The Health Consequences Of Smoking

CANCER

a report of the Surgeon General

1982

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office on Smoking and Health
Rockville, Maryland 20857

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON D.C. 20201

The Honorable Thomas P. O'Neill, Jr.
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

I hereby submit to you the 1982 Report on the Health Consequences of Smoking, prepared in accordance with the Public Health Cigarette Smoking Act of 1969 and its predecessor, the Federal Cigarette Labeling and Advertising Act. This is the first report in the series to focus on a single disease entity--cancer.

Scientists inside and outside of Government have evaluated the evidence presented in this report. It joins this Department's previous reports on smoking and health in making publicly available information about one of the major health risks of smoking. These reports reflect the important responsibility of Government to inform its citizens in order that they can make a considered decision about whether to smoke.

Sincerely,

Richard S. Schweiker
Secretary

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

The Honorable George Bush
President of the Senate
Washington, D. C. 20510

Dear Mr. President:

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FOREWORD

The 1982 report on *The Health Consequences of Smoking* presents a comprehensive evaluation of the relationship between cigarette smoking and cancer.

Since 1937, cancer has been the second most important cause of death in the United States and will account for an estimated 430,000 deaths this year. Surveys have shown that Americans fear dying of cancer more than any other disease. We have yet to observe, however, a decline in the cancer mortality rate as is currently occurring for other chronic diseases, such as the 30 percent decline in the cardiovascular disease mortality rate and the 50 percent decline in the cerebrovascular disease mortality rate observed over the last three decades. The mortality rate for cancer has changed little over two decades, and that change has been a small, but measurable, increase. This increase in mortality has occurred in the face of remarkable improvements in survival rates for some cancer sites through earlier or better diagnosis and treatment. Unfortunately, however, these advances have failed to counter the remarkable increases in mortality from smoking-related cancers, many of which have a poor prognosis for long-term survival or cures.

The Public Health Significance of this Report

Cigarette smoking is the major single cause of cancer mortality in the United States. Tobacco's contribution to *all* cancer deaths is estimated to be 30 percent. This means we can expect that 129,000 Americans will die of cancer this year because of the higher overall cancer death rates that exist among smokers as compared with nonsmokers. Cigarette smokers have total cancer death rates two times greater than do nonsmokers. Heavy smokers have a three to four times greater excess risk of cancer mortality. If large numbers of our population did not smoke, the cancer death rate in this country could be reduced, and instead of the small but continued increase in the total cancer death rate, there could be a substantial decline. There is no single action an individual can take to reduce the risk of cancer more effectively than quitting smoking, particularly cigarettes.

Cigarette smoking is a major cause of cancers of the lung, larynx, oral cavity, and esophagus, and is a contributory factor for the development of cancers of the bladder, pancreas, and kidney. The term contributory factor by no means excludes the possibility of a causal role for smoking in cancer of these sites.

Lung Cancer

Lung cancer, first correlated with smoking over 50 years ago, is the single largest contributor to the total cancer death rate. Lung cancer alone accounts for fully 25 percent of all cancer deaths in this country; it is estimated that 85 percent of lung cancer cases are due to cigarette smoking. Overall, smokers are 10 times more likely to die from lung cancer than are nonsmokers. Heavy smokers are 15 to 25 times more at risk than nonsmokers. The total number of lung cancer deaths in the United States increased from 18,313 in 1950 to 90,828 in 1977. The lung cancer death rate for women is currently rising faster than the lung cancer death rate for men, a fact that reflects the later adoption of smoking by large numbers of women. The lung cancer death rate for women will soon surpass that of breast cancer (perhaps as early as next year), currently the leading cause of cancer mortality in women. This remarkable increase in lung cancer mortality for women mimics that observed among men some 30 years ago. However, since the early 1960s, large numbers of men have given up cigarette smoking or have not begun to smoke, whereas only recently has the prevalence of cigarette smoking by women started to decline. These differences in patterns of smoking have a decided effect on lung cancer mortality trends in this country, with a decline in lung cancer mortality already apparent for younger men. These differences will clearly affect future lung cancer mortality experience by sex in the United States. The American Cancer Society estimates there will be 111,000 lung cancer-related deaths in 1982, of which 80,000 will be in men and 31,000 in women.

The 5-year survival rate for cancer of the lung is less than 10 percent. This rate has not changed in 20 years. Early diagnosis and treatment do not appreciably alter this dismal survival rate—the best preventive measure a smoker can take to reduce the risk of lung cancer is to quit smoking, and for a nonsmoker, to not take up the habit.

Larynx and Oral Cavity Cancer

Laryngeal and oral cancers will strike an estimated 40,000 individuals and will be responsible for approximately 13,000 deaths this year in the United States. These sites have 5-year survival rates of 60 and 40 percent, respectively. An estimated 50 to 70 percent of

oral and laryngeal cancer deaths are associated with smoking. These cancers are strongly associated with the use of cigars and pipes in addition to cigarettes. All carry approximately the same excess relative risk of at least fivefold. The use of alcohol in conjunction with smoking acts synergistically to greatly increase the risk of these cancers.

Esophageal Cancer

This year, 8,300 deaths due to cancer of the esophagus are expected. Cancer of the esophagus has one of the poorest survival rates of all cancers—only about 4 percent of esophageal cancer patients live 5 years after diagnosis and most die within 6 months. Cigarette smoking is estimated to be a factor in over half of esophageal cancer deaths. Smokers have mortality ratios approximately 4 to 5 times higher than nonsmokers. The use of alcohol has a synergistic interaction with smoking that greatly increases this risk.

Bladder and Kidney Cancers

Over 50,000 Americans are expected to develop bladder and kidney cancer this year. Bladder and kidney cancers will be responsible for a total of 20,000 deaths this year. The 5-year survival rates are approximately 50 to 60 percent. Various investigators have estimated that between 30 and 40 percent of bladder cancers are smoking related, with slightly higher estimates for males than for females.

Pancreatic Cancer

Approximately 24,000 people will develop cancer of the pancreas this year, and there will be an estimated 22,000 deaths. Like cancers of the lung and esophagus, cancer of the pancreas is often fatal, with a 5-year survival of less than 3 percent. While few estimates are available as to the proportion of these deaths attributable to smoking, it would appear to be about 30 percent. Pancreatic cancer appears to be increasing at a more rapid rate than most other cancer sites.

Stomach and Uterine Cervix Cancer

A link between smoking and stomach cancer and cancer of the uterine cervix is noted. However, no judgment can be reached on the significance of any association, because of insufficient data.

Involuntary Smoking and Lung Cancer

In recent months, the popular press has generated interest in the controversy of whether passive or involuntary smoking causes lung cancer in nonsmokers. Three epidemiological studies examined this issue in the past year. Evidence from two of the studies demonstrated a statistically significant correlation between involuntary smoking and lung cancer risk in nonsmoking wives of husbands who smoked. A third noted a positive association, but it was not statistically significant. While the nature of this association is unresolved, it does raise the concern that involuntary smoking may pose a carcinogenic risk to the nonsmoker. Any health risk resulting from involuntary smoke exposure is a serious public health concern because of the large numbers of nonsmokers in the population who are potentially exposed. Therefore, for the purpose of preventive medicine, prudence dictates that nonsmokers avoid exposure to second-hand tobacco smoke to the extent possible.

Lower Tar Cigarettes

This report also notes that smokers who use filtered or lower tar cigarettes have statistically lower death rates from lung cancer than do cigarette smokers who use nonfiltered or higher tar brands. This reduced risk was also noted for laryngeal cancer. However, cancer death rates for smokers of lower tar cigarettes were still significantly higher than those noted for nonsmokers.

Cessation of Smoking

Since cigarette smoking is a cause of many cancers, encouraging data about cessation are presented in this Report. Quitting smoking reduces one's cancer risk substantially, compared with the continuing smoker, even after many years of cigarette smoking. The more years one is off cigarettes, the greater the reduction in excess cancer risk. Fifteen years after quitting cigarette smoking, the former smoker's lung cancer risk, for example, is reduced close to that observed in nonsmokers. This same reduction in cancer risk is observed for the other cancer sites associated with smoking.

Part V of this Report contains a review of cessation research among adults and adolescents. In summary, many promising techniques are available to smokers who have been unable to quit on their own. It is nonetheless interesting to note that the vast majority of former smokers, probably close to 95 percent, quit on their own, without the aid of formal smoking cessation programs.

As a physician, I encourage all health care providers, particularly other physicians, to counsel cigarette smokers to quit and to give them as much support as possible. As this Report notes, a few

minutes' discussion with patients about their smoking behavior can have a decisive impact on whether they quit smoking or continue the habit.

Trends in Smoking Prevalence

I am encouraged by the recent decline in cigarette smoking rates in this country. Today, only one-third of adults smoke, a decline from 42 percent in 1965. Teenage smoking, particularly among adolescent girls, also appears to be declining.

While these figures are encouraging, there are still 53 million cigarette smokers in this country—about the same number of smokers as 20 years ago.

Furthermore, while per capita use of cigarettes has declined to its lowest level since 1957, there has been a substantial increase in the consumption of chewing tobacco and snuff, particularly among the young. What impact the use of these products will have on future cancer mortality is unclear; knowledge of the type and extent of the health effects of these tobacco products is limited. Current evidence indicates, however, that their use is not without risk. Studies conducted in this country and others have demonstrated an increased risk for oral cancer and other noncancerous oral diseases.

Educational Efforts

This Department is committed to continuing the programs of education and information for all our citizenry regarding the adverse health consequences of smoking. There is no more important aspect of this than the health education of our young, to convince them not to start smoking, or to quit the habit before it becomes difficult to break.

This problem cannot be left solely to government to solve. I call upon the rest of the health care community, the voluntary health agencies, and our schools to increase their efforts to control one of this country's most pressing health problems. Reducing smoking will reduce the devastating toll that cancer, as well as other smoking-related diseases, exacts on this Nation's health.

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

PREFACE

In July 1957, Dr. Leroy E. Burney issued the Public Health Service's first statement on cigarette smoking: it identified smoking as a cause of lung cancer. Each succeeding Surgeon General has had occasion to issue additional and stronger warnings. These have linked smoking with lung cancer, with heart disease, with chronic lung disease, with other cancers, and with increases in overall mortality.

With this 1982 statement on cigarette smoking and cancer, I am joining my distinguished predecessors, Drs. Burney, Luther Terry, William Stewart, Jesse Steinfeld, and Julius Richmond. Cigarette smoking, as this Report again makes clear, is the chief, single, avoidable cause of death in our society and the most important public health issue of our time.

Over the years, 14 reports on the health consequences of smoking have been prepared by the Public Health Service under the Federal Cigarette Labelling and Advertising Act and its successor, the Public Health Cigarette Smoking Act of 1969. These reports have contributed greatly to public understanding of the hazards that cigarette smoking poses to the health of this Nation.

In contrast with previous Public Health Service reports on smoking and health, the present document examines the relationship between smoking and a single category of disease, cancer. The relationships between smoking and lung cancer, as well as cancer of other sites, are carefully examined. This should not distract attention from the fact that smoking is related to many diseases, including cardiovascular disease, which exacts a greater toll than does cancer in disease and death. Cancer, however, was the first disease to be linked with tobacco use, and its association with smoking has been the subject of the most intense research. Much of the research within the past few years has not previously been examined in the detail presented here.

As in previous years, this Report has been prepared with the aid and critical review of experts from within and outside the Government. On behalf of the Public Health Service, I express here my respect for their expertise and gratitude for their help.

C. Everett Koop, M.D.
Surgeon General

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PART I. INTRODUCTION AND CONCLUSIONS

Introduction

Development and Organization of the 1982 Report

The content of this Report is the work of numerous scientists within the Department of Health and Human Services, as well as scientific experts outside the organization. Individual manuscripts were reviewed by experts, both outside and within the Public Health Service, and the entire Report was reviewed by a broad-based panel of 12 distinguished scientists. Many of these scientists are, or have been, directly involved in research on the health effects of smoking. The 1982 Report consists of a Preface by the Surgeon General, a Foreword by the Assistant Secretary for Health of the Department of Health and Human Services, and five Parts, as follows:

- Part I. Introduction and Conclusions
- Part II. Biomedical Evidence for Determining Causality
- Part III. Mechanisms of Carcinogenesis
- Part IV. Involuntary Smoking and Lung Cancer
- Part V. Cessation of Smoking

Historical Perspective

Tobacco use was associated with the possible development of cancer as early as 1761. According to one medical historian, Dr. John Hill (1716?-1775) should be credited with the first report documenting an association between tobacco use and cancer for his work *Cautions Against the Immoderate Use of Snuff.* Hill reported on two case histories and observed that "snuff is able to produce...swellings and excrescences" in the nose, and he believed these to be cancerous. Others credit Soemmerring in 1795 for noting a relationship between cancer of the lip and tobacco use.

It was not until the 1920s and 1930s that investigators began to examine scientifically the possible association of smoking and cancer. In 1928, Lombard and Doering, in the United States, found an association between heavy smoking and cancer in general. Muller and Schairer (Germany) in 1939 and 1944 respectively, and Porter (USA) in 1945, and others, noted higher percentages of smokers among lung cancer patients than among controls. The first major developments in the modern history of investigation of the effects of smoking on health occurred in 1950 with the publication of four retrospective studies on smoking habits of lung cancer patients and controls in the United States by Schrek et al., Mills and Porter, Levin et al., and Wynder and Graham. Each of these noted a consistent, statistically significant association between smoking and cancer of the lung. Other investigators proceeded to further examine the relationship by initiating prospective studies in which large numbers of healthy persons were followed over time and their subsequent mortality noted.

The first major prospective study encompassing total and cause-specific mortality was initiated in October 1951 by Doll and Hill in the United Kingdom among 40,000 British physicians. Hammond and Horn followed 188,000 males beginning in January 1952 in the United States. These and subsequent prospective studies conducted in the United States, Sweden, Canada, and Japan, found not only that smokers have substantially elevated cancer mortality rates, but also that smokers experience significantly elevated overall death rates.

Cancer has been the second ranking cause of death in the United States since 1937. Provisional vital statistics data for 1980 indicate cancer accounted for almost 21 percent of all deaths in the United States. This compares to 17 percent of all deaths in 1970 and 14.5 percent of all deaths in 1950. Various investigators have suggested that 22 to 38 percent of these deaths can be attributed to smoking, and therefore, are potentially "avoidable" if smoking did not exist as a human behavior. Since 1950, the age-adjusted overall cancer death rate has changed little, whereas the lung cancer death rate has increased dramatically for both males and females.

The male age-adjusted lung cancer rate increased 192 percent during the period 1950–1952 thru 1976–1978. Female lung cancer death rates during this same period increased even more: 263 percent. Since the 1950s, lung cancer has been the leading cause of cancer death among males in the United States, and if present trends continue, will become the leading cause of cancer death in females during this decade; the age-adjusted female lung cancer death rate is projected to possibly surpass the death rate for breast cancer next year. Today, deaths from cancer of the lung represent fully one quarter of all deaths due to cancer in the United States.

In 1962, the year when the Surgeon General's Advisory Committee on Smoking and Health began deliberating the evidence presented in its landmark report, slightly more than 41,000 persons died of lung cancer annually, compared to 18,300 lung cancer deaths in 1950. In 1982, the American Cancer Society estimates 111,000 Americans will die of lung cancer, nearly a three-fold increase in the number of deaths in a 20-year time span.

The Advisory Committee's Report of 1964 judged the causal significance of the association of cigarette smoking and disease by rigid criteria, no one of which alone was sufficient for a causal judgment. The epidemiologic criteria included:

a. The consistency of the association
b. The strength of the association
c. The specificity of the association
d. The temporal relationship of the association, and
e. The coherence of the association

Corroboration was also sought from other sources, such as clinical autopsy and experimental evidence.

Significant additional scientific evidence linking smoking to cancer, as well as to other tobacco-related diseases, has accumulated since the issuance of that Advisory Committee's Report in 1964. Much of this has been collected, reviewed, and published in annual reports by the Department of Health and Human Services.

The purpose of this Report is to review in depth the many sources of scientific evidence relating cigarette smoking to each cancer by anatomic site, and to evaluate this evidence by the same criteria first established by the Advisory Committee in its 1964 Report, including experimental carcinogenesis and human epidemiologic studies.

Conclusions of the 1982 Report

Overall Cancer Mortality

1. Cigarette smokers have overall mortality rates substantially greater than those of nonsmokers. Overall cancer death rates of male smokers are approximately double those of nonsmokers; overall cancer death rates of female smokers are approximately 30 percent higher than nonsmokers, and are increasing.
2. Overall cancer mortality rates among smokers are dose-related as measured by the number of cigarettes smoked per day. Heavy smokers (over one pack per day) have more than three times the overall cancer death rate of nonsmokers.
3. With increasing duration of smoking cessation, overall cancer death rates decline, approaching the death rate of nonsmokers.

Site-Specific Cancer Mortality

Lung Cancer

1. Cigarette smoking is the major cause of lung cancer in the United States.
2. Lung cancer mortality increases with increasing dosage of smoke exposure (as measured by the number of cigarettes smoked daily, the duration of smoking, and inhalation patterns) and is inversely related to age of initiation. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than nonsmokers.
3. Cigar and pipe smoking are also causal factors for lung cancer. However, the majority of lung cancer mortality in the United States is due to cigarette smoking.
4. Cessation of smoking reduces the risk of lung cancer mortality compared to that of the continuing smoker. Former smokers who have quit 15 or more years have lung cancer mortality rates only slightly above those for nonsmokers (about two times

greater). The residual risk of developing lung cancer is directly proportional to overall life-time exposure to cigarette smoke.

5. Filtered lower tar cigarette smokers have a lower lung cancer risk compared to nonfiltered, higher tar cigarette smokers. However, the risk for these smokers is still substantially elevated above the risk of nonsmokers.
6. Since the early 1950s, lung cancer has been the leading cause of cancer death among males in the United States. Among females, the lung cancer death rate is accelerating and will likely surpass that of breast cancer in the 1980s.
7. The economic impact of lung cancer to the nation is considerable. It is estimated that in 1975, lung cancer cost $3.8 billion in lost earnings, $379.5 million in short-term hospital costs, and $78 million in physician fees.
8. Lung cancer is largely a preventable disease. It is estimated that 85 percent of lung cancer mortality could have been avoided if individuals never took up smoking. Furthermore, substantial reductions in the number of deaths from lung cancer could be achieved if a major portion of the smoking population (particularly young persons) could be persuaded not to smoke.

Laryngeal Cancer

9. Cigarette smoking is the major cause of laryngeal cancer in the United States. Cigar and pipe smokers experience a risk for laryngeal cancer similar to that of a cigarette smoker.
10. The risk of developing laryngeal cancer increases with increased exposure as measured by the number of cigarettes smoked daily as well as other dose measurements. Heavy smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers.
11. Cessation of smoking reduces the risk of laryngeal cancer mortality compared to that of the continuing smoker. The longer a former smoker is off cigarettes the lower the risk.
12. Smokers who use filtered lower tar cigarettes have lower laryngeal cancer risks than those who use unfiltered higher tar cigarettes.
13. The use of alcohol in combination with cigarette smoking appears to act synergistically to greatly increase the risk for cancer of the larynx.

Oral Cancer

14. Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars

experience a risk for oral cancer similar to that of the cigarette smoker.

15. Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking.
16. Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers.
17. Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum.

Esophageal Cancer

18. Cigarette smoking is a major cause of esophageal cancer in the United States. Cigar and pipe smokers experience a risk of esophageal cancer similar to that of cigarette smokers.
19. The risk of esophageal cancer increases with increased smoke exposure, as measured by the number of cigarettes smoked daily, and is diminished by discontinuing the habit.
20. The use of alcohol in combination with smoking acts synergistically to greatly increase the risk for esophageal cancer mortality.

Bladder Cancer

21. Cigarette smoking is a contributory factor in the development of bladder cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Kidney Cancer

22. Cigarette smoking is a contributory factor in the development of kidney cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Pancreatic Cancer

23. Cigarette smoking is a contributory factor in the development of pancreatic cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Stomach Cancer

24. In epidemiological studies, an association between cigarette smoking and stomach cancer has been noted. The association is small in comparison with that noted for smoking and some other cancers.

Uterine Cervix Cancer

25. There are conflicting results in studies published to date on the existence of a relationship between smoking and cervical cancer; further research is necessary to define whether an association exists and, if so, whether that association is direct or indirect.

Mechanisms of Carcinogenesis

This overview presents evidence and observations on tobacco carcinogenesis primarily developed since 1978.

1. The biological activity of whole cigarette smoke and its tar and tar fractions can now be measured by improved inhalation assays in addition to tests for tumor-initiating, tumor-promoting, and cocarcinogenic activities on mouse skin.
2. Studies on smoke inhalation with the hamster now appear suitable for estimating the relative tumorigenic potential of whole smoke from commercial and experimental cigarettes. The identification of the smoke constituents that contribute to tumor induction in the respiratory tract is best achieved by fractionations of tar and by assays on mouse epidermis that determine the type and potency of the carcinogens. In combination with biochemical tests, mouse skin assays should also aid in evaluating the possible role of nicotine as a cocarcinogen.
3. The identification, formation, and metabolic activation of organ-specific carcinogens have been studied which help explain the increased risk to cigarette smokers of cancer of the esophagus, pancreas, kidney, and urinary bladder. In addition to certain aromatic amines, tobacco-specific N-nitrosamines appear to be an important group of organ specific carcinogens in tobacco and tobacco smoke. Little is known of the *in vivo* formation of organ-specific carcinogens from nicotine and other *Nicotiana* alkaloids. The modification of their enzymatic activation to ultimate carcinogenic forms needs to be explored by chemopreventive approaches.
4. Transplacental carcinogenesis as it may relate to effects of cigarette smoking should be investigated more fully. It has been known for some time that inhalation of tobacco smoke activates enzymes in the placenta and fetus and the consequences of such changes need to be studied.

5. The continuing modification of U.S. cigarettes has led to changes in the quantitative and perhaps also the qualitative composition of the smoke. This ongoing development requires continued monitoring of the toxic and carcinogenic potential of the smoke of new cigarettes.
6. The changes in cigarette composition lead generally to reduced emission of major toxic mainstream smoke constituents as measured in analytical laboratories under machine-smoking conditions. Many smokers intensify puff volume and degree of inhalation when smoking a lower-yield cigarette. Therefore, it should be determined what effect different techniques of air dilution and filtration have in counteracting the increased smoke exposure that results from intensified smoking.
7. Snuff tobaccos are increasingly used as an alternative to cigarette smoking. More information is needed regarding the carcinogenic activity of snuff tobaccos and the presence of tumorigenic agents in these products.

Involuntary Smoking and Lung Cancer

1. Mainstream and sidestream cigarette smoke contain similar chemical constituents. (Mainstream smoke is smoke that the smoker inhales directly during puffing. Sidestream smoke is smoke emitted from a smoldering cigarette into the ambient air.) These constituents include known carcinogens, some of which are present in higher concentrations in sidestream smoke than they are in mainstream smoke. Passive or involuntary smoking differs from voluntary cigarette smoking with respect to the concentration of smoke components inhaled, the duration and frequency of smoke exposure, and the pattern of inhalation.
2. In two epidemiologic studies, an increased risk of lung cancer in nonsmoking wives of smoking husbands was found. In these studies, the nonsmoking wife's risk of lung cancer increased in relation to the extent of the husband's smoking. In a third study, the risk of lung cancer among nonsmoking wives of smoking husbands was also increased, but the difference was not statistically significant.
3. Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem.

Cessation of Smoking

1. Ninety-five percent of those who have quit smoking have done so without the aid of an organized smoking cessation program, and most current smokers indicate a preference for quitting

with a procedure they may use on their own, and a disinclination to enter an organized, comprehensive program.

