approach: Ask = 95.4% vs. 85.8%; Advise = 87.5% vs. 59.4%; Assess = 63.8% vs. 37.9%; Assist = 58.6% vs. 34.0%; and Arrange = 14.9% vs. 5.2%.

Barriers that can prevent clinicians from consistently conducting brief cessation interventions include time constraints; a lack of knowledge, training, and confidence; inadequate clinical and/or institutional support; a lack of adequate reimbursement for delivering tobacco treatment; and inadequate or confusing insurance cessation coverage (Fiore et al. 2008; Sheffer et al. 2012). Concerns about the lack of adequate training to effectively deliver cessation interventions are also reported by other healthcare providers, such as nurses, psychologists, and social workers (Steinberg et al. 2006a,b; Applegate et al. 2008; Sheffer et al. 2012).

Alternative Approaches to the 5 A's

Research supports the value of alternative treatment approaches that do not deliver all steps of the 5 A's approach in the clinical setting. One such alternative that is widely used is the Ask-Advise-Refer (AAR) approach, which involves a provider in a clinical setting Asking about tobacco use; Advising patients to quit; and Referring interested patients to another cessation resource, such as a quitline (see Chapter 7), to complete the remaining "Assess," "Assist," and "Arrange" steps (Schroeder 2005; Gordon et al. 2010). Gordon and colleagues (2010) compared the use of the 5 A's with the use of the AAR approach in 68 dental clinics. At 12 months, participants receiving either the 5 A's or the AAR were more likely to report tobacco cessation than those who received only usual care. Additionally, there was no significant difference (using a threshold of $p < 0.05$) in rates of 9-month prolonged cessation between participants receiving the 5 A's method and the AAR approach (3% vs. 2%, $p < .10$ for 9 months of prolonged abstinence) (Gordon et al. 2010).

Limited research supports a third approach, Ask-Advise-Connect (AAC). Compared with AAR, AAC provides

a more active and direct connection to an outside cessation resource (Vidrine et al. 2013a,b). One example of providing such a direct connection is referring smokers to tobacco quitlines via an electronic referral or "eReferral" that securely transfers patient registration information from electronic health records to the quitlines (Boyle et al. 2011, 2014; Sheffer et al. 2012; Adsit et al. 2014; Tindle et al. 2016) (see Chapter 7 for more details on electronic health records and eReferrals). Some research suggests that AAC may be more effective than AAR in reaching smokers and engaging them in treatment. Specifically, in a pair-matched, two-treatment-arm, group-randomized study conducted in 10 family practice clinics in one metropolitan area, 7.8% of all identified smokers enrolled in treatment in the AAC arm compared with just 0.6% who enrolled in the AAR arm (OR = 11.6; 95% CI, 5.5–24.3) (Vidrine et al. 2013a).

Finally, because many smokers are ambivalent about quitting or have transient motivation to quit, a fourth hypothetical version of the 5 A's might build on such approaches as the 5 R's (Relevance, Risks, Rewards, Roadblocks, and Repetition) (Agency for Healthcare Research and Quality 2012), which is used for smokers who are not yet ready to quit and focuses on providing interventions and supports to all smokers, even those who are initially assessed as not ready to quit. This approach is appealing from a theoretical standpoint because of the lack of clear evidence demonstrating that a very brief assessment of readiness to quit is sufficient to withhold an offer of more robust cessation support to these individuals. One potential downside of this approach could be that providing support to smokers who are not ready to quit could turn out to be time-consuming and inefficient. To date, randomized trials have not assessed this approach.

As tobacco cessation interventions are increasingly integrated into inpatient care and into care in other settings, such as pharmacies and behavioral health treatment facilities, updates to the 5 A's model may emerge that more explicitly coordinate and distribute cessation interventions across an integrated care team and across different clinical environments.

Intensive Face-To-Face Counseling

Intensive in-person behavioral treatment, which is sometimes combined with pharmacologic interventions, typically consists of multiple face-to-face counseling sessions that last long periods of time (e.g., ≥ 10 minutes) by clinicians who have been trained in specialized smoking cessation interventions (Fiore et al. 2008). Although intensive interventions are intended primarily for moderately to heavily addicted smokers, the effectiveness and cost-effectiveness of such interventions are not limited to heavy or highly dependent smokers (Fiore et al. 2008; USPSTF 2015). A range of intensive treatment programs

are available at the individual and group levels in some communities, worksites, and healthcare systems (Institute of Medicine 2007). However, availability varies widely from community to community, and geographic location and temporal availability are major barriers to utilization. In practice, such intensive cessation approaches are generally the exception rather than the rule in the United States. Compared with the United States, some countries have invested more heavily to ensure that most smokers have access to intensive face-to-face counseling. For example, in addition to making brief cessation interventions delivered by primary care physicians and some pharmacists widely available, the United Kingdom has established Stop Smoking Services, which mainly target highly addicted smokers and are staffed by counselors who are trained in behavioral approaches to smoking cessation (Dobbie et al. 2015; Public Health England 2017). Both intensive individual and group cessation treatments have been shown to be effective when delivered outside of healthcare clinics, particularly in workplace settings. For example, Cahill and Lancaster (2014) reported on rates of tobacco cessation in eight trials in workplace settings that involved intensive group treatments (N = 1,309) and individual treatments (N = 3,516). Relative to controls, the OR for successful quitting among those in the intensive group treatments (OR = 1.71; 95% CI, 1.05–2.80) was generally comparable in magnitude to that for those receiving individual treatments (OR = 1.96; 95% CI, 1.51–2.54), suggesting that well-designed group counseling can be effective in workplace settings.

Although a strong evidence base exists for in-person behavioral approaches to treating tobacco use and nicotine dependence, few U.S. smokers use face-to-face individual and group counseling when trying to quit, possibly because of a lack of investment in these approaches and practical barriers to use (e.g., time, transportation, schedule, etc.) (Dobbie et al. 2015; Public Health England 2017). For example, in a U.S. study, Babb and colleagues (2017) found that in 2015 31.2% of U.S. adult cigarette smokers reported using cessation counseling and/or medication when trying to quit, 6.8% reported using counseling, 29.0% reported using medication, and 4.7% reported using both counseling and medication. In terms of specific types of counseling, 4.1% of smokers reported using a telephone quitline; 2.8% one-on-one counseling; and 2.4% a stop-smoking clinic, class, or support group (Babb et al. 2017).

Technology-Mediated Delivery Approaches

Evidence supports the effectiveness of certain non-face-to-face delivery approaches for tobacco cessation, including telephone-based quitlines (The Community Guide 2012a) and mHealth-based interventions (The Community Guide 2011b). These approaches have characteristics that

can remove or reduce time, transportation, and child care issues that may hinder face-to-face service delivery, thereby potentially leading to more widespread use. The following section reviews technology-mediated tobacco cessation intervention delivery approaches, including quitlines, SMS texting, web-based interventions, and smartphone applications. Telehealth approaches, which are discussed later in the “Emerging Behavioral Treatments” section of this chapter, are another emerging technology that can be used to deliver tobacco cessation interventions.

Tobacco Quitlines

Staffed by trained counselors or coaches, tobacco quitlines typically deliver a variety of services, including individual counseling, practical information on how to quit, referrals to other cessation or health-related resources, mailed self-help materials, information on FDA-approved cessation medications, and, in some cases, provision of limited quantities of free or discounted cessation medications (Keller et al. 2010; Anderson 2016). Publicly funded quitlines are available at no cost to U.S. residents in every state, the District of Columbia, Guam, and Puerto Rico (North American Quitline Consortium n.d.b). However, specific services vary across states, largely as a result of funding constraints that vary across states and jurisdictions and over time (Centers for Disease Control and Prevention [CDC] 2014; Anderson 2016). In addition to publicly funded state quitlines, some public and private health insurance plans and employers also offer quitline services (CDC 2014).

Since the 1990s, a large body of clinical literature has consistently demonstrated the effectiveness of tobacco quitlines (Zhu et al. 1996; Fiore et al. 2008). Although research on single- and multi-call quitline protocols has demonstrated that both are effective, better outcomes have been reported for multi-call approaches. Better outcomes have also been documented for proactive quitline services, which make multiple outbound calls to engage the tobacco user in ongoing treatment, compared with reactive quitline services, which simply respond to incoming calls from tobacco users. For example, in a meta-analysis of 49 studies that compared proactive quitlines with reactive quitlines, The Community Guide (2012b) estimated that proactive quitlines yielded a median 3.1-percentage-point increase (0.5–3.3 percentage points, 12 studies) in quitting and a 4.2 percentage-point increase when promoted through mass-reach health communication interventions.

Similarly, in a Cochrane Review of 77 trials that assessed counseling provided through quitlines, Stead and colleagues (2013b) concluded that multiple sessions of proactive telephone counseling significantly boosted rates of smoking cessation (nine studies; >24,000 participants; RR for cessation at longest follow-up = 1.37; 95% CI, 1.26–1.50). There was some evidence of a dose-response

effect—that is, more completed quitline counseling calls yielded higher rates of cessation. Even reactive calls to quitlines were effective in increasing cessation (51 studies, >30,000 participants, RR for cessation = 1.27; 95% CI, 1.20–1.36).

A toll-free national portal (1-800-QUIT-NOW) operated by the National Cancer Institute (NCI) links callers to their state quitline based on their area code. An electronic telecommunications device for the deaf (TDD) is also available to serve persons who are deaf or hard of hearing. From 2010 to 2015, state quitlines received an estimated 1.1–1.3 million calls annually and provided cessation counseling and/or cessation medications to an estimated 342,000–475,000 tobacco users each year (CDC, National Quitline Warehouse Database, unpublished data).

NCI also operates 1-855-DÉJELO-YA (1-855-335-3569), a national portal that routes Spanish-speaking callers to Spanish-language services available through their state quitlines. From February 2013 (the portal's inception) through December 2018, 1-855-DÉJELO-YA received more than 40,000 calls (CDC, NCI, unpublished data).

In addition, the Moores Cancer Center at the University of California–San Diego operates a nationwide Asian Smokers' Quitline, which offers direct counseling services in Chinese, Korean, and Vietnamese (Asian Smokers' Quitline n.d.). Nearly 5,800 callers from 48 states enrolled in the Asian Quitline between 2012 and 2014; 31% spoke Chinese (Cantonese or Mandarin), 38% spoke Korean, and 31% spoke Vietnamese (Kuiper et al. 2015). Nearly all eligible callers to the Asian Quitline (99%) received nicotine patches. Approximately 85% of smokers who called the Asian Quitline enrolled in counseling, completing an average of four sessions (Kuiper et al. 2015).

Quitline counseling is readily accessible because it is free, convenient, and confidential, and it removes or reduces barriers related to time, transportation, child care, and other factors (World Health Organization [WHO] 2011). As a result, quitline counseling has the potential for broad reach. Quitline counseling has also been found to be effective with an array of subpopulations (Baezconde-Garbanati et al. 2011). Tobacco users can be connected with a quitline in several ways: by calling directly; by having a healthcare provider's office fax, send an online referral, or submit an eReferral through the patient's electronic health record; by sending an e-mail; or by enrolling online. Most state quitlines provide at least one counseling session to any adult tobacco user who calls, and many state quitlines provide a multi-call program that includes both reactive and proactive calls. Some state quitlines prioritize multi-call services for subpopulations with a higher prevalence of tobacco use and/or limited access to other tobacco cessation services (e.g., persons who lack health insurance or are unemployed) (Anderson 2016). A study of quitline

eReferrals in Wisconsin randomized 23 primary care clinics from two healthcare systems to one of two methods for referring adult patients who smoked to the Wisconsin quitline: a paper-based, fax-to-quit referral process or an eReferral process (Fiore et al. 2019). The eReferral process involved sending referrals to the quitline from patients' electronic health records and receiving outcome reports from the quitline back into the electronic health records. The fax referral process transmitted the same information in both directions via fax. A total of 14,636 smokers were seen in the two systems. Compared with clinics that were randomized to the fax referral process, clinics that were randomized to the eReferral process generated quitline referral rates that were 3- to 4-times higher and also generated higher rates of connecting patients with quitlines (i.e., having patients accept a quitline call and at least begin the process of registering for quitline services). The eReferral method generated especially high rates of referrals among Medicaid recipients. The study, which was the first randomized study of this topic, concluded that eReferrals provide an effective means of referring patients who smoke to quitline services.

A major innovation in quitline services that occurred over the past decade was the integration of NRT and, in some cases, other FDA-approved cessation medications into state quitline services, along with counseling. A series of randomized and quasi-randomized trials (Cummings et al. 2006; Hollis et al. 2007; Tinkelman et al. 2007) demonstrated that quitlines can feasibly and safely provide NRT to callers, either directly via mail order or by pharmacy voucher. This involved having quitlines screen callers for the medical appropriateness of NRT use, educate callers on how to properly use the NRT, and continue to provide callers with behavioral counseling. Making cessation medication available to callers and promoting its availability results in more smokers calling quitlines and has the potential to increase quit rates among callers by providing them with the optimal combination of cessation counseling plus medications (An et al. 2006). Even 2-week NRT “starter kits” have demonstrable benefits, including increased call volume to quitlines, higher quit rates, and increased caller satisfaction with the quitline (Bush et al. 2008; Deprey et al. 2009; Kerr et al. 2018). Distributing NRT through quitlines can be cost-effective (Fellows et al. 2007; Cummings et al. 2011). For example, Fellows and colleagues (2007) estimated that the total cost per quit was \$2,688 lower for callers who received free NRT (\$1,050) compared with persons who called the Oregon quitline before it began offering the nicotine patch to callers (\$3,738).

The reach of state quitlines varies across states, over time, and by demographic factors, such as race/ethnicity (North American Quitline Consortium n.d.a). Despite reaching thousands of smokers each year in most states,

state quitlines reach an average of 1% of smokers annually (CDC 2014). Data suggest that even among smokers who tried to quit in the previous year and were aware of quitlines, quitline reach was around 8% (Schauer et al. 2014a). This limited awareness and reach, along with the variation in quitline services and eligibility for these services across states and over time, are largely the result of limited state funding for operating and promoting quitlines (e.g., state quitline expenditures) (CDC 2004; Schauer et al. 2014a). States have developed the capacity to carefully titrate their activities to promote quitlines and the level of quitline services they provide to match available funding. Some states have been able to temporarily attain higher levels of reach, in some cases higher than 6%, during periods when they can fund quitlines at higher levels, often while also conducting specific policy and promotional efforts that drive increased calls to the quitline (Woods and Haskins 2007; Mann et al. 2018).

Call volume to quitlines is highly sensitive to promotional activities (Anderson 2016). For example, *Tips From Former Smokers (Tips)*, a national tobacco education campaign conducted annually by CDC for varying periods of time from 2012 to 2019, includes a message on the majority of its television ads directing smokers to call 1-800-QUIT-NOW for free help quitting. From 2012 to 2018, this campaign generated more than 1.3 million additional calls to 1-800-QUIT-NOW (Nathan Mann, RTI International, personal communication, May 6, 2019). Call volume to 1-800-QUIT-NOW consistently increases when the campaign airs and decreases when it goes off the air (Zhang et al. 2016; McAfee et al. 2017; Murphy-Hoefer et al. 2018).

In part, to maintain or improve their reach, state quitlines increasingly offer ancillary cessation services, such as Internet interventions, e-mail, chat, texting, and the dispensing of NRT both alone and in combination with counseling (Anderson 2016; Keller et al. 2016). This shift in quitline practice stems in part from the recognition that many younger adults prefer to access cessation assistance through these alternative channels rather than over the telephone (Dreher et al. 2015). For example, to increase both reach and quitting behavior, Minnesota implemented a model for state quitline services in 2014 that expanded tobacco users' options for accessing cessation services, allowing tobacco users to enroll via telephone or online and to choose one or more cessation services from a menu of options that includes quitline counseling, a medication starter kit, text messaging, an e-mail program, and a quit guide (Keller et al. 2016). Between March 2014 and February 2015, 15,861 unique tobacco users registered for cessation services in the state—a 169% increase over calendar year 2013. More than four in five (83.7%) of the participants made a quit attempt, and the 30-day

point-prevalence abstinence rate (among responders) was 26.1% for the overall program (regardless of services used); 29.6% for quitline services; and 25.5% for individual non-quitline services. Thus, the reach of quitlines can be expanded, and new populations can be engaged in cessation services when quitlines (a) broaden their cessation service offerings beyond traditional telephone-based quitline services and (b) allow tobacco users to choose the service that best meets their needs and suits their preferences (Keller et al. 2016).

Mobile Health Intervention Strategies

Desktop or laptop computer-based interactive program modalities for delivering smoking cessation support have been developed and tested (USPSTF 2015), first via programs operated from a CD-ROM or hard drive, later via Internet downloads, and more recently from “the cloud” (Strecher et al. 2005; Haskins et al. 2017). The current state of science and technology also allows the leveraging of mobile phone and tablet applications (e.g., mHealth interventions) to deliver treatment for nicotine dependence (Whittaker et al. 2016). mHealth strategies can be broadly defined as the use of technology to remotely monitor, track, respond to, and/or deliver an intervention for health-related events. mHealth treatment platforms have expanded greatly during the past 20 years and especially in the past decade, with the development of electronic and mHealth technologies. These platforms include applications offered by for-profit and not-for-profit organizations and academic institutions and by federal agencies involving standardized text messages that enhance motivation to quit smoking or inform persons about quitting strategies, some of which offer real-time, live peer or professional advising or counseling (Smokefree.gov n.d.). Preliminary evaluations suggest that these applications benefit users (Cole-Lewis et al. 2016; Squiers et al. 2016, 2017; Taber et al. 2016) and that the cost of delivery is low.

Uptake of mobile technologies has been seen across almost all segments of the U.S. population (Pew Research Center 2017b). In 2016, cell phone ownership and usage were widespread: 95% of American adults owned a cell phone; 77% had a smartphone; and ownership levels were generally similar across all categories of race/ethnicity, age, education level, income level, and rural versus urban status (Pew Research Center 2017b). Texting is common among cell phone users, and many smartphone users report using their phones for texting, accessing the Internet, watching videos, and using apps (applications). Importantly, despite the widespread adoption of mobile technology, some populations—including some low-income and rural individuals and veterans—do not have equal access to mobile technology (Koutroumpisa and Leiponenb 2016; Markham et al. 2016).

Despite some remaining gaps in the availability and coverage of mobile technology, these technologies offer considerable potential to serve as platforms for delivering smoking cessation interventions. In 2011, the Community Preventive Services Task Force recommended mobile phone-based interventions, specifically automated texting programs, for tobacco cessation on the basis of sufficient evidence of their effectiveness in increasing tobacco use cessation among persons interested in quitting (The Community Guide 2011b).

Potential advantages of mHealth interventions include greater reach to some disproportionately impacted populations (Markham et al. 2016; Anguiano et al. 2017) and reduced costs because mHealth interventions can be less costly to provide than other behavioral interventions. In terms of reach, the Smokefree.gov initiative—a large federal mHealth behavioral intervention program that focuses primarily on smokers—reaches 5–6.5 million persons each year, including more than 3.6 million visitors to the Smokefree.gov website in 2018 (Yvonne Prutzman, NCI, personal communication, January 23, 2019). In addition, mHealth interventions may improve engagement through increased access to intervention services, decreased barriers to participation (e.g., by removing barriers related to scheduling, transportation, or child care), seamless integration of users' interactions with treatment into their daily lives, and the ability to personalize treatment based on passively (e.g., GPS [global positioning system] location) or actively (e.g., self-report of craving) gathered information (Atienza and Patrick 2011; Nilsen et al. 2012; Free et al. 2013; Borrelli et al. 2015; Marzano et al. 2015).

The potential benefits from mHealth interventions are tempered by several challenges, including (1) inconsistent access to cell phones among low-income populations (despite the increasing adoption of cell phones, low-income populations may still struggle to maintain cell phone contracts, have regular access to minutes, and have data plans that allow for repeated use of interventions), (2) different types of devices (e.g., cell phone vs. smartphone), (3) possible sharing of devices among multiple users, (4) differences in fee structures and costs for using cell phones, (5) the challenges of delivering content to populations with low literacy, and (6) lack of broadband coverage (Atienza and Patrick 2011; Katz et al. 2012; Free et al. 2013; Marzano et al. 2015; McClure et al. 2016; Federal Communications Commission n.d.).

At this time, optimal methods are not in place to fully assess the expanding array of available mHealth cessation interventions. Future research should address the components of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) impact model (addressed later in this chapter) to determine the

effectiveness of mobile cessation interventions under ideal conditions and their impact when used in real-world settings (Stearns et al. 2014). Research should include both process measures, such as engagement and reengagement, and measures of the interventions' impact on quit attempts and successful quitting. In addition, assessing the comparative effectiveness and cost-effectiveness of mHealth cessation interventions relative to other modalities, such as in-person and quitline interventions, will be important. Because of the rapid cycle of technological development, the use of adaptive and iterative research methods in assessing development and performing evaluations may be necessary. Although opportunities are available for conducting large cohort studies at a relatively low cost, the potential for selection bias and other types of bias in such studies underscores a need for RCTs in clinical settings.

Short Message Service Texting Interventions.

Interventions based on SMS texting—which involve sending automated, one-way messages—offer a low-cost, convenient method of delivering smoking cessation interventions. Text messaging is a basic feature of almost all cell phones, making the delivery of cessation interventions via SMS texts an accessible and promising mHealth platform. A series of three studies from New Zealand and the United Kingdom provided the initial evidence supporting the use of this platform for delivering smoking cessation interventions (Rodgers et al. 2005; Free et al. 2009, 2011). Notably, a large-scale RCT in the United Kingdom that compared smokers receiving a text-based intervention with controls who received SMS texts related to the importance of trial participation, found a significant difference in biochemically verified abstinence at 6-month follow-up: 9.2% of smokers in the texting intervention achieved abstinence versus 4.3% of smokers in the control group (RR = 2.14; 95% CI, 1.74–2.63) (Free et al. 2011). A subsequent meta-analysis of a limited number of text-based cessation interventions found that, compared with control conditions, such interventions improved the 7-day point-prevalence of abstinence (OR = 1.38; 95% CI, 1.22–1.55) and continuous abstinence (OR = 1.63; 95% CI, 1.19–2.24) (Scott-Sheldon et al. 2016).

Although the findings from studies of cessation texting interventions are generally encouraging, a review of these interventions found that, while smoking cessation outcomes measured at less than 6 months were better than those for controls, outcomes measured at 6 months or longer often failed to show differences between treatment and control groups (Scott-Sheldon et al. 2016). In addition, the review found that the studies' findings were mixed and the analyses were based on a small number of RCTs. One reason for these mixed findings may be the substantial variation in key features of the interventions, including frequency of messages per day and per week;

length of programs; use of unidirectional versus bidirectional messages; and, to a lesser extent, message content. Another reason may be variation in study design, such as the endpoint used for measuring abstinence (Free et al. 2013; Kong et al. 2014; Scott-Sheldon et al. 2016). This variability has presented a challenge when interpreting findings from specific studies. Nevertheless, the overall evidence supports the efficacy of text-based smoking cessation treatment programs. However, to inform the optimization of treatment, more research is needed to better understand the contributions of various treatment elements.

Web-Based Interventions. Web-based cessation interventions (i.e., cessation interventions delivered via the Internet) have the potential to achieve broad reach, as 88% of American adults report regularly accessing the Internet, including a majority of low-income Americans and members of various racial/ethnic groups (Pew Research Center 2017a). However, evidence on the effectiveness of web-based smoking cessation interventions is mixed. Such interventions date back to the early 2000s, with studies exploring several approaches for delivering treatment and examining user behavior (Etter 2005; Stoddard et al. 2005; Strecher et al. 2005; Cobb and Graham 2006). Initial research findings were inconsistent, and several reports found that websites frequently failed to deliver recommended elements of behavioral treatment for smoking cessation (Bock et al. 2004, 2008; Fiore et al. 2008).

In its 2011 review, the Community Preventive Services Task Force found insufficient evidence to determine the effectiveness of Internet-based interventions in increasing tobacco cessation (The Community Guide 2011a). Later, a study on web-based tobacco cessation interventions by Cijljak and colleagues (2013) concluded that some Internet-based interventions, particularly interventions that are interactive and tailored to individuals, can assist in achieving longer term smoking cessation. However, trials that compared Internet interventions with usual care or self-help did not show consistent effects. As web-based interventions have grown more sophisticated, incorporating better website design and improved functionality, the efficacy of such interventions for smoking cessation has improved significantly (Graham et al. 2016). A meta-analysis of web-based cessation interventions found that, although sites with largely static content did not perform significantly better than printed materials in increasing abstinence (RR = 0.83; 95% CI, 0.63–1.10), sites that incorporated interactive elements significantly increased abstinence (RR = 2.10; 95% CI, 1.25–3.52) (Graham et al. 2016). Comparisons of web-based cessation interventions with face-to-face counseling and quit-line counseling suggest that these different modalities have the potential to produce similar cessation outcomes (Graham et al. 2016; McCrabb et al. 2019).

In a meta-analysis, McCrabb and colleagues (2019) assessed the effectiveness of 45 RCTs of adult-focused Internet cessation programs, as well as the number and type of behavior change techniques employed in the intervention (Michie et al. 2013), to determine how behavior change techniques impact program effectiveness. The study found short-term effectiveness for all measured cessation outcomes (e.g., prolonged abstinence and 30-day point-prevalence abstinence) (OR = 1.29; 95% CI, 1.12–1.50) and for long-term outcomes (OR = 1.19; 95% CI, 1.06–1.35). Interventions used more behavior change techniques than comparison groups (6.6 vs. 3.1, $p < .0002$). Interventions that included goals and planning, social support, natural consequences, comparison of outcomes, reward and threat, or regulation were significantly associated with increased intervention effectiveness in the short and long terms, when compared with study arms that did not include the domain(s).

The fact that web technologies and web-based cessation interventions continue to evolve, along with the potential reach and customizability of web-based technologies, suggests that future interventions could further improve on current ones. For example, advances in web technologies could improve user experience, enhance content management, better incorporate interactive elements, and better integrate various types of media (e.g., videos and audio). The increasing penetration of smartphones and the broad availability of free Wi-Fi may also allow for access to the web in many nontraditional settings. In response to this changing landscape, many websites are using adaptive design (i.e., changing the format to match the type of device used) and are optimized for use on mobile devices (i.e., are designed to offer easy navigation and high-quality user experience when accessed via such devices). Such sites have the potential to achieve broad population-level reach and widespread engagement with target audiences. Taken as a whole, the available evidence suggests that web interventions with interactive components can increase abstinence to tobacco. As with text-based cessation programs, more research is needed to better understand the specific components that can further enhance the effectiveness of web-based interventions for smoking cessation.

Smartphone Applications. Although most mobile phone interventions have traditionally relied on text messaging platforms (Whittaker et al. 2016), the increasing use of smartphones offers a platform to combine elements of texting and the web to create more interactive and visual interventions (Abroms et al. 2011). In their 2013 review of smartphone apps for smoking cessation, Abroms and colleagues (2013) identified 252 such apps for Apple's iOS and 148 apps for Google's Android operating systems. The review then analyzed nearly 100 of the most popular

cessation apps and their adherence to an index criteria based on the *Clinical Practice Guideline* (Fiore et al. 2008). The average score suggested that overall levels of the apps' adherence to evidence-based cessation approaches were low (Abroms et al. 2011). However, smartphone apps for smoking cessation continue to evolve, both as standalone interventions and in combination with other approaches to cessation interventions. For example, in 2017 FDA granted marketing authorization for a carbon monoxide breath sensor system that can be paired with a smartphone via Bluetooth technology to measure carbon monoxide in exhaled breath and show smokers in real time how their cigarette smoking is impacting their levels of carbon monoxide (FDAnews 2017). The Smokefree.gov initiative now includes two free smoking cessation apps: QuitGuide, which helps smokers understand their smoking patterns and build skills to quit, and quitSTART, which gives smokers tailored tips and motivation to quit. These federally funded apps provide opportunities to learn more about the components that make a smoking cessation smartphone application effective. In particular, more research is needed to assess the efficacy of smartphone applications that combine texting and web-based features.

As reviewed, a variety of technology-mediated approaches exist to deliver behavioral interventions for smoking cessation, and these interventions stand to further increase the reach of cessation interventions. However, technologies are evolving, as are the ways in which people interact with and use technology. Therefore, ongoing research is warranted to ensure that technology-based approaches to cessation remain relevant and meet current user preferences. The elements that make a particular technology effective for cessation may shift as technologies evolve. For example, preferences for texting may shift as that technology becomes integrated into smartphone applications and user interfaces.

In summary, a variety of behavioral and counseling approaches are available through various delivery modalities to motivate and aid successful smoking cessation. However, most smokers still try to quit on their own without using behavioral or counseling interventions. Therefore, innovative, technology-based delivery modalities have the potential to help increase the reach and use of these interventions, but more research is needed to better understand the impact that different delivery modalities have on motivating and sustaining cessation in different subpopulations.

Pharmacologic Treatments

Nicotine is the drug in tobacco that leads to addiction (USDHHS 1988). Epidemiologic and laboratory evidence indicates that nicotine delivered in tobacco products is substantially more addictive than nicotine delivered through current medications (USDHHS 2010). In addition to behavioral and environmental components, constituents other than nicotine in tobacco products and product delivery methods play critical supporting roles in promoting nicotine addiction. A major conclusion from the 2010 Surgeon General's report is, "Sustained use and long-term exposures to tobacco smoke are due to the powerfully addicting effects of tobacco products, which are mediated by diverse actions of nicotine and perhaps other compounds, at multiple types of nicotinic receptors in the brain" (USDHHS 2010, p. 9). The general rationale for having smokers use smoking cessation medications as part of a quit attempt is to reduce physical symptoms resulting from nicotine withdrawal, thus allowing smokers to focus on the behavioral and psychological aspects of quitting smoking (Prochaska and Benowitz 2016). Cessation medications also have the additional benefit of eliminating or greatly reducing the immediate reinforcing effects of nicotine absorbed from tobacco smoke by desensitizing the nicotinic receptors (Prochaska and Benowitz 2016). Although not FDA-approved for smoking cessation,

the prescription medications clonidine hydrochloride and nortriptyline hydrochloride are recommended as second-line agents in the U.S. Public Health Service's *Clinical Practice Guideline* (Fiore et al. 2008). Lack of an FDA-approved indication for smoking cessation, as well as some side effects, currently preclude these medications from being classified as first-line agents; therefore, they are not reviewed in this report.

To date, seven FDA-approved, first-line medications have been found to be safe and effective for treating nicotine dependence—although there are some contraindications for use (e.g., recent myocardial infarction for most NRT formulations, seizure disorder for bupropion), as well as insufficient evidence of effectiveness and, in some cases, safety in certain populations (e.g., pregnant women, light smokers, adolescents, and smokeless tobacco users) (Fiore et al. 2008). The seven medications include five nicotine-based medications (the nicotine patch, gum, lozenge, nasal spray, and oral inhaler) and two non-nicotine oral medications, bupropion and varenicline. Table 6.2 offers in-depth information on these seven medications. The nicotine patch, gum, and lozenges are available over the counter; however, a prescription may still be required for insurance coverage of over-the-counter products. The nicotine nasal spray and oral inhaler, bupropion, and varenicline

Table 6.2 Pharmacologic product guide: FDA-approved medications for smoking cessation

Product	NRT formulations						Varenicline
	Gum	Lozenge	Transdermal patch	Nasal spray	Oral inhaler	Bupropion SR	
Product	Nicorette,^a ZONNIC,^b Generic OTC 2 mg, 4 mg original, cinnamon, fruit, mint	Nicorette Lozenge,^a Nicorette Mini Lozenge,^a Generic OTC 2 mg, 4 mg cherry, mint	NicoDerm CQ,^a Generic OTC (NicoDerm CQ, generic) Rx (generic) 7 mg, 14 mg, 21 mg (24-hour release)	Nicotrol NS^c Rx Metered spray 10 mg/ml aqueous solution	Nicotrol Inhaler^c Rx 10-mg cartridge delivers 4-mg inhaled vapor	Zyban,^a Generic Rx 150-mg sustained- release tablet	Chantix^c Rx 0.5-mg, 1-mg tablet
FDA approval	Nicorette: • 2 mg (Rx) 1984 • 4 mg (Rx) 1991 ZONNIC: • 2 mg (OTC) 1996 • 4 mg (OTC) 1996	Lozenge: • 2 mg (OTC) 2002 • 4 mg (OTC) 2002 Mini-lozenge: • 2 mg (OTC) 2009 • 4 mg (OTC) 2009	• Rx: 1991–1992 • OTC: 1996–2002	Rx: 1996	Rx: 1997	Rx: 1997	Rx: 2006

Table 6.2 Continued

	NRT formulations					Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal patch	Nasal spray	Oral inhaler		
Precautions	<ul style="list-style-type: none"> • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Temporomandibular joint disease • Pregnancy^d and breastfeeding • Adolescents (<18 years of age) 	<ul style="list-style-type: none"> • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy^d and breastfeeding • Adolescents (<18 years of age) 	<ul style="list-style-type: none"> • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy^d (Rx formulations, category D) and breastfeeding • Adolescents (<18 years of age) 	<ul style="list-style-type: none"> • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) • Severe reactive airway disease • Pregnancy^d (category D) and breastfeeding • Adolescents (<18 years of age) 	<ul style="list-style-type: none"> • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Bronchospastic disease • Pregnancy^d (category D) and breastfeeding • Adolescents (<18 years of age) 	<ul style="list-style-type: none"> • Concomitant therapy with medications/ conditions known to lower the seizure threshold • Hepatic impairment • Pregnancy^d (category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms^e: Boxed warning removed December 2016 <p>Contraindications:</p> <ul style="list-style-type: none"> • Seizure disorder • Concomitant bupropion (e.g., Wellbutrin) therapy • Current or prior diagnosis of bulimia or anorexia nervosa • Simultaneous abrupt discontinuation of alcohol or sedatives/ benzodiazepines • MAO inhibitors during preceding 14 days; concurrent use of reversible MAO inhibitors 	<ul style="list-style-type: none"> • Severe renal impairment (dosage adjustment is necessary) • Pregnancy^d (category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms^e: Boxed warning removed December 2016

Table 6.2 Continued

	NRT formulations						
	Gum	Lozenge	Transdermal patch	Nasal spray	Oral inhaler	Bupropion SR	Varenicline
Dosing	<ul style="list-style-type: none"> • 1st cigarette ≤30 minutes after waking: 4 mg • 1st cigarette >30 minutes after waking: 2 mg • Weeks 1–6: 1 piece every 1–2 hours • Weeks 7–9: 1 piece every 2–4 hours • Weeks 10–12: 1 piece every 4–8 hours • Maximum 24 pieces/day • Chew each piece slowly • Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) • Resume chewing when tingle fades • Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min) • Park in different areas of mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks 	<ul style="list-style-type: none"> • 1st cigarette ≤30 minutes after waking: 4 mg • 1st cigarette >30 minutes after waking: 2 mg • Weeks 1–6: 1 lozenge every 1–2 hours • Weeks 7–9: 1 lozenge every 2–4 hours • Weeks 10–12: 1 lozenge every 4–8 hours • Maximum 20 lozenges/day • Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini) • Nicotine release may cause a warm, tingling sensation • Do not chew or swallow • Occasionally rotate to different areas of the mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks 	<ul style="list-style-type: none"> • >10 cigarettes/day: <ul style="list-style-type: none"> – 21 mg/day for 4–6 weeks – 14 mg/day for 2 weeks – 7 mg/day for 2 weeks • ≤10 cigarettes/day: <ul style="list-style-type: none"> – 14 mg/day for 6 weeks – 7 mg/day for 2 weeks • Rotate patch application site daily; do not apply a new patch to the same skin site for at least 1 week • May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) • Duration: 8–10 weeks 	<ul style="list-style-type: none"> • 1–2 doses/hour (8–40 doses/day) • One dose = 2 sprays (1 in each nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa • Maximum: 5 doses/hour or 40 doses/day • For best results, initially use at least 8 doses/day • Do not sniff, swallow, or inhale through the nose as the spray is being administered • Duration: 3–6 months 	<ul style="list-style-type: none"> • 6–16 cartridges/day • Individualize dosing; initially use 1 cartridge every 1–2 hours • Best effects with continuous puffing for 20 minutes • Initially use at least 6 cartridges/day • Nicotine in cartridge is depleted after 20 minutes of active puffing • Inhale into back of throat or puff in short breaths • Do NOT inhale into the lungs (like a cigarette) but “puff” as if lighting a pipe • Open cartridge retains potency for 24 hours • No food or beverages 15 minutes before or during use • Duration: 3–6 months 	<ul style="list-style-type: none"> • 150 mg po every morning for 3 days, then 150 mg po bid • Do not exceed 300 mg/day • Begin therapy 1–2 weeks prior to quit date • Allow at least 8 hours between doses • Avoid bedtime dosing to minimize insomnia • Dose tapering is not necessary • Duration: 7–12 weeks, with maintenance up to 6 months in selected patients 	<ul style="list-style-type: none"> • Days 1–3: 0.5 mg po every morning • Days 4–7: 0.5 mg po bid • Weeks 2–12: 1 mg po bid • Begin therapy 1 week prior to quit date • Take dose after eating and with a full glass of water • Dose tapering is not necessary • Dosing adjustment is necessary for patients with severe renal impairment • Duration: 12 weeks; an additional 12-week course may be used in selected patients • May initiate up to 35 days before target quit date • May reduce smoking over a 12-week period of treatment prior to quitting and continue treatment for an additional 12 weeks

Table 6.2 Continued

	NRT formulations						
	Gum	Lozenge	Transdermal patch	Nasal spray	Oral inhaler	Bupropion SR	Varenicline
Adverse effects	<ul style="list-style-type: none"> • Mouth/jaw soreness • Hiccups • Dyspepsia • Hypersalivation • Effects associated with incorrect chewing technique: <ul style="list-style-type: none"> – Lightheadedness – Nausea/vomiting – Throat and mouth irritation 	<ul style="list-style-type: none"> • Nausea • Hiccups • Cough • Heartburn • Headache • Flatulence • Insomnia 	<ul style="list-style-type: none"> • Local skin reactions (erythema, pruritus, burning) • Headache • Sleep disturbances (insomnia, abnormal/vivid dreams); associated with nocturnal nicotine absorption 	<ul style="list-style-type: none"> • Nasal and/or throat irritation (hot, peppery, or burning sensation) • Rhinitis • Tearing • Sneezing • Cough • Headache 	<ul style="list-style-type: none"> • Mouth and/or throat irritation • Cough • Headache • Rhinitis • Dyspepsia • Hiccups 	<ul style="list-style-type: none"> • Insomnia • Dry mouth • Nervousness/difficulty concentrating • Nausea • Dizziness • Constipation • Rash • Seizures (risk is 0.1%) • Neuropsychiatric symptoms (rare; see PRECAUTIONS) 	<ul style="list-style-type: none"> • Nausea • Sleep disturbances (insomnia, abnormal/vivid dreams) • Constipation • Flatulence • Vomiting • Neuropsychiatric symptoms (rare; see PRECAUTIONS)
Advantages	<ul style="list-style-type: none"> • Might serve as an oral substitute for tobacco • Might delay weight gain • Can be titrated to manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges 	<ul style="list-style-type: none"> • Might serve as an oral substitute for tobacco • Might delay weight gain • Can be titrated to manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges 	<ul style="list-style-type: none"> • Once-daily dosing associated with fewer adherence problems • Of all NRT products, its use is least obvious to others • Can be used in combination with other agents; delivers consistent nicotine levels over 24 hours 	<ul style="list-style-type: none"> • Can be titrated to rapidly manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges 	<ul style="list-style-type: none"> • Might serve as an oral substitute for tobacco • Can be titrated to manage withdrawal symptoms • Mimics hand-to-mouth ritual of smoking • Can be used in combination with other agents to manage situational urges 	<ul style="list-style-type: none"> • Twice-daily oral dosing is simple and associated with fewer adherence problems • Might delay weight gain • Might be beneficial in patients with depression • Can be used in combination with NRT agents 	<ul style="list-style-type: none"> • Twice-daily oral dosing is simple and associated with fewer adherence problems • Offers a different mechanism of action for patients who have failed other agents

Table 6.2 Continued

	NRT formulations					Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal patch	Nasal spray	Oral inhaler		
Disadvantages	<ul style="list-style-type: none"> • Need for frequent dosing can compromise adherence • Might be problematic for patients with significant dental work • Proper chewing technique is necessary for effectiveness and to minimize adverse effects • Gum chewing might not be acceptable or desirable for some patients 	<ul style="list-style-type: none"> • Need for frequent dosing can compromise adherence • Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome 	<ul style="list-style-type: none"> • When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms • Not recommended for use by patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis) 	<ul style="list-style-type: none"> • Need for frequent dosing can compromise adherence • Nasal administration might not be acceptable or desirable for some patients; nasal irritation often problematic • Not recommended for use by patients with chronic nasal disorders or severe reactive airway disease 	<ul style="list-style-type: none"> • Need for frequent dosing can compromise adherence • Cartridges might be less effective in cold environments ($\leq 60^{\circ}\text{F}$) 	<ul style="list-style-type: none"> • Seizure risk is increased • Several contraindications and precautions preclude use in some patients (see PRECAUTIONS) • Patients should be monitored for potential neuropsychiatric symptomse (see PRECAUTIONS) 	<ul style="list-style-type: none"> • Should be taken with food or a full glass of water to reduce the incidence of nausea • Patients should be monitored for potential neuropsychiatric symptomse (see PRECAUTIONS)
Cost/day ^f	2 mg or 4 mg: \$1.90–\$3.70 (9 pieces)	2 mg or 4 mg: \$3.36–\$3.78 (9 pieces)	\$1.52–\$3.48 (1 patch)	\$6.67 (8 doses)	\$11.35 (6 cartridges)	\$2.58–\$7.87 (2 tablets)	\$11.86 (2 tablets)

Source: Reproduced with permission from Rx for Change: Clinician-Assisted Tobacco Cessation program. The Regents of the University of California. Copyright © 1999–2017.

Notes: For complete prescribing information and a comprehensive listing of warnings and precautions, please refer to the manufacturers' package inserts. **bid** = twice a day; **FDA** = U.S. Food and Drug Administration; **MAO** = monoamine oxidase; **mg** = milligram; **ml** = milliliter; **NRT** = nicotine replacement therapy; **OTC** = over the counter (nonprescription product); **po** = by mouth; **Rx** = prescription product; **SR** = sustained release.

^aMarketed by GlaxoSmithKline.

^bMarketed by Nicovum USA (a subsidiary of Reynolds American, Inc.).

^cMarketed by Pfizer.

^dThe *Clinical Practice Guideline* (Fiore et al. 2008) states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

^eIn July 2009, FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a healthcare provider immediately if they experience agitation, depressed mood, or any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve. Based on results of a mandated clinical trial, FDA removed this boxed warning in December 2016.

^fWholesale acquisition cost from Red Book Online. Thomson Reuters, December 2016.

are available by prescription only (FDA 2017). The use of FDA-approved cessation medications generally doubles quit rates relative to placebo, but results vary somewhat across products (ORs range from 1.82 for bupropion and 1.84 for NRTs to 2.88 for varenicline) (Cahill et al. 2013). Certain combinations of NRTs have been shown to further increase quit rates, including using the transdermal patch with any of the other forms of NRT (nicotine gum, lozenges, nasal spray, or inhalers).

The seven cessation medications vary in their mechanisms of action and modes of delivery. Each of the seven FDA-approved, first-line cessation medications is described below. In addition to a review of these medications and combination pharmacotherapy, this section also reviews evidence around longer term and pre-quit use of NRT.

Nicotine Replacement Therapy

NRT delivers nicotine to address physical nicotine dependence without exposing the person who is trying to quit to the toxic constituents generated by combustion or other additives. NRT delivers plasma nicotine concentrations that are lower than those in conventional cigarettes and that rise more slowly, thereby reducing the behaviorally reinforcing effect of smoking. Five forms of NRT are available in the United States: the transdermal nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, and nicotine inhaler; the latter two products are available only by prescription (Table 6.2).

The five forms of NRT are similar in efficacy. Lindson and colleagues (2019) observed similar quit rates among persons who used a fast-acting form of NRT, such as gum or lozenge. Similarly, a meta-analysis of 117 clinical trials found that the RR for 6 or more months of abstinence for any form of NRT versus controls was 1.60 (95% CI, 1.53–1.68), with an RR of 1.49 (95% CI, 1.40–1.60) for nicotine gum, 1.64 (95% CI, 1.52–1.78) for the nicotine patch, 1.95 (95% CI, 1.61–2.36) for nicotine lozenges, 2.48 (95% CI, 1.24–4.94) for the nasal spray, and 1.90 (95% CI, 1.36–2.67) for the inhaler (Stead et al. 2012). An older randomized study found that medication adherence was lowest for the nasal spray and inhaler, moderate for the gum, and greatest for the patch; the study did not include the lozenge (Hajek et al. 1999).

NRT is sold in different dosages (Table 6.2). Some healthcare providers recommend higher dosages of NRT or combinations of two forms of NRT for more dependent smokers, with dependence being defined by the number of cigarettes smoked per day or the time to first cigarette after awakening (Shiffman et al. 2013). Lindson and colleagues (2019) found that, compared with a 2-milligram (mg) dose of nicotine gum, using a 4-mg dose increases smokers'

chances of successfully stopping smoking. The review also found that higher dose nicotine patches appeared to be associated with higher rates of abstinence than lower dose patches, but this finding was less certain due to the quality of the evidence. Nicotine patches, which are applied in the morning, deliver nicotine slowly over 16–24 hours to achieve a continuous level of nicotine in the blood (Wadgave and Nagesh 2016). Several nicotine patches are marketed, some of which have tapering dosages (i.e., gradually lowering the dosage over time). The 24-hour patch can be removed at bedtime if it causes side effects, such as insomnia or bothersome dreams. Oral NRT formulations include the nicotine gum, lozenge, and inhaler (Table 6.2). The nicotine inhaler is a cigarette-like plastic device that delivers nicotine to the throat and upper airway. Nicotine in gum and lozenges is primarily absorbed in oral mucosa, with a rapid absorption of the nicotine when used properly (Wadgave and Nagesh 2016). However, these oral medications are “short acting” and result in relatively low levels of nicotine in the blood, initially requiring use every 1–2 hours to suppress withdrawal symptoms.

The nicotine nasal spray is administered with one spray per nostril; each spray contains 0.5 mg of nicotine (Wadgave and Nagesh 2016). The medication can be used every 20–60 minutes, with a maximum of 5 doses per hour or 40 doses per day. Dosage is based on the number of cigarettes smoked per day before starting the medication (Pfizer 2010). Of all NRT products, the nasal spray delivers nicotine most rapidly, but inhaling cigarette smoke still delivers nicotine faster (Wadgave and Nagesh 2016). During initial treatment, irritation of the nose commonly produces burning, sneezing, and watery eyes; users generally develop tolerance to these effects in 1–2 days (Pfizer 2010). Other side effects are minor and may include cough or headache (Table 6.2); however, NRT use, including long-term use, has been generally found to be safe for most adults (Fiore et al. 2008). Some users may opt to start the nasal spray a few days before their quit date to work through the initial nasal irritation (Wadgave and Nagesh 2016).

Persons with higher levels of nicotine dependence are at increased risk for difficulty quitting, abstinence distress, and relapse (Piper et al. 2008). NRT has been shown to be particularly effective in highly nicotine-dependent smokers (e.g., Stead et al. 2012) relative to smokers with lower levels of nicotine dependence and in trials of smoking cessation pharmacotherapy in which the majority of participants are at least moderately dependent on nicotine. The evidence regarding the efficacy and effectiveness of smoking cessation pharmacotherapies focuses mostly on highly dependent daily smokers (e.g., Stead et al. 2012). Lindson and colleagues (2019) note that there is little evidence on the role of NRT for persons smoking fewer than 15 cigarettes a day. Evidence supports the efficacy

of tailoring the dose of NRT to markers of dependence (e.g., time to first cigarette after waking) (e.g., Baker et al. 2007), given that more highly nicotine-dependent smokers benefit more from higher doses of NRT than less nicotine-dependent smokers (e.g., Stead et al. 2012).

Bupropion

Bupropion is a prescription medication that blocks reuptake of dopamine and, to a lesser extent, norepinephrine. It also has some nicotine receptor-blocking activity (Slemmer et al. 2000). Thus, bupropion increases levels of dopamine and norepinephrine in the brain, simulating nicotine's effects on these neurotransmitters. In studies with rats, bupropion in low doses was found to block nicotine's rewarding effects, as assessed by the intracranial self-stimulation threshold, and to reverse the negative affective actions of nicotine withdrawal (Cryan et al. 2003). For humans, bupropion's blocking of nicotine receptors could contribute to lessened reinforcement from cigarettes in the event of a lapse or relapse during a quit attempt (Prochaska and Benowitz 2016). Bupropion was originally marketed and is still widely used as an antidepressant. However, the sustained-release formulation of bupropion was found to help smokers quit independent of whether smokers had a history of depression (Hurt et al. 1997). Bupropion is initiated 1 week before the scheduled quit date to allow time for the smoker to reach steady state therapeutic levels (Corelli and Hudmon 2002). In the sustained release formulation, bupropion is started at 150 mg/day. If the initial dose is adequately tolerated, it is increased on day 4 to 300 mg/day (the recommended maximum daily dose), given as two 150-mg doses taken at least 8 hours apart. If the 300-mg dose is not well tolerated, the dose is reduced to 150 mg/day, which is still efficacious (Swan et al. 2003).

In a meta-analysis of 65 RCTs of bupropion for smoking cessation, Hughes and colleagues (2014) concluded that bupropion alone significantly increased long-term cessation of 6 months or greater (RR = 1.62; 95% CI, 1.49–1.76) relative to placebo; this level of efficacy was comparable to NRT (RR = 0.96; 95% CI, 0.85–1.09) and lower than varenicline (RR = 0.68; 95% CI, 0.56–0.83). In an RCT conducted in 2001, participants who had quit successfully by week 7 of the trial were randomized to receive bupropion or placebo for 1 year to prevent relapse (Hays et al. 2001). Bupropion was found to be safe and effective and significantly better than placebo at delaying relapse (median time to relapse 156 days vs. 65 days, $p = 0.021$). Bupropion also resulted in less weight gain among participants. However, 1 year after treatment, quit rates did not differ between the bupropion and placebo groups (41.6% vs. 40.0%) (Hays et al. 2001).

FDA continues to evaluate the safety and effectiveness of cessation medications after they enter the marketplace. Following the introduction of bupropion, the agency received and assessed case reports of serious changes in mood and behaviors in patients taking bupropion. As a result, in 2009 the agency required new boxed warnings for bupropion's product labeling (FDA 2018a). At the time, FDA also required the manufacturer to conduct a large clinical trial to evaluate the side effects. Based on FDA review of the findings from that clinical trial (Anthenelli et al. 2016), which is discussed further in the section on varenicline, the agency determined the risk of serious side effects on mood, behavior, or thinking was lower than previously suspected and determined the product labeling should be revised accordingly. FDA noted that while these mental health side effects were present, especially in those with current or mental illness, they were rare (Anthenelli et al. 2016). Additionally, side effects were rarely serious enough to result in hospitalization, and the occurrence of side effects was no greater for persons randomized to bupropion compared with those randomized to nicotine patch or placebo.

Varenicline

Varenicline is a prescription medicine marketed specifically for smoking cessation. The drug is a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype, which mediates dopamine release and is thought to be the major receptor involved in nicotine addiction. Varenicline activates the $\alpha 4\beta 2$ nicotinic cholinergic receptor, with a maximal effect about 50% that of nicotine, relieving the symptoms of nicotine withdrawal, including craving, and at the same time blocking the effects of nicotine on the receptor, thereby diminishing the rewarding effects of cigarettes (Aubin et al. 2014). Thus, the desire to smoke and, in the event of a lapse or relapse, the likelihood of continued smoking are reduced. As with bupropion, varenicline is initiated 1 week before the quit date (Pfizer 2018). The dose of varenicline starts at 0.5 mg/day and then increases on day 4 to 0.5 mg twice per day and on day 7 to 1 mg twice per day (the recommended maximum daily dose). This dosing regimen allows for gradual titration of the dose to minimize treatment-related nausea and insomnia (Pfizer 2018). The dosage can be lowered temporarily or permanently for patients experiencing intolerable, treatment-associated adverse effects (Pfizer 2018). Notably, smokers taking varenicline often reduce their smoking even before their target quit day (Ashare et al. 2012; Ebbert et al. 2015; Nakamura et al. 2017).

The largest clinical trial to date of approved tobacco cessation medications, the Evaluating Adverse Events

in a Global Smoking Cessation Study (EAGLES), which was primarily conducted to examine adverse effects, found that (a) varenicline was more effective for quitting smoking than placebo, the nicotine patch, or bupropion and (b) bupropion and the nicotine patch were more effective than placebo and were comparable to each other in efficacy (Anthenelli et al. 2016). This triple-blinded randomized trial enrolled 8,144 daily smokers, about half of whom had a stably treated but active psychotic disorder or a history of a psychiatric disorder. In the nonpsychiatric cohort, continuous abstinence rates (for weeks 9–24) at the 6-month follow-up were 25.5% for varenicline, 18.8% for bupropion, 18.5% for nicotine patch, and 10.5% for placebo. In the psychiatric cohort, continuous abstinence rates at the 6-month follow-up were 18.3% for varenicline, 13.7% for bupropion, 13.0% for nicotine patch, and 8.3% for placebo (Anthenelli et al. 2016).

Taking varenicline for 6 months has been shown to be effective in preventing relapse, including among smokers with schizophrenia (Evins et al. 2014). Varenicline is FDA-approved for extended (up to 6 months) treatment (Tonstad et al. 2006). Common side effects include nausea, vomiting, and insomnia (Cahill et al. 2013). Neuropsychiatric side effects—including depression, psychosis, aggression, and suicidality—have been reported to FDA, and the agency required that boxed warning labels for both varenicline and bupropion note those possible side effects (FDA 2018a). In the EAGLES trial, the primary endpoint was neuropsychiatric safety; the frequency of moderate to severe neuropsychiatric events was less than 3% in the nonpsychiatric cohort and less than 7% in the psychiatric cohort, with no significant difference by medication condition (Anthenelli et al. 2016). Notably, the findings in EAGLES were generally consistent with prior clinical trials and observational data. In previous clinical trials of varenicline conducted among smokers with depression and schizophrenia, neuropsychiatric side effects had not been observed at higher levels relative to those observed in control groups (Williams et al. 2012; Anthenelli et al. 2013; Cinciripini et al. 2013); this was also the case in large clinical cohort studies (Thomas et al. 2013; Kotz et al. 2015). Importantly, smoking itself has been found to be associated with mood disturbance, including suicidality (Oquendo et al. 2004; Li et al. 2012). Nicotine withdrawal experienced during quitting attempts is also characterized by disturbances in mood—including agitation, depressive symptoms, and anxiety—and can cause sleep disturbance with associated mood effects (Prochaska and Benowitz 2019).

With regard to the cardiovascular safety of varenicline, an initial meta-analysis raised concerns, showing a small but significant RR for serious adverse cardiovascular events compared with placebo (Singh et al. 2011). However, a second, larger meta-analysis found the absolute

risk to be small and statistically nonsignificant (Prochaska and Hilton 2012). In addition, a 52-week RCT that examined cardiovascular safety in the EAGLES cohort found no significant difference relative to placebo for varenicline, bupropion, or nicotine patch on the time to occurrence of a major adverse cardiovascular event (Benowitz et al. 2018). The three time points of interest were during the medication treatment period, 30 days post-medication use, and at 52 weeks (which marked the end of the study). At all three time points, the hazard ratio for major cardiovascular events associated with varenicline was less than 0.50, which was statistically nonsignificant and suggests a reduced risk compared with placebo (Benowitz et al. 2018). A biological mechanism by which varenicline could produce cardiovascular toxicity has not been identified.

Additional Approaches to Medication Therapy

The seven FDA-approved cessation medications have been evaluated in multiple research protocols, with many of the study variations aimed at improving our understanding of the reach and short- and long-term efficacy of treatment under conditions other than the labeled FDA-approved use. These approaches have included combination pharmacotherapy (i.e., using more than one form of medication at a time), pre-loading (starting the medication before the quit date), gradual reduction (using medication as part of an attempt to gradually reduce consumption of tobacco products as a prelude to quitting, instead of quitting abruptly), extended treatment (longer use of the medication aimed at preventing relapse), and precision medicine (tailoring the medication to differences in drug metabolism). The following sections discuss each of these approaches in detail.

Combination Pharmacotherapy

Combination pharmacotherapy combines the use of cessation drugs that have different mechanisms and/or different pharmacokinetic profiles. Dual regimens of NRT have generally demonstrated superior efficacy compared with a single form of NRT (Ebbert et al. 2010; Tulloch et al. 2016; Windle et al. 2016). Dual NRT regimens combine the use of a transdermal patch, which acts slow and provides a base level of nicotine, with any of the other forms of NRT (nicotine gum, lozenges, nasal spray, or inhalers)—all of which act faster and can be used to offset acute episodes of craving or other relapse triggers. Based on evidence in their review of 11,356 participants across 14 studies, Lindson and colleagues (2019) concluded that combining fast-acting forms of NRT with the nicotine patch results in

long-term quit rates that are higher than those observed among persons who use a single form of NRT (RR = 1.25; 95% CI, 1.15–1.36). Similarly, in a meta-analysis of nine trials, combining the nicotine patch with nicotine gum, lozenges, inhalers, or nasal spray was shown to be more effective than using individual NRT products (RR = 1.34; 95% CI, 1.18–1.51) (Stead et al. 2012). A different meta-analysis found that combination NRT had an effect comparable to that of varenicline (OR = 1.06; 95% CI, 0.75–1.48) (Cahill et al. 2013).

Emerging evidence also suggests that combining varenicline with bupropion or NRT may be more effective than taking varenicline alone, particularly among heavier smokers (Koegelenberg et al. 2014; Chang et al. 2015). Two trials examined the combined use of varenicline and the nicotine patch. One trial (N = 435) compared the nicotine patch with a placebo patch, both administered 2 weeks before the target quit date, followed by the addition of varenicline for 1 week before the target quit date; the nicotine patch and varenicline were continued for 12 additional weeks. Use of the nicotine patch plus varenicline resulted in significantly greater quit rates than use of the placebo patch plus varenicline at 12 weeks (55.4% vs. 40.9%, $p = 0.007$) and 24 weeks (49% vs. 36.2%, $p = 0.004$) (Koegelenberg et al. 2014). The other trial, which was smaller and likely underpowered (N = 117), tested varenicline alone 1 week before the target quit date and then with the nicotine patch added at the quit date. The trial found statistically nonsignificant differences at 12 weeks (38% vs. 29% quit, $p = 0.14$) (Hajek et al. 2013b). The mechanism of benefit from combining varenicline and NRT is unclear: varenicline may not fully block $\alpha 4\beta 2$ receptors or, compared with varenicline alone, the nicotine from NRT may affect additional nicotinic receptors that contribute to the addictive effects of nicotine. The combination was well tolerated by users in both studies, with vivid dreams being the most common side effect (Hajek et al. 2013b; Koegelenberg et al. 2014).

In addition, combination therapy with bupropion and NRT has been shown to produce better outcomes than either medication used by itself (Ebbert et al. 2010). In a meta-analysis of eight trials, use of bupropion plus the nicotine patch was more effective than use of bupropion alone (RR = 1.24; 95% CI, 1.06–1.45) (Stead et al. 2012), but a different meta-analysis that reviewed 12 studies in which bupropion was added to NRT reported insufficient evidence of long-term benefit (at least 6 months) over NRT alone (RR = 1.19; 95% CI, 0.94–1.51) (Hughes et al. 2014). One randomized trial compared the use of bupropion plus varenicline versus the use of varenicline alone for 12 weeks (Ebbert et al. 2014); the combination significantly increased continuous abstinence through 12 weeks (53.0% vs. 43.2%) and through 26 weeks (36.6% vs. 27.6%)

but not through 52 weeks (30.9% vs. 24.5%). In a different randomized trial, use of bupropion plus varenicline was associated with greater depressive symptoms over the first 2 weeks, but no differences in depressive symptoms were observed by week 4 (Hong et al. 2015).

Pre-Loading Medication

Pre-loading with NRT, or providing NRT in advance of a quit attempt, has been tested to see whether it increases abstinence rates. The underlying mechanism would be to saturate and/or desensitize nicotinic cholinergic receptors to decrease the reward from nicotine delivered by smoking. Lindson and colleagues (2019) found with a moderate level of certainty that using NRT before quitting, instead of using it from the quit date, may improve quit rates, but noted that more research is needed to confirm this finding. In a meta-analysis of four studies, pre-loading with the nicotine patch doubled the odds of quitting at 6 weeks (OR = 1.96; 95% CI, 1.31–2.93) and at 6 months (OR = 2.17; 95% CI, 1.46–3.22) (Shiffman and Ferguson 2008). In contrast, a large pragmatic randomized trial in New Zealand in which smokers called a quit-line found no boost in abstinence rates when NRT was pre-loaded, but such pre-loading was determined to be safe, acceptable, and easy to implement (Bullen et al. 2010). A meta-analysis of eight trials by Stead and colleagues (2012) found a moderate but statistically nonsignificant effect of pre-loading NRT on abstinence, but effects were significant when restricted to the six trials that tested pre-loading with a nicotine patch. These findings suggest that pre-loading in advance of a quit attempt, especially with the nicotine patch, can increase abstinence rates.

Gradual Reduction

Gradually reducing the number of cigarettes smoked per day leading up to a quit attempt, rather than quitting all at once, may be preferred by smokers who are unwilling to quit abruptly (Prochaska and Benowitz 2016). Nationally representative data from the 2010–2011 Tobacco Use Supplement to the Current Population Survey suggest that more than 40% of adult smokers in the United States who had tried to quit smoking in the past year reported gradually cutting down on their cigarette use as a cessation strategy (Schauer et al. 2015b). A meta-analysis of 10 trials evaluating gradual smoking reduction relative to quitting abruptly found comparable efficacy, with no difference by treatment approach (e.g., self-help, behavioral, pharmacologic) (Lindson-Hawley et al. 2012).

In a different placebo-controlled randomized trial of varenicline, Ebbert and colleagues (2015) studied smokers who were unwilling to quit in the next month but who were willing to reduce smoking immediately and to make a quit

attempt within 3 months. Participants received medication or placebo for 12 weeks before the quit attempt and were advised to reduce the number of cigarettes they smoked daily by 50% at 4 weeks, by 75% or more at 8 weeks, and then to quit completely at 12 weeks. Varenicline or placebo was continued for an additional 12 weeks after the quit date. Quit rates increased approximately threefold in the varenicline versus placebo-treated group from week 21 to 24 (37.8% vs. 12.5%) and from week 21 to 52 (27.0% vs. 9.9%). Pretreatment with varenicline may reduce craving for cigarettes and extinguish the rewarding effects of cigarettes, thus making it easier to quit. Importantly, gradual reduction of cigarette consumption should be used only as an interim strategy on the path to completely quitting smoking, since in the absence of quitting, reduction of cigarette consumption alone does not substantially reduce health risks (Stead and Lancaster 2007; USDHHS 2014, 2016; Lindson-Hawley et al. 2016).

Extended Treatment

Currently, NRT package inserts indicate that these products should be used for up to 8–12 weeks, depending on the type of product. However, studies have explored using cessation medications for much longer periods (up to 1 year) in an attempt to prevent relapse (Prochaska and Benowitz 2016). Similar to chronic disease management approaches, this approach underscores the idea that smoking is a chronic, relapsing disease that warrants ongoing treatment.

The literature is insufficient, however, to determine whether extended NRT is more efficacious than standard-duration NRT (Carpenter et al. 2013). For example, an RCT with older smokers found that extended cessation treatment—consisting of NRT gum and bupropion for 12 weeks combined with counseling (group and then individual) extending to 1 year—resulted in abstinence rates exceeding 50% at the 2-year follow-up (Hall et al. 2009). Notably, the study showed that extending NRT to 52 weeks (with no bupropion) did not increase abstinence beyond what was achieved with 12 weeks of NRT gum combined with bupropion. A trial that assessed point-prevalence abstinence in smokers randomized to receive 12 weeks of behavioral counseling plus 8, 24, or 52 weeks of nicotine patches found that, after 24 weeks of treatment, 21.7% of participants in the 8-week arm were abstinent compared with 27.2% ($p = 0.17$) in the 24- and 52-week arms (Schnoll et al. 2015). Participants in the 52-week arm did not report greater abstinence rates than those in the 24-week arm (20.3% vs. 23.8%, $p = 0.57$), suggesting that using NRT beyond 24 weeks may not confer added benefit.

In contrast, varenicline dosed over 6 months has been shown to be effective in preventing relapse (Tonstad et al. 2006; Evins et al. 2014). Currently, FDA labeling

recommends 12 weeks of therapy, but treatment can be extended another 12 weeks if needed. However, patients are encouraged to stop sooner if they feel ready. Livingstone-Banks and colleagues (2019) found that with a moderate level of certainty, because of unexplained statistical heterogeneity, extended treatment with varenicline helped to prevent relapse. In an RCT, Joseph and colleagues (2011) tested a chronic care model for smoking cessation. Participants in the extended care arm received counseling by telephone and NRT for 1 year, and participants in the usual care arm received counseling and NRT for 8 weeks. At 18 months, the proportion of subjects who were abstinent for 6 months or longer did not differ significantly by condition: 30% for extended treatment and 24% ($p = 0.13$) for usual care. Finally, in a meta-analysis of extended interventions for preventing relapse, Hajek and colleagues (2013c) reported insufficient evidence to support either extended cessation counseling or extended pharmacotherapies (NRT, varenicline, or bupropion). More research is warranted to continue to assess extended behavioral and/or pharmacological treatments for smoking cessation.

Precision Medicine

Precision medicine is an emerging approach to smoking cessation treatment (Prochaska and Benowitz 2016). The goal of precision medicine is to enable clinicians to quickly, efficiently, and accurately predict the most appropriate course of action for a patient based on genetic and lifestyle factors (Aronson and Rehm 2015). Cessation medications are effective in increasing abstinence, but with long-term quit rates rarely surpassing 30% (Perkins and Scott 2008), there is great interest in identifying differences in response to medications to inform personalized treatment, which could potentially increase quit rates. Smokers differ from each other in many ways. One is the rate at which they metabolize nicotine, which has been studied as a possible basis for selecting medications (Prochaska and Benowitz 2016). On average, a person who metabolizes nicotine rapidly smokes more heavily and appears to be more dependent on nicotine than a person who does not metabolize nicotine rapidly (Malaiyandi et al. 2005). CYP2A6, a liver enzyme, is the chief metabolizer of nicotine; CYP2A6 also metabolizes cotinine, the primary metabolite of nicotine, which is reduced to 3'-hydroxycotinine (USDHHS 2010).

The cotinine/3'-hydroxycotinine ratio, also termed the nicotine metabolite ratio, can be measured in urine, blood, or plasma as a biomarker for the rate at which a smoker metabolizes nicotine (USDHHS 2010). In retrospective studies, slow metabolizers received no incremental benefit from bupropion, but they responded well to the nicotine patch, while normal metabolizers responded better to bupropion than to the patch (Prochaska and

Benowitz 2016). In a clinical trial that stratified participants by slow or normal nicotine metabolite ratio and compared treatment with placebo, the nicotine patch, or varenicline (Lerman et al. 2015), slow metabolizers experienced more side effects from varenicline and evidenced no benefit in quitting when taking varenicline relative to using the nicotine patch (OR = 1.13, $p = 0.56$), but normal metabolizers had greater success with varenicline relative to the patch (OR = 2.17, $p = 0.001$). Thus, use of the nicotine metabolite ratio shows promise in aiding in treatment selection, given that the nicotine patch may be as effective as varenicline for slow metabolizers of nicotine, while costing less and exposing them to fewer side effects. However, use of the nicotine metabolite ratio in clinical practice is not yet possible because there is no widely available clinical test for this measure.

Other precision medicine approaches are under investigation, including pharmacogenomic variation and variance in both behavioral and pharmacologic responses between men and women and among persons with certain mental health conditions. For example, pharmacogenomic evidence suggests that variants in gene regions that impact dopaminergic neurotransmission, nicotine receptor expression, and nicotine and other drug metabolism may predict response to various cessation pharmacotherapies (Chenoweth and Tyndale 2017). Some evidence suggests that (a) the superior efficacy of varenicline relative to bupropion and NRT may be greater among women than among men and (b) certain mental health conditions may also alter responses to behavioral and pharmacological treatments (Luo et al. 2015; McKee et al. 2016; Piper et al. 2017; Smith et al. 2017).

Real-World Effectiveness of Cessation Medications

In RCTs, the provision of cessation medications has consistently increased successful quitting, particularly among heavy cigarette smokers. Several studies have reported similar findings in real-world settings (West and Zhou 2007; Kasza et al. 2013). For example, the International Tobacco Control Four Country Survey found increased 6-month continuous abstinence from smoking among smokers who reported using varenicline, bupropion, and the nicotine patch but not among those who reported using oral NRTs (Kasza et al. 2013). However, some population-based studies have found that smokers who used NRT (Pierce and Gilpin 2002), and in some cases bupropion and varenicline (Leas et al. 2018), reported similar or lower rates of quit success compared with those not using these medications. These studies have raised questions about the real-world effectiveness of these medications, and reviews

have highlighted conflicting results in the scientific literature (Hughes et al. 2011; Pierce et al. 2012).

Leas and colleagues (2018), using nationally representative data from the 2002–2003 and 2010–2011 waves of the Tobacco Use Supplement to the Current Population Survey, assessed the effectiveness of cessation medications among adults who smoked at baseline and attempted to quit prior to 1 year of follow-up. The study's authors used propensity score matching to control for 12 potential confounders, including smoking intensity, nicotine dependence, previous quit history, and self-efficacy to quit. The study did not find evidence that the use of varenicline, bupropion, or NRT increases the likelihood of smokers being quit for 30 or more days at 1-year follow-up. Similarly, a study by Kotz and colleagues (2014) conducted in the United Kingdom using cross-sectional data from aggregated monthly waves of the Smoking Toolkit Study, a household survey, found that smokers who purchased NRT over the counter with no behavioral support had similar odds of quitting as smokers who tried to quit with no quitting aids.

Several other studies have also found no effects of NRT on cessation. For example, a randomized study conducted in New Zealand among 1,410 adult smokers who called the national quitline, found that subjects who were randomized to receive a free 1-week supply of their choice of NRT, followed by a voucher for a free 8-week supply of that product, did not have higher rates of abstinence at 7 days or 6 months compared with those receiving usual care from the quitline (Walker et al. 2011). Similarly, a prospective cohort study of a probability sample of 787 adult smokers from Massachusetts who had quit smoking found that those who quit using NRT were just as likely to relapse over the following year as were those who had quit without using medications (Alpert et al. 2013). Finally, in a parallel group, factorial design RCT of 2,591 smokers 16 years of age and older in England, Ferguson and colleagues (2012) found, contrary to findings from multiple U.S. randomized trials in quitline settings (An et al. 2006; Hollis et al. 2007; Smith et al. 2013), that adding NRT to proactive counseling offered through a quitline had no additional effect on abstinence.

Several possible explanations exist for these contradictory findings. Some of the studies that have found limited impact of the real-world effectiveness of cessation medications have specific limitations. For example, Alpert and colleagues (2013) measured whether prior use of NRT had a residual benefit of preventing relapse, which differs from assessing whether use of NRT increases cessation success. McAfee (2012) noted several potential issues that could have impacted the findings of Ferguson and colleagues (2012), including (a) many differences and limitations in how NRT was provided in the Ferguson

trial compared with U.S. trials that found a positive effect (e.g., medications were provided through a voucher that had to be redeemed by telephone, adding an extra step for participants) and (b) caveats for interpreting the results. For example, in a large randomized trial with methods similar to those used for the Ferguson trial, which involved more than 4,600 U.S. adults who called a quitline, overall receipt of study medications was low (43%) compared with the 90% rate at initial intake and the 80% rate of medication receipt at 5 weeks. The trial also included youth smokers (16–18 years of age), for whom NRT has not been found to be effective (Hollis et al. 2007).

More broadly, most real-world studies have been nonrandomized cohort studies that have examined the association between self-selected use of cessation medications and quitting success. Without randomization, the study design cannot exclude the potential for residual confounding, even with multivariable adjustment. Researchers have suggested that conclusions about the real-world effectiveness of cessation medications may be the result of systematic biases that affect the outcomes of cross-sectional surveys (Borland et al. 2012). For example, participants may be more likely to recall failed medication-assisted quit attempts than failed unassisted quit attempts. Furthermore, smokers who choose to use medications as part of a quit attempt may smoke more heavily and be more addicted, and therefore may be less likely to succeed, than smokers who try to quit without medications. Either of these factors could lead to an overrepresentation of failed quit attempts among smokers using medications, even if these medications actually conferred benefits (Borland et al. 2012). However, Leas and colleagues (2018) used propensity score matching on 12 potential confounders, including nicotine dependence and smoking intensity, and concluded that confounding cannot explain the lack of effectiveness of cessation medications in increasing long-term cessation in real-world settings.

Another potential factor that could contribute to the findings of studies suggesting a lack of real-world effectiveness for cessation medications is the important role that behavioral support can play in complementing medication use to maximize cessation, in part by ensuring that smokers use cessation medications appropriately and effectively (Fiore et al. 2008; USPSTF 2015). While cessation medication and counseling are each effective alone, they are more effective when combined (Fiore et al. 2008; USPSTF 2015). In particular, providing counseling or decision support to help ensure that consumers use the appropriate medication correctly at the correct dose and for a recommended duration, could increase the effectiveness of over-the-counter (nonprescription) cessation medications in the general population. This type of support is typically present in RCTs but is often absent in real-world settings,

which could explain why many therapies, including cessation medications, might perform more poorly in the real world than in clinical trials. The study by Leas and colleagues (2018) supports this hypothesis. Using data from the Tobacco Use Supplement to the Current Population Survey, they found that only 32 of 186 adult smokers who used bupropion and only 9 of 118 smokers who used varenicline as part of a quit attempt, reported receiving any form of behavioral counseling. Similarly, Kotz and colleagues (2014) found that smokers who purchased NRT over the counter with no behavioral support had similar odds of quitting as smokers who tried to quit with no quitting aids—also highlighting the important role that behavioral support can play in enhancing the effectiveness of cessation medications. Further support for this explanation includes the markedly shorter duration of use of medications in real-world settings compared with study settings, averaging 1–2 weeks rather than the recommended 8–12 weeks (Pierce and Gilpin 2002; Zhang et al. 2015).

In the absence of behavioral support, tobacco users in the general population may not receive adequate information or education about how to use cessation medications and what to expect from them (as described previously), or they may face barriers to accessing information, including such financial barriers as lack of insurance, copays, and cost-prohibitive prices (Pacek et al. 2018). Smokers may also have misconceptions about the safety of using a medication that contains nicotine (Pierce and Gilpin 2002; Zhang et al. 2015). Furthermore, many tobacco users may not be aware of changes to the labeling of over-the-counter NRT products introduced in 2013, indicating that it is safe to use NRT (a) longer than the recommended period, in consultation with a physician if necessary to avoid relapsing, and (b) concurrently with smoking (e.g., following a lapse) or with another NRT product (*Federal Register* 2013; FDA 2013). These and other misconceptions about smoking cessation medications could lead people to use them ineffectively, for example, by stopping use prematurely or by not using enough of the medication.

Some researchers who have questioned the real-world effectiveness of cessation medications have suggested that an excessive emphasis on the role of medications in helping smokers quit may overmedicalize and mystify smoking cessation. They also suggest that such an approach may discourage smokers from quitting without help (i.e., quitting “cold turkey”), which remains the predominant way that smokers try to quit—and, as a result, the predominant way that smokers succeed in quitting—in the United States (Pierce et al. 2012). In addition, some evidence suggests that direct-to-consumer advertisements for smoking cessation medications may give smokers a false sense of security, suggesting that using these medications will make quitting easy (Frosch et al. 2007).

Combination Treatment—Behavioral Therapy and Pharmacotherapy

Although behavioral therapy and pharmacotherapy are each effective interventions for increasing quit rates when used alone, combining them is more effective (Fiore et al. 2008) and represents the “gold standard” in smoking cessation treatment. Use of cessation medications is more effective when accompanied by counseling, and use of cessation counseling is more effective when accompanied by medications (Fiore et al. 2008). USPSTF (2015) recommends combining medications with multisession, intensive group or individual counseling to achieve the highest quit rates; using medication to target physical addiction; and employing behavioral therapy and counseling to target psychological and behavioral addiction. A meta-analysis by Stead and colleagues (2016) found that behavioral therapy increased the efficacy of pharmacotherapy (RR = 1.27; 95% CI, 1.02–1.58), probably in part because it allows healthcare professionals who are delivering the behavioral therapy to instruct smokers on using cessation medications properly, managing side effects from the medications, understanding and managing cravings and withdrawal symptoms, and simultaneously addressing the behavioral aspects of tobacco dependence. Similarly, in the Smoking Toolkit study from the United Kingdom, Kotz and colleagues (2014) found that, compared with smokers who used neither cessation medications nor behavioral support, those who used prescription cessation medications combined with behavioral support from specialists had 3.25 times the adjusted odds (95% CI, 2.05–5.15) of remaining abstinent up to the time of the survey; those who used prescription cessation medications combined with brief advice to quit had 1.61 times the adjusted odds (95% CI, 1.33–1.94) of remaining abstinent; and those who used NRT purchased over the counter had 0.96 times the odds (95% CI, 0.81–1.13) of remaining abstinent. The authors concluded that smokers who use a combination of behavioral support and cessation medications in their quit attempts have almost three times the odds of successfully quitting than smokers who use neither.

Notably, evidence from 40 studies with more than 15,000 participants found a significant increase in smoking abstinence at 6 months or longer compared with controls when pharmacotherapy was added to behavioral treatment (RR = 1.82; 95% CI, 1.66–2.00) (Stead and Lancaster 2012b; Stead et al. 2016). Earlier, Mottillo and colleagues (2009) conducted a meta-analysis of individual, group, and telephone counseling in clinical settings from 50 RCTs (N = 26,927) and found that medications (the nicotine patch, bupropion, or nortriptyline) combined with counseling led to higher quit rates compared with

controls. The ORs were similar for individual counseling (1.49; 95% CI, 1.08–2.07), group counseling (1.76; 95% CI, 1.11–2.93), and telephone counseling (1.58; 95% CI, 1.15–2.29). These results suggest that the highest quit rates are achieved through intensive individual or group counseling combined with pharmacotherapy.

Modified and Alternative Tobacco Products

Very-Low-Nicotine-Content Cigarettes

Experimental very-low-nicotine-content (VLNC) cigarettes (also see Chapter 7) are engineered to have reduced content of nicotine in the tobacco used in the cigarette compared with conventionally manufactured cigarettes. The smoke of VLNC cigarettes delivers lower levels of nicotine compared with cigarettes that were marketed by the tobacco industry in the past as “light” or “ultra-light,” which did not have lower levels of nicotine in the tobacco itself (Benowitz and Henningfield 2013). Instead, light and ultra-light cigarettes relied on design features, such as ventilation holes in the filter, to allow these products to be rated as low nicotine (and low tar) when subjected to machine smoking employing a standardized method. However, through compensatory behaviors, such as blocking ventilation holes with lips and/or fingers, drawing larger puffs, and inhaling more deeply, smokers were able to obtain levels of nicotine (and tar) that were as high as those delivered by conventional (regular strength) cigarettes (Benowitz and Henningfield 1994). Scientists have suggested that reducing the nicotine content of cigarettes to approximately 0.5 mg per cigarette (compared with 10–15 mg per cigarette in most currently marketed cigarettes) would render cigarettes nonaddictive. This would potentially prevent adolescents from developing nicotine addiction and make it easier for adult smokers to quit, because cigarettes would be less reinforcing (Benowitz and Henningfield 1994).

Several clinical trials have compared the effects of experimental VLNC cigarettes and conventional cigarettes on smoking and cessation behaviors. These trials suggest that VLNC cigarettes may reduce smoking, reduce nicotine dependence, increase cessation rates, and reduce exposure to toxicants (Benowitz et al. 2007, 2012; Donny et al. 2007, 2014, 2015; Donny and Jones 2009; Hatsukami et al. 2010, 2013, 2018; Dermody et al. 2018). For example, Donny and colleagues (2015) and Fiore and Baker (2015) conducted a large, multisite clinical trial that randomized 840 daily smokers to their own cigarettes or to one of six variants of study-specific cigarettes with levels of nicotine ranging from 0.4 mg of nicotine per gram of tobacco to

15.8 mg of nicotine per gram of tobacco (levels typical of commercial brands). At 6 weeks, persons assigned to cigarettes with the lowest level of nicotine content smoked fewer cigarettes per day and reported less dependence and craving than those who smoked regular strength cigarettes (i.e., 15.8 mg of nicotine per gram of tobacco). In a randomized, parallel arm, semi-blind study in which 165 smokers were randomly assigned to either 0.3 mg nicotine yield cigarettes, 0.5 mg nicotine yield cigarettes, or 4 mg nicotine lozenges, Hatsukami and colleagues (2010) found that use of 0.5 mg nicotine yield cigarettes was associated with reduced carcinogen exposure and reduced nicotine dependence and product withdrawal scores, and led to a similar rate of cessation to the nicotine lozenge.

More recently, Hatsukami and colleagues (2018) published findings from another large, multisite clinical trial that assessed the effects of immediate versus gradual reductions in the levels of nicotine content in cigarettes. The authors randomized 1,250 smokers who were not interested in quitting into three groups: those who (a) continued to smoke conventional cigarettes containing 15.5 mg of nicotine per gram of tobacco; (b) smoked cigarettes in which the level of nicotine content was gradually reduced over 6 months from 15.5 mg to 0.4 mg of nicotine per gram of tobacco; or (c) switched immediately from conventional cigarettes to cigarettes with 0.4 mg of nicotine per gram of tobacco and continued to smoke those cigarettes for 6 months. The study found that smokers who switched immediately to cigarettes with low levels of nicotine tended to show greater benefits than smokers in the other two conditions. For instance, compared with gradual reduction of nicotine, immediate reduction yielded significantly lower levels of biomarkers of exposure to toxic smoke constituents, a greater reduction in the number of cigarettes smoked per day, a greater reduction in nicotine dependence, and more days entirely free of cigarettes. Those in the immediate reduction group had significantly lower levels of breath carbon monoxide compared with those in the gradual reduction group (difference = 4.1 parts per million; 95% CI, -4.89 to -3.23; $P < .0055$) and with those in the control group (difference = 3.4 parts per million; 95% CI, -4.40 to -2.36; $P < .0055$). Significantly lower levels in the immediate versus gradual and control groups were also observed for acrolein (difference = 17% and 19%, respectively) and phenanthrene tetraol (difference = 12% and 14%, respectively). However, for carbon monoxide, acrolein, and phenanthrene tetraol, there were no significant differences between the gradual reduction and control groups. Lower dependence scores (scale ranges from 0 to 10, with higher scores associated with greater dependence) were observed in (a) the immediate reduction group versus the gradual reduction group (mean = 4.27 [low dependence] vs. 5.13 [moderate dependence]; adjusted mean

difference = -0.99 [95% CI, -1.27 to -0.71]; $p < .00057$) and (b) the immediate reduction group versus the control group (mean = 4.27 [low dependence] vs. 5.48 [moderate dependence]; adjusted mean difference = -1.44 [95% CI, -1.75 to -1.12]; $p < .00057$). No differences were found in the gradual reduction group versus the control group (mean = 5.13 [moderate dependence] vs. 5.48 [moderate dependence]; adjusted mean difference = -0.45 [95% CI, -0.76 to -0.13]; $p = .006$) (Hatsukami et al. 2018).

However, a study with longer term follow-up reported that reducing the nicotine content in cigarettes over 12 months did not result in sustained reductions in nicotine intake or increases in smoking cessation over the subsequent 12 months (Benowitz et al. 2015). Experimental cigarettes were likely less acceptable because conventional cigarettes were readily available to the participants in the study. The lack of effect of nicotine intake on smoking cessation may be the result of compensatory behaviors, including consumption of regular-nicotine-content cigarettes. Compensatory smoking (i.e., altering smoking behaviors to continue to obtain enough nicotine to satisfy addiction) has been posited as a possible countervailing effect of setting a nicotine product standard (Gottlieb and Zeller 2017). However, in its advisory report on a global nicotine reduction strategy, which summarized the literature available at that time, WHO (2015) concluded that the use of cigarettes with a nicotine content of 0.4 mg/g (or less) of cigarette tobacco filler does not significantly increase craving or withdrawal and does not result in compensatory smoking behaviors. Studies have found this to be consistent in populations highly vulnerable to nicotine addiction, including individuals with serious mental illness (Denlinger-Apte et al. 2018). However, among participants in clinical trials, levels of acceptability have been lower for experimental VLNC cigarettes than for commercially available cigarettes; and nonadherence has been prevalent, with one trial reporting greater than 70% of participants having substituted traditional cigarette brands for VLNC cigarettes (Nardone et al. 2016). Additionally, 25–45% of participants dropped out of these studies (Nardone et al. 2016; Mercincavage et al. 2017).

Combining VLNC cigarettes with nicotine patches was hypothesized to perhaps aid with the transition to VLNC cigarettes and increase compliance. However, Hatsukami and colleagues (2013) did not find that such a combination improved long-term quit rates of conventional cigarettes. Furthermore, in a two-by-two factorial RCT, Smith and colleagues (2019) found that assignment to the patch, along with VLNC cigarettes, did not significantly reduce cigarette smoking compared with assignment to VLNC cigarettes alone (Smith et al. 2019).

If, as outlined by Benowitz and Henningfield (1994, 2013) and summarized by USDHHS (2014), potential

“end-game” options to complement existing, proven tobacco control interventions include reducing the nicotine content of *all* cigarettes to make them less addictive, then problems with adherence and attrition would not be an issue, unless there was widespread contraband, and long-term cessation rates would likely be higher than observed in the trials. Because a product standard reducing the nicotine content of cigarettes has not yet been implemented, studies have not examined the impact of a product standard that would reduce the level of nicotine in all cigarettes or other tobacco products would have on cessation.

Importantly, the advisory report from WHO (2015) noted that the ultimate health benefits of a nicotine reduction strategy aimed at individual smokers would require that the standard include all combustible tobacco products. The WHO report also noted that such a strategy needs to be accompanied by the provision of cessation treatments to help people quit, including behavioral support and NRT or other medications. In a randomized trial comparing the use of experimental VLNC cigarettes with the use of cigarettes with conventional levels of nicotine over an 8-week period, Hatsukami and colleagues (2017) found that smokers in the VLNC cigarette arm (a) had consumed fewer combustible products at almost all visits compared with those in the conventional nicotine arm ($p < .02$); (b) had higher rates of abstinence (VLNC cigarette arm vs. conventional nicotine arm: RR = 9.96; 95% CI, 5.01–19.81); and (c) used significantly more alternative tobacco products, including nonstudy cigarettes, noncigarette combustible products, and noncombustible products (RR = 2.18; 95% CI, 1.94–2.46 for the VLNC cigarette arm vs. RR = 1.64; 95% CI, 1.46–1.85 for the conventional nicotine arm). As outlined by WHO (2015), for persons who switched from cigarettes to noncombustible forms of tobacco to sustain their nicotine intake, the health benefits of not smoking conventional cigarettes depended on the level of tobacco-related toxicants delivered by the noncombustible products and the patterns and duration of use of such products.

Although evidence to date is suggestive but not sufficient to infer that VLNC cigarettes could reduce smoking and nicotine dependence and increase smoking cessation, further research could help better understand the impact that a nicotine product standard could have on increasing cessation from conventional cigarettes. Several issues warrant continued consideration regarding the impacts of a nicotine product standard on cigarette cessation, including whether compensatory behaviors would occur in the given policy framework (Gottlieb and Zeller 2017), whether there would be illicit trade for products with higher nicotine yield and how to minimize such effects (Ribisl et al. 2019), and how populations that are more vulnerable to

nicotine may be impacted, including those with mental illness and substance use disorders (USDHHS 2016).

Product standards to decrease nicotine in all cigarettes will likely have a greater impact on smoking cessation if they are accompanied by a comprehensive cessation strategy that promotes available cessation treatments, including FDA-approved medications and behavioral support.

E-Cigarettes

E-cigarettes (also called electronic nicotine delivery systems [ENDS], vapes, vape pens, tanks, mods, and pod-mods) are battery-powered devices designed to convert a liquid (often called e-liquid) into an aerosol for inhalation by the user (Figure 6.1). E-liquid contains solvents (propylene glycol and vegetable glycerin) to produce the aerosol and typically contains nicotine, flavorings, and other compounds. E-cigarettes, which have been available in the United States since at least 2007 (USDHHS 2016), have been discussed as a potential harm-reduction tool for current smokers (Fagerstrom et al. 2015). For this reason, smokers, scientists, clinicians, and policymakers have an interest in understanding how e-cigarettes will impact the smoking cessation landscape.

As e-cigarettes are products designed to deliver nicotine to the body through the pulmonary route, which results in more rapid absorption and delivery of nicotine to the brain than through other modes of administration (i.e., mouth, transdermal), it is useful to consider their ability to deliver nicotine in the context of a smoker attempting to use e-cigarettes to quit cigarette smoking. The design and components of many e-cigarettes are intended to generate aerosols that can rapidly deliver boluses of nicotine to the brain, similar to nicotine delivery by conventional cigarettes (Farsalinos et al. 2016). E-cigarettes vary in their ability to deliver nicotine to the body (Vansickel and Eissenberg 2013). However, the pharmacokinetics of nicotine delivery of certain e-cigarette products, such as more recent generation e-cigarettes, resemble those of conventional cigarettes, and thus have the potential to mirror the pharmacologic effects of conventional cigarettes (National Academies of Sciences, Engineering, and Medicine 2018). Therefore, for smokers of conventional cigarettes who seek a product with a rapid onset of the dose of nicotine similar to cigarettes, e-cigarettes that deliver nicotine in a similar way to conventional cigarettes could have greater appeal than current FDA-approved NRTs. However, although rapid boluses of nicotine could increase the appeal of these products relative to NRTs, whether this pharmacokinetic profile supports an effective method of cessation has not been extensively studied (Shihadeh and Eissenberg 2015). However, when considering e-cigarettes as a potential cessation aid

Figure 6.1 The evolution of e-cigarettes, by product generation and characteristics



Source: Photos by James Gathany and Lauren Bishop, CDC.

for adult smokers, it is also important to take into account factors related to both safety and efficacy. NRT has been proven safe and effective, whereas the same has not been proven for any e-cigarette. There is no safe tobacco product. Although e-cigarette aerosol generally contains fewer toxic chemicals than conventional cigarette smoke, all tobacco products, including e-cigarettes, carry risks.

Other features of e-cigarettes that may enhance their appeal to conventional cigarette smokers are the ways in which e-cigarettes mirror some of the sensorimotor features of conventional cigarette smoking, including stimulation of the airways, the sensation and taste of e-cigarette aerosol in the mouth and lungs, the hand-to-mouth movements and puffing in which e-cigarette users engage, and the exhalation of aerosol that may visually resemble cigarette smoking. Given the potentially important role of such sensorimotor factors in the reinforcing and addictive qualities of conventional cigarettes (Chaudhri et al. 2006), these attributes could make e-cigarettes more appealing to smokers than FDA-approved NRTs. However, the sensorimotor aspects of e-cigarettes could (a) facilitate uptake for use as a cessation aid, with the goal of attaining complete nicotine abstinence, similar to how NRTs are intended to be used or (b) facilitate the use of e-cigarettes as a long-term substitute for conventional cigarettes to sustain nicotine use. The potential abuse liability of e-cigarettes that deliver nicotine in a manner comparable, or higher

than, conventional cigarettes should also be considered, including long-term dual use and decreased likelihood of cessation through maintenance of addiction. When considering the potential role of e-cigarettes used in smoking cessation, it is important to consider the intent of therapeutic FDA-approved NRT (i.e., that they are intended to act as a support for attaining complete abstinence from smoking).

Two previous Surgeon General's reports have addressed e-cigarettes. However, to date, no Surgeon General's report has reviewed the available science related to e-cigarettes and cessation. E-cigarettes were first discussed in the 2014 Surgeon General's report (USDHHS 2014), which noted that the use of e-cigarettes could have positive and negative public health impacts at the individual and population levels. Additionally, the 2016 Surgeon General's report (USDHHS 2016), *E-Cigarette Use Among Youth and Young Adults*, examined many topics related to e-cigarettes, including patterns of use and health risks of e-cigarettes among young people, as well as the importance of population-based strategies to prevent and reduce the use of e-cigarettes among this population. USDHHS (2016) underscored the need to understand any effects of e-cigarettes on adult smoking cessation, as well as the risks that the products pose to youth and young adults. This is especially important in light of alarming increases in e-cigarette use among adolescents, which threaten decades of progress in tobacco control

(USDHHS 2016; Miech et al. 2018; Gentzke et al. 2019). Additionally, e-cigarette, or vaping, product use may be associated with other health risks beyond youth initiation and use. For example, CDC, FDA, state and local health departments, and public health and clinical partners have been investigating a multistate outbreak of e-cigarette, or vaping, product use associated lung injury (EVALI) (Siegel et al. 2019). The latest national and state findings show e-cigarette, or vaping, products containing THC—particularly those from informal sources, such as friends, family, or in-person or online dealers—are linked to most of the cases of lung injury and play a major role in the outbreak (Moritz et al. 2019; Navon et al. 2019). In particular, vitamin E acetate is closely associated with EVALI (Blount et al. 2019). Vitamin E acetate has been identified in several tested products used by EVALI patients, and has been identified in bronchoalveolar lavage (BAL) fluid samples from 48 of 51 assessed EVALI patients, but not in the BAL fluid from a control group. However, as of January 2020, evidence is not yet sufficient to rule out the contribution of other chemicals of concern among some EVALI patients.

Current use of e-cigarettes among adults rose through 2014 (Adkison et al. 2013; Dockrell et al. 2013; Goniewicz et al. 2013; Agaku et al. 2014; Kasza et al. 2017), but has since declined gradually through 2017 (Wang et al. 2018). In 2017, 2.8% of adults were current users of e-cigarettes (Wang et al. 2018). More than half of current adult e-cigarette users also currently smoke cigarettes, which is commonly known as “dual use” (CDC 2016; Mirbolouk et al. 2018). Among current e-cigarette users in 2016, 15.0% were never cigarette smokers, 30.4% were former smokers, and 54.6% were current smokers (Mirbolouk et al. 2018). Data from the National Youth Tobacco Survey showed that among high school students, current (past 30-day) e-cigarette use rose from 1.5% in 2011 to 20.8% in 2018 (Cullen et al. 2018), including a 78% increase from 2017 to 2018 (USDHHS 2018a). E-cigarette use among middle school students has also risen dramatically in the same time period, with a 49% increase from 2017 to 2018 (3.3% to 4.9%) (USDHHS 2018a). Dual use is also common among youth. In 2018, approximately half of youth who used tobacco products reported using two or more products; among high school students who reported currently using two or more tobacco products, the most common combinations reported were e-cigarettes and cigarettes (14.8%) (Gentzke et al. 2019).

Since its introduction into the U.S. marketplace in 2015, the JUUL brand e-cigarette has been increasingly popular among U.S. youth (USDHHS 2018a), and increases in sales in recent years have corresponded with the previously described increases in current e-cigarette use among U.S. youth in recent years. For example, sales of JUUL increased 600% during 2016–2017, largely driven

by uptake among youth and young adults, giving it the greatest market share of any e-cigarette in the United States by the end of 2017 (King et al. 2018b). Sales have continued to increase since that time; in the assessed channels by the end of 2018, JUUL held approximately 75% of the market share of total U.S. e-cigarette sales (Truth Initiative 2018). JUUL's popularity with youth appears to stem from several factors:

- Appearance of a flash drive,
- Ease of concealment (small and does not emit as much aerosol or odor as some other types of e-cigarettes),
- Availability in a variety of flavors,
- Widespread promotion through a variety of media, including social media, and
- High nicotine content delivered in a form (e.g., nicotine salt) that may facilitate easier initiation (Cullen et al. 2018; Goniewicz et al. 2018a; Spindle and Eissenberg 2018).

E-cigarettes may appeal to adult smokers of conventional cigarettes because they mimic cigarettes in several ways: size, appearance (at least in the case of first-generation e-cigarettes), method of inhalation, production of a smoke-like aerosol, and the taste and ritual behaviors associated with smoking (Prochaska and Benowitz 2016). In terms of exposure risks, as part of a comprehensive review on the public health consequences of e-cigarette use, the National Academies of Sciences, Engineering, and Medicine (2018) concluded that for current cigarette smokers, completely substituting e-cigarettes for combustible tobacco products would reduce exposure to several toxicants and carcinogens present in tobacco cigarettes. For example, an analysis of 12 first-generation brands of e-cigarettes found that toxicants (including carcinogenic compounds) were present in the e-cigarettes' aerosol across brands at varying levels, ranging from about 9- to 450-times lower than cigarette smoke to levels in some brands that were comparable to levels in the NRT inhaler (Goniewicz et al. 2014). In a separate analysis of urine samples from 5,105 adult participants in the 2013–2014 wave of the Population Assessment of Tobacco and Health (PATH) Study, Goniewicz and colleagues (2018b) concluded that the exclusive use of e-cigarettes was associated with exposure to known tobacco-related toxicants (e.g., tobacco-specific nitrosamines, such metals as cadmium and lead, and some volatile organic compounds), but that this exposure was markedly lower than that associated with both cigarette smoking and dual use of

cigarettes and e-cigarettes. However, depending on the toxicant analyzed, dual users ($n = 792$) had similar or higher exposures to toxicants compared with users of only conventional cigarettes ($n = 2,411$). Among dual users, the frequency of cigarette use was positively correlated with exposure to both nicotine and toxicants. These findings suggest that exclusive use of e-cigarettes can result in markedly lower exposure to tobacco-related toxicants compared with exclusive use of conventional cigarettes, but that using e-cigarettes concurrently with conventional cigarettes does not meaningfully reduce exposure to potentially harmful toxicants. Of note, ingredients unique to e-cigarettes (i.e., not found in conventional cigarettes) pose potential harms (Erythropel et al. 2019). It is important to note that the findings from the PATH Study analysis pertain to e-cigarette products used in 2013–2014, and because the landscape of e-cigarette products continues to diversify and evolve rapidly, the findings may or may not be generalizable to behaviors surrounding the use of these products years later (e.g., in 2019). Moreover, the National Academies of Science Engineering and Medicine (2018) concluded that exposure to nicotine and exposure to potentially toxic substances in aerosol from e-cigarettes are highly variable and depend on product characteristics (e.g., e-liquid constituents and device characteristics and settings), how the device is operated, and user behavior.

Although the available scientific evidence indicates that e-cigarettes generally have a markedly lower number and level of harmful toxicants than conventional cigarettes, use of the products is not without potential health risks; the long-term health effects of using these products remain unknown, and short-term risks are only slowly coming into focus (National Academies of Sciences, Engineering, and Medicine 2018). However, the National Academies of Sciences, Engineering, and Medicine (2018) concluded that there is substantial evidence that e-cigarette use is associated with several adverse health outcomes that are precursors to disease, including acute endothelial cell dysfunction, formation of reactive oxygen species/oxidative stress, and increased heart rate (National Academies of Sciences, Engineering, and Medicine 2018). The report also concluded that there is substantial evidence that some chemicals present in e-cigarette aerosols are capable of causing DNA damage and mutagenesis, which supports the biologic plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes; however, whether the levels of exposure are high enough to contribute to human carcinogenesis remains uncertain. The report further noted that there is no available evidence whether e-cigarette use is associated with certain longer term health outcomes, including clinical cardiovascular outcomes and subclinical atherosclerosis, intermediate cancer endpoints in humans,

respiratory diseases, and pregnancy outcomes (National Academies of Sciences, Engineering, and Medicine 2018). Additionally, Gotts and colleagues (2019) reviewed the available science to date on risks to the respiratory system from using e-cigarettes or being exposed to aerosol from e-cigarettes. The study found negative impacts on cellular and organ physiology and immune function (Gotts et al. 2019). Accordingly, more research is warranted to assess the extent to which e-cigarette use may impact the likelihood of these and other health outcomes. Of note, some studies have found that after accounting for conventional cigarette smoking, e-cigarette use is associated with increased risk of having had a myocardial infarction (Alzahrani et al. 2018; Alzahrani and Glantz 2019; Osei et al. 2019). However, the cross-sectional nature of these studies limits the ability to ascertain causality (Farsalinos and Niaura 2019a). A longitudinal study using data from the PATH Study found that having had a myocardial infarction at Wave 1 of the study did not predict e-cigarette use at Wave 2 (Bhatta and Glantz 2019). This finding, according to the study's authors, suggests that reverse causality cannot explain the cross-sectional association between e-cigarette use and myocardial infarction observed at Wave 1. However, further longitudinal research is warranted to fully account for the time period when myocardial infarction has occurred relative to e-cigarette use.

Research on the impact of e-cigarettes on smoking cessation is limited but growing. In addition to the review of this topic by the National Academies of Sciences, Engineering, and Medicine (2018), multiple systematic reviews have assessed the literature on e-cigarette use and smoking cessation, some of which conducted meta-analyses of RCT data and observational studies (Franck et al. 2014; Grana et al. 2014; Harrell et al. 2014; McRobbie et al. 2014; Lam and West 2015; Rahman et al. 2015; Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016; Khoudigian et al. 2016; Malas et al. 2016; El Dib et al. 2017).

Few RCTs have been conducted that directly investigate the utility of e-cigarettes for smoking cessation, and no RCTs on this topic have been conducted in the United States. Only four RCTs—a clinical trial of smokers in Italy who were not motivated to quit (Caponnetto et al. 2013), a clinical trial of smokers in New Zealand who were motivated to quit (Bullen et al. 2013), another clinical trial of smokers in New Zealand who were motivated to quit (Walker et al. 2019), and an RCT of adults using the stop-smoking service of the UK National Health Service (Hajek et al. 2019)—have directly tested the efficacy of using e-cigarettes for smoking cessation with a follow-up timepoint of at least 6 months; none were funded by the tobacco or e-cigarette industries. In a randomized clinical trial of smokers who were not motivated to quit, Caponnetto and colleagues (2013) found that the use of

first-generation e-cigarettes resulted in a nonsignificant ($p = 0.24$) increase in the likelihood of smoking abstinence at 52-weeks follow-up compared with those who used first-generation e-cigarettes that did not contain nicotine (placebo e-cigarette). Abstinence rates were 13% in Group A (12-weeks supply of 7.2 mg nicotine cartridges), 9% in Group B (one 6-week supply of 7.2-mg nicotine cartridges and one 6-week supply of 5.4-mg nicotine cartridges), and 4% in Group C (cartridges without nicotine). However, in an intention-to-treat analysis, a statistically significant increase in the abstinence rate was observed at 52-weeks follow-up: 11.0% when Groups A and B were combined compared with 4.0% in Group C ($p = 0.04$). The RCT by Bullen and colleagues (2013) also showed (a) a nonsignificant elevated RR of 6-month continuous abstinence rates for smokers who were assigned to use first generation e-cigarettes that contained nicotine compared with those who were assigned to use first generation e-cigarettes that did not contain nicotine (7.3% vs 4.1%, RR 1.77, $p = 0.44$) and (b) a nonsignificantly elevated RR for 6-month continuous abstinence (RR = 1.26; $p = 0.46$) between smokers who were assigned to use e-cigarettes that contained nicotine (7.3%) and those who were assigned to use nicotine patches (5.8%). As reviewed in National Academies of Sciences, Engineering, and Medicine (2018), the results of these two RCTs were pooled in two different, rigorous meta-analyses. A 2016 Cochrane review that pooled data from these two RCTs showed (a) no significant statistical heterogeneity between the two studies and (b) that use of nicotine-containing e-cigarettes was associated with statistically significant higher abstinence rates than use of placebo e-cigarettes (RR = 2.29; 95% CI, 1.05–4.96; 9% for nicotine e-cigarette group vs. 4% in placebo e-cigarette group, among 662 participants) (Hartmann-Boyce et al. 2016). El Dib and colleagues (2017) pooled the same two RCTs into a meta-analysis and found a nonsignificant increase in smoking cessation for nicotine e-cigarettes compared with placebo e-cigarettes (RR = 2.03; 95% CI, 0.94–4.38; $p = 0.07$). A notable difference in the methodology between these two reviews was that Hartmann-Boyce and colleagues (2016) considered participants with missing data as smokers and retained them in the analysis, increasing their sample size to 662 compared with the 481 cases analyzed by El Dib and colleagues (2017) (National Academies of Sciences, Engineering, and Medicine 2018).

A few notable limitations to two RCTs (Bullen et al. 2013; Caponnetto et al. 2013) should be noted: They both produced fairly low quit rates in all conditions (range: 4–13%) and used first generation e-cigarettes that do not have comparable nicotine pharmacokinetics as cigarettes. Furthermore, Bullen and colleagues (2013) found that rates of compliance were substantially lower among smokers in the nicotine patch condition than among

those in either of the e-cigarette conditions, suggesting that the similar efficacy among users of e-cigarettes with nicotine and of the nicotine patches might be mediated by different mechanisms of action. The greater adherence to e-cigarettes could be driven, in part, by past experience of failed quit attempts with patches and/or greater appeal of e-cigarettes.

The third RCT (Hajek et al. 2019) randomly assigned 886 adults attending stop-smoking services from the UK National Health Service. Participants received either an NRT medication of their choice or an e-cigarette starter pack, which included a newer generation refillable e-cigarette with one bottle of nicotine e-liquid (18 mg per milliliter [ml]). Both conditions received face-to-face smoking cessation counseling from a trained counselor for at least 4 weeks. At 1 year, the biochemically verified cigarette smoking abstinence rate was 18.0% in the e-cigarette group compared with 9.9% in the NRT group. Of note, participants in both the e-cigarette and NRT groups rated their assigned products as less satisfying than cigarettes. However, participants who were assigned to use e-cigarettes reported that e-cigarettes provided them with greater satisfaction and rated e-cigarettes as more helpful to refrain from smoking than participants in the NRT group rated NRT medications (Hajek et al. 2019). The study concluded that use of e-cigarettes was more effective than use of NRT for smoking cessation in the trial when both were accompanied by behavioral support. Of note, among participants with 1-year abstinence, 80% of participants in the e-cigarette group were using e-cigarettes at 52 weeks follow-up and 9% of participants in the NRT group were using NRT, suggesting greater likelihood of complete abstinence from all products in the long term from NRT use compared with e-cigarette use. This also suggests that, among those who use e-cigarettes for smoking cessation, cigarette abstinence may be predicated on long-term use of e-cigarettes, which may pose unknown long-term health risks, in addition to short-term risks that are only slowly coming into focus. Limitations of the study should also be considered. First, participants were enrolled through the UK National Health Service's stop-smoking service, so they were motivated to quit. Participants also received evidence-based cessation counseling in addition to e-cigarettes or NRT. Furthermore, the policy and regulatory environment regarding both e-cigarettes and tobacco products in the United Kingdom differs greatly from that of the United States. For example, compared with the United States, the United Kingdom limits the amount of nicotine permitted in e-cigarettes (maximum concentration 20 mg/ml) and has more restrictions on the advertising and marketing of e-cigarettes, which aligns with its advertising restrictions on tobacco products more generally. Further

well-designed RCTs will ultimately be important before any substantive conclusions can be made about the comparative efficacy of e-cigarettes relative to NRT, other cessation pharmacotherapies, or not using a cessation aid.

A fourth RCT conducted in 2016–2017 in New Zealand explored e-cigarettes, with and without nicotine, as an adjunct to the nicotine patch (Walker et al. 2019). The study randomized smokers motivated to quit ($n = 1,124$) to receive either nicotine patch, nicotine patch plus nicotine-containing e-cigarettes, or nicotine patch plus nicotine-free e-cigarettes. Participants randomized to the e-cigarette conditions received a tank-style device and tobacco-flavored e-liquid in either 0 mg/ml or 18 mg/ml concentration, depending on assigned group; and all participants received 21 mg nicotine patches. Smokers using nicotine-containing e-cigarettes were more likely to have biochemically verified, continuous cigarette abstinence at 6-month follow-up than those randomized to patch plus nicotine-free e-cigarettes or to nicotine patch alone (7%, 4%, and 2%, respectively). However, the study had higher than expected rates of attrition: 50% in the patch-only group, 32% in the patch plus nicotine-containing e-cigarettes group, and 33% in the patch plus nicotine-free e-cigarettes group. Moreover, quit rates were much lower than expected among all three randomized groups.

In addition to the aforementioned RCTs, an additional RCT assigned smokers employed by 54 companies to one of four workplace smoking-cessation interventions or to usual care (Halpern et al. 2018). Usual care consisted of access to information about the benefits of smoking cessation and to a motivational text-messaging service. The four interventions consisted of usual care and one of the following interventions: free access to cessation aids (NRT or pharmacotherapy, with e-cigarettes if standard therapies failed); free access to e-cigarettes, without a requirement that standard therapies had been tried; free access to cessation aids and \$600 in rewards for sustained abstinence; or free access to cessation aids plus \$600 in redeemable funds, with money removed from the account if cessation milestones were not met. The study found that rates of sustained abstinence through 6 months were 0.1% in the usual care group, 0.5% in the free cessation aids group, 1.0% in the free e-cigarettes group, 2.0% in the rewards group, and 2.9% in the redeemable funds group. Of note, the free e-cigarettes intervention was not superior to usual care ($p = 0.20$) or to the free cessation aids intervention ($p = 0.43$), and among smokers who received usual care, the addition of free cessation aids or e-cigarettes did not significantly enhance cessation efficacy. However, the study did not assess actual use of e-cigarettes, only access to the products, nor did it compare free access to e-cigarettes with free access to conventional cessation aids without any option for e-cigarettes (Halpern et al. 2018).

In addition to the data from the previously summarized RCTs, multiple observational studies have explored the effectiveness of using e-cigarettes for smoking cessation. Several systematic reviews have synthesized the observational literature on the impact of e-cigarette use on smoking cessation (Franck et al. 2014; Grana et al. 2014; Harrell et al. 2014; McRobbie et al. 2014; Lam and West 2015; Rahman et al. 2015; Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016; Khoudigian et al. 2016; Malas et al. 2016; El Dib et al. 2017). The review by El Dib and colleagues (2017), which used a methodology known as GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to formally assess the certainty of evidence by outcome, concluded that the findings on this topic from two RCTs (Bullen et al. 2013; Caponnetto et al. 2013) and eight observational studies (Vickerman et al. 2013; Borderud et al. 2014; Prochaska and Grana 2014; Al-Delaimy et al. 2015; Biener and Hargraves 2015; Brose et al. 2015; Harrington et al. 2015; Manzoli et al. 2015) were of very low quality. Several of the reviews noted that findings from the observational studies varied, and differences in study design and the selection of participants made it difficult to make conclusive comparisons. Similarly, a review conducted by USPSTF (2015), which also considered the existing RCTs, concluded that the current evidence was insufficient to recommend e-cigarettes for tobacco cessation in adults, including pregnant women.

In one of the prospective observational studies, Manzoli and colleagues (2015) reported that the rate of quitting smoking did not differ between smokers who had used e-cigarettes weekly for at least 6 months and smokers who did not use e-cigarettes. However, in a longitudinal study of a nationally representative population of adults surveyed in 2012 and 2014, Zhuang and colleagues (2016) found that long-term e-cigarette users appeared to have (a) higher rates of quit attempts than short-term e-cigarette users or nonusers of e-cigarettes (72.6% vs. 53.8% and 45.5%, respectively) and (b) higher rates of cigarette cessation (42.4% vs. 14.2% and 15.6%, respectively). Adjusting for smoking characteristics and demographics, long-term e-cigarette users were significantly more likely than nonusers of e-cigarettes to try to quit smoking (OR = 2.94; 95% CI, 1.34–6.44) and to do so successfully (OR = 4.14; 95% CI, 1.50–11.42); cessation outcomes for short-term e-cigarette users were similar to those for nonusers. The study also found that 43.7% of adults who were dual users of cigarettes and e-cigarettes at baseline were still using e-cigarettes at follow-up. In a study of multiple years of nationally representative data from the U.S. Current Population Survey Tobacco Use Supplement, Zhu and colleagues (2017) found that the smoking cessation rate for the overall population increased from 4.5% in 2010–2011 to 5.6% in 2014–2015,

and in 2014–2015, e-cigarette users were more likely than nonusers to attempt to quit smoking (65.1% vs. 40.1%; percentage point change = 25%; 95% CI, 23.2–26.9%) and to succeed in quitting (8.2% vs. 4.8%, $p < 0.001$). The study also examined the potential impact on cessation of other tobacco control efforts that were underway during the study period (e.g., mass media campaigns and increased taxation of cigarettes) and concluded that their effects could not fully account for the observed increase in the quit rate, leaving the use of e-cigarettes as a potential explanation. Finally, in a cross-sectional household survey of smokers 16 years of age and older in England, Beard and colleagues (2016) found that the success rate of attempts to quit cigarettes increased by 0.098% ($p < .001$) for every 1% increase in the prevalence of e-cigarette use among smokers, and by 0.058% for every 1% increase in the prevalence of e-cigarette use during a recent quit attempt. The study concluded that increases in e-cigarette use in England have been associated with increased success in quitting cigarette smoking.

As noted previously, some of the literature suggests potential utility of e-cigarettes for smoking cessation. However, the current literature is limited by small numbers of trials, low event rates, and wide confidence intervals. Moreover, interpretation of results is further complicated by the wide variation in e-cigarette products (i.e., types of devices and components and levels of nicotine content in e-liquids) and the contexts in which they are used, including the motivation of smokers to quit and whether the products are used with behavioral support. Accordingly, more well-designed RCTs and prospective observational studies are needed to determine whether and how e-cigarettes influence smoking cessation, including whether the type of e-cigarette and the setting in which it is used impacts the potential for e-cigarette use to help smokers quit.

Existing research suggests that the frequency of e-cigarette use and the type of product are important factors that influence the extent to which the products increase the likelihood of smoking cessation. As part of a comprehensive report on the public health consequences of e-cigarettes, the National Academies of Sciences, Engineering, and Medicine (2018) reviewed three RCTs (Bullen et al. 2013; Caponnetto et al. 2013; Adriaens et al. 2014)—one of which assessed smoking reduction and not actual cessation (Adriaens et al. 2014)—and results from several prospective cohort studies or repeated cross-sectional design studies (Biener and Hargraves 2015; Brose et al. 2015; Hitchman et al. 2015; Delnevo et al. 2016; Malas et al. 2016; Zhuang et al. 2016; Levy et al. 2018) on the effectiveness of e-cigarettes for smoking cessation. The review concluded that while the overall evidence from observational trials is mixed, there is moderate evidence

from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation. For example, in a cross-sectional study using data from the 2016 and 2017 National Health Interview Survey, Farsalinos and Niaura (2019b) found that daily e-cigarette use was not associated with being a former smoker when quit duration was ignored, but was positively associated with being a former smoker of less than 1 year (adjusted prevalence ratio [aPR] = 3.44; 95% CI, 2.63–4.49), 1–3 years (aPR = 2.51; 95% CI, 2.13–2.95), and 4–6 years (aPR = 1.84; 95% CI, 1.49–2.26). Moreover, using data from waves 1 (2013–2014) and 2 (2014–2015) of the Population Assessment of Tobacco and Health Study, Berry and colleagues (2019) found that after adjusting for covariates, (a) cigarette smokers who initiated e-cigarette use between waves and reported that they used e-cigarettes daily at wave 2, had 7.88 (95% CI, 4.45–13.95) times the odds of 30-day cigarette cessation compared with nonusers of e-cigarettes at wave 2, and (b) nondaily e-cigarette users had significantly lower odds of cessation compared with nonusers. Similarly, in a longitudinal sample from two U.S. municipalities, Biener and Hargraves (2015) found that after accounting for demographic characteristics and tobacco dependence, intensive users of e-cigarettes (used e-cigarettes daily for at least 1 month) were six times more likely than nonusers to quit smoking (OR = 6.07; 95% CI, 1.11–33.2); a comparable relationship was not observed between intermittent users (used e-cigarettes regularly but not daily for more than 1 month) and nonusers/riers (used e-cigarettes only once or twice). Furthermore, among a longitudinal sample of smokers in Great Britain, Hitchman and colleagues (2015) found that compared with smokers who did not report using e-cigarettes at follow-up, nondaily users of disposable e-cigarettes were less likely to have quit smoking since baseline ($p = 0.0002$); daily users of disposable e-cigarettes and nondaily users of tank-style e-cigarettes were no more or less likely to have quit ($p = 0.36$ and $p = 0.42$, respectively); and daily users of tank-style e-cigarettes were more likely to have quit ($p \leq 0.01$). These findings are consistent with findings from the RCT by Hajek and colleagues (2019), which found greater efficacy for cessation from the use of more recent generations of e-cigarettes with higher nicotine yield, and from studies showing that open tank e-cigarettes, which allow the user to refill the nicotine liquid and to titrate the dose of nicotine, result in greater nicotine absorption (Farsalinos et al. 2013a,b; 2015). Most recently, Gomajee and colleagues (2019) assessed longitudinal data from the CONSTANCES (Consultants des Centres d'Examens de Santé) cohort and found that among the 5,400 daily smokers, daily e-cigarette use was associated with a significantly higher decrease in the number of cigarettes smoked per day compared with daily smokers who did

not use e-cigarettes (-4.4 [95% CI, -4.8 to -3.9] vs. -2.7 [95% CI, -3.1 to -2.4]), as well as a higher adjusted RR of smoking cessation (1.67; 95% CI, 1.51–1.84)]. However, among 2,025 former smokers, e-cigarette use was associated with an increase in the rate of smoking relapse (adjusted hazard ratio = 1.70; 95% CI, 1.25–2.30) compared with former smokers who did not use e-cigarettes. In addition to frequency of use and product type, some data suggest that the reason for using e-cigarettes (e.g., to quit or reduce smoking vs. all other reasons) may be an important factor that influences the effectiveness of e-cigarettes for smoking cessation (Vickerman et al. 2017). Taken together, these findings suggest that the type and design of e-cigarettes (e.g., open tank systems vs. closed systems vs. disposable) and the way in which they are used (e.g., more frequent use vs. less frequent use) may affect their utility for cessation (Hitchman et al. 2015).

The landscape of e-cigarettes continues to evolve, with the arrival of a new generation of devices and e-liquids that can more efficiently deliver nicotine (Farsalinos et al. 2014; USDHHS 2018b). For example, some e-cigarettes contain nicotine salt e-liquids (also called nic salts); nicotine salts are created by adding an acid to the nicotine to lower the overall pH (Goniewicz et al. 2018a; Spindle and Eissenberg 2018). Nicotine salt-based liquids allow users to inhale aerosols with high levels of nicotine more easily and with less irritation than the freebase nicotine e-liquids that have been used in e-cigarettes since they were first introduced into the marketplace (USDHHS 2018b; O'Connell et al. 2019). Nicotine salt e-liquids may also help deliver nicotine to the brain faster and in a way that is more comparable to the nicotine delivery achieved via conventional cigarettes (Goniewicz et al. 2018a). Although justifiable concerns exist that nicotine salts could promote initiation of e-cigarette use among youth, this new product formulation also has the potential to enhance the dose and efficiency with which nicotine is delivered to adult smokers who may be attempting to quit smoking, thus potentially increasing the likelihood that they are able to transition completely to e-cigarettes. However, this formulation could also make it more difficult for those who fully transition to e-cigarettes to eventually quit using these products completely.

The 2014 Surgeon General's report noted that "the promotion of noncombustible products is much more likely to provide public health benefits only in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combusted tobacco products are being rapidly reduced" (USDHHS 2014, p. 874). Therefore, it is particularly important to consider both the potential benefits of e-cigarettes for smoking cessation and the high level of e-cigarette use among youth, which increased to unprecedented levels between 2017 and 2018 primarily

because of the introduction of JUUL and other e-cigarettes shaped like USB flash drives (Cullen et al. 2018). As noted by the National Academies of Sciences, Engineering, and Medicine (2018), the specific time frame and magnitude of population health effects of e-cigarettes will depend on their impact on the rates of initiation and net cessation of combustible tobacco cigarettes and their intrinsic harm, and the risks of the high level of e-cigarette use among youth. To date, a variety of modeling projections have estimated the potential magnitude of these effects, but it is important to note that results can vary greatly depending on parameter inputs, underlying assumptions, and other factors. Using a Mendez-Warner modeling approach, the National Academies of Sciences, Engineering, and Medicine (2018) found that the use of e-cigarettes will generate a net public health benefit, at least in the short term. The model found that the harms from increased initiation by youth will take time to manifest, occurring decades after the benefits of increased cessation are observed. However, for long-term projections, the net public health benefit was projected to be substantially less and was negative under some scenarios in the model. Importantly, irrespective of the range of assumptions used, the model projected a net public health harm in the short and long terms if the products do not increase net combustible tobacco cessation in adults. Warner and Mendez (2019) used a similar approach, concluding that potential life-years gained as a result of e-cigarette-induced smoking cessation are projected to exceed potential life-years lost due to e-cigarette-induced smoking initiation, and that these results held over a wide range of assessed parameters. In contrast, Soneji and colleagues (2018), using a Monte Carlo stochastic simulation model, found that 2,070 additional current cigarette smoking adults (25–69 years of age) (95% CI, -42,900–46,200) would, because of e-cigarette use in 2014, quit smoking in 2015 and remain continually abstinent from smoking for 7 or more years. The model also estimated 168,000 additional never-cigarette smoking adolescents (12–17 years of age) and young adults (18–29 years of age) (95% CI, 114,000–229,000) would, because of e-cigarette use in 2014, initiate cigarette smoking in 2015 and become daily cigarette smokers at 35–39 years of age. Based on the existing scientific evidence related to e-cigarettes and optimistic assumptions about the relative harm of e-cigarette use compared with cigarette smoking, the authors concluded that e-cigarette use currently represents more population-level harm than benefit.

In summary, the evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation; factors contributing to the uncertainty include the changing characteristics of e-cigarettes, the many different contexts in which they are used, and the limited number of studies conducted to date. However, the evidence is suggestive

but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine; of important note, the evidence to support this conclusion lacks comparison to standard evidence-based therapy, and more research on this topic is warranted. The evidence is also suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes; however, future research on this topic is also warranted because existing evidence is primarily from observational studies that did not control for confounding based on motivation to quit smoking or assess potential characteristics of e-cigarette use that may be correlated with frequency of use, such as duration of use and product nicotine levels. The effects of e-cigarette use on smoking cessation will likely be determined by a combination of the physical characteristics of these products; how they are used; and how society, policymakers, manufacturers, smokers, and clinicians approach such products. Well-controlled clinical trials and rigorous, large-scale observational studies with long-term follow-up will be critical to better understand the impact of various e-cigarettes under various conditions. E-cigarettes could help adult smokers, by reducing the risk of smoking-attributable disease, if they completely switch from conventional cigarettes to e-cigarettes and do not partake in an extended period of dual use that delays quitting. It is also important to consider the extent of health risks posed by ingredients that are unique to e-cigarettes but not present in conventional cigarettes (Clapp and Jaspers 2017; Gotts et al. 2019; Madison et al. 2019). Among those who have transitioned completely, the ultimate goal should be to also quit the use of e-cigarettes completely in order to achieve the maximum individual and public health benefit. However, at the population level, any potential benefits these products confer in terms of increasing cessation among adult smokers would need to outweigh potential risks related to use among youth (USDHHS 2014),

including the already unprecedented increase in the use of e-cigarettes among youth that has occurred in recent years (Cullen et al. 2018; Miech et al. 2019). It is particularly important to emphasize the current diversity of e-cigarette products: they do not comprise a homogenous product category, and they have changed rapidly in design and characteristics since first entering the U.S. marketplace in 2007. Consequently, much of the existing scientific literature on cessation relates to past generations of e-cigarette products. Therefore, further research is needed on the effects that e-cigarettes have on smoking cessation, including research on:

- Differential effects based on the type of e-cigarette product (e.g., newer vs. older devices),
- Comparison groups (e.g., e-cigarettes that do not contain nicotine, NRT, no cessation aid),
- Components in e-cigarette devices and the settings at which they are used (e.g., temperature of the heating coils),
- Frequency of use (e.g., daily vs. less frequent use),
- Informational context (e.g., forms of marketing and promotion, communication about risk and harm, behavioral support for use as a cessation aid),
- Potential variations in effects across geographies, and
- Real-world use of e-cigarettes in different regulatory contexts.

Such research will shed light on whether and how it may be possible to leverage e-cigarettes (or certain types of e-cigarette products) to maximize positive smoking cessation outcomes while minimizing adverse consequences related to youth initiation and use.

Teachable Moments

Teachable moments—including life changes, disease diagnoses, medical procedures, and screening results—can motivate patients to make and sustain a quit attempt. Smokers often come into contact with health-care professionals—including physicians, nurses, medical staff, dentists, and pharmacists—during such moments. In addition to the specific situations described below, several other situations can also serve as teachable moments (e.g., when a pharmacist is dispensing a drug that interacts

with cigarette smoking or when a dentist, periodontist, or dental hygienist is treating a smoker).

Hospitalization

Hospitalization can present an opportunity to change behavior, especially if the patient has been hospitalized for a condition caused or exacerbated by tobacco

use. In most cases, hospitalization involves a temporary stay in a smokefree (and sometimes tobacco-free) clinical environment, with ready access to smoking cessation counseling and pharmacotherapy, at a time when health concerns are acutely relevant. Patients who use cessation medications for relief of withdrawal symptoms while hospitalized also have the opportunity to familiarize themselves with these medications and their benefits while in a clinical setting, potentially leading to a greater likelihood that they will subsequently use them to quit smoking (Fiore et al. 2012). Research indicates that tobacco cessation interventions delivered in the hospital can reduce tobacco use, improve postsurgical outcomes, reduce readmissions, and improve overall patient survival (Cummings et al. 1989; Mullen et al. 2015; Mullen et al. 2017; Nolan and Warner 2017; Cartmell et al. 2018b).

Research also indicates that post-hospital follow-up is key to achieving and sustaining smoking abstinence, as reported in a 2012 Cochrane meta-analysis of 50 randomized or quasi-RCTs evaluating smoking cessation interventions initiated in hospital settings (Rigotti et al. 2012). The meta-analysis found that intensive counseling interventions that were initiated in an acute care hospital and included at least 1 month of supportive care after discharge from the hospital were effective in increasing smoking cessation rates postdischarge (RR = 1.37; 95% CI, 1.27–1.48); adding NRT further increased the treatment effect (RR = 1.54; 95% CI, 1.34–1.79). No benefit was found for less intensive programs, or for adding bupropion. However, a multicenter, double-blind, randomized, placebo-controlled trial in which smokers with acute coronary syndrome were randomized to receive varenicline initiated in hospital or placebo for 12 weeks, found that patients randomized to varenicline had significantly higher rates of smoking abstinence and reduction than patients randomized to placebo (47.3% 6-month point-prevalence abstinence vs. 32.5% in the placebo group, $p < .05$) (Eisenberg et al. 2016). All patients in this trial also received low-intensity counseling.

Rigotti and colleagues (2012) found a comparable effect for intensive counseling in rehabilitation hospitals after acute care for stroke, coronary heart disease, or cancer or chronic disorders, such as diabetes or asthma (RR = 1.71; 95% CI, 1.37–2.14). Although not included in Rigotti and colleagues (2012), other research has found that treatment of tobacco use during a visit to a smokefree psychiatric emergency room or during psychiatric hospitalization was associated with reductions in agitation, greater abstinence from smoking, and lower readmission rates (Allen et al. 2011; Prochaska et al. 2014). For example, Allen and colleagues (2011) found that at baseline, participants were at least moderately agitated, and 28% reported aggressive behavior during the previous week. The mean

Agitated Behavior Scale scores for the nicotine replacement group were 33% lower at 4 hours and 23% lower at 24 hours than the respective scores for the placebo group.

Trials designed to link hospitalized smokers with quitline services have shown mixed results relative to standard, brief stop-smoking interventions (Rigotti et al. 2014, 2016; Cummins et al. 2016; Warner et al. 2016). For example, in a 2014 RCT of 397 smokers who received a cessation intervention during hospitalization at Massachusetts General Hospital, those assigned to the treatment condition that included postdischarge follow-up care were significantly more likely to achieve biochemically validated abstinence 6 months after discharge than those assigned to usual care (a referral to the state tobacco quitline) (27% vs. 16%; RR = 1.70; 95% CI, 1.15–2.51; $p = 0.007$) (Rigotti et al. 2014). However, in a 2016 RCT, patients were randomized to receive brief, in-hospital cessation advice or a brief, 5-minute quitline facilitation intervention that consisted of either a fax referral or a “warm handoff” (direct phone call to enroll the patient and arrange for an initial counseling call) to a tobacco quitline. Compared to those who received the brief, 5-minute cessation advice, less than 50% of the intervention group completed the first quitline intervention call, and results suggested no difference in rates of abstinence 6 months after discharge (Warner et al. 2016).

Overall, studies suggest that hospital-based cessation programs can lower readmission rates and are cost-effective for hospitals. For example, the Ottawa Model for Smoking Cessation—which identifies hospitalized smokers and provides in-hospital cessation counseling and medications and post-hospitalization follow-up—demonstrated increased smoking abstinence; lower rates of all-cause readmissions, smoking-related readmissions, and all-cause emergency department visits; and reduced healthcare costs (Mullen et al. 2017). The continuous 6-month abstinence rate was 29.4% for the intervention group versus 18.3% for controls (Reid et al. 2010). The largest absolute risk reductions (ARRs) were for all-cause readmissions at 30 days (13% vs. 7%; ARR = 6% [3–9%]; $p < 0.001$); 1 year (38% vs. 27%; ARR = 12% [7–17%]; $p < 0.001$); and 2 years (45% vs. 34%; ARR = 12% [7–17%]; $p < 0.001$) (Mullen et al. 2017). The greatest reduction in risk for all-cause visits to the emergency department was at 30 days (21% vs. 16%; ARR = 5% [0.4–9%]; $p = 0.03$). Reduction in mortality was significant by year 1 (11% vs. 5%; ARR = 6% [3% to 9%]; $p < 0.001$) and continued to be significant at year 2 (15% vs. 8%; ARR = 7% [4–11%]; $p < 0.001$). From the hospital payer’s perspective, delivery of in-hospital cessation services was cost-effective, with 1-year cost per QALY gained of \$C1,386 (Canadian dollars), and lifetime cost per QALY gained of \$C68 (Mullen et al. 2015).

In a study of acute care patients who were current smokers and were admitted to and discharged from the Medical University of South Carolina between November 2014 and June 2015, researchers compared unplanned readmissions at 30, 90, and 180 days postdischarge between (a) current smokers who were exposed to a nicotine dependence treatment service while hospitalized with unplanned readmissions and (b) smokers who did not receive the service (Nahhas et al. 2017; Cartmell et al. 2018b). The treatment service consisted of at least a bedside consult and/or one interactive voice response (IVR) follow-up call. At 30 days postdischarge, smokers exposed to the nicotine dependence treatment service were about half as likely to be smoking as those who did not receive the service (51% abstinence vs. 27%) and had significantly lower odds of readmission (OR = 0.77, $p < .05$) than those who did not receive the service (Nahhas et al. 2017). Odds of readmission remained lower among smokers exposed to the intervention at both 90 and 180 days postdischarge but were no longer statistically significant (Cartmell et al. 2018b). In a separate follow-up study, Cartmell and colleagues (2018a) assessed cost savings to the hospital at 12 months postdischarge, finding that overall adjusted mean healthcare charges for smokers exposed to the intervention were about \$7,300 lower than charges for those who did not receive the intervention.

Based on evidence of the effectiveness and benefits of interventions to help hospitalized smokers quit, The Joint Commission released an updated set of performance measures on tobacco cessation for hospitals (Fiore et al. 2012) (also see Chapter 7), but the final measures no longer contain the postdischarge follow-up component. Despite the growing body of evidence that hospital-initiated tobacco cessation interventions, especially programs that continue postdischarge, can increase abstinence, reduce readmission rates, and lead to cost savings, only about 5% of accredited acute care hospitals in the United States have selected and are reporting on the tobacco cessation measures from The Joint Commission, even without the follow-up component, and the number of hospitals reporting on these measures has decreased in recent years (The Joint Commission, personal communication, March 18, 2019). This is likely due to the voluntary nature of the measures (they are not currently tied to payment)—coupled with the fact that certain other measure sets from The Joint Commission are required or tied to payment, with the fact that performance measures are increasingly being reported electronically and the Joint Commission cessation measures have still not been fully converted electronically, and with the perception that other measure sets may be easier to implement and report on (Freund et al. 2008, 2009). If the cessation measures from The Joint Commission are not included in a CMS

rule or otherwise tied to payment or required, then the number of acute care hospitals reporting on these measures is likely to continue to decline. In contrast, two of these measures (offering cessation counseling and medication during hospitalization and again at discharge) are embedded in the Inpatient Psychiatric Facility Quality Reporting Program, and inpatient psychiatric facilities are accordingly required to report on these measures.

Surgery

Like being hospitalized, undergoing surgery can be a source of motivation to quit smoking, especially if the surgery is related to a health condition caused by smoking and presents an opportunity for patients to quit and stay quit. Smoking is a risk factor for perioperative and postoperative complications (e.g., wound infection, respiratory failure, lengthy hospital stays, admission to intensive care unit, in-hospital mortality, and readmission) (Lavernia et al. 1999; Delgado-Rodriguez et al. 2003; Barrera et al. 2005; Warner 2006) across a variety of surgical specialties (Brooks-Brunn 1997; Glassman et al. 2000; Møller et al. 2002; Thomsen et al. 2010). Quitting smoking before surgery can improve outcomes and reduce healthcare costs (American College of Surgeons 2014). Surgery also presents an opportunity for patients to quit and stay quit. For example, a large cross-sectional study found that having a major surgery doubled the likelihood of quitting smoking—particularly for surgery related to conditions caused or exacerbated by smoking, such as cancer and heart disease (Shi and Warner 2010). Even having minor surgery increased quit rates by 28%—a finding that, because of the high occurrence of such surgeries, could have a substantial impact on population-level tobacco abstinence (Keenan 2009). Requiring tobacco cessation and offering cessation treatments before elective surgery could further increase this effect. In one study, perioperative patients who were given a brief consultation by a nurse, smoking cessation brochures, and access to 6 weeks of NRT and were referred to a quitline were 2.7 times more likely to achieve long-term cessation than patients who received usual treatment, which did not include such components (Lee et al. 2015). Although little research has focused on surgeons as providers of tobacco treatment, even brief counseling on smoking cessation by a vascular surgeon was found to increase patients' interest in cessation and awareness of the harms of smoking, and this effect was maintained 3 months after the intervention (Newhall et al. 2017).

The evidence suggests that cessation interventions delivered before and in connection with surgery can increase smoking cessation among patients and improve surgical outcomes. Based on data from observational

studies and systematic reviews of RCTs by Nolan and Warner (2017), offering evidence-based tobacco treatments before and/or immediately around the time of surgery improves surgical, cardiovascular, pulmonary, and wound-healing outcomes in the short and long terms. Across more than 400 studies, effect sizes for improvement of outcomes ranged from 1.56 to 2.73 in the treatment group compared with placebo, usual care, or brief advice. Thomsen and colleagues (2014) suggested that while the optimal intensity and timing of preoperative intervention remain unclear, based on indirect comparisons and evidence from two small trials, cessation interventions that begin 4–8 weeks before surgery, include weekly counseling, and use NRT are beneficial to reduce postoperative surgical complications and increase long-term smoking cessation.

Lung Cancer Screening

Lung cancer screening with low-dose computed tomography (LDCT) is associated with an estimated 20% lower mortality rate from lung cancer relative to chest x-ray because of earlier detection of the cancer (Aberle et al. 2011; Bach et al. 2012). Based on findings from large, well-controlled clinical trials, USPSTF (2015) recommends that LDCT screening be offered to patients at high risk for lung cancer, defined as adults 55–80 years of age with a 30-pack-year smoking history who currently smoke or have quit smoking within the past 15 years. USPSTF recommends that screening continue annually until the patient has remained abstinent from smoking for 15 years or reaches 80 years of age (Moyer 2014). In February 2015, CMS issued a national coverage determination requiring Medicare to cover LDCT screening for lung cancer if certain eligibility requirements are met, including being aged 55–77 years of age, having no signs or symptoms of lung cancer, having a tobacco smoking history of at least 30 pack-years, being a current smoker or one who has quit smoking within the past 15 years, and receiving a written order for LDCT that meets several criteria (CMS 2015). In 2015, an estimated 6.8 million current and former U.S. smokers met the criteria for LDCT lung cancer screening (Jemal and Fedewa 2017). Medicare reimbursement of lung cancer screening requires that smoking cessation be addressed (CMS 2015). The shared decision-making visit must include counseling on the importance of maintaining cigarette smoking abstinence (if the patient is a former smoker) or counseling on the importance of smoking cessation (if the patient is a current smoker), and providers must offer information about tobacco cessation interventions. In addition, eligibility criteria for radiology imaging facilities must include making smoking cessation interventions available for current smokers.

Because of the criteria for lung cancer screening, the population receiving screening by definition includes a large number of current longtime smokers. Given the heightened awareness of smoking-related cancers among patients presenting for LDCT screening, these men and women could be especially receptive to smoking cessation advice and interventions delivered throughout the screening process (including before, during, and after the screening). Research on the perceptions and beliefs about smoking and negative health outcomes among high-risk older smokers found high levels of awareness of the dangers of continued smoking and strong interest in quitting, even if the screening results showed no signs of lung cancer (Cataldo 2016).

Several studies of smokers undergoing a lung cancer screening trial found that (a) motivation to quit and quit rates were higher among study participants than among those in the general population and (b) persons with abnormal LDCT scans were significantly more likely to quit smoking than those without abnormal results (Taylor et al. 2007; Styn et al. 2009; Slatore et al. 2014; Tammemägi et al. 2014). For example, in the National Lung Screening Trial (a study of 53,454 current or former heavy smokers, 55–75 years of age, with 30 or more pack-years of smoking), participants with suspicious results (a nodule ≥ 4 mm on the computed tomography scan) reported approximately 6% lower rates of smoking compared with those with normal results from the scan (Slatore et al. 2014; Tammemägi et al. 2014).

Despite these findings, some researchers have posited that, in the absence of a comprehensive cessation component, lung cancer screening could potentially have a negative impact on smoking cessation, with smokers believing that they have already taken sufficient action to protect their health simply by undergoing screening (Harris 2015; Zeliadt et al. 2015). Such an impact could be especially pronounced among smokers who receive negative screening results (i.e., no sign of cancer), since they might interpret the results to mean that they have a clean bill of health and a green light to continue smoking (Harris 2015; Zeliadt et al. 2015). In the clinical guideline on *Pairing Smoking-Cessation Services with Lung Cancer Screening* issued by the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco, Fucito and colleagues (2016) reported that a limited amount of data are available on the topic. The small number of studies conducted to date have yielded mixed findings.

Several studies seeking to add cessation interventions to LDCT scans have not observed improved cessation outcomes (e.g., Clark et al. 2004; van der Aalst et al. 2012; Marshall et al. 2016). Most of these trials used minimally intensive cessation interventions (e.g., self-help

materials, lists of resources, tailored computer information), which may have contributed to the lack of significant findings. Some evidence suggests that more intensive cessation interventions delivered in this setting might be more effective, and that the timing of such interventions may matter. For example, in a pilot study in which 18 patients were offered one face-to-face counseling session and follow-up telephone counseling with medications, Ferketich and colleagues (2012) found biochemically confirmed quit rates of 33.3% when the cessation intervention was delivered before the lung cancer screening (vs. 22.2% when it was delivered later). In addition, Park and colleagues (2015) reported increased quit rates when patients undergoing lung cancer screening received multisession, more intensive visits that included providing assistance (e.g., providing cessation counseling and/or prescription medication) and arranging follow-up.

In summary, although studies of LDCT scans have had positive effects on cessation behaviors, the optimal smoking cessation strategy for smokers who undergo LDCT screening remains unclear (Marshall et al. 2016), and research on the effectiveness of cessation interventions among persons receiving LDCT is still limited (Piñeiro et al. 2016). More research is needed to identify the most effective types of messaging and other types of cessation interventions to increase motivation to quit, quit attempts, and successful cessation among smokers who undergo lung cancer screening. Eight large RCTs of smoking cessation interventions for patients undergoing lung cancer screening are underway (Joseph et al. 2018; Taylor et al. 2019). These studies, along with future surveillance of populations undergoing lung cancer screening, will be critical to better understanding the impact of lung cancer screening on smoking and smoking cessation behaviors. In the interim, it is important for clinicians and lung cancer screening sites to deliver cessation interventions to this high-risk population and to evaluate and report the results to inform best practices in this area.

Readiness to Quit and Approaches for Quitting Ambivalence

The *Clinical Practice Guideline* recommends providing brief motivational counseling to smokers who are ambivalent about quitting (Fiore et al. 2008). Although nearly 7 out of 10 adult cigarette smokers reported that they want to stop smoking completely (Babb et al. 2017), just over 5 out of 10 reported trying to quit in the past year (Babb et al. 2017), suggesting that a substantial number of smokers are not yet ready to quit or are ambivalent about quitting. The Stages of Change Model provides a framework for assessing readiness to quit and for tailoring

interventions accordingly. Cessation strategies tailored to a smoker's readiness to quit are less likely to be perceived as overwhelming because the smoker is less likely to feel that these strategies are rushing them into action (Hall et al. 2006; Fiore et al. 2008; Prochaska et al. 2014). Readiness to quit can be conceptualized as a continuum of stages proceeding from precontemplation (no immediate intention to stop smoking) to contemplation (intending to quit in the next 6 months) to preparation (considering quitting in the next month, with at least one quit attempt in the past year) to action (has quit smoking for less than 6 months) and finally to maintenance (has quit smoking for at least 6 months) (Prochaska and DiClemente 1983). It should be noted, however, that smokers' progression through the stages of change is not necessarily sequential or orderly. Rather, smokers' motivations and readiness to quit are transient and fluctuate over time, and smokers may make spontaneous, unplanned quit attempts without first passing through all the stages of change (West 2005).

Unlike clinically based models, tailoring treatments to a smoker's stage of readiness to change recognizes that individual smokers may not always be receptive to certain types of cessation interventions. Part of the utility of this model is that it identifies a patient's stage of readiness and suggests interventions that can help move the patient to a point where he or she is ready to take advantage of standard treatment models. Motivational interviewing and adaptations of this approach (reviewed previously in this chapter) follow an intervention framework that is distinct from, but generally consistent with, stage-based approaches.

Stage-based, computer-delivered interventions have demonstrated efficacy for supporting smokers through the process of quitting, including smokers with depression or serious mental illness (Prochaska et al. 1993, 2001a,b, 2014; Velicer et al. 1999; Hall et al. 2006). In their review of 22 stage-based cessation interventions, Riemsma and colleagues (2003) found stronger effects in higher quality studies and with interventions tailored to all constructs of the Transtheoretical Model (Prochaska and DiClemente 1983), not just to the stage of change (Spencer et al. 2002). The review noted generally positive outcomes of the interventions and indicated a clear relationship between study quality and statistical significance: only 1 of 5 (20%) low-quality studies, 8 of 14 (57%) moderate-quality studies, and 3 of 4 (75%) of the highest quality studies yielded a significant finding. However, 1 of the 4 studies in the highest quality group had a small sample and a short follow-up, and was group-matched on only one stage of the Transtheoretical Model.

Some have argued that applying the Transtheoretical Model and Stages of Change Model to smoking cessation assigns smokers to stages based on arbitrary time periods that are not rooted in the science of smoking cessation

(e.g., a smoker ready to quit in 30 days is considered to be in the preparation stage, but one ready to quit in 31 days is in the contemplation stage [West 2005]). Another potential limitation of a stage-based approach is that it assumes that smokers make coherent and stable plans about quitting, but other research suggests that intentions to quit may be unstable (Hughes et al. 2005) and that smokers may make spontaneous quit attempts with no planning or preparation (Larabie 2005; Cooper et al. 2010). Finally, because the Stages of Change Model prioritizes intervening with smokers who are preparing to quit or actively engaged in quitting, some have argued that this approach may fail to offer effective interventions to smokers who might have been receptive to them (e.g., smokers who are contemplating a quit attempt or who may be ambivalent [West 2005]). Indeed, some evidence suggests that cessation assistance should be offered to as broad a spectrum of

smokers as possible, because current motivation to quit does not necessarily predict future abstinence (Pisinger et al. 2005).

Although the Transtheoretical Model and the Stages of Change Model have been widely applied to the field of smoking cessation and can be used to assess interest in and ambivalence about quitting and to tailor cessation interventions accordingly, clinicians should also be advised that the manner in which smokers approach quitting at a population level may not map onto these models. Offering support to as wide a range of smokers as possible is likely the best approach to increase quit attempts and successful quitting. However, more research is needed on such an approach, including unintended consequences. For example, offering widespread support could reduce cost-effectiveness, as interventions could be given to more numbers of smokers who are not ready and, as a result, would not quit.

Considerations for Subpopulations

As the prevalence of cigarette smoking in the general U.S. population has declined over time, increased attention has been devoted to tobacco cessation interventions focused on certain subgroups that may be more likely to smoke, be heavier smokers, bear a disproportionate burden of smoking-related morbidity and mortality, and face special challenges in quitting. In some cases, certain populations or conditions may warrant specific cessation interventions and/or lack an indication for or have certain considerations or contraindications related to cessation medication. This section outlines the evidence and considerations for cessation interventions across specific populations and/or conditions for which existing interventions are not indicated and/or are less effective.

Pregnant Women

Pregnant women are a priority population for tobacco cessation because of the health risks that tobacco use during pregnancy poses to the mother and the fetus (USDHHS 2001, 2004, 2014). Furthermore, pregnancy can offer an opportunity to quit smoking because pregnant women are highly motivated to take actions to protect the health of their babies (DiClemente et al. 2000). The literature indicates that, among American women who smoked during the 3 months before they became pregnant, about 50% quit during pregnancy (Tong et al. 2013; Curtin and Mathews 2016). However, rates of postpartum relapse among women who quit smoking during pregnancy may be as high as 50% (Tong et al. 2013). Large variations in

rates of smoking during pregnancy are seen across subpopulations and states (Curtin and Mathews 2016; Drake et al. 2018). Rates of smoking during pregnancy are higher among younger women, women with lower levels of education, economically disadvantaged women, and women who have not planned their pregnancy (Mosher et al. 2012; Curtin and Mathews 2016; Drake et al. 2018). Pregnant women and women of reproductive age who smoke are also more likely to live in low-resource environments that potentially subject them to high levels of stress (Coleman-Cowger et al. 2016; Mazurek and England 2016), and being pregnant may represent an additional stressor for these women. This context provides important insights into the potential challenges of providing smoking cessation treatment during pregnancy.

The *Clinical Practice Guideline* concluded that there was insufficient evidence for the effectiveness of smoking cessation medications in pregnant women (Fiore et al. 2008). Similarly, USPSTF (2015) concluded that evidence is not sufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women. More research is needed before definitive guidance can be provided on this topic (Fiore et al. 2008; Coleman et al. 2012a, 2015; Myung et al. 2012). Results have been mixed in reviews of the use of cessation pharmacotherapies (with most of the studies focusing on NRT) in women who smoke during pregnancy. These findings suggest that adding NRT to behavioral interventions may not increase quitting in this population (Coleman et al. 2012a, 2015; Myung et al. 2012). This may be due in part to a low medication adherence rate in trials to

date (Wisborg et al. 2000; Pollak et al. 2007; Coleman et al. 2012b).

Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacologic approaches. In individual cases, however, women and their physicians may opt to use cessation medications, including such alternatives to NRT as bupropion or varenicline. However, these decisions should be made in consultation with a physician after carefully considering the specific circumstances and weighing the risks of using medication against the risks of continued smoking (Fiore et al. 2008).

With regard to behavioral cessation interventions for pregnant women, USPSTF (2015) recommends that, as a Grade A intervention, clinicians ask all pregnant women about tobacco use, advise pregnant women who use tobacco to stop, and provide behavioral cessation interventions to pregnant women who use tobacco. Recent studies have suggested that social support is highly predictive of successful smoking cessation during pregnancy (Smedberg et al. 2014; Boucher and Konkle 2016). In addition, intervention approaches that address the health of the mother and the health of the fetus may increase long-term abstinence (Flemming et al. 2015; Bauld et al. 2017). Cessation interventions that are more intensive, are tailored, and go beyond advice to quit are more effective in this population (Fiore et al. 2008; Lumley et al. 2009). WHO (2013) recommends behavioral cessation interventions—such as health education, counseling, social support, and incentives for abstinence—as effective approaches to increasing cessation during pregnancy and to improving health outcomes for both the baby and the mother. Quitline counseling may be a useful cessation intervention for pregnant smokers, but more research is needed on the specific features that make this intervention optimally effective (e.g., the timing and frequency of calls during pregnancy and/or postpartum for relapse prevention and tailoring approaches) (Bombard et al. 2013; Cummins et al. 2016).

A growing body of evidence suggests that incentives and contingency management techniques (reviewed in detail elsewhere in this chapter) are effective cessation interventions for pregnant women (Higgins et al. 2004, 2010b, 2014; Heil et al. 2008; Cahill et al. 2015). For example, Cahill and colleagues (2015) found that incentive-based smoking cessation programs produced better outcomes for pregnant women than among controls (OR = 3.6; 95% CI, 2.39–5.43), with assessments out to 3 months postpartum. The same review concluded that such programs improve abstinence while the incentives remain in place. Despite these promising results, more evidence is needed to fully understand the effectiveness of incentive interventions in producing sustained cessation outcomes in pregnant women who smoke. Although it may be challenging to convince

payers to implement incentive interventions on a population scale, they may be more willing to consider doing so in this case, given the high costs of smoking-related adverse birth outcomes and the short-term cost savings associated with preventing these outcomes.

Lesbian, Gay, Bisexual, and Transgender Populations

In part because the tobacco industry has directly targeted the lesbian, gay, bisexual, and transgender (LGBT) population with marketing and outreach (Washington 2002; Stevens et al. 2004; Dilley et al. 2008), the prevalence of cigarette smoking and other tobacco use is substantially higher in these groups than in non-LGBT populations (Hu et al. 2016). For example, in a large national health survey (Jamal et al. 2016), the prevalence of smoking was higher among adults who were lesbian, gay, or bisexual (20.6%) than among heterosexual adults (14.9%). In 2015, gay, lesbian, and bisexual adult smokers, as a group, reported a lower prevalence of cessation counseling and/or medication use (14.5%) when trying to quit than did straight smokers (31.7%) (Babb et al. 2017). In addition, transgender adults report higher use of cigarettes and other tobacco products than cisgender persons (people whose gender identity matches the sex they were assigned at birth). Data from a 2013 nationally representative survey found that 35.5% of transgender adults reported past-month cigarette use compared with 20.7% of cisgender adults (Buchting et al. 2017). Although data are not available on the use of tobacco cessation treatments by transgender adults, as a group they are more likely to postpone general medical care and to report barriers in accessing care, primarily because they encounter discrimination when seeking care and cannot afford care (Grant et al. 2010).

Reviews of cessation treatments in LGBT populations have found that such treatments can be effective, but data are limited (Lee et al. 2014; Berger and Mooney-Somers 2016). In addition to the inclusion of elements of standard behavioral cessation treatment, most studies of this topic have investigated the effect of cessation interventions that have been modified to address LGBT-specific issues, including providing information about the tobacco industry's targeting of LGBT communities, the role of tobacco use in LGBT social activities, LGBT-specific smoking triggers, and social justice considerations (Berger and Mooney-Somers 2016). Notably, a systematic review of 19 LGBT-focused cessation interventions reported cessation rates of 30–40% out to 3–6 months (Berger and Mooney-Somers 2016). Although these results appear promising, none of the studies used adequate control groups, so a rigorous evaluation of efficacy was not possible.

To more actively engage LGBT communities in smoking prevention and cessation, some national smoking cessation campaigns (e.g., *Tips From Former Smokers* [CDC]) have included multimedia promotional materials designed specifically for LGBT populations. In May 2016, FDA launched *This Free Life*, a tobacco public education campaign that aims to prevent the escalation to daily tobacco use among lesbian, gay, bisexual, and transgender (LGBT) young adults, 18- to 24 years of age, who are nondaily or occasional smokers (FDA 2019b). *This Free Life* uses a range of primarily digital marketing tactics, including social media and online advertisements, to deliver messages to diverse subpopulations of the LGBT community. Evaluations of the effect of these large-scale promotions are ongoing, but the data are not yet available.

Populations with Mental Health Conditions and Co-Occurring Substance Use Disorders

Mental health conditions and substance use disorders commonly co-occur with smoking. Adults with mental health or substance use disorders account for 40% of all cigarettes smoked (Substance Abuse and Mental Health Services Administration 2013). In 2012–2014, the prevalence of cigarette smoking was higher among adults with any mental illness than among adults with no mental illness (33.3% vs. 20.7%, respectively, $p < .05$) (Lipari and Van Horn 2017). Nationally representative data from 2017 suggest that tobacco is used by 40.8% of individuals with serious psychological distress and 18.5% of those without serious psychological distress (Wang et al. 2018). In 2013, 65.2% of adult cigarette smokers also reported using alcohol (vs. 48.7% of nonsmoking adults), and 18.9% reported past-month use of other drugs (vs. 4.2% of nonsmoking adults) (Substance Abuse and Mental Health Services Administration n.d.). Behavioral health conditions also affect smoking patterns in ways that can make quitting more difficult. For example, the average number of cigarettes smoked in the past month was higher among adult smokers with any mental illness (326) than among adult smokers with no mental illness (284) (Lipari and Van Horn 2017).

The high prevalence of smoking among persons with mental illness is due in part to their lower rates of quitting smoking over time (Prochaska et al. 2017). In addition, mental illness is associated with heavier smoking, greater nicotine dependence, more pronounced withdrawal symptoms when quitting, and lower quit rates (Hall and Prochaska 2009). Although research on smoking and mental illness has increased markedly in recent years,

cessation intervention studies on this population are still limited. A statistical analysis of the literature on tobacco and mental illness documented a steady increase in research publications in this area for three 2-year periods: 1993–1995 ($n = 65$), 2003–2005 ($n = 153$), and 2013–2015 ($n = 329$) (Metse et al. 2017). However, the study designs remained predominantly descriptive in form (>80%), and few experimental studies tested cessation interventions (<13%).

A meta-analysis of 26 tobacco intervention studies found that smoking cessation was significantly associated with decreases in anxiety, depression, and stress and with improvements in overall mood and quality of life (Taylor et al. 2014). Notably, the strength of these relationships did not vary based on the presence or absence of a psychiatric diagnosis. In trials of tobacco cessation interventions conducted among smokers with psychiatric disorders, quitting smoking was associated with reductions in depression, anxiety, and symptoms of posttraumatic stress disorder and psychosis and with rapid changes in mood (Potkin et al. 2003; McFall et al. 2010; Kahler et al. 2011; Krebs et al. 2016). A meta-analysis that focused on smokers in treatment for substance use disorders found that tobacco cessation interventions were associated with a 25% increased likelihood of abstinence from alcohol and other drugs relative to usual care (Prochaska et al. 2004). A randomized trial of smokers recruited from inpatient psychiatric facilities found that a tobacco cessation intervention was associated with a significantly lower likelihood of readmission (Prochaska et al. 2004). In the past, many behavioral health clinicians believed that treating nicotine dependence and tobacco cessation jeopardize sobriety or mental health recovery (Baca and Yahne 2009), a misconception that has been actively fostered by the tobacco industry (Prochaska et al. 2008; Hall and Prochaska 2009). However, smoking cessation and the delivery of tobacco cessation treatments are associated with enhanced clinical outcomes, including improved sobriety, fewer symptoms of posttraumatic stress disorder, and lower rates of hospitalization.

Another RCT was conducted in 10 community mental health centers to determine whether smokers with schizophrenia or bipolar disease have higher rates of tobacco abstinence with pharmacotherapy than with standard treatment (Evins et al. 2014). There were 87 smokers with schizophrenia or bipolar disease who received 12 weeks of varenicline and achieved 2 weeks or more of continuous abstinence by week 12 who were randomly assigned to receive cognitive behavioral therapy and varenicline or placebo. At week 52, biochemically verified 7-day point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) versus 19% (9 of 47) in the placebo group (OR = 6.2; 95% CI, 2.2–19.2; $P < .001$). The authors concluded that among smokers with serious mental illness who attained initial abstinence with standard treatment,

maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation (Evins et al. 2014).

Approaches to smoking cessation with demonstrated efficacy among smokers with mental illness or addictive disorders include motivational and stage-based treatments and behavioral therapy that is offered outside of or integrated within mental health or addictions treatment, delivered in person or via a quitline, and combined with cessation pharmacotherapy (Hall and Prochaska 2009). The California Smokers' Helpline reported that nearly 1 in 4 of 844 smokers who called the helpline in 2007 and were screened for depression, met criteria for a current major depressive disorder and that quit rates at the 2-month follow-up were lower in this group (19%) than among callers without depression (28%) (Hebert et al. 2011). More generally, the convenience and accessibility of quitlines make them an important option for clinician referrals among this population. Supplementary cessation services and treatments that can complement clinician and quitline interventions, such as in-person counseling and cessation medication, may further increase quit rates. A randomized trial of 577 mental health patients in the Veterans Health Administration found that a specialized quitline for smokers referred by a mental health provider outperformed standard state quitlines, with significantly greater 30-day abstinence at 6 months (26% vs. 18%) and greater patient satisfaction (Rogers et al. 2016).

A Cochrane Review of trials testing smoking cessation interventions that included specific mood management components for depression versus a standard intervention showed a significant positive effect for smokers with current depression (11 trials; $N = 1,844$; $RR = 1.47$; 95% CI, 1.13–1.92) or past depression (13 trials; $N = 1,496$; $RR = 1.41$; 95% CI, 1.13–1.77) (van der Meer et al. 2013). The interventions largely followed a behavioral therapy approach, offering group or individual counseling sessions. For example, the treatments encouraged participants to monitor their mood with a daily rating scale and to learn and apply skills to decrease negative moods and increase pleasant ones—such as by recognizing maladaptive thoughts, disputing negative thinking, engaging in pleasant activities, increasing positive social contacts, and setting realistic goals (Hall et al. 1994, 1996).

Researchers have also tested the use of medications for mood management when quitting smoking. In one systematic review, use of bupropion and nortriptyline, which are both antidepressants, resulted in a statistically significant increase in tobacco abstinence, irrespective of depression history, but selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline) and monoamine oxidase

inhibitors (MAOIs) were not found to increase smoking cessation (Hughes et al. 2014).

Postmarketing reports, which are mandated by FDA, have raised concerns that persons taking varenicline may experience increased intoxicating effects when consuming alcoholic beverages. However, these effects have not been observed in clinical trials. Instead, evidence suggests that varenicline may aid in quitting smoking while also reducing drinking in men who drink excessively. A double-blind RCT of 131 smokers (30% women) with alcohol use disorders found that varenicline with medical management resulted in an increased rate of smoking abstinence overall and in decreased heavy drinking among men (O'Malley et al. 2018). These findings are important in light of the high rate of comorbid smoking and heavy drinking, but more research is needed.

In conclusion, individuals with behavioral health conditions smoke at a significantly higher rate than the general population and generally have a more difficult time quitting, despite being equally interested in quitting. However, evidence increasingly suggests that quitting smoking does not jeopardize the success of treatment for mental health conditions or substance abuse and may actually enhance recovery outcomes (McKelvey et al. 2017). Additional research is needed on which tailored tobacco cessation interventions are most effective in helping persons with behavioral health conditions quit smoking.

Adolescents

Nearly 9 out of 10 smokers first try smoking by 18 years of age, with 99% of smokers doing so by age 26 (USDHHS 2012, 2014). Accordingly, tobacco use can be considered a pediatric disorder (USDHHS 2012). Other data suggest that initiating tobacco use at 13 years of age or younger is associated with continuous daily and non-daily use during adolescence and with the development of nicotine dependence, compared with initiating tobacco use at 14 years of age and older (Sharapova et al. 2018). Once adolescents progress to established smoking, few of them attempt to quit, few quit successfully when trying on their own (7%), very few seek help quitting, and success rates are low—even among those who obtain help (12%) (Sussman et al. 1999; USPSTF 2016). Estimates suggest that quitting smoking before 35 years of age prevents much of the harm from smoking (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013). However, the average age of quitting in the United States is approximately 40 years of age, and this age did not change significantly between 1997–98 and 2011–12 (Schauer et al. 2015a). Because most smokers start young and because quitting is difficult once smoking becomes established, efforts to prevent adolescents from

ever starting to smoke and to help adolescents who start smoking to quit as soon as possible are critical.

The evidence for the effectiveness of cessation interventions targeting youth is mixed. A 2013 systematic review by USPSTF found stronger evidence for interventions by primary care providers to prevent youth smoking initiation than for provider actions to help youth who already smoke quit. The review concluded that, while primary care-based behavioral interventions may prevent smoking initiation among youth, these interventions, alone or in combination with cessation medications (bupropion or bupropion plus NRT), have not been shown to increase rates of smoking cessation among youth (Patnode et al. 2013). The review included studies of smokeless tobacco cessation interventions and very brief advice, as well as limited print-based interventions. In a Cochrane Review of primary care- and school-based tobacco cessation interventions for young people, which had broader criteria for including trials, included smokers younger than 20 years of age, and pooled data from 28 controlled trials, Stanton and Grimshaw (2013) identified as “promising” those approaches that were based on the Stages of Change Model (pooled RR = 1.56 at 1 year; 95% CI, 1.21–2.01) or included motivational enhancement therapy (RR = 1.60; 95% CI, 1.28–2.01). Only 3 of the 28 trials tested pharmacologic approaches, and those trials reported limited efficacy.

Cessation medications are not approved by FDA for use with children or adolescents, and NRT cannot be purchased over-the-counter by persons younger than 18 years of age (Johnson et al. 2004; Karpinski et al. 2010). However, cessation medications can be prescribed for and used by youth under the supervision of a physician. The *Clinical Practice Guideline* found insufficient evidence for the effectiveness of cessation medications in adolescents (Fiore et al. 2008). A study of 120 smokers 13–17 years of age found that the nicotine patch, but not nicotine gum, had a statistically significant effect on prolonging abstinence relative to placebo (Moolchan et al. 2005). More explicit evidence-based recommendations are needed to guide clinicians and parents in weighing the potential benefits and risks of specific smoking cessation medications in adolescent patients (*Federal Register* 2018).

With regard to behavioral smoking cessation interventions for children and adolescents, a 2016 meta-analysis of such interventions in primary care settings found a 34% increase in quit rates relative to control conditions (RR = 1.34; 95% CI, 1.05–1.69), with an absolute effect of 7.98% for cessation and a number needed to treat of 13 (95% CI, 6–77) (Peirson et al. 2016). The review excluded studies of smokeless tobacco, brief counseling, print materials, and NRT. Of the four studies reviewed, the intervention with the strongest effect (a 24% reduction in smoking) was based on the Stages of Change Model and

was personalized, computer assisted, and motivationally tailored (Hollis et al. 2005). Adolescents were recruited in a clinic setting, and the intervention lasted 12 months. The intervention focused solely on tobacco use (rather than addressing tobacco use in conjunction with additional risk behaviors) and included educational components (Hollis et al. 2005). Further research is needed to identify and replicate best practices for tobacco cessation interventions with adolescent smokers. However, recruitment is a major challenge to research on cessation among youth, in part because of parental consent and youth emancipation laws that are in place in most states. At this juncture, focusing on prevention efforts in youth (USDHHS 2012) is likely to yield the greatest impact in terms of reducing the prevalence of tobacco use in future generations. However, continued efforts are warranted to develop effective cessation treatments and interventions for young people who are already established cigarette smokers or established users of e-cigarettes or other tobacco products and who may already be addicted to nicotine.

Dual Tobacco Product Users

Dual tobacco use, which is commonly defined as the use of cigarettes concurrently with other tobacco products (including e-cigarettes), has become increasingly common. Among current adult e-cigarette users in the 2017 National Health Interview (NHIS) Survey, 49.6% were current smokers of conventional cigarettes (NHIS public use data 2017). Per data from NHIS, nearly 60% of adult e-cigarette users in 2015 were also current cigarette smokers, suggesting that dual use of e-cigarettes and cigarettes is a common pattern (CDC 2016). In fact, this was the most common product combination among adults who reported using two or more tobacco products. A study using data from the PATH Study found that more than one-third (37.8%) of adult tobacco users in 2013–2014 were multiple-product (or polytobacco) users, with the most common combination being cigarettes plus e-cigarettes (Kasza et al. 2017). Among the sample of youth (12–17 years of age) in the PATH Study, 43% of those using tobacco in the previous 30 days were multiple-product users; again, cigarettes plus e-cigarettes was the most common combination, followed by cigarettes plus cigarillos. In the 2018 National Youth Tobacco Survey, the prevalence of multiple product use among current tobacco users of high school age was 37% for girls and 45% for boys (Gentzke et al. 2019). A probability-based survey of 1,836 cigarette smokers found that concurrent use of cigarettes and alternative tobacco products (loose leaf chewing tobacco, moist snuff, snus, dissolvable tobacco, or e-cigarettes) was positively associated

with making cessation attempts and having intentions to quit but was not associated with quit success (Popova and Ling 2013). A larger study of quit attempts and interest in quitting among 26,000 smokers found no clear differences between cigarette-only use versus dual use of cigarettes and cigars or smokeless tobacco (Schauer et al. 2016b).

A few studies have compared quitting behaviors between adult cigarette-only users and dual users. In the 2010–2011 Tobacco Use Supplement to the Current Population Survey, cigarette-only and dual users (defined as users of cigarettes plus cigars or smokeless tobacco) reported a comparable prevalence of attempts to quit cigarettes, with both groups making suboptimal use of evidence-based cessation treatments (Schauer et al. 2016b). Other studies have suggested that many cigarette smokers who are trying to quit are using e-cigarettes as one method of quitting, as discussed previously in this chapter (Caraballo et al. 2017; Zhu et al. 2017). An online survey of 1,324 adults found that dual use of cigarettes with smokeless tobacco was associated with past attempts to quit smoking by switching to smokeless products, while dual use of cigarettes with e-cigarettes was associated with prior use of cessation medications and strong sentiment against the tobacco industry (Kalkhoran et al. 2015).

Although at least one-third of tobacco users are dual users, most trials of tobacco treatments focus exclusively on cigarette smoking cessation and do not address cessation interventions for other types of tobacco products. While noting that all tobacco products deliver toxicants and pose health risks, the 2014 Surgeon General’s report concluded that the overwhelming burden of death and disease from tobacco use in the United States is caused by cigarettes and other combustible tobacco products (USDHHS 2014). The report also acknowledged that the recent shift in patterns of tobacco use could have several potential impacts, ranging from the positive effect of accelerating the rate at which smokers completely quit smoking cigarettes to the negative effect of delaying complete cessation of all tobacco products, especially cigarettes. Despite the general acceptance of a continuum of risk across tobacco products (USDHHS 2014), the specific risk posed by each class of tobacco products has not been established and is difficult to estimate with precision because of the wide spectrum of products within each product class and the differences in how they are used.

Although the use of noncombustible tobacco products does not expose users to the same mix of toxicants via the same mode of administration as cigarette smoking, all tobacco products carry inherent risks. Risks for dual users may be particularly harmful if they delay cessation from combustible tobacco (USDHHS 2014, 2016). For example, smokeless tobacco has been shown to cause cancers of the mouth, esophagus, and pancreas; diseases of

the mouth; and adverse reproductive outcomes (WHO and International Agency for Research on Cancer 2007; USDHHS 2014; NCI and CDC 2014). E-cigarettes emit fewer and lower levels of certain harmful substances than conventional cigarettes, but the long-term health risks of using these products remain unknown, and short-term risks are only slowly coming into focus. Several studies demonstrate e-cigarette aerosol contains fine and ultrafine particles, such that use of the products could potentially increase cardiovascular and respiratory risks (USDHHS 2016; Alzahrani et al. 2018; Nabavizadeh et al. 2018; National Academies of Sciences, Engineering, and Medicine 2018; Gotts et al. 2019). Therefore, only complete cessation of all tobacco products fully eliminates all tobacco-related health risks. Nevertheless, based on currently available evidence, nonpregnant adults would be expected to reduce their risk of smoking-attributable disease and death if they completely substituted all combustible tobacco products with noncombustible tobacco products. Whether these products will realize the potential of harm reduction depends in part on how their use affects smokers’ attempts to quit cigarettes—either by switching completely to a noncombustible tobacco product or by discontinuing all tobacco use—combined with their impact on youth uptake of e-cigarettes and other tobacco products.

The *Clinical Practice Guideline* called for more research on effective cessation medications and counseling interventions for persons who are dual users of cigarettes and smokeless tobacco (Fiore et al. 2008), but research in this area remains sparse more than 10 years after the *Guideline* was released. In one study, an interactive, tailored, web-based intervention for smokeless tobacco use was found to significantly increase (nearly double) the likelihood of participants abstaining from all tobacco products (Severson et al. 2008). Another study examined the impact of a 40-minute, single contact, tobacco cessation intervention among 1,055 airmen enrolled in technical training in the U.S. Air Force (USAF) (Little et al. 2016). The USAF intervention addressed cigarettes, smokeless tobacco, snus, cigars, cigarillos, pipes, e-cigarettes, “roll your own” cigarettes, and hookah. From before the training to immediately after the training, perceptions of harm increased for all nine tobacco products among both tobacco users and nonusers, but intention to consume tobacco products was reduced mainly among existing tobacco users. Behavioral outcomes were not assessed, given the short assessment window (Little et al. 2016).

Much remains to be learned about best practices for achieving and sustaining abstinence from all tobacco products among dual users. Although few interventions have been studied for cessation from all tobacco products, some cessation medications (bupropion, varenicline, NRT) have been found to be effective for cessation

from cigarettes and smokeless products (independently) (Ebbert et al. 2007; Fagerström et al. 2010; Cahill et al. 2016; Schwartz et al. 2016; Hartmann-Boyce et al. 2018). Such medications could be candidates for tobacco cessation efforts among dual users of those two products. More also needs to be learned about (a) the degree to which e-cigarettes may promote or impede efforts to quit smoking and (b) the relative health benefits or harms from cessation of one tobacco product, but not all tobacco products, among dual or multiple tobacco product users.

Light and Nondaily Tobacco Users

The prevalence of daily smoking has decreased over the past two decades, but the proportion of light cigarette smoking (usually defined as 10 or fewer cigarettes smoked per day) has generally increased (Pierce et al. 2009; Jamal et al. 2018) and the prevalence of nondaily smoking has been generally stable (Schauer et al. 2016a). For example, among current U.S. smokers, the proportion of daily smokers was 76.1% in 2016, which declined from 80.8% in 2005 (p trend <0.05) (Jamal et al. 2018). During 2005–2016, increases occurred in the proportion of daily smokers who smoked 1–9 cigarettes per day (16.4% to 25.0%) or 10–19 (36.0% to 39.0%) cigarettes per day, and decreases occurred in the proportion of daily smokers who smoked 20–29 (34.9% to 28.4%) or ≥ 30 (12.7% to 7.5%) cigarettes per day (p trend <0.05) (Jamal et al. 2018). Nationally representative data from 2015 indicate that 24.3% of all smokers were nondaily smokers, and 25.1% of current daily smokers were light smokers (defined in this study as smoking 1–9 cigarettes per day) (Jamal et al. 2016). Nondaily smokers often do not consider themselves to be smokers; up to 42% classify themselves as nonsmokers when asked (Fergusson and Horwood 1995). Consequently, nondaily smoking is under-recognized by clinicians (Schane et al. 2009), which might result in their being less likely to deliver cessation interventions to this group of smokers. Studies have also pointed to potential challenges in motivating light and nondaily smokers to quit, given they are more likely to concurrently use other tobacco products than are heavier smokers (Reyes-Guzman et al. 2016). On the other hand, some studies have found that nondaily smokers report greater intention to quit and are more likely to succeed in quitting than daily smokers (Hennrikus et al. 1996; Sargent et al. 1998). Whereas daily smokers' intentions to quit may be driven in part by their level of nicotine dependence, nondaily smokers' intentions to quit may be more related to situational cues and sociodemographic characteristics (Fagan et al. 2007; Shiffman et al. 2014).