2. Research evaluations of self-help aids have reported success rates up to 50 percent cessation at extended followups (6 to 15 months). Most estimates, however, fall below this, around 5 to 20 percent.
3. Brief and simple advice to quit smoking delivered by a physician has substantial potential for producing cessation in a cost-effective manner.
4. Televised smoking cessation clinics result in variable rates of abstinence at followup. The use of television and other mass media are a cost-effective intervention because of their large potential audiences.
5. Retrospective studies revealed greater use of self-reward and active problem-solving strategies among those who quit or reduced smoking on their own than among those who were unsuccessful in quitting or reducing smoking.
6. Until recently, the long-term outcome of intensive smoking cessation clinics has remained at 25 to 30 percent abstinence. New emphasis on techniques to improve the maintenance phase of cessation promises to improve these rates, with several reports of greater than 50 percent abstinence at followups of 6 months or longer.
7. To improve maintenance of nonsmoking after intensive treatment programs have ended, reinforcement should be built into the natural environment. Smoking cessation programs in the workplace may offer an opportunity for this.
8. Comprehensive self-management packages that have been shown to boost maintenance rates include a wide variety of techniques.
9. Treatment outcome may be improved by focusing on the antecedents of relapse. These include feelings of frustration, anxiety, anger, and depression as well as social models and smoking-related cues and settings. Behavioral and cognitive skills for dealing with such antecedents should be developed.
10. Social support interventions are promising. Reliable findings link social cues, smoking friends, and smoking spouses to relapse, whereas the presence of group support, nonsmoking spouses, and professional contact decreases recidivism.
11. Spontaneous smoking cessation among regular users (approximately once a week or more often) is estimated to be on the order of 25 percent during adolescence.
12. Probability of quitting was greater for those adolescent smokers first interviewed in 1974 who had at least started to attend college by 1979 than for those smokers who did not attend college (42.0 percent vs. 24.6 percent).

13. Probability of quitting decreases linearly with duration of the smoking practice, changing from 64.5 percent in the first year of smoking to 14.3 percent after 7 years.
14. Quitting "cold turkey" appears to be a more effective cessation strategy than cutting down without trying to stop entirely.
15. Success at quitting increased with the number of efforts made: about 73.4 percent of adolescents who kept trying eventually succeeded.
16. Smoking prevention programs are desirable alternatives to cessation programs aimed at youth. Successful programs have been based on social psychological theory and research, and are school based. Results have shown a 50 percent or more reduction in smoking onset.
17. The most successful programs were those emphasizing the social and immediate consequences of smoking rather than long-term health consequences. These programs have placed special emphasis on teaching skills in recognizing and resisting social pressures to smoke.

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PART II. BIOMEDICAL EVIDENCE FOR DETERMINING CAUSALITY

INTRODUCTION

Provisional mortality data for 1980 indicate that cancer was responsible for approximately 412,000 deaths in the United States (*199*). It is estimated that in 1982 there will be 430,000 deaths due to cancer, 233,000 among men and 197,000 among women (*2*). Various investigators (*70, 78, 106*) have suggested that 22 to 38 percent of these deaths can be attributed to smoking, and therefore are potentially "avoidable" if smoking did not exist as a human behavior.

A relationship between smoking and cancer was first suggested for neoplasms of the lung in scientific reports from the 1920s and early 1930s (*203, 266*). Muller (*191*) in 1935 and Schairer and Schoeniger (*237*) in 1943 reported that most lung cancer patients were smokers. Subsequently, 8 major prospective studies and more than 50 retrospective studies have examined this relationship. In 1964, the Advisory Committee to the Surgeon General of the U.S. Public Health Service (*272*) published a comprehensive review of the then available data. They concluded that "cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. Data for women, though less extensive, point in the same direction. The risk of developing lung cancer increases with the duration of smoking and the number of cigarettes smoked per day and is diminished by discontinuing smoking."

Over the last 17 years, thousands of scientific investigations have confirmed the Committee's conclusion and provided additional evidence concerning the relationship of cigarette smoking to lung cancers. Smoking has been implicated as a cause of cancer of the larynx, oral cavity, and esophagus, and associated with cancer of the urinary bladder, kidney, and pancreas. This is the first report devoted exclusively to a comprehensive assessment of the associations reported between smoking and various cancers. In the following sections of this Part of the Report, the nature of these associations is appraised in the light of currently available knowledge.

EPIDEMIOLOGIC CRITERIA FOR CAUSALITY

The concept of causality has been debated by students of philosophy since the days of Aristotle. David Hume (1711–1776) and John Stuart Mill (1806–1873) are credited with major contributions to contemporary insight and theory of causality. More recently, members of the Advisory Committee to the Surgeon General (*272*), Hill (*112*), MacMahon and Pugh (*168*), Susser (*260*), Evans (*80*), and Lilienfeld (*158*) have examined the concept of causality in the health sciences. The ability to totally control the experimental environment, to randomize exposure, and to measure discrete outcomes allows a clear experimental demonstration of causality. However, the application of these rigid laboratory techniques for establishing causality to the study of cancer in humans is clearly impossible. The idea of exposing human subjects to potentially cancer-producing agents in order to establish causality is morally and ethically unacceptable. Therefore, other criteria have been developed to establish causality with a very high degree of scientific probability (*80, 112, 158, 260, 272, 280*).

In practice, epidemiologic methods have been employed to study cancer in man. These studies result in observational data that may establish a statistically significant association between variables or attributes. This association may be artifactual, indirect, or direct. The possibility of an artifactual (or spurious) result can be eliminated if the design and conduct of the studies are adequate, and if studies conducted in different geographical areas and among different population groups produce the same or similar statistical associations. Once an artifactual association has been ruled out, it is then necessary to determine whether the association is an indirect or direct (causal) one.

Randomization is an attempt to eliminate the effect of all variables other than the one under study. However, a personal choice behavior such as smoking is impossible to randomize (i.e., to dictate smoking behavior). Therefore, in order to establish that an association between smoking and a disease is not due to a confounding variable, an entire body of data must exist to satisfy specific criteria, none of which by itself is an all-sufficient basis for judgment. Thus, when a scientific judgment is made that all plausible confounding variables have been considered, an association may be considered to be direct.

In this Report, the same definition of the term "cause" that was used in the Report of the Advisory Committee to the Surgeon General in 1964 has been adopted. "The word cause is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host" (*272*). The term "cause" should not be construed to

exclude other agents as causes; rather, it is used in full recognition that biological processes are complex and multiple in etiologies.

In this Report, as in the earlier one, the attribution of "causality" to a disease-associated variable (e.g., smoking) includes full recognition that "the causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between an attribute or agent and the disease, or the effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:

a. The consistency of the association
b. The strength of the association
c. The specificity of the association
d. The temporal relationship of the association, and
e. The coherence of the association"

These criteria are utilized herein for evaluation of the reported associations between cigarette smoking and cancers of various sites in humans.

Consistency of the Association

This criterion implies that diverse methods of approach in the study of an association will provide similar conclusions. Consistency requires that the association be repeatedly observed by multiple investigators, in different locations and situations, at different times, using different methods of study. Such replication assures that the association is not likely to be an artifact due to bias in study methodology or subject selection, and that it is not indirect due to confounding variables such as diet, occupation, or genetics.

Strength of the Association

The most direct measure of the strength of the association is the ratio of cancer rates for smokers to the rates for nonsmokers. The relative risk ratio yields evidence on the size of the effect of a factor on disease occurrence and which, even in the presence of another associated factor without causal effect but coincident with the causal agent, will not be obscured by the presence of the non-causal agent.

A relative risk ratio measures the strength of an association and provides an evaluation of the importance of that factor in the production of a disease.

If all cases of the disease under study, but none of the controls, have a history of exposure to the suspected etiologic agent or characteristic (assuming that an adequate number of cases and controls exist in the population under study), a one-to-one correspondence between the disease and the factor exists, and a causal hypothesis would be credible. Most diseases are influenced by many

factors, however, and therefore a one-to-one correspondence would not be expected. The strength of an association is measured by relative risk ratios, incidence ratios, or mortality ratios. The greater the relative risk ratio or the mortality ratio, the stronger the relationship between the etiologic agent and the disease. Prospective studies have shown that the death rate from cancer of the lung among cigarette smokers is approximately 10 times the rate in nonsmokers, and the rate in heavy cigarette smokers is 20 to 30 times greater than in nonsmokers. To account for such high relative risk in terms of an indirect association would require that an unknown causal factor be present at least 10 times more frequently in the smokers and 20 to 30 times more frequently among heavy smokers than among nonsmokers. Such a confounding factor should be easily detectable, and if it cannot be detected or reasonably inferred, the finding of such a strong association makes a conclusion concerning causality more probable. Important to the strength, as well as to the coherence of the association, is the presence of a dose-response phenomenon in which a positive gradient between degree of exposure to the agent and incidence or mortality rates of the disease can be demonstrated.

Specificity of the Association

This concept cannot be entirely dissociated from the concept inherent in the strength of the association. It implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other, i.e., how frequently the presence of one variable will predict, in the same individual, the presence of another.

Specificity implies that a causal agent invariably leads to a single specific disease, an event rarely observed. A one-to-one relationship between the presence of an etiologic agent and disease would reflect a causal relationship. However, several points must be kept in mind in interpreting specificity in biological systems. First, an agent may be associated with multiple diseases. Second, many responses considered to be disease states have multiple causes. Congenital malformations, for example, result from prenatal radiation as well as from some drugs administered during pregnancy and other factors. Variations in the relative risk of disease may be produced by variations in the number of causal agents as well as by the specificity of a given causal agent. Third, a single pure substance in the environment may produce a number of different diseases. The experimental production of a variety of diseases in mice by exposure to X-rays is a good example of this. Fourth, a single factor may be the vehicle for several different substances. Tobacco smoke is a complex mixture of several thousand individual constituents, and therefore it would not be surprising to find that these diverse substances are able

to produce more than one adverse biologic response. It is also not surprising that these constituents may have possible additive, synergistic, or competitive actions with each other and with other agents in the environment. And fifth, there is no reason to assume that the relationships between one factor and different diseases have similar explanations. The association between smoking and lung cancer, for example, is considered direct and causal, whereas that between cigarette smoking and cirrhosis of the liver is thought to be indirect, reflecting the association of cigarette smoking and heavy alcohol use by some segments of the population.

In summary, despite the fact that the demonstration of specificity in an association makes a causal hypothesis more acceptable, lack of specificity does not negate such an hypothesis, since many biologic and epidemiologic aspects of the association must be considered.

Temporal Relationship of the Association

In chronic diseases, insidious onset and the lack of knowledge of precise induction periods automatically present problems on which came first—the suspected agent or the disease. In any evaluation of the significance of an association, exposure to an agent presumed to be causal must precede, temporally, the onset of a disease which it is purported to produce.

The criterion of temporal relationship requires that exposure to the suspect etiologic factor precede the disease. Temporality is more difficult to establish for diseases with long latency periods, such as cancer. Prospective studies minimize this difficulty, although even prospective studies do not exclude the possibility that the disease was present in an undetected form prior to exposure to the agent. Histologic evidence demonstrating premalignant changes among individuals exposed to the agent, but not among unexposed controls, provides evidence that temporality is present. Experimental studies may also demonstrate a temporal association.

Coherence of the Association

The final criterion for the appraisal of causal significance of an association is its coherence with known facts in the natural history and biology of the disease.

Coherence requires that descriptive epidemiologic results on disease occurrence correlate with measures of exposure to the suspected agent. Perhaps the most important consideration here is the observation of a dose-response relationship between agent and disease, that is, the progressively increasing occurrence of disease in increasingly heavily exposed groups. In some cases, multiple measures of dosage are available. The natural history of disease would include observations on the progression of disease with continuing

exposure differing from its progression in those whose exposure is discontinued.

In order to establish the coherence of a specific association, other possible explanations for the association must be systematically considered and excluded or taken into account. Coherence is clearly established when the actual mechanism of disease production is defined. Coherence exists, nonetheless, although of a lesser magnitude, when there is enough evidence to support a plausible mechanism, but not a detailed understanding of each step in the chain of events by which a given etiologic agent produces disease.

Causality for Specific Forms of Cancer

The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.

In the following section, the relationship between smoking and several cancers is reappraised. Epidemiologic, pathologic, and experimental data form the basis for review. When a significant association between cigarette smoking and a specific cancer is noted, the nature of the association was assessed by applying the judgment criteria noted above. If all epidemiologic criteria were judged to be satisfied and pathological and experimental data are supportive, the term "causal" is applied to the association. The designation "major cause" is used when the relative risk for the cancer in cigarette smokers is high. The term "contributory factor" is used when the body of evidence is less compelling, the relative risk is lower, or the ancillary evidence (pathologic and experimental data) is not sufficient for a judgment of causality. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of those sites. The term "association" is used when a relationship between smoking and a cancer site exists, but the data are inadequate for an assessment of the character of that relationship.

SMOKING-RELATED CANCERS BY SITE

Lung Cancer

Introduction

Since the early 1950s, lung cancer has been the leading cause of cancer death among males in the United States; among females, the lung cancer death rate is accelerating faster than all other cancer death rates and, if present trends continue, will likely surpass that of breast cancer by the mid-1980s (*2*) (Figure 1).

Between 1950 and 1977 in the United States,[1] the total number of lung cancer deaths increased from 18,313 in 1950 to 90,828 in 1977 (the figure for 1977 includes ICD (International Classification of Diseases) Nos. 162–163.0). The American Cancer Society estimates there will be 129,000 new lung cancer cases diagnosed in 1982 and 111,000 deaths. Of this number, 80,000 will be men and 31,000 women. The age-adjusted lung cancer mortality rate for the total population nearly tripled, rising from 11.1 to 32.7. (All age-adjusted death rates, unless stated otherwise, were derived by applying the age-specific rates to the standard population distributed by age as enumerated in 1940.) Overall lung cancer mortality rates increased over this period at a decelerating pace. Thus, in the 1950–1957 interval, the average annual increase in the age-adjusted death rate was 5.2 percent; over the next 10 years, the average annual increase was 4.0 percent; and in the final 10-year interval, 1968–1977, the rate of increase was 3.1 percent.

These sex-aggregated figures hide differences in the lung cancer mortality trends of males and females (Figures 2, 3, and 4). In the 28-year period from 1950 to 1977, the age-adjusted lung cancer rate increased almost 200 percent for men and over 250 percent for women. The most striking aspect of this trend is the acceleration in lung cancer mortality among females. The age-adjusted death rate of white females increased by an average of 1.0 percent per year between 1950 and 1957, 5.5 percent per year between 1958 and 1967, and 6.7 percent per year between 1968 and 1977. The corresponding increases for all other females were 3.0, 5.1, and 6.6 percent per year. (The term "nonwhite" represents all races other than white and is used in most graphics throughout this Report for the sake of brevity.) In contrast to this trend in females, the rate of increase slowed down in males. After climbing an average of 6.1 percent a year from 1950 to 1957, the rate among white males rose 4.0 percent annually from 1958 to 1967, and 2.1 percent a year from 1968 to 1977. The rate of increase among all other males fell from 8.7 to 6.2 to 3.6 percent per year over these intervals. Even with this deceleration in the rising

[1] Unless otherwise stated, all cancer mortality data cited in this Report were extracted from the volume "Mortality From Diseases Associated With Smoking: United States, 1960–77" (*200*). For a detailed discussion of these data as well as trends for other diseases related to smoking the reader is referred to that volume.

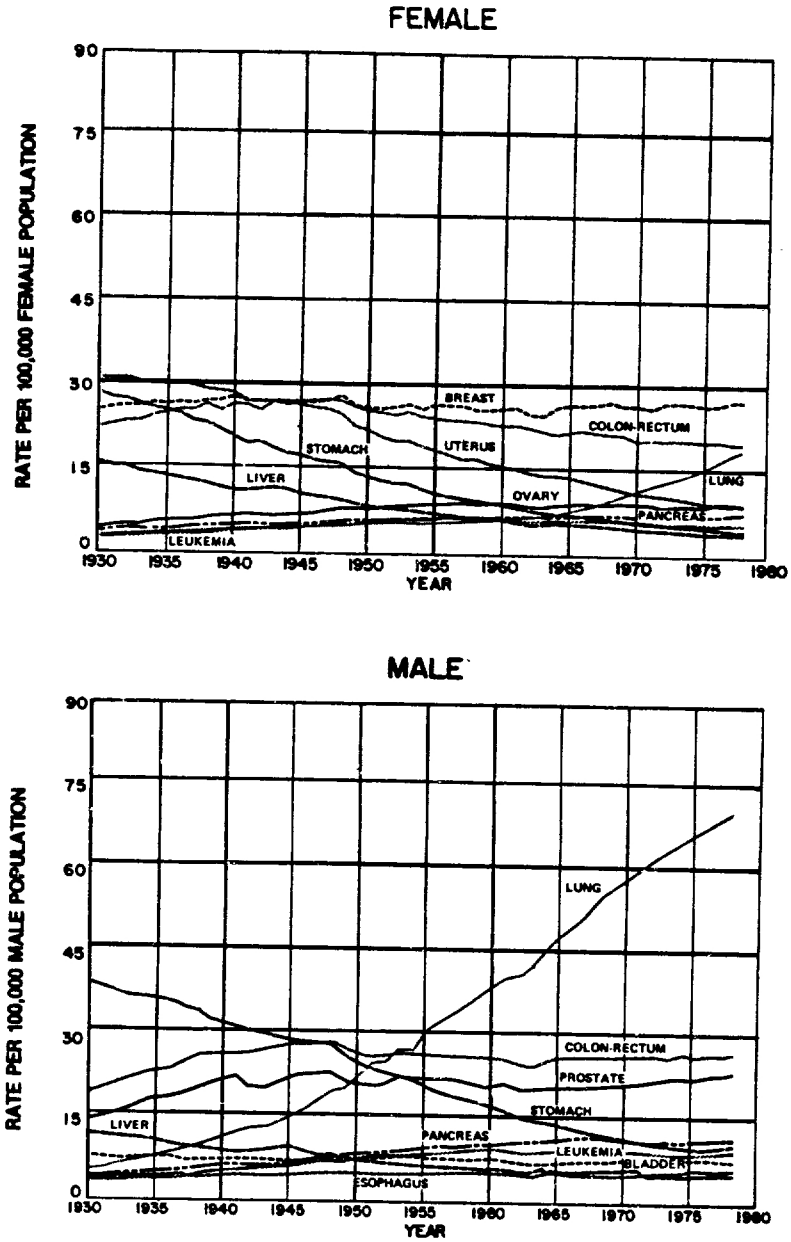

FIGURE 1.—Male and female cancer death rates* by site, United States, 1930–1978

* Age-adjusted to the U.S. population as enumerated in 1970.

SOURCE: American Cancer Society (2).

male lung cancer rate, an examination of the age-specific rates in Figures 3 and 4 reveals that the lung cancer rates are still markedly greater in males than in females.

In the white population, these trends resulted in a decrease in the sex ratio of lung cancer mortality rates between males and females. In 1950, the age-adjusted lung cancer death rate was 4.7 times higher in white males than in white females. By 1977, the mortality sex ratio had dropped to 3.6. In the white population 35 to 44 years of age, the mortality sex ratio decreased from 3.74 to 1.72 over this period. In contrast, the mortality sex ratio (male/female) of the other than white group increased from 4.11 to 4.54 from 1950 to 1977.

Particularly in the early part of the study period, mortality among males other than white climbed sharply. In 1950, the ratio of the age-adjusted death rate of all other males to that of white males was 0.77; by 1977, age-adjusted death rates of all other males had surpassed those of white males. The mortality color ratio (other-than-white/white) had risen to 1.25. Among females, the mortality color ratio shifted from 0.88 in 1950 to 1.00 in 1957, after which it remained stable. In females 35 to 44 years of age, however, rates were consistently higher in the other than white group than in the white group.

When age-specific lung cancer death rates are plotted by calendar year and age, a three-dimensional graph is produced (Figures 5 and 6) which can be examined from 1950–1977, or from the reverse (back side) perspective. The broad, ascending peaks reflect the dramatic rise in lung cancer rates for men and women over this time interval. The lower age-specific lung cancer death rates seen in the oldest age group (Figures 5 and 6) reflect changing cohort patterns of exposure. Thus, what appears to be a decline in mortality rates with old age is actually an artifact arising from the combining of cohorts with different cigarette smoke exposure and mortality experiences. As will be discussed later, the age-specific mortality rate for each specific birth cohort actually continues to increase steadily with increasing age in both men and women (Figures 13 and 15).

Lung cancer has a considerable economic impact. Rice and Hodgson (*218*) estimate that the health cost of lung cancer in 1975 was $3.8 billion in lost earnings, $379.5 million in short-term hospital charges, and $78 million in physician fees.

Less than 10 percent of patients with lung cancer will survive 5 or more years. This bleak survival rate has not changed significantly over the last 15 years. Hence, the prevention of lung cancer is of paramount importance. According to a recent study for the Congressional Office of Technology Assessment, approximately 85 percent of United States lung cancer deaths in 1978 were attributable to smoking, and thus were "avoidable" if individuals had not smoked cigarettes (*70*).

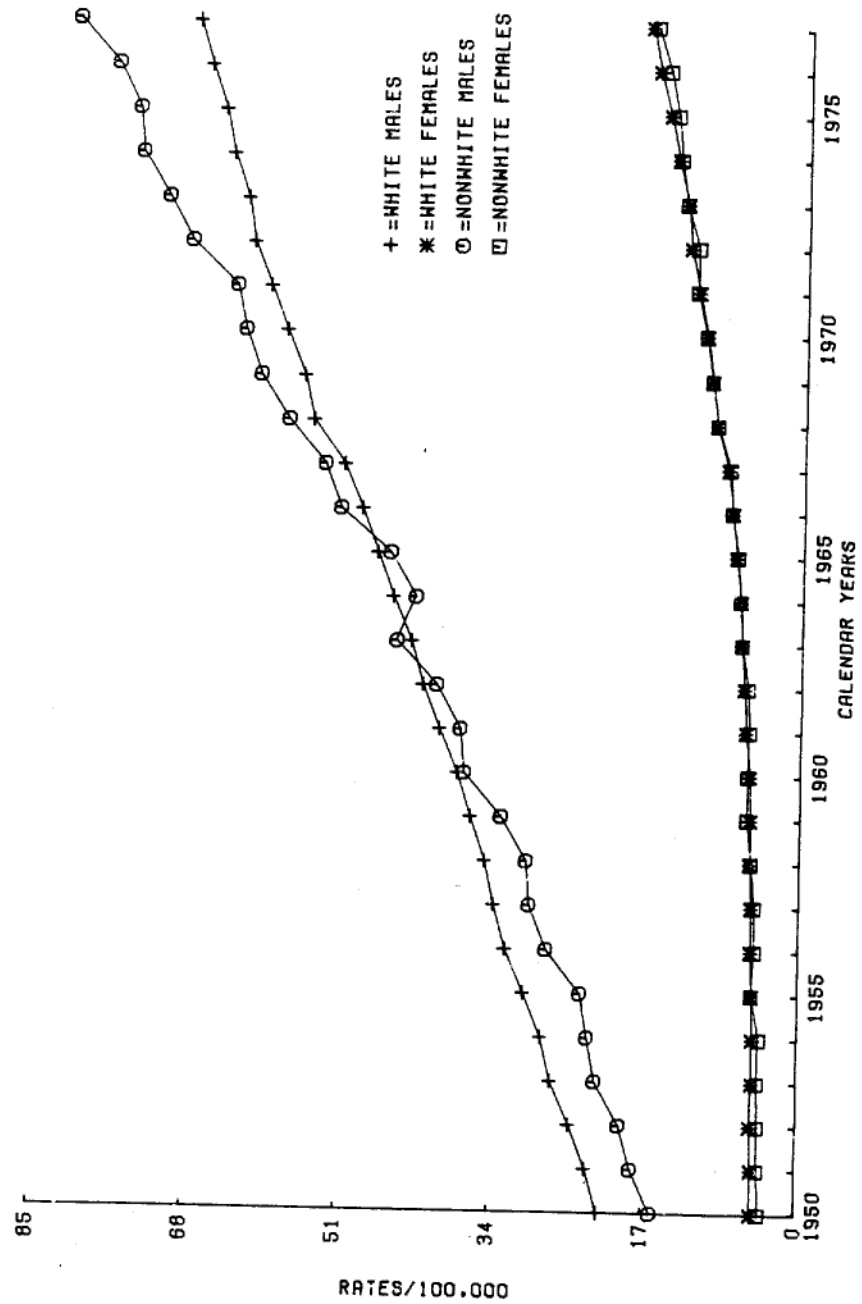

FIGURE 2.—Age-adjusted* mortality rates for cancer of the bronchus, trachea, and lung, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

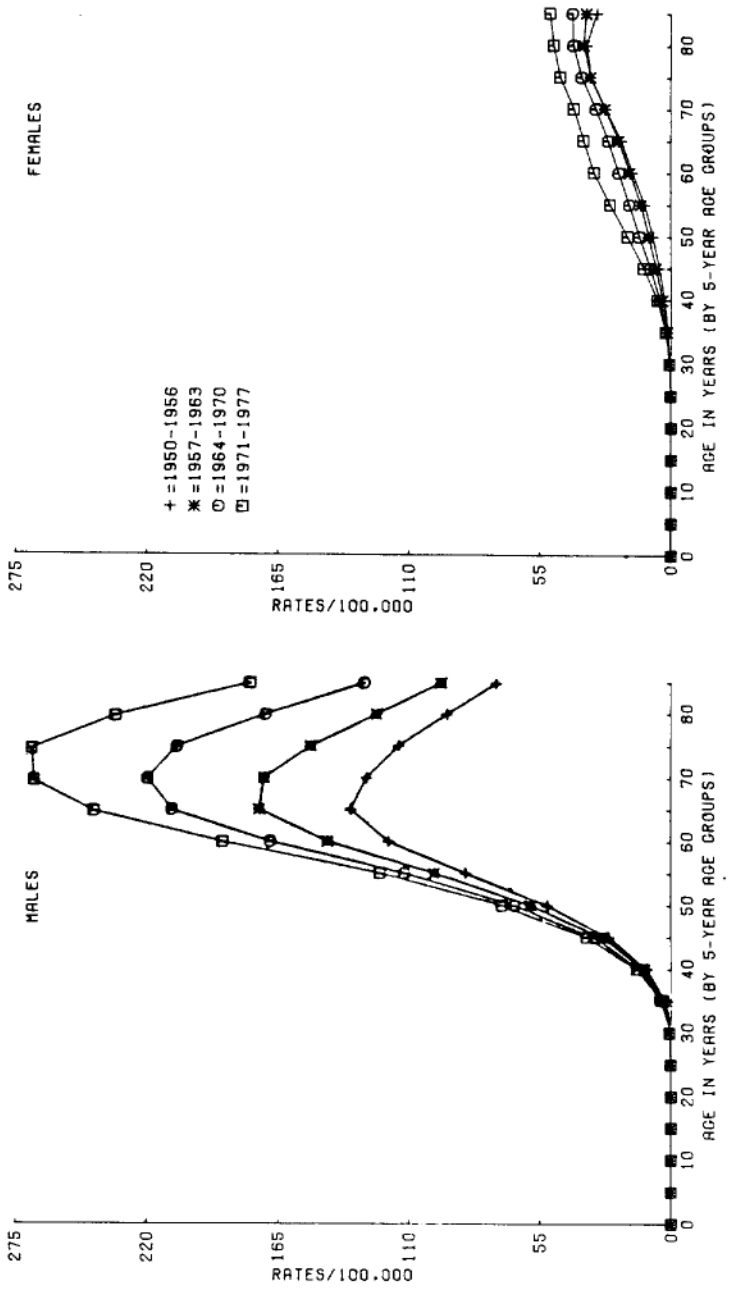

FIGURE 3.—Age-specific mortality rates for whites in the United States for cancer of the bronchus, trachea, and lung

SOURCE: National Cancer Institute (*198*).

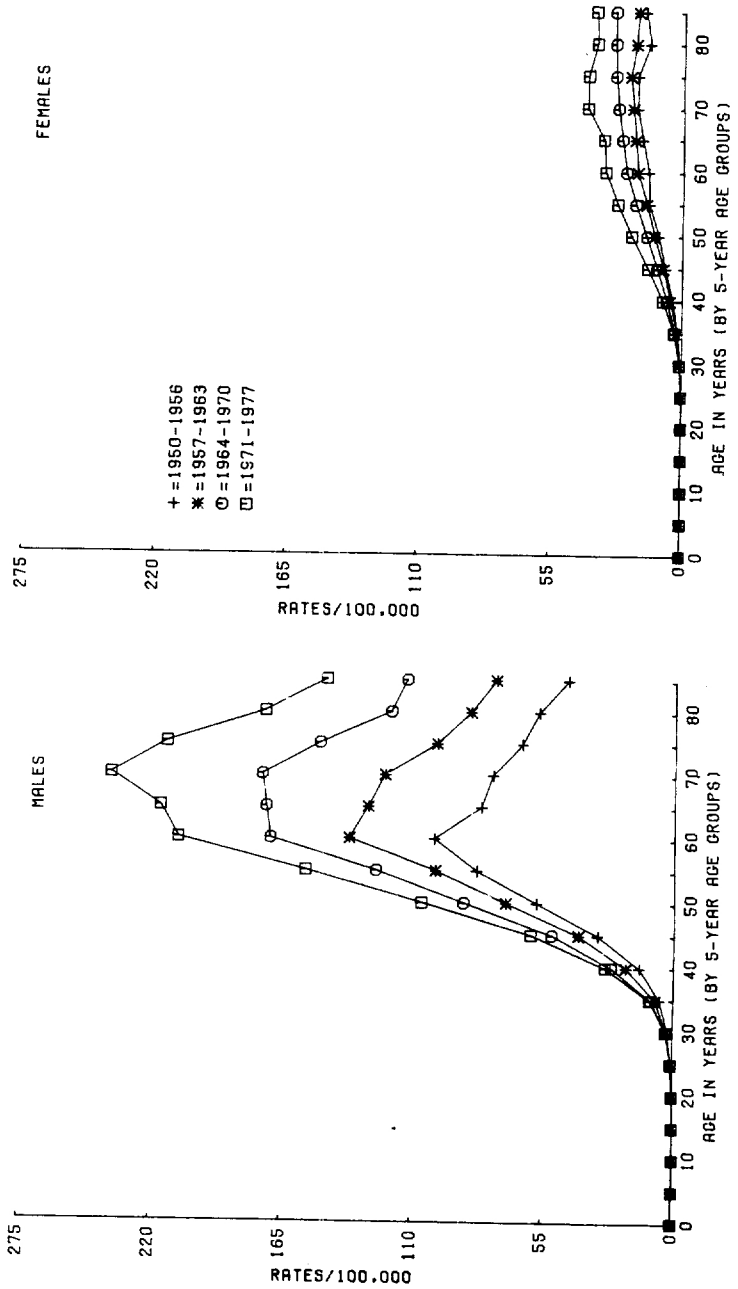

FIGURE 4.—Age-specific mortality rates for nonwhites in the United States for cancer of the bronchus, trachea, and lung

SOURCE: National Cancer Institute (*198*).

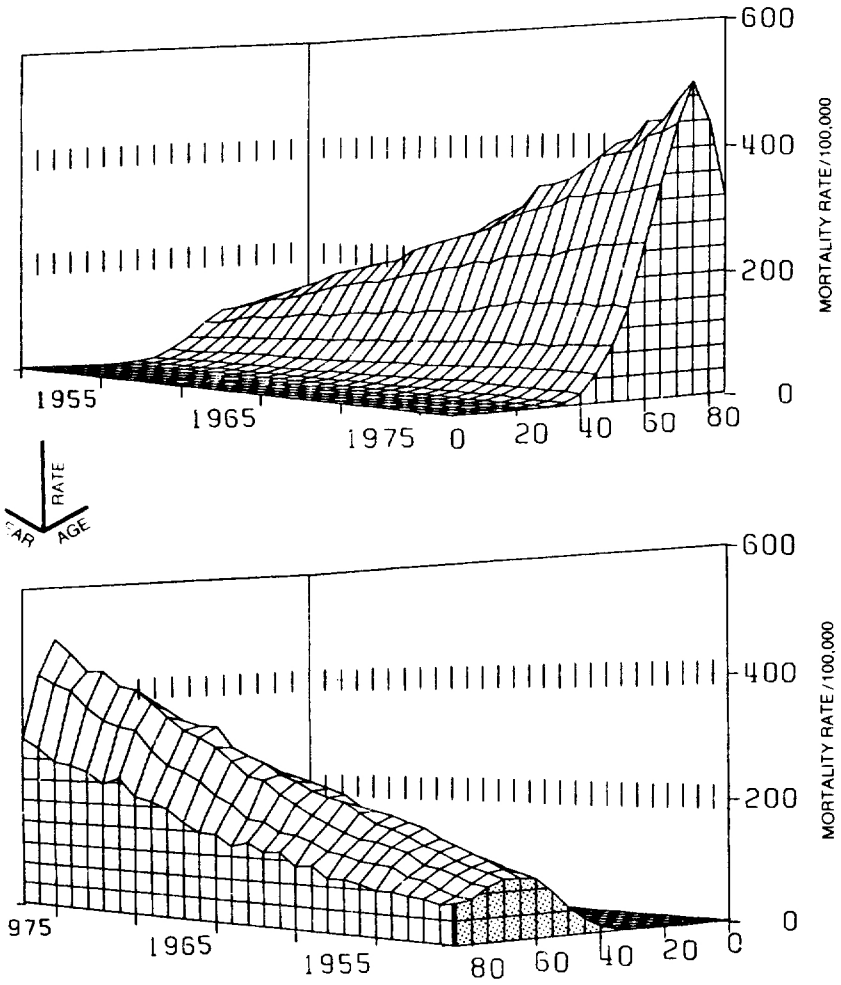

FIGURE 5.—Age-specific mortality rates by 5-year age groups for cancer of the bronchus, trachea, and lung for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

The term "lung cancer" refers to a number of specific malignant diseases involving the lungs. Several systems of classifying lung cancer have been proposed (Table 1).

Four cell types constitute the majority of lung cancers: epidermoid or squamous, adenocarcinoma, small cell (oat cell), and large cell. There are differences in the frequency distribution of the different

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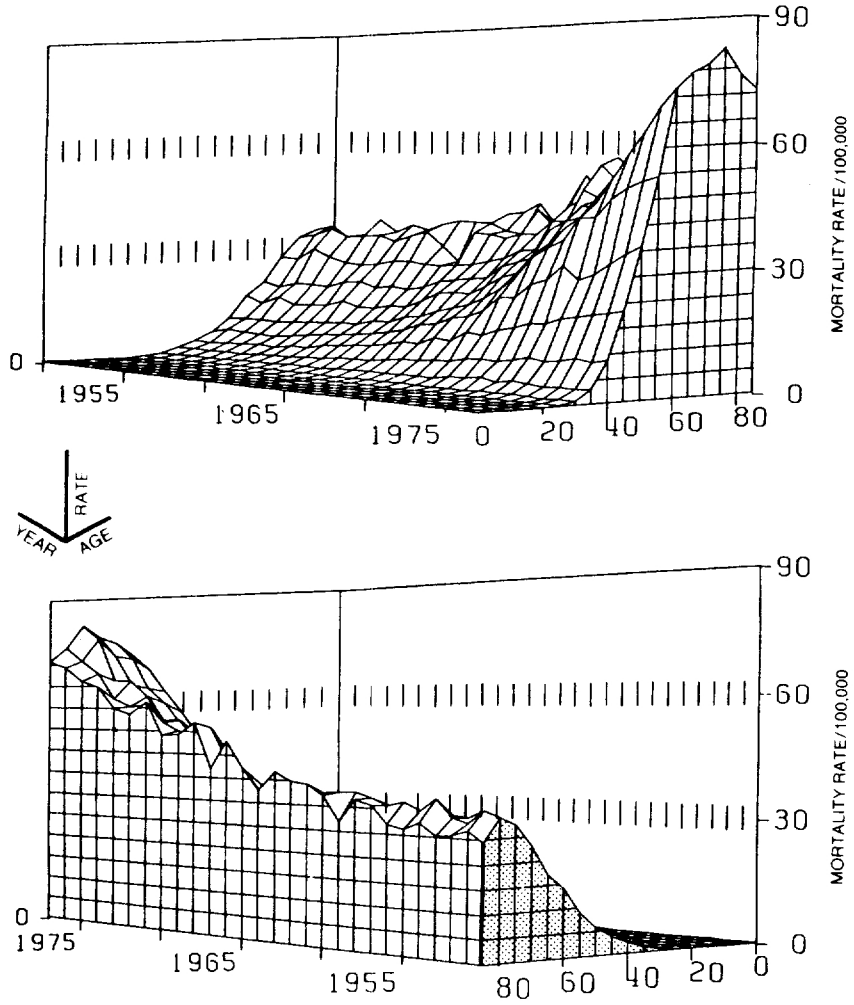

FIGURE 6.—Age-specific mortality rates by 5-year age groups for cancer of the bronchus, trachea, and lung for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

types of lung cancer in males and females and in smokers and nonsmokers. Epidermoid carcinoma was the most common histological type of lung cancer in the male smoker, while adenocarcinoma was most common in the female smoker and in nonsmokers of both sexes in a series recently published from the Mayo Clinic (Table 2) (*225*). Other centers have reported similar data, although the

TABLE 1.—Comparison of the World Health Organization (WHO), Veterans Administration Lung Cancer Chemotherapy Study Group (VALG), and Working Party for Therapy of Lung Cancer (WP-L) Lung Cancer Classifications

WHO	VALG	WP-L
I. Epidermoid carcinoma	1. Squamous cell carcinoma	10. Epidermoid carcinoma
	a. With abundant keratin	11. Well differentiated
	b. With intercellular bridges	12. Moderately differentiated
	c. Without keratin or bridges	13. Poorly differentiated
II. Small cell carcinoma	2. Small cell carcinoma	20. Small cell carcinoma
1. Fusiform	a. With oat-cell structure	21. Lymphocytelike
2. Polygonal	b. With polygonal cell structure	22. Intermediate cell
3. Lymphocytelike		
4. Others		
III. Adenocarcinoma	3. Adenocarcinoma	30. Adenocarcinoma
1. Bronchogenic	a. Acinar	31 Well differentiated
a. Acinar	b. Papillary	32. Moderately differentiated
b. Papillary	c. Poorly differentiated	33. Poorly differentiated
2. Bronchoalveolar		34. Bronchiolopapillary
IV. Large cell carcinoma	4. Large cell undifferentiated	40. Large cell carcinoma
1. Solid tumor with mucin		41. With stratification
2. Solid tumor without mucin		42. Giant cell
3. Giant cell		43. With mucin formation
4. Clear cell		44. Clear cell

SOURCE: Matthews and Gordon (*176*).

proportions by histological type vary with the pathological criteria used, the patient population, the geographic location, and other factors. Earlier epidemiologic studies suggested that cigarette smokers were more likely to develop squamous cell, large cell, and small cell lung carcinoma than other types (*67, 148*). This view has been supported by some investigators (*54, 284*) and disputed by others (*6, 18, 19, 137, 293, 329*). More recent investigations indicate that all four major histological types of lung cancer—including adenocarcinoma, which appears to be increasing in recent years—are related to cigarette smoking in both males and females (*8, 284, 293*).

Establishment of the Association Between Smoking and Lung Cancer

It is not ethical or feasible to perform a controlled experiment in humans to establish a causal relationship between tobacco smoking and lung cancer. Practically, epidemiological methods are employed to test a causal hypothesis. These methods, as discussed previously, when coupled with pathological and experimental data, provide the framework for a judgment of causality.

TABLE 2.—Histologic types of pulmonary cancers in smokers and nonsmokers

Type	Total	Male		Female	
		Smokers	Non-smokers	Smokers	Non-smokers
Epidermoid	992	892	7	80	13
Small cell	640	533	4	100	3
Adenocarcinoma	760	492	39	128	101
Large cell	466	389	16	46	15
Bronchioloalveolar	68	35	4	13	16
Total	2,926	2,341	70	367	148

SOURCE: Rosenow (225).

Numerous retrospective studies have examined smoking patterns among established cases of lung cancer and a variety of matched controls. These studies have been summarized and reviewed in previous reports from the Department of Health and Human Services (*270, 272–281*).

Eight prospective studies have measured lung cancer mortality rates among smokers and nonsmokers followed over various time intervals. In October 1951, Doll and Hill (*62, 63*) initiated the first major prospective study of the relationship between smoking habits and mortality in a cohort of more than 40,000 male and female physicians. By 1965, seven other major prospective studies in four countries had been initiated. These studies cumulatively represent more than 17 million person-years of observation and over 330,000 deaths. The study designs are summarized below and in Table 3.

The number of years of followup reported for the various major prospective studies ranges from a low of 4 years in the American Cancer Society Nine-State Study to 22 years for females in the British Physicians Study. Published reports for the varying followup periods differ substantially for each study with respect to the amount of information provided. Data from the Japanese study have been published presenting 5, 8, 10, and 13 years' results. For each followup period, site-specific cancer mortality is fragmented. Data for specific cancer sites are available only for males from the 13-year followup study; dosage analyses for other cancer sites for either males or females are intermittent among the many published reports cited. In all cases, the most current data from each of the prospective investigations are cited. In some instances, mortality rates (or ratios) for all smokers for a specific site may be from one study period while dosage information (usually expressed as the number of cigarettes smoked per day) may be from another (followup) period. The reader is referred to the references cited at the end of each study description for a complete bibliography.

The British Physicians Study

In 1951, the British Medical Association forwarded to all British doctors a questionnaire about their smoking habits. A total of 34,400 men and 6,207 women responded. With few exceptions, all physicians who replied in 1951 were followed to their deaths or for a minimum of 20 years (males) or 22 years (females). Further inquiries about changes in tobacco use and some additional demographic characteristics of the men were made in 1957, 1966, and 1972 and of the women in 1961 and 1973. By 1973 more than 11,000 deaths from all causes had occurred in this population (*62–66, 68, 69, 71*).

The American Cancer Society 25-State Study

In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women in a prospective study (*97–102, 155*). Although this was not a representative sample of the United States population, all segments of the population were included except groups that the planners believed could not be traced easily. An initial questionnaire was administered that contained information on age, sex, race, education, place of residence, family history, past diseases, present physical complaints, occupational exposures, and various habits. Information on smoking included type of tobacco used, number of cigarettes smoked per day, inhalation, age started smoking, and the brand of cigarettes used. Nearly 93 percent of the survivors were successfully followed for a 12-year period. Early reports of this study examined lung cancer mortality in relationship to several parameters of smoke exposure, including duration of habit and age at onset, among others. Two recent reports have examined the effects of general air pollution (*101*), the type of cigarette smoked (*155*), and lung cancer mortality. Cancer mortality data for 483,000 white females and 358,000 white males for the period 1967 to 1971 were also recently reported (*106*).

The U.S. Veterans Study

The U.S. Veterans study (*74, 131, 222–224*) followed the mortality experience of 290,000 U.S. veterans who held government life insurance policies in December 1953. Almost all policyholders were white males. The data for specific causes of death during a 16-year period were recently reported by Rogot (*224*) and are similar to earlier data published after only $8\frac{1}{2}$ years of observation of this population (*131*). Over 107,000 deaths have occurred in this population.

The Japanese Study of 29 Health Districts

In late 1965, a total of 265,118 men and women in 29 districts in Japan were enrolled in a prospective study (*115–120*). This represent-

ed from 91 to 99 percent of the population aged 40 and older in these districts. This study provided the unique opportunity to examine the relationship of cigarette smoking to death rates in a population with genetic, dietary, and cultural differences from previously examined Western populations. By the end of the 13th year of followup, almost 40,000 deaths had occurred, including 10,300 cancer deaths, and there were over 3,000,000 person-years of observation. For females, the main body of published data is based on 5 to 8 years of followup.

The Canadian Veterans Study

Beginning in 1955, the Canadian Department of National Health and Welfare enrolled 78,000 men and 14,000 women in a study of smoking-related mortality (*26, 27*). Information was obtained on age, detailed smoking history, residence, and occupation. During the first 6 years of followup, 9,491 males and 1,794 females died. No more recent followup has been reported.

The American Cancer Society Nine-State Study

In the American Cancer Society Nine-State Study (*104, 105*), 187,783 white males were followed for an average of 44 months. This study began in early 1952. There were 11,870 deaths in the age 50 to 70 population. The last major report of this study was published in 1958.

The California Men in Various Occupations Study

This study (*76, 290*) examined the mortality experience of 68,153 men, 35 to 64 years of age, over a period of 482,650 person-years of observation. A total of 4,706 deaths occurred. These men were in nine occupational groups. The last published report from this study was in 1970.

The Swedish Study

A national probability sample (*42*) of 55,000 Swedish men and women was surveyed in 1963 by mailed questionnaires, to which 89 percent of the sample responded. Information was collected on smoking status at the time of the initial query and for specific intervals during the previous 9 years according to type and amount of smoking and degree of inhalation. The questionnaire identified age, sex, location (urban, nonurban), income, and occupation of subjects. A 10-year followup on smoking-related mortality was published in 1975.

TABLE 3.—Outline of eight major prospective studies

Authors	Doll Hill Peto Pike	Hammond	Dorn Kahn Rogot	Hirayama	Best Josie Walker	Hammond Horn	Weir Dunn Linden Breslow	Cederlof Friberg Hrubec Lorich
Subjects	British doctors	Males and females in 25 States	U.S. veterans	Total population of 29 health districts in Japan	Canadian pensioners	White males in nine States	California males in various occupations	Probability sample of the Swedish population
Population size Females	40,000 6,000	1,000,000 562,671	290,000 <1%	265,000 142,857	92,000 14,000	187,000	68,000	55,000 27,700
Age range	20–85+	35–84	35–84	40 and up	30–90	50–69	33–64	18–69
Year of enrollment	1951	1960	1954 1957	1966	1955	1952	1954	1963
Years of followup reported	20–22 years	12 years	16 years	13 years	6 years	4 years	5–8 years	10 years
Number of deaths	11,166	150,000	107,500	39,100	11,000	12,000	4,700	4,500
Person years of experience	800,000	8,000,000	3,500,000	3,000,000	500,000	670,000	480,000	550,000

Causal Significance of the Association

It is apparent from retrospective and prospective data that a significant association exists between smoking and lung cancer (Tables 4 and 5). However, as noted above, proof of causality is a matter of judgment that goes beyond the simple statement of statistical probability. To judge this association, a number of criteria must be satisfied, no one of which is a *sine qua non* for judgment.

Consistency of the Association

More than 50 retrospective studies have reported smoking patterns (by type and quantity of tobacco smoked, duration of smoking, and inhalational practice) in a variety of subjects with lung cancer (e.g., males and females, different occupational groups, hospitalized patients, autopsy cases, all individuals who died from lung cancer in an area, nationwide sample of individuals who died from lung cancer, and different races and ethnic groups) (*276*). Many of these subjects have been compared with matched controls also drawn from a variety of groups (e.g., healthy individuals, patients hospitalized for cancer or other diseases, deaths from cancers of other sites, and samplings of the general population). Regardless of the method, these studies have consistently found an association between smoking and lung cancer. Relative risk ratios for smokers are consistently greater than for nonsmokers in the investigations up to 1971 (Table 4). Subsequent data show similar findings (*269*).

The Third National Cancer Survey (TNCS) and the Hawaiian Study of Five Ethnic Groups are two large population-based retrospective studies that were recently reported. In the TNCS, 7,518 subjects with invasive cancer (57 percent of those randomly selected) were interviewed in person; the data recorded included quantitative lifetime use of cigarettes, cigars, pipes, unsmoked tobacco, wine, beer, hard liquor, combined alcohol, and education and family income level (*299*). A significant independent positive association was found with cigarette smoking and lung cancer, with relative risks as high as 9.9 for the heaviest smokers. In the Hawaiian study, 9,920 subjects with cancer were interviewed in person. The data recorded included consumption rates for cigarettes, beer, wine, and hard liquor (*113*). A significant positive association was found with cigarette consumption and lung cancer for all ethnic groups.