Most tobacco cessation interventions target daily heavy smokers (Fiore et al. 2008). However, cessation

interventions are also critically important for nondaily and light smokers, but cessation approaches for these populations may require a new treatment paradigm (Hassmiller et al. 2003; Wortley et al. 2003). The *Clinical Practice Guideline* concluded that there was insufficient evidence for the effectiveness of using cessation medications in persons who smoke fewer than 5–10 cigarettes per day (Fiore et al. 2008). A review by Lindson and colleagues (2019) identified few studies on the role of NRT for persons smoking fewer than 15 cigarettes per day.

Furthermore, preliminary data suggest that standard cessation counseling that focuses on calling attention to personal health risks may not motivate nondaily or light smokers to quit, in part because they may believe that they have already minimized their health risks by using tobacco less intensively (Hyland et al. 2005; Tong et al. 2006). Despite these beliefs, studies indicate that light and nondaily smoking significantly increases risk for tobacco-related disease, especially cardiovascular and respiratory harms (Luoto et al. 2000; Hackshaw et al. 2018; Kameyama et al. 2018) and all-cause mortality (Inoue-Choi et al. 2017; Løchen et al. 2017). Moreover, the dose-response relationship between cigarette consumption and cardiovascular risk is not linear (USDHHS 2010).

Studies testing the impact of messages about the health harms associated with cigarette smoking generally have not focused on specific tobacco-related harms that are relevant to light and nondaily smoking. Messages about these effects could be more impactful for these groups of smokers, both clinically and at a population level, and should continue to be studied.

Data from observational and pilot studies of treatments suggest that counseling nondaily smokers on the dangers that their secondhand smoke poses to others could also be an effective approach for motivating them to quit (Tong et al. 2006; Schane and Glantz 2008; Schane et al. 2013). In the 1970s, research conducted by the tobacco industry concluded that social, infrequent, or nondaily smokers felt immune to the personal health effects of tobacco use but were concerned about the effects that their secondhand smoke might have on others (Schane et al. 2009).

Although further research on cessation interventions for nondaily smokers is needed, emerging evidence suggests that educating nondaily smokers about the dangers that secondhand smoke poses to nonsmokers is a powerful cessation message and may be more effective than traditional smoking cessation counseling that emphasizes the health consequences for the smoker (Schane et al. 2013). In addition, improved clinical identification of light and nondaily smokers is needed to help clinicians target these groups with strong messages emphasizing that no level of smoking is safe.

Emerging Intervention Approaches

Emerging Behavioral Treatments

In considering potential future directions for behavioral smoking cessation treatments, a wide variety of possible strategies exist to increase their reach while maintaining or improving their efficacy, thus increasing their impact. Two innovative approaches are (1) the expansion of treatment targets and (2) the use of emerging technologies to better time and personalize the delivery of behavioral cessation interventions.

Expanding Behavioral Treatment Targets

Although behavioral therapy is well established as the mainstay of most empirically based behavioral cessation interventions, applying constructs from other psychological theories could potentially enhance the efficacy of these interventions. Two examples are (1) treatments drawn from self-determination theory (SDT) (Ryan and Deci 2000; Ng et al. 2012) and (2) comprehensive, intensive group treatment for nicotine dependence (Hajek et al. 1999; Foulds et al. 2006; Hall and Prochaska 2009; Hall et al. 2011; Kotsen et al. 2017).

SDT postulates that a necessary condition for sustained change in health behavior is satisfaction of the basic psychological needs that a person has for autonomy, competence, and relatedness (Williams et al. 2016). Persons will be more motivated to change their behaviors and perceive themselves as more capable of successfully changing their behaviors in social contexts that support these needs (Ng et al. 2012). SDT-based interventions target adaptive and maladaptive behaviors and motivations for behavioral change. SDT-based treatments focus on shifting a patient's motivation for behavior change from the external (e.g., because others want the patient to change) to the internal (e.g., the patient wants to change because it is consistent with his or her personal values). SDT involves working with clients to better align their motivations and behaviors to enhance motivation that supports sustained behavioral change (Ryan et al. 2008). SDT-based interventions have demonstrated efficacy in a variety of contexts and populations, including among persons attempting to achieve long-term changes in health behavior, such as quitting smoking, losing weight, and engaging in physical activity (Williams et al. 2002, 2006a,b, 2009, 2011, 2016; Pesis-Katz et al. 2011; Teixeira et al. 2015).

Although not a new concept, intensive comprehensive tobacco use treatment at the group level likely brings to bear unique cessation mechanisms that have consistently led to high quit rates. Such treatment is professionally led

and addresses key mechanisms of behavior change, such as group interactions, intergroup discussions between smokers, development of cohesion among group members, and support for interventions that are unique to this cessation format (Hajek et al. 1985, 1989; Yalom and Leszcz 2005; Kotsen et al. 2017). Professionally led, group-based treatment has been a standard of care in all programs designed to treat other types of addictions, and has been shown to yield high rates of satisfaction and positive experiences for smokers (Dobbie et al. 2015). For more than two decades, these group smoking cessation interventions have shown robust feasibility, acceptability, and efficacy in a range of research and practice settings (Connett et al. 1993; Foulds et al. 2006; Hall et al. 2009; Dobbie et al. 2015; Kotsen et al. 2017; Public Health England September 2017), to the point that they can be applied in all healthcare settings (including primary and specialty care) and behavioral healthcare settings. However, group interventions have traditionally been limited by their reach, because having to travel to an in-person meeting at a set meeting time can be a barrier for many smokers, particularly those with lower incomes. Future research could explore whether combining medication with intensive group smoking cessation treatment led by a tobacco treatment specialist is feasible in a virtual telemedicine, telehealth, or other technology-based format, which could broaden the reach and availability of this approach.

Use of Emerging Technology

Given the dynamic, quickly evolving nature of the personal technology modalities used in mHealth, it is challenging to predict future developments in this area. More sophisticated applications are being developed that involve context-dependent, adaptive interventions and that are tailored to the needs of each individual. For example, just-in-time interventions are designed to prevent relapse when a smoker is at greatest risk, including using sensors (e.g., through GPS monitoring) that track a person's location and trigger support when the person enters a high-risk environment (e.g., when the person approaches a tobacco retailer) (Naughton 2016). Such innovations may lead to interventions that improve cessation outcomes in ways that could not have been achieved without such technology. Furthermore, the commercialization of smoking cessation interventions delivered by a variety of mobile applications may lead to some promising approaches. However, the proliferation of these applications has far surpassed the capacity for the scientific evaluation of their content and effectiveness—thus, raising

concerns about their effectiveness and about how these interventions adhere to evidence-based recommendations for cessation (Abroms et al. 2013).

Ongoing smoking cessation research is exploring the utility of two specific approaches that do not rely on a particular technology platform. The first approach involves improving both the personalization of mHealth platforms and engagement with these platforms via the *use of human-technology interactions* that mimic human-human interactions. Basic versions, which are already widely used in commercial settings for other purposes, include voice phone trees and web pop-ups that are designed to help triage the caller or website user to the appropriate customer service representative or salesperson. More complex versions help consumers make decisions about which product to buy in a manner that structures the interaction as a conversation (commonly called “chatbots”). Future mHealth cessation interventions may leverage these structured human-technology interactions to deliver highly personalized, real-time cessation support.

A second strategy involves *integrating treatment data* from multiple sources so that the person delivering the cessation intervention and the smoker have access to a broader array of information and treatment options across multiple contexts. One example is integrating data from a quitline’s database with a cessation application on a caller’s smartphone. Although many cessation treatment approaches, such as quitlines, employ mHealth resources, integration across multiple platforms is rare. As with integration across treatment resources, the wide availability of electronic health records has created the possibility for increased connectivity between healthcare providers engaged in cessation treatment (see Chapter 7).

A large number (>500) of smartphone apps for quitting smoking have been developed, and these apps have generated great interest (>20 million downloads globally) (Bricker et al. 2014b). These apps include interactive features, present content in various formats, and collect information that the smartphone then exchanges with external databases. Apps have many characteristics that can be leveraged to deliver behavioral treatment and to improve adherence to medication. Although reviews have identified some high-quality cessation apps, many cessation apps lack appropriate, empirically based clinical approaches that are consistent with cessation guidelines (Abroms et al. 2011, 2013; Choi et al. 2014; Hoepfner et al. 2016; Ubhi et al. 2016). As with SMS text programs, there is wide variability in content, functionality, and user experience across even those apps that use empirically based cessation treatment approaches, which makes evaluating their utility difficult.

Social media sites are visited by 80% of U.S. adults who have access to the Internet, and most of these adults

visit such sites daily (Greenwood et al. 2016). Research into the potential utility of social media platforms for delivering and supporting cessation treatment is in its early stages. One logical and promising strategy is to leverage social media’s potential for facilitating self-help groups. This potential has not been fully realized to date because, as with such previous technologies as online bulletin boards and listservs, prolonged engagement is often poor, with initially high levels of interest often waning over time (Danaher et al. 2006; An et al. 2008; Stoddard et al. 2008; Prochaska et al. 2012). In one example of an emerging cessation intervention, Twitter is being used to create small, private groups of 20 smokers who interact for 100 days, with twice-daily automessages sent to encourage group engagement among members (Lakon et al. 2016). The intervention builds on successful past work with “buddy interventions” in which smokers were assigned physically proximal “buddies” who were also trying to quit (West et al. 1998; May and West 2000; May et al. 2006). Preliminary results for the Twitter intervention indicate that participants in quit-smoking groups often form mutually reciprocated, strong, and enduring social bonds that support smoking cessation (Lakon et al. 2016).

In another intervention, which was assessed in an RCT pilot, all 160 participants were linked to Smokefree.gov and provided with nicotine patches. A subgroup of these participants was randomized to participate in a quit-smoking group on Twitter; the study found that they were twice as likely to report sustained abstinence as those who used the website and patch alone (40% vs. 20%, OR = 2.67; 95% CI, 1.19–5.99) (Pechmann et al. 2017). Similar efforts are underway to leverage Facebook and WhatsApp to engage young adults in cessation treatment. Cessation interventions leveraging these social media platforms have shown encouraging short-term effects (Cobb et al. 2014; Cheung et al. 2015; Haines-Saah et al. 2015; Ramo et al. 2015; Baskerville et al. 2016).

Emerging Pharmacologic Approaches

Cytisine, which is not currently approved for use in the United States, was first used for quitting smoking more than 50 years ago in Eastern and Central Europe, well before the approval of any smoking cessation aids in the United States. A plant alkaloid with high affinity for the $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype, cytisine is derived from the plant *Cytisus laburnum*. The course of treatment starts at one tablet every 2 hours (maximum of six tablets total per day) for days 1–3, with a scheduled quit date at day 5, tapered to one or two tablets daily by days 21–25 (Jeong et al. 2015). In meta-analyses, the

treatment effect of cytisine was comparable to published effects for NRT, bupropion, nortriptyline, and clonidine (Hajek et al. 2013a). Two randomized placebo-controlled trials also found that cytisine was effective for smoking cessation (pooled effect: RR = 3.98; 95% CI, 2.01–7.87) (Vinnikov et al. 2008; West et al. 2011), as reviewed by Cahill and colleagues (2016), but the quality of evidence from the reviewed trials was low, in part because of small sample sizes and loss to follow-up. Furthermore, the absolute sustained long-term quit rates were modest (8.5% for cytisine vs. 2.1% for placebo at 1 year), which is generally consistent with cessation rates in the United States (Babb et al. 2017; Wang et al. 2019). The modest sustained quit rates were attributed to the minimal behavioral support provided and to the study locations, which included countries with more limited tobacco control policies than the United States. In an open-label, randomized comparative effectiveness trial conducted in New Zealand, Walker and colleagues (2014) reported 22% sustained abstinence for

cytisine at the 6-month follow-up compared with 15% for the nicotine patch (RR = 1.4; 95% CI, 1.1–1.8).

The reported side effects of cytisine are primarily gastrointestinal, including abdominal discomfort, dry mouth, dyspepsia, and nausea. Notably, the cost of cytisine in places where it is available has increased, but it is still one-half to one-twentieth the cost of other cessation medications.

In February 2019, the FDA Center for Drug Evaluation and Research (2019) issued a draft version of guidance intended to assist sponsors in the clinical development of NRT drug products, including but not limited to products intended to help cigarette smokers stop smoking. This guidance incorporates feedback received from an FDA public hearing in January 2018 and from a notice in the *Federal Register* in November 2017 requesting comments on the FDA's approach to evaluating the safety and effectiveness of NRT products, including how these products should be used and labeled (*Federal Register* 2017; FDA 2019a).

Summary of the Evidence

The prevalence of cigarette smoking in the general U.S. population has declined steadily since the 1960s (USDHHS 2014), due in part to the development and concerted implementation of evidence-based tobacco control interventions, including cessation interventions. Since 2002 the number of former smokers has been greater than the number of current smokers (CDC 2005). However, as of 2017, there were still 34 million adult current cigarette smokers in the United States (Wang et al. 2018). This chapter highlighted key topics and developments associated with the content and delivery of smoking cessation interventions, with a focus on emerging evidence that can inform future smoking cessation efforts.

The evidence indicates that nicotine addiction is a chronic, relapsing disorder and that the chances of successfully sustaining a quit attempt and avoiding relapse increase with the use of evidence-based cessation treatments, with those chances generally increasing with higher dose, duration, and intensity of treatment. A large number of high-quality studies continues to support the use of behavioral counseling, pharmacologic interventions, and combined counseling and pharmacologic interventions for smoking cessation, with the latter combination being the most effective approach. Effective counseling interventions include diverse behavioral treatments that can be delivered effectively in a variety of formats, including individual, group, and telephone counseling. There are currently seven FDA-approved medications for use as first-line tobacco cessation treatments. Although

the products are not approved for combination use, there is clear scientific evidence that combinations of short- and long-acting forms of NRT are more effective in promoting cessation than individual forms of NRT (Lindson et al. 2019). Both behavioral and pharmacologic tobacco cessation treatments have been shown to be highly cost-effective (see Chapter 5).

Nationally representative data indicate that about three in five U.S. adults who ever smoked have quit successfully and that just over half of current smokers try to quit each year, but the success of any given quit attempt remains low (Babb et al. 2017). Despite progress over the past 30 years, the reach and use of smoking cessation interventions remain low, with less than one-third of smokers using any proven cessation treatments (counseling and/or medication) from 2000 to 2015 (Babb et al. 2017). Regardless of the generally wide availability of proven cessation treatments, about two-thirds of smokers still attempt to quit without using these treatments, contributing to low rates of success (Hughes et al. 2004; Fiore et al. 2008).

Increasing smoking cessation will require several strategies, including (1) increasing the appeal, reach, and use of existing evidence-based cessation interventions; (2) further increasing the effectiveness of those interventions; and (3) developing additional cessation interventions that have greater reach and/or effectiveness than existing interventions or that appeal to and are used by different populations of smokers. Increasing cessation at the population level will also require increasing quit

attempts (including the number of smokers making quit attempts and the number of quit attempts that individual smokers make) and quit success, with quit attempts being driven primarily by the reach of cessation interventions and quit success being driven primarily by the intensity of these interventions (Zhu et al. 2012).

Additional research is needed to better understand (a) how e-cigarette use impacts smoking cessation, including determining which types of e-cigarettes and which patterns and contexts of e-cigarette use may facilitate or hinder smoking cessation among adults, and (b) the negative impacts of e-cigarette use (e.g., increases in youth initiation of e-cigarettes, conventional cigarettes, and other tobacco products; dual use of e-cigarettes and other combusted tobacco products; decreased use of evidence-based cessation treatments; and decreased or

delayed complete cessation of conventional cigarettes and other combustible tobacco products). The research will need to track the changes in products over time.

Promising directions include leveraging emerging technologies to enhance the sustained engagement of smokers in cessation treatment, accelerating the integration of cessation services across multiple platforms and within healthcare systems, and developing new tobacco cessation medications and new indications for existing cessation medications. Although this chapter focuses on cessation interventions at the individual level, several population- and policy-based approaches (discussed in Chapter 7) have also been found to be effective in increasing tobacco cessation. Many of these broader approaches can be leveraged to complement and further increase the use of the cessation treatments described in this chapter.

Conclusions

1. The evidence is sufficient to infer that behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment.
2. The evidence is sufficient to infer that behavioral counseling and cessation medications are independently effective in increasing smoking cessation, and even more effective when used in combination.
3. The evidence is sufficient to infer that proactive quit-line counseling, when provided alone or in combination with cessation medications, increases smoking cessation.
4. The evidence is sufficient to infer that short text message services about cessation are independently effective in increasing smoking cessation, particularly if they are interactive or tailored to individual text responses.
5. The evidence is sufficient to infer that web or Internet-based interventions increase smoking cessation and can be more effective when they contain behavior change techniques and interactive components.
6. The evidence is inadequate to infer that smartphone apps for smoking cessation are independently effective in increasing smoking cessation.
7. The evidence is sufficient to infer that combining short- and long-acting forms of nicotine replacement therapy increases smoking cessation compared with using single forms of nicotine replacement therapy.
8. The evidence is suggestive but not sufficient to infer that pre-loading (e.g., initiating cessation medication in advance of a quit attempt), especially with the nicotine patch, can increase smoking cessation.
9. The evidence is suggestive but not sufficient to infer that very-low-nicotine-content cigarettes can reduce smoking and nicotine dependence and increase smoking cessation when full-nicotine cigarettes are readily available; the effects on cessation may be further strengthened in an environment in which conventional cigarettes and other combustible tobacco products are not readily available.
10. The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation. However, the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine, and the evidence is suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes.
11. The evidence is sufficient to infer that certain life events—including hospitalization, surgery, and lung cancer screening—can trigger attempts to quit

smoking, uptake of smoking cessation treatment, and smoking cessation.

12. The evidence is suggestive but not sufficient to infer that fully and consistently integrating standardized, evidence-based smoking cessation interventions

into lung cancer screening increases smoking cessation while avoiding potential adverse effects of this screening on cessation outcomes.

13. The evidence is suggestive but not sufficient to infer that cytisine increases smoking cessation.

References¹

- Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine* 2011;365(5):395–409.
- Abroms LC, Lee Westmaas J, Bontemps-Jones J, Ramani R, Mellerson J. A content analysis of popular smartphone apps for smoking cessation. *American Journal of Preventive Medicine* 2013;45(6):732–6.
- Abroms LC, Padmanabhan N, Thaweethai L, Phillips T. iPhone apps for smoking cessation: a content analysis. *American Journal of Preventive Medicine* 2011;40(3):279–85.
- Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, Cummings KM, McNeill A, Thrasher JF, Hammond D, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. *American Journal of Preventive Medicine* 2013;44(3):207–15.
- Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *International Journal of Environmental Research and Public Health* 2014;11(11):11220–48.
- Adsit RT, Fox BM, Tsiolis T, Ogland C, Simerson M, Vind LM, Bell SM, Skora AD, Baker TB, Fiore MC. Using the electronic health record to connect primary care patients to evidence-based telephonic tobacco quitline services: a closed-loop demonstration project. *Translational Behavioral Medicine* 2014;4(3):324–32.
- Agaku IT, King BA, Husten CG, Bunnell R, Ambrose BK, Hu SS, Holder-Hayes E, Day HR. Tobacco product use among adults—United States, 2012–2013. *Morbidity and Mortality Weekly Report* 2014;63(25):542–7.
- Agboola S, McNeill A, Coleman T, Leonardi Bee J. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. *Addiction* 2010;105(8):1362–80.
- Agency for Healthcare Research and Quality. Patients not ready to make a quit attempt now (The “5 R’s”). Rockville (MD): Agency for Healthcare Research and Quality, 2012; <<http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5rs.html>>; accessed: January 14, 2019.
- Ainscough TS, Brose LS, Strang J, McNeill A. Contingency management for tobacco smoking during opioid addiction treatment: a randomised pilot study. *BMJ Open* 2017;7(9):e017467.
- Al-Delaimy WK, Myers MG, Leas EC, Strong DR, Hofstetter CR. E-cigarette use in the past and quitting behavior in the future: a population-based study. *American Journal of Public Health* 2015;105(6):1213–9.
- Allen MH, Debanné M, Lazignac C, Adam E, Dickinson LM, Damsa C. Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: a double-blind, randomized, placebo-controlled study. *American Journal of Psychiatry* 2011;168(4):395–9.
- Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control* 2013;22(1):32–7.
- Alzahrani T, Glantz SA. The association between e-cigarette use and myocardial infarction is what one would expect based on the biological and clinical evidence. *American Journal of Preventive Medicine* 2019;56(4):627.
- Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. *American Journal of Preventive Medicine* 2018;55(4):455–61.
- American College of Surgeons. Statement on the effects of tobacco use on surgical complications and the utility of smoking cessation counseling, August 1, 2014; <<https://www.facs.org/about-ac/s/statements/71-tobacco-use>>; accessed: February 13, 2018.
- An LC, Bluhm JH, Foldes SS, Alesci NL, Klatt CM, Center BA, Nersesian WS, Larson ME, Ahluwalia JS, Manley MW. A randomized trial of a pay-for-performance program targeting clinician referral to a state tobacco quitline. *Archives of Internal Medicine* 2008;168(18):1993–9.
- An LC, Schillo BA, Kavanaugh AM, Lachter RB, Luxenberg MG, Wendling AH, Joseph AM. Increased reach and effectiveness of a statewide tobacco quitline after the addition of access to free nicotine replacement therapy. *Tobacco Control* 2006;15(4):286–93.
- Anderson CM. *Quitline Services: Current Practice and Evidence Base*. Phoenix (AZ): North American Quitline Consortium, 2016; <http://c.ymcdn.com/sites/www.naquitline.org/resource/resmgr/issue_papers/Quitline_Services_issue_pape.pdf>; accessed: May 24, 2017.
- Anguiano B, Brown-Johnson C, Rosas LG, Pechmann C, Prochaska JJ. Latino adults' perspectives on treating tobacco use via social media. *JMIR Mhealth and Uhealth* 2017;5(2):e12.

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387(10037):2507–20.
- Anthenelli RM, Morris C, Ramey TS, Dubrava SJ, Tsilkos K, Russ C, Yunis C. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Annals of Internal Medicine* 2013;159(6):390–400.
- Applegate BW, Sheffer CE, Crews KM, Payne TJ, Smith PO. A survey of tobacco-related knowledge, attitudes and behaviours of primary care providers in Mississippi. *Journal of Evaluation in Clinical Practice* 2008;14(4):537–44.
- Aronson SJ, Rehm HL. Building the foundation for genomics in precision medicine. *Nature* 2015;526(7573):336–42.
- Ashare RL, Tang KZ, Mesaros AC, Blair IA, Leone F, Strasser AA. Effects of 21 days of varenicline versus placebo on smoking behaviors and urges among non-treatment seeking smokers. *Journal of Psychopharmacology* 2012;26(10):1383–90.
- Asian Smokers' Quitline. Home page, n.d.; <<http://www.asiansmokersquitline.org>>; accessed: August 17, 2017.
- Atienza AA, Patrick K. Mobile health: the killer app for cyber-infrastructure and consumer health. *American Journal of Preventive Medicine* 2011;40(5 Suppl 2):S151–S153.
- Aubin HJ, Luquiens A, Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. *British Journal of Clinical Pharmacology* 2014;77(2):324–36.
- Augustine JM, Taylor AM, Pelger M, Schiefer D, Warholak TL. Smoking quit rates among patients receiving pharmacist-provided pharmacotherapy and telephonic smoking cessation counseling. *Journal of the American Pharmacists Association* 2016;56(2):129–36.
- Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;65(52):1457–64.
- Baca CT, Yahne CE. Smoking cessation during substance abuse treatment: what you need to know. *Journal of Substance Abuse Treatment* 2009;36(2):205–19.
- Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA: the Journal of the American Medical Association* 2012;307(22):2418–29.
- Baezconde-Garbanati L, Guy M, Soto C. *The Use of Quitlines Among Priority Populations in the U.S.: Lessons from the Scientific Evidence*. Oakland (CA): North American Quitline Consortium, 2011; <https://cdn.ymaws.com/www.naquitline.org/resource/resmgr/Issue_Papers/IssuePaperTheUseofQuitlinesA.pdf>; accessed: May 2, 2019.
- Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim SY, Colby S, Conti D, Giovino GA, Hatsukami D, et al. Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. *Nicotine and Tobacco Research* 2007;9(Suppl 4):S555–S570.
- Barrera R, Shi W, Amar D, Thaler HT, Gabovich N, Bains MS, White DA. Smoking and timing of cessation: impact on pulmonary complications after thoracotomy. *Chest* 2005;127(6):1977–83.
- Baskerville NB, Azagba S, Norman C, McKeown K, Brown KS. Effect of a digital social media campaign on young adult smoking cessation. *Nicotine and Tobacco Research* 2016;18(3):351–60.
- Bauld L, Graham H, Sinclair L, Flemming K, Naughton F, Ford A, McKell J, McCaughan D, Hopewell S, Angus K, et al. Barriers to and facilitators of smoking cessation in pregnancy and following childbirth: literature review and qualitative study. *Health Technology Assessment* 2017;21(36):1–158.
- Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ* 2016;354:i4645.
- Beck AT. Cognitive therapy: nature and relation to behavior therapy. *Behavior Therapy* 1970;1(2):184–200.
- Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiology, Biomarkers and Prevention* 2012;21(5):761–9.
- Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers and Prevention* 2007;16(11):2479–85.
- Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *New England Journal of Medicine* 1994;331(2):123–5.
- Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tobacco Control* 2013;22(Suppl 1):i14–i17.
- Benowitz NL, Nardone N, Dains KM, Hall SM, Stewart S, Dempsey D, Jacob P 3rd. Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior

- and tobacco smoke toxicant exposure: 2-year follow up. *Addiction* 2015;110(10):1667–75.
- Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Internal Medicine* 2018;178(5):622–31.
- Berger I, Mooney-Somers J. Smoking cessation programs for lesbian, gay, bisexual, transgender, and intersex people: a content-based systematic review. *Nicotine and Tobacco Research* 2016.
- Bernstein SL, Boudreaux ED. Emergency department-based tobacco interventions improve patient satisfaction. *Journal of Emergency Medicine* 2010;38(4):e35–e40.
- Berry KM, Reynolds LM, Collins JM, Siegel MB, Fetterman JL, Hamburg NM, Bhatnagar A, Benjamin EJ, Stokes A. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013–2015. *Tobacco Control* 2019;28(1):42–9.
- Bhatta DN, Glantz SA. Electronic cigarette use and myocardial infarction among adults in the U.S. Population Assessment of Tobacco and Health. *Journal of the American Heart Association* 2019;8(12):e012317.
- Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine and Tobacco Research* 2015;17(2):127–33.
- Bloom EL, Wing RR, Kahler CW, Thompson JK, Meltzer S, Hecht J, Minami H, Price LH, Brown RA. Distress tolerance treatment for weight concern in smoking cessation among women: the WE QUIT Pilot Study. *Behavior Modification* 2017;41(4):468–98.
- Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *New England Journal of Medicine* 2019.
- Blumenthal DS. Barriers to the provision of smoking cessation services reported by clinicians in underserved communities. *Journal of the American Board of Family Medicine* 2007;20(3):272–9.
- Bock B, Graham A, Sciamanna C, Krishnamoorthy J, Whiteley J, Carmona-Barros R, Niaura R, Abrams D. Smoking cessation treatment on the Internet: content, quality, and usability. *Nicotine and Tobacco Research* 2004;6(2):207–19.
- Bock BC, Graham AL, Whiteley JA, Stoddard JL. A review of web-assisted tobacco interventions (WATIs). *Journal of Medical Internet Research* 2008;10(5):e39.
- Bombard JM, Farr SL, Dietz PM, Tong VT, Zhang L, Rabius V. Telephone smoking cessation quitline use among pregnant and non-pregnant women. *Maternal and Child Health Journal* 2013;17(6):989–95.
- Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer* 2014;120(22):3527–35.
- Borland R, Partos TR, Cummings KM. Systematic biases in cross-sectional community studies may underestimate the effectiveness of stop-smoking medications. *Nicotine and Tobacco Research* 2012;14(12):1483–7.
- Borrelli B, Bartlett YK, Tooley E, Armitage CJ, Wearden A. Prevalence and frequency of mHealth and eHealth use among U.S. and UK smokers and differences by motivation to quit. *Journal of Medical Internet Research* 2015;17(7):e164.
- Boucher J, Konkle AT. Understanding inequalities of maternal smoking—bridging the gap with adapted intervention strategies. *International Journal of Environmental Research and Public Health* 2016;13(3):pii: E282.
- Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD008743. DOI: 10.1002/14651858.CD008743.pub2.
- Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD008743. DOI: 10.1002/14651858.CD008743.pub3.
- Bricker J, Wyszynski C, Comstock B, Heffner JL. Pilot randomized controlled trial of web-based acceptance and commitment therapy for smoking cessation. *Nicotine and Tobacco Research* 2013;15(10):1756–64.
- Bricker JB, Bush T, Zbikowski SM, Mercer LD, Heffner JL. Randomized trial of telephone-delivered acceptance and commitment therapy versus cognitive behavioral therapy for smoking cessation: a pilot study. *Nicotine and Tobacco Research* 2014a;16(11):1446–54.
- Bricker JB, Copeland W, Mull KE, Zeng EY, Watson NL, Akioka KJ, Heffner JL. Single-arm trial of the second version of an acceptance & commitment therapy smartphone application for smoking cessation. *Drug and Alcohol Dependence* 2017;170:37–42.
- Bricker JB, Mann SL, Marek PM, Liu J, Peterson AV. Telephone-delivered acceptance and commitment therapy for adult smoking cessation: a feasibility study. *Nicotine and Tobacco Research* 2010;12(4):454–8.
- Bricker JB, Mull KE, Kientz JA, Vilardaga R, Mercer LD, Akioka KJ, Heffner JL. Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy. *Drug and Alcohol Dependence* 2014b;143:87–94.
- Bricker JB, Sridharan V, Zhu Y, Mull KE, Heffner JL, Watson NL, McClure JB, Di C. Trajectories of 12-month

- usage patterns for two smoking cessation websites: exploring how users engage over time. *Journal of Medical Internet Research* 2018;20(4):e10143.
- Brody AL, Zorick T, Hubert R, Hellemann GS, Balali S, Kawasaki SS, Garcia LY, Enoki R, Abraham P, Young P, et al. Combination extended smoking cessation treatment plus home visits for smokers with schizophrenia: a randomized controlled trial. *Nicotine and Tobacco Research* 2017;19(1):68–76.
- Brooks-Brunn JA. Predictors of postoperative pulmonary complications following abdominal surgery. *Chest* 1997;111(3):564–71.
- Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction* 2015;110(7):1160–8.
- Buchting FO, Emory KT, Scout NFN, Kim Y, Fagan P, Vera LE, Emery S. Transgender use of cigarettes, cigars, and e-cigarettes in a national study. *American Journal of Preventive Medicine* 2017;53(1):e1–e7.
- Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013;382(9905):1629–37.
- Bullen C, Howe C, Lin RB, Grigg M, Laugesen M, McRobbie H, Glover M, Walker N, Wallace-Bell M, Whittaker R, et al. Pre-cessation nicotine replacement therapy: pragmatic randomized trial. *Addiction* 2010;105(8):1474–83.
- Bush TM, McAfee T, Deprey M, Mahoney L, Fellows JL, McClure J, Cushing C. The impact of a free nicotine patch starter kit on quit rates in a state quit line. *Nicotine and Tobacco Research* 2008;10(9):1511–6.
- Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical Psychology Review* 2006;26(1):17–31.
- Cahill K, Hartmann-Boyce J, Perera R. Incentives for smoking cessation. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub5.
- Cahill K, Lancaster T. Workplace interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD003440. DOI: 10.1002/14651858.CD003440.pub4.
- Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub7.
- Cahill K, Perera R. Competitions and incentives for smoking cessation. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub4.
- Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD009329. DOI: 10.1002/14651858.CD009329.pub2.
- Campaign for Tobacco-Free Kids. *Broken Promises to Our Children: A State-by-State Look at the 1998 Tobacco Settlement 20 Years Later, 2018*; <<https://www.tobaccofreekids.org/what-we-do/us/statereport>>; accessed: January 15, 2019.
- Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 2013;8(6):e66317.
- Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. Quit methods used by U.S. adult cigarette smokers, 2014–2016. *Preventing Chronic Disease* 2017;14:160600.
- Carpenter MJ, Jardin BF, Burris JL, Mathew AR, Schnoll RA, Rigotti NA, Cummings KM. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs* 2013;73(5):407–26.
- Carr AB, Ebbert J. Interventions for tobacco cessation in the dental setting. *Cochrane Database of Systematic Reviews* 2012, Issue 6. Art. No.: CD005084. DOI: 10.1002/14651858.CD005084.pub3.
- Carson KV, Verbiest MEA, Crone MR, Brinn MP, Esterman AJ, Assendelft WJJ, Smith BJ. Training health professionals in smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD000214. DOI: 10.1002/14651858.CD000214.pub2.
- Cartmell KB, Dismuke CE, Dooley M, Mueller M, Nahhas GJ, Warren GW, Fallis P, Cummings KM. Effect of an inpatient tobacco dependence treatment service on 1-year postdischarge health care costs. *Medical Care* 2018a;56(10):883–9.
- Cartmell KB, Dooley M, Mueller M, Nahhas GJ, Dismuke CE, Warren GW, Talbot V, Cummings KM. Effect of an evidence-based inpatient tobacco dependence treatment service on 30-, 90-, and 180-day hospital readmission rates. *Medical Care* 2018b;56(4):358–63.
- Cataldo JK. High-risk older smokers' perceptions, attitudes, and beliefs about lung cancer screening. *Cancer Medicine* 2016;5(4):753–9.
- Catley D, Goggin K, Harris KJ, Richter KP, Williams K, Patten C, Resnicow K, Ellerbeck EF, Bradley-Ewing A, Lee HS, et al. A randomized trial of motivational interviewing: cessation induction among smokers with low desire to quit. *American Journal of Preventive Medicine* 2016;50(5):573–83.

- Center for Drug Evaluation and Research. *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products*, February 2019; <<https://www.regulations.gov/document?D=FDA-2019-D-0297-0002>>; accessed: May 9, 2019.
- Center for Substance Abuse Treatment. Chapter 8. Intensive outpatient treatment approaches. In: *Substance Abuse: Clinical Issues in Intensive Outpatient Treatment*. Treatment Improvement Protocol (TIP) Series, No. 47. Rockville (MD): Substance Abuse and Mental Health Services Administration, 2006. DHHS Publication No. (SMA) 06-4182.
- Centers for Disease Control and Prevention. *Telephone Quitlines: A Resource for Development, Implementation, and Evaluation*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, September 2004.
- Centers for Disease Control and Prevention. State-specific prevalence of cigarette smoking and quitting among adults—United States, 2004. *Morbidity and Mortality Weekly Report* 2005;54(44):1124–7.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/comprehensive.pdf>; accessed: July 26, 2017.
- Centers for Disease Control and Prevention. QuickStats: cigarette smoking status among current adult e-cigarette users, by age group—National Health Interview Survey, United States, 2015. *Morbidity and Mortality Weekly Report* 2016;65(42):1177.
- Centers for Medicaid and Medicare Services. Medicaid Incentives for Prevention of Chronic Diseases grants [press release], September 13, 2011; <<https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2011-Fact-sheets-items/2011-09-13.html>>; accessed: February 23, 2018.
- Centers for Medicaid and Medicare Services. Medicaid Incentives for the Prevention of Chronic Diseases Model, January 8 2018; <<https://innovation.cms.gov/initiatives/MIPCD/>>; accessed: February 9, 2018.
- Centers for Medicare and Medicaid Services. Decision memo for screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439N), 2015; <<https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274>>; accessed: July 18, 2019.
- Chaiton M, Diemert L, Cohen JE, Bondy SJ, Selby P, Philipneri A, Schwartz R. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open* 2016;6(6):e011045.
- Chang PH, Chiang CH, Ho WC, Wu PZ, Tsai JS, Guo FR. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health* 2015;15:689.
- Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology* 2006;184(3-4):353–66.
- Chenoweth MJ, Tyndale RF. Pharmacogenetic optimization of smoking cessation treatment. *Trends in Pharmacological Sciences* 2017;38(1):55–66.
- Cheung YT, Chan CH, Lai CK, Chan WF, Wang MP, Li HC, Chan SS, Lam TH. Using WhatsApp and Facebook online social groups for smoking relapse prevention for recent quitters: a pilot pragmatic cluster randomized controlled trial. *Journal of Medical Internet Research* 2015;17(10):e238.
- Choi J, Noh GY, Park DJ. Smoking cessation apps for smartphones: content analysis with the self-determination theory. *Journal of Medical Internet Research* 2014;16(2):e44.
- Cinciripini PM, Robinson JD, Karam-Hage M, Minnix JA, Lam C, Versace F, Brown VL, Engelmann JM, Wetter DW. Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. *JAMA Psychiatry* 2013;70(5):522–33.
- Civiljak M, Stead LF, Hartmann-Boyce J, Sheikh A, Car J. Internet-based interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD007078. DOI: 10.1002/14651858.CD007078.pub4.
- Clapp PW, Jaspers I. Electronic cigarettes: their constituents and potential links to asthma. *Current Allergy and Asthma Reports* 2017;17(11):79.
- Clark MM, Cox LS, Jett JR, Patten CA, Schroeder DR, Nirelli LM, Vickers K, Hurt RD, Swensen SJ. Effectiveness of smoking cessation self-help materials in a lung cancer screening population. *Lung Cancer* 2004;44(1):13–21.
- Cobb NK, Graham AL. Characterizing Internet searchers of smoking cessation information. *Journal of Medical Internet Research* 2006;8(3):e17.
- Cobb NK, Jacobs MA, Saul J, Wileyto EP, Graham AL. Diffusion of an evidence-based smoking cessation intervention through Facebook: a randomised controlled trial study protocol. *BMJ Open* 2014;4(1):e004089.

- Cole-Lewis H, Augustson E, Sanders A, Schwarz M, Geng Y, Coa K, Hunt Y. Analysing user-reported data for enhancement of SmokefreeTXT: a national text message smoking cessation intervention. *Tobacco Control* 2016.
- Coleman-Cowger VH, Koszowski B, Rosenberry ZR, Terplan M. Factors associated with early pregnancy smoking status among low-income smokers. *Maternal and Child Health Journal* 2016;20(5):1054–60.
- Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2012a, Issue 9. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.
- Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.pub2.
- Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, Lewis S. A randomized trial of nicotine-replacement therapy patches in pregnancy. *New England Journal of Medicine* 2012b;366(9):808–18.
- Collins SE, Witkiewitz K, Kirouac M, Marlatt GA. Preventing relapse following smoking cessation. *Current Cardiovascular Risk Reports* 2010;4(6):421–8.
- Conklin CA, Salkeld RP, Perkins KA, Robin N. Do people serve as cues to smoke? *Nicotine and Tobacco Research* 2013;15(12):2081–7.
- Connett JE, Kusek JW, Bailey WC, O'Hara P, Wu M. Design of the Lung Health Study: a randomized clinical trial of early intervention for chronic obstructive pulmonary disease. *Controlled Clinical Trials* 1993;14(2 Suppl)3S–19S.
- Cooper J, Borland R, Yong HH, McNeill A, Murray RL, O'Connor RJ, Cummings KM. To what extent do smokers make spontaneous quit attempts and what are the implications for smoking cessation maintenance? Findings from the International Tobacco Control Four country survey. *Nicotine and Tobacco Research* 2010;12(Suppl):S51–S57.
- Corelli RL, Hudmon KS. Medications for smoking cessation. *Western Journal of Medicine* 2002;176(2):131–5.
- Corey CG, Chang JT, Rostron BL. Electronic nicotine delivery system (ENDS) battery-related burns presenting to US emergency departments, 2016. *Injury Epidemiology* 2018;5(1):4.
- Cristea IA, Gentili C, Cotet CD, Palomba D, Barbui C, Cuijpers P. Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;74(4):319–28.
- Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. *Psychopharmacology* 2003;168(3):347–58.
- Culbertson CS, Shulenberg S, De La Garza R, Newton TF, Brody AL. Virtual reality cue exposure therapy for the treatment of tobacco dependence. *Journal of Cyber Therapy and Rehabilitation* 2012;5(1):57–64.
- Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students—United States, 2011–2018. *Morbidity and Mortality Weekly Report* 2018;67(45):1276–7.
- Cummings KM, Fix B, Celestino P, Carlin-Menter S, O'Connor R, Hyland A. Reach, efficacy, and cost-effectiveness of free nicotine medication giveaway programs. *Journal of Public Health Management and Practice* 2006;12(1):37–43.
- Cummings KM, Hyland A, Carlin-Menter S, Mahoney MC, Willett J, Juster HR. Costs of giving out free nicotine patches through a telephone quit line. *Journal of Public Health Management and Practice* 2011;17(3):E16–E23.
- Cummings SR, Stein MJ, Hansen B, Richard RJ, Gerbert B, Coates TJ. Smoking counseling and preventive medicine. A survey of internists in private practices and a health maintenance organization. *Archives of Internal Medicine* 1989;149(2):345–9.
- Cummins SE, Tedeschi GJ, Anderson CM, Zhu SH. Telephone Intervention for pregnant smokers: a randomized controlled trial. *American Journal of Preventive Medicine* 2016;51(3):318–26.
- Curtin SC, Mathews TJ. Smoking prevalence and cessation before and during pregnancy: data from the birth certificate, 2014. *National Vital Statistics Reports* 2016;65(1):1–14.
- Danaher BG, Boles SM, Akers L, Gordon JS, Severson HH. Defining participant exposure measures in Web-based health behavior change programs. *Journal of Medical Internet Research* 2006;8(3):e15.
- Das S, Prochaska JJ. Innovative approaches to support smoking cessation for individuals with mental illness and co-occurring substance use disorders. *Expert Review of Respiratory Medicine* 2017;11(10):841–50.
- Delgado-Rodriguez M, Medina-Cuadros M, Martinez-Gallego G, Gómez-Ortega A, Mariscal-Ortiz M, Palma-Pérez S, Sillero-Arenas M. A prospective study of tobacco smoking as a predictor of complications in general surgery. *Infection Control and Hospital Epidemiology* 2003;24(1):37–43.
- Delnevo CD, Giovenco DP, Steinberg MB, Villanti AC, Pearson JL, Niaura RS, Abrams DB. Patterns of Electronic Cigarette Use Among Adults in the United States. *Nicotine and Tobacco Research* 2016;18(5):715–9.
- Denison E, Underland V, Mosdøl A, Vist GE. *Cognitive Therapies for Smoking Cessation: A Systematic Review*. Oslo (Norway): The Norwegian Institute of Public Health, 2017.

- Denlinger-Apte RL, Donny EC, Lindgren BR, Rubin N, Goodwin C, DeAtley T, Colby SM, Cioe PA, Hatsukami DK, Tidey JW. Smoking topography characteristics during a six-week trial of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine and Tobacco Research* 2019;ntz198.
- Deprey M, McAfee T, Bush T, McClure JB, Zbikowski S, Mahoney L. Using free patches to improve reach of the Oregon Quit Line. *Journal of Public Health Management and Practice* 2009;15(5):401–8.
- Dermody SS, McClernon FJ, Benowitz N, Luo X, Tidey JW, Smith TT, Vandrey R, Hatsukami D, Donny EC. Effects of reduced nicotine content cigarettes on individual withdrawal symptoms over time and during abstinence. *Experimental and Clinical Psychopharmacology* 2018;26(3):223–32.
- DiClemente CC, Dolan-Mullen P, Windsor RA. The process of pregnancy smoking cessation: implications for interventions. *Tobacco Control* 2000;9(Suppl 3):iii16–iii21.
- DiGiulio A, Jump Z, Yu A, Babb S, Schecter A, Williams KS, Yembra D, Armour BS. State Medicaid coverage for tobacco cessation treatments and barriers to accessing treatments—United States, 2015–2017. *Morbidity and Mortality Weekly Report* 2018;67(13):390–5.
- Dilley JA, Spigner C, Boysun MJ, Dent CW, Pizacani BA. Does tobacco industry marketing excessively impact lesbian, gay and bisexual communities? *Tobacco Control* 2008;17(6):385–90.
- Dobbie F, Hiscock R, Leonardi-Bee J, Murray S, Shahab L, Aveyard P, Coleman T, McEwen A, McRobbie H, Purves R, et al. Evaluating Long-term Outcomes of NHS Stop Smoking Services (ELONS): a prospective cohort study. *Health Technology Assessment* 2015;19(95):1–156.
- Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine and Tobacco Research* 2013;15(10):1737–44.
- Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328(7455):1519.
- Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, et al. Randomized trial of reduced-nicotine standards for cigarettes. *New England Journal of Medicine* 2015;373(14):1340–9.
- Donny EC, Hatsukami DK, Benowitz NL, Sved AF, Tidey JW, Cassidy RN. Reduced nicotine product standards for combustible tobacco: building an empirical basis for effective regulation. *Preventive Medicine* 2014;68:17–22.
- Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction* 2007;102(2):324–34.
- Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug and Alcohol Dependence* 2009;104(1–2):23–33.
- Drake P, Driscoll AK, Mathews TJ. *Cigarette Smoking During Pregnancy: United States, 2016*. NCHS Data Brief, Number 305. Hyattsville (MD): National Center for Health Statistics, 2018.
- Dreher M, Schillo BA, Hull M, Esqueda V, Mowery A. A case study for redesigning tobacco cessation services gaining critical insights from current and former smokers. *Social Marketing Quarterly* 2015;21(4):200–13.
- Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, Hurt RD. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA: the Journal of the American Medical Association* 2014;311(2):155–63.
- Ebbert JO, Hays JT, Hurt RD. Combination pharmacotherapy for stopping smoking: what advantages does it offer? *Drugs* 2010;70(6):643–50.
- Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu CR, Dutro MP, Park PW. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2015;313(7):687–94.
- Ebbert JO, Post JA, Moyer TP, Dale LC, Schroeder DR, Hurt RD. Nicotine percentage replacement among smokeless tobacco users with nicotine patch. *Drug and Alcohol Dependence* 2007;89(2–3):223–6.
- Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation* 2016;133(1):21–30.
- El Dib R, Suzumura EA, Akl EA, Gomaa H, Agarwal A, Chang Y, Prasad M, Ashoorion V, Heels-Ansdell D, Maziak W, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. *BMJ Open* 2017;7(2):e012680.
- Ellis A. *Reason and Emotion in Psychotherapy*. New York (NY): Lyle Stuart, 1962.
- Erythropel HC, Jabba SV, DeWinter TM, Mendizabal M, Anastas PT, Jordt SE, Zimmerman JB. Formation of flavorant-propylene glycol adducts with novel toxicological properties in chemically unstable e-cigarette liquids. *Nicotine and Tobacco Research* 2019;21(9):1248–58.
- Etter JF. Comparing the efficacy of two Internet-based, computer-tailored smoking cessation programs: a randomized trial. *Journal of Medical Internet Research* 2005;7(1):e2.
- Evins AE, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, Achtyes ED, Ayer D, Schoenfeld DA. Maintenance

- treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2014;311(2):145–54.
- Fagan P, Augustson E, Backinger CL, O’Connell ME, Vollinger RE Jr, Kaufman A, Gibson JT. Quit attempts and intention to quit cigarette smoking among young adults in the United States. *American Journal of Public Health* 2007;97(8):1412–20.
- Fagerström K, Etter JF, Unger JB. E-cigarettes: a disruptive technology that revolutionizes our field? *Nicotine and Tobacco Research* 2015;17(2):125–6.
- Fagerström K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ* 2010;341:c6549.
- Farsalinos K, Niaura R. E-cigarette use and myocardial infarction: association versus causal inference. *American Journal of Preventive Medicine* 2019a;56(4):626–7.
- Farsalinos K, Niaura R. E-cigarettes and smoking cessation in the United States according to frequency of e-cigarette use and quitting duration: analysis of the 2016 and 2017 National Health Interview Surveys. *Nicotine and Tobacco Research* 2019b.
- Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of “vapers” who had achieved complete substitution of smoking. *Substance Abuse* 2013a;7:139–46.
- Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities’ regulation. *International Journal of Environmental Research and Public Health* 2013b;10(6):2500–14.
- Farsalinos KE, Spyrou A, Stefopoulos C, Tsimopoulou K, Kourkouveli P, Tsiapras D, Kyrzopoulos S, Poulas K, Voudris V. Corrigendum: Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). *Scientific Reports* 2015;5:13506.
- Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific Reports* 2014;4:4133.
- Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Protocol proposal for, and evaluation of, consistency in nicotine delivery from the liquid to the aerosol of electronic cigarettes atomizers: regulatory implications. *Addiction* 2016;111(6):1069–76.
- FDAnews. Carrot lands FDA approval for smoking cessation mobile device, October 11, 2017; <<https://www.fdanews.com/articles/183905-carrot-lands-fda-approval-for-smoking-cessation-mobile-device>>; accessed: January 8, 2019.
- Federal Communications Commission. Mapping broadband health in America, n.d.; <<https://www.fcc.gov/health/maps>>; accessed: March 20, 2019.
- Federal Register*. U.S. Food and Drug Administration. The Food and Drug Administration’s Approach To Evaluating Nicotine Replacement Therapies; Public Hearing; Request for Comments. 82 *Fed. Reg.* 56759 (2017); <<https://www.federalregister.gov/d/2017-25671>>; accessed: May 9, 2019.
- Federal Register*. U.S. Food and Drug Administration. Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies; Public Hearing; Request for Comments. 83 *Fed. Reg.* 55318 (2018); <<https://www.federalregister.gov/d/2018-24126>>; accessed: January 9, 2019.
- Federal Register*. U.S. Department of Health and Human Services, Food and Drug Administration. Modifications to labeling of nicotine replacement therapy products for over-the-counter human use. 78 *Fed. Reg.* 19718 (2013).
- Fellows JL, Bush T, McAfee T, Dickerson J. Cost effectiveness of the Oregon quitline “free patch initiative”. *Tobacco Control* 2007;16(Suppl 1):i47–i52.
- Ferguson J, Docherty G, Bauld L, Lewis S, Lorgelly P, Boyd KA, McEwen A, Coleman T. Effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline: randomised controlled trial. *BMJ* 2012;344:e1696.
- Fergusson DM, Horwood LJ. Transitions to cigarette smoking during adolescence. *Addictive Behaviors* 1995;20(5):627–42.
- Ferketich AK, Otterson GA, King M, Hall N, Browning KK, Wewers ME. A pilot test of a combined tobacco dependence treatment and lung cancer screening program. *Lung Cancer* 2012;76(2):211–5.
- Fiore M, Adsit R, Zehner M, McCarthy D, Lundsten S, Hartlaub P, Mahr T, Gorrilla A, Skora A, Baker T. An electronic health record-based interoperable eReferral system to enhance smoking quitline treatment in primary care. *Journal of the American Medical Informatics Association* 2019.
- Fiore M, Baker T. Reduced-nicotine cigarettes—a promising regulatory pathway. *New England Journal of Medicine* 2015;373(14):1289–91.
- Fiore MC, Goplerud E, Schroeder SA. The Joint Commission’s new tobacco-cessation measures—will hospitals do the right thing? *New England Journal of Medicine* 2012;366(13):1172–4.
- Fiore MC, Jaen CR. A clinical blueprint to accelerate the elimination of tobacco use. *JAMA: the Journal of the American Medical Association* 2008;299(17):2083–5.

- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Flemming K, McCaughan D, Angus K, Graham H. Qualitative systematic review: barriers and facilitators to smoking cessation experienced by women in pregnancy and following childbirth. *Journal of Advanced Nursing* 2015;71(6):1210–26.
- Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke MV, Rhoads GG. Factors associated with quitting smoking at a tobacco dependence treatment clinic. *American Journal of Health Behavior* 2006;30(4):400–12.
- Foulds J, Schmelzer AC, Steinberg MB. Treating tobacco dependence as a chronic illness and a key modifiable predictor of disease. *International Journal of Clinical Practice* 2010;64(2):142–6.
- Franck C, Budlovsky T, Windle SB, Filion KB, Eisenberg MJ. Electronic cigarettes in North America: history, use, and implications for smoking cessation. *Circulation* 2014;129(19):1945–52.
- Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, Rodgers A, Cairns J, Kenward MG, Roberts I. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet* 2011;378(9785):49–55.
- Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, Patel V, Haines A. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. *PLoS Medicine* 2013;10(1):e1001362.
- Free C, Whittaker R, Knight R, Abramsky T, Rodgers A, Roberts IG. Txt2stop: a pilot randomised controlled trial of mobile phone-based smoking cessation support. *Tobacco Control* 2009;18(2):88–91.
- Freund M, Campbell E, Paul C, McElduff P, Walsh RA, Sakrouge R, Wiggers J, Knight J. Smoking care provision in hospitals: a review of prevalence. *Nicotine and Tobacco Research* 2008;10(5):757–74.
- Freund M, Campbell E, Paul C, Sakrouge R, McElduff P, Walsh RA, Wiggers J, Knight J, Girgis A. Increasing smoking cessation care provision in hospitals: a meta-analysis of intervention effect. *Nicotine and Tobacco Research* 2009;11(6):650–62.
- Friedman AS, Schpero WL, Busch SH. Evidence suggests that the ACA's tobacco surcharges reduced insurance take-up and did not increase smoking cessation. *Health Affairs* 2016;35(7):1176–83.
- Frosch DL, Krueger PM, Hornik RC, Cronholm PF, Barg FK. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. *Annals of Family Medicine* 2007;5(1):6–13.
- Fucito LM, Czabafy S, Hendricks PS, Kotsen C, Richardson D, Toll BA. Pairing smoking-cessation services with lung cancer screening: A clinical guideline from the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco. *Cancer* 2016;122(8):1150–9.
- Gallaway MS, Huang B, Chen Q, Tucker TC, McDowell JK, Durbin E, Stewart SL, Tai E. Smoking and smoking cessation among persons with tobacco- and non-tobacco-associated cancers. *Journal of Community Health* 2019.
- García-Rodríguez O, Secades-Villa R, Flórez-Salamanca L, Okuda M, Liu SM, Blanco C. Probability and predictors of relapse to smoking: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence* 2013;132(3):479–85.
- García-Vera MP, Sanz J. Análisis de la situación de los tratamientos para dejar de fumar basados en terapia cognitivo-conductual y en parches de Nicotina [Analysis of the situation of treatments for smoking cessation based on cognitive-behavioral therapy and nicotine patches]. *Psicooncología* 2006;3(2–3):269–89.
- Gelkopf M, Noam S, Rudinski D, Lerner A, Behrbalk P, Bleich A, Melamed Y. Nonmedication smoking reduction program for inpatients with chronic schizophrenia: a randomized control design study. *Journal of Nervous and Mental Disease* 2012;200(2):142–6.
- Genzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students, United States, 2011–2018. *Morbidity and Mortality Weekly Report* 2019;68(6):157–64.
- Glasgow RE, Dickinson P, Fisher L, Christiansen S, Toobert DJ, Bender BG, Dickinson LM, Jortberg B, Estabrooks PA. Use of RE-AIM to develop a multi-media facilitation tool for the patient-centered medical home. *Implementation Science* 2011;6:118.
- Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR. The effect of cigarette smoking and smoking cessation on spinal fusion. *Spine* 2000;25(20):2608–15.
- Gomajee R, El-Khoury F, Goldberg M, Zins M, Lemogne C, Wiernik E, Lequy-Flahault E, Romanello L, Kousignian I, Melchior M. Association between electronic cigarette use and smoking reduction in France. *JAMA Internal Medicine* 2019.
- Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use JUUL and other vape pod systems (“pods”). *Tobacco Control* 2018a.
- Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M,

- Rosik-Dulewska C, Havel C, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control* 2014;23(2):133–9.
- Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. *Drug and Alcohol Review* 2013;32(2):133–40.
- Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, Wang L, Christensen C, Ambrose B, Borek N, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Network Open* 2018b;1(8):e185937.
- Gordon JS, Andrews JA, Crews KM, Payne TJ, Severson HH, Lichtenstein E. Do faxed quitline referrals add value to dental office-based tobacco-use cessation interventions? *Journal of the American Dental Association* 2010;141(8):1000–7.
- Gottlieb S, Zeller M. A nicotine-focused framework for public health. *New England Journal of Medicine* 2017;377(12):1111–4.
- Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ* 2019;366:l5275.
- Graham AL, Carpenter KM, Cha S, Cole S, Jacobs MA, Raskob M, Cole-Lewis H. Systematic review and meta-analysis of Internet interventions for smoking cessation among adults. *Substance Abuse and Rehabilitation* 2016;7:55–69.
- Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014;129(19):1972–86.
- Grant JM, Mottet LA, Tanis J, Herman JL, Harrison J, Keisling M. *National Transgender Discrimination Survey Report on Health and Health Care: Findings of a Study by the National Center for Transgender Equality and the National Gay and Lesbian Task Force*. Washington (DC): National Center for Transgender Equality and the National Gay and Lesbian Task Force, October 2010.
- Greenhalgh T, Macfarlane F, Steed L, Walton R. What works for whom in pharmacist-led smoking cessation support: realist review. *BMC Medicine* 2016;14(1):209.
- Greenwood S, Perrin A, Duggan M. Social media update 2016: Facebook usage and engagement is on the rise, while adoption of other platforms holds steady, November 11, 2016; <<http://www.pewinternet.org/2016/11/11/social-media-update-2016/>>; accessed: June 5, 2017.
- Haas AL, Munoz RF, Humfleet GL, Reus VI, Hall SM. Influences of mood, depression history, and treatment modality on outcomes in smoking cessation. *Journal of Consulting and Clinical Psychology* 2004;72(4):563–70.
- Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ* 2018;360:j5855.
- Haines-Saah RJ, Kelly MT, Oliffe JL, Bottorff JL. Picture Me Smokefree: a qualitative study using social media and digital photography to engage young adults in tobacco reduction and cessation. *Journal of Medical Internet Research* 2015;17(1):e27.
- Hajek P. Withdrawal-oriented therapy for smokers. *British Journal of Addiction* 1989;84(6):591–8.
- Hajek P, Belcher M, Stapleton J. Enhancing the impact of groups: an evaluation of two group formats for smokers. *British Journal of Clinical Psychology* 1985;24(Pt 4):289–94.
- Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. *Thorax* 2013a;68(11):1037–42.
- Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine* 2019;380(7):629–37.
- Hajek P, Smith KM, Dhanji AR, McRobbie H. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. *BMC Medicine* 2013b;11:140.
- Hajek P, Stead LF, West R, Jarvis M, Hartmann-Boyce J, Lancaster T. Relapse prevention interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2013c, Issue 8. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub4.
- Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine* 1999;159(17):2033–8.
- Hall SM, Humfleet GL, Munoz RF, Reus VI, Prochaska JJ, Robbins JA. Using extended cognitive behavioral treatment and medication to treat dependent smokers. *American Journal of Public Health* 2011;101(12):2349–56.
- Hall SM, Humfleet GL, Munoz RF, Reus VI, Robbins JA, Prochaska JJ. Extended treatment of older cigarette smokers. *Addiction* 2009;104(6):1043–52.
- Hall SM, Munoz RF, Reus VI. Cognitive-behavioral intervention increases abstinence rates for depressive-history smokers. *Journal of Consulting and Clinical Psychology* 1994;62(1):141–6.
- Hall SM, Munoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, Hartz DT. Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. *Journal of Consulting and Clinical Psychology* 1996;64(5):1003–9.
- Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. *Annual Review of Clinical Psychology* 2009;5:409–31.

- Hall SM, Tsoh JY, Prochaska JJ, Eisendrath S, Rossi JS, Redding CA, Rosen AB, Meisner M, Humfleet GL, Gorecki JA. Treatment for cigarette smoking among depressed mental health outpatients: a randomized clinical trial. *American Journal of Public Health* 2006;96(10):1808–14.
- Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. *New England Journal of Medicine* 2018;378(24):2302–10.
- Harrell PT, Simmons VN, Correa JB, Padhya TA, Brandon TH. Electronic nicotine delivery systems (“e-cigarettes”): review of safety and smoking cessation efficacy. *Otolaryngology—Head and Neck Surgery* 2014;151(3):381–93.
- Harrington KF, Cheong J, Hendricks S, Kohler C, Bailey WC. E-cigarette and traditional cigarette use among smokers during hospitalization and 6 months later. *Cancer Epidemiology, Biomarkers, and Prevention* 2015;24(4):762.
- Harris RP. The psychological effects of lung cancer screening on heavy smokers: another reason for concern. *JAMA Internal Medicine* 2015;175(9):1537–8.
- Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub5.
- Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD001118. DOI: 10.1002/14651858.CD001118.pub3.
- Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub3.
- Haskins BL, Lesperance D, Gibbons P, Boudreaux ED. A systematic review of smartphone applications for smoking cessation. *Translational Behavioral Medicine* 2017;7(2):292–9.
- Hassmiller KM, Warner KE, Mendez D, Levy DT, Romano E. Nondaily smokers: who are they? *American Journal of Public Health* 2003;93(8):1321–7.
- Hatsukami DK, Hertsgaard LA, Vogel RI, Jensen JA, Murphy SE, Hecht SS, Carmella SG, al’Absi M, Joseph AM, Allen SS. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiology, Biomarkers and Prevention* 2013;22(6):1015–24.
- Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction* 2010;105(2):343–55.
- Hatsukami DK, Luo X, Dick L, Kangkum M, Allen SS, Murphy SE, Hecht SS, Shields PG, al’Absi M. Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction* 2017;112(1):156–67.
- Hatsukami DK, Luo X, Jensen JA, al’Absi M, Allen SS, Carmella SG, Chen M, Cinciripini PM, Denlinger-Apte R, Drobles DJ, et al. Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2018;320(9):880–91.
- Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the British Household Panel Survey. *Nicotine and Tobacco Research* 2010;12(12):1228–35.
- Hayes SC. Acceptance and commitment therapy, relational frame theory, and the third wave of behavior therapy. *Behavior Therapy* 2004;35:639–65.
- Hayes SC, Barnes-Holmes D, Roche B, editors. *Relational Frame Theory: A Post-Skinnerian Account of Human Language and Cognition*. New York (NY): Plenum Press, 2001.
- Hayes SC, Levin ME, Plumb-Villardaga J, Villatte JL, Pistorello J. Acceptance and commitment therapy and contextual behavioral science: examining the progress of a distinctive model of behavioral and cognitive therapy. *Behavior Therapy* 2013;44(2):180–98.
- Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behaviour Research and Therapy* 2006;44(1):1–25.
- Hayes SC, Strosahl K, Wilson KG. *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change*. 1st ed. New York: The Guilford Press, 1999.
- Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DP, Wolter TD, Buist AS, Johnston JA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Annals of Internal Medicine* 2001;135(6):423–33.
- Hebert KK, Cummins SE, Hernandez S, Tedeschi GJ, Zhu SH. Current major depression among smokers using a state quitline. *American Journal of Preventive Medicine* 2011;40(1):47–53.
- Heffner JL, McClure JB, Mull KE, Anthenelli RM, Bricker JB. Acceptance and commitment therapy and nicotine patch for smokers with bipolar disorder: preliminary evaluation of in-person and telephone-delivered treatment. *Bipolar Disorders* 2015;17(5):560–6.
- Heffner JL, Watson NL, McClure JB, Anthenelli RM, Hohl S, Bricker JB. “I smoke like this to suppress these issues that are flaws of my character”: challenges and

- facilitators of cessation among smokers with bipolar disorder. *Journal of Dual Diagnosis* 2018;14(1):32–9.
- Heil SH, Higgins ST, Bernstein IM, Solomon LJ, Rogers RE, Thomas CS, Badger GJ, Lynch ME. Effects of voucher-based incentives on abstinence from cigarette smoking and fetal growth among pregnant women. *Addiction* 2008;103(6):1009–18.
- Henningfield JE, Rose CA, Zeller M. Tobacco industry litigation position on addiction: continued dependence on past views. *Tobacco Control* 2006;15(Suppl 4):iv27–iv36.
- Hennrikus DJ, Jeffery RW, Lando HA. Occasional smoking in a Minnesota working population. *American Journal of Public Health* 1996;86(9):1260–6.
- Hernández-López M, Luciano MC, Bricker JB, Roales-Nieto JG, Montesinos F. Acceptance and commitment therapy for smoking cessation: a preliminary study of its effectiveness in comparison with cognitive behavioral therapy. *Psychology of Addictive Behaviors* 2009;23(4):723–30.
- Higgins ST, Heil SH, Solomon LJ, Bernstein IM, Lussier JP, Abel RL, Lynch ME, Badger GJ. A pilot study on voucher-based incentives to promote abstinence from cigarette smoking during pregnancy and postpartum. *Nicotine and Tobacco Research* 2004;6(6):1015–20.
- Higgins ST, Washio Y, Lopez AA, Heil SH, Solomon LJ, Lynch ME, Hanson JD, Higgins TM, Skelly JM, Redner R, et al. Examining two different schedules of financial incentives for smoking cessation among pregnant women. *Preventive Medicine* 2014;68:51–7.
- Higgins TM, Higgins ST, Heil SH, Badger GJ, Skelly JM, Bernstein IM, Solomon LJ, Washio Y, Preston AM. Effects of cigarette smoking cessation on breastfeeding duration. *Nicotine and Tobacco Research* 2010;12(5):483–8.
- Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. *Nicotine and Tobacco Research* 2015;17(10):1187–94.
- Hoepfner BB, Hoepfner SS, Seaboyer L, Schick MR, Wu GW, Bergman BG, Kelly JF. How smart are smartphone apps for smoking cessation? A content analysis. *Nicotine and Tobacco Research* 2016;18(5):1025–31.
- Hoerger T, Boland E, Acquah JK, Alva M, Kish Doto J, Farrell K, Gard Read J, Goodrich C, Perry R, Romaine M, et al. *Medicaid Incentives for Prevention of Chronic Diseases Model: Final Evaluation Report*. Research Triangle Park (NC): RTI International, April 2017.
- Hofmann SG, Asmundson GJ, Beck AT. The science of cognitive therapy. *Behavior Therapy* 2013;44(2):199–212.
- Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cognitive Therapy and Research* 2012;36(5):427–40.
- Holla N, Brantley E, Ku L. Physicians' recommendations to Medicaid patients about tobacco cessation. *American Journal of Preventive Medicine* 2018;55(6):762–9.
- Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tobacco Control* 2007;16(Suppl 1):i53–i59.
- Hollis JF, Polen MR, Whitlock EP, Lichtenstein E, Mullooly JP, Velicer WF, Redding CA. Teen reach: outcomes from a randomized, controlled trial of a tobacco reduction program for teens seen in primary medical care. *Pediatrics* 2005;115(4):981–9.
- Hong AS, Elrashidi MY, Schroeder DR, Ebbert JO. Depressive symptoms among patients receiving varenicline and bupropion for smoking cessation. *Journal of Substance Abuse Treatment* 2015;52:78–81.
- Hu SS, Neff L, Agaku IT, Cox S, Day HR, Holder-Hayes E, King BA. Tobacco product use among adults—United States, 2013–2014. *Morbidity and Mortality Weekly Report* 2016;65(27):685–91.
- Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;99(1):29–38.
- Hughes JR, Keely JP, Fagerstrom KO, Callas PW. Intentions to quit smoking change over short periods of time. *Addictive Behaviors* 2005;30(4):653–62.
- Hughes JR, Peters EN, Naud S. Effectiveness of over-the-counter nicotine replacement therapy: a qualitative review of nonrandomized trials. *Nicotine and Tobacco Research* 2011;13(7):512–22.
- Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub4.
- Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine* 1997;337(17):1195–202.
- Hyland A, Rezaishiraz H, Bauer J, Giovino GA, Cummings KM. Characteristics of low-level smokers. *Nicotine and Tobacco Research* 2005;7(3):461–8.
- Inoue-Choi M, Liao LM, Reyes-Guzman C, Hartge P, Caporaso N, Freedman ND. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP Diet and Health Study. *JAMA Internal Medicine* 2017;177(1):87–95.
- Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington (DC): National Academies Press, 2007.

- Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, King BA. Tobacco use among middle and high school students—United States, 2011–2016. *Morbidity and Mortality Weekly Report* 2017;66(23):597–603.
- Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005–2015. *Morbidity and Mortality Weekly Report* 2016;65(44):1205–11.
- Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, Neff LJ. Current cigarette smoking among adults—United States, 2016. *Morbidity and Mortality Weekly Report* 2018;67(2):53–9.
- Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015. *JAMA Oncology* 2017.
- Jeong SH, Newcombe D, Sheridan J, Tingle M. Pharmacokinetics of cytisine, an alpha4 beta2 nicotinic receptor partial agonist, in healthy smokers following a single dose. *Drug Testing and Analysis* 2015;7(6):475–82.
- Jha P, MacLennan M, Chaloupka FJ, Yurekli A, Ramasundarahettige C, Palipudi K, Zatonksi W, Asma S, Gupta PC. Chapter 10. Global hazards of tobacco and the benefits of smoking cessation and tobacco taxes. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. *Cancer: Disease Control Priorities*. 3rd ed., Vol. 3. Washington (DC):2015:175–94.
- Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. 21st-century hazards of smoking and benefits of cessation in the United States. *New England Journal of Medicine* 2013;368(4):341–50.
- Johnson KC, Klesges LM, Somes GW, Coday MC, DeBon M. Access of over-the-counter nicotine replacement therapy products to minors. *Archives of Pediatrics and Adolescent Medicine* 2004;158(3):212–6.
- Jones HA, Heffner JL, Mercer L, Wyszynski CM, Vilaradaga R, Bricker JB. Web-based acceptance and commitment therapy smoking cessation treatment for smokers with depressive symptoms. *Journal of Dual Diagnosis* 2015;11(1):56–62.
- Joseph AM, Fu SS, Lindgren B, Rothman AJ, Kodl M, Lando H, Doyle B, Hatsukami D. Chronic disease management for tobacco dependence: a randomized, controlled trial. *Archives of Internal Medicine* 2011;171(21):1894–900.
- Joseph AM, Rothman AJ, Almirall D, Begnaud A, Chiles C, Cinciripini PM, Fu SS, Graham AL, Lindgren BR, Melzer AC, et al. Lung cancer screening and smoking cessation clinical trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration. *American Journal of Respiratory Care Medicine* 2018;197(2):172–82.
- Kahler CW, Spillane NS, Busch AM, Leventhal AM. Time-varying smoking abstinence predicts lower depressive symptoms following smoking cessation treatment. *Nicotine and Tobacco Research* 2011;13(2):146–50.
- Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respiratory Medicine* 2016;4(2):116–28.
- Kalkhoran S, Grana RA, Neilands TB, Ling PM. Dual use of smokeless tobacco or e-cigarettes with cigarettes and cessation. *American Journal of Health Behavior* 2015;39(2):277–84.
- Kameyama N, Chubachi S, Hegab AE, Yasuda H, Kagawa S, Tsutsumi A, Fukunaga K, Shimoda M, Kanai Y, Soejima K, et al. Intermittent exposure to cigarette smoke increases lung tumors and the severity of emphysema more than continuous exposure. *American Journal of Respiratory Cell and Molecular Biology* 2018;59(2):179–88.
- Karpinski JP, Timpe EM, Lubsch L. Smoking cessation treatment for adolescents. *Journal of Pediatric and Pharmacology and Therapeutics* 2010;15(4):249–63.
- Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, et al. Tobacco-product use by adults and youths in the United States in 2013 and 2014. *New England Journal of Medicine* 2017;376(4):342–53.
- Kasza KA, Hyland AJ, Borland R, McNeill AD, Bansal-Travers M, Fix BV, Hammond D, Fong GT, Cummings KM. Effectiveness of stop-smoking medications: findings from the International Tobacco Control (ITC) Four Country Survey. *Addiction* 2013;108(1):193–202.
- Katz R, Mesfin T, Barr K. Lessons from a community-based mHealth diabetes self-management program: “it’s not just about the cell phone”. *Journal of Health Communication* 2012;17(Suppl 1):67–72.
- Keenan PS. Smoking and weight change after new health diagnoses in older adults. *Archives of Internal Medicine* 2009;169(3):237–42.
- Keller PA, Feltracco A, Bailey LA, Li Z, Niederdeppe J, Baker TB, Fiore MC. Changes in tobacco quitlines in the United States, 2005–2006. *Preventing Chronic Disease* 2010;7(2):A36.
- Keller PA, Schillo BA, Kerr AN, Lien RK, Saul J, Dreher M, Lachter RB. Increasing reach by offering choices: results from an innovative model for statewide services for smoking cessation. *Preventive Medicine* 2016;91:96–102.
- Kelly MM, Sido H, Forsyth JP, Ziedonis DM, Kalman D, Cooney JL. Acceptance and commitment therapy smoking cessation treatment for veterans with post-traumatic stress disorder: a pilot study. *Journal of Dual Diagnosis* 2015;11(1):50–5.
- Kerr AN, Schillo BA, Keller PA, Lachter RB, Lien RK, Zook HG. Impact and effectiveness of a stand-alone NRT

- starter kit in a statewide tobacco cessation program. *American Journal of Health Promotion* 2018.
- Khoudigian S, Devji T, Lytvyn L, Campbell K, Hopkins R, O'Reilly D. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. *International Journal of Public Health* 2016;61(2):257–67.
- Khoury B, Lecomte T, Fortin G, Masse M, Therien P, Bouchard V, Chapleau MA, Paquin K, Hofmann SG. Mindfulness-based therapy: a comprehensive meta-analysis. *Clinical Psychology Review* 2013;33(6):763–71.
- King BA, Creamer MR, Harrell M, Kelder S, Norman L, Perry CL. Surgeon General's reports on tobacco: a continued legacy of unbiased and rigorous synthesis of the scientific evidence. *Nicotine and Tobacco Research* 2018a;20(8):1033–6.
- King BA, Dube SR, Babb SD, McAfee TA. Patient-reported recall of smoking cessation interventions from a health professional. *Preventive Medicine* 2013;57(5):715–7.
- King BA, Gammon DG, Marynak KL, Rogers T. Electronic cigarette sales in the United States, 2013–2017. *JAMA: the Journal of the American Medical Association* 2018b;320(13):1379–80.
- Koegelenberg CF, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, Smith C, Abdool-Gaffar MS, Emanuel S, Esterhuizen TM, et al. Efficacy of varenicline combined with nicotine replacement therapy vs. varenicline alone for smoking cessation: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2014;312(2):155–61.
- Kong G, Ells DM, Camenga DR, Krishnan-Sarin S. Text messaging-based smoking cessation intervention: a narrative review. *Addictive Behaviors* 2014;39(5):907–17.
- Kotsen C, Santorelli ML, Bloom EL, Goldstein AO, Ripley-Moffitt C, Steinberg MB, Burke MV, Foulds J. A narrative review of intensive group tobacco treatment: clinical, research, and U.S. policy recommendations. *Nicotine & Tobacco Research* 2017:1–10.
- Kotz D, Brown J, West R. “Real-world” effectiveness of smoking cessation treatments: a population study. *Addiction* 2014;109(3):491–9.
- Kotz D, Viechtbauer W, Simpson C, van Schayck OC, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. *Lancet Respiratory Medicine* 2015;3(10):761–8.
- Koutroumpisa P, Leiponen A. Crowdsourcing mobile coverage. *Telecommunications Policy* 2016;40(6):532–44.
- Krebs P, Rogers E, Smelson D, Fu S, Wang B, Sherman S. Relationship between tobacco cessation and mental health outcomes in a tobacco cessation trial. *Journal of Health Psychology* 2016.
- Kruger J, O'Halloran A, Rosenthal AC, Babb SD, Fiore MC. Receipt of evidence-based brief cessation interventions by health professionals and use of cessation assisted treatments among current adult cigarette-only smokers: National Adult Tobacco Survey, 2009–2010. *BMC Public Health* 2016;16:141.
- Kuiper N, Zhang L, Lee J, Babb SD, Anderson CM, Shannon C, Welton M, Lew R, Zhu SH. A national Asian-language smokers' quitline—United States, 2012–2014. *Preventing Chronic Disease* 2015;12:E99.
- Lakon CM, Pechmann C, Wang C, Pan L, Delucchi K, Prochaska JJ. Mapping engagement in Twitter-based support networks for adult smoking cessation. *American Journal of Public Health* 2016;106(8):1374–80.
- Lam C, West A. Are electronic nicotine delivery systems an effective smoking cessation tool? *Canadian Journal of Respiratory Therapy* 2015;51(4):93–8.
- Lancaster T, Stead LF. Individual behavioural counseling for smoking cessation. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD001292. DOI: 10.1002/14651858.CD001292.pub3.
- Larabie LC. To what extent do smokers plan quit attempts? *Tobacco Control* 2005;14(6):425–8.
- Laude JR, Bailey SR, Crew E, Varady A, Lembke A, McFall D, Jeon A, Killen D, Killen JD, David SP. Extended treatment for cigarette smoking cessation: a randomized control trial. *Addiction* 2017;112(8):1451–9.
- Lavernia CJ, Sierra RJ, Gomez-Marin O. Smoking and joint replacement: resource consumption and short-term outcome. *Clinical Orthopaedics and Related Research* 1999;(367):172–80.
- Leas EC, Pierce JP, Benmarhnia T, White MM, Noble ML, Trinidad DR, Strong DR. Effectiveness of pharmaceutical smoking cessation aids in a nationally representative cohort of American smokers. *Journal of the National Cancer Institute* 2018;110(6):581–7.
- Lee JG, Matthews AK, McCullen CA, Melvin CL. Promotion of tobacco use cessation for lesbian, gay, bisexual, and transgender people: a systematic review. *American Journal of Preventive Medicine* 2014;47(6):823–31.
- Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P. Long-term quit rates after a perioperative smoking cessation randomized controlled trial. *Anesthesia and Analgesia* 2015;120(3):582–7.
- Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, Swan GE, Benowitz NL, Heitjan DF, Tyndale RF, et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomized, double-blind placebo-controlled trial. *Lancet Respiratory Medicine* 2015;3(2):131–8.
- Levy DT, Yuan Z, Luo Y, Abrams DB. The Relationship of E-Cigarette Use to Cigarette Quit Attempts and Cessation: Insights From a Large, Nationally Representative U.S. Survey. *Nicotine and Tobacco Research* 2018;20(8):931–9.

- Li S, Li Z, Pei L, Le AD, Liu F. The alpha7nACh-NMDA receptor complex is involved in cue-induced reinstatement of nicotine seeking. *Journal of Experimental Medicine* 2012;209(12):2141–7.
- Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD008033. DOI: 10.1002/14651858.CD008033.pub3.
- Lindson-Hawley N, Hartmann-Boyce J, Fanshawe TR, Begh R, Farley A, Lancaster T. Interventions to reduce harm from continued tobacco use. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD005231. DOI: 10.1002/14651858.CD005231.pub3.
- Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD006936. DOI: 10.1002/14651858.CD006936.pub3.
- Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013308. DOI: 10.1002/14651858.CD013308.
- Linehan MM, Korslund KE, Harned MS, Gallop RJ, Lungu A, Neacsiu AD, McDavid J, Comtois KA, Murray-Gregory AM. Dialectical behavior therapy for high suicide risk in individuals with borderline personality disorder: a randomized clinical trial and component analysis. *JAMA Psychiatry* 2015;72(5):475–82.
- Lipari RN, Van Horn SL. *Smoking and mental illness among adults in the United States*. Rockville (MD): Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, March 30, 2017.
- Little MA, Talcott GW, Bursac Z, Linde BD, Pagano LA, Messler EC, Ebbert JO, Klesges RC. Efficacy of a brief tobacco intervention for tobacco and nicotine containing product use in the U.S. Air Force. *Nicotine and Tobacco Research* 2016;18(5):1142–9.
- Liu X, Li R, Lanza ST, Vasilenko SA, Piper M. Understanding the role of cessation fatigue in the smoking cessation process. *Drug and Alcohol Dependence* 2013;133(2):548–55.
- Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Hajek P. Relapse prevention interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No.: CD003999. DOI: 10.1002/14651858.CD003999.pub5.
- Løchen ML, Gram IT, Mannsverk J, Mathiesen EB, Njølstad I, Schirmer H, Wilsgaard T, Jacobsen BK. Association of occasional smoking with total mortality in the population-based Tromsø study, 2001–2015. *BMJ Open* 2017;7(12):e019107.
- Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub3.
- Luo SX, Covey LS, Hu MC, Levin FR, Nunes EV, Winhusen TM. Toward personalized smoking-cessation treatment: Using a predictive modeling approach to guide decisions regarding stimulant medication treatment of attention-deficit/hyperactivity disorder (ADHD) in smokers. *American Journal on Addictions* 2015;24(4):348–56.
- Luoto R, Uutela A, Puska P. Occasional smoking increases total and cardiovascular mortality among men. *Nicotine and Tobacco Research* 2000;2(2):133–9.
- Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction* 2006;101(2):192–203.
- Maciosek MV, LaFrance AB, Dehmer SP, McGree DA, Flottemesch TJ, Xu Z, Solberg LI. Updated priorities among effective clinical preventive services. *Annals of Family Medicine* 2017a;15(1):14–22.
- Maciosek MV, LaFrance AB, Dehmer SP, McGree DA, Xu Z, Flottemesch TJ, Solberg LI. Health benefits and cost-effectiveness of brief clinician tobacco counseling for youth and adults. *Annals of Family Medicine* 2017b;15(1):37–47.
- Madison MC, Landers CT, Gu BH, Chang CY, Tung HY, You R, Hong MJ, Baghaei N, Song LZ, Porter P, et al. Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. *Journal of Clinical Investigation* 2019;129(10):4290–430.
- Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. *Journal of Studies on Alcohol and Drugs* 2009;70(4):516–27.
- Malaiyandi V, Sellers EM, Tyndale RF. Implications of CYP2A6 genetic variation for smoking behaviors and nicotine dependence. *Clinical Pharmacology and Therapeutics* 2005;77(3):145–58.
- Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, Andrews J, Zawertailo L, Ferrence R. Electronic Cigarettes for Smoking Cessation: A Systematic Review. *Nicotine and Tobacco Research* 2016;18(10):1926–36.
- Mann N, Nonnemaker J, Chapman L, Shaikh A, Thompson J, Juster H. Comparing the New York State Smokers' Quitline reach, services offered, and quit outcomes to 44 other state quitlines, 2010 to 2015. *American Journal of Health Promotion* 2018;32(5):1264–72.
- Manzoli L, Flacco ME, Fiore M, La Vecchia C, Marzuillo C, Gualano MR, Liguori G, Cicolini G, Capasso L, D'Amario C, et al. Electronic cigarettes efficacy

- and safety at 12 months: cohort study. *PLoS One* 2015;10(6):e0129443.
- Markham CM, Craig Rushing S, Jessen C, Gorman G, Torres J, Lambert WE, Prokhorov AV, Miller L, Allums-Featherston K, Addy RC, et al. Internet-based delivery of evidence-based health promotion programs among American Indian and Alaska Native Youth: a case study. *JMIR Research Protocols* 2016;5(4):e225.
- Marshall HM, Courtney DA, Passmore LH, McCaul EM, Yang IA, Bowman RV, Fong KM. Brief tailored smoking cessation counseling in a lung cancer screening population is feasible: a pilot randomized controlled trial. *Nicotine and Tobacco Research* 2016;18(7):1665–9.
- Marzano L, Bardill A, Fields B, Herd K, Veale D, Grey N, Moran P. The application of mHealth to mental health: opportunities and challenges. *Lancet Psychiatry* 2015;2(10):942–8.
- May S, West R. Do social support interventions (“buddy systems”) aid smoking cessation? A review. *Tobacco Control* 2000;9(4):415–22.
- May S, West R, Hajek P, McEwen A, McRobbie H. Randomized controlled trial of a social support (‘buddy’) intervention for smoking cessation. *Patient Education and Counseling* 2006;64(1–3):235–41.
- Mazurek JM, England LJ. Cigarette smoking among working women of reproductive age—United States, 2009–2013. *Nicotine and Tobacco Research* 2016;18(5):894–9.
- McAfee T. Re: effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline: randomised controlled trial [letter to the editor]. *BMJ* 2012;344:e1696.
- McAfee T, Davis KC, Shafer P, Patel D, Alexander R, Bunnell R. Increasing the dose of television advertising in a national antismoking media campaign: results from a randomised field trial. *Tobacco Control* 2017;26(1):19–28.
- McClure JB, Hartzler AL, Catz SL. Design considerations for smoking cessation apps: feedback from nicotine dependence treatment providers and smokers. *JMIR mHealth uHealth* 2016;4(1):e17.
- McCrabb S, Baker AL, Attia J, Skelton E, Twyman L, Palazzi K, McCarter K, Ku D, Bonevski B. Internet-based programs incorporating behavior change techniques are associated with increased smoking cessation in the general population: a systematic review and meta-analysis. *Annals of Behavioral Medicine* 2019;53(2):180–95.
- McFall M, Saxon AJ, Malte CA, Chow B, Bailey S, Baker DG, Beckham JC, Boardman KD, Carmody TP, Joseph AM, et al. Integrating tobacco cessation into mental health care for posttraumatic stress disorder: a randomized controlled trial. *JAMA: the Journal of the American Medical Association* 2010;304(22):2485–93.
- McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine and Tobacco Research* 2016;18(5):1002–11.
- McKelvey K, Thrul J, Ramo D. Impact of quitting smoking and smoking cessation treatment on substance use outcomes: an updated and narrative review. *Addictive Behaviors* 2017;65:161–70.
- McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub2.
- Mercincavage M, Wileyto EP, Saddleson ML, Lochbuehler K, Donny EC, Strasser AA. Attrition during a randomized controlled trial of reduced nicotine content cigarettes as a proxy for understanding acceptability of nicotine product standards. *Addiction* 2017;112(6):1095–103.
- Metse AP, Wiggers JH, Wye PM, Wolfenden L, Prochaska JJ, Stockings EA, Williams JM, Ansell K, Fehily C, Bowman JA. Smoking and mental illness: a bibliometric analysis of research output over time. *Nicotine and Tobacco Research* 2017;19(1):24–31.
- Meyers L, Voller EK, McCallum EB, Thuras P, Shallcross S, Velasquez T, Meis L. Treating veterans with PTSD and borderline personality symptoms in a 12-week intensive outpatient setting: findings from a pilot program. *Journal of Traumatic Stress* 2017;30(2):178–81.
- Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior. *Annals of Behavioral Medicine* 2013;46(1):81–95.
- Miech R, Johnston L, O’Malley PM, Bachman JG, Patrick ME. Adolescent vaping and nicotine use in 2017–2018—U.S. national estimates. *New England Journal of Medicine* 2019;380(2):192–3.
- Miech RA, Schulenberg JE, Johnston LD, Bachman JG, O’Malley PM, Patrick ME. National adolescent drug trends in 2018 [press release], December 17, 2018; <<http://monitoringthefuture.org/pressreleases/18drugpr.pdf>>; accessed: March 14, 2019.
- Miller WR. Motivational interviewing with drinkers. *Behavioural Psychotherapy* 1983;11:147–72.
- Miller WR, Rollnick S. *Motivational Interviewing: Preparing People for Change*. 2nd ed. New York: The Guilford Press, 2002.
- Mirbolouk M, Charkhchi P, Kianoush S, Uddin SMI, Orimoloye OA, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. Prevalence and distribution of e-cigarette use among U.S. adults: Behavioral Risk

- Factor Surveillance System, 2016. *Annals of Internal Medicine* 2018;169(7):429–38.
- Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 2002;359(9301):114–7.
- Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, Schroeder JR. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics* 2005;115(4):e407–14.
- Moritz ED, Zapata LB, Lekichvili A, Glidden E, Annor FB, Werner AK, Ussery EN, Hughes MM, Kimball A, DeSisto CL, et al. Update: characteristics of patients in a national outbreak of e-cigarette, or vaping, product use-associated lung injuries—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68(43):985–9.
- Mosher WD, Jones J, Abma JC. *Intended and unintended births in the United States: 1982–2010*. National Health Statistics Reports No. 55. Hyattsville (MD): National Center for Health Statistics, 2012.
- Mottillo S, Fillion KB, Belisle P, Joseph L, Gervais A, O’Loughlin J, Paradis G, Pihl R, Pilote L, Rinfret S, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. *European Heart Journal* 2009;30(6):718–30.
- Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* 2014;160(5):330–8.
- Mullen KA, Coyle D, Manuel D, Nguyen HV, Pham B, Pipe AL, Reid RD. Economic evaluation of a hospital-initiated intervention for smokers with chronic disease, in Ontario, Canada. *Tobacco Control* 2015;24(5):489–96.
- Mullen KA, Manuel DG, Hawken SJ, Pipe AL, Coyle D, Hobbler LA, Younger J, Wells GA, Reid RD. Effectiveness of a hospital-initiated smoking cessation programme: 2-year health and healthcare outcomes. *Tobacco Control* 2017;26(3):293–9.
- Murphy-Hoefer R, Davis KC, Beistle D, King BA, Duke J, Rodes R, Graffunder C. Impact of the Tips From Former Smokers campaign on population-level smoking cessation, 2012–2015. *Preventing Chronic Disease* 2018;15:E71.
- Myung SK, Ju W, Jung HS, Park CH, Oh SW, Seo H, Kim H. Efficacy and safety of pharmacotherapy for smoking cessation among pregnant smokers: a meta-analysis. *BJOG* 2012;119(9):1029–39.
- Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob P III, Springer ML. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tobacco Control* 2018;27(Suppl 1):S13–S19.
- Nahas GJ, Wilson D, Talbot V, Cartmell KB, Warren GW, Toll BA, Carpenter MJ, Cummings KM. Feasibility of implementing a hospital-based “opt-out” tobacco-cessation service. *Nicotine and Tobacco Research* 2017;19(8):937–43.
- Nakamura M, Abe M, Ohkura M, Treadow J, Yu CR, Park PW. Efficacy of varenicline for cigarette reduction before quitting in Japanese smokers: a subpopulation analysis of the Reduce to Quit Trial. *Clinical Therapeutics* 2017;39(4):863–72.
- Nardone N, Donny EC, Hatsukami DK, Koopmeiners JS, Murphy SE, Strasser AA, Tidey JW, Vandrey R, Benowitz NL. Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes. *Addiction* 2016;111(12):2208–16.
- Nathan Mann, RTI International. personal communication, May 6, 2019.
- National Academies of Sciences, Engineering, and Medicine. *Public Health Consequences of E-Cigarettes*. Washington (DC): The National Academies Press, 2018.
- National Cancer Institute and Centers for Disease Control and Prevention. *Smokeless Tobacco and Public Health: A Global Perspective*. Bethesda (MD): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute, 2014. NIH Publication No. 14-7983.
- National Center for Health Statistics. *Health, United States, 2017: With Special Feature on Mortality*. Hyattsville (MD): National Center for Health Statistics, 2018.
- Naughton F. Delivering “just-in-time” smoking cessation support via mobile phones: current knowledge and future directions. *Nicotine and Tobacco Research* 2016.
- Navon L, Jones CM, Ghinai I, King BA, Briss PA, Hacker KA, Layden JE. Risk factors for e-cigarette, or vaping, product use-associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products—Illinois, July–October 2019. *Morbidity and Mortality Weekly Report* 2019 Nov 15;68(45):1034–9.
- Newhall K, Suckow B, Spangler E, Brooke BS, Schanzer A, Tan TW, Burnette M, Edelen MO, Farber A, Goodney P. Impact and duration of brief surgeon-delivered smoking cessation advice on attitudes regarding nicotine dependence and tobacco harms for patients with peripheral arterial disease. *Annals of Vascular Surgery* 2017;38:113–21.
- Ng JY, Ntoumanis N, Thogersen-Ntoumani C, Deci EL, Ryan RM, Duda JL, Williams GC. Self-determination theory applied to health contexts: a meta-analysis. *Perspectives on Psychological Science* 2012;7(4):325–40.
- Nilsen W, Kumar S, Shar A, Varoquiens C, Wiley T, Riley WT, Pavel M, Atienza AA. Advancing the science of mHealth.