Eight major prospective studies have examined the relationship between smoking and lung cancer mortality in a large number of subjects, in different countries, and in different time periods. The results of these studies (presented in Table 5) are consistent with each other as well as with the retrospective studies.

The possibility of genetic predisposition toward both smoking and lung cancer has also been examined. One group of scientists (*43*) has

TABLE 4.—Relative risk ratios* for lung cancer mortality, retrospective studies, 1939–1970

Year/Author	Male**	Female**
1939 Müller (*191*)	5.4+	-
1943 Schairer and Schoniger (*237*)	5.7+	-
1945 Potter and Tully (*213*)	4.1+	-
1948 Wassink (*288*)	4.7	-
1950 Schrek et al. (*244*)	1.8	-
1950 Mills and Porter (*181*)	5.7	-
1950 Levin et al. (155a)	1.5	-
1950 Wynder and Graham (*315*)	13.0	2.9
1952 McConnell et al. (*178*)	1.2	2.8
1952 Doll and Hill (*61*)	9.4	2.1
1953 Sadowsky et al. (*230*)	3.9	-
1953 Wynder and Cornfield (*311*)	6.1+	-
1953 Koulumies (*147*)	36.0	-
1953 Lickint (*156*)	10.4+	5.3
1954 Breslow et al. (*34*)	3.2	-
1954 Watson and Conte (*289*)	5.6+	3.3
1954 Gsell (*90*)	26.8+	-
1954 Randig (*215*)	5.1+	2.2
1956 Wynder et al. (*308*)	-	1.4
1957 Segi et al. (*248*)	-	-
1957 Mills and Porter (*182*)	4.2	0.6
1957 Stocks (*259*)	4.9	1.6
1957 Schwartz and Denoix (*245*)	10.4	-
1958 Haenszel et al. (*94*)	-	2.5
1959 Lombard and Snegireff (*161*)	7.9	-
1960 Pernu (*209*)	8.4	1.9
1962 Haenszel et al. (*93*)	5.2	-
1962 Lancaster (*152*)	9.8	-
1964 Haenszel and Taeuber (*95*)	-	1.3
1966 Wicken (*295*)	3.9	
1968 Gelfand et al. (*87*)	25.3+	2.9
1968 Hitosugi (*121*)	2.6	2.3
1969 Bradshaw and Schonland (*33*)	-	-
1969 Ormos et al. (*205*)	9.3	0.2
1970 Wynder et al. (*319*)	20.8+	6.78

* Computed according to method of Cornfield (*49*).
** Ratio of smoker to nonsmoker.
\+ Based upon fewer than 5 case nonsmokers.

published data from the Swedish Twin Registry about monozygotic twins discordant for smoking, which showed a significant excess of lung cancer in the smoking twin of the pair. The authors state, "The well-documented evidence of a causal association between smoking and lung cancer found in other subjects has been further supported." Similar conclusions were reached in a retrospective study of families of lung cancer patients (*265*).

Strength of the Association

Relative risk ratios for lung cancer from the retrospective studies (Table 4) were strikingly elevated among smokers as compared with nonsmokers. Similar data were reported from the eight prospective

TABLE 5.—Lung cancer mortality ratios—prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British	34,000 males	441	1.00	14.0
Physicians	6,194 females	27	1.00	5.0
Swedish	27,000 males	55	1.00	7.0
Study	28,000 females	8	1.00	4.5
Japanese	122,000 males	940	1.00	3.76
Study	143,000 females	304	1.00	2.03
ACS 25-State	358,000 males	2018	1.00	8.53
Study	483,000 females	439	1.00	3.58
U.S. Veterans	290,000 males	3126	1.00	11.28
Canadian Veterans	78,000 males	331	1.00	14.2
ACS 9-State Study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

studies (Table 5). The mortality ratios for male smokers ranged from 3.76 for the Japanese study to 14.2 for the Canadian Veterans study. In general, lower mortality ratios were experienced by female smokers. The mortality ratios for females ranged from slightly more than 2.0 for the Japanese to 5.0 for the British female physicians. Combining the data from the prospective studies allows the conclusion that male cigarette smokers are about 10 times as likely to develop lung cancer as are nonsmokers, while the risk for heavier smokers considered alone is substantially higher (*272*).

The strength of the association between smoking and lung cancer is further enhanced by clear dose-response relationships. The strongest dose-response measured in most epidemiological studies was for the number of cigarettes smoked per day at the time of entry into the study. However, other important measures of dosage include the age at which smoking began, the duration of smoking, and inhalation practice. Several of the prospective studies have assessed these relationships.

The data, presented in Table 6, indicate that as the number of cigarettes smoked per day increases there is a gradient of risk for lung cancer mortality. This gradient increase was observed in each of the eight major prospective studies. Male smokers who smoked more than 20 cigarettes daily had lung cancer mortality ratios 15 to

25 times greater than nonsmokers. Similar findings were observed among female smokers, although proportionately fewer females were heavy smokers compared to males.

Four prospective studies which examined lung cancer mortality by age began smoking are presented in Table 7. These show a strong inverse relationship with age starting to smoke, i.e., the younger the age one began smoking, the greater the lung cancer mortality rate.

Three prospective studies reported data on the relationship between degree of inhalation and lung cancer mortality among smokers. Data from two of these studies are presented in Table 8. The third study (*68*) noted a relationship for light and moderate smokers (1–14 and 15–24 cigarettes per day) who reported that they inhaled as compared to smokers who said they did not inhale; but the reverse was found for heavier smokers ($\geq$ 25 cigarettes per day).

Another measure of smoke exposure is reflected by the tar and nicotine (T/N) content of the cigarette smoked. Filter cigarettes were introduced in the mid-1950s and were quickly adopted by smokers, particularly women. Generally, today's filtered cigarettes have lower tar and nicotine values compared to nonfiltered cigarettes (*81*). By 1981, 93 percent of the more than 600 billion cigarettes smoked in the United States were filtered (*177*). A few epidemiological studies have examined the relationship of lung cancer mortality by T/N content or by examining filtered versus nonfiltered cigarettes smoked. For the American Health Foundation, Wynder and Stellman conducted a retrospective study of the effects of filtered versus nonfiltered cigarettes (*326*). Relative risk ratios for smokers of filter cigarettes (which were assumed to be lower in tar and nicotine) were less than those for smokers of nonfilter cigarettes (Figures 7 and 8). Kunze and Vutuc (*149*) and Remington (*219*) reported similar data in Austrian and British studies, respectively. The largest of the prospective studies, the American Cancer Society 25-State Study (*155*), showed a decrease in risk for lung cancer among male and female smokers of lower T/N cigarettes as compared with smokers of higher yield cigarettes (Table 9), although the rates for lower T/N cigarette smokers were still considerably higher than the rates for nonsmokers.

Specificity of the Association

Tobacco smoke is a complex mixture consisting of several thousand chemical substances (*269, 277*). These diverse substances are capable of producing more than a single biological response. The specificity of the association between smoking and lung cancer is evidenced by comparison of the magnitude of lung cancer mortality ratios to those of other cancers, as has been done in most of the

TABLE 6.—Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day—prospective studies

Population	Men		Women	
	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-State Study	Nonsmoker	1.00	Nonsmoker	1.00
	1–9	4.62	1–9	1.30
	10–19	8.62	10–19	2.40
	20–39	14.69	20–39	4.90
	40+	18.71	40+	7.50
British Physicians Study	Nonsmoker	1.00	Nonsmoker	1.00
	1–14	7.80	1–14	1.28
	15–24	12.70	15–24	6.41
	25+	25.10	25+	29.71
Swedish Study	Nonsmoker	1.00	Nonsmoker	1.00
	1–7	2.30	1–7	1.80
	8–15	8.80	8–15	11.30
	16+	13.70	16+	—
Japanese Study All ages	Nonsmoker	1.00	Nonsmoker	1.0
	1–19	3.49	< 20	1.90
	20–39	5.69	20-29	4.20
	40+	6.45		
U.S. Veterans Study	Nonsmoker	1.00		
	1–9	3.89		
	10–20	9.63		
	21–39	16.70		
	≥ 40	23.70		
ACS 9-State Study	Nonsmoker	1.00		
	1–9	8.00		
	10–20	10.50		
	20+	23.40		
Canadian Veterans	Nonsmoker	1.00		
	1–9	9.50		
	10–20	15.80		
	20+	17.30		
California males in nine occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1 ½ pk	9.56		

prospective studies (see Appendix Tables A and B). The mortality ratios for lung cancer are very high when compared with those of other cancers.

TABLE 7.—Lung cancer mortality ratios for males, by age began smoking—prospective studies

Study	Age began smoking in years	Mortality ratio
ASC 25-State Study	Nonsmoker	1.00
	25+	4.08
	20–24	10.08
	15–19	19.69
	under 15	16.77
Japanese Study	Nonsmoker	1.00
	25+	2.87
	20–24	3.85
	under 20	4.44
U.S. Veterans	Nonsmoker	1.00
	25+	5.20
	20–24	9.50
	15–19	14.40
	Under 15	18.70
Swedish Study	Nonsmoker	1.00
	19+	6.5
	17–18	9.8
	Under 16	6.4

TABLE 8.—Lung cancer mortality ratios by degree of inhalation—prospective studies

Study	Degree of inhalation	Mortality ratio		Comments
		Males	Females	
ACS 25-State Study	Nonsmoker	1.00	1.00	
	None	8.00	1.78	
	Slight	8.92		
	Moderate	13.08	3.70	
	Deep	17.00		
Swedish Study	Nonsmoker	1.00	1.00	Female data
	None	3.70	—	based on only
	Light	7.80	7.20	9 total lung
	Deep	9.20	1.80	cancer deaths

Temporal Relationship of the Association

The criterion of temporality requires that cigarette smoking antedate the onset of cancer. Support for this criterion is provided by all the major prospective studies in which an enormous number of initially disease-free subjects were followed over varying time intervals.

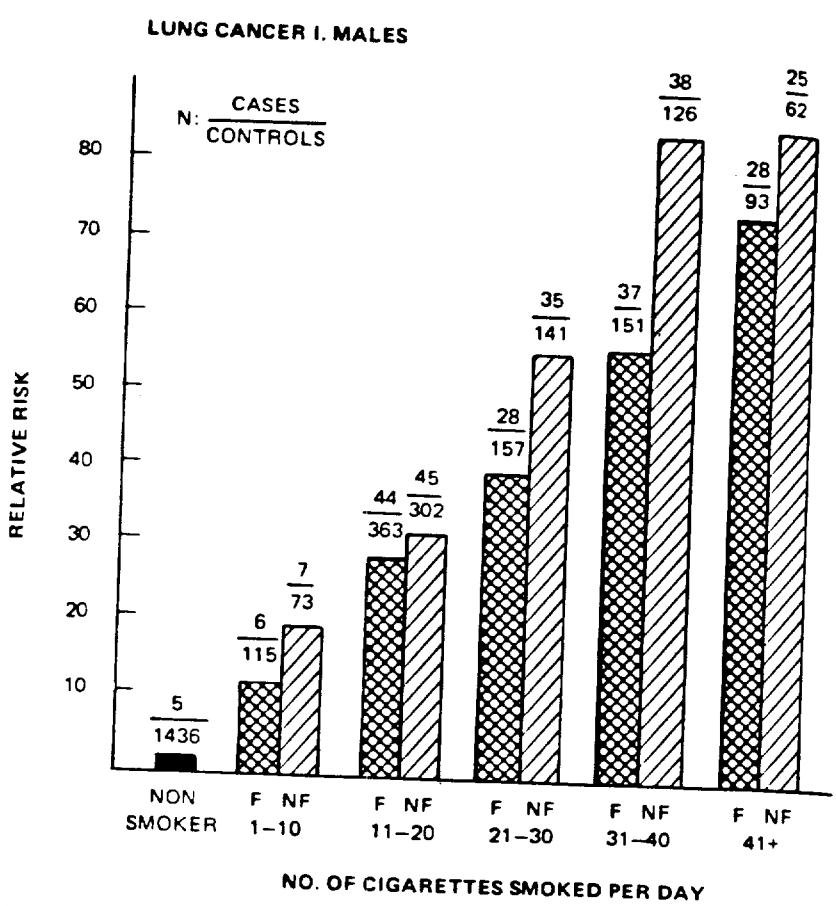

FIGURE 7.—Relative risk of lung cancer for males, by number of cigarettes smoked per day and long-term use of filter (F) or nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

Indirect support for the temporality of the association is provided by other studies (*57, 70*). One study (*57*) examined the relationship between per capita tobacco consumption in 1930 and male lung cancer death rates in 1950 in 11 different countries (Figure 9). This study encompassed the era prior to the advent of filter cigarettes. Assuming that the majority of tobacco consumption in 1930 occurred among males and that there was a 20-year latency period for the development of lung cancer, there was a strong positive correlation between tobacco consumption in 1930 and lung cancer death rates in 1950.

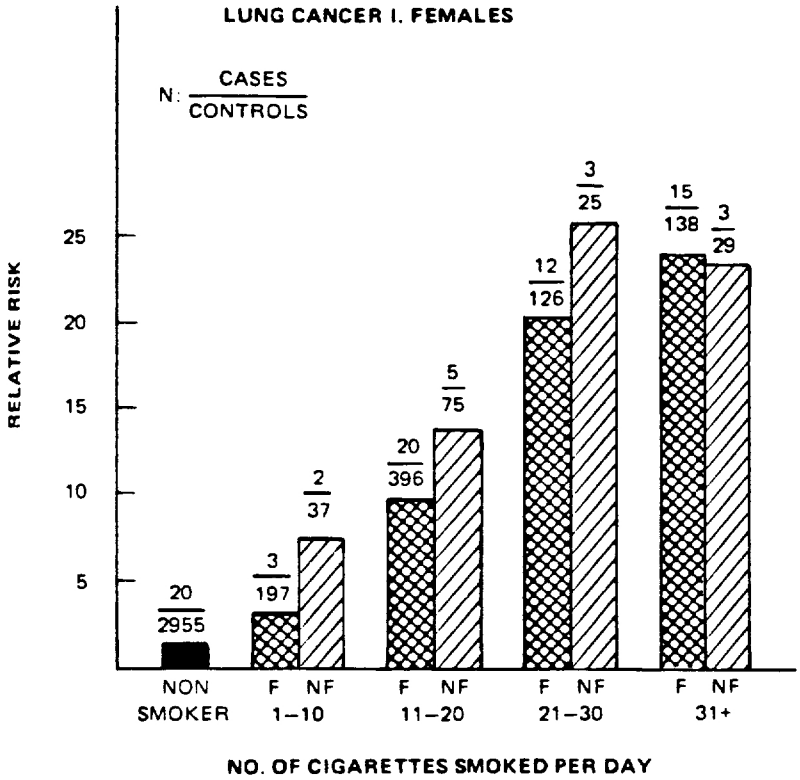

FIGURE 8.—Relative risk of lung cancer for females, by number of cigarettes smoked per day and long-term use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

A later study (*70*) examined the relationship between manufactured cigarette consumption per adult in 1950 and lung cancer death rates in males and females who were in the 35- to 44-year-old age group in the mid-1970s (who had entered adult life in 1950). There was a consistent correlation between cigarette consumption and lung cancer death rates in different countries (Figure 10), a finding which was "better than...expected in view of the possible international differences in cigarette composition, puff frequency, style of inhalation, butt length, additional use of nonmanufactured cigarettes (and other forms of tobacco), and national consumption of cigarettes in intervening years between 1950 and 1975."

TABLE 9.—Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine in cigarettes smoked

	Males	Females
High T/N	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

*The mortality ratio for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

SOURCE: Hammond et al. (*103*).

Additional evidence for the temporality of this association is advanced by a number of histological studies showing that smokers develop histologic changes interpreted by most pathologists as premalignant lesions in bronchial epithelium in much greater proportions than nonsmokers, and that these changes progress toward cancer in continuing smokers but reverse in ex-smokers (*9, 14, 15*) (Table 14).

Coherence of the Association

The final criterion is the coherence of the association between smoking and lung cancer with known facts in the biology and natural history of lung cancer. Coherence of the association has been noted with the following facts:

Dose-Response Relationship Between Smoking and Lung Cancer Mortality

The finding of a dose-response relationship between cigarette smoking and lung cancer provides great coherence with the known facts of the disease. Regardless of the measure of tobacco consumption employed (i.e., number of cigarettes smoked, inhalation practice, duration of smoking, age when smoking began, or type of cigarettes smoked), there was a gradient of disease consistent with a true dose-response relationship in every study.

Sex Differences in Lung Cancer Mortality Correlating With Corresponding Differences in Smoking Habits

Males have had higher lung cancer death rates than females. This observation has been interpreted by some as contradictory to the causal role of smoking in lung cancer (*82, 167*). However, a careful examination of smoking patterns and age-specific mortality data has

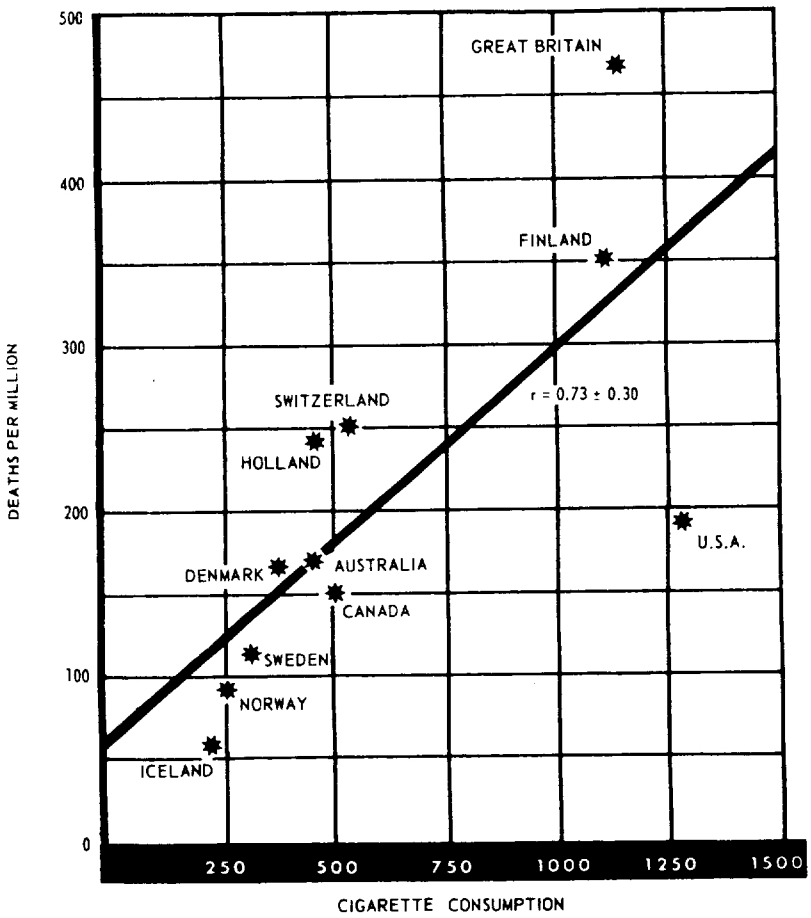

FIGURE 9.—Crude male death rate for lung cancer in 1950 and per capita consumption of cigarettes in 1930 in various countries

SOURCE: Doll (57).

been interpreted by most observers as support for the causality of smoking in lung cancer. Historically, males began to smoke in large numbers in the World War I period, and much of the increased cigarette use noted during this period reflected switching from other forms of tobacco (e.g., smokeless tobaccos, pipes, and cigars) to cigarettes. Females began to smoke in larger numbers about 20 to 25 years later, in the World War II era (*270*); at that time, a smaller proportion of females smoked compared to males, and those who did, generally smoked fewer cigarettes per day, inhaled less, started later in life, and were more likely to smoke lower tar and nicotine and filtered cigarettes. These differences in smoking habits of males and

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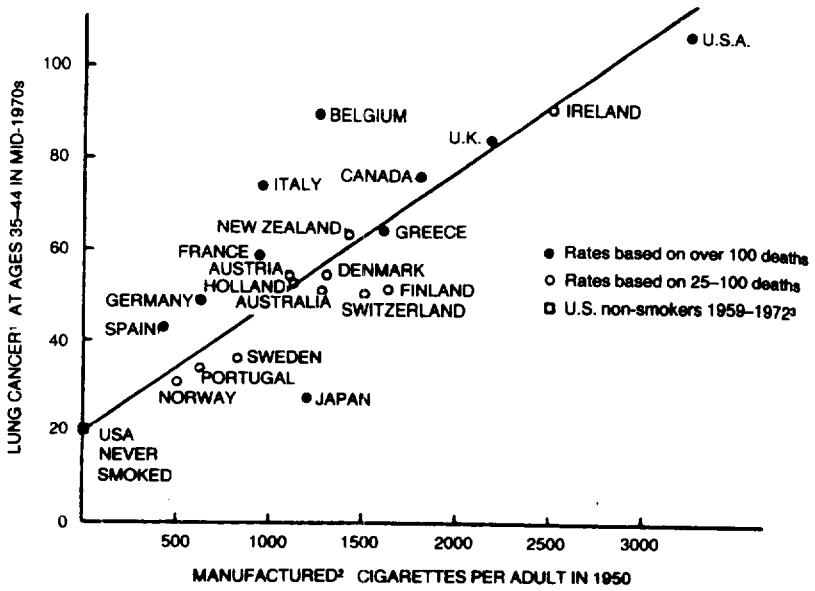

FIGURE 10.—International correlation between manufactured cigarette consumption per adult in 1950 while one particular generation was entering adult life (in 1950), and lung cancer rates in that generation as it enters middle age (in the mid-1970s)

NOTE: Comparison has been restricted to developed countries (i.e., excluding Africa, all of Asia except Japan, and all except North America), with populations >1 million, to improve the accuracy of the observed death certification rates as indicators of the underlying risks of lung cancer among people aged 35–44.

[1]Lung cancer death certification rates per million adults aged 35–44 are from WHO (*303, 304*). These rates are the means of the male and female rates for all years (1973, 1974, or 1975) reported in WHO (*303*), except for Greece (which was not reported in WHO (*303*) and thus was taken from WHO (*304*)) and Norway for which the rates in WHO (*303*) and WHO (*304*) were based on only 11 and 14 cases, respectively; for statistical stability, these were averaged.

[2]Manufactured cigarettes per adult are from Lee (*154*) for the year 1950 (except for Italy, where consumption data are available in 5-year groups only); to avoid the temporary postwar shortages, data for 1951–55 have been used. This excludes handrolled cigarettes, which in most countries accounted for only a small fraction of all cigarette tobacco in 1950.

[3]U.S. nonsmoker rates were estimated by fitting straight lines (on a double logarithmic scale) to the relationship between lung cancer mortality and age reported for male and for female lifelong nonsmokers by Garfinkel (*86*) and averaging the predicted values at age 40. (Although the average of the male and female rates actually observed at these ages is similar to this estimated value, these observed rates are each based on fewer than five cases (Garfinkel) (*86*) and so might have been inaccurate.)

SOURCE: Doll and Peto (*70*).

females correlate well with the observed sex differences in lung cancer mortality rates. In fact, the rise in female lung cancer mortality rates observed in the late 1950s and early 1960s appears to be reproducing the phenomena noted among males 20 to 30 years earlier. If one subtracts 25 years from the female cancer death rate, as noted previously in Figure 1, the rates for women are only slightly below the rates for men. Thus, close scrutiny of these trends reveals

no substantial difference in the risk of developing lung cancer between men and women.

Lung Cancer Mortality and Cessation of Smoking

Since cigarette smoking is significantly associated with lung cancer, it is logical to expect that cessation of smoking would lead to a decrease in mortality rates from lung cancer among quitters compared to persons who continue to smoke cigarettes. In fact, all of the major studies which examined cessation showed this decrease in lung cancer risk. Data from four of the major prospective studies are presented in Table 10 for illustration. After 15 to 20 years, the ex-smoker's risk of dying from lung cancer gradually decreases to a point where it more closely approximates the risk of the nonsmoker (*68, 224*), whereas for the continuing cigarette smoker, the lung cancer risk is more than 10 times that of the nonsmoker. The magnitude of the residual risk that ex-smokers experience is largely determined by the cumulative exposure to tobacco prior to smoking cessation (i.e., total amount the individual smoked, age when smoking began, and degree of inhalation), and varies with number of years since quitting smoking, as well as with the reasons for quitting smoking (e.g., quitting due to symptoms of disease).

Differences in Lung Cancer Mortality by Site of Residence (Urban Versus Rural)

A number of studies have examined the relationship of smoking to lung cancer mortality by site of residence (urban or rural) and air quality of a community. Eight of the earlier studies were reviewed in the 1971 Report of the Surgeon General (*276*). More recent publications include "Epidemiological Review of Lung Cancer in Man" (*111*) and the report of a task group, "Air Pollution and Cancer" (*41*). There have been studies in England and Wales (*59*), in 20 countries combined (*40, 291*), as well as in the United States (*101, 146, 164, 258*). The majority of these studies has found that lung cancer mortality is more common in urban than rural areas. This urban to rural gradient is primarily, but not exclusively, found among smokers. Since cigarette consumption is generally greater in urban areas than in rural areas, it is difficult to define conclusively what proportion, if any, of the excess lung cancer mortality in city dwellers can be accounted for by urban living independent of smoking.

One study (*164*) examined the risk of several cancers by religion and place of residence in 20,379 cases in the State of Utah. Members of the Church of Jesus Christ of Latter-Day Saints (Mormons) composed approximately 70 percent of the state's population in 1970. The use of tobacco and alcohol is prohibited by religious tenets, and it is documented that Mormons have a very low proportion of

TABLE 10.—Lung cancer mortality ratios in ex-cigarette smokers, by number of years stopped smoking

Study	Years stopped smoking	Mortality ratio	
British Physicians	1–4	16.0	
	5–9	5.9	
	10–14	5.3	
	15 +	2.0	
	Current smokers	14.0	
U.S. Veterans*	1–4	18.83	
	5–9	7.73	
	10–14	4.71	
	15–19	4.81	
	20 +	2.10	
	Current smokers	11.28	
Japanese Males	1–4	4.65	
	5–9	2.50	
	10 +	1.35	
	Current smokers	3.76	
		Number of cigarettes Smoked per day	
		1–19	20 +
ACS 25-State Study (males 50–69)	<1	7.20	29.13
	1–4	4.60	12.00
	5–9	1.00	7.20
	10 +	0.40	1.06
	Current smokers	6.47	13.67

* Includes data only for ex-cigarette smokers who stopped for other than physicians' orders.

smokers. Approximately 77 percent of Mormons live in urban areas and 23 percent live in rural areas. Non-Mormons, whose smoking habits and alcohol consumption more closely resemble those of the U.S. population in general, showed a similar distribution of urban and rural residence. These authors found substantial urban-rural differences in cancer mortality at a number of sites; the largest urban-rural difference observed, however, was found in lung cancer mortality among non-Mormons. There were almost no urban-rural differences in cancer mortality among Mormons (Figure 11). The authors concluded that the urban-rural gradient in lung cancer incidence among non-Mormons reflects differences in smoking habits or interaction of smoking and air pollution or occupational exposure.

Data from the American Cancer Society 25-State Study (*101*) have been reported recently. The data showed little, if any, effect of general air pollution on the lung cancer death rates of males, who in 1959 reported having lived in the same neighborhood for at least 10 years. Thus, the majority of epidemiological investigations indicates that the most important cause of lung cancer is cigarette smoking

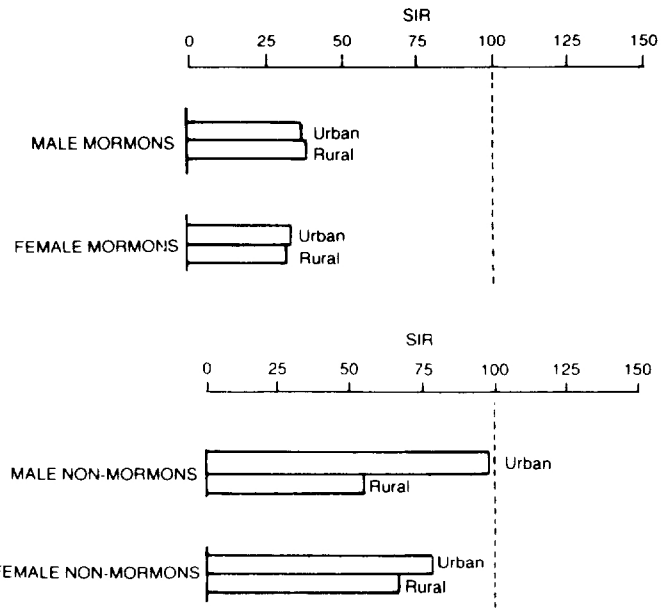

FIGURE 11.—Standard incidence ratios* (SIR) for lung cancer among Utah Mormons and non-Mormons by site of residence and sex

* Compared with the Third National Cancer Survey rates.
SOURCE: Adapted from Lyon et al. (*164*).

and that urban factors, such as air pollution, probably contribute less than 5 percent of the cases of lung cancer in the United States (*70*).

Lung Cancer Mortality and Occupation

Various investigators have estimated that occupational exposure to a variety of chemical substances is responsible for 1 to 15 percent of lung cancer mortality (*47, 58, 109, 110, 196, 314*). A higher estimate of 36 percent (*212*) resulted when differences in smoking patterns were disregarded. In the American Cancer Society 25-State Study (*101*), the mortality from lung cancer after standardization for smoking history was 13.5 percent greater among men with a reported history of occupational exposure to a variety of chemicals, dust, fumes, vapors, and radiation, as compared with those without such a history. Reviewing these data, other scientists (*70*) have suggested that, since "only 38 percent of lung cancer deaths occurred among men who gave a positive history, the total contribution of

TABLE 11.—Limiting factors for attributing cancer to environmental factors

1.	Inaccurate or incomplete knowledge of which industrial chemicals and/or physical agents are carcinogens, cocarcinogens, and promoters
2.	Lack of accurate knowledge of duration and levels of exposure
3.	Lack of accurate knowledge of numbers of workers exposed
4.	Lack of accurate knowledge of incidence and types of cancers occurring
5.	Probable multivariate nature of cancer causation
6.	Mixed and multiple exposures to carcinogenic conditions at the workplace and in daily living (e.g., lifestyle factors)

SOURCE: Adapted from Stellman and Stellman (*255*).

these factors to the production of the disease appears to have been 4.6 percent," a figure they consider too low to be of significance.

This wide range of estimates reflects the considerable complexity of attributing cancer risks to occupational factors, as noted by several authors (*210*). One study (*255*) recently discussed these limitations (Table 11) and concluded that "even if carcinogen dosage and cancer response among workers were available, the ability to detect and attribute occupationally caused cancer would be limited by the fragmented nature of production (i.e., relatively small numbers of workers in many locations) and the change in the exposed populations (i.e., employee turnover, plant shutdown, and production changes)."

Epidemiological and experimental data have established several occupational causes of lung cancer. The finding of a synergistic relationship between smoking and occupational agents (e.g., asbestos (Table 12) and possibly radioactive aerosols), is not surprising in view of the fact that cigarette smoke contains multiple chemical compounds, among which are known carcinogens, tumor initiators, and tumor promoters.

Correspondence of Lung Cancer Mortality Among Different Populations With Different Tobacco Consumption

Two studies (*57, 70*) have found a close correlation between cigarette consumption and lung cancer mortality in different countries (Figures 9 and 10). In the Utah Cancer Study (*165, 166, 294*), Mormons had much lower lung cancer mortality rates than did non-Mormons. One study (*79*) compared cancer mortality rates of a subgroup of "active" Mormon males (a subset of particularly religious Mormons that has an even lower proportion of smokers than among all Mormons) to those of ordinary California and Utah Mormons. Active Mormon males had less than one-half the standardized mortality ratio for lung cancer deaths compared with other Mormon males.

Phillips et al. (*211*) conducted a study of California Seventh Day Adventists (a religious group with a very small proportion of

TABLE 12.—Epidemiological and experimental evidence for carcinogenicity of industrial inhalants

	Agent	Years[a,b]	Evidences[a] Epidemiological	Experimental	Occupations[b]	Demonstrated Interaction with cigarette Smoking	Remarks
1.	Arsenic	1951	Established	Negative	Copper smelters, arsenic pesticide manufacturers, some gold mines	Unknown	Satterlee (*235*) reported an average of 46 mg of arsenic in several cigarettes in 1950–1951. Lee and Murphy (*153*) found the average reduced to 7.7 +0.5 mg by 1967.
2.	Asbestos	1935	Established	Established	Asbestos miners, asbestos textile manufacturers, asbestos insulation workers, certain shipyard workers	Established (*25, 107, 174, 180, 249, 250*)	Asbestos workers who smoked cigarettes had 5 times the risk for lung cancer of smokers without asbestos exposure and over 50 times the risk of individuals who neither smoked nor worked with asbestos.
3.	Chloromethyl ethers	1968	Established	Established	Makers of ion exchange resins	Unknown	Recent data from Weiss (*292*) suggest a protective effect of cigarette smoking. The use of this agent has been widely curtailed; future data are unlikely.
4.	Chromium	1936	Established	Established	Manufacturers of chromates from chromate ores	Unknown	
5.	Coke oven fumes	1971	Established	Established	Coke oven workers (steel mills), gas retort workers	Unknown	
6.	Nickel	1933	Established	Established	Nickel refiners	Unknown	
7.	Radioactive aerosols	1979	• Established	Established	Uranium miners	Established (*5, 285, 286, 287, 163, 229*)	Risk for cigarette smoking uranium miners is at least four times greater than for cigarette smokers who do not work in the mines (*163, 229*). Nonsmoking miners also have increased risk for lung cancer (*17*).

[a] Adapted from Hoffmann and Wynder (*123*).

[b] The year agent first suspected to be a human carcinogen for bronchi or lung.

SOURCE: Adapted from Doll and Peto (*70*) and Wynder and Gori (*314*).

smokers) and found that the lung cancer mortality rate among Seventh Day Adventists was only 20 percent of the rate of the control population (112,726 smoking and nonsmoking Californians enrolled in the American Cancer Society prospective study in 1960) (*98*).

Lung Cancer Mortality and Age-Specific Smoking Patterns

Male lung cancer death rates have to date been higher than female lung cancer death rates. Age-specific lung cancer death rates decline in the oldest age groups, although age-adjusted mortality rates continue to climb in both males and females in spite of the decline of smoking prevalence in both groups. Each of these facts appears to challenge the coherence between smoking behavior and the occurrence of lung cancer. However, smoking behavior is not uniform for different age and sex cohorts; therefore, in order to examine the coherence of this relationship, it is necessary to match the smoking behavior of an individual cohort with the lung cancer occurrence in that cohort. Figure 12 shows the prevalence of cigarette smoking over time among successive age cohorts of males, and it can be compared with Figure 13, which shows the specific mortality rates of cancer of the lung by birth cohort and age of death. Figures 14 and 15 are the corresponding graphs for females. Careful examination of these graphs resolves the apparent discrepancy between smoking prevalence data and lung cancer mortality data. Males began to take up smoking in large numbers some 25 years prior to females taking up the habit in large numbers. In addition, the cohorts of males with the peak prevalence of smoking were born between 1910 and 1930, whereas the peak prevalence in females occurred among those born between 1920 and 1950. These differences in the smoking prevalence among the different birth cohorts for males and females explain a large part of the difference in overall mortality rates. When the mortality rates are examined by birth cohorts (Figures 13 and 15), one can see that both male and female cohorts with increasing smoking prevalence also have increasing age-specific mortality rates. In the youngest cohorts, where the smoking prevalence of males and females is most comparable, the age-specific mortality experience is similar.

An examination of Figures 13 and 15 reveals that the age-specific mortality experience for each birth cohort continues to rise with advancing age. What appears to be a decline in lung cancer mortality with age (Figures 5 and 6) in the oldest age groups (75 years and older) is an artifact resulting from the combination of cohorts with differing cigarette smoking exposures and mortality experiences. Note the leftward shift of the age-specific mortality rates in each succeeding birth cohort.

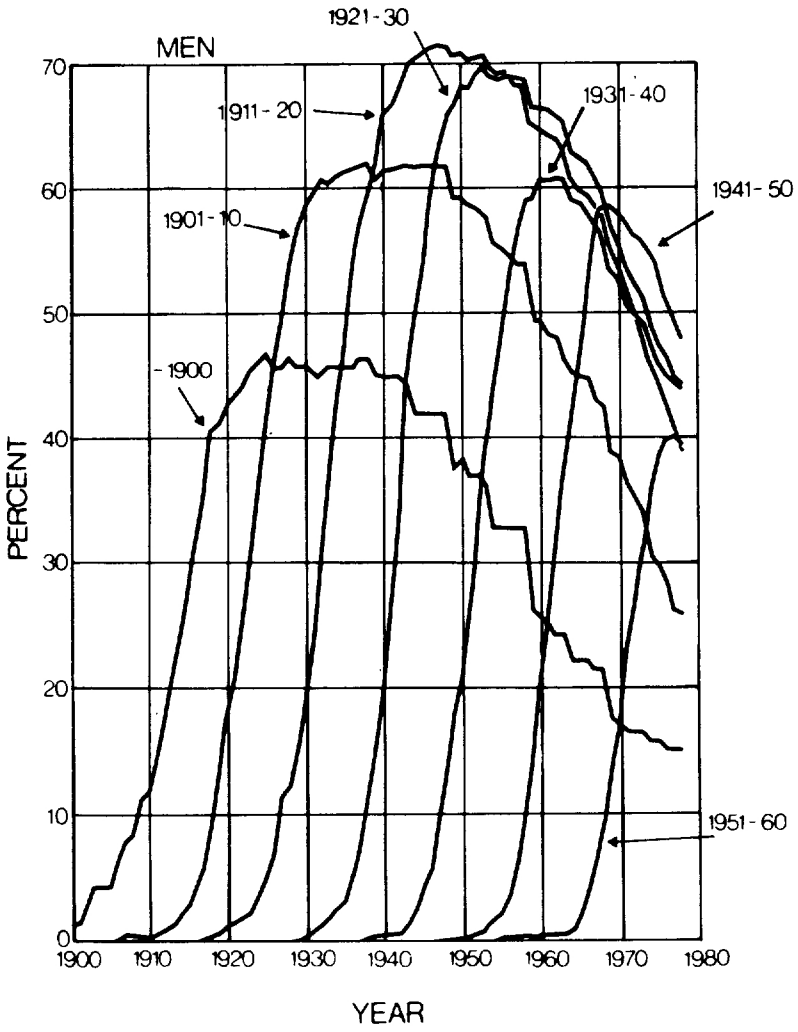

FIGURE 12.—Changes in the prevalence of cigarette smoking among successive birth cohorts of men, 1900–1978

NOTE: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics.

SOURCE: U.S. Department of Health, Education, and Welfare (*200*).

A third concern about the coherence of smoking behavior and lung cancer mortality has been that overall lung cancer mortality continues to rise at a time when the prevalence of cigarette smoking continues to decline, and the consumption of lower tar and nicotine cigarettes is increasing. Part of this apparent discrepancy can be accounted for by the relatively slow decline in the excess risk of

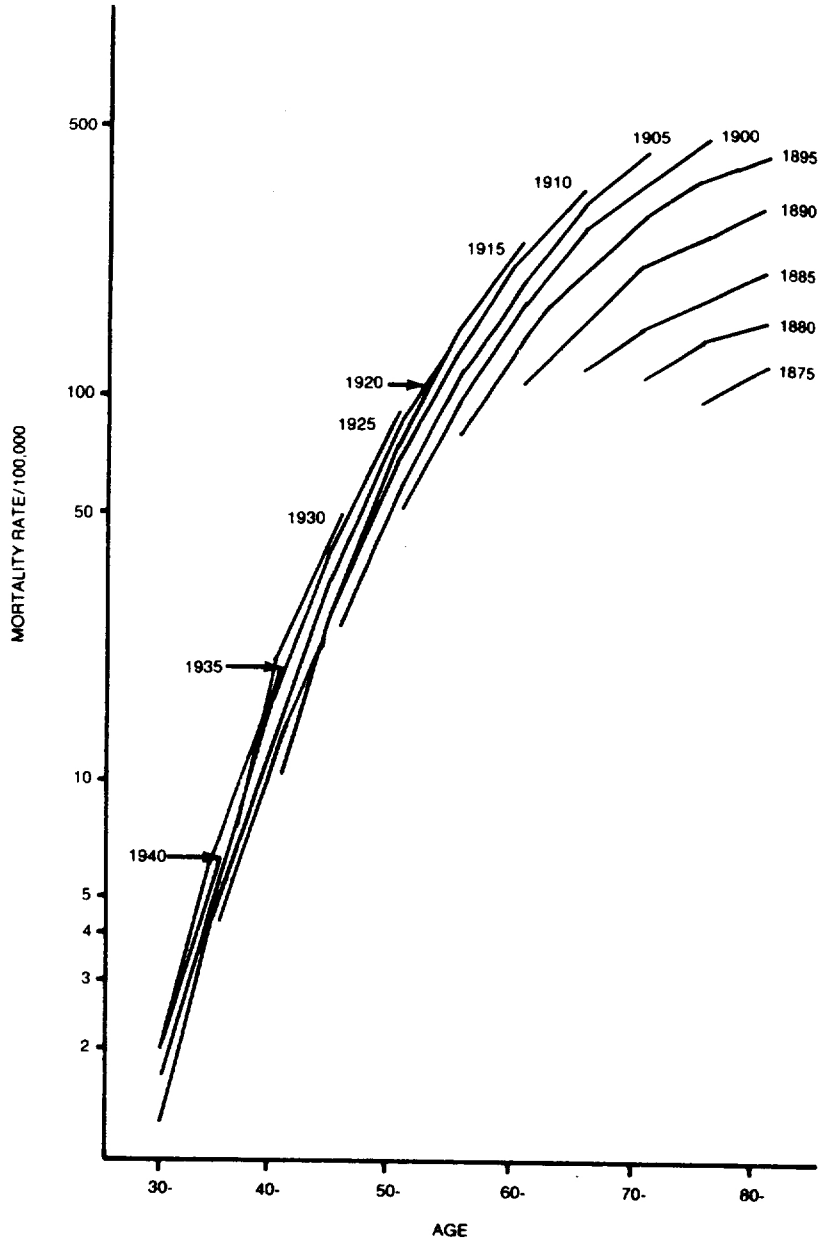

FIGURE 13.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death for males, United States, 1950–1975

SOURCE: Derived from data available in National Cancer Institute (*198*).

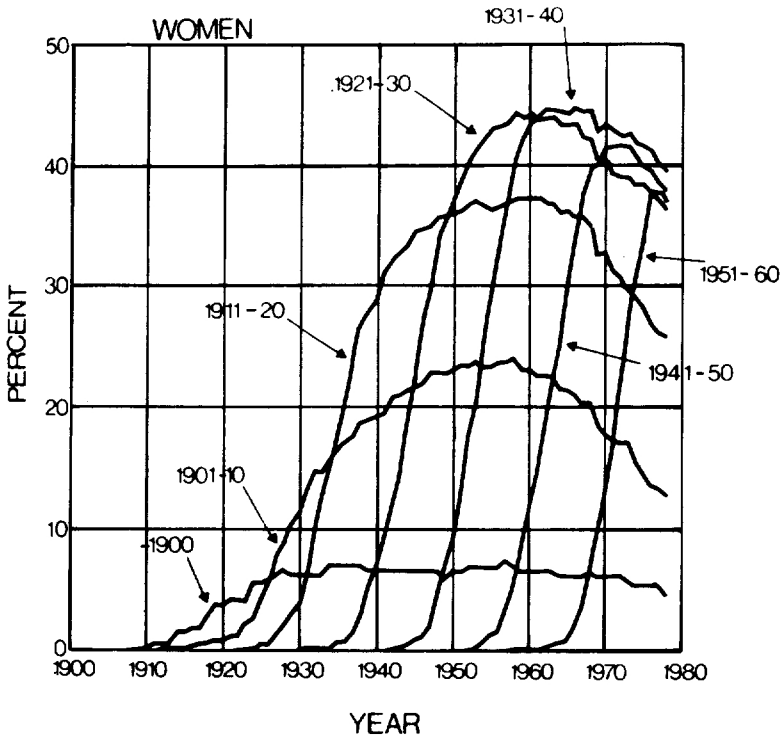

FIGURE 14.—Changes in the prevalence of cigarette smoking among successive birth cohorts of women, 1900–1978

NOTE: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics.
SOURCE: U.S. Department of Health, Education, and Welfare (*200*).

developing lung cancer once someone actually stops smoking, compared to persons who continue to smoke cigarettes. However, in the youngest male birth cohorts (birth years 1931–1940 and 1941–1950), there is a substantially lower peak prevalence of smoking which should result in a lower lung cancer mortality experience. From the smoking prevalence data and Figure 12, one would expect to see this declining mortality experience in those birth cohorts born after 1930, and the data in Figure 13 for 1935 and 1940 birth cohorts suggest that a decline in mortality experience is occurring. This trend can be visualized easily in Figure 16, which plots the age-specific lung cancer mortality rates for 5-year age groups over time, and reveals that the male rates for the youngest age groups do appear to be declining. No such trend can be seen in the female mortality experience, and this, too, is consistent with the smoking prevalence data presented in Figure 14.

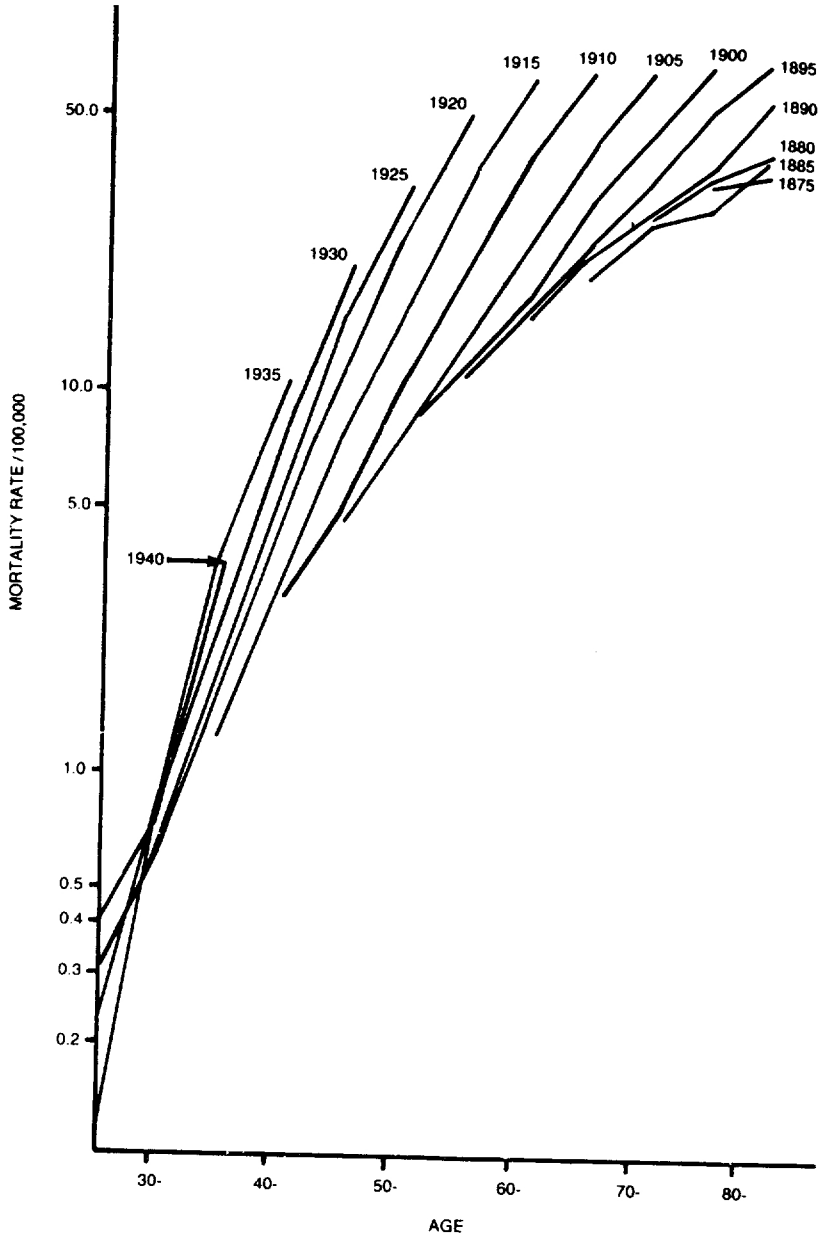

FIGURE 15.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death for females, United States, 1950–1975

SOURCE: Derived from data available in National Cancer Institute (*198*).