- Journal of Health Communication* 2012;17(Suppl 1):5–10.
- Nolan MB, Warner DO. Perioperative tobacco use treatments: putting them into practice. *BMJ* 2017;358:j3340.
- North American Quitline Consortium. 2015 survey, n.d.a; <<http://www.naquitline.org/?page=2015Survey>>; accessed: August 1, 2017.
- North American Quitline Consortium. Map: looking for data about quitlines?, n.d.b; <<http://map.naquitline.org/>>; accessed: August 1, 2017.
- O’Connell G, Pritchard JD, Prue C, Thompson J, Verron T, Graff D, Walele T. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in U.S. adult smokers. *Internal and Emergency Medicine* 2019.
- O’Malley SS, Zweben A, Fucito LM, Wu R, Piepmeier ME, Ockert DM, Bold KW, Petrakis I, Muvvala S, Jatlow P, et al. Effect of varenicline combined with medical management on alcohol use disorder with comorbid cigarette smoking: a randomized clinical trial. *JAMA Psychiatry* 2018;75(2):129–38.
- Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *American Journal of Psychiatry* 2004;161(8):1433–41.
- Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, et al. Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *American Journal of Medicine* 2019.
- Pacek LR, McClernon FJ, Bosworth HB. Adherence to pharmacological smoking cessation interventions: a literature review and synthesis of correlates and barriers. *Nicotine and Tobacco Research* 2018;20(10):1163–72.
- Park ER, Gareen IF, Japuntich S, Lennes I, Hyland K, DeMello S, Sicks JD, Rigotti NA. Primary care provider-delivered smoking cessation interventions and smoking cessation among participants in the National Lung Screening Trial. *JAMA Internal Medicine* 2015;175(9):1509–16.
- Patel K, Schlundt D, Larson C, Wang H, Brown A, Hargreaves M. Chronic illness and smoking cessation. *Nicotine and Tobacco Research* 2009;11(8):933–9.
- Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. *Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the U.S. Preventive Services Task Force*. Evidence Syntheses No. 134. Rockville (MD): Agency for Healthcare Research and Quality, 2015. Report No. 14-05200-EF-1.
- Patnode CD, O’Connor E, Whitlock EP, Perdue LA, Soh C, Hollis J. Primary care-relevant interventions for tobacco use prevention and cessation in children and adolescents: a systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2013;158(4):253–60.
- Pechmann C, Delucchi K, Lakon CM, Prochaska JJ. Randomised controlled trial evaluation of Tweet2Quit: a social network quit-smoking intervention. *Tobacco Control* 2017;26(2):188–94.
- Peirson L, Ali MU, Kenny M, Raina P, Sherifali D. Interventions for prevention and treatment of tobacco smoking in school-aged children and adolescents: a systematic review and meta-analysis. *Preventive Medicine* 2016;85:20–31.
- Perkins KA, Conklin CA, Levine MD. *Cognitive-Behavioral Therapy for Smoking Cessation: A Practical Guidebook to the Most Effective Treatments*. New York (NY): Routledge, 2008.
- Perkins KA, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine and Tobacco Research* 2008;10(7):1245–50.
- Pesis-Katz I, Williams GC, Niemiec CP, Fiscella K. Cost-effectiveness of intensive tobacco dependence intervention based on self-determination theory. *American Journal of Managed Care* 2011;17(10):e393–e398.
- Pew Research Center. Internet/broadband fact sheet, 2017a; <<http://www.pewinternet.org/fact-sheet/internet-broadband/>>; accessed: June 8, 2017.
- Pew Research Center. Mobile fact sheet, January 12, 2017b; <<http://www.pewinternet.org/fact-sheet/mobile/>>; accessed: March 6, 2017.
- Pfizer. Nicotrol® NS (nicotine nasal spray), June 2010; <https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020385s010lbl.pdf>; accessed: November 29, 2018.
- Pfizer. Medication guide: Chantix (varenicline) tablets, June 2018; <<http://labeling.pfizer.com/ShowLabeling.aspx?id=557§ion=MedGuide>>; accessed: January 8, 2019.
- Pierce JP, Cummins SE, White MM, Humphrey A, Messer K. Quitlines and nicotine replacement for smoking cessation: do we need to change policy? *Annual Review of Public Health* 2012;33:341–56.
- Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA: the Journal of the American Medical Association* 2002;288(10):1260–4.
- Pierce JP, White MM, Messer K. Changing age-specific patterns of cigarette consumption in the United States, 1992–2002: association with smoke-free homes

- and state-level tobacco control activity. *Nicotine and Tobacco Research* 2009;11(2):171–7.
- Piñeiro B, Simmons VN, Palmer AM, Correa JB, Brandon TH. Smoking cessation interventions within the context of Low-Dose Computed Tomography lung cancer screening: a systematic review. *Lung Cancer* 2016;98:91–8.
- Piper ME, Fiore MC, Smith SS, Fraser D, Bolt DM, Collins LM, Mermelstein R, Schlam TR, Cook JW, Jorenby DE, et al. Identifying effective intervention components for smoking cessation: a factorial screening experiment. *Addiction* 2016;111(1):129–41.
- Piper ME, McCarthy DE, Bolt DM, Smith SS, Lerman C, Benowitz N, Fiore MC, Baker TB. Assessing dimensions of nicotine dependence: an evaluation of the Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM). *Nicotine and Tobacco Research* 2008;10(6):1009–20.
- Piper ME, Schlam TR, Cook JW, Smith SS, Bolt DM, Loh WY, Mermelstein R, Collins LM, Fiore MC, Baker TB. Toward precision smoking cessation treatment I: moderator results from a factorial experiment. *Drug and Alcohol Dependence* 2017;171:59–65.
- Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* 2013;381(9861):133–41.
- Pisinger C, Vestbo J, Borch-Johnsen K, Jorgensen T. It is possible to help smokers in early motivational stages to quit. The Inter99 Study. *Preventive Medicine* 2005;40(3):278–84.
- Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, Peterson BL, Heine RP, Brouwer RJ, Fish L, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *American Journal of Preventive Medicine* 2007;33(4):297–305.
- Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *American Journal of Public Health* 2013;103(5):923–30.
- Potkin SG, Alphas L, Hsu C, Krishnan KR, Anand R, Young FK, Meltzer H, Green A. Predicting suicidal risk in schizophrenic and schizoaffective patients in a prospective two-year trial. *Biological Psychiatry* 2003;54(4):444–52.
- Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. *Annual Review of Medicine* 2016;67:467–86.
- Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: nicotine addiction. *Science Advances* 2019;5(10):eaay9763.
- Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annual Review of Public Health* 2017;38:165–85.
- Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *Journal of Consulting and Clinical Psychology* 2004;72(6):1144–56.
- Prochaska JJ, Grana RA. E-cigarette use among smokers with serious mental illness. *PLoS One* 2014;9(11):e113013.
- Prochaska JJ, Hall SE, Delucchi K, Hall SM. Efficacy of initiating tobacco dependence treatment in inpatient psychiatry: a randomized controlled trial. *American Journal of Public Health* 2014;104(8):1557–65.
- Prochaska JJ, Hall SM, Bero LA. Tobacco use among individuals with schizophrenia: what role has the tobacco industry played? *Schizophrenia Bulletin* 2008;34(3):555–67.
- Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ* 2012;344:e2856.
- Prochaska JJ, Pechmann C, Kim R, Leonhardt JM. Twitter=quitter? An analysis of Twitter quit smoking social networks. *Tobacco Control* 2012;21(4):447–9.
- Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *Journal of Consulting and Clinical Psychology* 1983;51(3):390–5.
- Prochaska JO, DiClemente CC, Velicer WF, Rossi JS. Standardized, individualized, interactive, and personalized self-help programs for smoking cessation. *Health Psychology* 1993;12(5):399–405.
- Prochaska JO, Velicer WF, Fava JL, Rossi JS, Tsoh JY. Evaluating a population-based recruitment approach and a stage-based expert system intervention for smoking cessation. *Addictive Behaviors* 2001a;26(4):583–602.
- Prochaska JO, Velicer WF, Fava JL, Ruggiero L, Laforge RG, Rossi JS, Johnson SS, Lee PA. Counselor and stimulus control enhancements of a stage-matched expert system intervention for smokers in a managed care setting. *Preventive Medicine* 2001b;32(1):23–32.
- Public Health England. *Models of Delivery for Stop Smoking Services: Options and Evidence*. London (UK): Public Health England, September 2017.
- Quinn VP, Hollis JF, Smith KS, Rigotti NA, Solberg LI, Hu W, Stevens VJ. Effectiveness of the 5-As tobacco cessation treatments in nine HMOs. *Journal of General Internal Medicine* 2009;24(2):149–54.
- Quinn VP, Stevens VJ, Hollis JF, Rigotti NA, Solberg LI, Gordon N, Ritzwoller D, Smith KS, Hu W, Zapka J. Tobacco-cessation services and patient satisfaction in nine nonprofit HMOs. *American Journal of Preventive Medicine* 2005;29(2):77–84.
- Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. E-cigarettes and smoking cessation: evidence

- from a systematic review and meta-analysis. *PLoS One* 2015;10(3):e0122544.
- Ramo DE, Liu H, Prochaska JJ. A mixed-methods study of young adults' receptivity to using Facebook for smoking cessation: if you build it, will they come? *American Journal of Health Promotion* 2015;29(4):e126–35.
- Reid RD, Mullen KA, Slovinec D'Angelo ME, Aitken DA, Papadakis S, Haley PM, McLaughlin CA, Pipe AL. Smoking cessation for hospitalized smokers: an evaluation of the "Ottawa Model". *Nicotine and Tobacco Research* 2010;12(1):11–8.
- Reyes-Guzman CM, Pfeiffer RM, Lubin J, Freedman ND, Cleary SD, Levine PH, Caporaso NE. Determinants of light and intermittent smoking in the United States: results from three pooled national health surveys. *Cancer Epidemiology, Biomarkers, and Prevention* 2017;26(2):228–39.
- Ribisl KM, Hatsukami DK, Huang J, Williams RS, Donny EC. Strategies to reduce illicit trade of regular nicotine tobacco products after introduction of a low-nicotine tobacco product standard. *American Journal of Public Health* 2019;109(7):1007–14.
- Rice VH, Heath L, Livingstone-Banks J, Hartmann-Boyce J. Nursing interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD001188. DOI: 10.1002/14651858.CD001188.pub5.
- Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, Walker A. Systematic review of the effectiveness of stage based interventions to promote smoking cessation. *BMJ* 2003;326(7400):1175–7.
- Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD001837. DOI: 10.1002/14651858.CD001837.pub3.
- Rigotti NA, Regan S, Levy DE, Japuntich S, Chang Y, Park ER, Viana JC, Kelley JH, Reyen M, Singer DE. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2014;312(7):719–28.
- Rigotti NA, Tindle HA, Regan S, Levy DE, Chang Y, Carpenter KM, Park ER, Kelley JH, Streck JM, Reid ZZ, et al. A post-discharge smoking-cessation intervention for hospital patients: Helping Hand 2 Randomized Clinical Trial. *American Journal of Preventive Medicine* 2016;51(4):597–608.
- Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin RB, Jones M. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. *Tobacco Control* 2005;14(4):255–61.
- Rogers ES, Smelson DA, Gillespie CC, Elbel B, Poole S, Hagedorn HJ, Kalman D, Krebs P, Fang Y, Wang B, et al. Telephone smoking-cessation counseling for smokers in mental health clinics: a patient-randomized controlled trial. *American Journal of Preventive Medicine* 2016;50(4):518–27.
- Rüther T, Bobes J, De Hert M, Svensson TH, Mann K, Batra A, Gorwood P, Möller HJ. EPA guidance on tobacco dependence and strategies for smoking cessation in people with mental illness. *European Psychiatry* 2014;29(2):65–82.
- Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *American Psychologist* 2000;55(1):68–78.
- Ryan RM, Patrick H, Deci EL, Williams GC. Facilitating health behaviour change and its maintenance: Interventions based on self-determination theory. *The European Health Psychologist* 2008;10:2–5.
- Sargent JD, Mott LA, Stevens M. Predictors of smoking cessation in adolescents. *Archives of Pediatrics and Adolescent Medicine* 1998;152(4):388–93.
- Schane RE, Glantz SA. Education on the dangers of passive smoking: a cessation strategy past due. *Circulation* 2008;118(15):1521–3.
- Schane RE, Glantz SA, Ling PM. Nondaily and social smoking: an increasingly prevalent pattern. *Archives of Internal Medicine* 2009;169(19):1742–4.
- Schane RE, Prochaska JJ, Glantz SA. Counseling nondaily smokers about secondhand smoke as a cessation message: a pilot randomized trial. *Nicotine and Tobacco Research* 2013;15(2):334–42.
- Schauer GL, Malarcher AM, Asman KJ. Trends in the average age of quitting among U.S. adult cigarette smokers. *American Journal of Preventive Medicine* 2015a;49(6):939–44.
- Schauer GL, Malarcher AM, Babb SD. Gradual reduction of cigarette consumption as a cessation strategy: prevalence, correlates, and relationship with quitting. *Nicotine and Tobacco Research* 2015b;17(5):530–8.
- Schauer GL, Malarcher AM, Mowery P. National trends in frequency and amount of nondaily smoking, and relation to quit attempts, 2000–2012. *Nicotine and Tobacco Research* 2016a;18(6):1539–44.
- Schauer GL, Malarcher AM, Zhang L, Engstrom MC, Zhu SH. Prevalence and correlates of quitline awareness and utilization in the United States: an update from the 2009–2010 National Adult Tobacco Survey. *Nicotine and Tobacco Research* 2014a;16(5):544–53.
- Schauer GL, Pederson LL, Malarcher AM. Past year quit attempts and use of cessation resources among cigarette-only smokers and cigarette smokers who use other tobacco products. *Nicotine and Tobacco Research* 2016b;18(1):41–7.
- Schauer GL, Wheaton AG, Malarcher AM, Croft JB. Smoking prevalence and cessation characteristics

- among U.S. adults with and without COPD: findings from the 2011 Behavioral Risk Factor Surveillance System. *COPD* 2014b;11(6):697–704.
- Schauer GL, Wheaton AG, Malarcher AM, Croft JB. Health-care provider screening and advice for smoking cessation among smokers with and without COPD: 2009–2010 National Adult Tobacco Survey. *Chest* 2016c;149(3):676–84.
- Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Internal Medicine* 2015;175(4):504–11.
- Schroeder SA. What to do with a patient who smokes. *JAMA: the Journal of the American Medical Association* 2005;294(4):482–7.
- Schwartz J, Fadahunsi O, Hingorani R, Mainali NR, Oluwasanjo A, Aryal MR, Donato A. Use of varenicline in smokeless tobacco cessation: a systematic review and meta-analysis. *Nicotine and Tobacco Research* 2016;18(1):10–6.
- Scott-Sheldon LA, Lantini R, Jennings EG, Thind H, Rosen RK, Salmoirago-Blotcher E, Bock BC. Text messaging-based interventions for smoking cessation: a systematic review and meta-analysis. *JMIR mHealth and uHealth* 2016;4(2):e49.
- Severson HH, Gordon JS, Danaher BG, Akers L. ChewFree.com: evaluation of a Web-based cessation program for smokeless tobacco users. *Nicotine and Tobacco Research* 2008;10(2):381–91.
- Sharapova S, Reyes-Guzman C, Singh T, Phillips E, Marynak KL, Agaku I. Age of tobacco use initiation and association with current use and nicotine dependence among U.S. middle and high school students, 2014–2016. *Tobacco Control* 2018.
- Sheffer MA, Baker TB, Fraser DL, Adsit RT, McAfee TA, Fiore MC. Fax referrals, academic detailing, and tobacco quitline use: a randomized trial. *American Journal of Preventive Medicine* 2012;42(1):21–8.
- Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology* 2010;112(1):102–7.
- Shiffman S, Dunbar MS, Li X, Scholl SM, Tindle HA, Anderson SJ, Ferguson SG. Smoking patterns and stimulus control in intermittent and daily smokers. *PLoS One* 2014;9(3):e89911.
- Shiffman S, Ferguson SG. Nicotine patch therapy prior to quitting smoking: a meta-analysis. *Addiction* 2008;103(4):557–63.
- Shiffman S, Sembower MA, Rohay JM, Gitchell JG, Garvey AJ. Assigning dose of nicotine gum by time to first cigarette. *Nicotine and Tobacco Research* 2013;15(2):407–12.
- Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. *Nicotine and Tobacco Research* 2015;17(2):158–62.
- Siegel DA, Jatlaoui TC, Koumans EH, Kiernan EA, Layer M, Cates JE, Kimball A, Weissman DN, Petersen EE, Reagan-Steiner S, et al. Update: Interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68:919–27.
- Simoyan OM, Badner VM, Freeman KD. Tobacco cessation services in dental offices. Are we doing all we can? *New York State Dental Journal* 2002;68(7):34–40.
- Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *Canadian Medical Association Journal* 2011;183(12):1359–66.
- Singh S, Starkey NJ, Sargisson RJ. Using SmartQuit®, an acceptance and commitment therapy smartphone application, to reduce smoking intake. *Digital Health* 2017;3.
- Slatore CG, Baumann C, Pappas M, Humphrey LL. Smoking behaviors among patients receiving computed tomography for lung cancer screening. Systematic review in support of the U.S. Preventive Services Task Force. *Annals of the American Thoracic Society* 2014;11(4):619–27.
- Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *Journal of Pharmacology and Experimental Therapeutics* 2000;295(1):321–7.
- Smedberg J, Lupattelli A, Mardby AC, Nordeng H. Characteristics of women who continue smoking during pregnancy: a cross-sectional study of pregnant women and new mothers in 15 European countries. *BMC Pregnancy and Childbirth* 2014;14:213.
- Smith PH, Weinberger AH, Zhang J, Emme E, Mazure CM, McKee SA. Sex differences in smoking cessation pharmacotherapy comparative efficacy: a network meta-analysis. *Nicotine and Tobacco Research* 2017;19(3):273–81.
- Smith SS, Keller PA, Kobinsky KH, Baker TB, Fraser DL, Bush T, Magnusson B, Zbikowski SM, McAfee TA, Fiore MC. Enhancing tobacco quitline effectiveness: identifying a superior pharmacotherapy adjuvant. *Nicotine and Tobacco Research* 2013;15(3):718–28.
- Smith TT, Koopmeiners JS, Tessier KM, Davis EM, Conklin CA, Denlinger-Apte RL, Lane T, Murphy SE, Tidey JW, Hatsukami DK, et al. Randomized trial of low-nicotine cigarettes and transdermal nicotine. *American Journal of Preventive Medicine* 2019;57(4):515–24.
- Smokefree.gov. Sign up for SmokefreeTXT, n.d.; <<https://smokefree.gov/smokefreetxt>>; accessed: August 17, 2017.
- Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One* 2018;13(3):e0193328.

- Spencer L, Pagell F, Hallion ME, Adams TB. Applying the transtheoretical model to tobacco cessation and prevention: a review of literature. *American Journal of Health Promotion* 2002;17(1):7–71.
- Spindle TR, Eissenberg T. Pod mod electronic cigarettes—an emerging threat to public health. *JAMA Network Open* 2018;1(6):e183518.
- Squiers L, Brown D, Parvanta S, Dolina S, Kelly B, Dever J, Southwell BG, Sanders A, Augustson E. The SmokefreeTXT (SFTXT) study: web and mobile data collection to evaluate smoking cessation for young adults. *JMIR Research Protocols* 2016;5(2):e134.
- Squiers LB, Augustson E, Brown D, Kelly B, Southwell B, Dever J, Dolina S, Tzeng J, Parvanta S, Holt S, et al. An experimental comparison of mobile texting programs to help young adults quit smoking. *Health Systems* 2017;6(1):1–14.
- Stanton A, Grimshaw G. Tobacco cessation interventions for young people. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD003289. DOI: 10.1002/14651858.CD003289.pub5.
- Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. *Cochrane Database of Systematic Reviews* 2013a, Issue 5. Art. No.: CD000165. DOI: 10.1002/14651858.CD000165.pub4.
- Stead LF, Carroll AJ, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD001007. DOI: 10.1002/14651858.CD001007.pub3.
- Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews* 2013b, Issue 8. Art. No.: CD002850. DOI: 10.1002/14651858.CD002850.pub3.
- Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD008286. DOI: 10.1002/14651858.CD008286.pub3.
- Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No.: CD009670. DOI: 10.1002/14651858.CD009670.pub3.
- Stead LF, Lancaster T. Interventions to reduce harm from continued tobacco use. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD005231. DOI: 10.1002/14651858.CD005231.pub2.
- Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2012a, Issue 10. Art. No.: CD009670. DOI: 10.1002/14651858.CD009670.pub3.
- Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2012b, Issue 10. Art. No.: CD008286. DOI: 10.1002/14651858.CD008286.pub2.
- Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub4.
- Stearns M, Nambiar S, Nikolaev A, Semenov A, McIntosh S. Towards evaluating and enhancing the reach of online health forums for smoking cessation. *Network Modeling and Analysis in Healthcare Informatics and Bioinformatics* 2014;3.
- Steinberg MB, Alvarez MS, Delnevo CD, Kaufman I, Cantor JC. Disparity of physicians' utilization of tobacco treatment services. *American Journal of Health Behavior* 2006a;30(4):375–86.
- Steinberg MB, Foulds J, Richardson DL, Burke MV, Shah P. Pharmacotherapy and smoking cessation at a tobacco dependence clinic. *Preventive Medicine* 2006b;42(2):114–9.
- Steinberg MB, Schmelzer AC, Richardson DL, Foulds J. The case for treating tobacco dependence as a chronic disease. *Annals of Internal Medicine* 2008;148(7):554–6.
- Stevens P, Carlson LM, Hinman JM. An analysis of tobacco industry marketing to lesbian, gay, bisexual, and transgender (LGBT) populations: strategies for mainstream tobacco control and prevention. *Health Promotion Practice* 2004;5(3 Suppl):129S–34S.
- Stoddard J, Delucchi K, Munoz R, Collins N, Stable EP, Augustson E, Lenert L. Smoking cessation research via the internet: a feasibility study. *Journal of Health Communication* 2005;10(1):27–41.
- Stoddard JL, Augustson EM, Moser RP. Effect of adding a virtual community (bulletin board) to smokefree.gov: randomized controlled trial. *Journal of Medical Internet Research* 2008;10(5):e53.
- Strecher VJ, Shiffman S, West R. Randomized controlled trial of a web-based computer-tailored smoking cessation program as a supplement to nicotine patch therapy. *Addiction* 2005;100(5):682–8.
- Styn MA, Land SR, Perkins KA, Wilson DO, Romkes M, Weissfeld JL. Smoking behavior 1 year after computed tomography screening for lung cancer: effect of physician referral for abnormal CT findings. *Cancer Epidemiology, Biomarkers, and Prevention* 2009;18(12):3484–9.
- Substance Abuse and Mental Health Services Administration. Adults with mental illness or substance use disorder account for 40 percent of all cigarettes smoked, March 20, 2013; <<https://www.samhsa.gov/data/sites/default/>

- files/spot104-cigarettes-mental-illness-substance-use-disorder/spot104-cigarettes-mental-illness-substance-use-disorder.pdf>; accessed: November 4, 2019.
- Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: detailed tables (tables 6.10B and 6.24B), n.d.; <<https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2013/NSDUH-DetTabs2013.htm>>; accessed: February 13, 2018.
- Sussman S, Lichtman K, Ritt A, Pallonen UE. Effects of thirty-four adolescent tobacco use cessation and prevention trials on regular users of tobacco products. *Substance Use and Misuse* 1999;34(11):1469–503.
- Swan GE, McAfee T, Curry SJ, Jack LM, Javitz H, Dacey S, Bergman K. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. *Archives of Internal Medicine* 2003;163(19):2337–44.
- Sykes CM, Marks DF. Effectiveness of a cognitive behaviour therapy self-help programme for smokers in London, UK. *Health Promotion International* 2001;16(3):255–60.
- Taber JM, Klein WM, Ferrer RA, Augustson E, Patrick H. A pilot test of self-affirmations to promote smoking cessation in a national smoking cessation text messaging program. *JMIR mHealth uHealth* 2016;4(2):e71.
- Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *Journal of the National Cancer Institute* 2014;106(6):dju084.
- Taylor KL, Deros DE, Fallon S, Stephens J, Kim E, Lobo T, Davis KM, Luta G, Jayasekera J, Meza R, et al. Study protocol for a telephone-based smoking cessation randomized controlled trial in the lung cancer screening setting: The lung screening, tobacco, and health trial. *Contemporary Clinical Trials* 2019;82:25–35.
- Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014;348:g1151.
- Taylor KL, Cox LS, Zincke N, Mehta L, McGuire C, Gelmann E. Lung cancer screening as a teachable moment for smoking cessation. *Lung Cancer* 2007;56(1):125–34.
- Teixeira PJ, Carraca EV, Marques MM, Rutter H, Oppert JM, De Bourdeaudhuij I, Lakerveld J, Brug J. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. *BMC Medicine* 2015;13:84.
- The Community Guide. Tobacco use and secondhand smoke exposure: internet-based cessation interventions, 2011a; <https://www.thecommunityguide.org/topic/tobacco?field_recommendation_tid=All&items_per_page=5>; accessed: May 24, 2017.
- The Community Guide. Tobacco use and secondhand smoke exposure: mobile phone-based cessation interventions, 2011b; <<https://www.thecommunityguide.org/findings/tobacco-use-and-secondhand-smoke-exposure-mobile-phone-based-cessation-interventions>>; accessed: May 24, 2017.
- The Community Guide. Tobacco, 2012a; <https://www.thecommunityguide.org/topic/tobacco?field_recommendation_tid=All&items_per_page=5>; accessed: May 24, 2017.
- The Community Guide. Tobacco use and secondhand smoke exposure: quitline interventions, 2012b; <<https://www.thecommunityguide.org/findings/tobacco-use-and-secondhand-smoke-exposure-quitline-interventions>>; accessed: August 1, 2017.
- The Joint Commission. personal communication, March 18, 2019.
- Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ* 2013;347:f5704.
- Thomsen T, Villebro N, Møller AM. Interventions for pre-operative smoking cessation. *Cochrane Database of Systematic Reviews* 2010, Issue 7. Art. No.: CD002294. DOI: 10.1002/14651858.CD002294.pub3.
- Thomsen T, Villebro N, Møller AM. Interventions for pre-operative smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD002294. DOI: 10.1002/14651858.CD002294.pub4.
- Tindle HA, Daigh R, Reddy VK, Bailey LA, Ochs JA, Maness MH, Davis EM, Schulze AE, Powers KM, Ylioja TE, et al. eReferral between hospitals and quitlines: an emerging tobacco control strategy. *American Journal of Preventive Medicine* 2016;51(4):522–6.
- Tinkelman D, Wilson SM, Willett J, Sweeney CT. Offering free NRT through a tobacco quitline: impact on utilization and quit rates. *Tobacco Control* 2007;16(Suppl 1):i42–i46.
- Tong EK, Ong MK, Vittinghoff E, Perez-Stable EJ. Nondaily smokers should be asked and advised to quit. *American Journal of Preventive Medicine* 2006;30(1):23–30.
- Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ. Trends in smoking before, during, and after pregnancy—Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000–2010. *Morbidity and Mortality Weekly Report: Surveillance Summaries* 2013;62(6):1–19.
- Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA: the Journal of the American Medical Association* 2006;296(1):64–71.

- Truth Initiative. *Behind the Explosive Growth of JUUL: Social Influences and Flavors Drive Rising Teen Use of the Top E-Cigarette*, December 2018; <<https://truthinitiative.org/sites/default/files/media/files/2019/03/Behind-the-explosive-growth-of-JUUL.pdf>>; accessed: July 25, 2019.
- Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD007253. DOI: 10.1002/14651858.CD007253.pub3.
- Tudor-Sfetea C, Rabee R, Najim M, Amin N, Chadha M, Jain M, Karia K, Kothari V, Patel T, Suseeharan M, et al. Evaluation of two mobile health apps in the context of smoking cessation: qualitative study of cognitive behavioral therapy (CBT) versus non-CBT-based digital solutions. *JMIR Mhealth and Uhealth* 2018;6(4):e98.
- Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. *BMC Medicine* 2016;14:80.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.
- U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
- U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2016.
- U.S. Department of Health and Human Services. Surgeon General releases advisory on e-cigarette epidemic among youth [press release], December 18, 2018a; <<https://www.hhs.gov/about/news/2018/12/18/surgeon-general-releases-advisory-e-cigarette-epidemic-among-youth.html>>.
- U.S. Department of Health and Human Services. *Surgeon General's Advisory on E-cigarette Use Among Youth*, 2018b; <<https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf>>; accessed: January 9, 2019.
- U.S. Food and Drug Administration. Nicotine replacement therapy labels may change, 2013; <https://www.integration.samhsa.gov/health-wellness/NRT_Label_Change_0413.pdf>; accessed: August 7, 2018.
- U.S. Food and Drug Administration. Want to Quit Smoking? FDA-Approved Products Can Help [consumer update], 2017; <<https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198176.htm>>; accessed: August 1, 2018.
- U.S. Food and Drug Administration. FDA drug safety communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings, 2018a; <<https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm>>; accessed: March 13, 2019.
- U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on pivotal public health step to dramatically reduce smoking rates by lowering nicotine in combustible cigarettes to minimally or non-addictive levels [press release], March 15, 2018b; <<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601039.htm>>; accessed: November 14, 2018.

- U.S. Food and Drug Administration. *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products; Draft Guidance for Industry; Availability*, February 2019a; <<https://www.regulations.gov/document?D=FDA-2019-D-0297-0001>>; accessed: May 9, 2019.
- U.S. Food and Drug Administration. This Free Life campaign, September 23, 2019b; < https://www.fda.gov/tobacco-products/free-life-campaign?utm_campaign=ctp-healthobservance&utm_medium=social&utm_source=CTPTwitter>; accessed: November 4, 2019.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions, September 2015; <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>>; accessed: May 24, 2017.
- U.S. Preventive Services Task Force. Final Recommendation Statement—Tobacco Use in Children and Adolescents: Primary Care Interventions, December 2016; <<https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-children-and-adolescents-primary-care-interventions>>; accessed: November 29, 2018.
- Ubhi HK, Kotz D, Michie S, van Schayck OC, Sheard D, Selladurai A, West R. Comparative analysis of smoking cessation smartphone applications available in 2012 versus 2014. *Addictive Behaviors* 2016;58:175–81.
- Ussher M, Beard E, Abikoye G, Hajek P, West R. Urge to smoke over 52 weeks of abstinence. *Psychopharmacology* 2013;226(1):83–9.
- van der Aalst CM, de Koning HJ, van den Bergh KA, Willemsen MC, van Klaveren RJ. The effectiveness of a computer-tailored smoking cessation intervention for participants in lung cancer screening: a randomised controlled trial. *Lung Cancer* 2012;76(2):204–10.
- van der Meer RM, Willemsen MC, Smit F, Cuijpers P. Smoking cessation interventions for smokers with current or past depression. *Cochrane Database of Systematic Reviews* 2013, 2013, Issue 8. Art. No.: CD006102. DOI: 10.1002/14651858.CD006102.pub2.
- Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine and Tobacco Research* 2013;15(1):267–70.
- Velicer WF, Prochaska JO, Fava JL, Laforge RG, Rossi JS. Interactive versus noninteractive interventions and dose-response relationships for stage-matched smoking cessation programs in a managed care setting. *Health Psychology* 1999;18(1):21–8.
- Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine and Tobacco Research* 2013;15(10):1787–91.
- Vickerman KA, Schauer GL, Malarcher AM, Zhang L, Mowery P, Nash CM. Reasons for electronic nicotine delivery system use and smoking abstinence at 6 months: a descriptive study of callers to employer and health plan-sponsored quitlines. *Tobacco Control* 2017;26(2):126–34.
- Vidrine JI, Shete S, Cao Y, Greisinger A, Harmonson P, Sharp B, Miles L, Zbikowski SM, Wetter DW. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. *JAMA Internal Medicine* 2013a;173(6):458–64.
- Vidrine JI, Shete S, Li Y, Cao Y, Alford MH, Galindo-Talton M, Rabius V, Sharp B, Harmonson P, Zbikowski SM, et al. The Ask-Advise-Connect approach for smokers in a safety net healthcare system: a group-randomized trial. *American Journal of Preventive Medicine* 2013b;45(6):737–41.
- Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind, randomised, placebo-controlled trial of cytosine for smoking cessation in medium-dependent workers. *Journal of Smoking Cessation* 2008;3(1):57–62.
- Volpp KG, Troxel AB, Pauly MV, Glick HA, Puig A, Asch DA, Galvin R, Zhu J, Wan F, DeGuzman J, et al. A randomized, controlled trial of financial incentives for smoking cessation. *New England Journal of Medicine* 2009;360(7):699–709.
- Wadgave U, Nagesh L. Nicotine replacement therapy: an overview. *International Journal of Health Sciences* 2016;10(3):425–35.
- Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, Laugesen M, Jiang J, Chen MH, Whittaker R, et al. Does improved access and greater choice of nicotine replacement therapy affect smoking cessation success? Findings from a randomized controlled trial. *Addiction* 2011;106(6):1176–85.
- Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, Parag V, Bassett B, Bullen C. Cytisine versus nicotine for smoking cessation. *New England Journal of Medicine* 2014;371(25):2353–62.
- Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respiratory Medicine* 2019
- Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults—United States, 2017. *Morbidity and Mortality Weekly Report* 2018;67(44):1225–32.
- Wang TW, Walton K, Jamal A, Babb SD, Schecter A, Prutzman YM, King BA. State-specific cessation behaviors among

- adult cigarette smokers—United States, 2014–2015. *Preventing Chronic Disease* 2019;16:E26.
- Warner DO. Perioperative abstinence from cigarettes: physiologic and clinical consequences. *Anesthesiology* 2006;104(2):356–67.
- Warner DO, Nolan MB, Kadimpati S, Burke MV, Hanson AC, Schroeder DR. Quitline Tobacco interventions in hospitalized patients: a randomized trial. *American Journal of Preventive Medicine* 2016;51(4):473–84.
- Warner KE, Mendez D. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine and Tobacco Research* 2019;21(1):41–7.
- Washington HA. Burning love: big tobacco takes aim at LGBT youths. *American Journal of Public Health* 2002;92(7):1086–95.
- Webb Hooper M, Antoni MH, Okuyemi K, Dietz NA, Resnicow K. Randomized controlled trial of group-based culturally specific cognitive behavioral therapy among African American smokers. *Nicotine and Tobacco Research* 2017;19(3):333–41.
- Webb MS, de Ybarra DR, Baker EA, Reis IM, Carey MP. Cognitive-behavioral therapy to promote smoking cessation among African American smokers: a randomized clinical trial. *Journal of Consulting and Clinical Psychology* 2010a;78(1):24–33.
- Webb TL, Sniehotta FF, Michie S. Using theories of behaviour change to inform interventions for addictive behaviours. *Addiction* 2010b;105(11):1879–92.
- West R. Time for a change: putting the Transtheoretical (Stages of Change) Model to rest. *Addiction* 2005;100(8):1036–9.
- West R, Edwards M, Hajek P. A randomized controlled trial of a “buddy” system to improve success at giving up smoking in general practice. *Addiction* 1998;93(7):1007–11.
- West R, Zatonski W, Cedzynska M, Lewandowska D, Pazik J, Aveyard P, Stapleton J. Placebo-controlled trial of cytisine for smoking cessation. *New England Journal of Medicine* 2011;365(13):1193–200.
- West R, Zhou X. Is nicotine replacement therapy for smoking cessation effective in the “real world”? Findings from a prospective multinational cohort study. *Thorax* 2007;62(11):998–1002.
- Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD006611. DOI: 10.1002/14651858.CD006611.pub4.
- Whittaker R, McRobbie H, Bullen C, Borland R, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD006611. DOI: 10.1002/14651858.CD006611.pub3.
- Williams GC, McGregor H, Sharp D, Kouldes RW, Levesque CS, Ryan RM, Deci EL. A self-determination multiple risk intervention trial to improve smokers’ health. *Journal of General Internal Medicine* 2006a;21(12):1288–94.
- Williams GC, McGregor HA, Sharp D, Levesque C, Kouides RW, Ryan RM, Deci EL. Testing a self-determination theory intervention for motivating tobacco cessation: supporting autonomy and competence in a clinical trial. *Health Psychology* 2006b;25(1):91–101.
- Williams GC, Minicucci DS, Kouides RW, Levesque CS, Chirkov VI, Ryan RM, Deci EL. Self-determination, smoking, diet and health. *Health Education Research* 2002;17(5):512–21.
- Williams GC, Niemiec CP, Patrick H, Ryan RM, Deci EL. The importance of supporting autonomy and perceived competence in facilitating long-term tobacco abstinence. *Annals of Behavioral Medicine* 2009;37(3):315–24.
- Williams GC, Niemiec CP, Patrick H, Ryan RM, Deci EL. Outcomes of the Smoker’s Health Project: a pragmatic comparative effectiveness trial of tobacco-dependence interventions based on self-determination theory. *Health Education Research* 2016;31(6):749–59.
- Williams GC, Patrick H, Niemiec CP, Ryan RM, Deci EL, Lavigne HM. The smoker’s health project: a self-determination theory intervention to facilitate maintenance of tobacco abstinence. *Contemporary Clinical Trials* 2011;32(4):535–43.
- Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, George TP. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychiatry* 2012;73(5):654–60.
- Windle SB, Filion KB, Mancini JG, Abye-White L, Joseph L, Gore GC, Habib B, Grad R, Pilote L, Eisenberg MJ. Combination therapies for smoking cessation: a hierarchical Bayesian meta-analysis. *American Journal of Preventive Medicine* 2016;51(6):1060–71.
- Winpenny E, Elliott MN, Haas A, Haviland AM, Orr N, Shadel WG, Ma S, Friedberg MW, Cleary PD. Advice to quit smoking and ratings of health care among Medicaid beneficiaries aged 65+. *Health Services Research* 2017;52(1):207–19.
- Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstetrics and Gynecology* 2000;96(6):967–71.
- Witman A, Acquah J, Alva M, Hoerger T, Romaine M. Medicaid incentives for preventing chronic disease: effects of financial incentives for smoking cessation. *Health Services Research* 2018;53(6):5016–34.
- Woods SS, Haskins AE. Increasing reach of quitline services in a U.S. state with comprehensive tobacco treatment. *Tobacco Control* 2007;16(Suppl 1):i33–i36.

- World Health Organization. 1. Benefits and rationale for establishing quit-line services. In: *Developing and Improving National Toll-Free Tobacco Quit Line Services: A World Health Organization Manual*. Geneva (Switzerland): World Health Organization, 2011:7–11.
- World Health Organization. Recommendations. In: *WHO Recommendations for the Prevention and Management of Tobacco Use and Second-Hand Smoke Exposure in Pregnancy*. Geneva (Switzerland): World Health Organization, 2013:44–9.
- World Health Organization. *Advisory Note: Global Nicotine Reduction Strategy*. Geneva (Switzerland): World Health Organization, 2015.
- World Health Organization and International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 89: Smokeless Tobacco and some Tobacco-Specific N-Nitrosamines* Lyon (France): International Agency for Research on Cancer, 2007.
- Wortley PM, Husten CG, Trosclair A, Chrismon J, Pederson LL. Nondaily smokers: a descriptive analysis. *Nicotine and Tobacco Research* 2003;5(5):755–9.
- Yalom ID, Leszcz M. *Theory and Practice of Group Psychotherapy*. 5th ed. New York (NY): Basic Books, 2005.
- Yvonne Prutzman, NCI. personal communication, January 23, 2019.
- Zapka JG, Fletcher K, Pbert L, Druker SK, Ockene JK, Chen L. The perceptions and practices of pediatricians: tobacco intervention. *Pediatrics* 1999;103(5):e65.
- Zeliadt SB, Heffner JL, Sayre G, Klein DE, Simons C, Williams J, Reinke LF, Au DH. Attitudes and perceptions about smoking cessation in the context of lung cancer screening. *JAMA Internal Medicine* 2015;175(9):1530–7.
- Zhang B, Cohen JE, Bondy SJ, Selby P. Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. *American Journal of Epidemiology* 2015;181(7):513–20.
- Zhang L, Malarcher A, Mann N, Campbell K, Davis K, Anderson C, Alexander R, Rodes R. The influence of state-specific quitline numbers on call volume during a national tobacco education campaign promoting 1-800-QUIT-NOW. *Nicotine and Tobacco Research* 2016;18(8):1780–5.
- Zhu SH, Lee M, Zhuang YL, Gamst A, Wolfson T. Interventions to increase smoking cessation at the population level: how much progress has been made in the last two decades? *Tobacco Control* 2012;21(2):110–8.
- Zhu SH, Stretch V, Balabanis M, Rosbrook B, Sadler G, Pierce JP. Telephone counseling for smoking cessation: effects of single-session and multiple-session interventions. *Journal of Consulting and Clinical Psychology* 1996;64(1):202–11.
- Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from U.S. current population surveys. *BMJ* 2017;358:j3262.
- Zhuang YL, Cummins SE, J YS, Zhu SH. Long-term e-cigarette use and smoking cessation: a longitudinal study with U.S. population. *Tobacco Control* 2016;25(Suppl 1)i90–i95.
- Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, Breslau N, Brown RA, George TP, Williams J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine and Tobacco Research* 2008;10(12):1691–715.

Chapter 7

Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation

Introduction 579

Literature Review Methods 579

Clinical- and Health System-Based Strategies on Smoking Cessation 581

Clinical Practice Guidelines 583

 Clinical Practice Guideline from the U.S. Public Health Service 583

 Recommendations from the U.S. Preventive Services Task Force 586

Improving and Promoting Coverage of Treatment for Tobacco Use and Dependence 587

 Health Insurance Coverage 588

 Removing Barriers to Access 592

 Promoting Coverage for Utilization of Smoking Cessation Treatments and Benefits 594

Quality and Performance Measures and Payment Reforms 594

 Linking Quality Measures to Payment 595

 Health Plan-Based Quality Measures 595

 Hospital-Based Performance Measures 595

 Realigning Payment Incentives 596

Enhancing the Technology of Electronic Health Records 597

Population-Based Strategies on Smoking Cessation 598

Quitlines 598

Increasing the Price of Tobacco Products 599

Smokefree Policies 601

Mass Media Campaigns 603

 Examples of Campaigns 603

 Features of Antismoking Campaigns that Support the Use of Cessation Resources 604

 Effectiveness of Campaigns 605

State Tobacco Control Programs 605

Pictorial Health Warnings 607

Plain Packaging 608

Reduced Retail Point-of-Sale Advertising and Retail Density 609

Restricting the Sale of Certain Types of Tobacco Products 610

Very-Low-Nicotine-Content Cigarettes 612

E-Cigarettes 612

Modeling to Assess the Impact of Policy and Regulatory Changes on Cessation 613

Limitations and Methodologic Gaps 617

Summary of the Evidence 618

Conclusions 619

References 620

Introduction

Clinical-, system-, and population-level strategies can broadly influence the behavior of smokers as they try to quit or think about quitting smoking. This chapter focuses on these broad strategies that can facilitate the integration of individual components of treatment for smoking cessation, as discussed in Chapter 6, into routine clinical care—making cessation interventions available and accessible to individual smokers and creating conditions whereby smokers become aware of these interventions and are motivated to use them. This chapter does not attempt to provide a review of all tobacco control policy actions that may result in smokers attempting to quit or that may increase quit success outside the context of cessation treatment interventions; these have been covered comprehensively in previous Surgeon General’s reports, including the 50th anniversary report, *The Health Consequences of Smoking—50 Years of Progress* (U.S. Department of Health and Human Services [USDHHS] 2014), as well as in other documents (National Cancer Institute [NCI] and World Health Organization [WHO] 2017; WHO 2019). Table 7.1 describes key findings from the 2014 Surgeon General’s report that are relevant to smoking cessation.

Strategies that encourage smoking cessation beyond the individual smoker generally involve actions at one of three levels: (1) the clinical setting, (2) the health system, or (3) the population. Actions taken at the clinical and health system levels typically target quitting behavior directly and generally focus on the use or effectiveness of treatments for smoking cessation (Fiore et al. 2008; Centers for Disease Control and Prevention [CDC] 2014b; U.S. Preventive Services Task Force [USPSTF] 2015). These actions include implementing policies that transform systems of care to better address tobacco use and dependence; promoting evidence-based treatments for tobacco cessation; and implementing policies that are clinically focused, address health insurance coverage, and promote cessation. These actions can reach a large proportion of Americans who smoke, considering nearly 70% of U.S. adults who smoke cigarettes visit a primary care clinician each year (CDC 2012c) and millions of U.S. adults see specialty clinicians and are hospitalized annually (National Center for Health Statistics 2018).

In contrast, population-based strategies are aimed at influencing tobacco cessation at a macro level by motivating smokers to quit and by providing an environment that supports or simplifies efforts to quit or lowers barriers that smokers might encounter. These strategies are broader than those at the clinical or health system levels, affecting the larger community or population, not just individuals engaged with the healthcare system. Population-based strategies include increasing the price of and/or the tax on cigarettes and other tobacco products; restricting where tobacco can be used by implementing smokefree and tobacco-free policies; adequately funding tobacco control programs at the state level; carrying out mass media campaigns (e.g., CDC’s *Tips From Former Smokers* campaign [Tips] [CDC 2018b] and the U.S. Food and Drug Administration’s [FDA’s] Real Cost Campaign [FDA 2018b]); making changes to the tobacco retail density and point-of-sale environments; and developing product regulations, including regulating nicotine content and requiring pictorial health warnings. Importantly, combining clinical and health system-based and macro-level strategies can have a synergistic effect on improving cessation outcomes. For example, in addition to motivating smokers to make a quit attempt, a mass media campaign (a macro-level strategy), such as the *Tips* campaign, can motivate smokers to use cessation resources, including state quitlines, web-based cessation support, and cessation interventions from healthcare providers.

This classification of strategies to promote smoking cessation is similar to CDC’s “three buckets framework,” in which prevention approaches include (1) traditional patient-level clinical interventions; (2) innovative clinical prevention provided outside of the clinical or health system setting; and (3) population- or community-wide interventions that reach a broader population, often defined geographically (Auerbach 2016) (Figure 7.1). With this framework in mind, a combination of strategies across the three buckets could potentially provide optimal cessation motivation and support for smokers by helping them quit and creating a broad environment that is conducive to and supportive of quitting.

Literature Review Methods

For the evidence presented in this chapter, PubMed/Medline, Scopus, and Google Scholar were searched for studies that focused on smoking cessation policies as

they are impacted by various strategies, technologies, and inducements at both the health system and population levels, with a specific focus on well-designed review articles

Table 7.1 Summary of policies from the 2014 Surgeon General’s report that encourage smoking cessation

Policy area	Results for smoking cessation
Tax or price	<ul style="list-style-type: none"> • A 10% increase in cigarette price is associated with a 3–5% decrease in cigarette consumption. • Increasing the price of tobacco products reduces initiation, prevalence, and intensity of smoking in youth and adults.
Smokefree policies	<p>In addition to protecting nonsmokers from exposure to secondhand smoke, strong evidence suggests that smokefree laws and policies:</p> <ul style="list-style-type: none"> • Reduce the prevalence of tobacco use, • Increase the number of tobacco users who quit, and • Reduce the initiation of smoking among youth and young adults. <p>Specifically, smokefree laws and policies are associated with a:</p> <ul style="list-style-type: none"> • 3.4% reduction in the prevalence of tobacco use, and • 6.4% increase in tobacco cessation.
Healthcare policies	<p>Federal regulations and legislation have included components to increase the delivery of evidence-based treatments for nicotine dependence in healthcare systems:</p> <ul style="list-style-type: none"> • The HITECH Act requires the identification and documentation of tobacco use in the EHRs of all patients 13 years of age and older who use tobacco. This has made the identification and documentation of tobacco use in EHRs nearly universal in the U.S. healthcare system. • The ACA contains several tobacco cessation elements: <ul style="list-style-type: none"> – Mandatory coverage for tobacco cessation medications in state Medicaid programs; – Coverage, without cost sharing, of treatment for nicotine dependence for pregnant smokers in state Medicaid programs; and – The elimination of copayments for preventive services rated A or B by USPSTF, including nicotine dependence treatment for all adults. • In 2010, Medicare expanded coverage of tobacco cessation to all beneficiaries who use tobacco, replacing previous coverage limited to beneficiaries with signs or symptoms of a tobacco-related disease.
Comprehensive statewide tobacco control programs	<p>States that have invested more funds in tobacco control have seen larger and faster declines in the prevalence of smoking. Several elements have been shown to be effective at promoting and facilitating tobacco cessation:</p> <ul style="list-style-type: none"> • Mass media health communications designed to discourage initiation and encourage cessation among youth. For example, CDC’s Tips campaign motivated an estimated 1.6 million additional smokers to make a quit attempt. • Healthcare system- and population-based interventions encouraged by state programs can promote tobacco cessation via increased delivery of evidence-based tobacco use treatments, such as: <ul style="list-style-type: none"> – Tobacco cessation quitlines and – Evidence-based tobacco cessation programs housed in healthcare delivery systems.

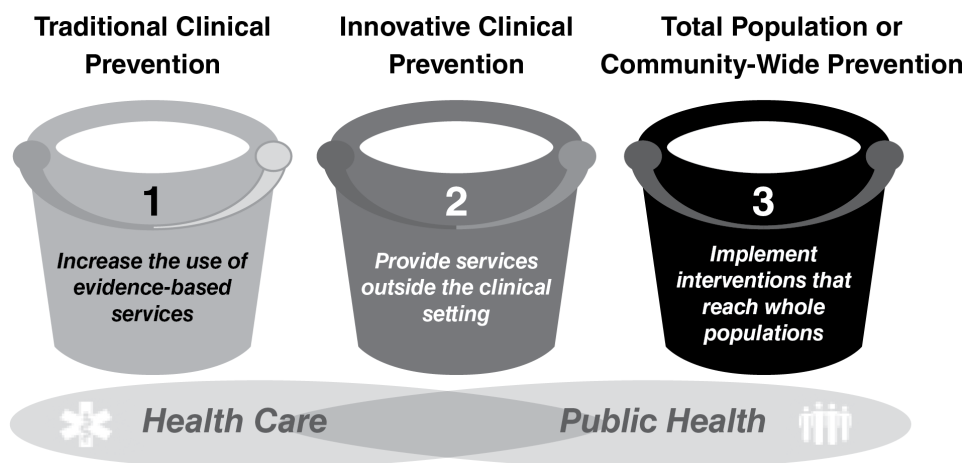
Source: USDHHS (2014).

Notes: **ACA** = Patient Protection and Affordable Care Act; **CDC** = Centers for Disease Control and Prevention; **EHRs** = electronic health records; **HITECH Act** = Health Information Technology Economic and Clinical Health Act; **USPSTF** = U.S. Preventive Services Task Force.

and meta-analysis, when available. Articles were published between January 1, 2002, and December 31, 2016, and included references to other sources (e.g., those in *Clinical Practice Guideline* [Fiore et al. 2008]) that predated 2002. Consistent with the longstanding process adhered to for the development of Surgeon General’s reports on tobacco (see Chapter 1), several additional studies published after 2016 were added during the review and clearance process to ensure that the volume includes the most updated scientific literature available. A combination of keywords and phrases were used in conjunction with “cessation” or “quit” to investigate the following topics as they relate to

smoking cessation: (1) clinic and health system strategies, including guidelines, insurance coverage, provider payments/incentives, performance measures, and electronic health records (EHRs); and (2) population-based policies, including tobacco taxes/price, quitlines, mass media campaigns, smokefree strategies, tobacco control programs, pictorial health warnings, plain packaging, retail density, low-nicotine-content cigarettes, and menthol or flavors. Chapter conclusions reflect evidence cited in previous Surgeon General’s reports and newly available evidence. Search results were limited to studies published in English and to original research.

Figure 7.1 CDC's conceptual population health and prevention framework



Source: Auerbach (2016), with permission.

One hundred sixty-five articles were initially identified for review for this chapter, with additional literature added that was published following completion of the initial literature review. For the first section on clinical and health system-based strategies, 75 articles were initially reviewed. These articles fell into the following categories: clinical guideline training and compliance (15 articles), provider and health system payments/incentives (22 articles), performance measures (4 articles), health information technology (12 articles), insurance coverage and benefits (13 articles), and health system enhancements (9 articles). For the second section on population-based strategies, 90 articles were initially reviewed. These articles fell into the following categories:

tobacco taxes/price (19 articles), quitlines (16 articles), EHR enhancement (3 articles), mass media campaigns (16 articles), smokefree policies (17 articles), and pictorial health warnings (5 articles). Subsequent to the initial review, additional reviews were performed that identified articles on the following categories: tobacco control programs, plain packaging, retail density and point-of-sale advertising, and flavor and product restrictions. Each article was screened for level of relevance to the topic, its recency, whether it provided novel or complementary information (relative to other articles), and the quality and soundness of its experimental methods given the goals of the research. Articles that did not meet these criteria were excluded.

Clinical- and Health System-Based Strategies on Smoking Cessation

Although significant progress has been made to integrate tobacco use and dependence treatment into clinical health systems, substantial opportunities remain for improvement. For example, in 2000, 52.4% of cigarette smokers who had seen a health professional during the previous year reported that they had received advice to quit. In 2015, that figure rose to 57.2% (Babb et al. 2017). This suggests that progress on this indicator has been slow, with more than 40% of smokers in healthcare settings not receiving basic tobacco cessation counseling from clinicians. Moreover, the rates at which physicians deliver more intensive interventions, such as cessation assistance and follow-up to help persons plan for and carry out quit attempts, are typically lower than the prevalence

of screening for tobacco use and delivering advice to quit (King et al. 2013b; Bartsch et al. 2016); these more intensive steps can play an important role in helping smokers carry out quit attempts (Fiore et al. 2008).

One way to increase smoking cessation interventions from clinicians is through health systems policies and protocols that make smoking cessation a standard of care (Fiore et al. 2008). Systemwide strategies and changes can increase the delivery of clinical cessation interventions by routinizing the approach to smoking cessation, making it easier for clinicians and their teams to consistently provide evidence-based cessation treatments (Fiore et al. 2007; Rigotti 2011; CDC 2014a). In particular, data and experiences from the field suggest that health

systems initiatives are most likely to increase the prevalence of clinical cessation interventions if these initiatives (a) embed policies and protocols for tobacco use screening and intervention into the clinical workflow, including provider reminder systems and support for clinical decisions; (b) embed decision support tools into health records, including EHRs¹; and (c) delegate specific components of the intervention to the broader healthcare team to reduce the burden on time-constrained physicians (Fiore et al. 2008; Lindholm et al. 2010; Land et al. 2012; Jansen et al. 2014; Moody-Thomas et al. 2015; Smith et al. 2015).

However, evidence is mixed on the impact of health systems change on overall cessation. For example, a 2017 Cochrane Review assessed the effectiveness of systems change interventions in healthcare settings for increasing smoking cessation and/or the provision of cessation care (Thomas et al. 2017). Evidence from the review indicated that systems change interventions improve performance on process outcomes, such as documenting smoking status and providing cessation counseling and treatment, but these interventions do not yet clearly demonstrate that they increase cessation rates. Conversely, a 2012 study of data from more than 100,000 patients in the Harvard Vanguard Medical system during 2005–2010 found that patients in clinics that implemented a systems change approach (defined as using a tobacco use identification system and screening at least half of all patients) had significant reductions in the prevalence of smoking and in the rate of office visits for smoking-related disease (Land et al. 2012).

Chapter 6 details the specific barriers that clinicians may face when delivering smoking cessation interventions to patients, along with approaches to overcoming these barriers. Barriers include time constraints, insufficient training on tobacco dependence and treatment, lack of confidence among clinicians on their ability to effectively deliver cessation interventions, a perception on the part of some clinicians that tobacco dependence treatment is not effective, limited clinician time and reimbursement to provide treatment to patients, and failure to fully engage other clinical staff in providing cessation support to patients (Rojewski et al. 2019). Many of these individual barriers can be overcome by implementing the system-wide policies discussed in this chapter.

In addition to strategies that seek to make the delivery of smoking cessation interventions in health systems more routine, those that remove cost and other barriers (which impede smokers' access to proven cessation

treatments) have been shown to increase the delivery and utilization of tobacco dependence treatment, especially when the covered treatments are proactively promoted to health plan beneficiaries. For example, standardized comprehensive, barrier-free cessation coverage by private and public insurers expedites smokers' access to evidence-based cessation treatments and removes confusion about which treatments are covered and related barriers for both smokers and providers, thereby increasing the chances that smokers and providers will make use of these treatments (Fiore et al. 2008; Kofman et al. 2012; CDC 2014b). Clinical guidelines and clinical quality measures also play an important role in ensuring that clinicians and health systems consistently intervene with tobacco users (Ward et al. 2003; Katz et al. 2004, 2014; Lesho et al. 2005; Smith et al. 2005, 2008; Caplan et al. 2011; Moody-Thomas et al. 2011; Shelley et al. 2011; Fiore et al. 2012; Kruger et al. 2015; Siu 2015).

During the past decade, numerous policy and regulatory efforts at the national, state, and local levels have been undertaken in the United States to encourage clinicians and health systems to identify, document, and treat persons who use tobacco (USDHHS 2014; McAfee et al. 2015; Fiore 2016; Thomas et al. 2017) and to encourage health insurers to cover smoking cessation and to promote the covered treatments. Generally, these efforts have focused on achieving several goals, including (1) increasing rates of cessation; (2) improving smokers' awareness of and access to evidence-based treatments; (3) improving patient health and healthcare quality; (4) reducing healthcare costs associated with tobacco use; (5) identifying and promoting evidence-based cessation treatments and programs; (6) establishing clinical standards for tobacco use and dependence treatment and making clinicians and health systems aware of such standards; (7) improving cessation insurance coverage and promoting it to smokers; (8) enhancing compensation for providers or health systems through pay-for-performance quality measures, payment reforms, and improved, simpler reimbursement procedures; and (9) leveraging health information technology to improve and routinize treatment for tobacco use and dependence (CDC 2014b; USDHHS 2014; McAfee et al. 2015; Fiore 2016).

Achieving these goals involves taking action at multiple levels and may involve government (at the local, state, and/or national levels) and nongovernmental entities (e.g., accreditation and nonprofit organizations, health system administrators, and insurers). This section

¹An EHR is a collection of health-related information for a patient that is generated by one or more visits in any healthcare setting. The EHR typically includes demographic information about the patient, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data, and radiology reports. EHRs focus on the total health of the patient and thus go beyond the standard clinical data that are collected in a healthcare provider's office, offering a broader view of the patient's care.

describes the major types of strategies at the clinical and health system levels and the evidence regarding their effects on cessation interventions. Because some of the specific strategies were developed relatively recently (McAfee et al. 2015; Fiore 2016), their effects on key endpoints, including increased access to clinical services for cessation and higher rates of cessation, are not yet fully known.

Clinical Practice Guidelines

Clinical practice guidelines from a variety of entities, including governmental, professional, and accrediting agencies, are relevant to clinical and health system policies in two ways. First, they contain best-practice recommendations for clinical treatment that are based on scientific evidence. As such, clinical practice guidelines can increase the likelihood that clinicians will use evidence-based approaches to help their patients quit using tobacco. Second, such guidelines seek to integrate evidence-based cessation interventions into routine clinical practice, serving as standards and laying the groundwork for the effective implementation of other policy levers, including insurance coverage policies and performance quality measures. Two examples of clinical practice guidelines will be described in this report—Clinical Practice Guidelines from the U.S. Public Health Service (Fiore et al. 2008) and the recommendations from the U.S. Preventive Services Task Force (USPSTF 2015). However, there are other guidelines, position statements, and consensus statements from a variety of organizations regarding the clinical treatment of tobacco use disorder (e.g., American Psychiatric Association 2010; Larzelere and Williams 2012; American Academy of Family Physicians 2014; Farber et al. 2015; Barua et al. 2018).

Clinical Practice Guideline from the U.S. Public Health Service

The U.S. Public Health Service first published in 1996 its Clinical Practice Guideline *Treating Tobacco Use and Dependence* (Fiore et al. 1996) and updated it in 2000 (Fiore et al. 2000) and 2008 (Fiore et al. 2008) (also discussed in Chapter 1). The *Clinical Practice Guideline* reviews extensive evidence indicating that health system changes can improve the delivery of treatment for smoking cessation in healthcare settings and can lead to improved downstream quitting behavior and quitting outcomes. Importantly, the findings and recommendations of the *Clinical Practice Guideline* are broadly applicable across most clinical settings, including primary care, specialty, and inpatient settings; dental care settings; and behavioral health settings (Hall et al. 1998; Hayford et al. 1999; Smith

et al. 2003; Wagena et al. 2005; Gordon et al. 2006, 2007, 2010). Moreover, the *Clinical Practice Guideline* recommends specific changes in healthcare systems and policies to enhance the delivery of cessation interventions in clinical settings (Fiore et al. 2008). Table 7.2 describes the systems and policy findings of the 2008 *Clinical Practice Guideline* and the evidence base supporting them.

The *Clinical Practice Guideline* (Fiore et al. 2008) identified (a) specific health system strategies and policies that can facilitate or complement clinical treatments for smokers who visit healthcare settings and (b) strategies that can enhance the likelihood that smokers receive evidence-based treatments for tobacco use and dependence and/or subsequently quit tobacco use. For example, the *Clinical Practice Guideline* found meta-analytic evidence that training clinicians increases the likelihood that they will provide cessation treatment (odds ratio [OR] = 3.2; 95% confidence interval [CI], 2.0–5.2) and that such training is associated with subsequent increases in cessation among their patients (OR = 2.0; 95% CI, 1.2–3.4). Similarly, in a Cochrane Review of training health professionals to conduct interventions in smoking cessation, Carson and colleagues (2012) concluded that clinicians who received training were more likely than untrained clinicians (control group) to ask patients to set a quit date, make follow-up appointments, and counsel smokers. However, in general, clinicians' follow-up with patients who are trying to quit remains suboptimal (King et al. 2013b; Bartsch et al. 2016).

Additionally, as outlined in Table 7.2, meta-analytic evidence from the *Clinical Practice Guideline* found that implementing systems to identify the smoking status of patients further increases clinicians' rates of intervention with patients (nine studies: OR = 3.1; 95% CI, 2.2–4.2) (Fiore et al. 2008). Because the prevalence of cigarette smoking remains high in certain subpopulations in the United States, such as persons of lower socioeconomic status (Wang et al. 2018) and those with comorbid mental health and other substance use diagnoses (Substance Abuse and Mental Health Services Administration 2013), specific types of healthcare providers or clinical environments that serve these subpopulations (e.g., psychiatrists, psychologists, social workers, federally qualified health centers) will likely play an increasingly important role in tobacco cessation.

Systems-level recommendations contained in the 2000 and 2008 *Clinical Practice Guidelines* have influenced numerous public and private sector policies and recommendations for treating tobacco use and dependence and have also served as the evidentiary basis for healthcare legislation (Torrijos and Glantz 2006). For example, evidence from the *Clinical Practice Guidelines* helped to inform cessation provisions in the 2010 *Patient Protection*

Table 7.2 Systems-level changes reviewed in the 2008 *Clinical Practice Guideline* to encourage smoking cessation

Strategy	Action	Strategies for implementation	Meta-analytic findings from the 2008 <i>Clinical Practice Guideline</i>
1. Implement a tobacco user identification system in every clinic	Implement an officewide system to ensure that tobacco use status is queried and documented for <i>every</i> patient at every visit to the clinic	<ul style="list-style-type: none"> • Office system change: Expand the review of vital signs to include tobacco use or implement an alternative universal identification system • Responsible staff (nurse, medical assistant, receptionist, or other person already responsible for recording the vital signs): Must be instructed on the importance of this activity and serve as nonsmoking role models • Frequency of utilization: Every visit for every patient, regardless of the reason for the visit • System-implementation steps: Routine smoker identification can be achieved by modifying data collection and documentation in EHRs to include tobacco use status as one of the vital signs 	<ul style="list-style-type: none"> • Impact of having a tobacco use status identification system in place on rates of clinician intervention with their patients who smoke (n = 9 studies): OR = 3.1; 95% CI, 2.2–4.2 • Impact of having a tobacco use status identification system in place on abstinence rates among patients who smoke (n = 3 studies): OR = 2.0; 95% CI, 0.8–4.8
2. Provide education, resources, and feedback to promote interventions by healthcare providers	Healthcare systems should ensure that clinicians have sufficient training to treat nicotine dependence; that clinicians and patients have resources; and that clinicians are given feedback about their nicotine dependence treatment practices	<ul style="list-style-type: none"> • Educate all staff on a regular basis by offering training (e.g., lectures, workshops, in-services) on nicotine dependence treatments and providing continuing education credits and/or other incentives for participation • Provide resources—such as having ready access to tobacco quitlines (800-QUIT-NOW and www.smokefree.gov) and establishing a tobacco quitline referral system—and other community resources, self-help materials, and information about effective tobacco use medications • Report the provision of nicotine dependence interventions on performance measures, report cards, and evaluative standards for healthcare organizations, insurers, accreditation organizations, and physician group practices • Provide feedback to clinicians about their performance, drawing on data from EHRs and quality reporting programs, and evaluate the degree to which clinicians are identifying, documenting, and treating patients who use tobacco 	<ul style="list-style-type: none"> • Effectiveness of clinician training on asking about smoking status (“Ask”) (n = 3 studies): OR = 2.1; 95% CI, 1.9–2.4 • Effectiveness of training on setting a quit date (“Assist”) (n = 2 studies): OR = 5.5; 95% CI, 4.1–7.4 • Effectiveness of training on rates of providing treatment (“Assist”) (n = 2 studies): OR = 3.2; 95% CI, 2.0–5.2 • Effectiveness of training on providing materials (“Assist”) (n = 2 studies): OR = 4.2; 95% CI, 3.4–5.3 • Effectiveness of training on arranging for follow-up (“Arrange”) (n = 2 studies): OR = 2.7; 95% CI, 1.9–3.9 • Effectiveness of training on abstinence rates (vs. no training) (n = 2 studies): OR = 2.0; 95% CI, 1.2–3.4

Table 7.2 Continued

Strategy	Action	Strategies for implementation	Meta-analytic findings from the 2008 <i>Clinical Practice Guideline</i>
3. Dedicate staff to provide nicotine dependence treatment and assess the delivery of this treatment in the performance evaluations of staff	Clinical sites should communicate to all staff the importance of intervening with tobacco users and should designate a staff person (e.g., nurse, medical assistant, or other clinician) to coordinate nicotine dependence treatments. Nonphysician personnel may serve as effective providers of nicotine dependence interventions	<ul style="list-style-type: none"> • Designate a nicotine dependence treatment coordinator for every clinical site • Delineate the responsibilities of the nicotine dependence treatment coordinator (e.g., ensuring the systematic identification of smokers, ready access to evidence-based cessation treatments [e.g., quitlines], and scheduling follow-up visits) • Communicate to each staff member (e.g., nurse, physician, medical assistant, pharmacist, or other clinician) his or her role and responsibility in the workflow and delivery of nicotine dependence services. Discuss these staff responsibilities during training of new staff 	No PHS <i>Guideline</i> meta-analysis.
4. Promote hospital policies that support and provide inpatient nicotine dependence services	Provide nicotine dependence treatment to all tobacco users who are admitted to a hospital	<ul style="list-style-type: none"> • Implement a system to identify and document the tobacco use status of all hospital patients • Identify a clinician(s) to deliver nicotine dependence services to inpatients at every hospital and reimburse hospitals for delivering such services • Offer nicotine dependence treatment to all hospital patients who use tobacco • Expand hospital formularies to include FDA-approved nicotine dependence medications • Ensure compliance with The Joint Commission's regulations mandating that all sections of the hospital be entirely smokefree and that patients receive cessation treatments • Educate hospital staff about medications that may be used to reduce nicotine withdrawal symptoms, even if the patient is not intending to quit at that time 	<ul style="list-style-type: none"> • No PHS <i>Guideline</i> meta-analysis • Rigotti and colleagues (2012), in a Cochrane review of in-hospital tobacco dependence treatment programs, concluded that intensive counseling interventions that began during the hospital stay and continued with supportive contacts for at least 1 month after discharge increased smoking cessation rates after discharge (n = 25 studies): OR = 1.37; 95% CI, 1.27–1.48 • Rigotti and colleagues (2012) also concluded that adding nicotine replacement therapy to an intensive counseling intervention increased rates of smoking cessation compared with intensive counseling alone (n = 6 studies): OR = 1.54; 95% CI, 1.34–1.79

Table 7.2 Continued

Strategy	Action	Strategies for implementation	Meta-analytic findings from the 2008 <i>Clinical Practice Guideline</i>
5. Include nicotine dependence treatments (both counseling and medication), identified as effective in the <i>Clinical Practice Guideline</i> , as paid or covered services for all subscribers or members of health insurance packages	Provide all insurance subscribers—including those covered by managed care organizations, workplace health plans, Medicaid, Medicare, and other government insurance programs—with comprehensive coverage for effective nicotine dependence treatments, including counseling and FDA-approved medications	<ul style="list-style-type: none"> • Cover evidence-based nicotine dependence treatments (counseling and medications) as part of the basic benefits package for all health insurance packages • Remove barriers to tobacco treatment benefits (e.g., copays, prior authorization) • Educate all subscribers and clinicians about the availability of covered nicotine dependence treatments (both counseling and medications) and encourage patients to use these services 	<ul style="list-style-type: none"> • Rates of intervention for persons who received tobacco use interventions as a covered health insurance benefit (vs. persons with no tobacco cessation health insurance benefit) (n = 3 studies): OR = 2.3; 95% CI, 1.8–2.9 • Rates of quit attempts for persons who received tobacco use interventions as a covered health insurance benefit (vs. persons with no tobacco cessation health insurance benefit) (n = 3 studies): OR = 1.3; 95% CI, 1.0–1.5 • Estimated abstinence rates for persons who received tobacco use interventions as a covered health insurance benefit (vs. persons with no tobacco cessation health insurance benefit) (n = 3 studies): OR = 1.6; 95% CI, 1.2–2.2

Source: Fiore and colleagues (2008).

Notes: **CI** = confidence interval; **EHR** = electronic health record; **FDA** = U.S. Food and Drug Administration; **OR** = odds ratio; **PHS** = U.S. Public Health Service.

and *Affordable Care Act* (ACA) and the approach for documenting tobacco use in EHRs in the *Health Information Technology for Economic and Clinical Health Act* (HITECH) (Table 7.2).

As noted previously in this chapter, the *Clinical Practice Guidelines* were intended to help shape clinical practice, and thereby increase cessation—not just to serve as a repository of evidence on clinical policies. Numerous studies have addressed the impact of the *Clinical Practice Guidelines* on clinical performance and outcomes (Katz et al. 2004, 2014; Lesho et al. 2005; Smith et al. 2005; Caplan et al. 2011; Institute of Medicine, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines 2011; Moody-Thomas et al. 2011; Shelley et al. 2011; Kruger et al. 2015). These studies have generally demonstrated that the implementation of guidelines (e.g., the *Clinical Practice Guidelines* or the “5 A’s” [Ask, Advise, Assess, Assist, Arrange] clinical intervention or its abbreviated version, the “AAR” [Ask, Advise, Refer])—via training, systems-level changes, or other actions—is associated with higher rates of delivery of guideline-recommended interventions for smoking cessation (see Chapter 6). Some studies have also demonstrated an association with higher rates of cessation and/or lower smoking prevalence. For example, Caplan and colleagues (2011) noted that training

primary care physicians to deliver the 5 A’s was associated with significantly greater compliance with the interventions recommended in the *Clinical Practice Guideline*. Data following the release of the guideline also revealed (a) a significant increase in the percentage of patients at U.S. Department of Veterans Affairs (VA) healthcare facilities who were counseled about smoking cigarettes and (b) a significant decrease in the percentage of VA patients who smoked cigarettes (Ward et al. 2003; Katz et al. 2004). Thus, the practices recommended in the *Clinical Practice Guideline* can enhance the provision of treatment for smoking and cessation-related outcomes.

Recommendations from the U.S. Preventive Services Task Force

Created in 1984, USPSTF is an independent, volunteer panel of national, nonfederal experts in prevention and evidence-based medicine who review relevant scientific evidence and make evidence-based recommendations about clinical preventive services, such as screenings, counseling services, and medications (USPSTF 2017).

In 2015, USPSTF conducted an evidence review and updated its recommendations regarding the clinical treatment of tobacco use in primary care practices (USPSTF 2015). The USPSTF recommended that clinicians (a) ask

all nonpregnant adults about their tobacco use, advise them to stop using tobacco, and provide both behavioral interventions and FDA-approved pharmacotherapy for cessation to nonpregnant adults who use tobacco; and (b) ask all pregnant women about their tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco. These recommendations are in the process of being updated. A draft research plan was posted on USPSTF's website for public comment in early 2018 (USPSTF 2018).

Although the 2015 USPSTF recommendations focus primarily on clinical cessation interventions, they are included in this chapter because the USPSTF guidelines increasingly serve as the basis for making decisions about insurance coverage and assessing performance and quality measures. The USPSTF "A" rankings have federal regulatory and reimbursement implications (USPSTF 2015). For example, the 2010 ACA used USPSTF's ratings as criteria for coverage requirements, requiring all non-grandfathered, private insurance plans to cover—without cost to the patient—preventive services that received "A" or "B" ratings (*Patient Protection and Affordable Care Act of 2010*), which included provision of tobacco cessation interventions to those who use tobacco (USPSTF 2009). As a result, a growing number of private insurers have included USPSTF "A" recommended preventive services as part of their basic package of covered health benefits; however, the administration and implementation of coverage for smoking cessation still varies widely across the insurance market, including among private insurers, state Medicaid programs, and Medicaid managed care plans (Kofman et al. 2012; American Lung Association 2015).

Overall, the evidence is sufficient to infer that the development and dissemination of evidence-based clinical practice guidelines increases the delivery of clinical interventions for smoking cessation.

Improving and Promoting Coverage of Treatment for Tobacco Use and Dependence

Treatments for tobacco use and dependence can be covered through (1) health insurance, which includes coverage through private insurance (both the individual market and the employer markets), Medicaid, or Medicare, or coverage provided to active-duty military and veterans; and/or (2) employer-based wellness programs that may be offered in conjunction with health insurance. Comprehensive coverage of tobacco cessation treatments includes coverage of evidence-based cessation treatments (individual, group, and telephone counseling) and

FDA-approved cessation medications (Fiore et al. 2008). Comprehensive coverage removes or minimizes barriers, such as cost-sharing and prior authorization, that can impede access to cessation treatments (CDC 2014a, 2015; McAfee et al. 2015; Singleterry et al. 2015). As an example, effective 2011, the U.S. Office of Personnel Management (OPM) implemented model comprehensive insurance coverage of evidence-based cessation interventions for federal employees (OPM 2010a,b,n.d.). The insurance covers individual, group, and telephone counseling and all seven FDA-approved cessation medications for at least two quit attempts per year with no copays, coinsurance, or deductibles and no annual or lifetime limits (OPM 2010a,b,n.d.; CDC 2014b). Despite the model coverage approach, one potential limitation of this benefit is that some federal prescription plans require a health risk assessment as a precondition to getting medications covered at 100%; otherwise, there are copays for medications. Additionally, these assessments are primarily completed online, which could diminish utilization, particularly by persons with limited or no access to the Internet (CDC 2014a). Another barrier is that many plans require a prescription for cessation medications, even if they can be purchased over the counter, so persons can be reimbursed.

In spring 2019, OPM included language in its annual call letter and technical guidance for Federal Employees Health Benefits (FEHB) program carriers that reaffirmed and updated the comprehensive tobacco cessation coverage benefit, which was originally introduced in 2011, for federal employees (OPM 2019b). This new language highlights

- The effectiveness of combination nicotine replacement therapy (NRT),
- The fact that the combination of counseling and medication gives smokers the best chance of quitting,
- The importance of making cessation coverage barrier free and of promoting this coverage so that members and providers are aware of it and use it, and
- Opportunities to partner with pharmacists to provide education and decision support on cessation medications.

The call letter (OPM 2019b) and technical guidance (OPM 2019a) also call for FEHB plans to educate parents and healthcare providers on approaches to help prevent youth from using all tobacco products, including e-cigarettes, and on approaches to help youth who already use tobacco products to quit. Beyond its direct impact on 8.2 million federal employees, family members, retirees, and annuitants, this

updated cessation coverage from OPM has the potential to provide a model for private health insurers and employers, and it creates an opportunity to promote the updated cessation coverage to federal employees.

Health insurance coverage for evidence-based treatment of tobacco use and dependence complements the efforts of health systems and healthcare providers by making it easier for them to connect patients with treatment (Fiore et al. 2008; CDC 2014a; McAfee et al. 2015). Regardless of how well designed a coverage benefit may be, coverage alone, without promotion, is insufficient. It is critical that benefits for smoking cessation, whether offered through a health insurer or an employee wellness program, be promoted to increase awareness and use of covered treatments. The next section outlines the scientific evidence base for the coverage and promotion of benefits that address smoking cessation.

Health Insurance Coverage

The availability of comprehensive health insurance coverage for evidence-based treatment of tobacco use and dependence has been associated with higher utilization of cessation treatment and with successful cessation. In an examination of four insurance plans (N = 90,005 enrollees), Curry and colleagues (1998) showed that the highest rates of cessation were achieved for the group of smokers that had no barriers to benefits (i.e., no cost for behavioral counseling and NRT). The study concluded that full insurance coverage, compared with coverage with copays, was associated with a doubling of the overall quit rate in this population. Later, the *Clinical Practice Guideline* (Fiore et al. 2008) reported that providing tobacco cessation treatments as a covered health insurance benefit was associated with a greater likelihood that smokers would make a quit attempt (OR = 1.3; 95% CI, 1.0–1.5); a greater likelihood that persons who smoke would receive treatments for tobacco use and dependence during a healthcare visit (OR = 2.3; 95% CI, 1.8–2.9); and greater odds that they would quit successfully (OR = 1.6; 95% CI, 1.2–2.2) (Table 7.2) (Alesci et al. 2004; Holtrop et al. 2005; Murphy et al. 2005). Using nationally representative data, another study reported that Medicaid enrollees in states with more comprehensive coverage of cessation treatment had higher-than-predicted successful quit rates (8.3%) compared with those living in states with more limited coverage (ranging from 4.0% for pharmacotherapy without copayment to 5.6% for pharmacotherapy with copayment) (Greene et al. 2014). In another study using nationally representative data, Kostova and colleagues (2018) found that state Medicaid coverage of both cessation counseling and cessation medication was associated with an estimated mean increase of 3.0 percentage points ($p < .10$) in past-year quitting among covered Medicaid beneficiaries compared

with persons without coverage. In addition, Ku and colleagues (2016) found that among Medicaid enrollees, state Medicaid coverage of at least one form of NRT, bupropion, and varenicline was associated with a 24–34% increase in the use of cessation medications.

Uniform implementation of comprehensive, evidence-based cessation coverage across health insurance products with minimal barriers (e.g., no prior authorizations) may also increase clinicians' delivery of cessation interventions by making it easier for them to understand their patients' coverage and increasing their confidence that their patients will be able to access the treatments they recommend (Kofman et al. 2012; McAfee et al. 2015; van den Brand et al. 2017).