TABLE 13.—Lung cancer mortality ratios for male and female smokers at 6- and 12-year followup, ACS 25-State Study

Sex	Mortality ratios		
	Non-smokers	6-year followup	12-year followup
Males	1.00	9.20	8.53
Females	1.00	2.20	3.58

When the prevalence of cigarette smoking by birth cohort is compared with the mortality experience by birth cohort, the relationship between cigarette smoking behavior and lung cancer mortality experience is extremely coherent.

This is also supported when lung cancer mortality ratios are examined at various periods of followup in the prospective studies. In the ACS 25-State Study, a different pattern of lung cancer mortality emerges for males compared to females. In contrast to lung cancer mortality ratios among male smokers, which remained almost constant during the 6-year followup interval, ratios for female smokers increased (Table 13). A similar trend is observed among male U.S. Veterans as noted above for males in the ACS 25-State Study. Figure 17 presents lung cancer mortality ratios by amount smoked for male veterans at $8^1/_2$ years compared to 16 years' followup. No differences between the two periods are evident and the pattern is constant at each level of exposure.

Lung Cancer Mortality and Premalignant Changes in Bronchial Epithelium

Since smoking is significantly associated with lung cancer, smokers could be expected to develop premalignant changes in bronchial epithelium more commonly than nonsmokers prior to the development of frank cancer. In the late 1950s, one scientist (*9, 14, 15*) examined the tracheobronchial tree of 402 males at post mortem in a controlled blinded study and found that several kinds of changes were much more common in the tracheobronchial tree of smokers as compared with nonsmokers (Table 14). The frequency and intensity of these epithelial changes (loss of cilia, basal cell hyperplasia, presence of atypia) correlated with the number of cigarettes smoked. The most severe lesions, aside from invasive cancer, were not seen among males who did not smoke regularly and were found only rarely among light smokers. They were present, however, in 4.3 percent of sections from males who smoked one to two packs a day,

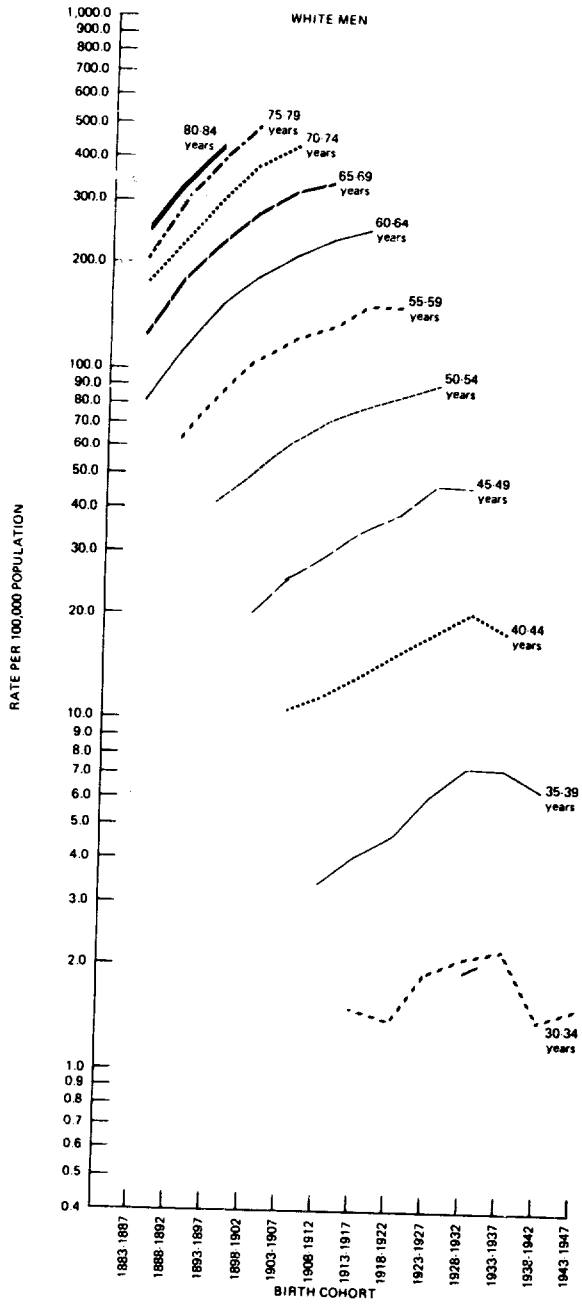

FIGURE 16.—Mortality rates for malignant neoplasm of the trachea, bronchus, and lung, for white men and white women, by birth cohort and age at death, United States, 5-year intervals during 1947–1977

SOURCE: National Center for Health Statistics (*200*).

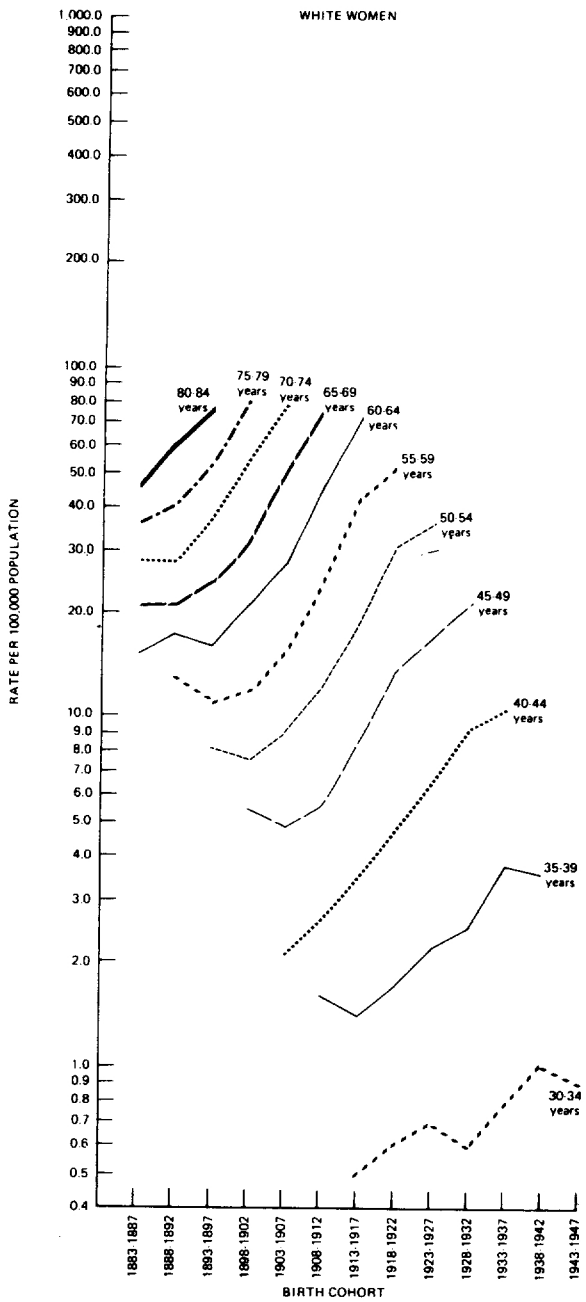

FIGURE 16, continued.—Mortality rates for malignant neoplasm of the trachea, bronchus, and lung, for white men and white women, by birth cohort and age at death, United States, 5-year intervals during 1947–1977

SOURCE: National Center for Health Statistics (*200*).

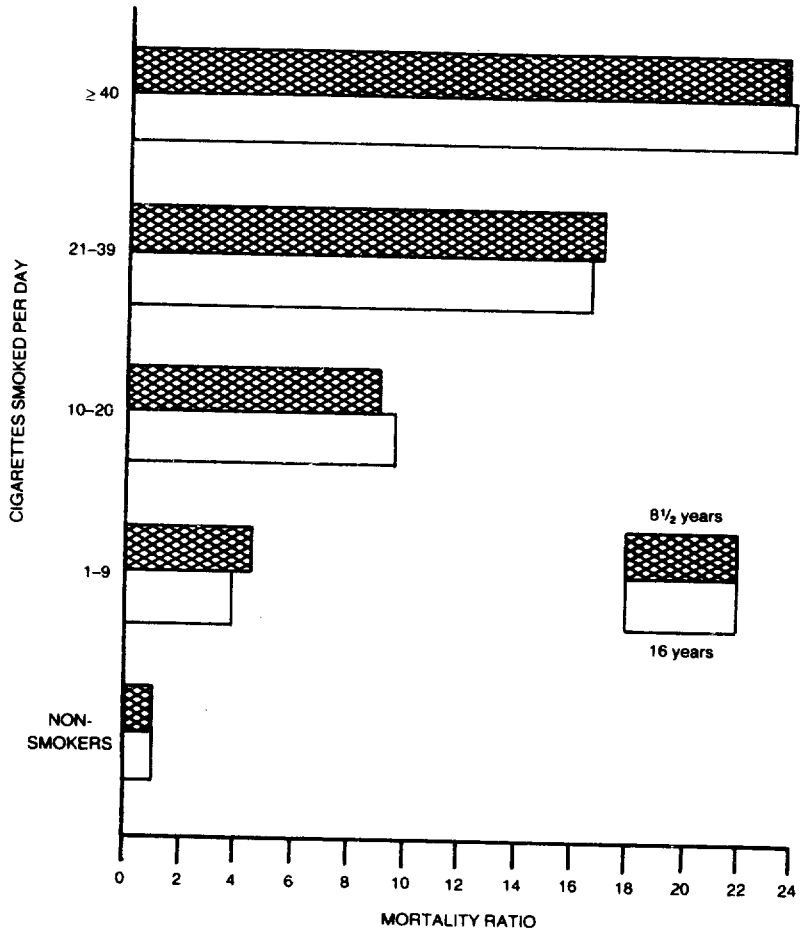

FIGURE 17.—Lung cancer mortality ratios for male smokers by amount smoked, 8½- and 16-year followup, U.S. Veterans Study

in 11.4 percent of sections from males who smoked two or more packs a day, and in 14.3 percent of sections from smokers who died of lung cancer. Studies by the same authors and others (*7, 10, 28, 39, 51, 89, 96, 144, 206, 217, 233, 268, 298, 319*) have confirmed this relationship between smoking and premalignant changes in bronchial epithelium in males and females, with and without lung cancer.

More recent investigations (*12*), which examined the histologic changes in the bronchial epithelium of male cigarette smokers who had died from causes other than lung cancer, found that changes occurred far less frequently in nonsmokers than in cigarette smokers. Changes in smokers correlated with the amount smoked. When comparing the degree of histologic changes of men who died in

TABLE 14.—Percent of slides with selected lesions,[a] by smoking status and presence of lung cancer

Group	Number cases	Number slides	Percent of slides with cilia absent and averaging 4 or more cell rows in depth			
			No cells atypical	Some cells atypical	All cells atypical[b]	Total
Cases without lung cancer						
Never smoked regularly	65	3,324	1.0	0.03	—	1.1
Ex-cigarette smokers	72	3,436	3.5	0.4	0.2	4.1
Cigarettes—½ pk. a day	36	1,824	0.2	4.2	0.3	4.7
Cigarettes—½—1 pk. a day	59	3,016	—	7.1	0.8	7.9
Cigarettes—1-2 pks. a day	143	7,062	—	12.6	4.3	16.9
Cigarettes—2+ pks. a day	36	1,787	—	26.2	11.4	37.5
Lung cancer cases[c]	63	2,784	—	12.5	14.3	26.8

[a] In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included in both individual columns and in the total column of the table. Lesions found at the edge of an ulcer were excluded.

[b] These lesions may be called carcinoma in-situ.

[c] Of the 63 who died of lung cancer, 55 regularly smoked cigarettes up to the time of diagnosis, 5 regularly smoked cigarettes but stopped before diagnosis, 1 smoked cigars, 1 smoked pipe and cigars, 1 was an occasional cigar smoker.

SOURCE: Auerbach (*9, 14, 15*).

the period 1955–1960 with those who died in 1970–1977, these investigators found the latter exhibited less advanced histologic changes. The authors attributed this finding to the reduced tar and nicotine yield of cigarettes smoked by this group when compared to the average tar and nicotine yield of those smoked by the earlier group (Table 15).

Several investigators have examined the relationship between smoking and cytological changes in respiratory epithelial cells shed into sputum in groups of smokers and nonsmokers. These studies (*171, 193, 220, 262*) have generally found increased proportions of sputum specimens showing atypical cells among smokers as compared with nonsmokers, and these changes have progressed toward cancer with increasing duration of the smoking habit. In addition, these changes have reverted toward normal in individuals who stopped smoking. These data support the causal nature of the association between smoking and lung cancer.

Experimental Studies

Over the past 30 years, a number of experimental models have been developed to study tobacco-induced carcinogenesis. These data are explored in detail in the Part of this Report on the mechanisms of carcinogenesis.

Lung Cancer and Non-Cigarette Tobacco Use

The relationship between lung cancer and other forms of tobacco was comprehensively reviewed in reports by the U.S. Public Health

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TABLE 15.—Percentage of sections with each of several categories of histologic change, classified according to smoking habit*

Histologic change	Adjusted % Never Smoked Regularly		Adjusted % Smoked 1–19 Cigarettes/ Day		Adjusted % Smoked 20–39 Cigarettes/ Day		Adjusted % Smoked 40+ Cigarettes/ Day	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Basal-cell hyperplasia:								
Total	3.8	5.8	87.8	63.1	93.2	76.2	98.8	86.3
6+ rows	0	0.1	2.1	0.4	5.7	0.5	13.0	0.8
10%+ cells with atypical nuclei	0.1	0.5	87.6	62.4	93.2	75.0	98.8	86.3
30%+ cells with atypical nuclei	0.1	0.4	77.2	53.9	92.6	72.5	98.8	85.1
50%+ cells with atypical nuclei	0	0.1	56.7	9.6	84.1	26.3	98.6	56.1
70%+ cells with atypical nuclei	0	0	0.1	0	12.2	0.1	66.6	<0.1
Lesion with cilia absent:								
Total	5.3	4.2	13.8	8.8	22.5	10.5	30.3	11.7
10%+ cells with atypical nuclei	0	<0.1	13.8	8.5	22.3	9.8	30.3	11.7
30%+ cells with atypical nuclei	0	<0.1	12.9	7.6	22.3	9.3	30.3	11.7
50%+ cells with atypical nuclei	0	0	10.0	2.2	21.9	6.0	30.3	9.3
70%+ cells with atypical nuclei	0	0	2.6	0.1	14.6	0.8	28.6	2.2
100% cells with atypical nuclei	0	0	2.6	0.1	13.2	0.8	22.5	2.2
No. of sections	2,580	2,628	2,208	3,026	2,881	3,471	1,413	2,217
No. of subjects	57	53	51	61	68	73	35	47

* Percentages adjusted for age to the distribution of age at death of all subjects in the study. An *A* denotes subjects who died in 1955–1960, a *B* denotes subjects who died in 1970–1977.
SOURCE: Auerbach et al. (*12*).

Service in 1973 and 1979 (*269, 278*). A brief summary follows. In contrast with cigarette smokers, most pipe and cigar smokers reported they did not inhale the smoke, and as a consequence, the total exposure of the lung to tobacco smoke was relatively lower. There was little evidence that lung cancer is associated with the use of chewing tobacco or "snuff." Several prospective epidemiological studies have demonstrated higher lung cancer mortality ratios for pipe and cigar smokers than for nonsmokers, but the risk of developing lung cancer for pipe and cigar smokers is less than for cigarette smokers. Table 16 presents a summary of these prospective studies. Two studies (*64, 131*) have reported (Table 17) that lung cancer mortality ratios for pipe and cigar smokers exhibited a dose-

TABLE 16.—Mortality ratios for lung cancer in male current smokers. A summary of prospective studies

Study	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
ACS 25-State Study	1.00	1.02	3.00	—	10.00	7.63
British Physicians	1.00	—	—	5.80	14.00	8.20
Canadian Veterans	1.00	2.94	4.35	—	14.20	—
U.S. Veterans	1.00	1.66	2.14	1.67	11.28	—

TABLE 17.—Lung cancer mortality ratios for cigar and pipe smokers by amount smoked

Smoking type	Mortality ratio	Number of deaths
Nonsmoker	1.00	78
Cigar smokers:		
< 5 cigars per day	1.14	12
5 to 8 cigars per day	2.64	11
> 8 cigars per day	2.07	2
Pipe smokers:		
< 5 pipefuls per day	.77	2
5 to 19 pipefuls per day	2.20	12
> 19 pipefuls per day	2.47	3
Cigar and pipe:		
8 or less cigars, 19 or less pipefuls	1.62	18
> 8 cigars, > 19 pipefuls	2.19	2

SOURCE: Kahn (*131*).

response relationship; however, the relationship is not as strong as that noted for cigarette smoking.

A few retrospective studies contain adequate numbers of smokers to allow an examination of dose-response relationships between pipe and cigar smoking and lung cancer (*1, 161, 215, 230*). An increased risk for developing lung cancer correlated with the increased use of pipes and cigars as measured by amount smoked and depth of inhalation.

Several investigators have examined histological changes in lungs of cigar and pipe smokers. One study (*15*) examined 36,340 histologic sections for various epithelial lesions obtained from 1,522 white adults. The numbers and types of pathological findings in the bronchial epithelium of pipe and cigar smokers were compared with those found in nonsmokers and cigarette smokers. Pipe and cigar smokers had abnormalities that were intermediate between those of nonsmokers and cigarette smokers, although cigar smokers had pathological changes that in some categories approached the changes seen in cigarette smokers. Others have reported similar findings (*144, 233*).

Several experimental investigations have been conducted to examine the relative tumorigenic activity of tobacco smoke condensates obtained from cigarettes, cigars, and pipes. Most of these studies were standardized in an attempt to make the results of the cigar and pipe experiments more directly comparable with cigarette data, and most used the shaved skin of mice for the application of tar. Tar from cigars, pipes, and cigarettes was usually applied on an equal weight basis so that qualitative differences in the tars could be determined. In several experiments, the nicotine was extracted from the pipe and cigar condensates in an attempt to reduce the acute toxic effects that resulted from the high concentration of nicotine frequently found in these products (*50, 53, 127, 138, 221, 328*). These experimental data suggest that cigar and pipe tobacco condensates have a carcinogenic activity that is comparable to cigarette condensates. This is supported by human epidemiologic data for those sites exposed equally to the smoke of cigars, pipes, and cigarettes. The alkaline smoke derived from pipes and cigars is generally not inhaled, and as a result there appears to be a lesser exposure of the lungs and possibly other organs to pipe and cigar smoke than that which occurs due to cigarette smoking.

Further, evidence from countries where smokers tend to inhale cigar smoke to a greater degree than smokers do in the United States (*1*) indicates that rates of lung cancer become elevated to levels approaching those of cigarette smokers.

Conclusion

1. Cigarette smoking is the major cause of lung cancer in the United States.
2. Lung cancer mortality increases with increasing dosage of smoke exposure (as measured by the number of cigarettes smoked daily, the duration of smoking, and inhalation patterns) and is inversely related to age of initiation. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than nonsmokers.

3. Cigar and pipe smoking are also causal factors for lung cancer. However, the majority of lung cancer mortality in the United States is due to cigarette smoking.
4. Cessation of smoking reduces the risk of lung cancer mortality compared to that of the continuing smoker. Former smokers who have quit 15 or more years have lung cancer mortality rates only slightly above those for nonsmokers (about two times greater). The residual risk of developing lung cancer is directly proportional to overall life-time exposure to cigarette smoke.
5. Filtered lower tar cigarette smokers have a lower lung cancer risk compared to nonfiltered, higher tar cigarette smokers. However, the risk for these smokers is still substantially elevated above the risk of nonsmokers.
6. Since the early 1950s, lung cancer has been the leading cause of cancer death among males in the United States. Among females, the lung cancer death rate is accelerating and will likely surpass that of breast cancer in the 1980s.
7. The economic impact of lung cancer to the nation is considerable. It is estimated that in 1975, lung cancer cost $3.8 billion in lost earnings, $379.5 million in short-term hospital costs, and $78 million in physician fees.
8. Lung cancer is largely a preventable disease. It is estimated that 85 percent of lung cancer mortality could have been avoided if individuals never took up smoking. Furthermore, substantial reductions in the number of deaths from lung cancer could be achieved if a major portion of the smoking population (particularly young persons) could be persuaded not to smoke.

Cancer of the Larynx

Introduction

Cancer of the larynx was responsible for about 1 percent of cancer deaths in the United States in 1977. It is estimated that in 1982 there will be 10,900 new cases and 3,700 deaths due to this disease (2). Males are affected more commonly than females, but the ratio of new cases and deaths in males and females (now about 6:1) has been narrowing over the last 20 years (*240, 312*). In 1950, 1,852 people died of cancer of the larynx. By 1977, this figure had nearly doubled, rising to 3,390. The age-adjusted death rate increased slightly, from 1.1 to 1.2 per 100,000 (Figure 18).

There is a considerable difference in this increased death rate when examined by sex and race. Among other than white males, the age-adjusted rate climbed from 1.6 to 3.5 per 100,000 between 1950 and 1977. By contrast, age-adjusted rates of white males rose less, from 2.0 to 2.1. As is seen with lung cancer, mortality rates of females were lower than those of males throughout the study period. Between 1950 and 1977, the age-adjusted mortality rate for white

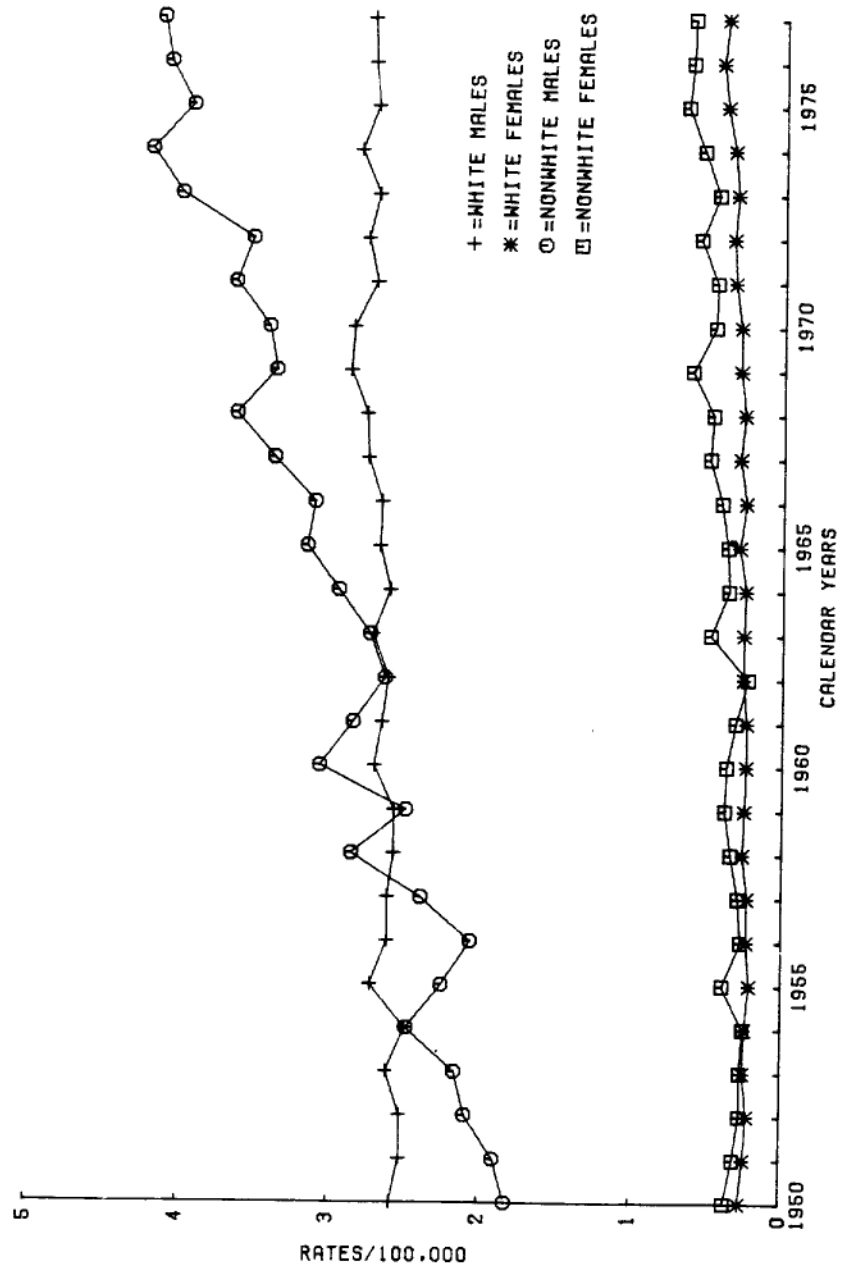

FIGURE 18.—Age-adjusted* mortality rates for cancer of the larynx, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

females increased from 0.2 to 0.3 per 100,000, while that of other than white females increased from 0.3 to 0.6 per 100,000.