Insurance coverage of tobacco cessation can also be a cost-effective benefit. For example, in 2006, the Massachusetts Medicaid program (MassHealth) began offering and intensely promoting comprehensive coverage for tobacco cessation with minimal barriers to all Medicaid enrollees. During the first 3 years of the program, more than 75,000 MassHealth members who smoked cigarettes (nearly 40% of MassHealth smokers) had used covered cessation treatments, with far more using cessation medications than counseling (Land et al. 2010a,b; CDC n.d.). Use of the benefit substantially influenced cessation, as the rate of cigarette smoking among MassHealth members decreased from 38.3% to 28.3% over 2-1/2 years (Land et al. 2010b). In another Massachusetts-based study, Land and colleagues (2010a) found that coverage for smoking cessation was associated with substantial decreases in hospitalization rates for cardiovascular disease, with annualized declines of 46% and 49% in admissions for acute myocardial infarction and other acute coronary heart disease diagnoses, respectively, among Medicaid smokers who used the benefit. An economic analysis focusing on the costs and savings from the perspective of the Medicaid program indicated that every \$1.00 spent on medications, counseling, and promotional outreach was associated with a reduction of \$3.12 in cardiovascular-related hospitalization expenditures, resulting in net savings between \$2.00 and \$2.25 (Richard et al. 2012).

Despite this evidence, numerous insurers have offered several reasons why they believe coverage should not be required, including

- Lack of evidence for effectiveness of interventions;
- Lack of evidence that coverage increases utilization;
- Coverage could decrease participant motivation by removing personal financial commitment to the cessation treatment program, thus potentially decreasing the odds of success;

- Lack of interest from smokers and institutional purchasers;
- The perception that smoking is a societal problem, rather than a healthcare problem;
- Concern that provision of coverage could make insurance unaffordable; and
- Concern that some of the health benefits of smoking cessation take years to be fully realized (e.g., reducing the risk of lung cancer or chronic obstructive pulmonary disease), and therefore this benefit may not accrue to the insurer, since the smoker may no longer be in the health plan when the benefit is realized (Gollust et al. 2008).

Over time, many of these rationales have been systematically refuted, often through large-scale research trials (Curry et al. 1998; Joyce et al. 2008; Hamlett-Berry et al. 2009; Smith et al. 2010; Fu et al. 2014, 2016). Nonetheless, adoption of smoking cessation coverage remains limited and varies widely (Kofman et al. 2012). Coverage mandates at the state and national levels can provide an important lever to encourage the delivery and use of evidence-based treatments and clinical services for smoking cessation and to standardize a minimum level of coverage. Such mandates often have components that are designed to influence the behaviors of both the beneficiary and the clinician or health system.

Examples of current insurance coverage in the United States and considerations for coverage across the major health insurance categories are outlined below, including for private insurance, Medicaid, Medicare, and Military Health System and Veteran's Health Administration. Specific epidemiologic data on the prevalence of quit

attempts, use of cessation treatments, and recent cessation success is not covered in this chapter but can be found in Chapter 2.

Private Insurance

In 2017, 67% of insured U.S. adults were covered through the private market, 56% were insured through their employers, and 16% were insured through nongroup plans or health insurance exchanges; these figures do not total 100% because persons may have had more than one type of coverage during the calendar year (Berchick et al. 2018). The 2010 ACA included components designed to increase rates of tobacco cessation among members of private, non-grandfathered health plans via improved coverage for cessation treatments (Kofman et al. 2012; McAfee et al. 2015). Further subregulatory guidance (U.S. Department of Labor 2014; McAfee et al. 2015) clarified that insurers should provide a minimum of two courses of evidence-based treatment for tobacco cessation per year that include both cessation counseling and cessation medication with no cost sharing or prior authorization (Table 7.3).

The limited evidence available suggests that much private insurance coverage continues to fall short of this standard. Bloom and colleagues (2018) reported that some insurance plans may not recognize certain types of clinicians as providers of tobacco counseling for reimbursement purposes. In addition, some plans may explicitly exclude intensive preventive counseling or may charge high copays for longer, more intensive counseling visits. This may be because of a reliance on the 2009 USPSTF tobacco cessation recommendations, which did not clearly define intensive treatment, instead of a reliance on the more detailed 2014 subregulatory guidance from the U.S. Department of Labor (2014). However, the 2015 tobacco cessation recommendations from USPSTF clarified that

Table 7.3 Affordable Care Act guidance of coverage of tobacco cessation treatment^a

“A group health plan or health insurance issuer will be considered in compliance with the ACA's requirement to cover tobacco-use counseling and interventions if, for example, it covers the following, without cost sharing or prior authorization:

- Screening of all patients for tobacco use; and
- For enrollees who use tobacco products, at least two tobacco cessation attempts per year, with coverage of each quit attempt including:
 - Four tobacco-cessation counseling sessions, each at least 10 minutes long (including telephone, group, and individual counseling); and
 - All FDA-approved tobacco-cessation medications (including prescription and over-the-counter) for a 90-day treatment regimen when prescribed by a health care provider”

Source: McAfee and colleagues (2015, p. 6) and U.S. Department of Labor (2014).

Notes: **ACA** = Patient Protection and Affordable Care Act; **FDA** = U.S. Food and Drug Administration.

^aFDA has approved seven smoking cessation medications: five nicotine medications (patch, gum, lozenge, nasal spray, and inhaler) and two non-nicotine pills (bupropion and varenicline). Information is adapted from U.S. Department of Labor (2014); additional information is available at American Lung Association (n.d.a).

intensive visits should last at least 20 minutes, multiple sessions should be provided (at least four in-person counseling visits), and cessation rates may plateau after 90 minutes of total counseling contact time (USPSTF 2015).

Public Health England (2017) outlined an example of a model benefit that offers intensive counseling (i.e., individual and group counseling with more frequent and longer visits than outlined in the subregulatory guidance in the United States) and robust medication benefits (e.g., combination short- and long-acting NRT) for every smoker in the country. Table 7.4 includes some examples of cessation benefit models. These models have strengths and weaknesses, with MassHealth and Public Health England having the most comprehensive and intensive models. As noted in Chapter 6, it is important for insurers to adequately and fairly reimburse or “incentivize” health-care systems and clinicians at a macro level for the costs of providing cessation counseling (Nolan and Warner 2017). Increasing clinician reimbursement for cessation counseling time (including high-intensity counseling) could help to increase reach and quit rates.

Medicaid

Medicaid is a joint federal and state program that provides health coverage for some individuals and families with low-incomes, qualified pregnant women and children, senior citizens, and people with disabilities (Medicaid.gov n.d.). Given that Medicaid enrollees comprise a low-income, disadvantaged population with disproportionately high rates of cigarette smoking (CDC 2014a, 2015; Jamal et al. 2016), and that smoking-related disease is a major driver of Medicaid costs (Xu et al. 2015b), comprehensive Medicaid coverage for tobacco use and dependence treatment is especially important. In 2016, almost 20% of insured U.S. adults were covered through Medicaid (Kaiser Family Foundation n.d.b). Smokers who are enrolled in Medicaid are more likely than privately insured and uninsured smokers to have chronic diseases and to experience severe psychological distress (Zhu et al. 2017). In 2017, 24.5% of adult Medicaid enrollees were current cigarette smokers, compared with 10.5% of adults with private health insurance (Wang et al. 2018) amounting to nearly 7.2 million Medicaid recipients, who make up about 21% of all U.S. adult smokers (NHIS, 2017 data). As discussed in Chapter 6, the smoking rate among Medicaid enrollees remained unchanged from 1998 to 2013 (Zhu et al. 2017). During 2006–2010, smoking-related diseases accounted for about 15% (or more than \$39 billion) of annual Medicaid spending (Xu et al. 2015b).

National health objectives include a target for all state Medicaid programs to adopt comprehensive coverage of treatments for smoking cessation, including coverage of individual, group, and telephone cessation counseling and

all seven FDA-approved cessation medications (DiGiulio et al. 2018). Although Medicaid cessation coverage varies by state, it has been gradually improving in recent years, especially with regard to cessation medications (DiGiulio et al. 2016, 2018). Changes in Medicaid policies have contributed, in part, to improved cessation coverage. For example, the Section 4107 of the 2010 ACA requires traditional (non-expansion) state Medicaid programs to cover cessation counseling and FDA-approved cessation medications for pregnant women with no cost-sharing (effective October 2010), and Section 2502 of the 2010 ACA prohibits these programs from excluding cessation medications from coverage for all traditional adult Medicaid enrollees (effective January 2014) (McAfee et al. 2015). In addition, in 2011, the Centers for Medicare & Medicaid Services (CMS) provided guidance that tobacco quitlines qualified as an allowable Medicaid administrative activity. As a result, state Medicaid programs became eligible to receive a 50% administrative match for quitline services provided to Medicaid beneficiaries (CMS 2011). While this policy does not impact state Medicaid cessation coverage per se, it provides Medicaid enrollees with increased access to evidence-based forms of cessation counseling.

Currently, all states (including the District of Columbia) cover at least some proven cessation treatments for all Medicaid enrollees; about three-fifths of states cover individual cessation counseling, and only about one-fifth of states cover group counseling; and about three-fifths of states cover all seven FDA-approved cessation medications (DiGiulio et al. 2018). Almost all states impose coverage barriers which restrict access to covered cessation treatments, especially cessation medications; common barriers include prior authorization, limits on duration, annual limits on quit attempts, and copayments.

Medicare

Medicare is a health insurance program for people aged 65 or older, people under age 65 with certain disabilities, and people of all ages with permanent kidney failure requiring dialysis or a kidney transplant (CMS 2019). In 2016, about 15% of insured U.S. adults received coverage through Medicare (Kaiser Family Foundation n.d.b). Medicare coverage of tobacco cessation affects a smaller number of beneficiaries compared with Medicaid, but it is still important, particularly because tobacco-related diseases often first become evident or worsen among older smokers, and cessation at any age is beneficial to health (USDHHS 2010). In recent years, Medicare has taken steps to improve coverage for cessation. For example, Medicare now covers—without cost sharing—multisession, individual counseling for two quit attempts per year (eight total visits). However, Medicare does not cover group or telephone counseling (Medicare Interactive n.d.).

Table 7.4 Models of comprehensive tobacco cessation coverage and health insurance benefits

Benefit plan	Counseling visits	Counseling format	Counseling dose/time	Setting	Clinician type	Medications
Mass Medicaid (Massachusetts Department of Public Health 2014)	Up to 16 face-to-face visits per year; more visits with prior authorization ^a	At least two 45-minute intake visits; 14 individual or group visits	Individual >30 minutes; group >60 minutes	Massachusetts	Physicians or nurses, certified tobacco treatment specialists, etc.	Seven FDA-approved medications, 180 days each, combinations
U.S. Office of Personnel Management (n.d.)	At least 8 visits per year	Individual, group, and telephone	>30 minutes for individual visits	Federal employee health benefit	Not specified	Seven FDA-approved medications, ^b 180 days each, combinations
Patient Protection and Affordable Care Act, U.S. Department of Labor (2014)	At least 8 visits per year	Individual, group, and telephone	>10 minutes for each visit	Applicable to group health plans and U.S. private health insurance	Not specified	Seven FDA-approved medications, 180 days each, combinations
Grade A Recommendation (U.S. Preventive Services Task Force 2015)	Multiple sessions, dose response, more or longer sessions improve cessation rates; >4 in-person visits per year; >8 visits largest effect (quit rate)	Individual, group, and telephone	Intensive in-person counseling for >20 minutes per visit ^c ; minimal or brief visits also covered	Applicable to U.S. health insurance plans; best and most effective combinations are those that are acceptable and feasible to the patient	Specialized cessation counselors, psychologists, social workers, physicians, nurses, etc.	Seven FDA-approved medications, combinations
Public Health England (2017)	6–12 group ^d visits, 6–12 individual ^d visits, and 6–12 telephone visits	Group, individual, telephone with pharmacotherapy, brief physician or pharmacist with pharmacotherapy	Approximately 60 minutes per group, 30–45 minutes per person, and 15–30 minutes for telephone	England National Health Service primary care, and Stop Smoking Specialist clinics	Tobacco treatment specialists, ^d primary care physicians, and pharmacists	Seven medications and combination medications
Veterans and Military, U.S. Department of Defense (Huang et al. 2018)	Not specified	Individual, group, telephone, and brief primary care	Brief primary care; intensive counseling time not specified	U.S. Department of Defense; Veterans Affairs health system	Not specified	Seven FDA-approved medications, combinations

Notes: **FDA** = U.S. Food and Drug Administration.

^aIn Massachusetts, the telephone quitline is independent of face-to-face treatment, and Mass Medicaid patients can access unlimited phone counseling via the quitline.

^bFor smokers to receive quitting medications covered at 100%, some federal plans require them to complete an online health risk assessment as a precondition. Otherwise, smokers have copayments.

^cSixteen of 38 studies reported more than 300 total minutes of counseling. For studies examining combinations of behavioral and pharmacotherapy interventions, the intensity of behavioral counseling was more than 300 minutes in 60% of the studies.

^dBreath carbon monoxide testing—a validated biomedical outcome measure—occurs at each intensive individual or group visit with a tobacco treatment specialist, which assists with treatment planning and motivation. Clinicians are trained to the standards of the National Centre for Smoking Cessation and Training and receive continued supervision.

Medicare Part D covers prescription cessation medications but not over-the-counter cessation medications (Medicare Interactive n.d.); the covered prescription medications are subject to copays.

Military Health Systems and Veteran's Health Administration

Veterans and active-duty military personnel smoke cigarettes at higher rates than the general U.S. adult population (Bray et al. 2009), making coverage of smoking cessation through health plans from VA and the U.S. Department of Defense (DoD) important. Tobacco use can affect military readiness and is costly to the health-care systems of the DoD and VA. A DoD (2013) survey estimated that nearly half of all military service members (49.2%) had used a tobacco product (cigarettes, smokeless tobacco, cigars, pipes, or e-cigarettes) during the previous 12 months. Moreover, an estimated 171,000 persons who were active-duty service members in 2014 are projected to die in the coming decades because of tobacco-related disease (Roulo 2014). DoD spends more than \$1.6 billion annually on tobacco-related health expenses (Institute of Medicine 2009). Tobacco cessation coverage through DoD's Military Health System or Defense Health Agency is complicated due to varying health policies across the services. Coverage across all services generally includes cessation counseling, a dedicated telephone quitline that serves the military, online support, and access to over-the-counter and prescription cessation medications.

In 2016, VA provided healthcare for approximately 1.3 million enrollees (14.9% of its total enrollment) who currently smoked cigarettes (Huang et al. 2017). Enrollees have access to several evidence-based benefits, including screening for tobacco use, brief counseling in primary care settings and more intensive counseling through clinics that specialize in treating tobacco use, all FDA-approved cessation medications, a dedicated national quitline (1-855-QUIT-VET) that serves veterans who are enrolled in the VA Health Care system, and a mobile texting program (SmokeFreeVET) (Huang et al. 2017). Once found eligible, veterans can receive all their health services from a VA facility or a VA networked facility, which can further help to enhance the provision of and continuity in care to this population.

Removing Barriers to Access

Insurance coverage and benefits can be designed in ways that encourage persons to seek out specific types of care or specific types of clinicians to provide such care. For example, removing barriers to access (e.g., copays, coverage limits, prior authorization) encourages individuals to use covered cessation treatments (Curry et al. 1998; Fiore

et al. 2008; Land et al. 2010b; Greene et al. 2014; Friedman et al. 2016; van den Brand et al. 2017). The manner in which care is structured and reimbursed in clinical settings can also improve access to tobacco use and dependence treatment. Several incentive programs and quality measures have been put in place at the federal level to remove barriers and improve access to care. However, because many of these initiatives have been implemented in only the past 5–10 years, limited evidence exists on the effects they can have on cessation, particularly at a national level. Furthermore, evidence is unclear on the extent to which recent policy changes have been successful at removing these barriers. Table 7.5 lists each of these policy initiatives, their enactment date, and the specific provisions designed to encourage cessation through increased access to care or removal of barriers. Although specific studies on these recent policy initiatives have not been conducted, studies generally suggest that removing barriers to access increases the use of evidence-based cessation treatments and rates of quitting (Curry et al. 1998; Fiore et al. 2008; Land et al. 2010b; Greene et al. 2014; van den Brand et al. 2017).

Health insurance premium differentials, which allow insurers to charge higher premiums for tobacco users, could be another barrier to accessing cessation coverage and treatment. Tobacco use is one of only four factors that can be considered in setting health insurance premiums under the ACA (*Patient Protection and Affordable Care Act of 2010*); the other factors are individual (vs. family) coverage, rating area, and age (Curtis and Neuschler 2012; American Lung Association n.d.b). Although charging persons who use tobacco more for health insurance could motivate them to quit, such charges could also cause persons to avoid obtaining health insurance or to conceal their smoking status to avoid the additional charges, which would make it harder to identify smokers and engage them in cessation treatment (Kaplan et al. 2014). Based in part on these potential concerns, as of October 16, 2019, four states and the District of Columbia have barred insurers in both the individual and small group markets from charging smokers more for insurance premiums (Kaiser Family Foundation n.d.a). Because premium differentials based on tobacco use status are a recent phenomenon, only limited data are available on their effect on tobacco use and cessation and on ways to design differentials that can minimize their potential negative impacts and promote tobacco cessation.

Friedman and colleagues (2016) used data from the 2011–2014 Behavioral Risk Factor Surveillance System to examine the effects of surcharges for tobacco use on insurance status and smoking cessation among adults who were the most likely to purchase insurance from health insurance exchanges. The study found that, compared with smokers who faced no surcharges, smokers facing

Table 7.5 Healthcare system approaches designed to encourage smoking cessation

Organization	Date enacted	Provision
Quality Payment Program (n.d.b), part of the Medicare Access and Children's Health Insurance Program Reauthorization Act, provides incentives to providers and health systems to deliver quality, evidence-based clinical care to treat Medicare patients.	2017	Requires the screening of all patients, 18 years of age and older, for tobacco use at least once within 24 months AND the provision of a tobacco cessation intervention if the patient is identified as a tobacco user
Comprehensive Primary Care is a collaboration between CMS and private and public payers that aims to improve the delivery of primary care and achieve better care, smarter spending, and healthier people (CMS 2017c).	2012	Requires the screening of all patients, 18 years of age and older, for tobacco use at least once within 24 months AND the provision of a tobacco cessation intervention if the patient is identified as a tobacco user
Accountable Care Organizations are groups of doctors, hospitals, and other healthcare providers that come together to give coordinated, high-quality care to patients. The goal of coordinated care is to ensure that patients, especially the chronically ill, get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors (CMS 2017a).	2010	Identifies and treats all patients who use tobacco
National Quality Forum (n.d.b) is a nonprofit, nonpartisan, public service organization that reviews, endorses, and recommends the use of standardized healthcare performance measures that are frequently used to assess performance in outpatient settings.	2009	Endorses a measure that screens all patients 18 years of age and older for tobacco use at least once within 24 months AND the provision of a tobacco cessation intervention if the patient is identified as a tobacco user. This performance measure is used in numerous programs that measure the quality of performance, including Meaningful Use, Medicare Shared Savings Program, CMS's Accountable Care Organization Program, and Physician Quality Reporting System.
Patient-Centered Medical Home is a care delivery model in which primary care physicians are responsible for coordinating necessary care for their patients (CMS n.d.).	2006	Recommends the use of registries, including a tobacco registry, to drive patient care, including the tracking of patient tobacco use and quit attempts
National Committee for Quality Assurance (n.d.a,b) is a private, not-for-profit organization dedicated to improving healthcare quality and developing quality standards and performance measures for a broad range of healthcare entities.	2000	Measures performance on medical assistance with smoking and tobacco use cessation, including advising smokers and tobacco users to quit, discussing cessation medications, and discussing cessation strategies
Inpatient Prospective Payment System is the Medicare payment program for hospitals tied to performance measurement of: <ul style="list-style-type: none"> • Acute care hospitals PPS (CMS 2017b) and • Inpatient psychiatric facilities (CMS 2017d). 	1983	Uses The Joint Commission's Tobacco Inpatient Measures 1 (in 2015) and 2 and 3 (in 2016) for the prospective payment system for inpatient psychiatric facilities

Notes: CMS = Centers for Medicare & Medicaid Services.

medium or high surcharges had significantly reduced insurance coverage (reductions of 4.3 percentage points and 11.6 percentage points, respectively) and no significant change in smoking cessation. However, compared with smokers with no surcharges, smokers facing low (but non-zero) surcharges were significantly less likely to quit smoking, and smokers in groups with high surcharges were more likely to quit smoking. In addition to these data suggesting reduced insurance among smokers who are charged surcharges, premium differentials could

also cause financial hardship for tobacco users by substantially increasing the cost of health insurance coverage (see Chapter 6). To decrease the potential negative impact of this barrier on smokers, insurers could offer policyholders access to a comprehensive smoking cessation benefit program, promote the program to increase awareness and use, and waive the differential for those who are making an assisted quit attempt. As of 2017, insurers in the small-group market were required to waive the differential for tobacco users who are participating in a cessation

program, but this requirement does not apply to the individual market (CMS 2013).

Another approach to decreasing barriers is widespread implementation of cessation programs at worksites (Cahill and Lancaster 2014), which can increase employees' access to high-quality treatment, boost employee morale, and give tools to smokers that help them successfully quit (Castellan et al. 2015). Employers and governments are two major purchasers of health insurance, so employers are also a key driver of health insurance coverage. Employers have an even greater economic incentive than insurers to help smokers quit because they stand to benefit from increased worker productivity and reduced healthcare costs; in particular, large self-insured employers have an especially strong incentive to reduce employee smoking rates because they often bear the risk for smoking-related disease costs (Bunn et al. 2006; Gollust et al. 2008; Berman et al. 2014; Xu et al. 2015b). Large employers are also well-positioned to insist that insurers include cessation coverage in standard insurance policies, rather than limiting this coverage to riders.

Promoting Coverage for Utilization of Smoking Cessation Treatments and Benefits

Coverage of proven cessation treatments by insurers and employers is a necessary but not sufficient condition for increasing smokers' use of these treatments and their cessation rates. For such coverage to have an impact, it must be systematically promoted to smokers and healthcare providers to ensure that both groups are aware of the coverage and use the covered treatments (Land et al. 2010b; CDC 2014a, 2015; McAfee et al. 2015). Promotion of coverage benefits is vital to increase use of these interventions, which in turn helps more smokers quit (McMenamin et al. 2004, 2006; Keller et al. 2011). For example, in the MassHealth example discussed previously, widespread promotion of the benefit to members and providers was viewed as central to the program's success (Land et al. 2010b). Similarly, the state Medicaid program in Wisconsin conducted a promotional campaign that targeted both Medicaid-certified providers and Medicaid enrollees. That campaign led to increases in the use of cessation medications and in the number of Medicaid members enrolling in the Wisconsin Tobacco Quit Line (Keller et al. 2011). Finally, following an increase in Minnesota's tobacco tax, ClearWay Minnesota conducted a 6-week media campaign to promote its quitline services (QUITPLAN). This campaign resulted in a 160% increase

in calls and web visits combined and an 81% increase in enrollment for QUITPLAN services (Keller et al. 2015). For greatest impact, promotions should target both tobacco users and their healthcare providers, as was done in Massachusetts and Wisconsin. Ideally, states should track utilization of the covered treatments to gauge the effectiveness of the coverage and to encourage improvements in the promotional efforts (Land et al. 2010b; CDC 2014a; McAfee et al. 2015; Singleterry et al. 2015).

Taken together, the evidence is sufficient to infer that with adequate promotion, comprehensive, barrier-free, evidence-based cessation insurance coverage increases the availability and utilization of treatment services for smoking cessation.

Quality and Performance Measures and Payment Reforms

In general, performance measures can motivate quality improvements and create accountability for decisions and behaviors (Smith et al. 2008). Tobacco-related quality measures are tools that can be used to evaluate how well healthcare providers, practices, and systems are doing on the delivery of tobacco use and dependence treatment. Quality measures also exist for health plans. The most widely used tobacco-related quality measures are endorsed by the National Quality Forum (NQF)—a nonprofit, nonpartisan, public service organization that reviews, endorses, and recommends the use of standardized measures of healthcare performance (Kizer 2000). For example, NQF Number 0028 is one of the most widely used measures for tobacco use screening and cessation (NQF n.d.a). It measures the percentage of patients 18 years of age and older who are screened for tobacco use at least once during a 2-year measurement period and, among those who are tobacco users, the percentage who have received an intervention (brief counseling [3 minutes or less] and/or pharmacotherapy). Currently, this measure is used in several performance and quality measurement programs, including Medicare and Medicaid Electronic Health Record Incentive Programs (commonly referred to as “Meaningful Use”²); the Medicare Shared Savings Program; CMS' Accountable Care Organization Program; CMS' Merit-based Incentive Payment System and Medicare Access and Children's Health Insurance Program (or CHIP) Reauthorization Act of 2015; and the Physician Quality Reporting System. Although NQF Number 0028 includes both screening for

²*Meaningful Use* is defined as the use of certified EHR technology to improve the quality, safety, and efficiency of healthcare and reduce health disparities; engage patients and families; improve the coordination of care for both population and public health; and maintain the privacy and security of patient health information.

tobacco use and receipt of a counseling intervention, it does not include or require referral to other, more intensive interventions with follow-up (e.g., quitlines, specific behavioral counseling, or coaching).

Linking Quality Measures to Payment

Quality measures can influence the frequency and consistency with which specific interventions are delivered. This effect may be strengthened when quality measurement is linked to payment. Payment-based strategies include (a) performance-based measures that provide financial incentives (or penalties) if a clinician or health system provides (or neglects to provide) the targeted clinical intervention and (b) innovative payment and delivery models that link payment to the outcomes of care rather than the quantity of care provided (i.e., value-based as opposed to volume-based healthcare payment models). The Quality Payment Program (n.d.a) provides a tangible example of this. Substantial scientific evidence shows that “pay-for-performance” programs that target clinicians, clinics, and health systems are associated with higher rates of delivery of clinical interventions for tobacco use and dependence than programs that do not offer an incentive (Kruse et al. 2013). However, the evidence is mixed as to whether such programs are associated with increases in quit rates (Roski et al. 2003; Millett et al. 2007; Twardella and Brenner 2007; An et al. 2008; Hung and Green 2012; Hamilton et al. 2013; Kruse et al. 2013; McLeod et al. 2015). For example, in a systematic review, Hamilton and colleagues (2013) identified 18 studies (including 3 randomized studies and 15 observational studies) that explored the effects of pay-for-performance programs on smoking cessation. The review found that financial incentives appeared to increase the recording of smoking status and the provision of advice to quit and referral to cessation services, but results for quit rates and long-term abstinence were mixed in the five studies that reported these outcomes.

Overall, the evidence is sufficient to infer that strategies that link smoking cessation-related quality measures to payments to clinicians, clinics, or health systems increase the rate of delivery of clinical treatments for smoking cessation.

Health Plan-Based Quality Measures

The National Committee for Quality Assurance (NCQA) works with health plans and others to improve the quality of healthcare. To be accredited by NCQA, health plans must report data for more than 40 performance standards. Health plans in every state, the District of Columbia, and Puerto Rico are NCQA accredited, and recent data indicate that those plans cover 109 million Americans, or 70.5% of all Americans enrolled in

health plans (NCQA n.d.a). The Healthcare Effectiveness Data and Information Set (HEDIS) is an NCQA program that measures health plan performance and patient satisfaction; more than 90% of America's health plans use HEDIS. With regard to performance on tobacco use and dependence treatment, HEDIS measures the provision of tobacco cessation advice offered to tobacco users and discussions about cessation medications and other tobacco use and dependence treatment strategies (NCQA n.d.c). Because so many plans collect HEDIS data and the measures are so specifically defined and collected over time, the use of HEDIS makes it possible to compare performance across health plans.

Hospital-Based Performance Measures

The Joint Commission is an independent, nonprofit organization that accredits more than 21,000 healthcare organizations and programs in the United States (The Joint Commission n.d.). Typically, payment by insurers, including CMS and other federal payers, is contingent upon successful accreditation by a certifying organization, such as The Joint Commission. One criterion in the accreditation process for hospitals is to successfully meet selected performance measures. For certification by The Joint Commission, hospitals must select and report on 6 of 14 performance domains; 1 of these domains is tobacco cessation.

In 2012, The Joint Commission released an updated set of performance measures on tobacco cessation for hospitals (Fiore et al. 2012). To meet these performance measures, hospitals must (1) identify and document tobacco use status for all hospital patients 18 years of age and older, (2) demonstrate that evidence-based cessation counseling and medication are provided or offered to identified tobacco users during hospitalization, and (3) demonstrate that evidence-based cessation counseling and medication are provided or offered to identified tobacco users at discharge. Within certain constraints, hospitals may choose which performance measures they report. As of September 2018, only about 5% of accredited acute care hospitals in the United States (170 of 3,328 reporting hospitals, including 13 VA and 11 DoD hospitals) had selected the tobacco use identification and treatment delivery measures and were reporting relevant data to The Joint Commission (personal correspondence with The Joint Commission, March 18, 2019). This is likely because these performance measures (a) are voluntary and certain other measures are required or tied to payment; (b) are increasingly being reported electronically, and the cessation measures from The Joint Commission have not been fully converted electronically; and (c) may be more difficult to implement and report on than other measure sets (Freund et al. 2008, 2009). If the Joint Commission

cessation measures are not included in a CMS rule, otherwise tied to payment, or required, the number of acute care hospitals reporting on these measures will likely continue to decline. In contrast, two of these measures (offering cessation counseling and medication during hospitalization and again at discharge) are embedded in the Inpatient Psychiatric Facility Quality Reporting Program, and inpatient psychiatric facilities are required to report on these measures (CMS 2006).

Effective October 1, 2016, as part of its fiscal year 2017 payment determination, CMS required inpatient psychiatric facilities to begin reporting on the first two tobacco cessation performance measures from The Joint Commission. CMS extended this requirement to the third Joint Commission cessation measure effective October 1, 2017, as part of its fiscal year 2018 payment determination, and then discontinued the first measure for fiscal year 2019. These requirements, which embedded The Joint Commission's measures in the Inpatient Psychiatric Facility Quality Reporting Program, are associated with an increase in the delivery of tobacco cessation treatments in psychiatric facilities. Specifically, Carrillo and colleagues (2017) documented a 10-fold increase in the number of smokers who received inpatient tobacco cessation treatment after CMS implemented the requirement.

To realize the full potential of The Joint Commission's tobacco measures, reporting on those measures must be tied to payment. Currently, for acute care general hospitals, these measures are available for selection on a voluntary basis. As described previously, hospitals have several other sets of measures to pick from, and there is no incentive for them to select the tobacco cessation measures. Nonetheless, voluntary implementation of The Joint Commission's cessation measures in acute care general hospitals has been associated with increased intervention rates. For example, between 2014 and 2015, among 365 hospitals reporting data on The Joint Commission's tobacco measures in place at that time, the rate of screening for tobacco use increased from 94.1% to 97.8%; the rate at which treatment (brief counseling or NRT) was provided or offered during hospitalization increased from 51.2% to 60.5%; and the rate at which treatment was provided or offered at discharge increased from 36.4% to 40.6% (The Joint Commission 2016). A 2017 study found that EHRs can be leveraged to facilitate integration of The Joint Commission's tobacco measures into routine inpatient care; the study reported a modest increase in orders for cessation medications (OR = 1.35; 95% CI, 1.07–1.70) and a 10-fold increase in rates of cessation counseling (OR = 10.54; 95% CI, 7.87–14.12) (Shelley et al. 2017). Although only limited data are available to assess the impact that The Joint Commission's tobacco measures have had on increasing quit attempts and successful

cessation, brief interventions that include screening for tobacco use and provision of brief counseling and/or medication have been shown to double the likelihood of successful quitting (Fiore et al. 2008).

Chapter 6 discusses the benefits of intensive bedside treatment (Rigotti et al. 2014; Mullen et al. 2015; Nahhas et al. 2017; Cartmell et al. 2018). Requiring hospitals to provide bedside counseling to patients who use tobacco and to provide these patients with cessation prescriptions and follow-up appointments for cessation counseling at discharge could facilitate the adoption of tobacco treatment across the continuum of acute care, rehabilitation treatment, and outpatient treatment (Fiore et al. 2012). This approach would make the treatment of tobacco dependence consistent with the treatment of other chronic conditions and could also generate increased patient referrals to face-to-face outpatient programs in hospitals and to state quitlines.

Realigning Payment Incentives

Another approach that has the potential to increase the availability, delivery, and efficacy of treatment for tobacco use and dependence in healthcare settings is the implementation of policies that align clinician and facility payment with the quality of care provided. Although tobacco-specific data are not yet available, broad-based payment reforms, such as value-based purchasing and bundled payments (i.e., payment for what a defined episode of care is predicted to cost), seek to reimburse clinicians or hospitals for the outcomes of care, rather than for separate services provided (as is the case with fee-for-service approaches). Although not designed expressly for tobacco dependence treatment, new payment models could make such treatment more of a focus for clinicians and hospitals because tobacco use causes and exacerbates many common and costly diseases, may lead to hospital readmissions, and delays and complicates healing—all of which increase costs for the healthcare system (USDHHS 2014). Two other approaches of reimbursement for hospitals and physicians also have the potential to increase the delivery of evidence-based cessation interventions: (a) allowing a wider variety of clinicians to bill for brief tobacco interventions and (b) expanding scope of practice to allow pharmacists to write prescriptions for cessation medications.

Alternative quality contracts (AQC) are another policy mechanism that could enhance and improve the provision of tobacco use and dependence treatment. Such contracts, which are initiated by insurers, combine incentives to reduce healthcare spending with incentives to improve the quality of healthcare. Clinician groups share (a) the benefits of reducing costs (savings) and the financial risks of increased expenditures and (b) the opportunity to earn bonuses for improved quality of care. National data

are not yet available on AQCs, but early regional findings suggest that such strategies may increase rates of delivering tobacco cessation treatments. For example, in 2009, Blue Cross Blue Shield of Massachusetts established an AQC that was designed to pay healthcare service delivery systems a global fixed payment for all the services used by a covered population. Because they face a fixed budget for care delivered, health systems participating in AQCs have an incentive to emphasize preventive interventions, including those for tobacco use and dependence, that have been shown to reduce downstream healthcare costs. Huskamp and colleagues (2016) assessed the impact of the Massachusetts AQC on rates of the use of clinical smoking cessation services. The study found that rates of tobacco cessation treatment use were modestly higher among persons in AQC provider organizations than among those in non-AQC provider organizations: 2.02% vs. 1.87%, overall; 4.97% vs. 4.66 %, among enrollees at risk for tobacco-related complications; and 3.67% vs. 3.25%, among users of behavioral health services.

Enhancing the Technology of Electronic Health Records

EHRs are an important tool to improve the frequency, quality, and consistency of screening for tobacco use and dependence treatment, thereby increasing adherence to the *Clinical Practice Guideline* (Linder et al. 2009; Boyle et al. 2014). EHRs can also be used to connect persons who use tobacco with tobacco quitlines, text message-based support for cessation, and other clinical or community-based treatment resources by electronically referring patients to those services (i.e., through electronic referrals or eReferrals) (Greenwood et al. 2012; Kruse et al. 2012). Federal and state programs to promote the adoption and use of EHRs and health information technology have provided incentives to clinicians and healthcare systems to transition from paper records to EHRs and to use EHRs in ways that are intended to improve the quality, safety, efficiency, and coordination of healthcare while reducing health disparities (The Commonwealth Fund n.d.). For example, the HITECH Act of 2009 was designed, in part, to promote the adoption and use of health information technology, including EHRs. Early on, HITECH provided financial incentives to Medicare- and Medicaid-eligible professionals and hospitals that adopted and demonstrated “Meaningful Use” of EHRs through the Medicare and Medicaid EHR Incentive Programs (Berwick et al. 2008; Institute for Healthcare Improvement 2009), and Medicaid continues to provide those incentives. Meaningful Use criteria have included

requirements regarding the documentation of patients’ tobacco use and, for outpatient tobacco clinical quality measures, the delivery of cessation treatments for patients who use tobacco.

By 2017, 86% of office-based physicians had adopted EHRs, up from 42% in 2008 (Office of the National Coordinator for Health Information Technology 2019). In addition, 56% of eligible professionals and 97% of eligible hospitals and critical access hospitals (a designation given to eligible rural hospitals designed to improve access to healthcare in these communities) have participated in the Medicare and Medicaid EHR Incentive Programs. Through October 2018, eligible professionals and hospitals had received more than \$38 billion from the program as part of incentive payments through Medicare and Medicaid reimbursement for adopting certified EHR technology and for using EHRs to achieve specified performance and technology objectives (i.e., demonstrating meaningful use) (CMS 2018).

As part of the EHR Incentive Programs, eligible professionals and hospitals are evaluated on their rates of asking about and documenting (in their EHRs) cigarette smoking status for patients 13 years of age and older. Meeting this measure has been a requirement for receiving payments through the Medicare and Medicaid EHR Incentive Programs, which is important because the assessment of smoking status is a critical first step for engaging patients in cessation treatment (see Chapter 6). For established users of EHR technology (Stage 2 of Meaningful Use), eligible professionals and hospitals must demonstrate that they use their EHRs to document the smoking status of at least 80% of their patients, 13 years of age and older, to receive performance payments through the program. By 2016, more than 97% of hospitals and eligible professionals that were reporting to the EHR Incentive Programs had met the requirement of documenting smoking status for patients visiting their healthcare facilities (CMS 2016).

In addition to encouraging the identification of patients who use tobacco, the EHR Incentive Programs include an electronic clinical quality measure to assess whether eligible professionals and hospitals provide cessation counseling services to patients identified as smokers and whether that counseling is documented in patients’ EHRs. Although not required, this clinical quality measure encourages eligible professionals and hospitals to move beyond documenting tobacco use status to delivering evidence-based cessation counseling. In the United States, clinical quality measures and related financial incentives have been major influences on clinician performance for more than a decade (Papadakis et al. 2010; Thomas et al. 2017). Clinical quality measures help to drive accountability for eligible professionals and hospitals, and the resulting feedback helps to improve medical

care. Accordingly, the EHR Incentive Programs and other incentive-based efforts to increase and improve the use of EHRs have the potential to increase the rates at which tobacco use is identified, documented, and treated when these initiatives are structured to integrate proven clinical tobacco cessation interventions into EHRs (Boyle et al. 2014; Schindler-Ruwisch et al. 2017).

Fiore and colleagues (2019) studied eReferrals to the Wisconsin quitline in which 23 primary care clinics from two healthcare systems were randomized to one of two methods for referring to the quitline adult patients who smoke: a paper-based fax-to-quit referral process or an eReferral process. The eReferral process involved sending referrals from patients' EHRs to the quitline and receiving back into these EHRs outcome reports from the quitline. The fax referral process involved transmitting the same

information in both directions via fax. The two systems saw a combined 14,636 smokers. Compared with clinics that were randomized to the fax referral process, clinics that were randomized to the eReferral process generated quitline referral rates 3–4 times higher and also connected patients with quitlines at higher rates (i.e., having patients accept a quitline call and at least begin the process or registering for quitline services). The eReferral method generated especially high rates of referrals among Medicaid recipients. The study, which was the first randomized study on this topic, concluded that eReferrals provide an effective way to refer patients who smoke to quitline services (Fiore et al. 2019).

Overall, the evidence is suggestive, but not sufficient, to infer that EHR technology increases the rate of delivery of smoking cessation treatments.

Population-Based Strategies on Smoking Cessation

In addition to strategies that can be implemented to increase the provision of clinical interventions to help smokers quit, broader population-level tobacco control strategies can also have important effects on tobacco cessation. This section reviews (1) strategies and programs that increase access to and use of evidence-based cessation treatments at the population level (e.g., funding tobacco quitlines) and (2) strategies that affect quit attempt rates, quit success rates, and smoking prevalence at the population level, without necessarily directly influencing cessation support or treatment at the individual level (e.g., price or smokefree laws). Several interventions can fit into both of these categories (e.g., mass media campaigns, state tobacco control programs, pictorial health warnings, very-low-nicotine-content cigarettes). Policy and regulatory details related to very-low-nicotine-content cigarettes and e-cigarettes are also described in this chapter. (Chapter 6 presents details about very-low-nicotine-content cigarettes and e-cigarettes as they relate to cessation outcomes.) The population-based strategies discussed in this chapter are reviewed in the context of their effects on smoking cessation. However, many of these strategies have broader effects. A review of these broader effects is beyond the scope of this report. The 2014 Surgeon General's report includes additional information on the broader effects of many of these strategies (USDHHS 2014).

Quitlines

Although telephone quitlines are a cessation treatment, they are included in this section on macro-level

policy actions because they are designed to be accessed on a population-wide basis and are supported through broad policies, including funding at the state and federal levels. This chapter focuses on quitlines as an evidence-based, population-level strategy and on their relationships with cessation insurance coverage requirements and measures of treatment quality. Chapter 6 also addresses quitline services but focuses on their role as cessation treatments and discusses their effectiveness and reach.

Tobacco quitlines have typically been funded at the state level (Beyer et al. 2010), but they can also be used and funded by employers, health plans, and health systems. Quitlines offer a convenient solution to helping health insurers partially meet the ACA requirements for tobacco cessation coverage (Lemaire et al. 2015); they can be used by employers as an employee benefit to promote quitting, help increase employee productivity, and reduce health expenditures related to tobacco use (Hughes et al. 2011). Similarly, health systems can use quitlines as an adjunct to clinical care and to provide ongoing follow-up support to patients who are engaged in a quit attempt (Warner et al. 2012). Finally, health systems can leverage quitlines as a means to reduce hospital readmission rates and to meet tobacco use and dependence treatment quality measures.

A variety of models exist for employers, health plans, and health systems to establish and leverage quitline services, including (1) contracting directly with quitline vendors and other entities for their services; (2) providing funds to the state quitline to cover the costs incurred from directing employees, members, and patients to the state quitline; or (3) having their employees, members, or patients use state-funded quitline services without cost

sharing. The third model is less than ideal for the financial sustainability of state quitlines. Although this has been the default approach in many states, several states have sought to bring health plans and employers to the table to share costs and help sustain quitline services, especially in times of funding reductions for state quitlines. Funding for both service provision and promotion is a primary factor that can limit the reach of quitlines (North American Quitline Consortium 2016).

As briefly described in Chapter 6, quitlines are increasingly serving as “extended treatment” for busy clinicians. The first method that healthcare providers used to refer patients to quitlines is the passive approach of simply giving patients information on how to contact the quitline (e.g., a card or brochure with the quitline’s number). In practice, few patients follow through and call the quitline. This method gradually gave way to a second approach: having healthcare personnel fax contact information for patients to the quitline (the “fax-to-quit” method). Quitlines then proactively call patients to deliver treatment. By 2009, all 50 states, the District of Columbia, Puerto Rico, and Guam reported offering fax referral services, although fax referral programs and implementation varied widely across locations. Despite including a proactive step to connect patients with the quitline, fax referrals can be cumbersome and time-consuming (Cantrell and Shelley 2009). For example, staff at quitlines sometimes had trouble reading clinicians’ handwriting. In addition, clinic staff often used fax referrals inconsistently (Sheffer et al. 2012), or required an intensive program to promote and routinize the use of fax referrals (Redmond et al. 2010; Schauer et al. 2012; Warner et al. 2012).

Recent efforts have focused on using EHR technology to “eRefer” patients who smoke to the state’s quitline (Boyle et al. 2011; Vidrine et al. 2013; Sharifi et al. 2014). This involves having clinicians make a HIPAA (Health Insurance Portability and Accountability Act of 1996)-compliant eReferral to a quitline, which may be operated by a vendor contracting with the state tobacco control program, health plan, employer, wellness vendor, or other entity. The healthcare provider sends an eReferral to the quitline with key information that identifies the patient (e.g., name, telephone number, best time to call). This prompts staff at the quitline to attempt to call the patient to deliver cessation services. Finally, the quitline closes the loop by sending an eReferral back to the patient’s EHR with information about the outcome of the referral (e.g., was the patient successfully contacted, did the patient set a quit date, did the patient receive counseling or medication, did the patient make a quit attempt and successfully quit). This type of bidirectional, closed-loop approach is the most effective approach to implementing eReferrals (North American Quitline Consortium

2015), in part because hearing back from the quitline enables the provider to follow up with the patient and support any tobacco cessation attempt.

Data suggest that direct eReferrals to a quitline are more effective in connecting patients with that quitline than either traditional fax referral or passive referral, in which a tobacco user receives a business card or other materials featuring the phone number of the quitline; and both eReferral and fax referral offer benefits over passive referral because they proactively contact the patient to begin services. In a pilot study of eReferrals, Adsit and colleagues (2014) found that 14% of adult smokers who had visited an outpatient clinic were referred to the quitline via eReferral, while only 0.3% were referred using the traditional fax method. Elsewhere, Vidrine and colleagues (2013) conducted a two-arm, group-randomized study of 10 matched family practice clinics that compared eReferral to a quitline that used the passive referral approach of handing patients business cards for the quitline. Of all identified smokers in treatment, 7.8% were referred using eReferral, and 0.6% were referred through a passive referral (OR = 11.6; 95% CI, 5.5–24.3). EReferral serves as a good example of the complementary effects that can occur when healthcare systems respond to policy initiatives. The Meaningful Use program was effective in accelerating healthcare systems’ adoption of EHR systems. In turn, eReferrals leverage these EHR systems to link healthcare systems with quitline services in a more seamless, consistent, and effective way.

Overall, the evidence is sufficient to infer that tobacco quitlines are an effective population-based approach to motivate quit attempts and to increase smoking cessation. Quitlines can be connected to health systems with EHRs to further facilitate and routinize the use and utility of quitlines.

Increasing the Price of Tobacco Products

Increasing the price of cigarettes, such as through taxation, is one of the most effective strategies for reducing cigarette consumption (USDHHS 2014). Cigarette price increases reduce cigarette consumption and smoking prevalence by leading some smokers to quit and some smokers to smoke fewer cigarettes per day and also reduce the number of young persons who initiate smoking (DeCicca and McLeod 2008; Reed et al. 2008; Bader et al. 2011; Chaloupka et al. 2011; Ross et al. 2011; Vijayaraghavan et al. 2013; Ross et al. 2014; USDHHS 2014; NCI and WHO 2016; Stevens et al. 2017). A comprehensive review by Chaloupka and colleagues (2011), which was summarized in the 2014 Surgeon General’s report (USDHHS 2014), concluded that a 10% increase in cigarette price

would result in a 3–5% reduction in overall cigarette consumption. That review also concluded that increases in cigarette prices would result in decreases in the prevalence of smoking and in the average number of cigarettes smoked. In its report on the global tobacco epidemic, WHO (2017) concluded that raising taxes to increase the price of tobacco products is the most effective and cost-effective means to reduce tobacco use and encourage cessation. Moreover, reports from WHO (2017) and the U.S. Surgeon General (USDHHS 2012b, 2014) have concluded that youth and lower income populations are especially sensitive to price increases.

Research has demonstrated that price increases can also influence tobacco cessation at the national and state levels. Specifically, data indicate that price increases are associated with increases in motivation to quit, quit attempts, and rates of cessation at the population level (Chaloupka et al. 2002; Ross et al. 2011; Bush et al. 2012; Chaloupka et al. 2012; Choi and Boyle 2013; Scollo et al. 2013). For example, Stevens and colleagues (2017) found that each \$1.00 increase in the average price of cigarettes was associated with a 6% increase in the quit rate of U.S. smokers 50 years of age and older.

The U.S. Community Preventive Services Task Force recommended increasing the unit price of tobacco products based on strong evidence that such a price increase is effective at reducing tobacco use (The Community Guide 2012a). The Task Force reported that this effect is driven, in part, by an increase in the number of persons who quit. The Task Force reported that for every 10% increase in price, there is a 3.8-percentage-point increase in cessation (The Community Guide 2013). More recently, NCI and WHO (2016) noted that only a few studies have used longitudinal data to examine the specific relationship between taxes or prices and cessation. Those studies generally found that higher prices increase the likelihood of smoking cessation (Tauras and Chaloupka 1999; Tauras 2004; Hyland et al. 2006; DeCicca et al. 2008; Ross et al. 2014). In particular, longitudinal data from the United States and Canada found evidence that (a) smokers living in areas with higher cigarette prices are significantly more motivated to quit, (b) price increases for cigarettes over time appear to increase motivation to quit, and (c) higher cigarette prices increase the likelihood of actual quitting (Ross et al. 2011).

In addition to national examples, robust findings for price-related outcomes at the state level indicate that price increases have both short- and long-term effects. For example, Reed and colleagues (2008) assessed rates of smoking cessation in California after an increase in the state's cigarette excise tax and a subsequent increase in retail prices by a cigarette manufacturer. For the months immediately following cigarette price increases, data from the 1996 and 1999 California Tobacco Surveys showed a

significant increase in the proportion of smokers reporting quit attempts (a 45% year-over-year increase from 1995 to 1996 and a 140% increase after the excise tax went into effect in December 1998, $p < 0.05$), and a significant increase in abstinence rates (a 94% year-over-year increase from 1995 to 1996 and a 120% increase after the excise tax went into effect in December 1998, $p < 0.05$). In addition, Tseng and colleagues (2014) used a health informatics system to assess the impact of an increase in the federal cigarette tax on readiness to quit among low-income smokers in Louisiana. In the month following the increase, readiness to quit rose from 22% before the increase to 33%.

Increasing the price of cigarettes would also be expected to lead to smoking fewer cigarettes per day; however, the design of cigarettes has also changed over time in ways that allow smokers to more easily modify their nicotine intake (USDHHS 2010; Land et al. 2014). Jarvis and colleagues (2014) reported that today's smokers may smoke fewer cigarettes, but the nicotine yield per cigarette (based on cotinine levels) has increased 42% from 1988 to 2012. Thus, future research should address (a) how much smokers are compensating for reduced cigarette consumption by smoking more efficiently, (b) the effects of contemporary cigarettes, and (c) how these factors affect overall population health.

Although price increases have a strong impact on cessation at the population level, some recent data suggest that impacts may differ across subpopulations. For example, an analysis of data from the Tobacco Use Supplement to the Current Population Survey in the United States found that price is positively associated with (a) intention to quit among non-Hispanic White smokers ($p < .001$) and non-Hispanic African American smokers ($p < .001$) and (b) quit attempts among non-Hispanic White smokers ($p < .001$) but not among non-Hispanic African American smokers (Keeler et al. 2018). As another example, qualitative studies conducted in New York suggest that some low-income smokers may circumvent price increases by purchasing untaxed cigarettes from Native American reservations, bootlegged cigarettes, and/or single cigarettes or by taking advantage of discounts and coupons from the tobacco industry (Shelley et al. 2007; Curry et al. 2018). However, it is important to note that increasing the price of tobacco products does not automatically result in the creation of substantial black markets (National Research Council 2015). Although taxes and price differentials on tobacco products can create incentives for tax evasion, several environmental and administrative factors play an equal or greater role, including high levels of corruption, lack of commitment to addressing illicit trade, and ineffective administration of customs charges and taxes (NCI and WHO 2016). Substantial evidence from many countries shows that illicit trade can be prevented as the price

of tobacco rises, resulting in increased tax revenues and reduced tobacco use (NCI and WHO 2016).

U.S. tobacco price increases in the form of excise taxes have become an important source of state government revenues (Boonn 2017, 2018), contributing \$13–\$15 billion annually to state and federal government revenues (Orzechowski and Walker 2017), but little of that tax revenue is invested in tobacco control and cessation efforts (CDC 2012b). Because state tobacco control expenditures are correlated with decreased prevalence of tobacco use and increased use of evidence-based cessation treatments, funding of public education and treatment support related to tobacco cessation through excise taxes, along with funds from the Master Settlement Agreement (MSA) and other funds, could have a large impact on cessation (Ossip-Klein and McIntosh 2003; Farrelly et al. 2008; USDHHS 2014).

In summary, policies increasing the price of tobacco products have two important outcomes for tobacco cessation: (1) they provide incentives that can increase motivation to quit, decrease cigarette consumption, and drive smokers to make quit attempts; and (2) they provide a possible revenue stream to support evidence-based tobacco control strategies, including tobacco cessation activities. As policy makers consider increases in the price of tobacco products, they may consider ensuring that cessation services are funded and available to meet the increased demand. Large increases in price can be particularly effective in reducing smoking among vulnerable populations, including young people and individuals with lower socioeconomic status. Overall, the evidence is sufficient to infer that increasing the price of cigarettes reduces the prevalence of smoking, reduces cigarette consumption, reduces the average number of cigarettes smoked, and increases smoking cessation.

Smokefree Policies

The number of state and local laws that prohibit smoking in indoor public places and workplaces—including restaurants and bars—has increased rapidly in the past two decades (USDHHS 2014). As of June 30, 2018, 27 states and the District of Columbia had implemented comprehensive smokefree laws that prohibit smoking in all indoor areas of private sector worksites, restaurants, and bars (Centers for Disease Control and Prevention 2018a). In many states without comprehensive smokefree laws, local smokefree ordinances have protected substantial proportions of the state population (Tynan et al. 2016). As of October 1, 2019, 61% of the U.S. population is protected by a comprehensive state or local smokefree law (American Nonsmokers' Rights Foundation 2019b). Additionally, several jurisdictions have removed exemptions and included

such areas as casinos and other gaming facilities in these laws (American Nonsmokers' Rights Foundation 2019a).

Although smokefree laws are primarily intended to eliminate involuntary exposure to secondhand smoke indoors, thereby protecting nonsmokers from the health risks of exposure to secondhand smoke, a substantial body of evidence has documented an association between the implementation of smokefree laws at the local, state, and national levels and decreased smoking among populations influenced by smokefree policies (USDHHS 2014). For example, USDHHS (2006) concluded that smoking restrictions in the workplace lead to less smoking among workers, and WHO (2009) concluded that smokefree workplaces reduce cigarette consumption among continuing smokers and lead to increased successful cessation. The impact of smokefree policies on cessation can be maximized when these policies are coupled with the promotion of free cessation resources (USDHHS 2006; International Agency for Research on Cancer [IARC] 2009).

The Community Guide (2012b) presented a systematic review on the effects of smokefree policies and concluded that smokefree policies increase the number of tobacco users willing to quit (reported as a mean absolute increase of 3.8 percentage points). Hopkins and colleagues (2010) reviewed 57 studies published between 1976 and 2005 and found that smokefree policies were associated with a median decrease of 3.4 percentage points (interquartile interval: -6.3 to -1.4 percentage points) in the prevalence of cigarette use and an absolute increase of 6.4 percentage points (interquartile interval: 1.3–7.9 percentage points) in cessation. The authors concluded that “the results of this review suggest that smokefree policies reduce consumption by continuing smokers, increase smoking cessation attempts, increase the number of smokers who successfully quit, and reduce the prevalence of tobacco use among workers” (p. S285).

Fichtenberg and Glantz (2002) reviewed 26 studies that evaluated the impact of smokefree ordinances at worksites and found that such ordinances were associated with a 3.8% (95% CI, 2.8–4.7%) reduction in the prevalence of smoking and 3.1% (95% CI, 2.4–3.8%) fewer cigarettes smoked among persons who continued to smoke. Other analyses found higher rates of smoking cessation at worksites that implemented smokefree policies (Longo et al. 2001); greater self-reported interest in quitting (Hammond et al. 2004); and a greater likelihood of smoking cessation the longer the smokefree policy was in effect (comparing rates of quitting at 18 and 36 months after implementation of a smokefree ordinance) (Hahn et al. 2009).

With the increasing adoption of smokefree policies in indoor public places and workplaces, private settings are becoming the major remaining source of exposure to secondhand smoke for many individuals. Residents of multiunit

housing are particularly likely to be exposed to secondhand smoke in their homes. An estimated 80 million people in the United States, or 25% of the U.S. population, reside in multiunit housing (King et al. 2013a). A subset of those individuals resides in government-subsidized housing, including public housing. Recent data indicate increases in the implementation of smokefree policies for subsidized, multiunit housing sites (Pizacani et al. 2012). Notably, the U.S. Department of Housing and Urban Development (2016) finalized a rule requiring public housing authorities to prohibit smoking in their buildings, including inside residents' units. The policy was coupled with promotion of tobacco cessation and cessation resources. This policy could help motivate many smokers to quit and may also encourage more private multiunit housing facilities to adopt similar policies (Levy et al. 2017a).

Promoting cessation resources in conjunction with the implementation of smokefree multiunit housing policies can help to facilitate the successful implementation of such policies and maximizes their impact on cessation. Increasing the adoption of smokefree policies in public and private multiunit housing and the availability of free cessation services to residents of multiunit housing is also important from a health equity standpoint because many residents of multiunit housing are from disadvantaged populations, including low-income persons, persons with behavioral health conditions, persons of minority racial/ethnic groups, persons with disabilities, elderly persons, and children. These populations are more likely to smoke cigarettes and/or to be exposed to secondhand smoke due to a variety of factors, and they often have less access to healthcare, including smoking cessation treatments (USDHHS 2006; CDC 2014a; Jamal et al. 2018).

In addition to federal progress making government subsidized housing smokefree, as of October 1, 2019, more than 56 cities and counties have local laws requiring smokefree policies in all multiunit housing, including both government or subsidized and private-market rate housing (American Nonsmokers' Rights Foundation 2019c). Data have shown that the adoption and maintenance of household smokefree rules in private single-family homes and smokefree policies in subsidized and public multiunit housing are associated with decreased consumption of cigarettes, increased confidence in achieving cessation, increased potentially considerable cost savings, and greater prevalence of successful cessation (Messer et al. 2008; Hyland et al. 2009; Kegler et al. 2012, 2015; King et al. 2014).

Smokefree restrictions can also be established in single-family homes to protect household members and to create an environment that can promote and support cessation (USDHHS 2006; IARC 2009). Household rules are voluntarily made by the occupants of the home (USDHHS

2006). Several studies have found that having rules in place for a smokefree home helps to prevent smoking relapse and increases other cessation behaviors, including quit attempts and successful cessation (Farkas et al. 1999, 2000; Gilpin et al. 1999; Borland et al. 2006; USDHHS 2006; Hyland et al. 2009; IARC 2009). Rules for a smokefree home can also support smoking cessation by making smoking more inconvenient, delaying smoking initiation, disrupting smoking rituals, and causing smokers to reduce their daily cigarette consumption (USDHHS 2006; IARC 2009). Coaching interventions can be (a) an effective way to motivate persons to establish rules for a smokefree home (Kegler et al. 2012; Escoffery et al. 2017; Bundy et al. 2018) and (b) delivered in a brief format through 2-1-1 telephone helplines that are set up with the primary goal of providing low-income populations with support and linkages to essential health and human services (Kegler et al. 2015; Mullen et al. 2016; Williams et al. 2016; Bundy et al. 2018; Thompson et al. 2019). Although beyond the scope of this report, a smaller body of research suggests that rules for a smokefree home can also prevent youth from starting to smoke and perhaps help youth quit smoking, in part by functioning as an expression of antismoking norms (Farkas et al. 2000). IARC (2009) concluded that policies for a smokefree home reduce adult smoking, youth smoking, and children's exposure to secondhand smoke.

Healthcare facilities are another important setting in which to implement smokefree or tobacco-free policies (Sheffer et al. 2009). Behavioral health treatment facilities, including mental health and substance use treatment facilities, are important because of the disproportional impact of tobacco use on populations with behavioral health comorbidities (Marynak et al. 2018). Despite attempts in the 1990s to explore the feasibility and acceptability of implementing smokefree policies in mental health and substance use treatment settings and taking other steps to address the high rates of smoking among persons with behavioral health conditions (Patten et al. 1996), many mental health and substance use providers and treatment facilities have been reluctant to implement tobacco-free facility policies and to integrate tobacco use and dependence treatment into routine clinical care (Schroeder et al. 2017). This may be due, in part, to some misconceptions implying that persons with behavioral health conditions do not want to quit and/or are not able to quit, and that helping smokers quit might undermine recovery from mental health problems and substance use (Schroeder and Morris 2010; American Legacy Foundation 2011; Prochaska 2011; CDC 2013b; USDHHS 2014). In addition, the tobacco industry has opposed smokefree policies in psychiatric hospitals, donated cigarettes to mental health facilities, and funded research suggesting that patients with psychiatric illnesses need tobacco for self-medication

(CDC 2013b; Prochaska et al. 2017; Marynak et al. 2018). However, attitudes toward such policies are changing, and mental health and substance use treatment facilities have increasingly begun to incorporate tobacco cessation into their missions, driven by greater efforts to integrate behavioral healthcare with primary healthcare, an increasing emphasis by behavioral health providers on a holistic approach that addresses patients' overall health and well-being, and the recognition that persons with behavioral health conditions are disproportionately likely to die prematurely of a smoking-related disease (USDHHS 2014; Schroeder et al. 2017). These efforts have coincided with increased adoption of smokefree and tobacco-free policies, including campuswide policies, by state behavioral health facilities (Marynak et al. 2018).

Overall, the evidence is sufficient to infer that smokefree policies reduce the prevalence of smoking, reduce cigarette consumption, and increase smoking cessation. Coupled with the aforementioned evidence, data also indicate that smokefree policies are particularly effective when coupled with the promotion of resources for cessation. Specifically, the Community Guide (2012b) notes that to maximize cessation outcomes, the implementation of smokefree policies should include the provision and promotion, including through quitlines, of proven cessation resources, such as counseling and medication.

Mass Media Campaigns

Scientific evidence shows that mass media educational campaigns can effectively motivate tobacco users to make quit attempts and promote tobacco cessation at the population level (NCI 2008; USDHHS 2014). Some hard-hitting advertisements (ads) seek to motivate smokers to quit by depicting the health consequences of continued smoking in emotionally compelling ways through graphic pictorial images and/or personal testimonials (Durkin et al. 2012). Other ads take a gain-frame approach by emphasizing the benefits of quitting rather than the losses associated with smoking (Toll et al. 2007). The latter type of ads is generally not as effective in motivating quit attempts as the type of ads that focuses on the health consequences of smoking and evokes fear or negative emotions (Durkin et al. 2012, 2018). Very few ads and no ad campaigns have attempted to systematically provide smokers with evidence-based recommendations on how to quit smoking, as recommended in the *Clinical Practice Guideline* (i.e., set a quit date in the near future; abstain from all cigarettes; remove all smoking-related paraphernalia; consider use of counseling and medications; and avoid high-risk social situations, especially use of alcohol, during the first weeks of a quit attempt [Fiore et al. 2008]).

Examples of Campaigns

The Fairness Doctrine campaign of 1967–1970 required stations broadcasting cigarette commercials to donate air time for antismoking messages that would provide the public, for the first time on television, with advertisements that countered messages from the tobacco industry (USDHHS 2014). In 2008, following a number of media campaigns in individual states, the Legacy Foundation (now known as Truth Initiative) launched EX, the first national adult cessation campaign since the Fairness Doctrine (Vallone et al. 2011). EX ran on television and radio from March 31 to September 28, 2008, and was targeted to adult smokers 25–49 years of age (Villanti et al. 2012).

In 2012, CDC launched *Tips From Former Smokers*, the first federally funded, national tobacco education campaign. This campaign provides a particularly strong example of the impact that mass media campaigns can have on adult smoking cessation at the national level. The *Tips* campaign has been on air from 2012 to 2019 for varying durations, ranging from 12 weeks in 2012 to 29 weeks in 2017. The hard-hitting, graphic testimonial campaign profiles real people who are living with serious long-term health effects from smoking and exposure to secondhand smoke (McAfee et al. 2017). Media placements vary from year to year, and the national ad buy has included placements on national broadcast, cable television, and digital properties. The national media campaign has been supplemented with additional ad placements in local media markets that have the highest rates of smoking. The media placements are designed to reach low-income and other groups that have the highest rates of smoking.

In addition to motivating smokers to quit, the *Tips* campaign also directs smokers to services that can provide them help with quitting. All ads in the *Tips* campaign promote a free source of cessation assistance: either the national quitline portal, 1-800-QUIT-NOW, which routes callers, based on their area code, to the quitline in their state, or a website that contains information to help smokers quit.

In January 2018, FDA launched *Every Try Counts*, the agency's first smoking cessation campaign. *Every Try Counts* builds on research that shows it takes many smokers multiple attempts to achieve long-term cessation (USDHHS 2014). The campaign aims to increase motivation to quit among adult smokers, 25–54 years of age, who have tried to quit smoking in the past but were unsuccessful. Complementary to *Tips From Former Smokers*, *Every Try Counts* uses positive messaging to reframe past quit attempts as important steps toward future success and to underscore that quitting is a process. The campaign is active in media markets with a high prevalence of smoking among adults, and messages are delivered through geotargeted digital, radio, and outdoor print

advertisements. Each ad includes a call to action to drive smokers to the campaign’s website, which was developed in partnership with NCI, and features quitting tips, text message programs to help smokers “practice the quit,” and online cessation counseling.

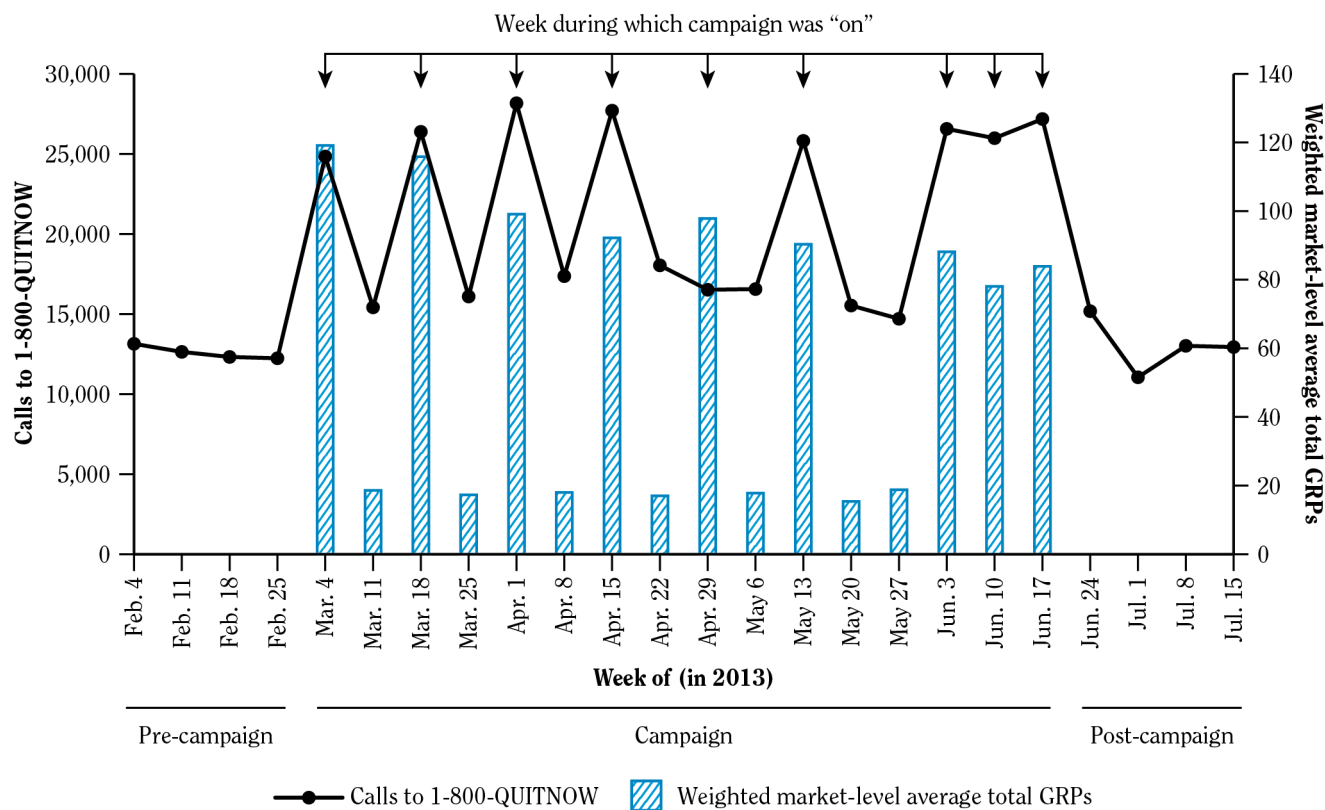
Features of Antismoking Campaigns that Support the Use of Cessation Resources

Mass media antismoking campaigns are frequently tagged with phone numbers for quitlines, an approach that serves several purposes. From a marketing and psychological perspective, inclusion of the quitline number extends a helping hand to smokers and serves to soften the message of hard-hitting campaigns that feature emotional ads with graphic images or personal testimonials about the consequences of smoking. Studies of antismoking media campaigns have found this approach to advertising to be most effective (Wakefield et al. 2008). Marketing research suggests that when ads offer cessation help,

smokers are more likely to consider and accept messages about negative smoking-related health consequences. From the quitline perspective, tagging mass media anti-smoking ads with quitline numbers is a cost-effective means of increasing calls to quitlines (CDC 2006; Sheffer et al. 2010). The effectiveness of tagging ads with a quitline number is illustrated in Figure 7.2.

In addition to quitline numbers, mass media anti-smoking ads have been tagged with website addresses that provide cessation support, including information about referral centers that can direct interested persons to a range of cessation resources, including in-person services (ClearWay Minnesota n.d.). Other means of advertising quitline services that have been shown to be effective include systematic encouragement of referrals from healthcare providers (Curry et al. 1998; Redmond et al. 2010), which may also result in an improved capacity of healthcare systems to identify and engage with smokers because the quitline assists in follow-up. In addition, promotion of services emphasizing the availability of cessation

Figure 7.2 Intensity of ad placement for *Tips From Former Smokers (Tips)* campaign and call volume to 1-800-QUIT-NOW, 2013



Source: National Cancer Institute (unpublished data); The Nielsen Company (unpublished data).

Notes: Call volume for 1-800 QUIT-NOW and 2013 *Tips* campaign gross ratings points (GRPs) are measures of the intensity of ad media placement.

medications has been shown to increase quit success and increase calls (An et al. 2006; CDC 2006; Hollis et al. 2007; USPSTF 2015).

Effectiveness of Campaigns

The Fairness Doctrine campaign was associated with significant declines in cigarette smoking rates among both adults and youth (Hamilton 1972). An evaluation of the EX campaign that focused on adult smokers who were aware of the campaign in eight media market areas at baseline and approximately 6 months later found that EX had significantly increased quit attempts (OR = 1.24; $p = .048$) (Vallone et al. 2011).

In several studies, the *Tips* campaign was found to be associated with rapid and substantial increases in calls to states' quitlines, which persisted for the duration of each *Tips* campaign cycle (CDC 2012a, 2013a; Davis et al. 2015). The *Tips* campaign has also been associated with increases in visitors to the websites featured in *Tips* ads (CDC 2012a, 2013a; Shafer et al. 2016). Although call volumes to quitlines provide a tangible early indicator of the *Tips* campaign's impact, the campaign has a much broader impact on cessation, with many smokers indicating that they intend to quit smoking, that they tried to quit, or finally succeeded in quitting without ever calling a quitline. An analysis of nationally representative cohorts of 3,051 smokers who completed baseline and follow-up assessments during the first 3 months of the 2012 *Tips* campaign, found that quit attempts among smokers increased significantly from 31.1% (95% CI, 30.3–31.9) to 34.8% (95% CI, 34.0–35.7). Moreover, 13.4% of smokers who reported making a quit attempt reported abstinence at follow-up. Although the 3.2% absolute increase in quit attempts observed may seem small, this translates into an estimated 1.6 million additional smokers making a quit attempt, and an estimated 220,000 of these smokers remained abstinent at 3-month follow-up (McAfee et al. 2013; USDHHS 2014). Analyses from the first year of the *Tips* campaign suggest that the campaign saved an estimated 179,099 quality-adjusted life-years (QALYs) and prevented 17,109 premature deaths. The campaign was also cost-effective, costing an estimated \$480 per quitter, \$2,819 per premature death averted, \$393 per life-year saved, and \$268 per QALY gained (Grosse 2008; Xu et al. 2015a). In the United States, a commonly used threshold to consider an intervention cost-effective from a societal perspective is \$50,000 per QALY gained (Xu et al. 2015a). In their evaluation of *Tips*, Neff and colleagues (2016) found that (a) exposure to the campaign was associated with increased odds of making a quit attempt in the previous 3 months (OR = 1.17; 95% CI, 1.02–1.36, $p < 0.05$) compared with baseline and (b) *Tips* was associated with an estimated 1.8 million additional quit attempts, suggesting that the effectiveness of the

campaign was not diminishing over time. Murphy-Hoefer and colleagues (2018) found that during 2012–2015, the *Tips* campaign was associated with approximately 9.15 million total additional persons who made a quit attempt and approximately 522,000 persons who quit smoking.

In 1997, Australia began a national tobacco cessation campaign with an intense and long-running mass media component that targeted adults (Hill and Carroll 2003). An analysis of quit attempts in a cohort of 3,047 Australian smokers exposed to the national tobacco cessation television ad campaign between 2002 and 2008 found that exposure to tobacco control advertising in the previous 3 months was associated with a greater likelihood of making a quit attempt, with each 1,000 increase in gross ratings points per quarter corresponding to an 11% increase in making a quit attempt (Wakefield et al. 2011).

In a detailed review of 70 studies (from January 2000 to July 2012) about mass-reach health communications campaigns for tobacco cessation, The Community Preventive Services Task Force identified 64 studies that assessed intervention campaigns in which television was the primary medium. Overall, the mass-reach campaigns were associated with decreased prevalence of tobacco use, increased cessation, and increased use of available cessation services and decreased tobacco use initiation among young persons. The campaigns were associated with an average 3.5-percentage-point absolute increase in cessation rates (2.0–5.0 in 12 studies); this translates to an approximate 14% relative increase (The Community Guide 2013).

Studies also showed that a dose-response relationship between quitting rates and greater exposure to mass media campaigns was associated with increased calls to a quitline and increased quit rates (The Community Guide 2013). Since that review, Davis and colleagues (2012) reported a 13% relative reduction in the prevalence of smoking and a 35% increase in quit attempts after a smoking cessation campaign in New York. Minnesota has also conducted extensive media campaigns to promote cessation, noting “a positive relation between weekly broadcast targeted rating points and the number of weekly calls to a cessation quitline and the number of weekly registrations to a web-based cessation program” (Schillo et al. 2011, p. 1).

Overall, the evidence is sufficient to infer that mass media campaigns increase the number of calls to quitlines and increase smoking cessation.

State Tobacco Control Programs

CDC's Office on Smoking and Health created the National Tobacco Control Program (NTCP) in 1999 to provide funding and technical support to U.S. state and territorial health departments, with the goal of encouraging

coordinated, national efforts to reduce tobacco use and tobacco-related disease and death. In particular, NTCP-funded state programs seek to achieve the four core goals of a comprehensive tobacco control program outlined in *Best Practices for Comprehensive Tobacco Control Programs* (or *Best Practices*):

- Prevent initiation among youth and young adults,
- Promote quitting among adults and youth,
- Eliminate exposure to secondhand smoke, and
- Identify and eliminate tobacco-related disparities among population groups (CDC 2014a).

To achieve the goal of promoting quitting among adults and youth, as well as the other three goals, comprehensive state tobacco control programs should include the following components: state and community interventions; mass-reach health communication interventions; cessation interventions; surveillance and evaluation; and infrastructure, administration, and management (CDC 2014a). As recommended in CDC's *Best Practices*, support for both direct provision of treatment and support for health systems and population-based tobacco control policies is what contributes to a comprehensive program (CDC 2014a), which has the greatest impact on increasing quit success.

The Community Preventive Services Task Force concluded that, based on the evidence, comprehensive tobacco control programs are effective in reducing tobacco use and exposure to secondhand smoke (The Community Guide 2014). Evidence indicates that such programs reduce the prevalence of tobacco use among adults and young people, increase the rate of quitting, and contribute to reductions in tobacco-related diseases and deaths. The Task Force concluded that comprehensive tobacco control programs are cost-effective, with savings from averted healthcare costs exceeding the costs of cessation interventions (The Community Guide 2014).

The Task Force reviewed 61 studies (through August 2014) on the impact of comprehensive tobacco control programs (The Community Guide 2014). Fifty-six of the studies evaluated the effects of such programs on cigarette use. Comprehensive tobacco control programs implemented over a median of 9 years were associated with an overall median decrease of 3.9 percentage points (-5.6 to -2.6 percentage points in 16 studies) in the prevalence of smoking among adults. More specifically, national studies showed a median decrease of 2.8 percentage points (-3.5 to -2.4 percentage points in 12 studies) in the prevalence of smoking among adults.

One of the studies reviewed by the Task Force compared California, a state with a comprehensive tobacco control program, with two states (New Jersey and New York) with similar policy climates but without comprehensive tobacco control programs from 1992 to 2002. The study found that long-term smoking cessation rates among adults were significantly higher in California compared with the other two states (Messer et al. 2007). In another study, Farrelly and colleagues (2008) examined the association between cumulative expenditures for state-specific antitobacco programs and changes in the prevalence of smoking among adults from 1985 to 2003. The authors concluded that expenditures on state tobacco control programs were associated with overall reductions in adult smoking. Rhoads (2012) used data from 1991 to 2006 in the Behavioral Risk Factor Surveillance System to examine the effects of comprehensive state tobacco control programs on cigarette smoking among adults. This study found that state programs had a significant impact on reducing the prevalence of cigarette smoking among adults, and that if all states had funded comprehensive tobacco control programs at the CDC-recommended level every year from 1991 to 2006, the prevalence of adult smoking in 2006 would have been between 18.5% and 19.8% instead of the observed prevalence of 20.07% (i.e., a 1.4–8.8% change), which translates into 635,000–3.7 million fewer cigarette smokers.

Despite the strong evidence base for many components of comprehensive tobacco control programs, the specific effects of state-funded clinical treatment programs for smoking cessation are less clear, and these effects appear to depend, in part, on sustained funding, availability, and promotion of cessation services. For example, two states have demonstrated that clinical cessation programs can yield high quit rates. New Jersey, with minimal funding, demonstrated high quit rates among moderate-to-heavy tobacco users who were treated at 15 clinics, worksites, or state-funded community cessation centers (Foulds et al. 2006; University of Medicine & Dentistry of New Jersey and School of Public Health 2007). Similarly, Minnesota developed QUITPLAN cessation treatment centers that operated for approximately 6 years (An et al. 2010). In an observational study of cohorts of participants of the service in 2004, 616 adults enrolled in the treatment centers, and 2,351 adults contacted the telephone-based helpline. Smokers at the treatment centers had a higher level of nicotine dependence than those who used a worksite, phone, or web-based treatment program. The 30-day quit rate was higher among smokers who contacted the telephone-based helpline (29.3%) than among smokers who attended the treatment centers (25.8%) (An et al. 2010). In another example, England's Stop Smoking Services have demonstrated high long-term quit rates with sustained funding for clinical treatment (>16 years) (Public Health England

2017). Existing evidence suggests that states that sustain adequate funding for comprehensive tobacco control programs can achieve higher rates of cessation.

Overall, the evidence is sufficient to infer that comprehensive state tobacco control programs can reduce the prevalence of smoking among adults, increase quit attempts, and increase smoking cessation. Because state tobacco control programs typically involve multiple strategies and components, it is difficult to attribute their effects to specific cessation strategies (such as support for clinical or onsite cessation services). The final section of this chapter describes how simulation studies can be used to evaluate the individual and synergistic effects of multiple tobacco control strategies.

Pictorial Health Warnings

Since 1965, Congress has enacted legislation requiring cigarette packages in the United States to carry small, text-based health warnings. Health warnings on cigarette packages can be an important means of conveying information to smokers about the health effects of smoking and available cessation resources. Nearly 50 countries now require large pictorial health warnings (also called graphic warning labels), often covering 50% or more of the cigarette package, that feature graphic depictions of smoking-related disease and a phone number for a tobacco cessation quitline (Hammond 2011; USDHHS 2014). However, health warnings on cigarette packages in the United States are weaker and less prominent than health warnings used on packages in many other countries (USDHHS 2000, 2014).

Evidence suggests that large, pictorial health warnings are a more effective means of reaching smokers than small, text-based messages (Hammond 2011). Furthermore, substantial evidence suggests that large pictorial health warnings that highlight the health risks of smoking are associated with increased knowledge of the harms of smoking, increased perceptions of risk associated with smoking, increased interest in quitting and motivation to quit, increased number of quit attempts, increased likelihood of remaining abstinent after a quit attempt, and reduced prevalence of smoking (Borland et al. 2009; Hammond 2011; USDHHS 2012; NCI and WHO 2016; Noar et al. 2016a,b; Reid et al. 2017). Given this evidence, the NCI-WHO Monograph 21 concluded that “Large pictorial health warning labels on tobacco packages are effective in increasing smokers’ knowledge, stimulating their interest in quitting, and reducing smoking prevalence” (NCI and WHO 2016, p. 13).

Noar and colleagues (2016b) conducted a meta-analysis of 37 experimental studies about the effects of

pictorial health warnings on tobacco packages in 16 countries. The study reported that “relative to text-only warnings, pictorial warnings (1) attracted and held attention better, (2) garnered stronger cognitive and emotional reactions, (3) elicited more negative pack attitudes and negative smoking attitudes, and (4) more effectively increased intentions to not start smoking and to quit smoking” (p. 341).

In a separate meta-analysis of longitudinal studies, Noar and colleagues (2016a) found that pictorial health warnings were associated with a 13% relative reduction in the prevalence of smoking among adults and with increased quit attempts. In another study with a nationally representative sample of Canadians, Azagba and colleagues (2013) assessed the impact of pictorial health warnings on smoking and quitting and found that the implementation of such warnings nationwide in Canada was associated with decreased prevalence of smoking (OR = 0.875; 95% CI: 0.82–0.93) and increased odds of making a quit attempt (OR = 1.33; 95% CI: 1.19–1.49). In a study of 14 countries that implemented graphic pictorial warnings, CDC (2011) found that the percentage of smokers thinking about quitting increased by at least 25% in 13 of the 14 countries.

Studies have also found that pictorial health warnings can lead to increased engagement in cessation treatment (Willemsen et al. 2002; International Tobacco Control Policy Evaluation Project 2009; Wilson et al. 2010; Noar et al. 2016a; Guydish et al. 2018). For example, in an experimental study, Guydish and colleagues (2018) found that smokers exposed to pictorial health warnings on their cigarette packages were significantly more likely to engage in a cessation group program compared with controls who did not receive pictorial warnings on their cigarette packages. Additionally, Australia, Brazil, the Netherlands, New Zealand, and the United Kingdom reported significant increases in calls to their national quitlines after the telephone numbers for the quitlines were included on pictorial health warnings (Willemsen et al. 2002; Miller et al. 2009; Hammond 2011, 2012; Noar et al. 2016a).

In summary, the evidence is sufficient to infer that pictorial health warnings increase smokers’ knowledge of health harms from smoking, motivation and intention to quit, and quit attempts, and decrease the prevalence of smoking, particularly when the labels cover at least 50% of the cigarette package and identify specific resources and contact information for cessation support, such as a phone number for a tobacco quitline.

Although pictorial health warnings have been implemented in numerous countries worldwide as part of recommendations from the WHO Framework Convention on Tobacco Control (FCTC), the United States is not a party to the FCTC. In the United States, the *Family Smoking*

Prevention and Tobacco Control Act of 2009 (or Tobacco Control Act) (2009) requires FDA to implement pictorial health warnings on cigarette packages and advertisements. On June 22, 2011, FDA published a final rule requiring color graphics depicting the negative health consequences of smoking to accompany the nine textual warning statements set out in the *Tobacco Control Act*. However, several tobacco companies challenged the final rule in court, and on August 24, 2012, the U.S. Court of Appeals for the District of Columbia Circuit vacated the rule on First Amendment grounds and remanded the matter to the agency (*R.J. Reynolds Tobacco Co., et al. v. FDA et al.* 2012).

FDA conducted further research on pictorial health warnings. A subsequent lawsuit by public health groups filed in 2016 resulted in a September 2018 decision by the U.S. District Court of Massachusetts that ordered FDA to expedite the issuance of a final rule for cigarette health warnings, after finding that FDA had unlawfully withheld and unreasonably delayed execution of the provision in the *Tobacco Control Act* that requires the implementation of such warnings (*American Academy of Pediatrics v. FDA 2018; FDA 2018a*). In March 2019, the U.S. District Court of Massachusetts ordered FDA to submit the proposed rule for publication in the *Federal Register* by August 15, 2019, and to submit the final rule for publication in the *Federal Register* by March 25, 2020 (*American Academy of Pediatrics v. FDA 2019a*).

FDA issued new cigarette health warnings through a proposed rule on August 16, 2019 (*Federal Register 2019*). When finalized, the new health warnings on cigarette packages and in advertisements would promote greater

public understanding of the negative health consequences of smoking. The 13 proposed warnings, which feature text statements and photo-realistic color images of the lesser-known health risks of cigarette smoking, stand to represent the most significant change to cigarette labels in the United States in 35 years.

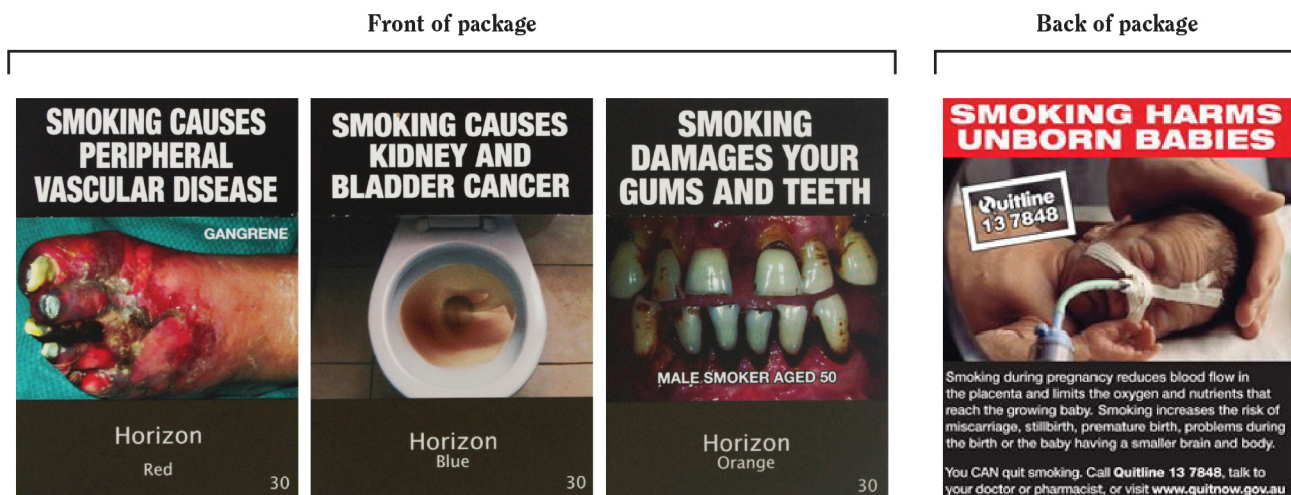
Plain Packaging

Plain packaging requirements standardize the appearance of cigarette packages by removing all brand imagery; using a standard background color and specific text size, font, and position; and including government-mandated information, such as health warnings (Figure 7.3) (USDHHS 2012b). In 2011, Australia became the first country to enact plain packaging requirements. Since then, some countries have passed similar laws standardizing the packaging of tobacco and/or cigarette products—including France, Ireland, New Zealand, Norway, Saudi Arabia, and the United Kingdom—and other countries are in the process of implementing such laws (Campaign for Tobacco-Free Kids 2019a). These laws are often combined with laws about pictorial health warnings.

Plain packaging can have several possible effects, particularly with regard to reducing the appeal of tobacco products (USDHHS 2012b; WHO 2016b). Plain packaging can:

- Make smoking less appealing because plain packages are less attractive and engaging than packages with normal branding (USDHHS 2012b; Hughes et al. 2016; WHO 2016b);

Figure 7.3 Pictorial warning on cigarette packages in Australia



Source: Tobacco Labelling Resource Centre (n.d.a,b), with permission.

- Enhance the effectiveness of health warnings by increasing their noticeability (Hammond 2010; WHO 2016b); and
- Reduce false beliefs about the absolute risks of different tobacco products (Hammond 2010; WHO 2016b).

Taken together, the scientific literature indicates that removing the color and brand imagery from cigarette packages reduces the appeal of cigarettes, enhances the effectiveness of health warnings, and may reduce the consumption of cigarettes (USDHHS 2012b; NCI and WHO 2016; WHO 2016b). Evaluation studies indicate that these reductions may, in turn, result in increased quit attempts and decreased prevalence of smoking (Durkin et al. 2015; McNeill et al. 2017).

Plain packaging can further support and enhance cessation efforts by removing misleading packaging and labeling and reducing false beliefs about the relative risks of different brands of cigarettes. The 2012 Surgeon General's report found that plain packaging has the potential to reduce false beliefs on the part of youth and adults that one cigarette brand is less harmful or easier to quit than another (USDHHS 2012b). In addition, plain packaging could counteract efforts by tobacco companies to color-code packages as a way to communicate a hierarchy of supposed relative harm within brand families (Dewhirst 2018). This activity occurs in countries, including the United States, that prohibit the use of unauthorized modified risk descriptors, such as "light," "mild," or "low tar" (*United States v. Philip Morris USA, Inc.* 2015; Dewhirst 2018). Reducing false beliefs about differences in risks between brands and within brand families could increase the number of current smokers who quit entirely instead of switching to other perceived "less risky" brands of cigarettes.

The tobacco industry has filed lawsuits alleging violations of domestic laws and international laws and treaties in response to regulatory proposals to remove brand imagery in the United States and in other countries (USDHHS 2012b; WHO 2016b). This speaks to the importance of brand imagery in sustaining purchases and, thus, tobacco use (Wakefield et al. 2002). Studies have concluded that plain packaging requirements can reduce cigarette consumption (WHO 2016b); and Australia's plain packaging requirements, which were implemented in conjunction with requirements around pictorial health warnings, have helped to reduce the national prevalence of smoking (Chipty 2016; Australian Department of Health n.d.).

The evidence is suggestive, but not sufficient, to infer that plain packaging increases smoking cessation (Moodie et al. 2011; Mannocci et al. 2013; USDHHS 2014;

WHO 2014; McNeill et al. 2017). Although the body of evidence on the efficacy of plain packaging continues to grow, further evaluation of these policies is required to better understand the specific impacts of plain packaging requirements on smoking cessation behavior.

Reduced Retail Point-of-Sale Advertising and Retail Density

Population-based policies linked to the sale and retailing of tobacco products have the potential to increase rates of smoking cessation, but the level of evidence is not yet sufficient to draw broad conclusions about their impacts on cessation behavior. These policies include decreasing point-of-sale tobacco marketing or exposure to advertising and decreasing the retail availability of tobacco products.

The 1998 MSA between 46 U.S. states and the four largest tobacco companies in the United States requires those companies to make payments to the settling states in perpetuity to offset medical costs associated with smoking. The MSA also restricts the advertising, marketing, and promotional activities of the four companies, including the use of cartoons, billboards, or merchandise branding to advertise cigarettes (National Association of Attorneys General n.d.). Although smoking rates in the United States have continued to decline since 1998 (USDHHS 2014), evidence suggests that the tobacco industry has shifted its marketing strategy to focus on the retail environment in direct response to the MSA (Ruel et al. 2004). Retail stores are now the primary means by which the tobacco industry advertises and promotes its products. In 2017, the tobacco industry spent more than \$1 million per hour marketing cigarettes and smokeless tobacco, a large majority of which was spent on discounts to help retailers reduce the price of tobacco products for consumers (Federal Trade Commission 2019a,b). In addition to offering price discounts, the tobacco industry advertises its products in the interior and on the exterior of retail stores (USDHHS 2012b; Center for Public Health Systems Science 2016).

Several policies that regulate the advertising of tobacco products in retail spaces have the potential to reduce the affordability, availability, and attractiveness of tobacco products (Center for Public Health Systems Science 2016) and to help support persons who are trying to quit using tobacco (Clattenburg et al. 2013; Mantey et al. 2017). For example, in addition to increasing smoking initiation among youth (USDHHS 2012b, 2014), the advertising of tobacco products in retail stores may undermine cessation attempts among adult smokers by increasing their cravings or prompting them to make unplanned purchases (McCarville and Bee 1999). The number and

location of tobacco retail stores (retail density) also can influence cessation. Proximity to tobacco retail outlets and higher retailer density are associated with reduced quit attempts for adults and can foster disparities in tobacco use and cessation behaviors (Chuang et al. 2005; Henriksen et al. 2008; Center for Public Health Systems Science 2014, 2016; Lipperman-Kreda et al. 2014; Young-Wolff et al. 2014).

Regarding exposure to point-of-sale tobacco marketing, in a study of 999 adult smokers in Nebraska, Siahpush and colleagues (2016) found that exposure to greater amounts of point-of-sale advertising in one's neighborhoods was associated with a lower probability of quit success among smokers who reported making a quit attempt in the previous 6 months. In a study of adult smokers in Australia, Germain and colleagues (2010) found a negative association between sensitivity to point-of-sale tobacco marketing and making a quit attempt. Some jurisdictions have also restricted the use of coupons and discounts, because evidence clearly shows that increasing price is the single most effective policy strategy to reduce tobacco use (USDHHS 2000, 2012b).

Reducing the number of retailers is another policy strategy that may reduce tobacco use, given the relationship between tobacco retailer density and tobacco use (Institute of Medicine 2007; Luke et al. 2017). Several studies have associated decreased long-term tobacco cessation with the increased availability of tobacco in retail markets, after considering retail density (i.e., the number of retailers per area or population) and retail proximity (i.e., the distance to the nearest retailer from one's home or school). For example, in a study of more than 400 adult smokers in Houston, Texas, Reitzel and colleagues (2011) found that even after adjusting for several sociodemographic variables, residential proximity to tobacco outlets provided unique information for predicting long-term continuous abstinence from smoking during a specific quit attempt. Those living less than 250 meters or less than 500 meters from a tobacco outlet were less likely to sustain a quit attempt than those living farther than 250 or 500 meters ($p = 0.01$ and $p = 0.04$, respectively). In the United Kingdom, Han and colleagues (2014) could not replicate Reitzel and colleagues' (2011) findings; however, the location and coding of retail outlets differed between the two studies. In a study of 8,751 adult smokers in Finland, Halonen and colleagues (2014) found that, among men who were moderate to heavy smokers at baseline, those living less than 0.5 kilometers (km) from the nearest tobacco store had a 27% lower likelihood of cessation at follow-up compared with those living 0.5 km or more from such a store, and that having a store within 0.5 km of one's home decreased cessation in men who were moderate or heavy smokers.

In summary, the evidence is suggestive, but not sufficient, to infer that decreasing the retail availability of tobacco products and exposure to point-of-sale tobacco marketing and advertising increases smoking cessation. Although causal conclusions cannot be drawn at this time, these findings should not prevent tobacco control practitioners from taking action to reduce the retail density of tobacco outlets and the impact of point-of-sale tobacco marketing and product offerings and to evaluate and report the results of such actions. A strong theoretical basis exists for limiting tobacco retail density, in part, because of the causal relationship between tobacco marketing and increased tobacco consumption (NCI 2008). Furthermore, evidence from alcohol control research indicates that limiting alcohol retail density can reduce excessive alcohol consumption (Campbell et al. 2009); this relationship may translate to tobacco.

Restricting the Sale of Certain Types of Tobacco Products

The 2014 Surgeon General's report concluded that imposing greater restrictions on the sale of certain types of tobacco products may also help to accelerate the decline of tobacco use (USDHHS 2014), particularly when coupled with other cessation strategies. This may include restricting the sale of certain tobacco products (e.g., menthol-flavored tobacco products, products with other flavors) or restricting the sale of all tobacco products in a setting (e.g., a pharmacy). The appeal of flavored tobacco products to youth and young adults is well-documented (USDHHS 2012b, 2016). Congress, concerned about tobacco use among youth, enacted the *Tobacco Control Act* of 2009, which banned cigarettes with characterizing flavors (e.g., cherry, chocolate, etc.) other than menthol (USDHHS 2012a). Menthol is a widely used flavor-characterizing additive in cigarettes among all age groups (Rose et al. 2019), with approximately 39% of all smokers reporting use of menthol cigarettes in 2012–2014 (Villanti et al. 2016). Use of menthol cigarettes is more prevalent among African Americans, Hispanics, smokers of lower socioeconomic status, and women (Delnevo et al. 2011; Giovino et al. 2015; Rath et al. 2016).

Menthol has been found to impede tobacco cessation (FDA n.d.; Villanti et al. 2017). In a rigorous review of the scientific evidence, FDA's Tobacco Products Scientific Advisory Committee concluded that menthol in cigarettes is associated with increased dependence and reduced success in smoking cessation, especially among African American smokers (Stahre et al. 2010; Hoffman and Miceli 2011; Levy et al. 2011a; FDA n.d.). Several reviews (Foulds et al. 2010; Villanti et al. 2017; FDA n.d.) and randomized

controlled trials (Faseru et al. 2013; Rojewski et al. 2014; Smith et al. 2014) have reached the same conclusions. Specifically, smokers of menthol cigarettes make more quit attempts than smokers of nonmenthol cigarettes but have a more difficult time quitting successfully (Trinidad et al. 2010; Delnevo et al. 2011; Levy et al. 2011a; Villanti et al. 2017). Potential explanations for the negative impact of menthol on cessation is that menthol leads to greater nicotine exposure and dependence (Benowitz et al. 2004; Giovino et al. 2004) or enhances the rewarding effects of nicotine (Wickham et al. 2015; Henderson et al. 2017).

However, not all studies have found an association between menthol use and cessation (Hyland et al. 2002; Fu et al. 2008; Steinberg et al. 2011). Differences in sampled populations, settings, study designs, and control variables may account for inconsistencies (Smith et al. 2019). Although, a meta-analysis of 19 studies of nearly 150,000 cigarette smokers did not find a significant association between menthol use and cessation (adjusted OR = 0.95; 95% CI, 0.89–1.03), it found that Black or African American menthol users were significantly less likely to quit than their nonmenthol-using counterparts (adjusted OR: 0.88, $p < .05$) (Smith et al. 2019). Many studies that have not found an association between menthol cigarette use and cessation in the general population have found an association by race/ethnicity, with African American menthol smokers having a lower likelihood of smoking cessation (Lewis et al. 2014; Smith et al. 2019; FDA n.d.). Use of menthol cigarettes has been shown to contribute to tobacco cessation-related disparities in the United States (Gardiner and Clark 2010; Garrett et al. 2016; FDA n.d.). Smith and colleagues (2019) concluded that menthol bans will have a favorable impact on smoking cessation rates among Black or African American smokers.

In 2016, WHO conducted a review of menthol in tobacco products and based on the evidence, recommended a ban on menthol in cigarettes, including menthol analogues, precursors, and derivatives (WHO 2016a). WHO also recommended prohibiting menthol in products other than cigarettes. Several countries have since adopted these WHO recommendations (WHO 2016a; 2018). In the United States in 2013, the city of Chicago was the first U.S. jurisdiction to restrict the sale of menthol tobacco products. After local retailers sued the city to block the policy, the court found that local governments have the authority to restrict the sale of menthol tobacco products (*Independents Gas & Service Stations Associations, Inc. v. City of Chicago* 2015; Tobacco Control Legal Consortium 2018). As of October 2019, more than 50 U.S. municipalities have restricted the sale of menthol tobacco products (Campaign for Tobacco-Free Kids 2019b).

In several studies, menthol smokers reported that they would quit smoking if the sale of menthol cigarettes

was prohibited (Tobacco Products Scientific Advisory Committee 2011; Pearson et al. 2012; Wackowski et al. 2014, 2018; Zatonski et al. 2018; Rose et al. 2019; FDA n.d.), but cessation and health impacts could be diminished if other types of menthol-flavored tobacco products were still available (Wackowski et al. 2015; Pacek et al. 2019; Rose et al. 2019). For example, initial evaluations of quit behaviors and restrictions on the sales of menthol tobacco products in Ontario, Canada, suggested that such restrictions may impact cessation (Chaiton et al. 2018a,b; 2019a). Another study that evaluated the long-term, population-level impact of the menthol restriction in Ontario showed that during the first year of implementation, a significantly higher percentage of persons who smoked menthol cigarettes quit smoking than those who smoked nonmenthol cigarettes and quit that same year (Chaiton et al. 2019b).

Less is known about the potential impacts that broader flavor bans could have on cessation. However, the role of flavors in promoting initiation of tobacco product use among youth is well established. Youth are more likely than adults to initiate tobacco product use with flavored tobacco products (Villanti et al. 2017, 2019), and appealing flavor is cited by youth as one of the main reasons for using e-cigarettes (USDHHS 2016; Villanti et al. 2017). Moreover, longitudinal analyses of data from the PATH Study show that first use of a flavored tobacco product is associated with an increased likelihood of subsequently using tobacco products (flavored or unflavored) compared with those who initiate tobacco use with an unflavored tobacco product (Villanti et al. 2019). Given the role of flavors in promoting tobacco product initiation among youth, more than 220 U.S. municipalities have restricted the sale of flavored tobacco products, including e-cigarettes, and several states have adopted partial restrictions on the sale of flavored tobacco products, including those that passed emergency rules in 2019 to restrict the sale of flavored e-cigarettes (Campaign for Tobacco Free Kids 2019b; Public Health Law Center 2019). Most studies to date about restrictions on the sale of flavored tobacco products have focused on the impact of restrictions on sales, product availability, and use by youth (Courtemanche et al. 2017; Farley and Johns 2017; Rogers et al. 2017, 2019; Brock et al. 2019; Czaplicki et al. 2019; Kingsley et al. 2019). More research is needed to understand the impacts that these types of policies have on cessation behaviors, and the implementation of such policies should be accompanied by a comprehensive cessation approach that seeks to make available and promote evidence-based cessation treatment.

Policies restricting the sale of certain tobacco products may extend beyond flavors and encompass restrictions on the sale of all tobacco products in certain retail settings. A limited amount of evidence exists on the impacts that these policies may have on cessation, and their impact

likely depends on the level of evidence-based cessation support made available to smokers in conjunction with enacting such policies. For example, in September 2014, CVS Health stopped selling tobacco products in its pharmacies and launched a comprehensive program to support smokers in their efforts to quit, including smoking cessation counseling offered through healthcare providers and retail pharmacists, promotion of NRT products, a dedicated quitline, and other resources (Brennan et al. 2014). Nearly 1 year after the policy change, an evaluation found that in states in which the intervention was implemented, the average smoker purchased five fewer packs of cigarettes each month compared with three control states with no CVS stores (Polinski et al. 2015). Moreover, smokers who had purchased cigarettes exclusively at CVS were 38% more likely to stop buying them (Polinski et al. 2017). Cessation and quitting outcomes were not directly assessed.

Overall, the evidence is suggestive, but not sufficient, to infer that restricting the sale of certain types of tobacco products, such as menthol and flavored products, increases smoking cessation. Rigorous evaluation of policies addressing this topic in the United States and abroad would be useful to better understand the effects that such policies have on tobacco cessation.

Very-Low-Nicotine-Content Cigarettes

Benowitz and Henningfield (1994) first proposed the idea of systematically reducing the levels of nicotine content in cigarettes as a way to prevent the development of nicotine addiction in youth. However, the authors noted that this strategy might also increase the likelihood that addicted (adult) smokers would stop smoking, because as the nicotine in cigarettes was lowered to nonaddictive levels, they would become less reinforcing and less satisfying. The authors estimated that, to avert addiction, daily intake of nicotine should be limited to 5 milligrams or less. Assuming a 30-cigarette-per-day smoker, this translates to less than 0.5 milligrams of nicotine per cigarette. Thus, very-low-nicotine-content cigarettes could achieve the dual goals of promoting cessation and preventing smoking initiation.

Since that time, several studies have tested the effects of experimental very-low-nicotine-content cigarettes on key relevant outcomes, and have suggested that such products may reduce smoking and dependence, increase abstinence, and reduce exposure to toxicants (Benowitz et al. 2007, 2012; Donny et al. 2007, 2014, 2015; Donny and Jones 2009; Hatsukami et al. 2013; Dermody et al. 2018). This approach was noted as one of several potential “end game” strategies in the 2014 Surgeon General’s

report (USDHHS 2014). Furthermore, the growing body of evidence (see Chapter 6 for a full review) has led to recent regulatory actions.

Although the *Tobacco Control Act* (2009) bars FDA from requiring nicotine yields of a tobacco product to be reduced to zero, it allows FDA to promulgate regulations regarding the construction; components; ingredients; additives; constituents, including smoke constituents; and properties of tobacco products if such regulations are appropriate for the protection of the public health. In July 2017, Dr. Scott Gottlieb, then Commissioner of FDA, announced “a new comprehensive plan for tobacco and nicotine regulation that will serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death. The approach places nicotine, and the issue of addiction, at the center of the agency’s tobacco regulation efforts” (FDA 2017). With that policy proposal, FDA had planned to “begin a public dialogue about lowering nicotine levels in combustible cigarettes to nonaddictive levels through achievable product standards” (FDA 2017). In 2018, the agency issued an Advance Notice of Proposed Rulemaking to seek input on the potential public health benefits and any possible adverse effects of lowering the level of nicotine in cigarettes (FDA 2018c). As outlined in the evidence review in Chapter 6 of this report, such regulatory action could reduce nicotine dependence and increase tobacco abstinence. No country, to date, has implemented such a policy around cigarettes.

E-Cigarettes

The scientific evidence surrounding e-cigarettes and cessation occurs within a broader environmental context with important policy and regulatory considerations. E-cigarette use has increased considerably among U.S. youth since 2011, with the U.S. Surgeon General declaring it an epidemic in 2018 (Office of the U.S. Surgeon General n.d.). By contrast, based on currently available evidence, e-cigarettes could benefit adult smokers if the products are used as a complete substitute for conventional cigarettes (see Chapter 6). However, the health effects of e-cigarettes to date remain uncertain. Furthermore, CDC, FDA, state and local health departments, and public health and clinical partners have been investigating a multistate outbreak of lung injury associated with the use of e-cigarette, or vaping, products since August 2019. The latest national and state findings suggest e-cigarette, or vaping, products containing tetrahydrocannabinol (or THC), particularly those obtained off the street or from other informal sources (e.g., friends, family members, illicit dealers), are linked to most of the cases and play a major role in the outbreak (Siegel et al. 2019). Federal, state, and local

governments have implemented, or are considering, regulations and other policy activities related to e-cigarettes in an effort to respond to this outbreak.

In the United States, e-cigarettes can be regulated as either tobacco products or, when marketed for therapeutic purposes, as medical products (*Federal Register* 2016). The *Tobacco Control Act* defines the term “tobacco product,” in part, as any product, “made or derived from tobacco,” including component, parts or accessories of a tobacco product that is not a “drug,” “device,” or “combination product” as defined by the *Food, Drug, and Cosmetic Act* (21 U.S.C. 321 (rr)) (*Family Smoking Prevention and Tobacco Control Act* 2009, §101(a)). In 2010, the U.S. Court of Appeals for the D.C. Circuit held that FDA has the authority to regulate customarily marketed tobacco products under the *Tobacco Control Act* and products made or derived from tobacco that are marketed for a therapeutic purpose under the medical product provisions of the *Food, Drug, and Cosmetic Act* (*Sottera, Inc. v. Food & Drug Administration* 2010).

The Center for Tobacco Products (CTP) issued a final rule (the “deeming rule”) in May 2016 extending the FDA’s authority to regulate tobacco products to all products meeting the definition of a “tobacco product” under the *Food, Drug, and Cosmetic Act*, except accessories of tobacco products. Therefore, all newly deemed tobacco products, including e-cigarettes must undergo premarket review and authorization by FDA (FDA 2016). In July 2017, FDA extended the compliance period for premarket applications to August 2022 for electronic nicotine delivery systems (or ENDS) and removed the “sunset policy,” whereby FDA deferred enforcement for products on the market while their application is reviewed. A lawsuit filed by American Academy of Pediatrics (AAP) and other public health groups challenged this compliance period. On July 12, 2019, the court issued the final order in the AAP case as follows: Premarket applications must be submitted within 10 months of the order (May 12, 2020) for deemed products on the market as of the Deeming Rule (August 8, 2016). Deemed products that submit an application by the deadline might remain on the market for up to 1 year

while FDA reviews the application and then would be required to come off the market (sunset provision) if the products have not yet received a marketing authorization (*American Academy of Pediatrics v. FDA* 2019b).

The statutory standards for tobacco products differ from those applied to FDA-approved NRTs, which are approved by the Center for Drug Evaluation and Research (CDER). For example, CDER requires evidence for the safety and efficacy of drugs, including cessation medications, generally coming from randomized controlled trials. By contrast, CTP employs a public health standard, which considers risks and benefits to users and nonusers of tobacco products and the population effects, for evaluating the evidence base to support commercial marketing of tobacco products. Regarding the potential for regulation of an e-cigarette product as a tobacco product, on October 11, 2019, one tobacco company announced the submission of a Premarket Tobacco Product Application (PMTA) to the FDA seeking orders authorizing the marketing of an ENDS product (Reynolds American 2019). E-cigarettes currently on the market that meet the definition of tobacco product under the federal *Food, Drug, and Cosmetic Act* are classified as tobacco products.

Under the *Tobacco Control Act*, states, localities, territories, and tribes maintain broad authority to adopt additional or more stringent requirements regarding tobacco product use, sales, marketing, and other topics. Accordingly, several states have enacted laws related to e-cigarettes in recent years, primarily to reduce youth initiation and use (Marynak et al. 2017). State, local, and territorial strategies to reduce initiation of e-cigarettes among youth and population-level exposure to e-cigarette aerosol, including educational initiatives, coupled with federal regulations around tobacco product manufacturing, labeling, and marketing, could help to reduce the risks of e-cigarettes on population health, especially among young persons (USDHHS 2016; Office of the U.S. Surgeon General n.d.). However, the extent to which population-based policies focused on e-cigarettes impact adult use of e-cigarettes or conventional cigarettes, including cessation behaviors, is unknown.

Modeling to Assess the Impact of Policy and Regulatory Changes on Cessation

As part of empirical policy evaluations, statistical analyses can generally identify the effects of a single strategy or group of strategies over a time period soon after the strategies are implemented. Simulation modeling, an alternative approach, generally synthesizes information

from empirical strategy evaluations and other sources to predict the long-term effects of a policy or a combination of strategies. In the context of tobacco use and cessation, simulation modeling estimates the individual and combined effects of strategies on such outcomes as

quit attempts, smoking prevalence, smoking-attributable deaths, and other health variables.

Most policy-oriented simulation models used for the United States have focused on the effects of implementing stronger tobacco control strategies, either individually or in combination, on the prevalence of future smoking and cessation (NCI 2007; USDHHS 2014). This section focuses on simulation models that examine the effects of strategies that are relevant to tobacco cessation in the United States. The Appendix to Chapter 15 of the 2014 Surgeon General's report (USDHHS 2014) offers an in-depth summary of tobacco control simulation models.

The most widely modeled policies are tax- and price-related strategies (USDHHS 2014). The SimSmoke model is a commonly used model. It utilizes a discrete Markov model that projects smoking prevalence and smoking-attributable deaths in the absence of policy change, and then estimates the effect of tobacco control policies on those outcomes; the policy effects are based on published reviews of the literature and the advice of an expert panel. The model has been described extensively in the scientific literature, as well as in previous U.S. Surgeon General's reports, and has been shown to predict well at the national and state levels (Levy et al. 2000; USDHHS 2014). The SimSmoke model (Levy et al. 2000) predicts that a \$1.00 tax increase applied to an initial price of \$2.00 would yield a 13% reduction in the prevalence of cigarette smoking among adults after 5 years (short-term) and a 30% reduction after 40 years. Other models have projected similar reductions in smoking prevalence associated with comparable tax increases (Emery et al. 2001; Kaplan et al. 2001; Ahmad 2005; Ahmad and Franz 2008), and one study of Latino smokers in California predicted a larger effect (Emery et al. 2001). A review of tax simulations found a linear relationship between the dollar amount of the tax and the relative reduction in the prevalence of smoking through both a reduction in initiation and an increase in cessation (Feirman et al. 2017). The decrease in smoking prevalence attributable to a tax on cigarettes ranged from 8% (from a \$0.71 tax) to 46% (from a \$4.63 tax).

In analyses that focused on the use of cessation treatments rather than on taxes or price, Apelberg and colleagues (2010) estimated that there would be 40,000 fewer smoking-attributable deaths in the United States with a gradual increase in the proportion of NRT-aided quit attempts to 100% by 2025, and the BENESCO (Benefits of Smoking Cessation on Outcomes) model projected that the provision of bupropion and varenicline to a hypothetical cohort of U.S. adult smokers, who made a one-time quit attempt, would increase the cessation rate from 5% (unaided) to about 15% and 22%, respectively, and the provision would be cost-effective (Howard et al. 2008; Knight et al. 2010). Importantly, some of the assumptions in both of

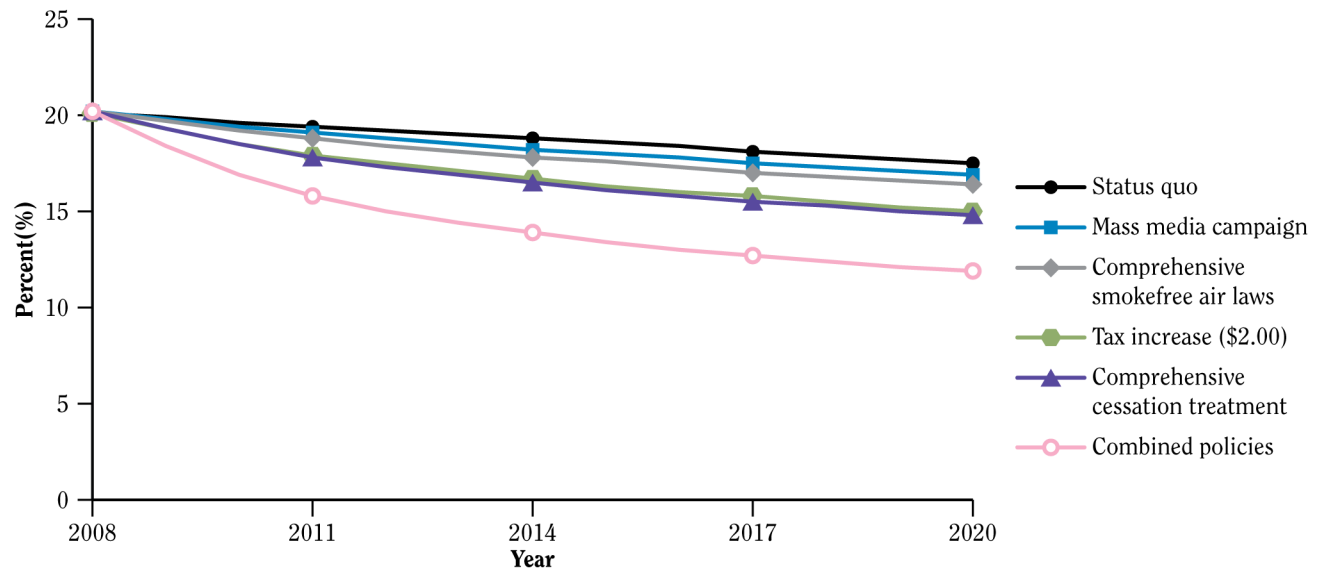
these models, especially assumptions related to the utilization of medications, were based on data from clinical trials and are unlikely to correspond to findings on the effectiveness of medications outside of a clinical trial setting.

In contrast to these studies, which focused on policies involving specific cessation treatments, the SimSmoke model considers a set of more comprehensive government cessation policies, including expansion of cessation treatment coverage and provider reimbursement; adequate funding for the use and promotion of evidence-based state quitlines; and support for health system changes to prompt, guide, and incentivize tobacco treatment (Abrams et al. 2010; Levy et al. 2010) (Figure 7.4). The SimSmoke model projected that, if these evidence-based policies for cessation were undertaken in 2008, the prevalence of cigarette smoking would be reduced from 20.1% in 2008 to 9.7% in 2020 (a 10.4-percentage-point change) (Levy et al. 2010). Finally, Ong and Glantz (2005) estimated that a free NRT program could reduce the prevalence of smoking by 20% among smokers in Minnesota.

Simulation models have also been used to consider the impact of smokefree air laws and mass media campaigns on smoking and smoking cessation behaviors. The SimSmoke model projected that implementing comprehensive smokefree laws would reduce the prevalence of cigarette smoking by 10% in the short term and 13% in the long term (Levy and Friend 2001), and Ong and Glantz (2005) estimated that 14.7% of current smokers would quit smoking if all U.S. indoor workplaces went smoke-free. The SimSmoke model has predicted that large-scale mass media campaigns can reduce the prevalence of smoking by 6% in the short term and 10% in the long term (Levy and Friend 2001). Elsewhere, Rivara and colleagues (2004) estimated that a hypothetical multimedia campaign implemented for a cohort of 18-year-olds in the year 2000 would produce a 9% decrease in the prevalence of smoking in this cohort by 2067.

In an assessment of the historical impacts of combined strategies, a SimSmoke model for the United States attributed a 53% reduction in the prevalence of cigarette smoking by adults to strategies that were implemented between 1964 and 2012 (Levy et al. 2016). In terms of relative reductions in the prevalence of smoking for states with relatively comprehensive cessation strategies, SimSmoke models predicted a 25% reduction from strategies implemented in California between 1988 and 2003 (Levy et al. 2007a), a 20% reduction from strategies implemented in Arizona between 1993 and 2002 (Levy et al. 2007b), and a 29% reduction from strategies implemented in Minnesota between 1993 and 2011 (Levy et al. 2012). All of these models were validated against actual rates of smoking by age and sex during the time periods considered and were found to have high predictability.

Figure 7.4 Effects of individual and combined policies on the prevalence of smoking among men and women 18 years of age and older, using the SimSmoke Model



Notes: Model is described in Levy and colleagues (2010). The authors examined three evidence-based treatment policies related to cessation: (1) expand cessation treatment coverage and provider reimbursement; (2) mandate adequate funding for the use and promotion of evidence-based, state-sponsored tobacco quitlines; and (3) support healthcare system changes to prompt, guide, and incentivize tobacco treatment.

The aforementioned simulation models focused on strategies that directly affect cigarette use by individual smokers, but other simulation models have examined the effects of strategies at the population level. For example, in a recent modeling study, Apelberg and colleagues (2018) assessed the impact that reducing the nicotine content in cigarettes to minimally addictive levels would have on smoking cessation. The study predicted that approximately 5 million additional smokers would quit smoking within 1 year after implementing such a strategy and that this number would increase to 13 million within 5 years. The model accounted for dual use and switching behaviors by assuming that certain other combustible and noncombustible tobacco products (e.g., premium cigars, hookah, e-cigarettes), which might serve as substitutes for conventional cigarettes, would be excluded from the hypothetical nicotine reduction strategy. An older model of the potential impact of reducing the nicotine content in cigarettes projected a 75% reduction in the prevalence of smoking among adults over the long term (Tengs et al. 2005). Another model, which estimated the impact over time of a ban on menthol cigarettes, predicted a 4–8% reduction in the prevalence of smoking among adults in the short term and a 5–10% reduction in the long term; percentage reductions were larger among African Americans (Levy et al. 2011b).

The *Tobacco Control Act* (2009) provides a regulatory framework in which companies may introduce and market tobacco products with lower exposure or risk claims, but only after such products have been reviewed and their marketing authorized by FDA. These products are classified as modified risk tobacco products (MRTPs) (i.e., products “sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products” [*Family Smoking Prevention and Tobacco Control Act of 2009*, p. 1812]). Products such as heated tobacco products, snus, and e-cigarettes may have the potential to reduce the individual- and population-level harms associated with tobacco use, and several companies have submitted applications to FDA seeking authorization to market specific products as MRTPs (Murphy et al. 2017). On October 22, 2019, FDA (2019) granted the first-ever modified risk orders to Swedish Match USA, Inc., for eight snus smokeless tobacco products sold under the “General” brand name.

Several models have assessed the projected population-level impact of potential reduced-harm products relative to cigarettes (Bachand and Sulsky 2013; Vugrin et al. 2015; Weitkunat et al. 2015), including e-cigarettes (Cobb et al. 2015; Kalkhoran and Glantz 2015; Cherng et al. 2016; Levy et al. 2017b) and smokeless

tobacco (Near et al. 2014). These models vary in structure, population focus, and modeling methods.

Three simulation models estimated the population health impact after introduction of a potentially reduced-harm product that is associated with lower health risks than cigarettes. Bachand and Sulsky (2013) estimated changes in all-cause mortality when potential or actual cigarette smokers substitute some or all of their cigarettes with a potentially reduced-harm product. The study concluded that partial or complete substitution of cigarettes with a lower risk product should provide some overall health benefit at the individual level. Vugrin and colleagues (2015) provided a range of scenarios using a multiple product model that included product switching and dual use. The authors found a potential population-level benefit if cigarette smokers switched to a lower risk product, but the benefit could be offset over time through increased initiation of the new product. Another model, developed by researchers at Philip Morris International, estimated a hypothetical reduction in smoking-attributable deaths in a 20-year period following the introduction of a reduced-harm product (Weitkunat et al. 2015). This model suggests a reduction of approximately 935,000 smoking-attributable deaths if cigarette smoking were to completely disappear. If a reduced-harm product completely replaced cigarette smoking, there would be an expected decrease of 516,944–780,433 deaths, provided a new, similarly harmful alternative was not introduced. Near and colleagues (2014) examined the effects of tobacco control strategies on the prevalence of cigarette smoking, use of smokeless tobacco (snus), and premature mortality in Sweden. The authors adapted the SimSmoke model with data from Sweden and found that significant reductions in the prevalence of smoking, use of snus, and premature mortality could be achieved through tax increases, especially when combined with other strategies. The prevalence of smoking could decrease by as much as 26% in the first few years, reaching a 37% reduction within 30 years.

Several models have estimated the impact of e-cigarettes on population health. However, results can vary greatly depending on parameter inputs, underlying assumptions, and other factors. Cobb and colleagues (2015) demonstrated a limited impact on patterns of current and former cigarette use. The model also projected that prevalence of e-cigarette use and dual use would be low (1% at Years 1 and 5 and 2% at Year 10). According to the authors, this limited transition between e-cigarette, dual, and former use suggests that this model may have been based on insufficient data or that it may have been too early to draw inferences regarding the public health impact of e-cigarettes. Kalkhoran and Glantz (2015) estimated a wide range of population health effects from the increased promotion and use of e-cigarettes. Population

health benefits are found in scenarios where (1) the use of e-cigarettes increases only among smokers who are interested in quitting, (2) there is no increased initiation of e-cigarette use among nonsmokers, and (3) e-cigarettes are used only by youth who would otherwise have smoked conventional cigarettes. However, net population harms were predicted in scenarios where (1) e-cigarette promotion leads to the renormalization of cigarette smoking and (2) e-cigarettes are used primarily by youth who never would have smoked. Cherng and colleagues (2016) concluded that e-cigarettes could have a greater effect on smoking cessation than on smoking initiation. However, the rapid increase in e-cigarette use among youth in recent years and the substantial proportion of youth and young adults who use e-cigarettes but never smoked conventional cigarettes (Mirbolouk et al. 2018) suggest that this conclusion may need to be re-evaluated. The study also suggested that if the use of e-cigarettes led to smoking initiation in never smokers, even small increases in smoking cessation due to the use of e-cigarettes could counteract any potential impact on the prevalence of smoking. The study also found that if e-cigarettes decreased smoking cessation by allowing current dual users to continue to smoke cigarettes, then the prevalence of smoking at the population level could increase considerably.

More recently, using a Mendez-Warner modeling approach, the National Academies of Sciences, Engineering, and Medicine (2018) found that the use of e-cigarettes will generate a net public health benefit, at least in the short term. The model found that the harms from increased initiation by youth will take time to manifest, occurring decades after the benefits of increased cessation are observed. However, for long-term projections, the net public health benefit was projected to be substantially less and was negative under some scenarios in the model. Importantly, irrespective of the range of assumptions used, the model projected a net public health harm in the short and long terms if the products do not increase net combustible tobacco cessation in adults. Warner and Mendez (2019) used a similar approach, concluding that potential life-years gained as a result of e-cigarette-induced smoking cessation would exceed potential life-years lost due to e-cigarette-induced smoking initiation, and that these results would hold over a wide range of assessed parameters. In contrast, Soneji and colleagues (2018), using a Monte Carlo simulation model, found that 2,070 additional current cigarette smoking adults (25–69 years of age) (95% CI, -42,900–46,200) would, because of e-cigarette use in 2014, quit smoking in 2015 and remain continually abstinent from smoking for 7 or more years. The model also estimated 168,000 additional never-cigarette smoking adolescents (12–17 years of age) and young adults (18–29 years of age) (95% CI,

114,000–229,000) would, because of e-cigarette use in 2014, initiate cigarette smoking in 2015 and become daily cigarette smokers at 35–39 years of age. Based on the existing scientific evidence related to e-cigarettes and optimistic assumptions about the relative harm of e-cigarette use compared with cigarette smoking, the authors concluded that e-cigarette use currently represents more population-level harm than benefit.

Overall, simulation models generally indicate greater effects of individual strategies as the effects fully unfold over time. The models also indicate that comprehensive, multicomponent, evidence-based tobacco control strategies have the potential to yield substantial reductions in

the prevalence of smoking. Such reductions are driven more by increases in smoking cessation than by reduced smoking initiation, but models are subject to some limitations (Levy et al. 2001). Simulation models are useful and can often be the most reliable sources for estimating long-term effects of interventions, but the projections are only as valid as their underlying assumptions and their input and transitional probability parameters, which are generally based on available data and sensitivity analysis (see Appendix 15.1 in USDHHS 2014). More research is warranted to assess the effects of strategies on specific cessation behaviors and to distinguish between their effects on quit attempts, successful quitting, and relapse.

Limitations and Methodologic Gaps

Despite considerable evidence about the effects of certain strategies (e.g., media campaigns, price increases, and smokefree policies) on the population-wide prevalence of cigarette smoking and cessation, the available evidence for some strategies is not adequate to reach conclusions about the extent to which they influence quit attempts and successful quitting. Some analyses can generate estimates of the effects of certain policies on these and other specific outcomes, but for many policies, this evidence is limited. For example, some healthcare strategies (e.g., modifying EHRs and adopting EHR-based referral systems) have been shown to improve the identification of smokers and the delivery of tobacco use and dependence treatment, but there is less evidence on the degree to which they directly influence quit attempts and successful quitting.

In theory, both healthcare- or clinically oriented tobacco use and dependence treatment strategies and population-based tobacco control strategies should influence successful cessation, and thus ultimately improve health and reduce healthcare costs. Although it is well documented that any strategy that reduces the prevalence of smoking by a meaningful amount will improve health and thus reduce cost, specific information on strategies' effects on those outcomes would be beneficial. For example, strategies may differ in their relative effects on increasing successful quitting versus reducing smoking initiation, and such differences would affect how soon effects on health outcomes and health-related costs would be expected to occur.

The effects of population-based strategies on rates of cessation reflect many factors, such as the types of effects the strategy produces (e.g., effects on initiation vs. cessation), the time lag between the strategy's implementation and its effects, and the maintenance or duration of its effects (e.g., the elasticity between the price of cigarettes

and cigarette consumption appears to change over time [NCI and WHO 2016]). Thus, although some evidence is available on the effects of certain policies on certain health outcomes (e.g., the effects of smokefree policies on the occurrence of coronary events [Meyers et al. 2009; Hahn 2010; Institute of Medicine 2010; Mackay et al. 2010; USDHHS 2014]), the scarcity of data on some potential outcomes of specific policies has made comprehensive evaluation strategies challenging.

A further limitation to better understanding the effects of policies—particularly population-level strategies—on tobacco cessation is the challenge of isolating the effects of a particular strategy from those of other past or current strategies. The attempt to identify the contribution of a specific strategy to an outcome is complicated by the fact that these strategies are rarely implemented in isolation. Specifically, the joint effects of new strategies may involve additive or interactive effects among similar or apparently dissimilar strategies at the federal, state, and local levels. A similar complexity is often encountered in analyzing strategies surrounding healthcare policies because healthcare systems often adopt a suite of tobacco-related strategies at the same time (Papadakis et al. 2010).

Progress is being made in addressing these analytic challenges, in part by taking advantage of the greater availability of relevant data and methodologic advances. For example, in the area of econometrics, the availability of improved longitudinal data for such key variables as income, cigarette consumption, cessation, tax avoidance, and tobacco price makes some analytic approaches more feasible (e.g., advanced time series analyses). Progress is aided by the greater availability of higher quality data, longitudinal data, and more comprehensive data (e.g., data that include measures of key covariates). In addition,

uniform approaches to data collection are increasingly being used across different sampling units, such as states and nations (International Tobacco Control Policy Evaluation Project 2017; WHO n.d.). The greater availability of uniform data across states and countries permits more powerful pooled analyses, which have the potential to permit statistical control of unmeasured factors that might otherwise bias results.

The greater availability of data and methodological advances could enhance the ability to accurately estimate the effects of different policies on tobacco use and cessation. Still, heightened focus on the effects of certain policies is needed because of their potential impacts on public

health. These include policies applying to the use of cigarettes and noncigarette tobacco products and strategies addressing populations that have limited access to cessation interventions (e.g., the rural poor, psychiatric populations, low-income and unemployed persons, homeless populations, and individuals who are incarcerated). More research is also needed on the effects of the mechanisms through which policies ultimately influence outcomes for smoking cessation; on the interactive effects of strategies used to implement various policies; and on how strategies that are carried out to implement certain policies affect the use of nontraditional resources for promoting cessation (e.g., cessation apps, social media).

Summary of the Evidence

Strategies at the clinical, system, and population levels can influence the behavior of smokers in ways that increase their likelihood of attempting to quit smoking and/or of successful smoking cessation.

At the clinical level, important milestones in the evolution of a health systems approach to increasing tobacco cessation include the relevant recommendations and clinical guidelines issued by The Community Preventive Services Task Force, notably its recommendations on provider reminder systems (Hopkins et al. 2001), the recommendations in the *Clinical Practice Guideline* (Fiore et al. 2008), and the guidelines issued by USPSTF (2015).

At the systems level, a growing body of research has documented the effectiveness of a health systems approach in increasing tobacco screening and cessation interventions and in increasing cessation and reducing smoking rates at the health system and/or population level. Several studies have taken this a step further, reporting reductions in primary care office visits for and healthcare-related costs from smoking-related diseases (Land et al. 2012; Moody-Thomas et al. 2015).

At the population level, several evidence-based tobacco control strategies—including tobacco quitlines; policies that raise the price of tobacco; smokefree policies; government-funded mass media and public education campaigns; pictorial health warnings; and adequately funded, sustained, comprehensive state tobacco control

programs—have been shown to reduce the prevalence of smoking among adults by increasing quit attempts and successful quitting. Although additional strategies—including those focused on retail density, point-of-sale tobacco advertising, and very-low-nicotine-content cigarettes—have been associated with reductions in the prevalence of smoking, more research could further clarify the impact of these policies on cessation behavior.

Overall, a landscape that combines both clinical and treatment-oriented strategies, as well as systems- and population-level strategy changes, is likely to create the most supportive environment for quit attempts and successful cessation. The clinical strategies and interventions described here and in Chapter 6 focus primarily on behaviors at the individual level, and such behaviors become more routine and consistent when strategies and systems are put in place that reinforce the delivery of clinical cessation interventions. The systems- and population-level strategies described in this chapter have a broad impact, can change the context and environment to make it easier for individuals to quit, and are more likely to be effective in helping people quit and stay quit when coupled with individual-level clinical interventions. Accordingly, clinicians and public health practitioners should seek to better bridge clinical work with population-based policy approaches to maximize tobacco cessation and reduce the overall prevalence of tobacco use.

Conclusions

1. The evidence is sufficient to infer that the development and dissemination of evidence-based clinical practice guidelines increase the delivery of clinical interventions for smoking cessation.
2. The evidence is sufficient to infer that with adequate promotion, comprehensive, barrier-free, evidence-based cessation insurance coverage increases the availability and utilization of treatment services for smoking cessation.
3. The evidence is sufficient to infer that strategies that link smoking cessation-related quality measures with payments to clinicians, clinics, or health systems increase the rate of delivery of clinical treatments for smoking cessation.
4. The evidence is sufficient to infer that tobacco quitlines are an effective population-based approach to motivate quit attempts and increase smoking cessation.
5. The evidence is suggestive but not sufficient to infer that electronic health record technology increases the rate of delivery of smoking cessation treatments.
6. The evidence is sufficient to infer that increasing the price of cigarettes reduces smoking prevalence, reduces cigarette consumption, and increases smoking cessation.
7. The evidence is sufficient to infer that smokefree policies reduce smoking prevalence, reduce cigarette consumption, and increase smoking cessation.
8. The evidence is sufficient to infer that mass media campaigns increase the number of calls to quitlines and increase smoking cessation.
9. The evidence is sufficient to infer that comprehensive state tobacco control programs reduce smoking prevalence, increase quit attempts, and increase smoking cessation.
10. The evidence is sufficient to infer that large, pictorial health warnings increase smokers' knowledge about the health harms of smoking, interest in quitting, and quit attempts and decrease smoking prevalence.
11. The evidence is suggestive but not sufficient to infer that plain packaging increases smoking cessation.
12. The evidence is suggestive but not sufficient to infer that decreasing the retail availability of tobacco products and exposure to point-of-sale tobacco marketing and advertising increases smoking cessation.
13. The evidence is suggestive but not sufficient to infer that restricting the sale of certain types of tobacco products, such as menthol and other flavored products, increases smoking cessation, especially among certain populations.

References³

- Abrams DB, Graham AL, Levy DT, Mabry PL, Orleans CT. Boosting population quits through evidence-based cessation treatment and policy. *American Journal of Preventive Medicine* 2010;38(3 Suppl):S351–S363.
- Adsit RT, Fox BM, Tsiolis T, Ogland C, Simerson M, Vind LM, Bell SM, Skora AD, Baker TB, Fiore MC. Using the electronic health record to connect primary care patients to evidence-based telephonic tobacco quitline services: a closed-loop demonstration project. *Translational Behavioral Medicine* 2014;4(3):324–32.
- Ahmad S. Increasing excise taxes on cigarettes in California: a dynamic simulation of health and economic impacts. *Preventive Medicine* 2005;41(1):276–83.
- Ahmad S, Franz GA. Raising taxes to reduce smoking prevalence in the U.S.: a simulation of the anticipated health and economic impacts. *Public Health* 2008;122(1):3–10.
- Alesci NL, Boyle RG, Davidson G, Solberg LI, Magnan S. Does a health plan effort to increase smokers' awareness of cessation medication coverage increase utilization and cessation? *American Journal of Health Promotion* 2004;18(5):366–9.
- American Academy of Family Physicians. Tobacco: preventing and treating nicotine dependence and tobacco use (position paper), 2014; <<https://www.aafp.org/about/policies/all/nicotine-tobacco-prevention.html>>; accessed: April 4, 2019.
- American Academy of Pediatrics v. FDA*, 330 F. Supp. 3d 657 (D. Mass 2018).
- American Academy of Pediatrics v. FDA*, No. 16-cv-11985, 2019 U.S. Dist. LEXIS 34946 (D. Mass. Mar. 5, 2019a).
- American Academy of Pediatrics v. FDA*, No. 18-cv-00883-PWG, U.S. Dist. (South D. Md. Jul. 12, 2019b).
- American Legacy Foundation. *A Hidden Epidemic: Tobacco Use and Mental Illness*. Washington (DC): American Legacy Foundation, 2011.
- American Lung Association. *State Health Insurance Marketplace Plans: New Opportunities to Help Smokers Quit*, August 2015; <<http://www.lung.org/assets/documents/tobacco/state-health-insurance-opportunities.pdf>>; accessed: July 26, 2017.
- American Lung Association. *Tobacco Cessation as a Preventive Service: New Guidance Clarifies Affordable Care Act Provision*, n.d.a; <<http://www.lung.org/assets/documents/tobacco/tobacco-cessation-preventive-service.pdf>>; accessed: August 29, 2017.
- American Lung Association. Tobacco surcharges, n.d.b; <<http://www.lung.org/assets/documents/tobacco/factsheet-tobacco-surcharges-v2.pdf>>; accessed: July 26, 2017.
- American Nonsmokers' Rights Foundation. *Statewide Laws Requiring 100% Smokefree Gambling Venues as of January 2, 2019*, 2019a; <<https://no-smoke.org/wp-content/uploads/pdf/100smokefreecasinos.pdf>>; accessed: March 26, 2019.
- American Nonsmokers' Rights Foundation. *Summary of 100% Smokefree State Laws and Population Protected by 100% U.S. Smokefree Laws*, October 1, 2019b; <<https://no-smoke.org/wp-content/uploads/pdf/WRBPercentMap.pdf>>; accessed: November 4, 2019.
- American Nonsmokers' Rights Foundation. *U.S. Laws for 100% Smokefree Multi-Unit Housing*, October 1, 2019c; <<https://no-smoke.org/wp-content/uploads/pdf/smokefreemuh.pdf>>; accessed: November 4, 2019.
- American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Substance Use Disorders*. 2nd ed. Washington (DC): American Psychiatric Association, 2010.
- An LC, Betzner A, Schillo B, Luxenberg MG, Christenson M, Wendling A, Saul JE, Kavanaugh A. The comparative effectiveness of clinic, work-site, phone, and Web-based tobacco treatment programs. *Nicotine and Tobacco Research* 2010;12(10):989–96.
- An LC, Bluhm JH, Foldes SS, Alesci NL, Klatt CM, Center BA, Nersesian WS, Larson ME, Ahluwalia JS, Manley MW. A randomized trial of a pay-for-performance program targeting clinician referral to a state tobacco quitline. *Archives of Internal Medicine* 2008;168(18):1993–9.
- An LC, Schillo BA, Kavanaugh AM, Lachter RB, Luxenberg MG, Wendling AH, Joseph AM. Increased reach and effectiveness of a statewide tobacco quitline after the addition of access to free nicotine replacement therapy. *Tobacco Control* 2006;15(4):286–93.
- Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A, Richman E, Verzi SJ, Vugrin ED, Brodsky NS, et al. Potential public health effects of reducing nicotine levels in cigarettes in the United States. *New England Journal of Medicine* 2018;378(18):1725–33.
- Apelberg BJ, Onicescu G, Avila-Tang E, Samet JM. Estimating the risks and benefits of nicotine replacement therapy for smoking cessation in the United States. *American Journal of Public Health* 2010;100(2):341–8.
- Auerbach J. The 3 buckets of prevention. *Journal of Public Health Management and Practice* 2016;22(3):215–8.

³For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- Australian Department of Health. Evaluation of tobacco plain packaging in Australia, n.d.; <<http://www.health.gov.au/internet/main/publishing.nsf/Content/tobacco-plain-packaging-evaluation>>; accessed: November 14, 2018.
- Azagba S, Sharaf MF. The effect of graphic cigarette warning labels on smoking behavior: evidence from the Canadian experience. *Nicotine and Tobacco Research* 2013;15(3):708–17.
- Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;65(52):1457–64.
- Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. *Regulatory Toxicology and Pharmacology* 2013;67(2):246–51.
- Bader P, Boisclair D, Ferrence R. Effects of tobacco taxation and pricing on smoking behavior in high risk populations: a knowledge synthesis. *International Journal of Environmental Research and Public Health* 2011;8(11):4118–39.
- Bartsch AL, Harter M, Niedrich J, Brutt AL, Buchholz A. A systematic literature review of self-reported smoking cessation counseling by primary care physicians. *PLoS One* 2016;11(12):e0168482.
- Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, Ratchford EV, Sarna L, Stecker EC, Wiggins BS. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology* 2018;72(25):3332–65.
- Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiology, Biomarkers and Prevention* 2012;21(5):761–9.
- Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers and Prevention* 2007;16(11):2479–85.
- Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *New England Journal of Medicine* 1994;331(2):123–5.
- Benowitz NL, Herrera B, Jacob P III. Mentholated cigarette smoking inhibits nicotine metabolism. *Journal of Pharmacology and Experimental Therapeutics* 2004;310(3):1208–15.
- Berchick ER, Hood E, Barnett JC. *Health Insurance Coverage in the United States: 2017*. Current Population Reports, P60-264. Washington (DC): U.S. Government Printing Office, 2018.
- Berman M, Crane R, Seiber E, Munur M. Estimating the cost of a smoking employee. *Tobacco Control* 2014;23(5):428–33.
- Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. *Health Affairs* 2008;27(3):759–69.
- Beyer EJ, Keller PA, Bailey LA, Baker TB, Fiore MC. State-level factors influencing tobacco cessation quitline spending in 2008. *Preventive Medicine* 2010;51(2):191–2.
- Bloom EL, Burke MV, Kotsen C, Goldstein AO, Ripley-Moffitt C, Steinberg MB, Dailey M, Hunt LE, Bars MP. Billing practices among U.S. tobacco use treatment providers. *Journal of Addiction Medicine* 2018.
- Boonn A. *Tobacco Tax Increases Are a Reliable Source of Substantial New State Revenue*. Washington (DC): Campaign for Tobacco-Free Kids, 2017; <<http://www.tobaccofreekids.org/research/factsheets/pdf/0303.pdf>>; accessed: October 18, 2018.
- Boonn A. *Raising State Cigarette Taxes Always Increases State Revenues (and Always Reduces Smoking)*. Washington (DC): Campaign for Tobacco-Free Kids, 2018; <<http://www.tobaccofreekids.org/research/factsheets/pdf/0098.pdf>>; accessed: October 18, 2018.
- Borland R, Yong HH, Cummings KM, Hyland A, Anderson S, Fong GT. Determinants and consequences of smoke-free homes: findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control* 2006;15(Suppl 3):iii42–iii50.
- Borland R, Yong H, Wilson N, Fong GT, Hammond D, Cummings KM, Hosking W, McNeill A. How reactions to cigarette packet health warnings influence quitting: findings from the ITC Four-Country survey. *Addiction* 2009;104(4):669–75.
- Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database of Systematic Reviews* 2011, Issue 12. Art. No.: CD008743. DOI: 10.1002/14651858.CD008743.pub2.
- Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD008743. DOI: 10.1002/14651858.CD008743.pub3.
- Bray RM, Pemberton MR, Hourani LL, Witt M, Olmsted KLR, Brown JM, Weimer B, Lane ME, Marsden ME, Scheffler S, et al. *2008 Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel: A Component of the Defense Lifestyle Assessment Program (DLAP)*. Research Triangle Park (NC): RTI International, 2009.
- Brennan TA, Shrank WH, Sussman A, Purvis MC, Hartman T, Kymes SM, Sullivan C, Matlin OS. *The Effect of a Policy to*

- Eliminate Sales of Tobacco in Pharmacies on the Number of Smokers in the Region*, 2014; <https://cvshealth.com/sites/default/files/styles/TobaccoPolicyResearchLetter_Final.pdf>; accessed: October 25, 2018.
- Brock B, Carlson SC, Leizinger A, D'Silva J, Matter CM, Schillo BA. A tale of two cities: exploring the retail impact of flavoured tobacco restrictions in the twin cities of Minneapolis and Saint Paul, Minnesota. *Tobacco Control* 2019;28(2):176–180
- Bundy LT, Haardörfer R, Kegler MC, Owolabi S, Berg CJ, Escoffery C, Thompson T, Mullen PD, Williams R, Hovell M, et al. Disseminating a Smoke Free Homes program to low SES households in the U.S. through 2-1-1: results of a national impact evaluation. *Nicotine and Tobacco Research* 2018.
- Bunn WB 3rd, Stave GM, Downs KE, Alvir JM, Dirani R. Effect of smoking status on productivity loss. *Journal of Occupational and Environmental Medicine* 2006;48(10):1099–108.
- Bush T, Zbikowski S, Mahoney L, Deprey M, Mowery PD, Magnusson B. The 2009 U.S. federal cigarette tax increase and quitline utilization in 16 states. *Journal of Environmental and Public Health* 2012;2012:314740.
- Cahill K, Lancaster T. Workplace interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD003440. DOI: 10.1002/14651858.CD003440.pub4.
- Campbell CA, Hahn RA, Elder R, Brewer R, Chattopadhyay S, Fielding J, Naimi TS, Toomey T, Lawrence B, Middleton JC. The effectiveness of limiting alcohol outlet density as a means of reducing excessive alcohol consumption and alcohol-related harms. *American Journal of Preventive Medicine* 2009;37(6):556–69.
- Campaign for Tobacco-Free Kids. *Standardized or Plain Tobacco Packaging: International Developments*, July 1, 2019a; <https://www.tobaccofreekids.org/assets/global/pdfs/en/standardized_packaging_developments_en.pdf>; accessed: November 4, 2019.
- Campaign for Tobacco-Free Kids. *States & Localities that Have Restricted the Sale of Flavored Tobacco Products*, January 22, 2019b; <<https://www.tobaccofreekids.org/assets/factsheets/0398.pdf>>; accessed: March 13, 2019.
- Cantrell J, Shelley D. Implementing a fax referral program for quitline smoking cessation services in urban health centers: a qualitative study. *BMC Family Practice* 2009;10:81.
- Caplan L, Stout C, Blumenthal DS. Training physicians to do office-based smoking cessation increases adherence to PHS guidelines. *Journal of Community Health* 2011;36(2):238–43.
- Carrillo S, Nazir N, Howser E, Shenkman L, Laxson M, Scheuermann TS, Richter KP. Impact of the 2015 CMS inpatient psychiatric facility quality reporting rule on tobacco treatment. *Nicotine and Tobacco Research* 2017;19(8):976–82.
- Carson KV, Verbiest MEA, Crone MR, Brinn MP, Esterman AJ, Assendelft WJJ, Smith BJ. Training health professionals in smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD000214. DOI: 10.1002/14651858.CD000214.pub2.
- Cartmell KB, Dooley M, Mueller M, Nahhas GJ, Dismuke CE, Warren GW, Talbot V, Cummings KM. Effect of an evidence-based inpatient tobacco dependence treatment service on 30-, 90-, and 180-day hospital readmission rates. *Medical Care* 2018;56(4):358–63.
- Castellan RM, Chosewood LC, Trout D, Wagner GR, Caruso CC, Mazurek J, McCrone SH, Weissman DN. *Promoting Health and Preventing Disease and Injury Through Workplace Tobacco Policies*. *Current Intelligence Bulletin 67*. Morgantown (WV): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, April 2015. DHHS (NIOSH) Publication No. 2015-113.
- Center for Public Health Systems Science. *Point-of-Sale Report to the Nation: The Tobacco Retail and Policy Landscape*. St. Louis (MO): Center for Public Health Systems Science at the Brown School at Washington University in St. Louis and the National Cancer Institute, State and Community Tobacco Control Research Initiative, 2014.
- Center for Public Health Systems Science. *Point-of-Sale Report to the Nation: Realizing the Power of States and Communities to Change the Tobacco Retail and Policy Landscape*. St. Louis (MO): Center for Public Health Systems Science at the Brown School at Washington University in St. Louis and the National Cancer Institute, State and Community Tobacco Control Research Initiative, 2016.
- Centers for Disease Control and Prevention. *A Practical Guide to Working with Health-Care Systems on Tobacco-Use Treatment*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
- Centers for Disease Control and Prevention. CDC grand rounds: current opportunities in tobacco control. *Morbidity and Mortality Weekly Report* 2010;59(16):487–92.
- Centers for Disease Control and Prevention. Cigarette package health warnings and interest in quitting smoking—14 countries, 2008–2010. *Morbidity and Mortality Weekly Report* 2011;60(20):645–51.
- Centers for Disease Control and Prevention. Increases in quitline calls and smoking cessation website visitors

- during a national tobacco education campaign—March 19–June 10, 2012. *Morbidity and Mortality Weekly Report* 2012a;61(34):667–70.
- Centers for Disease Control and Prevention. State tobacco revenues compared with tobacco control appropriations—United States, 1998–2010. *Morbidity and Mortality Weekly Report* 2012b;61(20):370–4.
- Centers for Disease Control and Prevention. Tobacco use screening and counseling during physician office visits among adults—National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005–2009. *Morbidity and Mortality Weekly Report: Supplement* 2012c;61(2):38–45.
- Centers for Disease Control and Prevention. Impact of a national tobacco education campaign on weekly numbers of quitline calls and website visitors—United States, March 4–June 23, 2013. *Morbidity and Mortality Weekly Report* 2013a;62(37):763–7.
- Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥18 years with mental illness—United States, 2009–2011. *Morbidity and Mortality Weekly Report* 2013b;62:81–7.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014a; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/comprehensive.pdf>; accessed: July 26, 2017.
- Centers for Disease Control and Prevention. III. Cessation interventions. In: *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014b; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/sectionA-III.pdf>; accessed: July 26, 2017.
- Centers for Disease Control and Prevention. Patient perspectives on tobacco use treatment in primary care. *Preventing Chronic Disease* 2015;12:140408.
- Centers for Disease Control and Prevention. *STATE System Smokefree Indoor Air Fact Sheet*, August 28, 2018a; <<https://chronicdata.cdc.gov/Legislation/STATE-System-Smokefree-Indoor-Air-Fact-Sheet/vgq2-kkcg>>; accessed: October 18, 2018.
- Centers for Disease Control and Prevention. Tips from former smokers, 2018b; <<https://www.cdc.gov/tobacco/campaign/tips/>>; accessed: October 17, 2018.
- Centers for Disease Control and Prevention. *Case Study: The Effect of Expanding Cessation Coverage—The Massachusetts Medicaid Cessation Benefit*, n.d.; <https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/ma_casestudy.pdf>; accessed: August 28, 2017.
- Centers for Medicare & Medicaid Services. Overview of Specifications of Measures Displayed on Hospital Compare as of December 14, 2006, 2006; <<https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/Downloads/HospitalOverviewOfSpecs200512.pdf>>; accessed: May 23, 2019.
- Centers for Medicare & Medicaid Services. *Promoting Interoperability (PI) program*, 2018; <https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Downloads/October2018_SummaryReport.pdf>; accessed: May 23, 2019.
- Centers for Medicare and Medicaid Services. New Medicaid tobacco cessation services (SDL 11-007, ACA 17), 2011; <<https://downloads.cms.gov/cmssgov/archived-downloads/SMDL/downloads/smd11-007.pdf>>; accessed: July 26, 2017.
- Centers for Medicare and Medicaid Services. Overview: final rule for health insurance market reforms, 2013; <<https://www.cms.gov/CCIIO/Resources/Files/Downloads/market-rules-technical-summary-2-27-2013.pdf>>; accessed: December 7, 2017.
- Centers for Medicare and Medicaid Services. Accountable Care Organizations (ACO), 2017a; <<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO/index.html?redirect=/aco>>; accessed: July 27, 2017.
- Centers for Medicare and Medicaid Services. Acute inpatient PPS, 2017b; <<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/index.html>>; accessed: July 27, 2017.
- Centers for Medicare and Medicaid Services. Comprehensive primary care plus, 2017c; <<https://innovation.cms.gov/initiatives/comprehensive-primary-care-plus/index.html>>; accessed: July 27, 2017.
- Centers for Medicare and Medicaid Services. Inpatient psychiatric facility PPS, 2017d; <<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/InpatientPsychFacilPPS/index.html>>; accessed: July 27, 2017.
- Centers for Medicare and Medicaid Services. Medicare Program: general information, November 13, 2019; <<https://www.cms.gov/Medicare/Medicare-General-Information/MedicareGenInfo/index>>; accessed: December 10, 2019.
- Centers for Medicare and Medicaid Services. Sec. 204. Medicare Medical Home Demonstration Project n.d.; <https://innovation.cms.gov/files/migrated-medicare-demonstration-x/medhome_taxrelief_healthcare.pdf>; accessed: July 27, 2017.

- Centers for Medicare and Medicaid Services, Health Information Technology Policy Committee. Medicare & Medicaid EHR incentive programs, 2016; <https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Downloads/HITPC_March2016_Fulldeck.pdf>; accessed: March 29, 2017.
- Chaiton M, Schwartz R, Cohen JE, Soule E, Eissenberg T. Association of Ontario's ban on menthol cigarettes with smoking behavior 1 month after implementation. *JAMA Internal Medicine* 2018a;178(5):710–1.
- Chaiton M, Schwartz R, Eissenberg T, Soule E, Cohen J. Effects of a real world menthol ban: changes in smoking behaviour and cigarette branding. *Tobacco Induced Diseases* 2018b;16(Suppl 1):A485.
- Chaiton M, Schwartz R, Shuldiner J, Tremblay G, Nugent R. Evaluating a real world ban on menthol cigarettes: an interrupted time series analysis of sales. *Nicotine and Tobacco Research* 2019a.
- Chaiton MO, Nicolau I, Schwartz R, Cohen JE, Soule E, Zhang B, Eissenberg T. Ban on menthol-flavoured tobacco products predicts cigarette cessation at 1 year: a population cohort study. *Tobacco Control* 2019b.
- Chaloupka FJ, Cummings KM, Morley CP, Horan JK. Tax, price and cigarette smoking: evidence from the tobacco documents and implications for tobacco company marketing strategies. *Tobacco Control* 2002;11(Suppl 1):I62–I72.
- Chaloupka FJ, Straif K, Leon ME. Effectiveness of tax and price policies in tobacco control. *Tobacco Control* 2011;20(3):235–8.
- Chaloupka FJ, Yurekli A, Fong GT. Tobacco taxes as a tobacco control strategy. *Tobacco Control* 2012;21(2):172–80.
- Cherng ST, Tam J, Christine PJ, Meza R. Modeling the effects of e-cigarettes on smoking behavior: implications for future adult smoking prevalence. *Epidemiology* 2016;27(6):819–26.
- Chipty T. Study of the Impact of the Tobacco Plain Packaging Measure on Smoking Prevalence in Australia, January 24, 2016; <<https://ris.pmc.gov.au/sites/default/files/posts/2016/02/Tobacco-Plain-Packaging-PIR-%E2%80%93Appendix-A.pdf>>; accessed: November 14, 2018.
- Choi K, Boyle RG. Minnesota smokers' perceived helpfulness of 2009 federal tobacco tax increase in assisting smoking cessation: a prospective cohort study. *BMC Public Health* 2013;13:965.
- Chuang YC, Cubbin C, Ahn D, Winkleby MA. Effects of neighbourhood socioeconomic status and convenience store concentration on individual level smoking. *Journal of Epidemiology and Community Health* 2005;59(7):568–73.
- Clattenburg EJ, Elf JL, Apelberg BJ. Unplanned cigarette purchases and tobacco point of sale advertising: a potential barrier to smoking cessation. *Tobacco Control* 2013;22(6):376–81.
- ClearWay Minnesota. About QUITPLAN® services, n.d.; <<http://clearwaymn.org/quitting/quitplan-services/>>; accessed: September 6, 2017.
- Cobb CO, Villanti AC, Graham AL, Pearson JL, Glasser AM, Rath JM, Stanton CA, Levy DT, Abrams DB, Niaura R. Markov Modeling to estimate the population impact of emerging tobacco products: a proof-of-concept study. *Tobacco Regulatory Science* 2015;2:129–41.
- Courtemanche CJ, Palmer MK, Pesko MF. Influence of the flavored cigarette ban on adolescent tobacco use. *American Journal of Preventive Medicine* 2017;52(5):e139–e146.
- Curry L, Schmitt CL, Henes A, Ortega-Peluso C, Battles H. How low-income smokers in New York access cheaper cigarettes. *American Journal of Health Promotion* 2018.
- Curry SJ, Grothaus LC, McAfee T, Pabiniak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *New England Journal of Medicine* 1998;339(10):673–9.
- Curtis R, Neuschler E. *Tobacco rating issues and options for California under the ACA*. Washington (DC): Institute for Health Policy Solutions, 2012; <http://www.ihps.org/pubs/Tobacco_Rating_Issue_Brief_21June2012.pdf>; accessed: July 26, 2017.
- Czaplicki L, Cohen JE, Jones MR, Clegg Smith K, Rutkow L, Owczarzak J. Compliance with the city of Chicago's partial ban on menthol cigarette sales. *Tobacco Control* 2019;28(2):161–7.
- Davis KC, Alexander RL Jr, Shafer P, Mann N, Malarcher A, Zhang L. The dose-response relationship between tobacco education advertising and calls to quitlines in the United States, March–June, 2012. *Preventing Chronic Disease* 2015;12:E191.
- Davis KC, Farrelly MC, Duke J, Kelly L, Willett J. Antismoking media campaign and smoking cessation outcomes, New York State, 2003–2009. *Preventing Chronic Disease* 2012;9:E40.
- DeCicca P, Kenkel D, Mathios A. Cigarette taxes and the transition from youth to adult smoking: smoking initiation, cessation, and participation. *Journal of Health Economics* 2008;27(4):904–17.
- DeCicca P, McLeod L. Cigarette taxes and older adult smoking: evidence from recent large tax increases. *Journal of Health Economics* 2008;27(4):918–29.
- Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB. Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes. *American Journal of Preventive Medicine* 2011;41(4):357–65.
- Dermody SS, McClernon FJ, Benowitz N, Luo X, Tidey JW, Smith TT, Vandrey R, Hatsukami D, Donny EC.

- Effects of reduced nicotine content cigarettes on individual withdrawal symptoms over time and during abstinence. *Experimental and Clinical Psychopharmacology* 2018;26(3):223–32.
- Dewhirst T. Into the black: Marlboro brand architecture, packaging and marketing communication of relative harm. *Tobacco Control* 2018;27(2):240–2.
- DiGiulio A, Haddix M, Jump Z, Babb S, Schechter A, Williams KS, Asman K, Armour BS. State Medicaid expansion tobacco cessation coverage and number of adult smokers enrolled in expansion coverage—United States, 2016. *Morbidity and Mortality Weekly Report* 2016;65(48):1364–9.
- DiGiulio A, Jump Z, Yu A, Babb S, Schechter A, Williams KS, Yembra D, Armour BS. State Medicaid coverage for tobacco cessation treatments and barriers to accessing treatments—United States, 2015–2017. *Morbidity and Mortality Weekly Report* 2018;67(13):390–5.
- Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al’Absi M, Carmella SG, Cinciripini PM, Dermody SS, et al. Randomized trial of reduced-nicotine standards for cigarettes. *New England Journal of Medicine* 2015;373(14):1340–9.
- Donny EC, Hatsukami DK, Benowitz NL, Sved AF, Tidey JW, Cassidy RN. Reduced nicotine product standards for combustible tobacco: building an empirical basis for effective regulation. *Preventive Medicine* 2014;68:17–22.
- Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction* 2007;102(2):324–34.
- Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug and Alcohol Dependence* 2009;104(1–2):23–33.
- Durkin S, Bayly M, Brennan E, Biener L, Wakefield M. Fear, sadness and hope: which emotions maximize impact of anti-tobacco mass media advertisements among lower and higher SES groups? *Journal of Health Communication* 2018;23(5):445–61.
- Durkin S, Brennan E, Coomber K, Zacher M, Scollo M, Wakefield M. Short-term changes in quitting-related cognitions and behaviours after the implementation of plain packaging with larger health warnings: findings from a national cohort study with Australian adult smokers. *Tobacco Control* 2015;24(Suppl 2):ii26–ii32.
- Durkin S, Brennan E, Wakefield M. Mass media campaigns to promote smoking cessation among adults: an integrative review. *Tobacco Control* 2012;21(2):127–38.
- Emery S, Ake CF, Navarro AM, Kaplan RM. Simulated effect of tobacco tax variation on Latino health in California. *American Journal of Preventive Medicine* 2001;21(4):278–83.
- Escoffery C, Mullen P, Genkin B, Bundy L, Owolabi S, Haardörfer R, Williams R, Savas L, Kegler M. Coaching to create a smoke-free home in a brief secondhand smoke intervention. *Health Education Research* 2017;32(6):555–68.
- Family Smoking Prevention and Tobacco Control Act*, Public Law 111-31, 123 U.S. Statutes at Large 1776 (2009).
- Farber HJ, Walley SC, Groner JA, Nelson KE. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke (section on tobacco control) *Pediatrics* 2015;136(5):1008–17.
- Farkas AJ, Gilpin EA, Distefan JM, Pierce JP. The effects of household and workplace smoking restrictions on quitting behaviours. *Tobacco Control* 1999;8(3):261–5.
- Farkas AJ, Gilpin EA, White MM, Pierce JP. Association between household and workplace smoking restrictions and adolescent smoking. *JAMA: the Journal of the American Medical Association* 2000;284(6):717–22.
- Farley SM, Johns M. New York City flavoured tobacco product sales ban evaluation. *Tobacco Control* 2017;26(1):78–84.
- Farrelly MC, Pechacek TF, Thomas KY, Nelson D. The impact of tobacco control programs on adult smoking. *American Journal of Public Health* 2008;98(2):304–9.
- Faseru B, Nollen NL, Mayo MS, Krebill R, Choi WS, Benowitz NL, Tyndale RF, Okuyemi KS, Ahluwalia JS, Sanderson Cox L. Predictors of cessation in African American light smokers enrolled in a bupropion clinical trial. *Addictive Behaviors* 2013;38(3):1796–803.
- Federal Register*. U.S. Food and Drug Administration. Tobacco Products; Required Warnings for Cigarette Packages and Advertisements. 84 *Fed. Reg.* 42754 (2019); <<https://www.federalregister.gov/d/2019-17481>>; accessed: January 9, 2019.
- Federal Register*. U.S. Department of Health and Human Services, Food and Drug Administration. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 81 *Fed. Reg.* 28974 (2016); <<https://federalregister.gov/a/2016-10685>>; accessed: January 9, 2019.
- Federal Trade Commission. *Federal Trade Commission Cigarette Report for 2017*. Washington (DC): Federal Trade Commission, 2019a.
- Federal Trade Commission. *Federal Trade Commission Smokeless Tobacco Report for 2017*. Washington (DC): Federal Trade Commission, 2019b.
- Feirman SP, Glasser AM, Rose S, Niaura R, Abrams DB, Teplitzskaya L, Villanti AC. Computational models used to assess U.S. tobacco control policies. *Nicotine and Tobacco Research* 2017;19(11):1257–67.