Generally, there was a pattern of increasing mortality after middle age (Figures 19 and 20). Among white males 55 years of age or older, mortality rates from cancer of the larynx were higher in 1977 than in 1950. Among other than white males, this pattern was evident for those 35 years of age or older. Both white and other females 45 to 74 years of age had higher mortality rates in 1977 than in 1950.

Squamous cell carcinoma is the most common cell type among laryngeal cancers. Approximately 70 percent of the cases involve the glottis and 25 percent involve the supraglottic region.

In contrast to lung cancer, the 5-year survival for cancer of the larynx is at present about 60 percent (*2*), and has been improving over the past 15 years. As a result, the trend over time in death rates from cancer of the larynx is not an accurate reflection of the incidence of this disease.

Over the last 30 years, numerous epidemiological, pathological, and experimental investigations have established a strong association between smoking and cancer of the larynx. One group of scientists (*296*) conducted a retrospective study of 3,924 patients attending a cancer clinic in Alberta, Canada. The authors estimated that 84 percent of laryngeal cancer among men could be attributed to smoking.

Causal Significance of the Association

Consistency of the Association

More than 25 retrospective studies have examined the relationship between smoking and laryngeal cancer. These studies have employed diverse methodology and have been performed in different time periods and in different countries. Regardless of the study design, these studies have found a positive association between smoking and cancer of the larynx. Relative risk ratios for 12 studies up to 1968 (Table 18) were consistently above 2.0. Subsequent studies show similar findings (*30, 35, 44, 52, 113, 114, 134, 142, 202, 254, 296, 299, 316, 327*). The TNCS study (*299*) and the Hawaiian Study of Five Ethnic Groups (*113*) have also reported a positive association. Data from studies of populations with low proportions of smokers (e.g., Mormons (*165, 166, 294*) and Seventh Day Adventists (*211*)) show low laryngeal cancer rates. Six of the major prospective studies have examined the relationship between smoking and laryngeal cancer (Table 19); as in the retrospective studies, a large positive association was consistently noted.

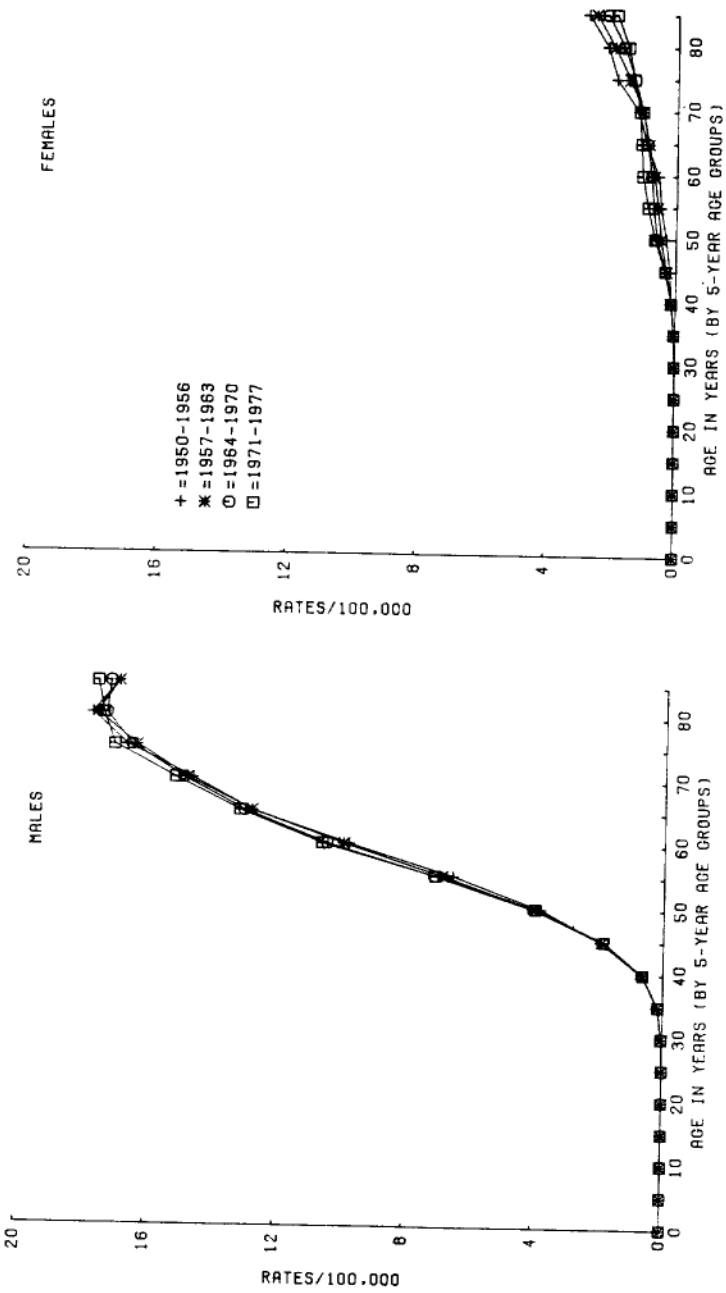

FIGURE 19.—Age-specific mortality rates for whites in the United States for cancer of the larynx

SOURCE: National Cancer Institute (*198*).

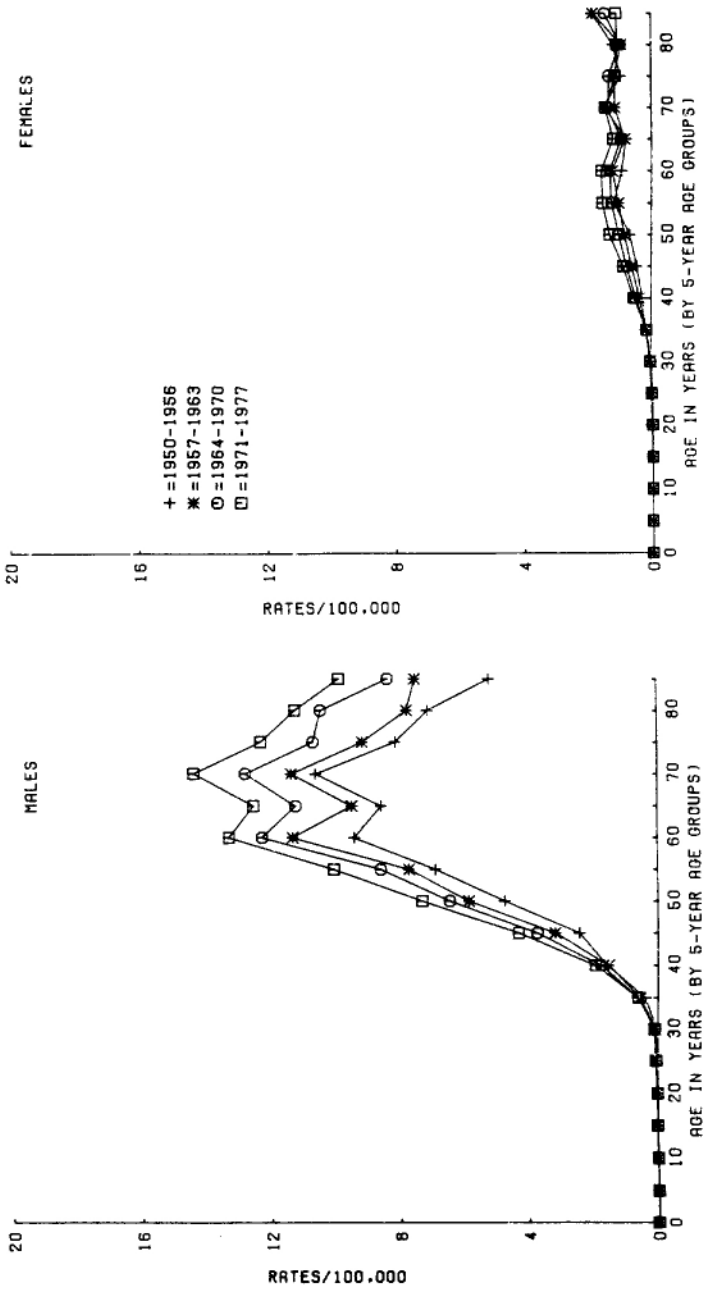

FIGURE 20.—Age-specific mortality rates for nonwhites in the United States for cancer of the larynx

SOURCE: National Cancer Institute (*198*).

TABLE 18.—Summary of results of retrospective studies of tobacco use and cancer of the larynx

Investigator, (reference)	Relative risk ratio[a] all smokers to nonsmokers
Schrek et al., U.S.A. (*244*)	2.0
Valko, Czechoslovakia (*282*)	3.5
Sadowsky et al., U.S.A. (*230*)	3.7
Blümlein, Germany (*31*)	27.5
Wynder et al., U.S.A. (*309*)	23.6
Wynder et al., India (*309*)	3.1
Schwartz et al., France (*246*)	4.6
Wynder et al., Sweden (*317*)	6.0
Wynder et al., Cuba (*324*)	(18.9)[b] (males only)
Dutta-Choudhuri et al., India (*77*)	4.3
Stazewski, Poland (*252*)	(40.0) (males only)
Svoboda, Czechoslovakia (*261*)	8.3

[a] Computed according to the method of J. Cornfield (*49*).
[b] Figures in parentheses represent ratios based on less than five case nonsmokers.

TABLE 19.—Mortality ratios for cancer of the larynx—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
ACS 9-State Study	188,000 males	24	—	—	All larynx cancer deaths occurred in smokers
British Physicians	34,000 males	38	1.00	13.00	Includes cancer of larynx and other upper respiratory sites
U.S. Veterans	290,000 males	116	1.00	11.49	
ACS 25-State Study	358,000 males	67	1.00	6.52	Includes buccal, pharyngeal, and laryngeal cancers
	483,000 females	11	1.00	3.25	
California males in 9 occupations	68,000 males	11	—	>2.90	All larynx cancer deaths occurred in smokers[a]
Japanese Study	122,000 males	38	1.00	13.59	
	142,800 females	6	1.00	6.52	

[a] Ratio derived by comparing smokers of half a pack with all other smokers

TABLE 20.—Relative risk of laryngeal cancer for males and females by amount smoked per day*

Number of Cigarettes Per Day	Number	Relative Risk	Confidence Limits
	Males (N = 243)		
1-10	16	4.4	1.6 ~ 12.6
11-20	87	13.5	5.3 ~ 33.1
21-40	99	17.3	6.8 ~ 44.2
41+	41	34.4	12.3 ~ 96.1
	Females (N = 48)		
1-20	19	4.4	
21+	29	28.2	

* Risk relative to 1.0 for nonsmokers.
SOURCE: Wynder and Hoffmann (*316*).

Strength of the Association

In the retrospective studies, the relative risk of laryngeal cancer (Table 18) ranged from 2.0 in a study of 73 U.S. veterans (*244*) to 40.0 in a Polish study of 207 males admitted to a chronic disease hospital (*252*). Two other studies (*30, 316*) found substantial increases in relative risk among smokers as compared with nonsmokers. Several studies have reported a strong dose-response relationship between the number of cigarettes smoked per day and laryngeal cancer mortality (*299, 316*). The mortality ratios for male and female cigarette smokers from one of these studies (*316*) are summarized by daily consumption in Table 20.

One study (*327*) examined the impact of long-term filter cigarette usage on laryngeal cancer risk. After adjustment for duration of smoking, inhalation, and butt length, the relative risk for developing laryngeal cancer was decreased in male and female users of filter cigarettes compared to users of unfiltered cigarettes, although this risk was still substantially greater than that for nonsmokers (Figures 21 and 22). The American Cancer Society 25-State Study data (*155*) also showed a reduced risk of laryngeal cancer among smokers of lower tar and nicotine cigarettes, but this reduction was not statistically significant.

In the prospective studies, the mortality ratios for smokers ranged from over 3 among U.S. females to 13 or greater among Japanese males and British male physicians (Table 19). In two of the prospective studies, mortality ratios could not be accurately calculated because all the deaths occurred in smokers. Several of these prospective studies have confirmed the strong dose-response relationship reported in the retrospective studies (Table 21).

Specificity of the Association

The prospective studies have measured mortality data for a large number of diseases. The specificity of the association is evidenced by

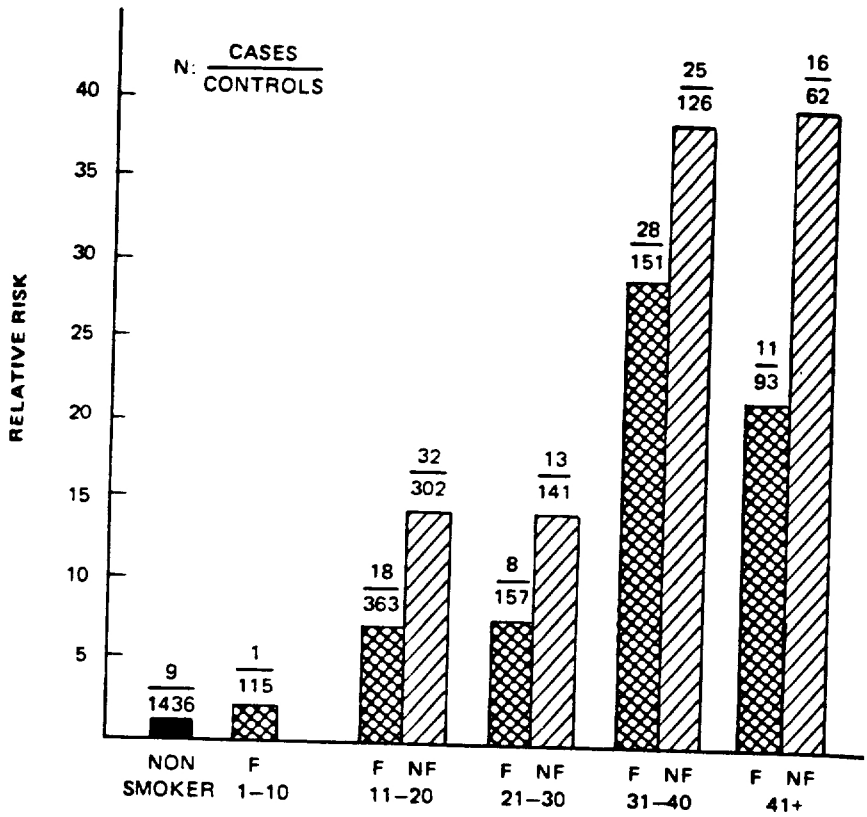

FIGURE 21.—Relative risk of developing larynx cancer for males, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

the mortality ratios of laryngeal cancer in comparison with other cancers (Appendix Tables A and B).

Temporal Relationship of the Association

This criterion is supported by the major prospective studies (Table 19) that examined the occurrence of laryngeal cancer in initially healthy groups of smokers and nonsmokers. The temporal relationship of the association is strengthened by data from post mortem studies that have evaluated vocal cord histology in groups of smokers and nonsmokers (*11, 56, 190, 228*). A spectrum of premalignant changes is seen in laryngeal tissue of smokers; this is not found in nonsmokers (see below).

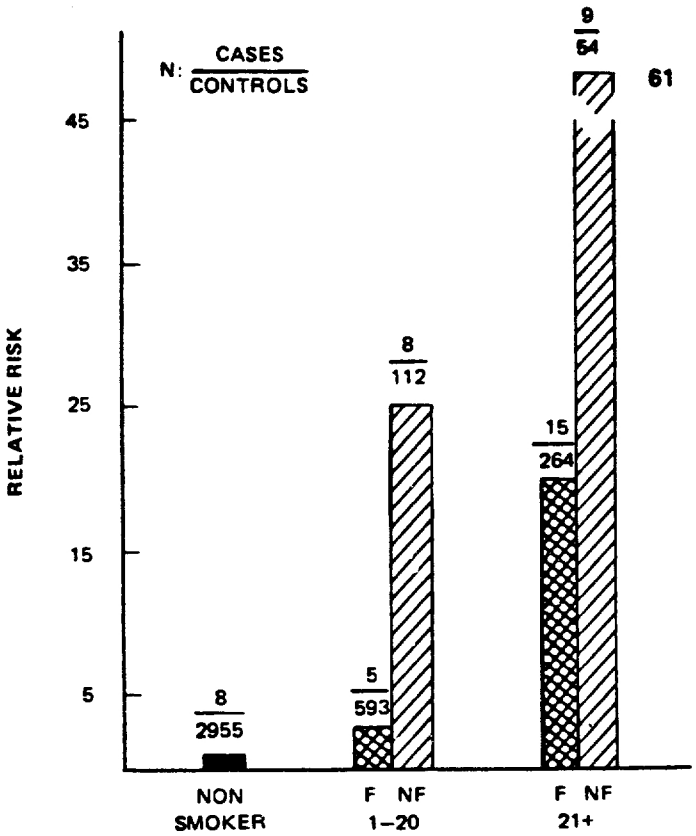

FIGURE 22.—Relative risk of developing larynx cancer for females, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship between smoking and laryngeal cancer incidence and mortality in retrospective and prospective studies strongly supports a causal association. Smoke exposure has been measured by the number of cigarettes smoked per day, the tar and nicotine content of the cigarettes smoked, the depth of inhalation, the number of years smoked, and the age at initiation (*269, 276*), all of which support a direct causal relationship.

TABLE 21.—Laryngeal cancer mortality ratios, by amount smoked

Population	Cigarettes/day	Mortality rates		Comments
U.S. Veterans Study	Nonsmoker	1.00		
	1–9	5.28*		*Based on less than 20 deaths
	10–20	9.20		
	21–39	14.78		
	> 40	32.14*		
Japanese Study	Nonsmoker	1.00		
	1–19	19.23		
	20–39	27.43		
	40+	34.13		
British Physicians		Male	Female	
	Nonsmoker	1.00	1.00	Includes larynx and other respiratory sites
	1–14	5.00	—	
	15–24	7.00	4.00	
	25+	33.00	6.50	

Correlation of Sex Differences in Laryngeal Cancer With Different Smoking Habits

Laryngeal cancer is predominantly a disease of males, although the mortality among females has increased over the past 20 years. A male-to-female ratio of 14.9:1 was reported in 1956 (*312*). The sex ratio decreased to 4.6:1 by 1976. This time trend is consistent with the later adoption of cigarette smoking by females (*270*) and a possible increase in female alcohol consumption, given the synergy between the two exposures. The greater alcohol consumption among males and the strong association between laryngeal cancer and alcohol consumption (see below) are considered to contribute to the excess of male to female laryngeal cancer mortality.

Correlation of Laryngeal Cancer Mortality Among Populations With Different Tobacco Consumption

In studies of populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the incidence of laryngeal cancer is substantially lower (*79, 165, 166, 211, 294*), supporting the causal relationship between smoking and laryngeal cancer.

Laryngeal Cancer Mortality and Cessation of Smoking

A few studies have examined the relationship between cigarette smoking cessation and risk for laryngeal cancer. One retrospective study found a marked reduction in risk following cessation among males and females (Figures 23 and 24) and suggested that "10 to 15 years of cessation are required before the long-term smoker's risk approaches that of a nonsmoker" (*327*). In the U.S. Veterans and British Physicians studies, ex-smokers had approximately 40 percent

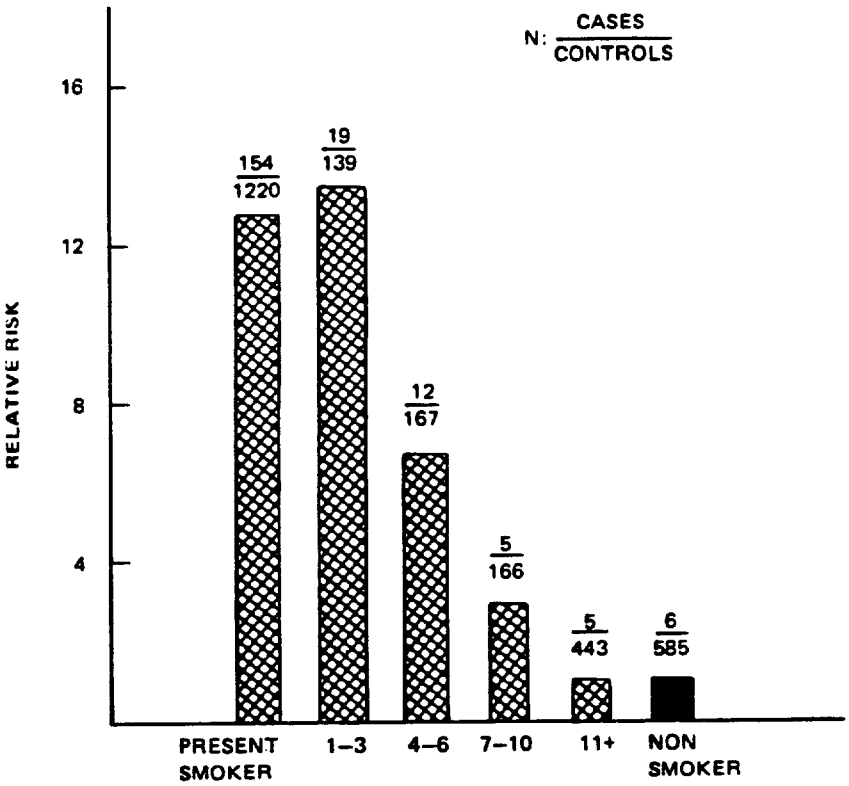

FIGURE 23.—Relative risk of developing larynx cancer for male ex-smokers, by years of smoking cessation

SOURCE: Wynder (*327*).

of the risk of current smokers for laryngeal cancer; however, the risk was still roughly five times that of the nonsmoker (*68, 224*). Because data were not presented by the number of years off cigarettes, the higher relative risk may be due to higher mortality rates often observed in former smokers (even compared to continuing smokers) during the initial years of smoking cessation.