- Fichtenberg CM, Glantz SA. Effect of smoke-free workplaces on smoking behaviour: systematic review. *BMJ* 2002;325(7357):188.
- Fiore M, Adsit R, Zehner M, McCarthy D, Lundsten S, Hartlaub P, Mahr T, Gorrilla A, Skora A, Baker T. An electronic health record-based interoperable eReferral system to enhance smoking quitline treatment in primary care. *Journal of the American Medical Informatics Association* 2019.
- Fiore MC. Tobacco control in the Obama era—substantial progress, remaining challenges. *New England Journal of Medicine* 2016;375(15):1410–2.
- Fiore MC, Bailey WC, Cohen SJ. *Treating Tobacco Use and Dependence: Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, U.S. Public Health Service, 2000.
- Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, Heyman RB, Holbrook J, Jaen CR, Kottke TE, et al. *Smoking Cessation: Clinical Practice Guideline No. 18*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1996. AHCPR Publication No. 96-0692.
- Fiore MC, Goplerud E, Schroeder SA. The Joint Commission's new tobacco-cessation measures—will hospitals do the right thing? *New England Journal of Medicine* 2012;366(13):1172–4.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Fiore MC, Keller PA, Curry SJ. Health system changes to facilitate the delivery of tobacco-dependence treatment. *American Journal of Preventive Medicine* 2007;33(6 Suppl):S349–S356.
- Foulds J, Gandhi KK, Steinberg MB, Richardson DL, Williams JM, Burke MV, Rhoads GG. Factors associated with quitting smoking at a tobacco dependence treatment clinic. *American Journal of Health Behavior* 2006;30(4):400–12.
- Foulds J, Hooper MW, Pletcher MJ, Okuyemi KS. Do smokers of menthol cigarettes find it harder to quit smoking? *Nicotine and Tobacco Research* 2010;12(Suppl 2):S102–S109.
- Freund M, Campbell E, Paul C, McElduff P, Walsh RA, Sakrouge R, Wiggers J, Knight J. Smoking care provision in hospitals: a review of prevalence. *Nicotine and Tobacco Research* 2008;10(5):757–74.
- Freund M, Campbell E, Paul C, Sakrouge R, Lecathelinais C, Knight J, Wiggers J, Walsh RA, Jones T, Girgis A, et al. Increasing hospital-wide delivery of smoking cessation care for nicotine-dependent in-patients: a multi-strategic intervention trial. *Addiction* 2009;104(5):839–49.
- Friedman AS, Schpero WL, Busch SH. Evidence suggests that the ACA's tobacco surcharges reduced insurance take-up and did not increase smoking cessation. *Health Affairs* 2016;35(7):1176–83.
- Fu SS, Okuyemi KS, Partin MR, Ahluwalia JS, Nelson DB, Clothier BA, Joseph AM. Menthol cigarettes and smoking cessation during an aided quit attempt. *Nicotine and Tobacco Research* 2008;10(3):457–62.
- Fu SS, van Ryn M, Nelson D, Burgess DJ, Thomas JL, Saul J, Clothier B, Nyman JA, Hammett P, Joseph AM. Proactive tobacco treatment offering free nicotine replacement therapy and telephone counselling for socioeconomically disadvantaged smokers: a randomised clinical trial. *Thorax* 2016;71(5):446–53.
- Fu SS, van Ryn M, Sherman SE, Burgess DJ, Noorbaloochi S, Clothier B, Taylor BC, Schleder CM, Burke RS, Joseph AM. Proactive tobacco treatment and population-level cessation: a pragmatic randomized clinical trial. *JAMA Internal Medicine* 2014;174(5):671–7.
- Gardiner P, Clark PI. Menthol cigarettes: moving toward a broader definition of harm. *Nicotine and Tobacco Research* 2010;12(Suppl 2):S85–S93.
- Garrett BE, Gardiner PS, Wright LT, Pechacek TF. The African American youth smoking experience: an overview. *Nicotine and Tobacco Research* 2016;18(Suppl 1):S11–S15.
- Germain D, McCarthy M, Wakefield M. Smoker sensitivity to retail tobacco displays and quitting: a cohort study. *Addiction* 2010;105(1):159–63.
- Gilpin EA, White MM, Farkas AJ, Pierce JP. Home smoking restrictions: which smokers have them and how they are associated with smoking behavior. *Nicotine and Tobacco Research* 1999;1(2):153–62.
- Giovino GA, Sidney S, Gfroerer JC, O'Malley PM, Allen JA, Richter PA, Cummings KM. Epidemiology of menthol cigarette use. *Nicotine and Tobacco Research* 2004;6(Suppl 1):S67–S81.
- Giovino GA, Villanti AC, Mowery PD, Sevilimedu V, Niaura RS, Vallone DM, Abrams DB. Differential trends in cigarette smoking in the USA: is menthol slowing progress? *Tobacco Control* 2015;24(1):28–37.
- Gollust SE, Schroeder SA, Warner KE. Helping smokers quit: understanding the barriers to utilization of smoking cessation services. *Milbank Quarterly* 2008;86(4):601–27.
- Gordon JS, Andrews JA, Albert DA, Crews KM, Payne TJ, Severson HH. Tobacco cessation via public dental clinics: results of a randomized trial. *American Journal of Public Health* 2010;100(7):1307–12.
- Gordon JS, Andrews JA, Crews KM, Payne TJ, Severson HH. The 5A's vs 3A's plus proactive quitline referral

- in private practice dental offices: preliminary results. *Tobacco Control* 2007;16(4):285–8.
- Gordon JS, Lichtenstein E, Severson HH, Andrews JA. Tobacco cessation in dental settings: research findings and future directions. *Drug and Alcohol Reviews* 2006;25(1):27–37.
- Greene J, Sacks RM, McMenamin SB. The impact of tobacco dependence treatment coverage and copayments in Medicaid. *American Journal of Preventive Medicine* 2014;46(4):331–6.
- Greenwood DA, Parise CA, MacAller TA, Hankins AI, Harms KR, Pratt LS, Olveda JE, Buss KA. Utilizing clinical support staff and electronic health records to increase tobacco use documentation and referrals to a state quitline. *Journal of Vascular Nursing* 2012;30(4):107–11.
- Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert Review of Pharmacoeconomics & Outcomes Research* 2008;8(2):165–78.
- Guydish J, Tajima B, Le T, Henderson C, Yip D, Gruber V, Garcia W, Delucchi KL. Do cigarette graphic warnings encourage smokers to attend a smoking cessation programme: a quasi-experimental study. *Tobacco Control* 2018;27(1):43–9.
- Hahn EJ. Smokefree legislation: a review of health and economic outcomes research. *American Journal of Preventive Medicine* 2010;39(6 Suppl 1):S66–S76.
- Hahn EJ, Rayens MK, Langley RE, Darville A, Dignan M. Time since smoke-free law and smoking cessation behaviors. *Nicotine and Tobacco Research* 2009;11(8):1011–5.
- Hall SM, Reus VI, Munoz RF, Sees KL, Humfleet G, Hartz DT, Frederick S, Triffleman E. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Archives of General Psychiatry* 1998;55(8):683–90.
- Halonon JI, Kivimaki M, Kouvonen A, Pentti J, Kawachi I, Subramanian SV, Vahtera J. Proximity to a tobacco store and smoking cessation: a cohort study. *Tobacco Control* 2014;23(2):146–51.
- Hamilton FL, Greaves F, Majeed A, Millett C. Effectiveness of providing financial incentives to healthcare professionals for smoking cessation activities: systematic review. *Tobacco Control* 2013;22(1):3–8.
- Hamilton JL. The demand for cigarettes: advertising, the health scare, and the cigarette advertising ban. *The Review of Economics and Statistics* 1972;54(4):401–11.
- Hamlett-Berry K, Davison J, Kivlahan DR, Matthews MH, Hendrickson JE, Almenoff PL. Evidence-based national initiatives to address tobacco use as a public health priority in the Veterans Health Administration. *Military Medicine* 2009;174(1):29–34.
- Hammond D. “Plain packaging” regulations for tobacco products: the impact of standardizing the color and design of cigarette packs. *Salud Publica de México* 2010;52(Suppl 2):S226–S232.
- Hammond D. Health warning messages on tobacco products: a review. *Tobacco Control* 2011;20(5):327–37.
- Hammond D. Tobacco packaging and labeling policies under the U.S. Tobacco Control Act: research needs and priorities. *Nicotine and Tobacco Research* 2012;14(1):62–74.
- Hammond D, McDonald PW, Fong GT, Brown KS, Cameron R. The impact of cigarette warning labels and smoke-free bylaws on smoking cessation: evidence from former smokers. *Canadian Journal of Public Health* 2004;95(3):201–4.
- Han T, Alexander M, Niggebrugge A, Hollands GJ, Marteau TM. Impact of tobacco outlet density and proximity on smoking cessation: a longitudinal observational study in two English cities. *Health Place* 2014;27:45–50.
- Hatsukami DK, Hertsgaard LA, Vogel RI, Jensen JA, Murphy SE, Hecht SS, Carmella SG, al’Absi M, Joseph AM, Allen SS. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiology, Biomarkers and Prevention* 2013;22(6):1015–24.
- Hayford KE, Patten CA, Rummans TA, Schroeder DR, Offord KP, Croghan IT, Glover ED, Sachs DP, Hurt RD. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *British Journal of Psychiatry* 1999;174:173–8.
- Henderson BJ, Wall TR, Henley BM, Kim CH, McKinney S, Lester HA. Menthol enhances nicotine reward-related behavior by potentiating nicotine-induced changes in nAChR function, nAChR upregulation, and DA neuron excitability. *Neuropsychopharmacology* 2017;42(12):2285–91.
- Henriksen L, Feighery EC, Schleicher NC, Cowling DW, Kline RS, Fortmann SP. Is adolescent smoking related to the density and proximity of tobacco outlets and retail cigarette advertising near schools? *Preventive Medicine* 2008;47(2):210–4.
- Hill D, Carroll T. Australia’s National Tobacco Campaign. *Tobacco Control* 2003;12(Suppl 2):ii9–ii14.
- Hoffman AC, Miceli D. Menthol cigarettes and smoking cessation behavior. *Tobacco Induced Diseases* 2011;9 Suppl 1:S6.
- Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tobacco Control* 2007;16(Suppl 1):i53–i59.
- Holtrop JS, Wadland WC, Vansen S, Weismantel D, Fadel H. Recruiting health plan members receiving pharmacotherapy into smoking cessation counseling. *American Journal of Managed Care* 2005;11(8):501–7.
- Hopkins DP, Husten CG, Fielding JE, Rosenquist JN, Westphal LL. Evidence reviews and recommendations

- on interventions to reduce tobacco use and exposure to environmental tobacco smoke: a summary of selected guidelines. *American Journal of Preventive Medicine* 2001;20(2 Suppl):67–87.
- Hopkins DP, Razi S, Leeks KD, Priya Kalra G, Chattopadhyay SK, Soler RE. Smokefree policies to reduce tobacco use. A systematic review. *American Journal of Preventive Medicine* 2010;38(2 Suppl):S275–S289.
- Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model: application to a population of U.S. adult smokers. *Pharmacoeconomics* 2008;26(6):497–511.
- Huang G, Kim S, Gasper J, Xu Y, Bosworth T, May L. 2016 Survey of Veteran Enrollees' Health and Use of Health Care: Main Results Report, March 2017; <https://www.va.gov/HEALTHPOLICYPLANNING/SoE2016/2016_Survey_of_Veteran_Enrollees_Health_and_Health_Care.pdf>; accessed: July 26, 2017.
- Huang G, Muz B, Kim S, Gasper J. 2017 Survey of Veteran Enrollees' Health and Use of Health Care Data Findings Report. Washington (DC): U.S. Department of Veterans Affairs, April 2018.
- Hughes MC, Yette EM, Hannon PA, Harris JR, Tran NM, Reid TR. Promoting tobacco cessation via the workplace: opportunities for improvement. *Tobacco Control* 2011;20(4):305–8.
- Hughes N, Arora M, Grills N. Perceptions and impact of plain packaging of tobacco products in low and middle income countries, middle to upper income countries and low-income settings in high-income countries: a systematic review of the literature. *BMJ Open* 2016;6(3):e010391.
- Hung DY, Green LA. Paying for prevention: associations between pay for performance and cessation counseling in primary care practices. *American Journal of Health Promotion* 2012;26(4):230–4.
- Huskamp HA, Greenfield SF, Stuart EA, Donohue JM, Duckworth K, Kouri EM, Song Z, Chernew ME, Barry CL. Effects of global payment and accountable care on tobacco cessation service use: an observational study. *Journal of General Internal Medicine* 2016;31(10):1134–40.
- Hyland A, Garten S, Giovino GA, Cummings KM. Mentholated cigarettes and smoking cessation: findings from COMMIT. Community Intervention Trial for Smoking Cessation. *Tobacco Control* 2002;11(2):135–9.
- Hyland A, Higbee C, Travers MJ, Van Deusen A, Bansal-Travers M, King B, Cummings KM. Smoke-free homes and smoking cessation and relapse in a longitudinal population of adults. *Nicotine and Tobacco Research* 2009;11(6):614–8.
- Hyland A, Laux FL, Higbee C, Hastings G, Ross H, Chaloupka FJ, Fong GT, Cummings KM. Cigarette purchase patterns in four countries and the relationship with cessation: findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control* 2006;15(Suppl 3):iii59–iii64.
- Independents Gas & Service Stations Associations, Inc. v. City of Chicago*, 112 F. Supp. 3d 749, 754 (N.D. Ill. 2015).
- Institute for Healthcare Improvement. The triple aim. Optimizing health, care and cost. *Healthcare Executive* 2009;24(1):64–6.
- Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington (DC): National Academies Press, 2007.
- Institute of Medicine. *Combating Tobacco Use in Military and Veteran Populations*. Washington (DC): The National Academies Press, 2009.
- Institute of Medicine. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. Washington (DC): The National Academies Press, 2010.
- Institute of Medicine, Committee on Standards for Developing Trustworthy *Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust*. Washington (DC): National Academies Press, 2011.
- International Agency for Research on Cancer. *Evaluating the Effectiveness of Smoke-Free Policies*. IARC Handbooks of Cancer Prevention, Volume 13. Lyon (France): IARC Press, 2009.
- International Tobacco Control Policy Evaluation Project. About ITC, 2017; <<http://www.itcproject.org/about>>; accessed: March 29, 2017.
- International Tobacco Control Policy Evaluation Project. *FCTC Article 11—Tobacco Warning Labels: Evidence and Recommendations from the ITC Project*, May 2009; <https://itcproject.org/files/ITC_Tobacco_Labels_Bro_V3.pdf>; accessed: November 4, 2019.
- Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005–2015. *Morbidity and Mortality Weekly Report* 2016;65(44):1205–11.
- Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, Neff LJ. Current cigarette smoking among adults—United States, 2016. *Morbidity and Mortality Weekly Report* 2018;67(2):53–9.
- Jansen AL, Capesius TR, Lachter R, Greenfield LO, Keller PA. Facilitators of health systems change for tobacco dependence treatment: a qualitative study of stakeholders' perceptions. *BMC Health Services Research* 2014;14:575.
- Jarvis MJ, Giovino GA, O'Connor RJ, Kozlowski LT, Bernert JT. Variation in nicotine intake among U.S. cigarette smokers during the past 25 years: evidence from NHANES surveys. *Nicotine and Tobacco Research* 2014;16(12):1620–8.
- Joyce GF, Niaura R, Maglione M, Mongoven J, Larson-Rotter C, Coan J, Lapin P, Morton S. The effectiveness of

- covering smoking cessation services for Medicare beneficiaries. *Health Services Research* 2008;43(6):2106–23.
- Kaiser Family Foundation. FAQs: Health insurance marketplace and the ACA—tobacco surcharge for premiums, n.d.a; <<https://www.kff.org/health-reform/faq/health-insurance-marketplace-aca/#section-tobacco-surcharge-for-premiums>>; accessed: November 4, 2019.
- Kaiser Family Foundation. State health facts: health insurance coverage of the total population, 2016, n.d.b; <<https://www.kff.org/other/state-indicator/total-population/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D>>; accessed: January 18, 2018.
- Kalkhoran S, Glantz SA. Modeling the health effects of expanding e-cigarette sales in the United States and United Kingdom: a Monte Carlo analysis. *JAMA Internal Medicine* 2015;175(10):1671–80.
- Kaplan CM, Graetz I, Waters TM. Most exchange plans charge lower tobacco surcharges than allowed, but many tobacco users lack affordable coverage. *Health Affairs* 2014;33(8):1466–73.
- Kaplan RM, Ake CF, Emery SL, Navarro AM. Simulated effect of tobacco tax variation on population health in California. *American Journal of Public Health* 2001;91(2):239–44.
- Katz DA, Brown RB, Muehlenbruch DR, Fiore MC, Baker TB. Implementing guidelines for smoking cessation: comparing the efforts of nurses and medical assistants. *American Journal of Preventive Medicine* 2004;27(5):411–6.
- Katz DA, Holman JE, Johnson SR, Hillis SL, Adams SL, Fu SS, Grant KM, Buchanan LM, Prochazka A, Battaglia CT, et al. Implementing best evidence in smoking cessation treatment for hospitalized veterans: results from the VA-BEST Trial. *Joint Commission Journal on Quality and Patient Safety* 2014;40(11):493–1.
- Keeler C, Max W, Yerger VB, Yao T, Wang Y, Ong MK, Sung HY. Effects of cigarette prices on intention to quit, quit attempts, and successful cessation among African American smokers. *Nicotine and Tobacco Research* 2018.
- Kegler MC, Bundy L, Haardörfer R, Escoffery C, Berg C, Yembra D, Kreuter M, Hovell M, Williams R, Mullen PD, et al. A minimal intervention to promote smoke-free homes among 2-1-1 callers: a randomized controlled trial. *American Journal of Public Health* 2015;105(3):530–7.
- Kegler MC, Escoffery C, Bundy L, Berg CJ, Haardörfer R, Yembra D, Schauer G. Pilot study results from a brief intervention to create smoke-free homes. *Journal of Environmental and Public Health* 2012;2012:951426.
- Keller PA, Christiansen B, Kim SY, Piper ME, Redmond L, Adsit R, Fiore MC. Increasing consumer demand among Medicaid enrollees for tobacco dependence treatment: the Wisconsin “Medicaid Covers It” campaign. *American Journal of Health Promotion* 2011;25(6):392–5.
- Keller PA, Greenseed LO, Christenson M, Boyle RG, Schillo BA. Seizing an opportunity: increasing use of cessation services following a tobacco tax increase. *BMC Public Health* 2015;15:354.
- King BA, Babb SD, Tynan MA, Gerzoff RB. National and state estimates of secondhand smoke infiltration among U.S. multiunit housing residents. *Nicotine and Tobacco Research* 2013a;15(7):1316–21.
- King BA, Dube SR, Babb SD, McAfee TA. Patient-reported recall of smoking cessation interventions from a health professional. *Preventive Medicine* 2013b;57(5):715–7.
- King BA, Peck RM, Babb SD. National and state cost savings associated with prohibiting smoking in subsidized and public housing in the United States. *Preventing Chronic Disease* 2014;11:E171.
- Kingsley M, Song G, Robertson J, Henley P, Ursprung WWS. Impact of flavoured tobacco restriction policies on flavoured product availability in Massachusetts. *Tobacco Control* 2019.
- Kizer KW. The National Quality Forum seeks to improve health care. *Academic Medicine* 2000;75(4):320–1.
- Knight C, Howard P, Baker CL, Marton JP. The cost-effectiveness of an extended course (12+12 weeks) of varenicline compared with other available smoking cessation strategies in the United States: an extension and update to the BENESCO model. *Value in Health* 2010;13(2):209–14.
- Kofman M, Dunton K, Senkewicz MB. *Implementation of Tobacco Cessation Coverage Under the Affordable Care Act: Understanding How Private Health Insurance Policies Cover Tobacco Cessation Treatments*. Washington (DC): Health Policy Institute, Georgetown University, 2012.
- Kostova D, Xu X, Babb S, McMenamin SB, King BA. Does state Medicaid coverage of smoking cessation treatments affect quitting? *Health Services Research* 2018;53(6):4725–46.
- Kruger J, O’Halloran A, Rosenthal A. Assessment of compliance with U.S. Public Health Service clinical practice guideline for tobacco by primary care physicians. *Harm Reduction Journal* 2015;12:7.
- Kruse GR, Chang Y, Kelley JH, Linder JA, Einbinder JS, Rigotti NA. Healthcare system effects of pay-for-performance for smoking status documentation. *American Journal of Managed Care* 2013;19(7):554–61.
- Kruse GR, Kelley JH, Linder JA, Park ER, Rigotti NA. Implementation of an electronic health record-based care management system to improve tobacco treatment. *Journal of General Internal Medicine* 2012;27(12):1690–6.
- Ku L, Brantley E, Bysshe T, Steinmetz E, Bruen BK. How Medicaid and other public policies affect use of tobacco

- cessation therapy, United States, 2010–2014. *Preventing Chronic Disease* 2016;13:E150.
- Land T, Keithly L, Kane K, Chen L, Paskowsky M, Cullen D, Hayes RB, Li W. Recent increases in efficiency in cigarette nicotine delivery: implications for tobacco control. *Nicotine and Tobacco Research* 2014;16(6):753–8.
- Land T, Rigotti NA, Levy DE, Paskowsky M, Warner D, Kwass JA, Wetherell L, Keithly L. A longitudinal study of Medicaid coverage for tobacco dependence treatments in Massachusetts and associated decreases in hospitalizations for cardiovascular disease. *PLoS Medicine* 2010a;7(12):e1000375.
- Land T, Warner D, Paskowsky M, Cammaerts A, Wetherell L, Kaufmann R, Zhang L, Malarcher A, Pechacek T, Keithly L. Medicaid coverage for tobacco dependence treatments in Massachusetts and associated decreases in smoking prevalence. *PLoS One* 2010b;5(3):e9770.
- Land TG, Rigotti NA, Levy DE, Schilling T, Warner D, Li W. The effect of systematic clinical interventions with cigarette smokers on quit status and the rates of smoking-related primary care office visits. *PLoS One* 2012;7(7):e41649.
- Larzelere MM, Williams DE. Promoting smoking cessation. *American Family Physician* 2012;85(6):591–8.
- Lemaire RH, Bailey L, Leischow SJ. Meeting the tobacco cessation coverage requirement of the Patient Protection and Affordable Care Act: state smoking cessation quitlines and cost sharing. *American Journal of Public Health* 2015;105(Suppl 5):S699–S705.
- Lesho EP, Myers CP, Ott M, Winslow C, Brown JE. Do clinical practice guidelines improve processes or outcomes in primary care? *Military Medicine* 2005;170(3):243–6.
- Levy DE, Adams IF, Adamkiewicz G. Delivering on the promise of smoke-free public housing. *American Journal of Public Health* 2017a;107(3):380–3.
- Levy DT, Blackman K, Tauras J, Chaloupka FJ, Villanti AC, Niaura RS, Vallone DM, Abrams DB. Quit attempts and quit rates among menthol and nonmenthol smokers in the United States. *American Journal of Public Health* 2011a;101(7):1241–7.
- Levy DT, Borland R, Villanti AC, Niaura R, Yuan Z, Zhang Y, Meza R, Holford TR, Fong GT, Cummings KM, et al. The application of a decision-theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. *Nicotine and Tobacco Research* 2017b;19(2):149–59.
- Levy DT, Boyle RG, Abrams DB. The role of public policies in reducing smoking: the Minnesota SimSmoke tobacco policy model. *American Journal of Preventive Medicine* 2012;435(Suppl 3):S179–S186.
- Levy DT, Cummings KM, Hyland A. Increasing taxes as a strategy to reduce cigarette use and deaths: results of a simulation model. *Preventive Medicine* 2000;31(3):279–86.
- Levy DT, Friend K. A computer simulation model of mass media interventions directed at tobacco use. *Preventive Medicine* 2001;32(3):284–94.
- Levy DT, Friend K, Holder H, Carmona M. Effect of policies directed at youth access to smoking: results from the SimSmoke computer simulation model. *Tobacco Control* 2001;10(2):108–16.
- Levy DT, Hyland A, Higbee C, Remer L, Compton C. The role of public policies in reducing smoking prevalence in California: results from the California tobacco policy simulation model. *Health Policy* 2007a;82(2):167–85.
- Levy DT, Mabry PL, Graham AL, Orleans CT, Abrams DB. Reaching Healthy People 2010 by 2013: a SimSmoke simulation. *American Journal of Preventive Medicine* 2010;38(3 Suppl):S373–S381.
- Levy DT, Meza R, Zhang Y, Holford TR. Gauging the effect of U.S. tobacco control policies from 1965 through 2014 using SimSmoke. *American Journal of Preventive Medicine* 2016;50(4):535–42.
- Levy DT, Pearson JL, Villanti AC, Blackman K, Vallone DM, Niaura RS, Abrams DB. Modeling the future effects of a menthol ban on smoking prevalence and smoking-attributable deaths in the United States. *American Journal of Public Health* 2011b;101(7):1236–40.
- Levy DT, Ross H, Powell L, Bauer JE, Lee HR. The role of public policies in reducing smoking prevalence and deaths caused by smoking in Arizona: results from the Arizona tobacco policy simulation model. *Journal of Public Health Management and Practice* 2007b;13(1):59–67.
- Lewis M, Wang Y, Berg CJ. Tobacco control environment in the United States and individual consumer characteristics in relation to continued smoking: differential responses among menthol smokers? *Preventive Medicine* 2014;65:47–51.
- Linder JA, Rigotti NA, Schneider LI, Kelley JH, Brawarsky P, Haas JS. An electronic health record-based intervention to improve tobacco treatment in primary care: a cluster-randomized controlled trial. *Archives of Internal Medicine* 2009;169(8):781–7.
- Lindholm C, Adsit R, Bain P, Reber PM, Brein T, Redmond L, Smith SS, Fiore MC. A demonstration project for using the electronic health record to identify and treat tobacco users. *WMJ* 2010;109(6):335–40.
- Lipperman-Kreda S, Mair C, Grube JW, Friend KB, Jackson P, Watson D. Density and proximity of tobacco outlets to homes and schools: relations with youth cigarette smoking. *Prevention Science* 2014;15(5):738–44.
- Longo DR, Johnson JC, Kruse RL, Brownson RC, Hewett JE. A prospective investigation of the impact of smoking bans on tobacco cessation and relapse. *Tobacco Control* 2001;10(3):267–72.
- Luke DA, Hammond RA, Combs T, Sorg A, Kasman M, Mack-Crane A, Ribisl KM, Henriksen L. Tobacco town:

- computational modeling of policy options to reduce tobacco retailer density. *American Journal of Public Health* 2017;107(5):740–6.
- Mackay DF, Irfan MO, Haw S, Pell JP. Meta-analysis of the effect of comprehensive smoke-free legislation on acute coronary events. *Heart* 2010;96(19):1525–30.
- Mannocci A, Colamesta V, Mipatrini D, Boccia A, Terzano C, La Torre G. How would plain packaging and pictorial warning impact on smoking reduction, cessation and initiation? [Italian]. *Epidemiologia e Prevenzione* 2013;37(6):400–5.
- Mantey DS, Pasch KE, Loukas A, Perry CL. Exposure to point-of-sale marketing of cigarettes and e-cigarettes as predictors of smoking cessation behaviors. *Nicotine and Tobacco Research* 2017.
- Marynak K, Kenemer B, King BA, Tynan MA, MacNeil A, Reimels E. State laws regarding indoor public use, retail sales, and prices of electronic cigarettes—U.S. States, Guam, Puerto Rico, and U.S. Virgin Islands, September 30, 2017. *Morbidity and Mortality Weekly Report* 2017;66(49):1341–6.
- Marynak K, VanFrank B, Tetlow S, Mahoney M, Phillips E, Jamal A, Schecter A, Tipperman D, Babb S. Tobacco cessation interventions and smoke-free policies in mental health and substance abuse treatment facilities—United States, 2016. *Morbidity and Mortality Weekly Report* 2018;67(18):519–23.
- Massachusetts Department of Public Health. *Massachusetts Department of Public Health. Information for Providers About the MassHealth Tobacco Cessation Program Benefit*, April 2014; <<http://massclearinghouse.ehs.state.ma.us/TOB/TC3406.html>>; accessed: August 16, 2018.
- McAfee T, Babb S, McNabb S, Fiore MC. Helping smokers quit—opportunities created by the Affordable Care Act. *New England Journal of Medicine* 2015;372(1):5–7.
- McAfee T, Davis KC, Alexander RL Jr, Pechacek TF, Bunnell R. Effect of the first federally funded U.S. antismoking national media campaign. *Lancet* 2013;382(9909):2003–11.
- McAfee T, Davis KC, Shafer P, Patel D, Alexander R, Bunnell R. Increasing the dose of television advertising in a national antismoking media campaign: results from a randomised field trial. *Tobacco Control* 2017;26(1):19–28.
- McCarville R, Bee C. *Point-of-Purchase Techniques and Their Influence on Tobacco Consumption: A Review of Literature in Private Sector Journals*. Waterloo, Ontario (Canada): Centre for Behavioral Research and Program Evaluation, University of Waterloo, 1999.
- McLeod H, Blissett D, Wyatt S, Mohammed MA. Effect of pay-for-outcomes and encouraging new providers on national health service smoking cessation services in England: a cluster controlled study. *PLoS One* 2015;10(4):e0123349.
- McMenamin SB, Halpin HA, Bellows NM. Knowledge of Medicaid coverage and effectiveness of smoking treatments. *American Journal of Preventive Medicine* 2006;31(5):369–74.
- McMenamin SB, Halpin HA, Ibrahim JK, Orleans CT. Physician and enrollee knowledge of Medicaid coverage for tobacco dependence treatments. *American Journal of Preventive Medicine* 2004;26(2):99–104.
- McNeill A, Gravelly S, Hitchman SC, Bauld L, Hammond D, Hartmann-Boyce J. Tobacco packaging design for reducing tobacco use. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD011244. DOI: 10.1002/14651858.CD011244.pub2.
- Medicaid.gov. Eligibility, n.d.; <<https://www.medicaid.gov/medicaid/eligibility/index.html>>; accessed: December 12, 2019.
- Medicare Interactive. Medicare coverage to help you quit smoking, n.d.; <<https://www.medicareinteractive.org/get-answers/medicare-covered-services/preventive-care-services/medicare-coverage-to-help-you-quit-smoking>>; accessed: July 26, 2017.
- Messer K, Mills AL, White MM, Pierce JP. The effect of smoke-free homes on smoking behavior in the U.S. *American Journal of Preventive Medicine* 2008;35(3):210–6.
- Messer K, Pierce JP, Zhu SH, Hartman AM, Al-Delaimy WK, Trinidad DR, Gilpin EA. The California Tobacco Control Program's effect on adult smokers: (1) Smoking cessation. *Tobacco Control* 2007;16(2):85–90.
- Meyers DG, Neuberger JS, He J. Cardiovascular effect of bans on smoking in public places: a systematic review and meta-analysis. *Journal of the American College of Cardiology* 2009;54(14):1249–55.
- Miller CL, Hill DJ, Quester PG, Hiller JE. Impact on the Australian Quitline of new graphic cigarette pack warnings including the quitline number. *Tobacco Control* 2009;18(3):235–7.
- Millett C, Gray J, Saxena S, Netuveli G, Majeed A. Impact of a pay-for-performance incentive on support for smoking cessation and on smoking prevalence among people with diabetes. *Canadian Medical Association Journal* 2007;176(12):1705–10.
- Mirbolouk M, Charkhchi P, Kianoush S, Uddin SMI, Orimoloye OA, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP, et al. Prevalence and distribution of e-cigarette use among U.S. adults: Behavioral Risk Factor Surveillance System, 2016. *Annals of Internal Medicine* 2018;169(7):429–38.
- Moodie C, Stead M, Bauld L, McNeill A, Angus K, Hinds K, Kwan I, Thomas J, Hastings G, O'Mara-Eves A. *Plain tobacco packaging: a systematic review*, 2011; <http://phrc.lshtm.ac.uk/papers/PHRC_006_Final_Report.pdf>; accessed: November 14, 2018.

- Moody-Thomas S, Horswell R, Celestin MD, Dellinger AB, Kaiser M, Butler M. Awareness and implementation of the 2000 United States public health service tobacco dependence treatment guideline in a public hospital system. *Population Health Management* 2011;14(2):79–85.
- Moody-Thomas S, Nasuti L, Yi Y, Celestin MD Jr, Horswell R, Land TG. Effect of systems change and use of electronic health records on quit rates among tobacco users in a public hospital system. *American Journal of Public Health* 2015;105(Suppl 2):e1–e7.
- Mullen KA, Coyle D, Manuel D, Nguyen HV, Pham B, Pipe AL, Reid RD. Economic evaluation of a hospital-initiated intervention for smokers with chronic disease, in Ontario, Canada. *Tobacco Control* 2015;24(5):489–96.
- Mullen PD, Savas LS, Bundy LT, Haardörfer R, Hovell M, Fernández ME, Monroy JA, Williams RS, Kreuter MW, Jobe D, et al. Minimal intervention delivered by 2-1-1 information and referral specialists promotes smoke-free homes among 2-1-1 callers: a Texas generalisation trial. *Tobacco Control* 2016;25(Suppl 1):i10–i18.
- Murphy-Hoefer R, Davis KC, Beistle D, King BA, Duke J, Rodes R, Graffunder C. Impact of the Tips From Former Smokers campaign on population-level smoking cessation, 2012–2015. *Preventing Chronic Disease* 2018;15:E71.
- Murphy J, Gaca M, Lowe F, Minet E, Breheny D, Prasad K, Camacho O, Fearon IM, Liu C, Wright C, et al. Assessing modified risk tobacco and nicotine products: description of the scientific framework and assessment of a closed modular electronic cigarette. *Regulatory Toxicology and Pharmacology* 2017;90:342–57.
- Murphy JM, Mahoney MC, Cummings KM, Hyland AJ, Lawvere S. A randomized trial to promote pharmacotherapy use and smoking cessation in a Medicaid population (United States). *Cancer Causes and Control* 2005;16(4):373–82.
- Nahas GJ, Wilson D, Talbot V, Cartmell KB, Warren GW, Toll BA, Carpenter MJ, Cummings KM. Feasibility of implementing a hospital-based “opt-out” tobacco-cessation service. *Nicotine and Tobacco Research* 2017;19(8):937–43.
- National Academies of Sciences, Engineering, and Medicine. *Public Health Consequences of E-Cigarettes*. Washington (DC): The National Academies Press, 2018.
- National Association of Attorneys General. NAAG Center for Tobacco and Public Health, n.d.; <http://www.naag.org/naag/about_naag/naag-center-for-tobacco-and-public-health.php>; accessed: March 12, 2019.
- National Cancer Institute. *Greater than the Sum: Systems Thinking in Tobacco Control*. Tobacco Control Monograph No. 18. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2007. NIH Pub. No. 06-6085.
- National Cancer Institute. *The Role of the Media in Promoting and Reducing Tobacco Use*. Smoking and Tobacco Control Monograph No. 19. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2008. NIH Publication No. 07-6242.
- National Cancer Institute and World Health Organization. *The Economics of Tobacco and Tobacco Control*. National Cancer Institute Tobacco Control Monograph 21. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; and World Health Organization, 2016. NIH Publication No. 16-CA-8029A.
- National Center for Health Statistics. *Health, United States, 2017: With Special Feature on Mortality*. Hyattsville (MD): National Center for Health Statistics, 2018.
- National Committee for Quality Assurance. About NCQA, n.d.a; <<http://www.ncqa.org/>>; accessed: December 7, 2017.
- National Committee for Quality Assurance. HEDIS and performance measurement, n.d.b; <<http://www.ncqa.org/hedis-quality-measurement>>; accessed: July 26, 2017.
- National Committee for Quality Assurance. Medical assistance with smoking and tobacco use cessation, n.d.c; <<http://www.ncqa.org/report-cards/health-plans/state-of-health-care-quality/2016-table-of-contents/smoking-cessation>>; accessed: July 26, 2017.
- National Quality Forum. NQF number 0028—preventive care & screening: tobacco use: screening & cessation intervention. Washington (DC): National Quality Forum, n.d.a.
- National Quality Forum. Home page, n.d.b; <<http://www.qualityforum.org/Home.aspx>>; accessed: July 27, 2017.
- National Research Council. *Understanding the U.S. Illicit Tobacco Market: Characteristics, Policy Context, and Lessons from International Experiences*. Washington (DC): The National Academies Press, 2015.
- Near AM, Blackman K, Currie LM, Levy DT. Sweden SimSmoke: the effect of tobacco control policies on smoking and snus prevalence and attributable deaths. *European Journal of Public Health* 2014;24(3):451–8.
- Neff LJ, Patel D, Davis K, Ridgeway W, Shafer P, Cox S. Evaluation of the National Tips from Former Smokers Campaign: the 2014 longitudinal cohort. *Preventing Chronic Disease* 2016;13:E42.
- Noar SM, Francis DB, Bridges C, Sontag JM, Ribisl KM, Brewer NT. The impact of strengthening cigarette pack warnings: Systematic review of longitudinal observational studies. *Social Science and Medicine* 2016a;164:118–29.
- Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial cigarette pack warnings: a meta-analysis of experimental studies. *Tobacco Control* 2016b;25(3):341–54.
- Nolan MB, Warner DO. Perioperative tobacco use treatments: putting them into practice. *BMJ* 2017;358:j3340.

- North American Quitline Consortium. *Guide for Implementing eReferral Using Certified EHR*. Phoenix (AZ): North American Quitline Consortium, 2015; <<https://c.ymcdn.com/sites/naquitline.site-ym.com/resource/resmgr/eRef/GuideforImpeRefFeb2016.pdf>>; accessed: July 26, 2017.
- North American Quitline Consortium. *A Promising Practices Report—Public-Private Partnership Initiative: Working to Advance Cessation Coverage Among Private and Public Insurers*, 2016; <<https://c.ymcdn.com/sites/www.naquitline.org/resource/resmgr/ppp/PPPReportSeptember2016.pdf>>; accessed: October 18, 2018.
- Office of the National Coordinator for Health Information Technology. Office-based physician electronic health record adoption—Health IT Quick-Stat #50, January 2019; <dashboard.healthit.gov/quickstats/pages/physician-ehr-adoption-trends.php>; accessed: May 23, 2019.
- Office of the U.S. Surgeon General. *Surgeon General's Advisory on E-Cigarette Use Among Youth*, n.d.; <<https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf>>; accessed: January 9, 2019.
- Ong MK, Glantz SA. Free nicotine replacement therapy programs vs implementing smoke-free workplaces: a cost-effectiveness comparison. *American Journal of Public Health* 2005;95(6):969–75.
- Orzechowski and Walker. *The Tax Burden on Tobacco: Historical Compilation, Volume 52, 2017*. Fairfax (VA): Orzechowski & Walker, 2017.
- Ossip-Klein DJ, McIntosh S. Quitlines in North America: evidence base and applications. *American Journal of the Medical Sciences* 2003;326(4):201–5.
- Pacek LR, Oliver JA, Sweitzer MM, McClernon FJ. Young adult dual combusted cigarette and e-cigarette users' anticipated responses to a nicotine reduction policy and menthol ban in combusted cigarettes. *Drug and Alcohol Dependence* 2019;194:40–4.
- Papadakis S, McDonald P, Mullen KA, Reid R, Skulsky K, Pipe A. Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis. *Preventive Medicine* 2010;51(3-4):199–213.
- Patient Protection and Affordable Care Act of 2010*. Public Law 111-148, U.S. Statutes at Large 124 (2010):119–1024.
- Patten CA, Martin JE, Owen N. Can psychiatric and chemical dependency treatment units be smoke free? *Journal of Substance Abuse Treatment* 1996;13(2):107–18.
- Pearson J, Abrams D, Niaura R, Richardson A, Vallone D. A ban on menthol cigarettes: impact on public opinion and smokers' intention to quit. *American Journal of Public Health* 2012;102:e107–e114.
- Pizacani BA, Maher JE, Rohde K, Drach L, Stark MJ. Implementation of a smoke-free policy in subsidized multiunit housing: effects on smoking cessation and secondhand smoke exposure. *Nicotine and Tobacco Research* 2012;14(9):1027–34.
- Polinski JM, Howell B, Brennan TA, Shrank WH. *Impact of the CVS Tobacco Sales Removal on Smoking Cessation: When CVS Health Quit Tobacco, Many Smokers Quit, Too*, 2015; <<https://cvshealth.com/sites/default/files/%20Impact%20of%20the%20CVS%20Tobacco%20Sales%20Removal%20on%20Smoking%20Cessation.pdf>>; accessed: October 25, 2018.
- Polinski JM, Howell B, Gagnon MA, Kymes SM, Brennan TA, Shrank WH. Impact of CVS Pharmacy's discontinuance of tobacco sales on cigarette purchasing (2012–2014). *American Journal of Public Health* 2017;107(4):556–62.
- Prochaska JJ. Smoking and mental illness—breaking the link. *New England Journal of Medicine* 2011;365(3):196–8.
- Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annual Review of Public Health* 2017;38:165–85.
- Public Health England. *Models of Delivery for Stop Smoking Services: Options and Evidence*. London (UK): Public Health England, September 2017.
- Public Health Law Center. States and tribes stepping in to protect communities from the dangers of e-cigarettes: actions and options (2019), October 30, 2019; <<https://www.publichealthlawcenter.org/resources/states-and-tribes-stepping-protect-communities-dangers-e-cigarettes-actions-and-options>>; accessed: November 5, 2019.
- Quality Payment Program. How to use this tool, n.d.a; <<https://qpp.cms.gov/mips/explore-measures/quality-measures>>; accessed: May 23, 2019.
- Quality Payment Program. Quality payment program, n.d.b; <<https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/MACRA-MIPS-and-APMs/Quality-Payment-Program-Long-Version-Executive-Deck.pdf>>; accessed: January 25, 2018.
- R.J. Reynolds Tobacco Co., et al., v. Food & Drug Administration, et al.*, 696 F.3d 1205 (D.C. Cir. 2012).
- Rath JM, Villanti AC, Williams VF, Richardson A, Pearson JL, Vallone DM. Correlates of current menthol cigarette and flavored other tobacco product use among U.S. young adults. *Addictive Behaviors* 2016;62:35–41.
- Redmond LA, Adsit R, Kobinsky KH, Theobald W, Fiore MC. A decade of experience promoting the clinical treatment of tobacco dependence in Wisconsin. *Wisconsin Medical Journal* 2010;109(2):71–8.
- Reed MB, Anderson CM, Vaughn JW, Burns DM. The effect of cigarette price increases on smoking cessation in California. *Prevention Science* 2008;9(1):47–54.

- Reid JL, Mutti-Packer S, Gupta PC, Li Q, Yuan J, Nargis N, Hussain AKMG, Hammond D. Influence of health warnings on beliefs about the health effects of cigarette smoking, in the context of an experimental study in four Asian countries. *International Journal of Environmental Research and Public Health* 2017;14(8):E868.
- Reitzel LR, Cromley EK, Li Y, Cao Y, Dela Mater R, Mazas CA, Cofta-Woerpel L, Cinciripini PM, Wetter DW. The effect of tobacco outlet density and proximity on smoking cessation. *American Journal of Public Health* 2011;101(2):315–20.
- Reynolds American. Reynolds American Inc. submits Premarket Tobacco Product Application for VUSE products, October 11, 2019; <<https://www.reynoldsameric.com/about-us/press-releases/Press-Release-Details-/2019/Reynolds-American-Inc-submits-Premarket-Tobacco-Application-for-VUSE-products/default.aspx>>; accessed: December 10, 2019.
- Rhoads JK. The effect of comprehensive state tobacco control programs on adult cigarette smoking. *Journal of Health Economics* 2012;31(2):393–405.
- Richard P, West K, Ku L. The return on investment of a Medicaid tobacco cessation program in Massachusetts. *PLoS One* 2012;7(1):e29665.
- Rigotti NA. Integrating comprehensive tobacco treatment into the evolving U.S. health care system: it's time to act: comment on "A randomized trial of Internet and telephone treatment for smoking cessation". *Archives of Internal Medicine* 2011;171(1):53–5.
- Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD001837. DOI: 10.1002/14651858.CD001837.pub3.
- Rigotti NA, Regan S, Levy DE, Japuntich S, Chang Y, Park ER, Viana JC, Kelley JH, Reyem M, Singer DE. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. *JAMA: the Journal of the American Medical Association* 2014;312(7):719–28.
- Rivara FP, Ebel BE, Garrison MM, Christakis DA, Wiehe SE, Levy DT. Prevention of smoking-related deaths in the United States. *American Journal of Preventive Medicine* 2004;27(2):118–25.
- Rogers T, Brown EM, McCrae TM, Gammon DG, Eggers ME, Watson K, Engstrom MC, Tworek C, Holder-Hayes E, Nonnemaker J. Compliance with a sales policy on flavored non-cigarette tobacco products. *Tobacco Regulatory Science* 2017;3(2 Suppl 1):S84–S93.
- Rogers T, Feld A, Gammon DG, Coats EM, Brown EM, Olson LT, Nonnemaker JM, Engstrom M, McCrae T, Holder-Hayes E. Changes in cigar sales following implementation of a local policy restricting sales of flavored non-cigarette tobacco products. *Tobacco Control* 2019.
- Rojewski AM, Bailey SR, Bernstein SL, Cooperman NA, Gritz ER, Karam-Hage MA, Piper ME, Rigotti NA, Warren GW. Considering systemic barriers to treating tobacco use in clinical settings in the United States. *Nicotine and Tobacco Research* 2019;21(11):1453–61.
- Rojewski AM, Toll BA, O'Malley SS. Menthol cigarette use predicts treatment outcomes of weight-concerned smokers. *Nicotine and Tobacco Research* 2014;16(1):115–9.
- Rose SW, Ganz O, Zhou Y, Carnegie BE, Villanti AC, Rath J, Hair EC. Longitudinal response to restrictions on menthol cigarettes among young adult U.S. menthol smokers, 2011–2016. *American Journal of Public Health* 2019;109:1400–3.
- Rose SW, Johnson AL, Glasser AM, Villanti AC, Ambrose BK, Conway K, Cummings KM, Stanton CA, Delnevo C, Wackowski OA, et al. Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014–2015. *Tobacco Control* 2019.
- Roski J, Jeddeloh R, An L, Lando H, Hannan P, Hall C, Zhu SH. The impact of financial incentives and a patient registry on preventive care quality: increasing provider adherence to evidence-based smoking cessation practice guidelines. *Preventive Medicine* 2003;36(3):291–9.
- Ross H, Blecher E, Yan L, Hyland A. Do cigarette prices motivate smokers to quit? New evidence from the ITC survey. *Addiction* 2011;106(3):609–19.
- Ross H, Kostova D, Stoklosa M, Leon M. The impact of cigarette excise taxes on smoking cessation rates from 1994 to 2010 in Poland, Russia, and Ukraine. *Nicotine and Tobacco Research* 2014;16(Suppl 1):S37–S43.
- Roulo C. Tobacco use harms military readiness, official says, August 12, 2014; <<https://www.defense.gov/News/Article/Article/603055/tobacco-use-harms-military-readiness-official-says/>>; accessed: July 26, 2017.
- Ruel E, Mani N, Sandoval A, Terry-McElrath Y, Slater SJ, Tworek C, Chaloupka FJ. After the Master Settlement Agreement: trends in the American tobacco retail environment from 1999 to 2002. *Health Promotion Practice* 2004;5(3 Suppl):99S–110S.
- Schauer GL, Thompson JR, Zbikowski SM. Results from an outreach program for health systems change in tobacco cessation. *Health Promotion Practice* 2012;13(5):657–65.
- Schillo BA, Mowery A, Greenseed LO, Luxenberg MG, Zieffler A, Christenson M, Boyle RG. The relation between media promotions and service volume for a statewide tobacco quitline and a web-based cessation program. *BMC Public Health* 2011;11:939.
- Schindler-Ruwisch JM, Abroms LC, Bernstein SL, Heminger CL. A content analysis of electronic health record (EHR) functionality to support tobacco treatment. *Translational Behavioral Medicine* 2017;7(2):148–56.

- Schroeder SA, Clark B, Cheng C, Saucedo CB. Helping smokers quit: the Smoking Cessation Leadership Center engages behavioral health by challenging old myths and traditions. *Journal of Psychoactive Drugs* 2017;1–8.
- Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. *Annual Review of Public Health* 2010;31:297–314.
- Scollo M, Hayes L, Wakefield M. What price quitting? the price of cigarettes at which smokers say they would seriously consider trying to quit. *BMC Public Health* 2013;13:650.
- Shafer PR, Davis KC, Patel D, Rodes R, Beistle D. Association between media dose, ad tagging, and changes in web traffic for a national tobacco education campaign: a market-level longitudinal study. *Journal of Medical Internet Research* 2016;18(2):e39.
- Sharifi M, Adams WG, Winickoff JP, Guo J, Reid M, Boynton-Jarrett R. Enhancing the electronic health record to increase counseling and quit-line referral for parents who smoke. *Academic Pediatrics* 2014;14(5):478–84.
- Sheffer C, Stitzer M, Wheeler JG. Smoke-free medical facility campus legislation: support, resistance, difficulties and cost. *International Journal of Environmental Research and Public Health* 2009;6(1):246–58.
- Sheffer MA, Baker TB, Fraser DL, Adsit RT, McAfee TA, Fiore MC. Fax referrals, academic detailing, and tobacco quitline use: a randomized trial. *American Journal of Preventive Medicine* 2012;42(1):21–8.
- Sheffer MA, Redmond LA, Kobinsky KH, Keller PA, McAfee T, Fiore MC. Creating a perfect storm to increase consumer demand for Wisconsin's Tobacco Quitline. *American Journal of Preventive Medicine* 2010;38(3 Suppl):S343–S346.
- Shelley D, Anno J, Tseng TY, Calip G, Wedeles J, Lloyd M, Wolff MS. Implementing tobacco use treatment guidelines in public health dental clinics in New York City. *Journal of Dental Education* 2011;75(4):527–33.
- Shelley D, Cantrell MJ, Moon-Howard J, Ramjohn DQ, VanDevanter N. The \$5 man: the underground economic response to a large cigarette tax increase in New York City. *American Journal of Public Health* 2007;97(8):1483–8.
- Shelley D, Goldfeld KS, Park H, Mola A, Sullivan R, Austrian J. System changes to implement The Joint Commission Tobacco Treatment (TOB) performance measures for improving the treatment of tobacco use among hospitalized patients. *Joint Commission Journal on Quality and Patient Safety* 2017;43(5):234–40.
- Shahpush M, Shaikh RA, Smith D, Hyland A, Cummings KM, Kessler AS, Dodd MD, Carlson L, Meza J, Wakefield M. The association of exposure to point-of-sale tobacco marketing with quit attempt and quit success: results from a prospective study of smokers in the United States. *International Journal of Environmental Research and Public Health* 2016;13(2):203.
- Siegel DA, Jatlaoui TC, Koumans EH, Kiernan EA, Layer M, Cates JE, Kimball A, Weissman DN, Petersen EE, Reagan-Steiner S, et al. Update: interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68:919–27.
- Singleterry J, Jump Z, DiGiulio A, Babb S, Sneegas K, MacNeil A, Zhang L, Williams KA. State Medicaid coverage for tobacco cessation treatments and barriers to coverage—United States, 2014–2015. *Morbidity and Mortality Weekly Report* 2015;64(42):1194–9.
- Siu AL. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 2015;163(8):622–34.
- Smith BK, Adsit RT, Jorenby DE, Matsumura JS, Fiore MC. Utilization of the electronic health record to improve provision of smoking cessation resources for vascular surgery inpatients. *International Journal of Cardiovascular Research* 2015;4(5).
- Smith MW, Chen S, Siroka AM, Hamlett-Berry K. Using policy to increase prescribing of smoking cessation medications in the VA healthcare system. *Tobacco Control* 2010;19(6):507–11.
- Smith PC, Mossialos E, Papanicolas I. Performance Measurement for Health System Improvement: Experiences, Challenges and Prospects. Copenhagen (Denmark): World Health Organization, 2008; <<http://www.who.int/management/district/performance/PerformanceMeasurementHealthSystemImprovement2.pdf>>; accessed: July 26, 2017.
- Smith PH, Assefa B, Kainth S, Salas-Ramirez KY, McKee SA, Giovino GA. Use of mentholated cigarettes and likelihood of smoking cessation in the United States: a meta-analysis. *Nicotine and Tobacco Research* 2019.
- Smith SS, Beckley T, Fiore MC. Health care provider use of guideline-based smoking cessation interventions: results from the 2003 Wisconsin Tobacco Survey. *WMJ* 2005;104(4):28–31.
- Smith SS, Fiore MC, Baker TB. Smoking cessation in smokers who smoke menthol and non-menthol cigarettes. *Addiction* 2014;109(12):2107–17.
- Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Jamerson B, Fiore MC, Baker TB. Targeting smokers at increased risk for relapse: treating women and those with a history of depression. *Nicotine and Tobacco Research* 2003;5(1):99–109.
- Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms

- of e-cigarette use in the United States. *PLoS One* 2018;13(3):e0193328.
- Sottera, Inc. v. Food and Drug Administration*, No. 627 F.3d 891 (D.C. Cir. 2010).
- Stahre M, Okuyemi KS, Joseph AM, Fu SS. Racial/ethnic differences in menthol cigarette smoking, population quit ratios and utilization of evidence-based tobacco cessation treatments. *Addiction* 2010;105(Suppl 1):75–83.
- Steinberg MB, Bover MT, Richardson DL, Schmelzer AC, Williams JM, Foulds J. Abstinence and psychological distress in co-morbid smokers using various pharmacotherapies. *Drug and Alcohol Dependence* 2011;114(1):77–81.
- Stevens VL, Diver WR, Stoklosa M, Flanders WD, Westmaas JL, Jemal A, Drope JM, Gapstur SM, Jacobs EJ. A prospective cohort study of cigarette prices and smoking cessation in older smokers. *Cancer Epidemiology, Biomarkers and Prevention* 2017;26(7):1071–7.
- Substance Abuse and Mental Health Services Administration. *Adults with Mental Illness or Substance Use Disorder Account for 40 Percent of All Cigarettes Smoked*, March 30, 2013; <<https://www.samhsa.gov/data/sites/default/files/spot104-cigarettes-mental-illness-substance-use-disorder/spot104-cigarettes-mental-illness-substance-use-disorder.pdf>>; accessed: December 7, 2017.
- Tauras JA. Public policy and smoking cessation among young adults in the United States. *Health Policy* 2004;68(3):321–32.
- Tauras JA, Chaloupka FJ. *Determinants of smoking cessation: An analysis of young adult men and women*. NBER Working Paper Series No. 7262, 1999; <<http://www.nber.org/papers/w7262>>; accessed: June 21, 2018.
- Tengs TO, Ahmad S, Savage JM, Moore R, Gage E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts. *Preventive Medicine* 2005;40(2):170–80.
- The Commonwealth Fund. States' role in promoting meaningful use of electronic health records, n.d.; <<https://www.commonwealthfund.org/publications/newsletter-article/states-role-promoting-meaningful-use-electronic-health-records>>; accessed: March 25, 2019.
- The Community Guide. Reducing tobacco use and secondhand smoke exposure: interventions to increase the unit price for tobacco products—task force finding and rationale statement, 2012a; <<https://www.thecommunityguide.org/sites/default/files/assets/Tobacco-Increasing-Unit-Price.pdf>>; accessed: July 26, 2017.
- The Community Guide. Tobacco use and secondhand smoke exposure: smoke-free policies, 2012b; <<https://www.thecommunityguide.org/findings/tobacco-use-and-secondhand-smoke-exposure-smoke-free-policies>>; accessed: January 29, 2018.
- The Community Guide. Tobacco use and secondhand smoke exposure: mass-reach health communication interventions, 2013; <<https://www.thecommunityguide.org/findings/tobacco-use-and-secondhand-smoke-exposure-mass-reach-health-communication-interventions>>; accessed: April 1, 2017.
- The Community Guide. Reducing tobacco use and secondhand smoke exposure: comprehensive tobacco control programs—task force finding and rationale statement, September 29, 2014; <<https://www.thecommunityguide.org/sites/default/files/assets/TFFRS-Tobacco-Comprehensive-Control-Programs.pdf>>; accessed: August 29, 2017.
- The Joint Commission. *2016 Annual Report: America's hospitals: improving quality and safety*, 2016; <http://www.new-media-release.com/jointcommission/2016_annual_report/2016-annual-report.pdf>; accessed: March 27, 2017.
- The Joint Commission. About The Joint Commission, n.d.; <https://www.jointcommission.org/about_us/about_the_joint_commission_main.aspx>; accessed: July 26, 2017.
- Thomas D, Abramson MJ, Bonevski B, George J. System change interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD010742. DOI: 10.1002/14651858.CD010742.pub2.
- Thompson T, Kreuter MW, Caito N, Williams RS, Escoffery C, Fernández ME, Kegler MC. Implementing an evidence-based tobacco control program at five 2-1-1 call centers: an evaluation using the consolidated framework for implementation research. *Nicotine and Tobacco Research* 2019;21(2):180–7.
- Tobacco Control Legal Consortium. *U.S. Sales Restrictions on Flavored Tobacco Products*. St. Paul (MN): Public Health Law Center at Mitchell Hamline School of Law, September 2018.
- Tobacco Labelling Resource Centre. Plain packaging images: Horizon Australia 2014, n.d.a; <http://www.tobaccolabels.ca/wp/wp-content/uploads/2016/07/2014_Horizon3.jpg>; accessed: November 21, 2018.
- Tobacco Labelling Resource Centre. Smoking harms unborn babies, n.d.b; <<http://www.tobaccolabels.ca/wp/wp-content/uploads/2014/04/Australia-2012-ETS-baby-targets-pregnant-women-back.jpg>>; accessed: November 21, 2018.
- Tobacco Products Scientific Advisory Committee. *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*. Washington (DC): U.S. Food and Drug Administration, 2011.
- Toll BA, O'Malley SS, Katulak NA, Wu R, Dubin JA, Latimer A, Meandzija B, George TP, Jatlow P, Cooney JL, et al. Comparing gain- and loss-framed messages for smoking cessation with sustained-release bupropion: a randomized controlled trial. *Psychology of Addictive Behaviors* 2007;21(4):534–44.

- Torrijos RM, Glantz SA. The U.S. Public Health Service “treating tobacco use and dependence clinical practice guidelines” as a legal standard of care. *Tobacco Control* 2006;15(6):447–51.
- Trinidad DR, Perez-Stable EJ, Messer K, White MM, Pierce JP. Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. *Addiction* 2010;105(Suppl 1):84–94.
- Tseng TS, Moody-Thomas S, Horswell R, Yi Y, Celestin MD, Jones KD. Using a health informatics system to assess effect of a federal cigarette tax increase on readiness to quit among low-income smokers, Louisiana, 2009. *Preventing Chronic Disease* 2014;11:E52.
- Twardella D, Brenner H. Effects of practitioner education, practitioner payment and reimbursement of patients’ drug costs on smoking cessation in primary care: a cluster randomised trial. *Tobacco Control* 2007;16(1):15–21.
- Tynan MA, Holmes CB, Promoff G, Hallett C, Hopkins M, Frick B. State and local comprehensive smoke-free laws for worksites, restaurants, and bars—United States, 2015. *Morbidity and Mortality Weekly Report* 2016;65(24):623–6.
- U.S. Department of Defense. *2011 Department of Defense Health Related Behaviors Survey of Active Duty Military Personnel*, February 2013; <https://www.murray.senate.gov/public/_cache/files/889efd07-2475-40ee-b3b0-508947957a0f/final-2011-hrb-active-duty-survey-report.pdf>; accessed: August 14, 2017.
- U.S. Department of Health and Human Services. *Reducing Tobacco Use. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2000.
- U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
- U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
- U.S. Department of Health and Human Services. *A Report of the Surgeon General: Preventing Tobacco Use Among Youth and Young Adults—We CAN Make the Next Generation Tobacco-Free* [Consumer Booklet]. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Office on Smoking and Health, 2012a.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012b.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
- U.S. Department of Housing and Urban Development. Instituting Smoke-Free Public Housing. 81 *Fed. Reg.* 87430, 2016; <<https://www.federalregister.gov/documents/2016/12/05/2016-28986/instituting-smoke-free-public-housing>>; accessed: January 18, 2018.
- U.S. Department of Labor. FAQs about Affordable Care Act implementation (part XIX), May 2, 2014; <<http://www.dol.gov/ebsa/faqs/faq-aca19.html>>; accessed: July 27, 2017.
- U.S. Food and Drug Administration. FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death: agency to pursue lowering nicotine in cigarettes to non-addictive levels and create more predictability in tobacco regulation [news release], July 28, 2017; <<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm568923.htm>>; accessed: August 18, 2017.
- U.S. Food and Drug Administration. FDA takes significant steps to protect Americans from dangers of tobacco through new regulation [press release], 2016; <<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm499234.htm>>; accessed: May 16, 2016.
- U.S. Food and Drug Administration. Cigarette graphic health warnings, 2018a; <<https://www.fda.gov/tobacco-products/labeling/labeling/ucm257774.htm>>; accessed: October 19, 2018.
- U.S. Food and Drug Administration. The Real Cost Campaign, 2018b; <<https://www.fda.gov/tobaccoproducts/publichealtheducation/publiceducationcampaigns/therealcostcampaign/default.htm/>>; accessed: October 17, 2018.
- U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on pivotal public health step to dramatically reduce smoking rates by lowering nicotine in combustible cigarettes to minimally or non-addictive levels [press release], March 15, 2018c; <<https://www.fda.gov/oc/2018/03/15-statement-fda-commissioner-scott-gottlieb-m-d-on-pivotal-public-health-step-to-dramatically-reduce-smoking-rates-by-lowering-nicotine-in-combustible-cigarettes-to-minimally-or-non-addictive-levels>>; accessed: October 17, 2018.

- fd.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601039.htm>; accessed: November 14, 2018.
- U.S. Food and Drug Administration. Swedish Match USA, Inc., MRTP applications, November 19, 2019; <<https://www.fda.gov/tobacco-products/advertising-and-promotion/swedish-match-usa-inc-mrtp-applications>>; accessed: December 10, 2019.
- U.S. Food and Drug Administration. *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes*, n.d.; <<https://www.fda.gov/downloads/ucm361598.pdf>>; accessed: November 15, 2018.
- U.S. Office of Personnel Management. Additional information and instructions on the technical guidance for the 2011 contract year (FEHB Program Carrier Letter No. 2010—12[c]), May 17, 2010a; <<https://www.opm.gov/healthcare-insurance/healthcare/carriers/2010/2010-12c.pdf>>; accessed: November 16, 2018.
- U.S. Office of Personnel Management. Federal employees health benefits program call letter (FEHB Program Carrier Letter No. 2010-06), April 7, 2010b; <<https://www.opm.gov/healthcare-insurance/healthcare/carriers/2010/2010-06.pdf>>; accessed: November 16, 2018.
- U.S. Office of Personnel Management. 2020 technical guidance and instructions for preparing HMO benefit and service area proposals (FEHB Program Carrier Letter No. 2019-05 (a)), April 30, 2019a; <<https://www.opm.gov/healthcare-insurance/healthcare/carriers/2019/2019-05a.pdf>>; accessed: July 24, 2019.
- U.S. Office of Personnel Management. [Annual call for benefit and rate proposals from Federal Employees Health Benefits (FEHB) Program Carriers] (FEHB Program Carrier Letter No. 2019-01), March 14, 2019b; <<https://www.opm.gov/healthcare-insurance/healthcare/carriers/2019/2019-01.pdf>>; accessed: May 23, 2019.
- U.S. Office of Personnel Management. Special initiatives: quit smoking, n.d.; <<https://www.opm.gov/healthcare-insurance/special-initiatives/quit-smoking/>>; accessed: July 26, 2017.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Use in Adults and Pregnant Women: Counseling and Interventions, April 2009; <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions>>; accessed: July 19, 2018.
- U.S. Preventive Services Task Force. Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions, September 2015; <<https://www.uspreventiveservices-taskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1>>; accessed: May 24, 2017.
- U.S. Preventive Services Task Force. About the USPSTF, 2017; <<https://www.uspreventiveservicestaskforce.org/Page/Name/about-the-uspstf>>; accessed: July 26, 2017.
- U.S. Preventive Services Task Force. Draft update summary: tobacco smoking cessation in adults, including pregnant women: interventions, March 2018; <<https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/tobacco-smoking-cessation-in-adults-including-pregnant-women-interventions>>; accessed: November 13, 2018.
- United States v. Philip Morris USA, Inc.*, 801 F.3d 250, 260 (D.C. Cir. 2015).
- University of Medicine & Dentistry of New Jersey, School of Public Health. *Data Brief: A Profile of New Jersey Quitcenter Clients*. Trenton (NJ): New Jersey Department of Health and Senior Services, July 2007.
- Vallone DM, Duke JC, Cullen J, McCausland KL, Allen JA. Evaluation of EX: a national mass media smoking cessation campaign. *American Journal of Public Health* 2011;101(2):302–9.
- van den Brand FA, Nagelhout GE, Reda AA, Winkens B, Evers S, Kotz D, van Schayck OC. Healthcare financing systems for increasing the use of tobacco dependence treatment. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD004305. DOI: 10.1002/14651858.CD004305.pub5.
- Vidrine JI, Shete S, Cao Y, Greisinger A, Harmonson P, Sharp B, Miles L, Zbikowski SM, Wetter DW. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. *JAMA Internal Medicine* 2013;173(6):458–64.
- Vijayaraghavan M, Messer K, White MM, Pierce JP. The effectiveness of cigarette price and smoke-free homes on low-income smokers in the United States. *American Journal of Public Health* 2013;103(12):2276–83.
- Villanti AC, Collins LK, Niaura RS, Gagosian SY, Abrams DB. Menthol cigarettes and the public health standard: a systematic review. *BMC Public Health* 2017;17(1):983.
- Villanti AC, Curry LE, Richardson A, Vallone DM, Holtgrave DR. Analysis of media campaign promoting smoking cessation suggests it was cost-effective in prompting quit attempts. *Health Affairs* 2012;31(12):2708–16.
- Villanti AC, Johnson AL, Glasser AM, Rose SW, Ambrose BK, Conway KP, Cummings KM, Stanton CA, Edwards KC, Delnevo CD, et al. Association of flavored tobacco use with tobacco initiation and subsequent use among U.S. youth and adults, 2013–2015. *JAMA Network Open* 2019;2(10):e1913804.
- Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004–2014. *Tobacco Control* 2016;25(Suppl 2):ii14–ii20.

- Vugrin ED, Rostron BL, Verzi SJ, Brodsky NS, Brown TJ, Choiniere CJ, Coleman BN, Paredes A, Apelberg BJ. Modeling the potential effects of new tobacco products and policies: a dynamic population model for multiple product use and harm. *PLoS One* 2015;10(3):e0121008.
- Wackowski O, Manderski M, Delnevo C. Young adults' behavioral intentions surrounding a potential menthol cigarette ban. *Nicotine and Tobacco Research* 2014;16:876–80.
- Wackowski OA, Delnevo CD, Pearson JL. Switching to e-cigarettes in the event of a menthol cigarette ban. *Nicotine and Tobacco Research* 2015;17(10):1286–7.
- Wackowski OA, Evans KR, Harrell MB, Loukas A, Lewis MJ, Delnevo CD, Perry CL. In their own words: young adults' menthol cigarette initiation, perceptions, experiences and regulation perspectives. *Nicotine and Tobacco Research* 2018;20(9):1076–84.
- Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. *Archives of Internal Medicine* 2005;165(19):2286–92.
- Wakefield M, Morley C, Horan JK, Cummings KM. The cigarette pack as image: new evidence from tobacco industry documents. *Tobacco Control* 2002;11(Suppl 1):I73–I80.
- Wakefield MA, Durkin S, Spittal MJ, Siahpush M, Scollo M, Simpson JA, Chapman S, White V, Hill D. Impact of tobacco control policies and mass media campaigns on monthly adult smoking prevalence. *American Journal of Public Health* 2008;98(8):1443–50.
- Wakefield MA, Spittal MJ, Yong HH, Durkin SJ, Borland R. Effects of mass media campaign exposure intensity and durability on quit attempts in a population-based cohort study. *Health Education Research* 2011;26(6):988–97.
- Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults—United States, 2017. *Morbidity and Mortality Weekly Report* 2018;67(44):1225–32.
- Ward MM, Doebbeling BN, Vaughn TE, Uden-Holman T, Clarke WR, Woolson RF, Letuchy E, Branch LG, Perlin J. Effectiveness of a nationally implemented smoking cessation guideline on provider and patient practices. *Preventive Medicine* 2003;36(3):265–71.
- Warner DD, Land TG, Rodgers AB, Keithly L. Integrating tobacco cessation quitlines into health care: Massachusetts, 2002–2011. *Preventing Chronic Disease* 2012;9:E133.
- Warner KE, Mendez D. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine and Tobacco Research* 2019;21(1):41–7.
- Weitkunat R, Lee PN, Baker G, Sponsiello-Wang Z, Gonzalez-Zuloeta Ladd AM, Ludicke F. A novel approach to assess the population health impact of introducing a modified risk tobacco product. *Regulatory Toxicology and Pharmacology* 2015;72(1):87–93.
- Wickham RJ. How menthol alters tobacco-smoking behavior: a biological perspective. *Yale Journal of Biology and Medicine* 2015;88(3):279–87.
- Willemsen MC, Simons C, Zeeman G. Impact of the new EU health warnings on the Dutch quit line. *Tobacco Control* 2002;11(4):381–2.
- Williams RS, Stollings JH, Bundy L, Haardörfer R, Kreuter MW, Mullen PD, Hovell M, Morris M, Kegler MC. A minimal intervention to promote smoke-free homes among 2-1-1 callers: North Carolina Randomized Effectiveness Trial. *PLoS One* 2016;11(11):e0165086.
- Wilson N, Li J, Hoek J, Edwards R, Peace J. Long-term benefit of increasing the prominence of a quitline number on cigarette packaging: 3 years of quitline call data. *New Zealand Medical Journal* 2010;123(1321):109–11.
- World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2009: Implementing Smoke-Free Environments*. Geneva (Switzerland): World Health Organization, 2009.
- World Health Organization. *Evidence Brief. Plain Packaging of Tobacco Products: Measures to Decrease Smoking Initiation and Increase Cessation*. Copenhagen (Denmark): WHO Regional Office for Europe, 2014.
- World Health Organization. *Advisory Note: Banning Menthol in Tobacco Products*. Geneva (Switzerland): WHO Study Group on Tobacco Product Regulation, 2016a.
- World Health Organization. *Plain Packaging of Tobacco Products: Evidence, Design and Implementation*. Geneva (Switzerland): World Health Organization, 2016b.
- World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2017: Monitoring Tobacco Use and Prevention Policies*. Geneva (Switzerland): World Health Organization, 2017.
- World Health Organization. *Case Studies for Regulatory Approaches to Tobacco Products: Menthol in Tobacco Products*. Geneva (Switzerland): World Health Organization, 2018.
- World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2019: Offer Help to Quit Tobacco Use*. Geneva (Switzerland): World Health Organization, 2019.
- World Health Organization. Global Adult Tobacco Survey (GATS), n.d.; <<http://www.who.int/tobacco/surveillance/survey/gats/en/>>; accessed: March 29, 2017.
- Xu X, Alexander RL Jr, Simpson SA, Goates S, Nonnemaker JM, Davis KC, McAfee T. A cost-effectiveness analysis of the first federally funded antismoking

- campaign. *American Journal of Preventive Medicine* 2015a;48(3):318–25.
- Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *American Journal of Preventive Medicine* 2015b;48(3):326–33.
- Young-Wolff KC, Henriksen L, Delucchi K, Prochaska JJ. Tobacco retailer proximity and density and nicotine dependence among smokers with serious mental illness. *American Journal of Public Health* 2014;104(8):1454–63.
- Zatonski M, Herbec A, Zatonski W, Przewozniak K, Janik-Konieczny K, Mons U, Fong GT, Demjén T, Tountas Y, Trofor AC, et al. Characterising smokers of menthol and flavoured cigarettes, their attitudes towards tobacco regulation, and the anticipated impact of the Tobacco Products Directive on their smoking and quitting behaviours: The EUREST-PLUS ITC Europe Surveys. *Tobacco Induced Diseases* 2018;16:A4.
- Zhu SH, Anderson CM, Zhuang YL, Gamst AC, Kohatsu ND. Smoking prevalence in Medicaid has been declining at a negligible rate. *PLoS One* 2017;12(5):e0178279.

Chapter 8

A Vision for the Future

Introduction 643

Past: Historical Perspective 643

Present: Health Benefits of Cessation 649

Future: Ending the Tobacco Use Epidemic 651

Progress and Challenges 651

End-Game Strategies 653

Advancing Cessation 656

Accelerating National Momentum to Promote Cessation 658

References 661

Introduction

The progress made in reducing cigarette smoking in the United States over the past five decades represents one of the most notable public health achievements of the past century (Ward and Warren 2007; U.S. Department of Health and Human Services [USDHHS] 2014). Since the first Surgeon General's report on smoking and health was released in 1964, current cigarette smoking among U.S. adults 18 years of age and older has declined from 42.6% in 1964 to a low of 14.0% in 2017 (Wang et al. 2018). This decline has brought within reach USDHHS' national *Healthy People 2020* goal of reducing adult cigarette smoking prevalence to 12.0% (Office of Disease Prevention and Health Promotion n.d.). Similarly, current cigarette smoking among youth in grades 9–12 has declined from 36.4% in 1997 to 8.8% in 2017, a decline that has persisted in the two decades since the Master Settlement Agreement of 1998 and has surpassed the national *Healthy People 2020* target of 16.0% (Centers for Disease Control and Prevention [CDC] n.d.). This commendable progress has been accomplished through the implementation of evidence-based tobacco control programs and policies at the federal, state, and local levels that effectively combat the tobacco use epidemic in the United States (Figure 8.1 and Table 8.1) (USDHHS 2012, 2014). However, it is important to acknowledge that the tobacco product landscape has diversified in recent years. Although cigarettes remain the most commonly used tobacco product among U.S. adults (Wang et al. 2018), e-cigarettes have been the most commonly used tobacco product among youth since 2014, and recent increases in e-cigarette use have offset declines in cigarette smoking and led to a net increase in overall tobacco product use among youth (Gentzke et al. 2019).

The decline in cigarette smoking among adults have been driven, in part, by reductions in initiation among youth in recent years, especially over the past two decades (USDHHS 2012, 2014). For example, since 2002, cigarette smoking initiation and daily smoking initiation has decreased among youth 12–17 years of age of both sexes

and among nearly all races/ethnicities (Cantrell et al. 2018). Preventing tobacco use among youth is therefore critical to reduce the overall prevalence of tobacco use because the vast majority of adult smokers initiate tobacco use as youth or young adults (USDHHS 2012). However, despite these notable accomplishments, motivating and helping people to quit smoking remains essential to (a) protecting the nation's approximately 34 million adult cigarette smokers from a lifetime of addiction and tobacco-related disease and death (Wang et al. 2018) and (b) curbing the substantial financial costs incurred by society because of smoking-attributable healthcare spending and lost productivity (USDHHS 2014; Xu et al. 2015). Accordingly, sustained efforts to increase access to and use of evidence-based cessation treatments among adult smokers, in coordination with population-based interventions, are essential to effectively address the full continuum of tobacco use from initiation to intermittent or routine use (USDHHS 2012, 2014).

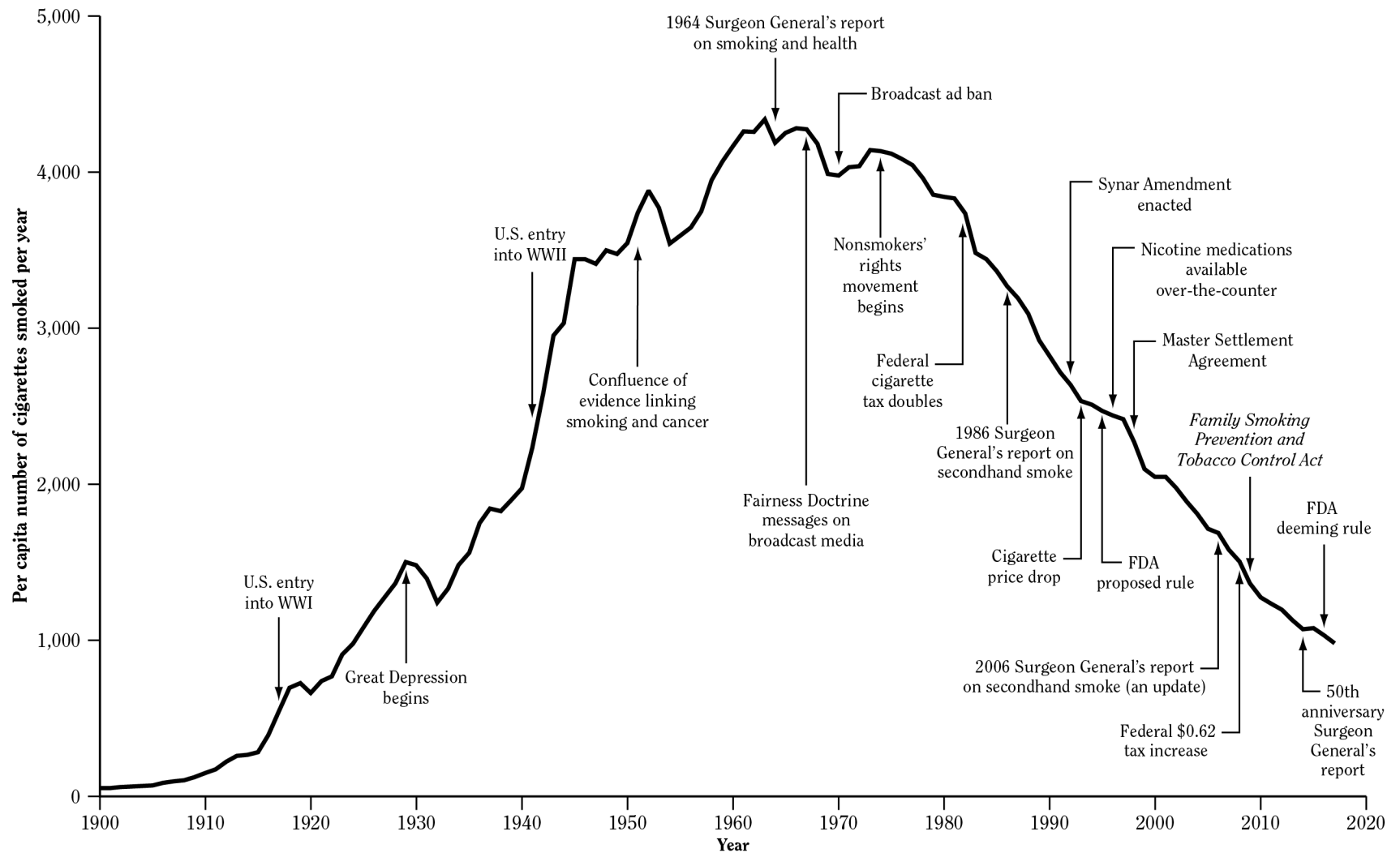
Three decades after the first Surgeon General's report to focus specifically on the health benefits of cessation, this report reviews and updates evidence on the importance of cessation in the context of a comprehensive tobacco control strategy. The report discusses historical patterns of smoking cessation in the United States, as well as the immediate and long-term health and economic benefits of smoking cessation at the individual and societal levels. The report also presents updated findings on biological insights into smoking cessation, including findings on nicotine addiction and genetic factors that may impact smoking behaviors. Finally, the report discusses the extensive array of clinical and population-based interventions that have been scientifically shown to effectively increase smoking cessation. The following sections discuss the past, present, and future of tobacco cessation in the United States. Specifically, these sections provide a historical perspective, discuss the current tobacco control landscape, and provide a vision for enhancing tobacco cessation in the United States.

Past: Historical Perspective

In 2010, USDHHS published the first tobacco control strategic action plan for the United States, *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services* (USDHHS 2010). The main intent of this action plan was

to reinvigorate national momentum toward advancing tobacco prevention and control by applying proven methods to reduce the burden of tobacco use and dependence. The 50th anniversary Surgeon General's report provided further scientific evidence for the effectiveness of the interventions

Figure 8.1 Per capita annual cigarette consumption among adults, 18 years of age and older, and major smoking and health events in the United States, 1900–2017



Source: Adapted from Warner (1985) with permission from Massachusetts Medical Society, © 1985; as cited in USDHHS (2014).

Table 8.1 Summary of milestones aimed at increasing tobacco cessation in the United States

Year	Event
1964	<ul style="list-style-type: none"> The first Surgeon General's report, <i>Smoking and Health</i>, is released.
1967–1970	<ul style="list-style-type: none"> Regulation from the Federal Communications Commission requires broadcasters to apply the Fairness Doctrine to cigarette advertising to counter messages in advertising from the tobacco industry.
1971	<ul style="list-style-type: none"> Broadcast advertising of cigarettes ends. Surgeon General Jesse Steinfeld called for a national “Bill of Rights for the Non-Smoker.”
1979	<ul style="list-style-type: none"> The Surgeon General's report, <i>Smoking and Health</i>, is released. This report offers detailed reviews of major diseases and concludes that compared with smokers, risks are lower among former smokers for all-cause mortality, atherosclerosis and coronary heart disease, lung cancer, larynx cancer, lung function, and respiratory symptoms.
1984	<ul style="list-style-type: none"> Nicotine gum, available by prescription only, becomes the first FDA-approved cessation medication.
1986	<ul style="list-style-type: none"> The Surgeon General's report, <i>The Health Consequences of Involuntary Smoking</i>, is released.
1987	<ul style="list-style-type: none"> The United States House of Representatives passed an amendment to the <i>Federal Aviation Act</i>, making domestic flights of 2 hours or less smokefree.
1988	<ul style="list-style-type: none"> The Surgeon General's report, <i>The Health Consequences of Smoking—Nicotine Addiction</i>, is released.
1990	<ul style="list-style-type: none"> A congressionally mandated smoking ban takes effect on all domestic airline flights of 6 hours or less. The Surgeon General's report, <i>The Health Benefits of Smoking Cessation</i>, is released. San Luis Obispo, California, becomes the first city in the world to eliminate smoking in all public buildings, including bars and restaurants.
1992	<ul style="list-style-type: none"> California launches the first state-sponsored smoking cessation quitline.
1996	<ul style="list-style-type: none"> FDA approves the nicotine patch and gum for over-the-counter use and the nicotine nasal spray for prescription use. The U.S. Public Health Service issues the first clinical practice guideline on <i>Treating Tobacco Use and Dependence</i>.
1997	<ul style="list-style-type: none"> FDA approves the nicotine inhaler and bupropion for prescription use for cessation. (Bupropion had previously been available as an antidepressant and continues to be available for this indication.)
1998	<ul style="list-style-type: none"> Attorneys General of 46 states sign the Master Settlement Agreement with the four largest tobacco companies in the United States. Among its provisions, the agreement prohibits tobacco advertising that targets people younger than 18 years of age. California becomes the first state to pass a comprehensive statewide smokefree air law.
1999	<ul style="list-style-type: none"> CDC releases <i>Best Practices for Comprehensive Tobacco Control</i> with recommendations for tobacco cessation activities at the state level.
2000	<ul style="list-style-type: none"> The U.S. Public Health Service issues the second clinical practice guideline on <i>Treating Tobacco Use and Dependence</i>.
2002	<ul style="list-style-type: none"> The Joint Commission (on Accreditation of Healthcare Organizations) adds quality measures for treating tobacco dependence to accreditation requirements for hospitals. FDA approves the nicotine lozenge for over-the-counter use.
2003	<ul style="list-style-type: none"> NCI launches the smokefree.gov cessation website. University of California, San Francisco establishes the Smoking Cessation Leadership Center.
2004	<ul style="list-style-type: none"> USDHHS announces National Network of Quitlines; NCI's 1-800-QUIT-NOW portal becomes operational; and CDC begins to dedicate funding for state quitlines. The North American Quitline Consortium begins activities. The Surgeon General's report, <i>The Health Consequences of Smoking</i>, is released.
2006	<ul style="list-style-type: none"> The Surgeon General's report, <i>The Health Consequences of Involuntary Exposure to Tobacco Smoke</i>, is released. All 50 states, the District of Columbia, and Puerto Rico have publicly funded quitlines in place. Massachusetts implements an evidence-based, heavily promoted Medicaid cessation benefit. FDA approves varenicline for prescription use, making it the seventh FDA-approved cessation medication.
2007	<ul style="list-style-type: none"> The Multistate Collaborative for Health Systems Change is established.
2008	<ul style="list-style-type: none"> The U.S. Public Health Service issues the third clinical practice guideline on <i>Treating Tobacco Use and Dependence, 2008 Update</i>.
2009	<ul style="list-style-type: none"> Federal tax increase of \$0.62 per pack of cigarettes raises the federal tax to \$1.01 per pack of cigarettes. The <i>Family Smoking Prevention and Tobacco Control Act</i> is enacted.

Table 8.1 Continued

Year	Event
2010	<ul style="list-style-type: none"> • President Obama signs the <i>Patient Protection and Affordable Care Act</i> into law. The law includes important provisions that expand tobacco cessation benefits and establishes the Prevention and Public Health Fund, which provides funds to prevent and reduce tobacco use. • Recording the smoking status in the electronic health records of all patients 13 years of age and older becomes a required measure to track and report as part of the <i>Patient Protection and Affordable Care Act</i>. • The first tobacco control strategic action plan for the United States, <i>Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services</i>, is published.
2011	<ul style="list-style-type: none"> • OPM implements an evidence-based cessation benefit for federal employees. • NCI launches SmokefreeTXT, a cessation program administered via mobile text messaging.
2012	<ul style="list-style-type: none"> • The Joint Commission's set of tobacco cessation measures for hospitals is strengthened to define required components of evidence-based treatment for tobacco dependence and becomes available for voluntary adoption by hospitals. • CDC launches <i>Tips From Former Smokers</i>, the first federally funded, national tobacco education campaign. • The University of California, San Diego, launches the Asian Smokers' Quitline.
2013	<ul style="list-style-type: none"> • NCI and CDC launch 1-855-DEJELLO-YA portal for Spanish speakers.
2014	<ul style="list-style-type: none"> • The Surgeon General's report <i>The Health Consequences of Smoking—50 Years of Progress</i> is released. • CDC publishes a new edition of <i>Best Practices for Comprehensive Tobacco Control Programs</i> that includes updated recommendations for tobacco cessation activities at the state level. • The U.S. Departments of Labor, Health and Human Services, and the Treasury issue subregulatory guidance that clarifies the tobacco cessation coverage requirements in the <i>Patient Protection and Affordable Care Act</i>. • Major components of the <i>Patient Protection and Affordable Care Act</i> are implemented, including new health insurance options and requirements that most private health plans must cover preventive services, including a comprehensive quit smoking benefit. As part of another key component, Medicaid is expanded to provide a comprehensive quit smoking benefit to millions of low-income Americans.
2015	<ul style="list-style-type: none"> • The U.S. Preventive Services Task Force issues updated recommendations for tobacco cessation. • CDC launches the 6/18 initiative, partnering with healthcare purchasers, payers, and providers to improve health and control costs. The initiative focuses on the reduction of tobacco use, which is a costly health condition with proven interventions.
2017	<ul style="list-style-type: none"> • Inpatient psychiatric facilities are required, as part of the Inpatient Psychiatric Facility Quality Reporting program, to report on the Joint Commission's set of tobacco cessation measures for hospitals.
2018	<ul style="list-style-type: none"> • FDA launches the <i>Every Try Counts</i> media campaign that encourages smokers to quit smoking.

Notes: **CDC** = Centers for Disease Control and Prevention; **FDA** = U.S. Food and Drug Administration; **NCI** = National Cancer Institute; **OPM** = Office of Personnel Management; **USDHHS** = U.S. Department of Health and Human Services.

described in the national action plan (USDHHS 2014). The report concluded that, “Comprehensive tobacco control programs and policies have been proven effective for controlling tobacco use. Further gains can be made with the full, forceful, and sustained use of these measures” (USDHHS 2014, p. 7). The evidence outlined in this Surgeon General's report reinforces that conclusion and provides compelling evidence related to the successes of these measures in the context of cessation:

- More than three out of every five U.S. adults who were ever cigarette smokers have quit smoking;
- More than two-thirds of U.S. adult cigarette smokers report interest in quitting cigarette smoking; and
- The majority of adult cigarette smokers in the United States have tried to quit during the past year, and

the percentage who have tried to quit has increased slowly over the past two decades.

However, several key findings of this report highlight the tragic public health history of tobacco use in this country, including the continued legacy of millions of lives prematurely lost from this deadly and completely preventable health risk factor:

- Each year, less than 1 in 10 U.S. adult cigarette smokers successfully quits smoking (defined as being quit for at least 6 months at the time of the survey interview);
- Disparities in cessation remain by age, race/ethnicity, educational attainment, socioeconomic status, healthcare insurance coverage, geography, and other factors;

- Interest in quitting is declining among high school students who are smokers, and the proportion who made a quit attempt during the past year has decreased over the past two decades;
- Support to quit smoking, in the form of advice from health professionals and assistance from clinicians, remains inadequate; and
- More than two-thirds of adult cigarette smokers in the United States who tried to quit during the past year did not use evidence-based cessation counseling or medication.

Despite progress over the past half century, challenges persist with regard to ensuring that the risks of cigarette smoking and the benefits of cessation are addressed by implementing evidence-based strategies in a timely manner and by sustaining these strategies over time. In 2000, Surgeon General Dr. David Satcher acknowledged a recurring theme that still plagues the tobacco control movement today: “Our lack of greater progress in tobacco control is more the result of failure to implement proven strategies than it is the lack of knowledge about what to do” (USDHHS 2000). To that end, several advances have been made to better understand the immediate and long-term benefits of smoking cessation and of effective cessation interventions. However, these strategies have not necessarily been implemented in a timely, equitable, and sustainable manner (USDHHS 2014). The comprehensive body of scientific evidence that has emerged since the first Surgeon General’s report on cessation nearly three decades ago (USDHHS 1990) makes it even more important that we act on this knowledge and immediately implement effective cessation strategies.

When first introduced in the U.S. marketplace in the mid-1980s and early 1990s, nicotine replacement therapy (NRT) was available only by prescription (USDHHS 1990; *JAMA: the Journal of the American Medical Association* 2000). However, a growing body of scientific evidence on the safety of NRT led the U.S. Food and Drug Administration (FDA) to make certain NRT products available over the counter. In 1996, FDA approved the transition of certain NRT products from being available by prescription only to being available over the counter to enhance their availability and use (*JAMA: the Journal of the American Medical Association* 2000). In the same year, the U.S. Agency for Health Care Policy and Research formally recommended that NRT be part of standard care for every adult smoker (Fiore et al. 1996).

As evidence on the efficacy of tobacco cessation interventions continued to grow, the U.S. Public Health Service (*JAMA: the Journal of the American Medical Association*

2000) released *A Clinical Practice Guideline for Treating Tobacco Use and Dependence*. As noted in the guideline, a considerable increase in research during the previous two decades had clarified the nature of tobacco dependence as a chronic disease, the addictive nature of nicotine, and the availability of multiple effective behavioral counseling and pharmacological strategies for treating tobacco use and dependence (*JAMA: the Journal of the American Medical Association* 2000). Based on this evidence, the guideline provided specific recommendations regarding brief and intensive tobacco cessation interventions, as well as systems-level changes designed to promote the assessment and treatment of tobacco use. These recommendations were updated in *Treating Tobacco Use and Dependence: 2008 Update* (Fiore et al. 2008). The 2008 guideline concluded that “tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit” (Fiore et al. 2008, p. vi). It provided healthcare professionals with additional effective treatment strategies that had not been identified in the 2000 guideline, such as stronger evidence on the effectiveness of counseling, evidence that quitline counseling is effective, and recommendations related to the efficacy of all seven first-line pharmacotherapies that are approved by FDA for smoking cessation. These seven medications include five nicotine-based medications (the nicotine patch, gum, lozenge, nasal spray, and oral inhaler) and two non-nicotine oral medications (bupropion and varenicline). Of note, the 2008 guideline also reinforced the increasing body of evidence demonstrating that the successful implementation of nicotine dependence treatment strategies depends on support from the healthcare system in which the strategies are embedded. To that end, the guideline presented new evidence about the critical role the healthcare system plays in increasing the likelihood that clinicians consistently identify and intervene with smokers and that smokers receive and use effective nicotine dependence treatments and successfully quit. The 2008 guideline also underlines the failure to fully implement proven tobacco cessation interventions: “Indeed, it is difficult to identify any other condition that presents such a mix of lethality, prevalence, and neglect, despite effective and readily available interventions” (Fiore et al. 2008, p. 12).

In 2009, following the release of the 2008 guideline, landmark advancements helped to shape the regulatory landscape for tobacco products in the United States. In June 2009, the *Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act)* gave, for the first time in history, FDA the authority to regulate the manufacturing, marketing, and sale of tobacco products. The statute empowered FDA to regulate tobacco products in a manner that is “appropriate for the protection of public health” (*Tobacco Control Act* 2009, §907(a)(3)(A)), which

was an unprecedented and critical departure from the standard of safety and efficacy that had governed the regulation of human drugs and medical devices. For example, the *Tobacco Control Act* gives FDA the authority to promulgate regulations respecting the construction; components; ingredients; additives; constituents, including smoke constituents; and properties of cigarettes, but the Act prohibits the agency from reducing nicotine yields in these products to zero. The Act also requires FDA to consider the individual- and population-level health effects of its regulatory actions, including their impact on cessation. Despite these provisions, FDA has faced some legal challenges (Public Health Law Center 2019). Nonetheless, FDA authority over tobacco products has been, and continues to be, an instrumental lever to reduce tobacco use and its harms using a population-based standard. Ongoing FDA actions related to this authority have the potential to advance population-based cessation efforts, including

- Regulating existing tobacco products and their constituents;
- Conducting a premarket review of new tobacco products before they can be introduced into the marketplace;
- Evaluating modified risk claims and products and requiring premarket testing and postmarket surveillance to evaluate the potential consequences of introducing these products into the marketplace;
- Educating the public about the harms of tobacco products (Zeller 2012; USDHHS 2014).

In March 2010, the *Patient Protection and Affordable Care Act (Affordable Care Act)* (2010) was signed into law. In the context of cessation, the law

- Requires most private insurance plans and all Medicaid expansion plans to cover in-network tobacco cessation with no cost-sharing;
- Requires state Medicaid programs to cover all seven FDA-approved tobacco cessation medications;
- Requires states to provide a comprehensive cessation benefit, including coverage of cessation counseling and medication, for pregnant women enrolled in Medicaid; and
- Provides Medicare beneficiaries with an annual wellness visit that includes referrals for tobacco cessation services.

By contributing to improved Medicaid and private cessation coverage and increasing the number of smokers who have insurance coverage, the *Affordable Care Act* has increased smokers' access to proven cessation treatments, which will improve their chances of quitting (McAfee et al. 2015). Specifically, the Act requires Grade A or B recommendations from the U.S. Preventive Services Task Force to be covered without cost-sharing. Since the implementation of the *Affordable Care Act*, some progress has occurred in traditional state Medicaid coverage of proven tobacco cessation treatments: The number of states covering individual and group counseling and all seven FDA-approved cessation medications increased from 7 states at the end of 2008 to 15 states at the end of 2018, and the number of states covering all seven FDA-approved cessation medications increased from 20 states at the end of 2008 to 36 states at the end of 2018. However, cessation coverage still falls short of a comprehensive benefit across all 50 states and the District of Columbia, and nearly all states retain barriers—such as prior authorization, duration limits, and copayments—that make it difficult for Medicaid enrollees to access cessation treatments (DiGiulio et al. 2018).

Effective August 2016, FDA finalized a rule that extended its regulatory authority to all tobacco products, except for accessories of newly deemed products, including electronic cigarettes (e-cigarettes), cigars, hookah and pipe tobacco, and future tobacco products, as part of its goal to improve public health. Known as the “deeming rule,” the rule makes these products subject to regulatory requirements imposed by or authorized under the *Tobacco Control Act*, including federal prohibition on free sampling for most tobacco products, federal requirements for health warnings, and the requirement that tobacco manufacturers register with FDA and seek the agency's review of new tobacco products (FDA 2018a). Of important note, the deeming rule does not preempt states and localities from implementing laws related to tobacco product sales, use, distribution, and advertising, as long as the laws are in addition to, or more stringent than, the requirements of the *Tobacco Control Act* (FDA 2018a). Expanding the diversity of tobacco products under the regulatory jurisdiction of FDA enhanced the agency's ability to effectively regulate these products in a manner that is appropriate for the protection of public health, as directed by the U.S. Congress. As was concluded in the 50th anniversary Surgeon General's report, “The burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products” (USDHHS 2014, p. 7), thus reinforcing the importance of regulatory actions to address the variety of combustible tobacco products being sold and used in the United States. The report further noted that “the cigarette is also a defective product, meaning not just dangerous but unreasonably dangerous,

killing half of its long-term users” (Proctor 2013, p. i27, as cited in USDHHS 2014). The report also noted that a variety of noncombustible and electronic tobacco products with the potential for modified risk are being developed and aggressively marketed. Further, it noted that the shift in patterns of tobacco use could have several potential impacts, ranging from the positive effect of accelerating the rates of complete cessation among adult smokers to the negative effects of delaying cessation and diminishing progress in reducing the use of all forms of tobacco products, especially among youth and young adults. However, the impact of these products on population health is considerably more likely to be beneficial in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combustible tobacco products are being rapidly reduced and effectively regulated, most notably among youth and young adults (USDHHS 2014).

These major developments in the federal regulatory landscape since the release of the last Surgeon General’s report on cessation in 1990, coupled with the extensive and growing body of science documenting evidence-based clinical and population-based strategies for reducing tobacco use and motivating and helping tobacco users to quit, have created a strong foundation for achieving success in helping the nation’s 34 million adult cigarette smokers quit for good. Increased implementation of proven tobacco

control strategies would accelerate progress; however, the present levels of implementation of these strategies are unacceptably low and fall well below optimally effective levels based on the existing body of scientific evidence. Of particular note, state funding for tobacco control programs has been declining for more than a decade (CDC 2014; Campaign for Tobacco-Free Kids 2018); this funding includes support for state cessation interventions, which is one of CDC’s five recommended components of a comprehensive state tobacco control program (CDC 2014). For example, in fiscal year 2019, states will collect \$27.3 billion from taxes and payments as a result of the tobacco Master Settlement Agreement of 1998. However, states will spend just 2.4% of this revenue—\$655 million—on tobacco control programs, including efforts to help smokers quit (Campaign for Tobacco-Free Kids 2018). The enormous health and financial burden of smoking-attributable disease, disability, and death in the United States will continue for decades unless comprehensive, meaningful, sufficiently funded, and evidence-based actions take hold at the national, state, and local levels. Although the nation is on the cusp of reaching the *Healthy People 2020* objective of reducing the prevalence of smoking among adults 18 years of age and older to 12.0% (Wang et al. 2018), more can and should be done to help implement the proven interventions that are readily available.

Present: Health Benefits of Cessation

Even more than 50 years after the first Surgeon General’s report on smoking, the number of diseases and other adverse health effects caused by smoking continues to grow as the available scientific evidence has expanded with time (U.S. Department of Health, Education, and Welfare 1964; USDHHS 2004, 2010, 2014). The conclusions in earlier Surgeon General’s reports on tobacco use have focused primarily on causal associations between smoking and increased risk of disease and other adverse health outcomes, largely because of the lack of a sufficient body of scientific evidence at the time on the link between smoking cessation and decreased risk of such outcomes. The 1990 report was the first Surgeon General’s report to comprehensively synthesize the available scientific evidence on the health benefits of smoking cessation. That report concluded that smoking cessation has major and immediate health benefits for men and women of all ages (USDHHS 1990). Specifically, the report concluded that compared with continued smoking, smoking cessation reduces rates of respiratory symptoms and respiratory infections, such as bronchitis and pneumonia. The report also reached conclusions related to the short- and

long-term benefits of cessation. For example, smoking cessation improves pulmonary function by about 5% in only a few months after quitting smoking. Moreover, with sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers, and mortality rates from chronic obstructive pulmonary disease decline among former smokers compared with rates among persons who continue to smoke (USDHHS 1990). This report expands on the findings of the 1990 report, reaching several important new conclusions about the specific health benefits of smoking cessation, including

- Smoking cessation benefits persons at any age, but the benefits are greater at younger ages compared with older ages;
- Smoking cessation improves well-being, including higher quality of life and improved health status;
- Smoking cessation reduces the risk of the following cancers: lung, larynx, oral cavity and pharynx,

esophagus, pancreas, bladder, stomach, liver, cervix, kidney, colorectal, and acute myeloid leukemia;

- Smoking cessation substantially reduces the risk of coronary heart disease among men and women of all ages and reduces risk of morbidity and mortality from stroke and cardiovascular diseases; and
- Smoking cessation by pregnant women benefits their health and that of their fetuses and newborns.

In addition to significant health benefits to individual smokers and society, smoking cessation also has considerable economic benefits. Smoking cessation can reduce the costs of smoking for individual smokers, health systems, and society. Moreover, the report finds that smoking cessation interventions are cost-effective. The report documents an array of effective clinical and health systems interventions for increasing smoking cessation and treating tobacco use and dependence:

- Behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment.
- Behavioral counseling and cessation medications are each effective alone in treating tobacco use and nicotine addiction but are most effective when used in combination.
- Combination pharmacotherapy, including combining short- and long-acting forms of NRT, increases smoking cessation compared with the use of single forms of NRT.
- Tobacco quitline counseling increases smoking cessation, when provided alone or in combination with medication.
- Insurance coverage of cessation interventions that are comprehensive, barrier-free, and evidence-based increases the availability and utilization of treatment services for smoking cessation.

This report further reinforces the importance of interventions promoting cessation at the individual and population levels. Specifically, actions at the clinical and health system levels are typically designed to integrate tobacco cessation interventions into routine clinical care, increase the use and effectiveness of smoking cessation treatments, or directly help smokers quit. However, such interventions should not function in isolation. Instead, they should complement population-based interventions that have already been shown in multiple previous

Surgeon General's reports (USDHHS 2004, 2014) and other major reports to reduce tobacco use and tobacco-related morbidity and mortality. Given the critical importance and impact of population-based interventions in combating the tobacco use epidemic, King and Graffunder (2018) described the importance of such strategies in the context of a "tobacco control vaccine," whose ultimate impact on public health is contingent on its combination of individual components (including a "cessation access" component), robust population-level protection, and the extent to which these components are supported and advanced by key stakeholders at an adequate dose. In addition to preventing initiation of tobacco product use, population-based interventions can also influence cessation at a macro level by motivating tobacco users to quit and by providing an environment that makes it easier for them to do so (CDC 2014). Although previous Surgeon General's reports have documented the efficacy of these interventions for reducing tobacco use, this is the first Surgeon General's report to document the impact of such interventions on smoking cessation:

- Increasing the price of cigarettes reduces cigarette consumption, reduces the prevalence of smoking, and increases smoking cessation;
- Mass media campaigns increase the number of calls to quitlines and increase smoking cessation;
- Smokefree policies lead to decreased prevalence of smoking, decreased cigarette consumption, and increased smoking cessation among adults; and
- Comprehensive state tobacco control programs reduce the prevalence of smoking and increase smoking cessation.

Predictive models described in this report show that evidence-based tobacco control policies can yield substantial reductions in the prevalence of smoking. Moreover, cessation treatment policies and other policies—including tax increases, smokefree laws, and media campaigns—have complementary effects by increasing quit attempts and improving quitting success. Taken together, the preponderance of available data on the benefits of cessation and the efficacy of available clinical and population-based interventions reinforces the importance of a comprehensive approach to promoting tobacco cessation in the United States. While acknowledging the importance of the individual components, it is critical to recognize that these individual components must work together synergistically to most effectively prevent initiation of tobacco use and promote cessation (CDC 2014; USDHHS 2014).

Future: Ending the Tobacco Use Epidemic

Progress and Challenges

Tobacco use could remain the leading cause of preventable disease, disability, and death in the United States unless the prevalence of tobacco use, especially use of combustible products, is reduced more rapidly than the current trajectory (USDHHS 2014). Such reductions will require coordinated efforts to prevent initiation of tobacco use and nicotine addiction among young people and to create an environment that promotes and supports cessation among current tobacco users (USDHHS 2014). Considerable progress has been made but more can be done—and with enhanced expediency. To end the tobacco use epidemic, the evidence-based strategies articulated in this report must be implemented fully and sustained with sufficient intensity and duration. If this does not happen, nearly half a million Americans will continue to die each year from smoking-related diseases and exposure to secondhand smoke, and millions of Americans will continue to live with serious smoking-related diseases, costing society hundreds of billions of dollars in smoking-attributable healthcare expenditures and lost productivity (USDHHS 2014).

Challenges remain to accomplish the goal of a society free of tobacco-related death and disease. For example, marked disparities exist in the use of tobacco products, and some subpopulations face a considerably higher burden of tobacco use and tobacco-associated morbidity and mortality. Use of tobacco products remains higher among males, middle-aged adults, American Indians/Alaska Natives, persons with lower levels of education, persons living below the poverty level, persons living in the Midwest and South, persons with no health insurance or who are insured through Medicaid, sexual and gender minorities, persons with disabilities, and persons with behavioral health conditions (Wang et al. 2018). Additionally, as noted in this report, marked disparities in cessation persist across population groups. Disparities also persist regarding access to and use of proven cessation treatments (National Cancer Institute [NCI] 2017). The prevalence of key indicators of cessation—quit attempts, advice to quit from a health professional, and access to cessation therapies—varies across populations, with lower prevalence among some vulnerable subgroups. For example, uninsured smokers and Hispanic smokers are less likely than their respective counterparts to report receiving advice to quit from a health professional; uninsured smokers, Hispanic smokers, and gay/lesbian/bisexual smokers are less likely than their counterparts to report using cessation counseling and/or medication as part of a quit attempt (Babb et al. 2017). To eliminate tobacco-related disparities,

tobacco control programs and policies, including barrier-free access to cessation treatments, must be implemented in a way that achieves equitable benefits for all (CDC 2014). Such efforts would ultimately enhance access to effective cessation treatments and accelerate the decline in the prevalence of smoking across all population groups, thus alleviating the disproportionate health and economic burden experienced by vulnerable population groups (CDC 2014; NCI 2017).

Disparities in tobacco use and cessation are compounded by the fact that the tobacco industry continues to aggressively market and promote addictive and lethal products with the goals of retaining current users of these products and of recruiting new consumers, including youth and young adults (USDHHS 2012). Such marketing and promotional activities, including decades of coordinated efforts targeting various vulnerable population groups, have contributed to the disparities in cigarette smoking and cessation that exist in the United States (USDHHS 1998, 2014; NCI 2008, 2017). The 50th anniversary Surgeon General's report further underscored the deceptive nature of the tobacco industry's efforts, reaching the following major conclusion: "The tobacco epidemic was initiated and has been sustained by the aggressive strategies of the tobacco industry, which has deliberately misled the public on the risks of smoking cigarettes" (USDHHS 2014, p. 7).

The landscape of tobacco products continues to evolve to include an array of combustible, noncombustible, and electronic products (Cullen et al. 2018; Wang et al. 2018). For example, heated tobacco products have recently reentered the U.S. marketplace, with IQOS being authorized by FDA for sale in April 2019 (FDA 2019). More research is needed to better understand the long-term health effects of heated tobacco products. Although preliminary data from the tobacco industry suggest certain heated tobacco products generally have lower levels of harmful ingredients than conventional cigarettes (St. Helen et al. 2018), concerns remain around sustained dual use of heated products and conventional cigarettes, youth initiation, and the limited number of independent studies assessing the constituents in these products and the potential population-level health risks (Leigh et al. 2018; Max et al. 2018; McKelvey et al. 2018; Nabavizadeh et al. 2018). At present, data are not available on the long-term health effects of these products.

The continued diversification of the tobacco product landscape could have several different potential impacts, ranging from accelerating the rates of complete cessation among adult smokers to delaying cessation and

diminishing progress in reducing the use of all forms of tobacco products among youth and young adults (USDHHS 2014). Moreover, as the landscape of tobacco products continues to evolve, so does the tobacco industry. For example, during the past decade, three categories of e-cigarette brands have emerged in the U.S. market: brands developed by cigarette manufacturers, brands that were ultimately acquired by cigarette manufacturers, and brands that have no affiliation with cigarette manufacturers (USDHHS 2016). In recent years, the majority of e-cigarettes sold in traditional retail stores are those manufactured by major cigarette companies (King et al. 2018). More recently, the tobacco industry has also made more prominent efforts to acquire a stake in e-cigarette companies not previously affiliated with the traditional tobacco industry. For example, in December 2018, Altria Group, the parent company of Philip Morris USA, purchased a 35% stake in JUUL Labs, the maker of the most commonly sold e-cigarette in the United States (Altria Group 2018).

The increasing availability and use of novel tobacco products, most notably e-cigarettes, raise questions about the potential impact that such products could have on efforts to eliminate the individual- and population-level disease and death caused by tobacco use. However, when considering the impact of e-cigarettes on public health, it's critical to acknowledge their potential benefits and their potential risks, including the recognition that population-level increases in youth using e-cigarettes and becoming addicted to nicotine could offset any potential benefits realized among adult smokers using these products to quit. Additionally, e-cigarette, or vaping, product use may be associated with other health risks beyond youth initiation and use. For example, CDC, FDA, state and local health departments, and public health and clinical partners have been investigating a multistate outbreak of e-cigarette, or vaping, product use associated lung injury (EVALI) (Siegel et al. 2019). The latest national and state findings show e-cigarette, or vaping, products containing THC—particularly those from informal sources, such as friends, family, or in-person or online dealers—are linked to most of the cases of lung injury and play a major role in the outbreak (Moritz et al. 2019; Navon et al. 2019). In particular, vitamin E acetate is closely associated with EVALI (Blount et al. 2019). Vitamin E acetate has been identified in several tested products used by EVALI patients, and has been identified in bronchoalveolar lavage (BAL) fluid samples from 48 of 51 assessed EVALI patients, but not in the BAL fluid from a control group. However, as of January 2020, evidence is not yet sufficient to rule out the contribution of other chemicals of concern among some EVALI patients.

The *Tobacco Control Act* is governed by a requirement to protect the overall public health. Such a

population-level public health standard is essential because exposure to harmful toxicants from e-cigarettes at the individual level could adversely affect public health at the population level by (a) increasing initiation of e-cigarette use and nicotine addiction among vulnerable populations, including young people, and (b) increasing the number of adult users of both combustible tobacco products and e-cigarettes (i.e., dual users) without necessarily increasing the number of successful adult quitters. Weighing the relative benefits and risks to individuals and the population as a whole is essential when considering the potential role that any noncombustible tobacco product may play in reducing the occurrence of smoking-attributable disease and death (USDHHS 2014). E-cigarettes could help individual adult smokers if they completely switch from conventional cigarettes to e-cigarettes. Among those who have transitioned completely, the ultimate goal should be to also quit the use of e-cigarettes completely to achieve the maximal individual and public health benefit. However, at the population level, any potential benefits these products confer in terms of increasing cessation among adult smokers would need to outweigh potential risks related to increased initiation of tobacco product use among youth (USDHHS 2014). E-cigarette use among U.S. high school students increased 78% during 2017–2018, as 1 in 4 high school students reported currently using e-cigarettes in 2019 (Cullen et al. 2019). This increase coincided with the growing popularity of e-cigarettes shaped like a USB flash drive, including JUUL (King et al. 2018; Gentzke et al. 2019). Many of these e-cigarettes deliver nicotine in the form of nicotine salts, which allow users to inhale particularly high levels of nicotine more easily and with less irritation than the freebase nicotine that is used traditionally in tobacco products, including older generation e-cigarettes (USDHHS 2018). These high levels of nicotine introduce additional population-level risks because nicotine is extremely addictive, can harm the developing brain in adolescents, and can prime the brain for addiction to other drugs (USDHHS 2016).

It is also critical to acknowledge that for e-cigarettes or other noncombustible tobacco products to be effective harm-reduction tools, they must help smokers completely quit conventional cigarettes. Specifically, users must transition completely from combustible tobacco products to lower risk alternatives in order to realize a reduction in risk at the individual level. As noted in the major conclusions of this report, e-cigarettes, a continually changing and heterogeneous group of products, are used in a variety of ways; and there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation. Moreover, the available evidence indicates that a majority of e-cigarette users also smoke conventional cigarettes—a pattern of use that does not confer a substantial

risk reduction benefit to the individual (USDHHS 2014; Goniewicz et al. 2018). However, the number and scientific rigor of studies on e-cigarettes and smoking cessation among adults continue to increase (Hajek et al. 2019), and a growing body of scientific evidence suggests that multiple factors related to e-cigarettes—including product type, frequency of use, and efficiency of nicotine delivery—could affect the efficacy of these products for successful smoking cessation. Of note, the diversification of the e-cigarette landscape is especially important to consider in the context of cessation efficacy, as various aspects of these products—including their ability to efficiently deliver nicotine to the user—have evolved with each generation of e-cigarette product that has entered the marketplace. For example, although justifiable concerns exist that nicotine salts could promote initiation of e-cigarette use among youth, this new product formulation also has the potential to enhance the dose and efficiency with which nicotine is delivered to adult smokers who may be attempting to quit smoking, thus potentially increasing the likelihood that they are able to transition completely to e-cigarettes. However, this formulation could also make it more difficult for those who fully transition to e-cigarettes to eventually quit using these products completely.

Studies on the relationship between e-cigarettes and smoking cessation continue to emerge, including randomized clinical trials that will be critical to providing a comprehensive and evidence-based understanding of this topic. When considering current and future studies on e-cigarettes, it is important to note that findings may not be generalizable to all settings, including smokers who have different levels of dependency than those included in the reported research; smokers who try or use e-cigarettes for reasons other than quitting smoking; and smokers who live in countries that have different policy and regulatory environments, including limitations on the amount of nicotine permitted in e-cigarettes and restrictions on e-cigarette advertising and marketing. Also, e-cigarettes are not a uniform product category; the generalizability of research on their efficacy for smoking cessation is complicated by the diversity of products available, the volatile nature of the marketplace, and the extent to which the products can be modified by the user—including modifications that affect the level of nicotine the products deliver. More longitudinal research is needed on the long-term health effects of using e-cigarettes and on the effects of e-cigarette use on cessation, including research addressing internal validity and generalizability to real-world usage. Additionally, given the volatility of the e-cigarette landscape, including the introduction of nicotine salts, research on different types of e-cigarette products and frequency of use is essential.

As studies on e-cigarettes and cessation continue to emerge, it is critical that public health recommendations be based on a robust and scientifically rigorous evidence base that takes into account the potential detrimental impacts that the widespread availability and promotion of e-cigarettes for cessation could have on youth initiation of e-cigarettes, as well as other tobacco products (USDHHS 2016). When considering public health, in order for a net gain to occur, any benefit of e-cigarette use among adult smokers would have to outweigh the risks of increased initiation among young people at the population level.

End-Game Strategies

Faced with the challenge of realizing the vision of a society free of tobacco-related death and disease, and especially given the increasing variety of tobacco products in the marketplace, the patterns of use of these products among adults and youth, and the changing demographics of users of these products, the 50th anniversary Surgeon General's report summarized several potential end-game strategies and emphasized those judged most relevant for the United States (Table 8.2) (USDHHS 2014). These proposed strategies, in conjunction with the accelerated implementation of proven tobacco control interventions, are intended to end the epidemic of disease and premature death caused by tobacco use. The development of various end-game strategies by scholars around the world has taken place in the absence of a broad consensus on how to define the *end* related to tobacco. For example, some end-game strategies have focused on the elimination of all tobacco use and the use of any nicotine-containing products, including e-cigarettes; others have focused on eliminating the use of combustible tobacco products because to date, these products have been responsible for the overwhelming burden of death and disease caused by tobacco use (USDHHS 2014). Nonetheless, there is generally broad recognition and consensus that the overriding objective is to maximize health (USDHHS 2014).

Benowitz and Henningfield (1994) made one of the first end-game proposals, describing a policy approach of gradually reducing the levels of nicotine content in cigarettes to nonaddictive levels, so as to prevent the development of nicotine addiction in youth. The authors also noted that this strategy could increase the likelihood that adult smokers would stop smoking—as cigarettes would become “less satisfying.” In the decades since that 1994 publication, several studies have assessed the potential impact of experimental very-low-nicotine-content cigarettes on adult smokers. Based on these studies, this report finds that reducing the level of nicotine content in cigarettes could have the potential to reduce smoking:

Table 8.2 Potential end-game strategies discussed in the 50th anniversary Surgeon General’s report, 2014

Potential end-game strategy	Description
Reduce nicotine yield in cigarettes and other tobacco products	Use government regulations to gradually reduce the level of nicotine in cigarettes, and possibly other tobacco products, to nonaddictive levels
Reduce toxicity in tobacco products	Implement regulatory standards that require manufacturers to create tobacco products with very low toxicity
Gradually reduce the supply of tobacco products	Phase out over time the use of tobacco products via systematic reduction of supply to zero or to some other minimal level
Prohibit the sale of tobacco products to future generations	Prohibit the sale of tobacco products to persons born after a specific date, essentially creating tobacco-free cohorts that progressively increase in coverage and size over time
Prohibit cigarettes and/or cigarettes and other tobacco products	Prohibit the production and sale of cigarettes and possibly other types of tobacco products
Sell tobacco products through a not-for-profit agency	Transfer control of the supply and sales of tobacco products to a not-for-profit agency that has the goal of reducing consumption

Sources: Benowitz and Henningfield 1994, 2013; Borland 2003, 2013; Callard et al. 2005a,b; Daynard et al. 2010; Hatsukami et al. 2010, 2012, 2013; Khoo et al. 2010; Thomson et al. 2010; Proctor 2011, 2013; Berrick 2013; Callard and Collishaw 2013; Wilson et al. 2013; USDHHS 2014.

The evidence is suggestive but not sufficient to infer that very-low-nicotine-content cigarettes can reduce smoking and nicotine dependence and increase smoking cessation when full-nicotine cigarettes are readily available; the effects on cessation may be further strengthened in an environment in which conventional cigarettes and other combustible tobacco products are not readily available.

Moreover, a simulation model by Apelberg and colleagues (2018) suggested that if conventional cigarettes were not available, lowering the level of nicotine content in cigarettes to minimally addictive levels in the United States would decrease the prevalence of cigarette smoking to 1.4% by 2060, prevent 16 million people from initiating smoking, and avert an estimated 2.8 million tobacco-related deaths. Of all end-game strategies proposed to date, nicotine reduction has received the greatest interest and attention in the United States, in part because the regulatory structure required to implement it is already in place and is explicitly articulated in the *Tobacco Control Act*. In 2018, FDA issued an advance notice of proposed rulemaking that specifically requested data and other information to inform a potential tobacco product standard to reduce nicotine in cigarettes to minimally addictive or nonaddictive levels for the protection of public health (*Federal Register* 2018; FDA 2018a). The *Tobacco Control Act* gives FDA several tools to regulate cigarettes, including the ability to establish product standards, which could include reducing nicotine content to levels so low that they would be insufficient to cause or sustain nicotine addiction, but the Act expressly prohibits FDA from requiring the reduction of nicotine yields of

cigarettes to zero. However, questions of potential interest related to a standard could include whether such a nicotine standard would lead to smokers inhaling more deeply to compensate for the reduced nicotine yield; would lead to illicit trade in products with higher nicotine yield; and would impact vulnerable populations with higher rates of smoking, such as those with mental illness and substance use disorders (USDHHS 2014; Gottlieb and Zeller 2017).

In addition to a potential standard around the level of nicotine content, several other end-game proposals also have the potential to contribute to increases in smoking cessation and reductions in the disease and premature death caused by tobacco. For example, strict standards for ingredients in tobacco products could be established to make some or all tobacco products less toxic and less appealing, particularly to young people (Table 8.2). The *Tobacco Control Act* authorizes FDA to implement product standards to control levels of chemicals and other ingredients in tobacco products or their emissions for the protection of public health (USDHHS 2014). Other potential end-game strategies could aim to reduce the supply of tobacco products, which could also influence cessation among current users of such products, or to prohibit the sale of cigarettes and/or other tobacco products. Although the *Tobacco Control Act* prohibits FDA from banning the sale of cigarettes, it does authorize the agency to set standards for tobacco products that could significantly impact the marketing of tobacco products. Specifically, the act allows FDA to issue a product standard to prohibit menthol in cigarettes, or any other tobacco product, to protect public health. Moreover, the *Tobacco*

Control Act does not preempt states and localities from prohibiting the sale of cigarettes or other tobacco products. However, other factors may preclude such actions, including state constitutions or other state laws, which could prevent the implementation of such measures at the local level. Additionally, prohibiting specific types of tobacco products (e.g., flavored tobacco products) could also impact population-level cessation. In November 2018, FDA indicated its intent to prohibit menthol in combustible tobacco products, prohibit flavored cigars, and prohibit flavored e-cigarettes (excluding tobacco and menthol flavors), except those sold in age-restricted, in-person locations (FDA 2018b). Several jurisdictions in California, Illinois, Massachusetts, Minnesota, New York, and Rhode Island have restricted the sale of flavored tobacco products, with some of these policies not exempting menthol flavors (Campaign for Tobacco-Free Kids 2019). Prohibiting flavors, including menthol, in tobacco products can benefit public health by reducing initiation among young people and promoting cessation among adults (USDHHS 2014). For example, studies show that a sizable portion of adults who smoke menthol cigarettes report that they would try to quit smoking if menthol cigarettes were prohibited (O'Connor et al. 2012; Pearson et al. 2012). In 2011, the Tobacco Product Scientific Advisory Committee (TPSAC) to the FDA conducted an extensive review of the state of the science on menthol, concluding that the “[r]emoval of menthol cigarettes from the marketplace would benefit public health in the United States” (TPSAC 2011, p. 225). Furthermore, FDA conducted a subsequent independent review of the science and concluded, “From the available studies, the weight of evidence supports the conclusion that menthol in cigarettes is likely associated with reduced success in smoking cessation, especially among African American menthol smokers” (FDA n.d., p. 6).

But end-game strategies cannot function in isolation and should not be seen as a panacea or as a substitute for the accelerated implementation of established population-based strategies. To that end, an integrated national tobacco control strategy is essential—one that is based on a foundation of enhanced implementation of the traditional strategies that have been shown to be effective, including taxation, smokefree policies, barrier-free cessation support, and hard-hitting mass media campaigns (USDHHS 2014; King and Graffunder 2018). The most feasible end-game strategies—such as reducing the nicotine content in cigarettes to make them less addictive and placing greater restrictions on sales of tobacco products, including prohibitions on entire categories of tobacco products—could then be integrated into this foundational platform (Van der Eijk 2015). Using this paradigm, a more aggressive implementation of the proven population-based interventions outlined in Chapter 7 would reinforce

cessation efforts nationally and enhance the feasibility and impact of end-game strategies.

The pursuit of an integrated strategy of accelerated implementation of proven interventions coupled with the introduction of novel end-game interventions is likely to encounter unique challenges (Isett 2013; Rabe 2013; Thomas and Gostin 2013). These challenges are likely to come from two key groups. The first group is those with a financial stake in the continued widespread use of cigarettes and other tobacco products, including the traditional tobacco industry and the emerging array of e-cigarette companies and related entities advocating for their interests (USDHHS 2014). The tobacco industry has an extensive history of attempting to influence decision makers to oppose evidence-based tobacco control strategies, and because local control is so integral to galvanizing evidence-based policies and shifting social norms, the tobacco industry and its allies have used strategies to preempt local smokefree laws and other types of tobacco control policies (USDHHS 2014). The second group is users of tobacco products and others who would be ideologically opposed to any policy or strategy that would jeopardize the availability and sale of cigarettes and other tobacco products and the ability of adults to obtain and consume these products (USDHHS 2014). However, innovation spurred by the proliferation of subnational policies has been a hallmark of tobacco control for decades, at times giving rise to approaches that have been emulated by practitioners in other disciplines. As noted in the 50th anniversary Surgeon General’s report, “It is important to remember that many policy innovations, once thought inconceivable, have now become the law of the land” (USDHHS 2014, p. 858). Just two decades ago, it would have been difficult to envision that more than half of U.S. states and more than 1,000 communities would be covered by comprehensive smokefree laws, and even a decade ago, most public health experts would not have predicted that more than a dozen states and several hundred communities would increase the legal age of sale for tobacco to 21 years of age (CDC 2018). Indeed, the profound and dynamic history of tobacco control over more than 50 years suggests that continued innovation is a key tenet of success. Therefore, the public health community must remain nimble and capable of evolving as quickly as the rapidly changing landscape of tobacco products. New developments and innovations will continue to occur, as has been the case for decades, but the public health community need not reinvent the wheel. Proven interventions can continue to be modernized with time. Additionally, new end-game strategies offer unprecedented opportunities to complement these interventions to end the epidemic of disease and premature death caused by tobacco use.

Advancing Cessation

As documented in Chapter 6, a comprehensive body of scientific evidence, which has grown stronger over time, supports the use of behavioral counseling and pharmacologic interventions for smoking cessation, with the combination of both being the most effective approach. Effective counseling interventions include an array of behavioral treatments that can be delivered effectively by a variety of qualified personnel in many formats, including individual, group, and telephone counseling. Additionally, emerging evidence suggests that text messaging and web interventions are also effective modalities for delivering cessation behavioral interventions. As documented in Chapter 5, strong evidence exists for the cost-effectiveness of both behavioral and pharmacologic tobacco cessation treatments. However, although more than half of current smokers try to quit each year, the success rate of these quit attempts remains low, and successful cessation is typically preceded by multiple prior attempts (Babb et al. 2017). Moreover, despite gains over the past three decades, both the reach and use of existing smoking cessation interventions also remain low, with less than one-third of smokers using behavioral and/or pharmacologic interventions when trying to quit. The current state of the cessation landscape in the United States underscores the fact that more can and should be done to help smokers quit for good.

Two factors drive the rate of cessation in the population: the rate of quit attempts and the rate of successful cessation among smokers who try to quit. Thus, increases in quit attempts and quit success rates can each drive increases in population-level cessation. Moreover, increasing the reach and intensity of cessation interventions can each increase the cessation rate in the population (CDC 2014). Of note, some strategies address only one of these factors, and others address both. For example, a mass media campaign can motivate more smokers to try to quit, and the development of a new, more effective cessation medication can increase the success rate for smokers who try to quit. In contrast, a mass media campaign that drives smokers to a quitline or a promotional campaign that drives smokers enrolled in Medicaid to take advantage of newly improved Medicaid cessation coverage in their state can (a) motivate more smokers to try to quit and (b) by connecting these smokers with proven cessation treatments, increase their chances of quitting successfully. Therefore, strategies that increase the rate of quit attempts and the rate of successful cessation are especially important.

As noted in this report, increasing quit rates requires several strategies that include increasing the appeal and reach of existing evidence-based interventions to smokers. Promising directions to increase appeal and reach could

include expanding treatment targets, leveraging emerging technologies to enhance the initial and sustained engagement of smokers in treatment, and accelerating the integration of cessation services across multiple platforms and in healthcare systems. Given shifts in the manner in which people communicate and obtain information, possible emerging technologies that could be considered include (a) mobile health platforms with applications that involve adaptive interventions that are tailored to the needs of each person and (b) social media and other applications that deliver behavioral treatment and improve adherence to medication.

In addition to enhancing the reach of behavioral support, the enhanced availability of generic versions of FDA-approved brand-name drugs could enhance access to and the reach of these medications, particularly with regard to increased affordability among persons in lower socioeconomic groups, who traditionally have high rates of smoking (Wang et al. 2018). It is anticipated that health insurers would be more likely to cover generic cessation medications with no or minimal barriers because generic medications are typically less expensive; this would increase the affordability of and access to these medications among smokers, especially low-income smokers. Additionally, Leischow (2019) proposed enhancing access to and the reach of proven pharmacotherapies by making varenicline and other prescription medications for smoking cessation available over the counter. The conversion of pharmacotherapies to over-the-counter medicines requires careful weighing of risks and benefits at the individual and population levels.

Increasing quit rates could also be achieved by increasing the effectiveness of existing interventions. Chapter 6 of this report concluded, “The evidence is sufficient to infer that combining short- and long-acting forms of nicotine replacement therapy increases smoking cessation compared with using single forms of nicotine replacement therapy.” Emerging evidence also suggests that combining varenicline with bupropion or NRT may be more effective than taking varenicline alone, particularly among heavy smokers. In addition, combination therapy involving bupropion and NRT has been shown to produce better outcomes than either medication used by itself. Reaching a better understanding of both behavioral and pharmacological interventions that can safely and effectively promote cessation among youth is becoming increasingly important because of the dearth of evidence on this issue and because of recent surges in e-cigarette use and frequency among youth, particularly products that utilize nicotine salts (USDHHS 2018).

Efforts can also be made to increase quit rates through the development of cessation interventions that have greater reach and/or effectiveness than existing

interventions or that appeal to and are used by different populations of smokers. For example, according to this report, evidence is suggestive but not sufficient to conclude that varenicline is effective for smoking cessation (Chapter 6). Varenicline is used for cessation in several Eastern European countries but is not yet approved by FDA for use as a cessation medication in the United States. More research is needed to further assess the safety and efficacy of varenicline for smoking cessation and its possible utility in the United States.

Similarly, more research is needed on the potential of using e-cigarettes as a smoking cessation aid, including determining what types of e-cigarettes and what aspects of use may maximize positive cessation outcomes and minimize adverse consequences, especially related to use among young people. Chapter 6 of this report concluded that the evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation. It also concluded that the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine, and the evidence is suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes. It is also important to note that the e-cigarette landscape continues to evolve, and existing research has not assessed newer types of e-cigarettes, including those that use nicotine salts. Such products may deliver nicotine content more efficiently and, therefore, may be more effective for smoking cessation than earlier generations of e-cigarettes. However, this formulation could also make it more difficult for those who fully transition to e-cigarettes to eventually quit using these products completely.

The aforementioned individual treatments for smoking cessation are necessary but not sufficient to fully achieve meaningful population-based cessation outcomes. As discussed in Chapter 7, these interventions are most effective when complemented by actions taken at the clinical and health systems levels to create environments that support the use of cessation treatments and successful cessation by smokers—including policies to transform systems of care to better address tobacco use and dependence, the promotion of evidence-based treatments for tobacco use and dependence, and the implementation of policies (e.g., covering all evidence-based cessation treatments; removing barriers to treatments, such as prior authorization; and promoting covered treatments to smokers and providers so that they are aware of and use these treatments) to increase smokers' access to clinical interventions and cessation treatments that could help them quit. Although considerable progress has been made to integrate nicotine dependence treatment into clinical

health systems over the past several decades, substantial opportunities for improvement remain, for example:

- Embedding policies and protocols for tobacco use screening and interventions into the clinical workflow;
- Embedding prompts, decision support, and documentation tools into health records, including electronic health records; and
- Distributing specific components of the intervention across the broader healthcare team to reduce the burden on time-constrained physicians and to reinforce the importance of cessation to patients.

Because cigarette smoking remains high and quitting smoking may be more difficult among certain subpopulations in the United States, including persons of lower socioeconomic status and those with comorbid mental health and other substance use disorders (Wang et al. 2018), specific types of healthcare providers or clinical environments could become increasingly important in promoting cessation and delivering targeted cessation support. In addition to policies that seek to make the delivery of clinical cessation interventions in health systems more consistent and routine, policies that remove cost and other barriers to access for patients are also essential to increase the delivery and utilization of nicotine dependence treatment, especially when barrier-free coverage is well promoted to health plan beneficiaries. Timely and relevant clinical guidelines and clinical quality measures also play critical roles in ensuring that clinicians and staff from healthcare systems intervene consistently with tobacco users. Improving and promoting insurance coverage of treatment for tobacco use and dependence are also essential. Cessation benefits should cover all evidence-based cessation interventions, including brief and intensive counseling and all FDA-approved medications, including combination NRT therapy. This coverage should be provided with no or minimal barriers, such as prior authorization, duration limits, or cost-sharing. Regardless of how well designed a coverage benefit may be, coverage alone, without promotion, is not sufficient. Benefits for smoking cessation, whether offered through a health insurer or an employee wellness program, must be promoted to increase awareness.

In addition to the individual and clinical health systems interventions cited previously, population-based policy and program actions also serve critical roles in broadly influencing the behavior of smokers as they try to quit or think about quitting smoking. As noted in Chapter 7, population-level policy and program actions

can facilitate the integration of individual treatments into routine clinical care, thus making cessation interventions available and accessible to individual smokers and motivating smokers to use them. Such actions can occur at multiple levels—national, state, and local—and may involve government and nongovernment entities. These policies and programs include quitlines, which are an evidence-based, population-level strategy to increase the accessibility and uptake of scientifically proven cessation support, including the optimal combination of cessation counseling and medication.

Tobacco quitlines have typically been funded at the state level, but they can also be used by and funded through employers, health plans, and health systems. Quitlines offer convenient mechanisms through which health insurers and employers can partially meet federal requirements for coverage of tobacco cessation and reduce tobacco-related health expenditures. Employers can offer a tobacco quitline as an employee benefit to promote tobacco cessation and to help increase the productivity of employees who use tobacco by helping them to quit. Health systems can use quitlines as a complement to clinical care and to provide more intensive follow-up to patients engaged in a quit attempt. Provider referrals offer a less expensive and potentially more sustainable approach to drive smokers to quitline services, although developing and maintaining relationships with health systems and putting referral systems in place can be time- and staff-intensive. As described in Chapter 6, quitlines are increasingly linked to the delivery of cessation treatment by primary care providers, and enhanced use of electronic health records to electronically refer patients who smoke to quitlines is warranted. Beyond quitline e-referrals, electronic health records can be a critical tool for improving the frequency, quality, and consistency of screening and treatment for tobacco use and dependence, thereby increasing adherence to clinical practice guidelines. However, it is important that careful and intentional efforts must be made to integrate appropriate, evidence-based cessation content into the electronic health record system and to make parallel changes to the clinical work flow.

Although telephone quitlines are a clinical treatment, they are supported through broad policies at the local, state, and national levels and are designed to be accessed on a population-wide basis to address quit attempts, successful quitting, and the prevalence of smoking. Supportive policies include price increases (e.g., increasing excise taxes); restrictions on where tobacco can be used (e.g., smokefree policies); adequately funding state programs for tobacco control; carrying out mass media campaigns (e.g., CDC's *Tips From Former Smokers* campaign [*Tips*], FDA's *Every Try Counts*

campaign); and developing product regulations, such as requiring pictorial health warnings. Additionally, promising policies discussed in Chapter 7 include those focused on limiting retail density and point-of-sale tobacco advertising and on policies seeking to regulate the nicotine content in cigarettes to very low, nonaddictive levels.

Population-level policies have a broad impact, can change the context and environment to make it easier for persons to quit, and are more likely to help people quit and stay quit when coupled with clinical interventions at the individual level. Specifically, combining clinical and health system-based and population-level policy actions can improve cessation outcomes. For example, in addition to motivating smokers to make a quit attempt, a mass media campaign, such as the *Tips* campaign and the *Every Try Counts* campaign, can connect smokers to evidence-based resources for cessation treatment, such as a quitline or, in some cases, a healthcare provider. Therefore, clinicians and public health practitioners should connect clinical work with macro-level policy work to maximize the impact of tobacco-control interventions at the population level on tobacco cessation and to facilitate the implementation of these interventions.

Accelerating National Momentum to Promote Cessation

As noted in the 50th anniversary Surgeon General's report, the scientific evidence is undeniable: inhaling the combusted compounds from tobacco smoke is deadly (USDHHS 2014). Although substantial progress has been made to reduce smoking in the United States over the past five decades, by increasing adult smoking cessation and by reducing youth smoking initiation, more can and should be done. The following major conclusions from this report provide evidence that points to an urgent need for intensified and coordinated actions to reduce the considerable—and preventable—human and financial burden of smoking in the United States:

- More than three out of five U.S. adults who have ever smoked cigarettes have quit. Although a majority of cigarette smokers make a quit attempt each year, less than one-third use FDA-approved cessation medications or behavioral counseling to support these attempts.
- Smoking places a substantial financial burden on smokers, healthcare systems, and society. Smoking cessation reduces this burden, including smoking-attributable healthcare expenditures.

- Considerable disparities exist in the prevalence of smoking across the U.S. population; such prevalence is higher in some subgroups. Similarly, the prevalence of key indicators of smoking cessation—quit attempts, receiving advice to quit from a health professional, and using cessation therapies—also varies across the population, with lower prevalence among some subgroups.

To increase smoking cessation and reduce smoking in the United States, this report outlines a broad range of well-defined and effective population-based interventions that are necessary, at present, to help the 34 million American adults who currently smoke cigarettes quit:

- Fully funded, comprehensive statewide tobacco control programs;
- Higher average retail prices of cigarettes—at least \$10 a pack;
- Complete protection of the entire U.S. population from exposure to secondhand smoke through comprehensive indoor smokefree policies in workplaces, restaurants, and bars;
- High-impact media campaigns, such as CDC's *Tips From Former Smokers*, that run with sufficient reach, frequency, and duration—ideally for 12 months a year; and
- Product regulations, such as requiring pictorial health warnings.

However, these population-based actions and the more aggressive use of the evidence-based policies and programs reviewed in Chapter 7 are not enough. An array of effective clinical and health system-based interventions should also be implemented to increase smoking cessation and treat tobacco use and dependence in the United States:

- Increasing the appeal and reach of existing evidence-based interventions to individuals, including leveraging emerging technologies and accelerating the integration of cessation services across multiple platforms and in healthcare systems;
- Increasing the effectiveness of existing interventions, including recommending the combination of short- and long-acting forms of NRT, combined with behavioral support interventions, as first-line treatment for tobacco use;

- Conducting research to develop and better understand cessation interventions that have the potential for greater reach and/or effectiveness than existing interventions or that appeal to and are used by different populations of smokers;
- Conducting research to develop and better understand cessation interventions that are safe and effective among both youth and adults, including those that address the diversity of tobacco products being used by these populations, including e-cigarettes;
- Embedding policies and protocols for tobacco use screening and intervention into the clinical workflow; embedding prompts, decision support, and documentation tools into health records, such as electronic health records; and distributing specific components of the intervention across the broader healthcare team to reduce the burden on time-constrained physicians and to reinforce the importance of cessation to patients;
- Adopting policies to make the provision of cessation care in health systems more routine, as well as policies that remove cost and barriers to access for patients to increase the delivery and utilization of tobacco dependence treatment;
- Providing timely and relevant clinical guidelines and clinical quality measures to ensure that clinicians and health systems intervene consistently with tobacco users;
- Providing barrier-free cessation insurance coverage—without prior authorization, duration limits, cost-sharing, or other barriers that impede smokers' access to cessation treatments—to increase the availability and utilization of treatment services for smoking cessation;
- Ensuring comprehensive cessation insurance benefits for all smokers that include coverage of all evidence-based cessation interventions, including brief and intensive counseling and all FDA-approved medications, including combination NRT therapy;
- Promoting cessation coverage and services, whether offered through a health insurer or an employee wellness program, to smokers and healthcare providers to increase awareness and use of the covered treatments; coverage alone, without promotion, is not sufficient; and

- Adequately funding and promoting tobacco quitlines to enable their operations and services to function at levels sufficient to maximize their reach and impact.

The implementation of scientifically proven interventions has been a hallmark of the successes made in combating the tobacco use epidemic in the United States for more than 50 years. However, the tobacco control community must remain nimble and vigilant in conducting and disseminating timely, high-quality scientific studies on best practices; in modernizing existing interventions to keep pace with the rapidly diversifying landscape of tobacco products; and in identifying emerging strategies to ensure more rapid elimination of the health and economic burden of tobacco use in the United States. To that end, several end-game strategies could help to increase cessation and reduce the disease and premature death caused by tobacco use. Strategies that have been proposed include:

- Implementing a tobacco product standard to lower the level of nicotine in cigarettes to minimally addictive or nonaddictive levels, and
- Restricting the sale of tobacco products, such as prohibitions on entire categories of flavored tobacco products, including menthol.

Such actions have the potential to accelerate increases in smoking cessation and declines in the prevalence of smoking in the United States, thus hastening the end of the tobacco epidemic. However, these actions and the extensive body of evidence-based clinical, health system, and population-based tobacco prevention, control, and cessation strategies that are outlined in this report are a necessary but insufficient means to end the tobacco epidemic. Reaching the finish line will require coordination across federal government agencies and other stakeholders at the national, state, and local levels. To achieve success, we must work together to maximize resources and coordinate efforts across a wide range of stakeholders. Stakeholders who have a role to play include federal, state, local, tribal, and territorial governments; voluntary health agencies; nongovernmental and community-based organizations; civic and community leaders; public health and healthcare professionals; researchers; and individuals

(USDHHS 2016). Stakeholders must also continue to hold the tobacco industry accountable for its role in creating, obscuring, and perpetuating the tobacco use epidemic in the United States (USDHHS 2014). For example, beginning in 2017, the major U.S. tobacco companies were required by the U.S. District Court for the District of Columbia to run “corrective statements” via television and newspaper ads and to publish statements on their websites and cigarette packs that tell the American public the truth about the dangers of smoking and secondhand smoke (U.S. Department of Justice 2017; Farber et al. 2018). The tobacco control movement has achieved remarkable progress over time through coordinated actions by diverse stakeholders. The most effective interventions frequently originate at the local level before percolating to higher levels and ultimately becoming recognized as evidence-based practices (CDC 2014; USDHHS 2014). Action at the federal level is a key lever to success, but such action must be complemented by subnational and nongovernmental efforts to continue to denormalize tobacco use and advance the strategies that we know work to combat the devastating effects of tobacco use on society (USDHHS 2014). Each stakeholder can make unique and critical contributions toward reducing tobacco-related disease and death in the United States. In particular, there are opportunities for practitioners, experts, and researchers who have traditionally focused primarily on population-based tobacco control policy interventions, to collaborate more closely with their counterparts who have traditionally focused on cessation interventions as part of a broader effort to build linkages.

We are at the precipice of a critical period in the more-than-half-century history of the tobacco control movement in the United States. The considerable reduction in the prevalence of smoking since the mid-1960s is an important public health achievement, which has been driven in part by increases in adult smoking cessation and the multiple advances in smoking cessation interventions since the last Surgeon General’s report on this topic nearly three decades ago (USDHHS 1990). However, we cannot rest on our laurels. More work must be done, and we have the experience and wherewithal to do it. Equipped with both science and resolve, we will continue to move forward to end the tobacco epidemic in the United States. Working together, we can make tobacco-related disease and death a thing of the past.

References¹

- Altria Group. Altria makes \$12.8 billion minority investment in JUUL to accelerate harm reduction and drive growth [press release], December 20, 2018; <<http://investor.altria.com/file/Index?KeyFile=396169695>>; accessed: March 11, 2019.
- Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A, Richman E, Verzi SJ, Vugrin ED, Brodsky NS, et al. Potential public health effects of reducing nicotine levels in cigarettes in the United States. *New England Journal of Medicine* 2018;378(18):1725–33.
- Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. *Morbidity and Mortality Weekly Report* 2017;65(52):1457–64.
- Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *New England Journal of Medicine* 1994;331(2):123–5.
- Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tobacco Control* 2013;22(Suppl 1):i14–i17.
- Berrick AJ. The tobacco-free generation proposal. *Tobacco Control* 2013;22(Suppl 1):i22–i26.
- Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *New England Journal of Medicine* 2019.
- Borland R. A strategy for controlling the marketing of tobacco products: a regulated market model. *Tobacco Control* 2003;12(4):374–82.
- Borland R. Minimising the harm from nicotine use: finding the right regulatory framework. *Tobacco Control* 2013;22(Suppl 1):i6–i9.
- Callard C, Thompson D, Collishaw N. Transforming the tobacco market: why the supply of cigarettes should be transferred from for-profit corporations to non-profit enterprises with a public health mandate. *Tobacco Control* 2005a;14(4):278–83.
- Callard CD, Thompson D, Collishaw N. *Curing the addiction to profits: a supply-side approach to phasing out tobacco*. Ottawa (Ontario, Canada): Canadian Centre for Policy Alternatives, 2005b.
- Callard CD, Collishaw NE. Supply-side options for an endgame for the tobacco industry. *Tobacco Control* 2013; 22(Suppl 1):i10–i13.
- Campaign for Tobacco-Free Kids. *Broken Promises to Our Children: A State-by-State Look at the 1998 Tobacco Settlement 20 Years Later*, 2018; <<https://www.tobaccofreekids.org/what-we-do/us/statereport>>; accessed: January 15, 2019.
- Campaign for Tobacco-Free Kids. *States & Localities that Have Restricted the Sale of Flavored Tobacco Products*, January 22, 2019; <<https://www.tobaccofreekids.org/assets/factsheets/0398.pdf>>; accessed: March 13, 2019.
- Cantrell J, Bennett M, Mowery P, Xiao H, Rath J, Hair E, Vallone D. Patterns in first and daily cigarette initiation among youth and young adults from 2002 to 2015. *PLoS One* 2018;13(8):e0200827.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014; <https://www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2014/comprehensive.pdf>; accessed: July 26, 2017.
- Centers for Disease Control and Prevention. *STATE System Smokefree Indoor Air Fact Sheet*, August 28, 2018; <<https://chronicdata.cdc.gov/Legislation/STATE-System-Smokefree-Indoor-Air-Fact-Sheet/vgq2-kkcg>>; accessed: October 18, 2018.
- Centers for Disease Control and Prevention. 1991–2017 High School Youth Risk Behavior Survey data, n.d.; <<https://nccd.cdc.gov/youthonline/App/Default.aspx>>; accessed: March 11, 2019.
- Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students—United States, 2011–2018. *Morbidity and Mortality Weekly Report* 2018;67(45):1276–7.
- Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW, Creamer MR, Jamal A, Ambrose BK, King BA. E-cigarette use among youth in the United States, 2019. *JAMA: the Journal of the American Medical Association* 2019.
- Daynard RA. Doing the unthinkable (and saving millions of lives). *Tobacco Control* 2009;18(1):2–3.
- DiGiulio A, Jump Z, Yu A, Babb S, Schecter A, Williams KS, Yembra D, Armour BS. State Medicaid coverage for tobacco cessation treatments and barriers to accessing treatments—United States, 2015–2017. *Morbidity and Mortality Weekly Report* 2018;67(13):390–5.
- Family Smoking Prevention and Tobacco Control Act*, Public Law 111-31, 123 U.S. Statutes at Large 1776 (2009).

¹For reference entries that contain URLs, those URLs were active on the access date presented in the respective reference entry.

- Farber HJ, Neptune ER, Ewart GW. Corrective statements from the tobacco industry: more evidence for why we need effective tobacco control. *Annals of the American Thoracic Society* 2018;15(2):127–30.
- Federal Register. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Tobacco product standard for nicotine level of combusted cigarettes, 83 *Fed. Reg.* 11818 (2018).
- Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, Heyman RB, Holbrook J, Jaen CR, Kottke TE, et al. *Smoking Cessation: Clinical Practice Guideline No. 18*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1996. AHCPR Publication No. 96-0692.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, et al. *Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service Clinical Practice Guideline*. Rockville (MD): U.S. Department of Health and Human Services, 2008.
- Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital signs: tobacco product use among middle and high school students, United States, 2011–2018. *Morbidity and Mortality Weekly Report* 2019;68(6):157–64.
- Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, Wang L, Christensen C, Ambrose B, Borek N, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Network Open* 2018;1(8):e185937.
- Gottlieb S, Zeller M. A nicotine-focused framework for public health. *New England Journal of Medicine* 2017;377(12):1111–4.
- Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine* 2019;380(7):629–37.
- Hatsukami DK. Ending tobacco-caused mortality and morbidity: the case for performance standards for tobacco products. *Tobacco Control* 2013;22(Suppl 1):i36–i37.
- Hatsukami DK, Benowitz NL, Donny E, Henningfield J, Zeller M. Nicotine reduction: strategic research plan. *Nicotine and Tobacco Research* 2013;15(6):1003–13.
- Isett KR. In and across bureaucracy: structural and administrative issues for the tobacco endgame. *Tobacco Control* 2013;22(Suppl 1):i58–i60.
- JAMA: the Journal of the American Medical Association*. A clinical practice guideline for treating tobacco use and dependence: A U.S. Public Health Service report. *JAMA: the Journal of the American Medical Association* 2000;283(24):3244–54.
- Khoo D, Chiam Y, Ng P, Berrick AJ, Koong HN. Phasing-out tobacco: proposal to deny access to tobacco for those born from 2000. *Tobacco Control* 2010;19(5):355–60.
- King BA, Gammon DG, Marynak KL, Rogers T. Electronic cigarette sales in the United States, 2013–2017. *JAMA: the Journal of the American Medical Association* 2018;320(13):1379–80.
- King BA, Graffunder C. The tobacco control vaccine: a population-based framework for preventing tobacco-related disease and death. *Tobacco Control* 2018;27(2):123–4.
- Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tobacco Control* 2018;27(Suppl 1):S37–S38.
- Leischow SJ. Increasing smoking cessation in the United States: expanding the availability of over-the-counter medication. *JAMA: the Journal of the American Medical Association* 2019;321(6):541–2.
- Max WB, Sung HY, Lightwood J, Wang Y, Yao T. Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. *Tobacco Control* 2018;27(Suppl 1):S82–S86.
- McAfee T, Babb S, McNabb S, Fiore MC. Helping smokers quit—opportunities created by the Affordable Care Act. *New England Journal of Medicine* 2015;372(1):5–7.
- McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P, Halpern-Felsher B. Heated tobacco products likely appeal to adolescents and young adults. *Tobacco Control* 2018;(Suppl 1):S41–S47.
- Moritz ED, Zapata LB, Lekhiachvili A, Glidden E, Annor FB, Werner AK, Ussery EN, Hughes MM, Kimball A, DeSisto CL, et al. Update: characteristics of patients in a national outbreak of e-cigarette, or vaping, product use-associated lung injuries—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68(43):985–9.
- Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob P III, Springer ML. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tobacco Control* 2018;27(Suppl 1):S13–S19.
- National Cancer Institute. *The Role of the Media in Promoting and Reducing Tobacco Use*. Smoking and Tobacco Control Monograph No. 19. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2008. NIH Publication No. 07-6242.
- National Cancer Institute. *A Socioecological Approach to Addressing Tobacco-Related Health Disparities*. National Cancer Institute Tobacco Control Monograph 22. Bethesda (MD): U.S. Department of Health and Human

- Services, National Institutes of Health, National Cancer Institute, 2017. NIH Publication No. 17-CA-8035A.
- Navon L, Jones CM, Ghinai I, King BA, Briss PA, Hacker KA, Layden JE. Risk factors for e-cigarette, or vaping, product use-associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products—Illinois, July–October 2019. *Morbidity and Mortality Weekly Report* 2019 Nov 15;68(45):1034–9.
- O'Connor RJ, Bansal-Travers M, Carter LP, Cummings KM. What would menthol smokers do if menthol in cigarettes were banned? Behavioral intentions and simulated demand. *Addiction* 2012;107(7):1330–8.
- Office of Disease Prevention and Health Promotion. Tobacco use: objectives, n.d.; <<https://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use/objectives>>; accessed: July 26, 2017.
- Patient Protection and Affordable Care Act*, Public Law 111-148, *U.S. Statutes at Large* 124 (2010):100.
- Pearson JL, Abrams DB, Niaura RS, Richardson A, Vallone DM. A ban on menthol cigarettes: impact on public opinion and smokers' intention to quit. *American Journal of Public Health* 2012;102(11):e107–14.
- Proctor RN. *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition*. Berkeley (CA): University of California Press, 2011.
- Proctor RN. Why ban the sale of cigarettes? The case for abolition. *Tobacco Control* 2013;22(Suppl 1):i27–i30.
- Public Health Law Center. Lawsuits challenging the FDA's deeming rule (2019), March 5, 2019; <<https://www.publichealthlawcenter.org/resources/lawsuits-challenging-fda-deeming-rule>>; accessed: May 14, 2019.
- Rabe BG. Political impediments to a tobacco endgame. *Tobacco Control* 2013;22(Suppl 1):i52–i54.
- Siegel DA, Jatlaoui TC, Koumans EH, Kiernan EA, Lauer M, Cates JE, Kimball A, Weissman DN, Petersen EE, Reagan-Steiner S, et al. Update: interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68:919–27.
- St. Helen G, Jacob P III, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. *Tobacco Control* 2018;27(Suppl 1):S30–S36.
- Thomas BP, Gostin LO. Tobacco endgame strategies: challenges in ethics and law. *Tobacco Control* 2013;22(Suppl 1):i55–i57.
- Thomson G, Wilson N, Blakely T, Edwards R. Ending appreciable tobacco use in a nation: using a sinking lid on supply. *Tobacco Control* 2010;19(5):431–5.
- Tobacco Products Scientific Advisory Committee. *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*. Washington (DC): U.S. Food and Drug Administration, 2011.
- U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.
- U.S. Department of Health and Human Services. *Tobacco Use Among U.S. Racial/Ethnic Minority Groups—African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1998.
- U.S. Department of Health and Human Services. Reducing Tobacco Use: A Report of the Surgeon General. Highlights: At a Glance, 2000; <https://www.cdc.gov/tobacco/data_statistics/sgr/2000/highlights/ata glance/index.htm>; accessed: March 12, 2019.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
- U.S. Department of Health and Human Services. *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services*. Washington (DC): Office of the Assistant Secretary for Health, 2010.
- U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

- U.S. Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2016.
- U.S. Department of Health and Human Services. *Surgeon General's Advisory on E-Cigarette Use Among Youth*, 2018; <<https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf>>; accessed: January 9, 2019.
- U.S. Department of Justice. Print corrective statements—exhibit 3: newspaper exemplars, October 2, 2017; <<https://www.justice.gov/opa/press-release/file/1013581/download>>; accessed: April 11, 2019.
- U.S. Food and Drug Administration. FDA's deeming regulations for e-cigarettes, cigars, and all other tobacco products, 2018a; <<https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm394909.htm>>; accessed: March 11, 2019.
- U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes, November 15, 2018b; <<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm625884.htm>>; accessed: March 12, 2019.
- U.S. Food and Drug Administration. FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway [press release], April 30, 2019; <<https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway>>; accessed: June 13, 2019.
- U.S. Food and Drug Administration. *Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes*, n.d.; <<https://www.fda.gov/downloads/ucm361598.pdf>>; accessed: November 15, 2018.
- U.S. Public Health Service. *Treating Tobacco Use and Dependence: 2008 Update. Tobacco Use and Dependence Guidelines Panel*. Rockville (MD): U.S. Department of Health and Human Services, 2008; <<https://www.ncbi.nlm.nih.gov/books/NBK63952/>>; accessed: January 30, 2019.
- Van der Eijk Y. Development of an integrated tobacco end-game strategy. *Tobacco Control* 2015;24(4):336–40.
- Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA. Tobacco product use among adults—United States, 2017. *Morbidity and Mortality Weekly Report* 2018;67(44):1225–32.
- Ward JW, Warren C, editors. *Silent Victories: The History and Practice of Public Health in Twentieth-Century America*. New York (NY): Oxford University Press, 2007.
- Warner KE. Cigarette advertising and media coverage of smoking and health. *New England Journal of Medicine* 1985;312(6):384–8.
- Wilson N, Thomson GW, Edwards R, Blakely T. Potential advantages and disadvantages of an endgame strategy: a 'sinking lid' on tobacco supply. *Tobacco Control* 2013;22(Suppl 1):i18–i21.
- Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *American Journal of Preventive Medicine* 2015;48(3):326–33.
- Zeller M. Three years later: an assessment of the implementation of the Family Smoking Prevention and Tobacco Control Act. *Tobacco Control* 2012;21(5):453–4.

List of Abbreviations

α	alpha	ASSET	AngloScandinavian Study of Early Thrombolysis
β	beta	BAL	bronchoalveolar lavage
δ	delta	BENESCO	Benefits of Smoking Cessation on Outcomes
κ	kappa	bid	twice a day
μ	mu	BMI	body mass index
$\mu\text{g/ml}$	microgram per milliliter	BRFSS	Behavioral Risk Factor Surveillance System
15-D	15 dimensions [generic, self-administered measure of HRQoL]	C3I	Cancer Center Cessation Initiative
2-SORA	selective receptor 2 antagonist	CABG	coronary artery bypass grafting
5 A's	Ask, Advise, Assess, Assist, Arrange	CAC	coronary artery calcification
AAA	abdominal aortic aneurysm	CAD	coronary artery disease
AAC	Ask, Advise, Connect	CAGE 50	number of segments with coronary artery stenosis of greater than or equal to 50%
AACR	American Association for Cancer Research	CALIBER	Clinical research using Linked Bespoke studies and Electronic health Records
AAR	Ask, Advise, Refer	CASS	Coronary Artery Surgery Study
AARP	American Association of Retired Persons	CAST	Cardiac Arrhythmia Suppression Trial
ABI	ankle-brachial index	CBT	cognitive behavioral therapy
ACA	Patient Protection and Affordable Care Act	CCA	common carotid artery
ACC	anterior cingulate	CCQ	Clinical COPD Questionnaire
ACE	angiotensin-converting enzyme	CCS	Cancer Control Supplement
ACT	acceptance-based therapy	CDC	Centers for Disease Control and Prevention
ADHD	attention-deficit/hyperactivity disorder	CDER	Center for Drug Evaluation and Research
AF	atrial fibrillation	CHANCES	Consortium on Health and Ageing: Network of Cohorts in Europe and the United States
aFRs	adjusted fecundability ratios	CHD	coronary heart disease
AGS	additive genetic score	CHDA	coronary heart disease hard, definite angina, probable angina if followed by revascularization
AHRR	aryl-hydrocarbon receptor repressor	CHDH	coronary heart disease hard [myocardial infarction, resuscitated cardiac arrest, coronary heart disease death]
AMI	acute myocardial infarction	CHF	congestive heart failure
AML	acute myeloid leukemia	CHIP	Children's Health Insurance Program
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	CI	confidence interval
ANOVA	analysis of variance	CIMP-high	CpG island methylator phenotype
AoAC	aortic artery calcium	CIN3	cervical intraepithelial cancer grade 3
aOR	adjusted odds ratio	CIS	carcinoma in situ
APO	apolipoprotein	cm	centimeter
APPROACH	Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease		
aPR	adjusted prevalence ratio		
AQCs	alternative quality contracts		
ARIC	Atherosclerosis Risk in Communities		
ARR	absolute risk reduction		
ASCO	American Society of Clinical Oncology		

CMS	Centers for Medicare and Medicaid Services	EORTC-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer Module
CO	carbon monoxide	EPIC	European Prospective Investigation into Cancer and Nutrition
COLD	chronic obstructive lung disease	eReferral	electronic referral
CONSTANCES	Consultants des Centres d'Examens de Santé	ESTHER	Epidemiological Investigations on Opportunities for Prevention, Early Detection and Optimised Treatment of Chronic Diseases in the Elderly Population
COPD	chronic obstructive pulmonary disease	EURQoL	European quality of life
cpd	cigarettes smoked per day	EVALI	e-cigarette- or vaping-associated lung injury
CpG	cytosine-phosphate-guanine	F	females
CPP	conditioned place preference	F2:Cr	F2 isoprostane:creatinine
CPS	Cancer Prevention Study	F2RL3	factor II receptor-like 3
CRF	corticotropin-releasing factor	FCTC	Framework Convention on Tobacco Control
CRP	C-reactive protein	FDA	U.S. Food and Drug Administration
CT	computed tomography	FEV₁	forced expiratory volume at 1 second
CTP	Center for Tobacco Products	FINRISK	Large Finnish population survey on Risk factors on chronic, noncommunicable diseases
CVA	cerebrovascular accident	FMD	flow-mediated dilation
CVD	cardiovascular disease	fMRI	functional magnetic resonance imaging
CVDA	CVDH, CHDH, atherosclerotic death, CVD death	FRENA	Factores de Riesgo y Enfermedad Arterial [Registry]
CVDH	CHDH, stroke death, stroke	FSH	follicular-stimulating hormone
dACC	dorsal anterior cingulate cortex	FTND	Fagerström Test for Nicotine Dependence
DALYs	disability-adjusted life-years	FVC	forced vital capacity
DART	Diet and Reinfarction Trial	g	gram
dIPFC	dorsolateral prefrontal cortex	GDM	gestational diabetes mellitus
DM	diabetes mellitus	GED	General Education Development
DMN	default mode network	GLT	glutamate transporter
dmPFC	dorsomedial prefrontal cortex	GPR15	G protein-coupled receptor 15
DNA	deoxyribonucleic acid	GPS	global positioning system
DoD	U.S. Department of Defense	GRADE	Grading of Recommendations Assessment, Development, and Evaluation
DORs	delta opioid receptors	GWAS	genomewide association study
DRD2	dopamine receptor D2	HAPIEE	Health, Alcohol, and Psychosocial factors In Eastern Europe
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation Study	HB-IPN	habenula-interpeduncular
e-cigarettes	electronic cigarettes	HDL	high-density lipoprotein
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints	HDL-C	high-density lipoprotein cholesterol
ED	erectile dysfunction	HEDIS	Healthcare Effectiveness Data and Information Set
EHRs	electronic health records	HELLP	hemolysis, elevated liver enzymes, and low platelet count
ELSA	English Longitudinal Study of Aging		
ELSA-Brazil	Brazilian Longitudinal Study of Adult Health		
EMS	emergency management system		
ENDS	electronic nicotine delivery systems		
EORTC	European Organisation for Research and Treatment of Cancer		
EORTC-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module		

HINTS	Health Information National Trends Survey	LVEF	left ventricular ejection fraction
HIPAA	Health Insurance Portability and Accountability Act of 1996	M	males
HITECH	Health Information Technology for Economic and Clinical Health	MAO	monoamine oxidase
HMO	health maintenance organization	MAOI	monoamine oxidase inhibitor
HPV	human papillomavirus	MassHealth	Massachusetts Medicaid
HR	hazard ratio	MCS	Mental Component Summary
HRQoL	health-related quality of life	MEPS	Medical Expenditure Panel Survey
HT	hypertension	MESA	Multi-Ethnic Study of Atherosclerosis
IARC	International Agency for Research on Cancer	MeSH	Medical Subject Headings
IASLC	International Association for the Study of Lung Cancer	MF	males and females
ICAM-1	intercellular adhesion molecule-1	mg	milligram
ICC	invasive cervical cancer	mg/dL	milligram per deciliter
ICD	International Classification of Diseases	mGluR	metabotropic glutamate receptor
ICESCC	International Collaboration of Epidemiological Studies of Cervical Cancer	Mh	to search Medical Subjects Headings in MEDLINE or PubMed
ICH	intracerebral hemorrhage	MHb	medial habenula
IL	interleukin	MHb-IPN	medial habenulo-interpeduncular nucleus
IMT	intimal-media thickness	mHealth	mobile health
IOM	Institute of Medicine	MI	myocardial infarction
IPAQ	International Physical Activity Questionnaire	MILIS	Multicenter Investigation of Limitation of Infarct Size
IPN	interpeduncular nucleus	mL	milliliter
ISFAMI	Israel Study of First Acute Myocardial Infarction	mm	millimeter
IVF	in vitro fertilization	mmol	millimole
IVR	interactive voice response	MORGAM	Monica Risk Genetics Archiving and Monograph
KAROLA	Langzeiterfolge der Kardiologischen Anschlussheilbehandlung [Long Term Success of Cardiologic Rehabilitation Therapy]	MORs	mu opioid receptors
kg	kilogram	MPEP	2-methyl-6-(phenylethynyl) pyridine
km	kilometer	MRFIT	Multiple Risk Factor Intervention Trial
KORA	Kooperative Gesundheitsforschung in der Region Augsburg [Cooperative Health Research in the Augsburg Region]	MRI	magnetic resonance imaging
KORs	kappa opioid receptors	M RTP	modified risk tobacco product
L	liter	MSA	Master Settlement Agreement
lbs	pounds	MSI-high	microsatellite instability
LDCT	low-dose computed tomography	MTF	Monitoring the Future
LDL	low-density lipoprotein	NA	not applicable
LDL-C	low-density lipoprotein cholesterol	NA	not available
LDTg	laterodorsal tegmental nucleus	NAC	nucleus accumbens
LGBT	lesbian, gay, bisexual, and transgender	nAChR	nicotinic acetylcholine receptor
		NAM	negative allosteric modulator
		NAMCS	National Ambulatory Medical Care Survey
		NATS	National Adult Tobacco Survey
		NCCN	National Comprehensive Cancer Network
		NCHS	National Center for Health Statistics
		NCI	National Cancer Institute

NCQA	National Committee for Quality Assurance	PRAMS	Pregnancy Risk Assessment Monitoring System
ng/mL	nanogram per milliliter	PROM	premature rupture of the membranes
NHANES	National Health and Nutrition Examination Survey	PTCA	percutaneous transluminal coronary angioplasty
NHIS	National Health Interview Survey	PVD	peripheral vascular disease
NIBS	noninvasive brain stimulation	q	every
NICU	neonatal intensive care unit	QALYs	quality-adjusted life years
NIH	National Institutes of Health	QLQ-30	quality of life questionnaire 30 items
NIH-AARP	National Institutes of Health-American Association of Retired Persons	QoL	quality of life
NMDA	N-methyl-D-aspartate	RCT	randomized controlled trial
NMR	nicotine metabolite ratio	RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance
NQF	National Quality Forum	RIVM	chronic disease model developed at the National Institute of Public Health and the Environment in The Netherlands
NRT	nicotine replacement therapy	RNA	ribonucleic acid
NSDUH	National Survey on Drug Use and Health	RR	relative risk
NTCP	National Tobacco Control Program	RR	risk ratio
NYTS	National Youth Tobacco Survey	RSE	relative standard error
OACIS	Osaka Acute Coronary Insufficiency Study	RV	residual volume
OASIS	Organization to Assess Strategies in Ischemic Syndromes	Rx	prescription product
OFC	orbitofrontal cortex	SAH	subarachnoid hemorrhage
OR	odds ratio	SAMMEC	Smoking-Attributable Mortality, Morbidity and Economic Costs
OTC	over the counter	SAST	serum aspartate amino transferase
PAD	peripheral artery disease	SAVE	Sleep Apnea Cardiovascular Endpoints Trial
PAM	positive allosteric modulator	SBRT	stereotactic body radiation therapy
PAS	pharmacists action on smoking	SCD	sudden cardiac death
PATH	Population Assessment of Tobacco and Health	SCHIP	State Children's Health Insurance Program
PCASRM	Practice Committee of American Society for Reproductive Medicine	SCQoL	Smoking Cessation Quality of Life
PCC	posterior cingulate cortex	SD	standard deviation
PCI	percutaneous coronary intervention	SDT	self-determination therapy
PCS	Physical Component Summary	SE	standard error
PEF	peak expiratory flow	SENECA	Survey Europe on Nutrition in the Elderly
PEFR	peak expiratory flow rate	sEng	soluble endoglin
PET	positron emission tomography	SF	Short Form [survey]
PFC	prefrontal cortex	sFlt-1	soluble fms-like tyrosine kinase 1
PHS	U.S. Public Health Service	SGA	small-for-gestational age
PIGF	placental growth factor	SHARE	Survey of Health, Aging, and Retirement in Europe
PLCO	Prostate, Lung, Colorectal, and Ovarian cancer screening	SMC	Swedish Mammography Cohort
PMTA	Premarket Tobacco Product Application	SMS	short text message
po	by mouth	SNP	single nucleotide polymorphism
PPROM	preterm premature rupture of the membranes	SNpc	substantia nigra pars compacta
PPTg	pedunculo-pontine tegmental nucleus		

SP-A	surface protein A	USDHHS	U.S. Department of Health and Human Services
SR	sustained release	USPSTF	U.S. Preventive Services Task Force
sRAGE	soluble Receptor for Advanced Glycation End [product]	VA	U.S. Department of Veterans Affairs
SYNTAX	Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Trial	VascuQoL	Vascular Quality of Life [questionnaire]
TDD	telecommunications device for the deaf	VC	vital capacity
THC	tetrahydrocannabinol	VEGF	vascular endothelial growth factor
TLC	total lung capacity	VLNC	very-low-nicotine-content
TPSAC	Tobacco Product Scientific Advisory Committee	VTA	ventral tegmental area
TUS-CPS	Tobacco Use Supplement to the Current Population Survey	VTE	venous thromboembolism
UCSD	University of California–San Diego	WHO	World Health Organization
UK	United Kingdom	WHOQoL-BREF	World Health Organization Quality of Life-BREF
USAF	United States Air Force	WPS	Work Performance Scale
USDHEW	U.S. Department of Health, Education, and Welfare	xCT	cystine/glutamate exchanger
		YRBS	Youth Risk Behavior Survey
		YRBSS	Youth Risk Behavior Surveillance System

List of Tables and Figures

Executive Summary¹

Figure ES.1 Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1965–2017; United States 2

Chapter 1. Introduction, Conclusions, and the Evolving Landscape of Smoking Cessation

Figure 1.1 Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1965–2017; United States 4

Chapter 2. Patterns of Smoking Cessation Among U.S. Adults, Young Adults, and Youth

Table 2.1 Sources of national survey data on smoking cessation used for this report, 1965–2017; United States 38

Table 2.2 Distribution of selected demographic characteristics of adult current cigarette smokers 18 years of age and older; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States 49

Table 2.3 Distribution of tobacco use characteristics among adult current cigarette smokers 18 years of age and older; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States 52

Table 2.4 Distribution of selected demographic characteristics of young adult current cigarette smokers 18–24 years of age; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States 53

Table 2.5 Distribution of tobacco use characteristics of young adult current cigarette smokers 18–24 years of age; National Health Interview Survey (NHIS) 2000, 2005, 2010, 2015, and 2017; United States 54

Table 2.6 Distribution of demographic characteristics of high school students who are frequent cigarette smokers; National Youth Risk Behavior Survey (YRBS) 2001, 2005, 2009, 2015, and 2017; United States 55

Table 2.7 Prevalence of use of other tobacco products among high school students who are frequent cigarette smokers; National Youth Risk Behavior Survey (YRBS) 2001, 2005, 2009, 2015, and 2017; United States 56

Table 2.8 Prevalence of use of menthol cigarettes among high school students who currently smoke cigarettes, by frequency of smoking; National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States 56

Table 2.9 Percentage of ever cigarette smokers 18 years of age and older who have recently successfully quit and quit smoking (quit ratio), by selected characteristics; National Health Interview Survey (NHIS) 2017; United States 62

Table 2.10 Percentage of current and ever smokers 18 years of age and older who quit smoking (quit ratio) and prevalence of recent successful cessation and a past-year quit attempt, by state; Behavioral Risk Factor Surveillance System (BRFSS) 2017; United States 63

Table 2.11 Prevalence of a past-year quit attempt and interest in quitting smoking among adult cigarette smokers 18 years of age and older, by selected characteristics; National Health Interview Survey (NHIS) 2015; United States 68

Table 2.12 Prevalence of a past-year quit attempt among adult current cigarette smokers 18 years of age and older, by selected smoking-related and demographic characteristics; National Health Interview Survey (NHIS) 2015; United States 69

Table 2.13a Quitting behaviors among current cigarette smokers in high school (grades 9–12); National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States 72

Table 2.13b Quitting behaviors among current cigarette smokers in middle school (grades 6–8); National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, 2015, and 2017; United States 73

Table 2.14 Quitting behaviors among current cigarette smokers 18 years of age and older, by year; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2001–2002, 2006–2007, 2010–2011, and 2014–2015; United States 76

¹The Executive Summary is not part of the main report. Instead, it is available online at <https://www.hhs.gov/surgeongeneral/reports-and-publications/index.html>

Table 2.15	Quitting behaviors among current cigarette smokers 18–24 years of age, by year; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2001–2002, 2006–2007, 2010–2011, 2014–2015; United States 77	Table 2.24	Prevalence of using strategies to quit cigarette smoking among current cigarette smokers 18 years of age and older who tried to quit during the past year, by selected characteristics; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2014–2015; United States 96
Table 2.16	Prevalence of cessation behaviors and attitudes among high school seniors who are current cigarette smokers; Monitoring the Future (MTF) Study 2011–2017 combined data; United States 79	Table 2.25	Strategies used to quit smoking among high school and middle school current cigarette smokers who tried to quit during the past year; National Youth Tobacco Survey (NYTS) 2000, 2004, 2009, and 2015; United States 97
Table 2.17	Prevalence of cessation behaviors and attitudes among high school seniors who are current cigarette smokers, by year; Monitoring the Future (MTF) Study 2000–2004, 2005–2009, 2010–2014, and 2015–2017 combined data; United States 80	Table 2.26	Percentage of ever cigarette smokers 18 years of age and older who quit smoking (quit ratio) and prevalence of recent successful cessation and a past-year quit attempt, by urban or rural status; Behavioral Risk Factor Surveillance System (BRFSS) 2017; United States 101
Table 2.18	Prevalence of a past-year quit attempt for cigarette smoking and all tobacco use by type of tobacco used among adult current tobacco users 18 years of age and older, by selected demographic characteristics; National Health Interview Survey (NHIS) 2012–2014; United States 83	Figure 2.1	Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1965–2017; United States 44
Table 2.19	Quitting behaviors among current users of two or more tobacco products, by grade in school; National Youth Tobacco Survey (NYTS) 2017; United States 85	Figure 2.2	Trends in prevalence (%) of current and former cigarette smoking among adults 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 1965–2017; United States 44
Table 2.20	Receipt of screening for tobacco use, counseling, and a prescription for a cessation medication during outpatient visits to office-based physicians among adults 18 years of age and older, by patient and physician characteristics; National Ambulatory Medical Care Survey (NAMCS) 2009–2011 combined data; United States 87	Figure 2.3	Trends in prevalence (%) of current and former cigarette smoking among young adults 18–24 years of age, by sex; National Health Interview Survey (NHIS) 1965–2017; United States 45
Table 2.21	Prevalence of receiving a health professional’s advice to quit smoking and use of counseling and medications for cessation among cigarette smokers 18 years of age and older, by selected characteristics; National Health Interview Survey (NHIS) 2015; United States 89	Figure 2.4	Trends in prevalence (%) of current and former cigarette smoking among young adults 18–24 years of age, by race/ethnicity; National Health Interview Survey (NHIS) 1965–2017; United States 46
Table 2.22	Prevalence of interest in quitting, past-year quit attempt, receipt of a health professional’s advice to quit, use of counseling and/or medication, quit ratio, and recent successful cessation among smokers 18 years of age and older, by selected subpopulations; National Health Interview Survey (NHIS) 2015, 2017; United States 91	Figure 2.5	Trends in prevalence (%) of current frequent, former daily, and former nondaily cigarette smoking among high school students; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States 47
Table 2.23a	Prevalence of being asked about tobacco use and being advised not to use tobacco among high school students (grades 9–12) who saw a healthcare provider during the past year, by grade in school; National Youth Tobacco Survey (NYTS) 2015; United States 94	Figure 2.6a	Trends in prevalence (%) of current frequent cigarette smoking among high school students, by race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States 48
Table 2.23b	Prevalence of being asked about tobacco use and being advised not to use tobacco among middle school students (grades 6–8) who saw a healthcare provider during the past year, by grade in school; National Youth Tobacco Survey (NYTS) 2015; United States 94	Figure 2.6b	Trends in prevalence (%) of former daily and former nondaily cigarette smoking among high school students, by race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1991–2017; United States 48
		Figure 2.7a	Prevalence of current cigarette smoking by level of education and presence or absence of serious psychological distress and poverty status among adults 25 years of age and older; National Health Interview Survey (NHIS) 2017; United States 60

Figure 2.7b	Prevalence of current cigarette smoking by level of education and status of health insurance among adults 25 years of age and older; National Health Interview Survey (NHIS) 2017; United States 60
Figure 2.8a	Percentage of ever smokers 18 years of age and older who quit smoking (quit ratio), by age group; National Health Interview Survey (NHIS), 1965–2017; United States 65
Figure 2.8b	Percentage of ever smokers 18 years of age and older who quit smoking (quit ratio), by race/ethnicity; National Health Interview Survey (NHIS), 1965–2017; United States 65
Figure 2.9	Cessation continuum for current cigarette smokers 18 years of age and older; Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2006–2007, 2010–2011, 2014–2015; United States 67
Figure 2.10	Prevalence of past-year quit attempts among adult cigarette smokers 18 years of age and older, by sex; National Health Interview Survey (NHIS) 1997–2017; United States 74
Figure 2.11	Prevalence of past-year quit attempts among adult cigarette smokers 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 1997–2017; United States 74
Figure 2.12	Prevalence of past-year quit attempts among students in grades 9–12 who currently smoke cigarettes, by sex; National Youth Risk Behavior Survey (YRBS) 2001–2015; United States 75
Figure 2.13	Prevalence of use of counseling or medications for cessation among adult smokers 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 2000–2015; United States 98
Figure 2.14	Quarterly, inflation-adjusted dollar sales of over-the-counter nicotine replacement therapy, by type; Quarter 2, 2014–Quarter 4, 2018; United States 99

Chapter 3. New Biological Insights into Smoking Cessation

Table 3.1	Current pharmacotherapies for smoking cessation 130
Table 3.2	Novel pharmacologic targets for smoking cessation 133
Figure 3.1	Stages of the addiction cycle 127
Figure 3.2	Structure and properties of nAChRs 128
Figure 3.3	Neuronal mechanisms involved in nicotine addiction: A model 145

Chapter 4. The Health Benefits of Smoking Cessation

Table 4.1	Conclusions from the 1990 Surgeon General's report on the health benefits of smoking cessation and cancer 178
Table 4.2	Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with continued smoking, in three large U.S. cohorts 181
Table 4.3	Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with never smokers, in three large U.S. cohorts 182
Table 4.4	Cohort studies of stomach cancer incidence or mortality, by number of years since smoking cessation 183
Table 4.5	Cohort studies of colorectal cancer incidence or mortality, by number of years since smoking cessation 189
Table 4.6	Studies of liver cancer incidence or mortality, by number of years since smoking cessation 196
Table 4.7	Studies of cervical cancer incidence by years since smoking cessation 198
Table 4.8	Studies of kidney cancer incidence by number of years since smoking cessation 200
Table 4.9	Cohort studies that compared all-cause mortality in persons who were smokers at the time of a cancer diagnosis but had quit smoking after the diagnosis with those who continued smoking after the diagnosis 208
Table 4.10	Conclusions from previous Surgeon General's reports on smoking cessation and cardiovascular disease 215
Table 4.11	Studies on the association between smoking cessation and subclinical atherosclerosis 221
Table 4.12	Meta-analyses of observational studies on smoking cessation and incidence of total cardiovascular disease 228
Table 4.13	Observational studies on smoking cessation and cardiovascular disease 231
Table 4.14	Meta-analyses and a pooled analysis of observational studies on smoking cessation and incidence of coronary heart disease 235
Table 4.15	Observational studies on smoking cessation and incident coronary heart disease 237
Table 4.16	Observational studies (meta-analyses and pooled analyses) on smoking cessation and cerebrovascular disease 240
Table 4.17	Observational studies on smoking cessation and cerebrovascular disease 244

Table 5.3	Prospective studies of populations undergoing cessation treatment	451	Table 7.2	Systems-level changes reviewed in the 2008 <i>Clinical Practice Guideline</i> to encourage smoking cessation	584
Table 5.4	Prospective studies of special populations	454	Table 7.3	<i>Affordable Care Act</i> guidance of coverage of tobacco cessation treatment	589
Table 5.5a	Relative risks by smoking status and age group among adult men 35 years of age and older, United States	463	Table 7.4	Models of comprehensive tobacco cessation coverage and health insurance benefits	591
Table 5.5b	Relative risks by smoking status and age group among adult women 35 years of age and older, United States	464	Table 7.5	Healthcare system approaches designed to encourage smoking cessation	593
Table 5.6	Summary of economic evaluations of nicotine-based pharmacotherapies for smoking cessation	469	Figure 7.1	CDC's conceptual population health and prevention framework	581
Table 5.7	Summary of economic evaluations of non-nicotine-based pharmacotherapies for smoking cessation	474	Figure 7.2	Intensity of ad placement for <i>Tips From Former Smokers (Tips)</i> campaign and call volume to 1-800-QUIT-NOW, 2013	604
Table 5.8	Summary of economic evaluations of brief counseling for smoking cessation	478	Figure 7.3	Pictorial warning on cigarette packages in Australia	608
Table 5.9	Summary of economic evaluations of nonclinical interventions for smoking cessation	483	Figure 7.4	Effects of individual and combined policies on the prevalence of smoking among men and women 18 years of age and older, using the SimSmoke Model	615
Figure 5.1a	Incidence rate ratios for death from any cause, by smoking status	462			
Figure 5.1b	Incidence rate ratios for death from lung cancer, by smoking status	462			

Chapter 6. Interventions for Smoking Cessation and Treatments for Nicotine Dependence

Table 6.1	The 5 A's model for treating tobacco use and dependence	502
Table 6.2	Pharmacologic product guide: FDA-approved medications for smoking cessation	510
Figure 6.1	The evolution of e-cigarettes, by product generation and characteristics	525

Chapter 7. Clinical-, System-, and Population-Level Strategies that Promote Smoking Cessation

Table 7.1	Summary of policies from the 2014 Surgeon General's report that encourage smoking cessation	580
-----------	---	-----

Chapter 8. A Vision for the Future

Table 8.1	Summary of milestones aimed at increasing tobacco cessation in the United States	645
Table 8.2	Potential end-game strategies discussed in the 50th anniversary Surgeon General's report, 2014	654
Figure 8.1	Per capita annual cigarette consumption among adults, 18 years of age and older, and major smoking and health events in the United States, 1900–2017	644



U.S. Department of Health and Human Services