Smoking and Histologic Changes in the Larynx

The relationship of smoking habits to precancerous lesions of the larynx was examined in an autopsy series of 148 cases, 24 of whom were nonsmokers (*190*). Precancerous lesions (dysplasia and carcinoma *in situ*) and carcinoma occurred least frequently among nonsmokers (4.2 percent). The frequency of these lesions increased from 12.5 percent in light smokers to 22.9 percent in moderate smokers and to 47.2 percent in heavy smokers. Similar findings were reported

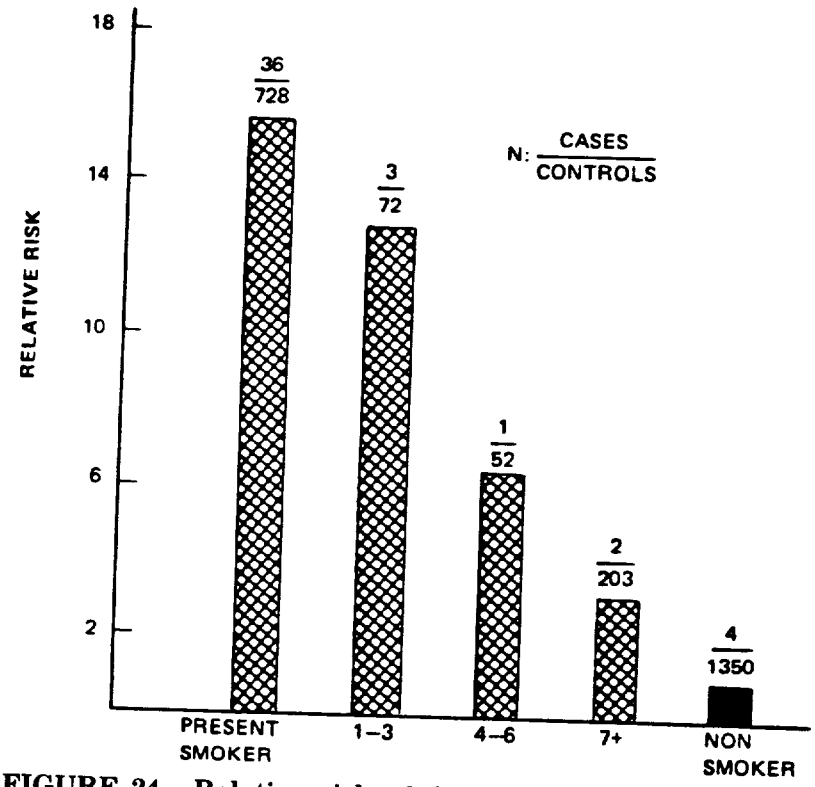

FIGURE 24.—Relative risk of developing larynx cancer for female ex-smokers, by years of smoking cessation

SOURCE: Wynder (*327*).

from a study of histological changes in the larynx of 942 males aged 21 to 95 (*11*). These findings lend support to a causal nature of the relationship.

Laryngeal Cancer and Non-Cigarette Tobacco Use

A few epidemiological studies have examined the relationship between other forms of tobacco use and cancer of the larynx (*60, 68, 98, 131*). Pipe and cigar smokers develop cancer of the larynx at rates comparable to those of cigarette smokers (i.e., several times those of nonsmokers) (Tables 22 and 23). The similarities of the mortality ratios of cancer of the larynx for smoking of non-cigarette tobacco products suggests that the carcinogenic potentials of smoke from cigars, pipes, and cigarettes are quite similar at this site.

The association of smoking of non-cigarette tobacco products to histological changes in the larynx has been examined (*11*). Among males who smoked cigars and pipes but not cigarettes, only 1 percent

TABLE 22.—Mortality ratios for cancer of the larynx in cigar and pipe smokers. A summary of prospective epidemiological studies

Study	Smoking Type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
ACS 9-State Study [1]	1.00	5.00	3.50	—	5.06	—
British Physicians [2]	1.00	—	—	2.00	1.00	0.60
ACS 25-State Study	1.00	—	—	3.37	[3]6.09	—
U.S. Veterans	1.00	10.33	—	7.28	11.49	—

[1] Combines data for oral, larynx, and esophagus.
[2] Ratios: relative to cigarette smokers.
[3] Only mortality ratios for ages 45 to 64 are presented.

had no atypical cells and more than 75 percent of the subjects had lesions with 50 to 69 percent atypical cells. Four of the cigar and pipe smokers had carcinoma *in situ*. Of those who never smoked regularly, 75 percent had no atypical cells. The cigar and pipe smokers had a percentage of cells with atypical nuclei similar to that of cigarette smokers who smoked one to two packs per day.

Synergistic Role of Alcohol for Laryngeal Cancer

Laryngeal cancer occurs much more frequently in alcoholics than in nonalcoholics (*183, 208, 239*). Although part of this increased risk for laryngeal cancer among alcohol abusers may be attributed to heavier smoking by this group, there remains a substantial excess risk associated with alcohol use (*227*). The relative risks of laryngeal cancer by daily consumption of alcohol and cigarettes in 239 male cases and 4,725 controls (Figure 25) suggest a synergy when tobacco usage is combined with chronic alcohol consumption (*179*). Male smokers of from 11 to 20 and from 21 or more cigarettes per day who consumed 7 ounces or more of alcohol per day had relative risks for laryngeal cancer of 26.8 and 27.2 respectively. The corresponding risks for nondrinking smokers were 6.6 and 12.0. This synergy has also been demonstrated using the Third National Cancer Survey, which suggests that the laryngeal cancer risk for smoking drinkers is approximately 50 percent greater than the sum of the excess risks posed by either behavior alone (*85*). The mechanism(s) by which these two factors interact is unclear (*179, 226, 242*).

Experimental Studies

The Syrian golden hamster has been found to be a suitable species for the investigation of cancer of the larynx. The distribution of malignant lesions in the upper airway of the hamster is due not to an unusual susceptibility of the larynx for tumor induction, but rather to the distribution of smoke aerosol precipitation within the upper

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TABLE 23.—Relative risk of cancer of the larynx for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

Author (Reference)	Number		Relative Risk Ratio and Percentage of Cases and Controls by Type of Smoking					
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Schrek et al. (*244*):		Relative risk	1.0	0	1.1	.....	2.3	.....
Cases	73	Percent cases	14	0	7	.....	80	.....
Controls	522	Percent controls	24	10	11	.....	59	.....
Sadowsky et al. (*230*):		Relative risk	1.0	2.2	2.3	.....	3.7	4.1
Cases	273	Percent cases	4	2	5	.....	60	29
Controls	615	Percent controls	13	3	7	.....	53	23
Wynder et al. (*309*):		Relative risk	1.0	15.5	27.7	11.1	24.6	.....
Cases	209	Percent cases	.5	8	5	1	86	.....
Controls	209	Percent controls	11	10	4	2	74	.....
Wynder et al. (*317*):		Relative risk	1.0	9.7	4.5	.....	6.3	6.3
Cases	60	Percent cases	5	17	15	.....	47	17
Controls	271	Percent controls	24	9	16	.....	36	13
Wynder et al. (*324*):		Relative risk	1.0	14.5	16.0	.....	22.0	16.0
Cases	142	Percent cases	1	20	1	.....	62	16
Controls	220	Percent controls	16	22	1	.....	45	16
Pernu (*209*):		Relative risk	1.0	.....	4.5	.....	8.7	3.2
Cases	546	Percent cases	7	.....	4	.....	78	4
Controls	713	Percent controls	39	.....	5	.....	50	7
Staszewski (*252*):		Relative risk	1.0	.....	.....	5.9	50.2	.....
Cases	207	Percent cases	.5	.....	.....	2	88	.....
Controls	912	Percent controls	17	.....	.....	11	61	.....
Svoboda (*261*):		Relative risk	1.0	.....	2.6	.....	10.0	.....
Cases	205	Percent cases	3	.....	3	.....	95	.....
Controls	320	Percent controls	22	.....	7	.....	71	.....
Stell (*254*):		Relative risk	1.0	.....	.....	1.3	2.4	.....
Cases	190	Percent cases	11	.....	.....	8	79	.....
Controls	190	Percent controls	17	.....	.....	10	50	.....

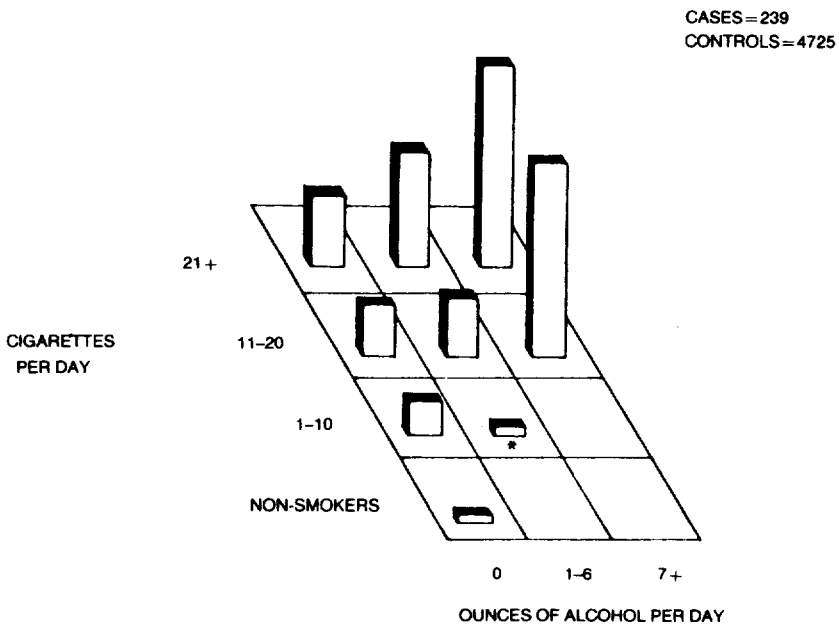

FIGURE 25.—Relative risks of larynx cancer by daily consumption of alcohol and cigarettes for males

* Not significant.
SOURCE: McCoy et al. (*179*).

respiratory tract. Several recent experiments have been performed (*23, 24, 72, 73, 125, 126, 133*).

Cigarette smoke inhalation has not been found to induce laryngeal tumors in other rodents. Such tumors have been induced, however, by direct application of carcinogens known to be present in cigarette smoke. This is accomplished by the intratracheal instillation of benzo[a]pyrene in combination with particulates into hamster lungs. In this animal model, laryngeal tumors, as well as tumors in other parts of the respiratory tract, are induced (*184, 231, 232*). One study has recently reported a synergy of alcohol and benzo[a]pyrene injection (*257*).

Conclusion

1. Cigarette smoking is the major cause of laryngeal cancer in the United States. Cigar and pipe smokers experience a risk for laryngeal cancer similar to that of a cigarette smoker.
2. The risk of developing laryngeal cancer increases with increased exposure as measured by the number of cigarettes smoked daily as well as other dose measurements. Heavy

smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers.

3. Cessation of smoking reduces the risk of laryngeal cancer mortality compared to that of the continuing smoker. The longer a former smoker is off cigarettes the lower the risk.
4. Smokers who use filtered lower tar cigarettes have lower laryngeal cancer risks than those who use unfiltered higher tar cigarettes.
5. The use of alcohol in combination with cigarette smoking appears to act synergistically to greatly increase the risk for cancer of the larynx.

Oral Cancer

Introduction

Cancers of the oral cavity include malignant tumors of the lip, tongue, salivary gland, floor of the mouth, mesopharynx, and hypopharynx. It is estimated that in 1982 there will be 26,800 new cases and 9,150 deaths due to these tumors (*2*). Males are affected more commonly than females (by about threefold). Several authors (*29, 175*) have reported geographic differences in mortality. In the southeast, females living in urban and rural areas have mortality rates that exceed those of northern females by 30 and 90 percent respectively.

Cancer of the Buccal Cavity and Pharynx, Excluding Lip[2]

From 1950 to 1967, the age-adjusted rate remained stable at 2.8 per 100,000. The increase in the age-adjusted death rate from 2.8 to 2.9 per 100,000 between 1967 and 1968 resulted in part from changes in coding procedures in the International Classification of Diseases. From 1968 to 1977, the age-adjusted rate rose from 2.9 to 3.1. Total deaths from cancer of these sites increased from 1,461 in 1950 to 8,291 in 1977.

While the age-adjusted death rate of white males fell slightly over the study period (Figure 26), rates of white females and of males and females of races other than white increased. The largest increases occurred among other than white males, whose mortality rates rose from 4.1 to 7.7 per 100,000 between 1950 and 1977. The white male to female mortality ratio fell gradually over the study period, from 4.09 to 2.93. In contrast, the mortality sex ratio (male/female) in the other than white population increased from 2.56 to 3.85. The mortality ratio of other than white males to white males increased from 0.91 to 1.75, while the mortality ratio of other than white females to white females decreased slightly, from 1.45 to 1.33.

[2] Cancer of the lip is causally associated with smoking, particularly pipe smoking. However, because this cancer site represents so few deaths in the United States, only 163 in 1977, it is excluded from this review.

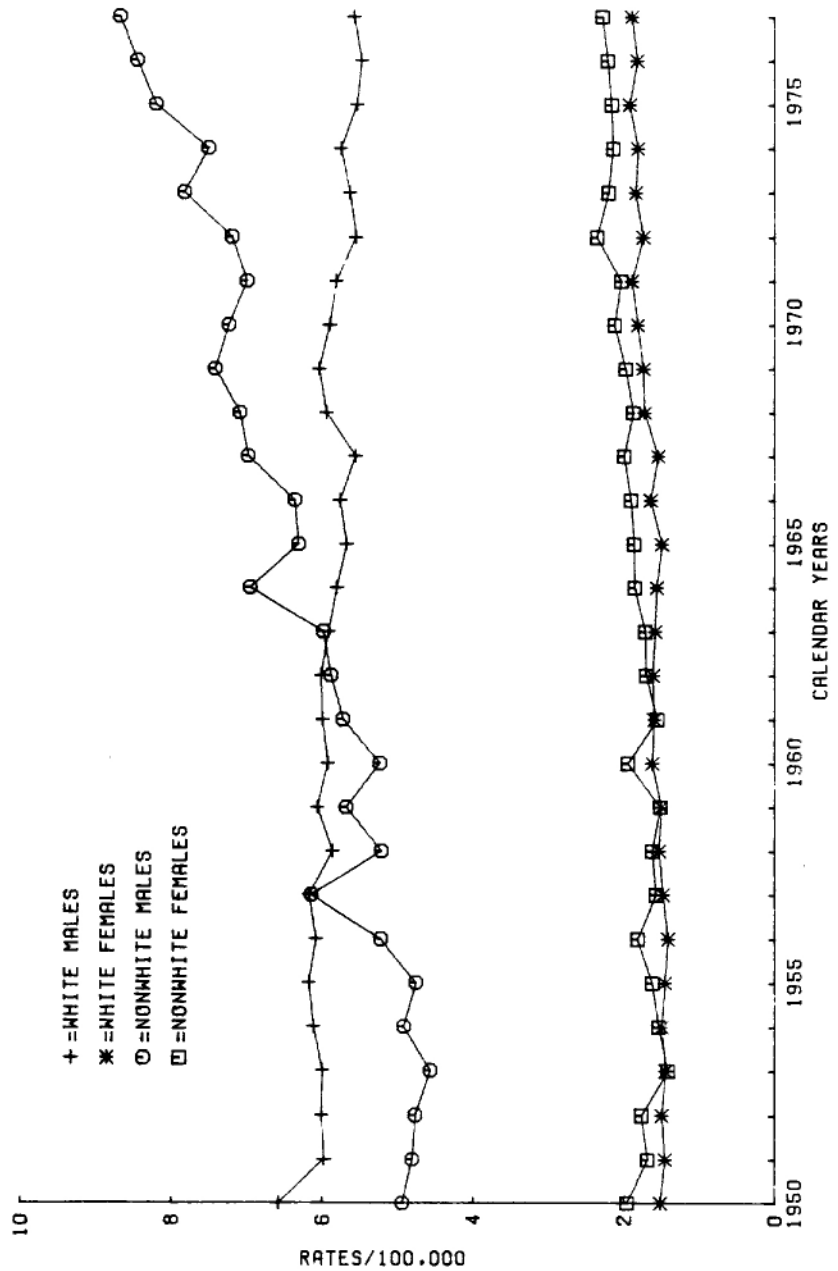

FIGURE 26.—Age-adjusted* mortality rates for cancer of the buccal cavity plus oral pharynx, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

The death rates of white males 35 to 54 years of age and of those at least 75 years old were lower in 1977 than in 1960 (Figure 27), but rates were higher among white males between 55 and 74 years of age, as well as among white females in the same age range. In contrast, among other than white males in every 10-year age group from 35 through 84, as well as among females between 35 and 64, death rates were higher in 1977 than in 1960; the average increase in mortality in these age groups was 60 percent (Figure 28).

When age-specific death rates are plotted by calendar year and age (Figures 29 and 30), a three-dimensional graph is produced, which can be examined from 1950 to 1977, or from the reverse perspective.

Squamous cell cancer is the most common histological type of oral cancer and comprises about 90 percent of these tumors. The 5-year survival for cancer of the floor of the mouth, tongue, and pharynx ranges from 25 to 45 percent.

Numerous epidemiological and experimental studies have established a close association between smoking and oral cancer. Alcohol has an incompletely understood but important synergistic role with tobacco in increasing disease incidence and mortality.

Causal Significance of the Association

Consistency of the Association

More than 25 retrospective studies have examined the relationship between smoking and the development of cancer of the oral cavity (*269, 276*).

These studies have been done in many countries, in different areas, and have involved diverse study methods. Almost uniformly, they show an association between cigarettes and other forms of tobacco use and cancer of the oral cavity and pharynx. The TNCS study (*299*) and the Hawaiian Study of Five Ethnic Groups (*113*) reported similar findings.

Six of the major prospective studies examined the relationship between smoking and oral cancer. These data, presented in Table 24, show a close association between smoking and oral cancer.

Strength of the Association

The relative risks for oral cancer among smokers were substantially greater compared with nonsmokers in the retrospective studies. Similarly, in the prospective studies, the mortality ratios for cancer of the oral cavity among smokers ranged from 1.22 among Japanese females to over 13 in the U.S. Veterans and British Physicians studies (Table 24).

A dose-response relationship was noted in many of the retrospective and prospective studies (Table 25) (*64, 98, 120, 131, 276*). The American Cancer Society 25-State Study (*155*) reported a reduction

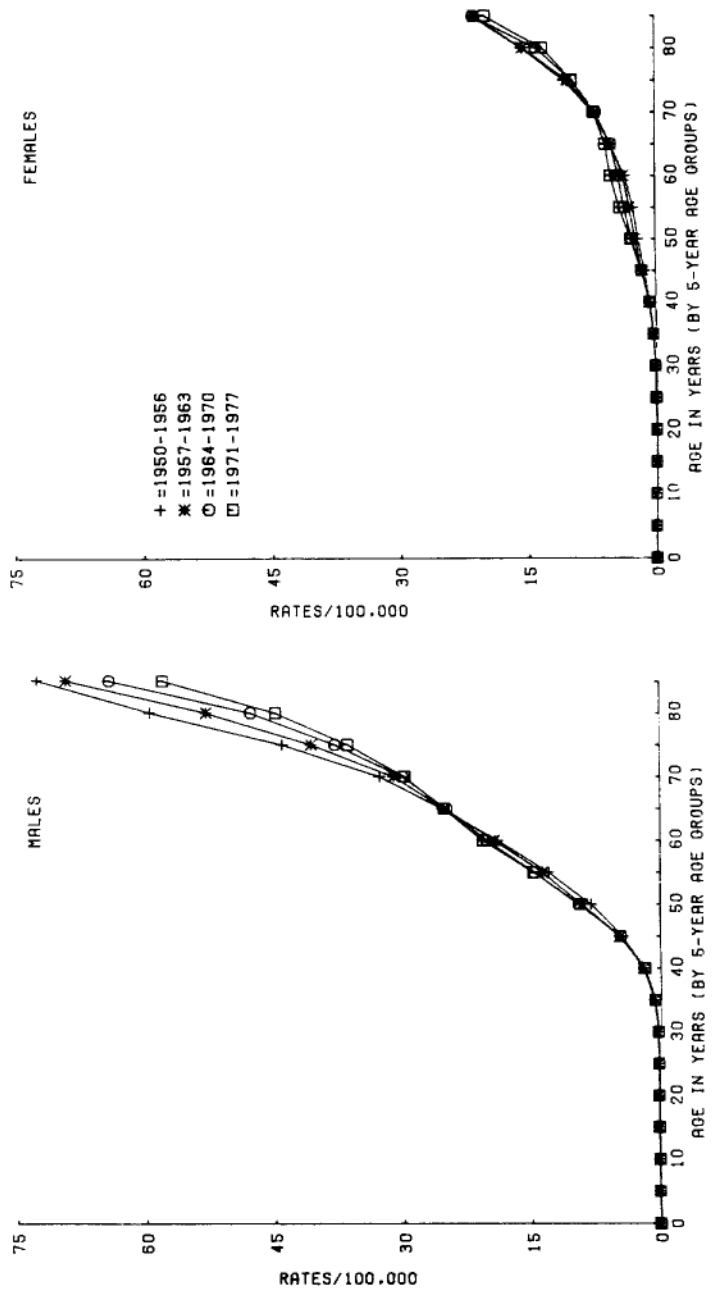

FIGURE 27.—Age-specific mortality rates for whites in the United States for cancer of the buccal cavity plus oral pharynx

SOURCE: National Cancer Institute (*198*).

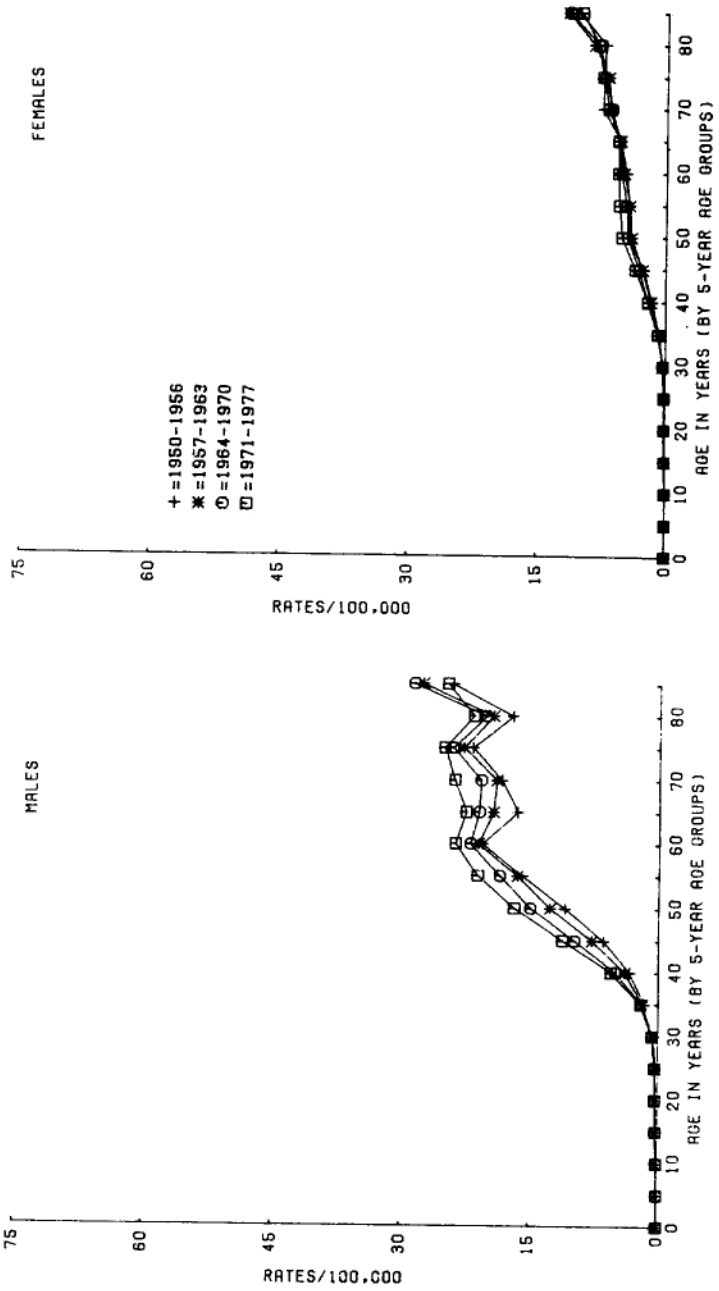

FIGURE 28.—Age-specific mortality rates for nonwhites in the United States for cancer of the buccal cavity plus oral pharynx

SOURCE: National Cancer Institute (*198*).

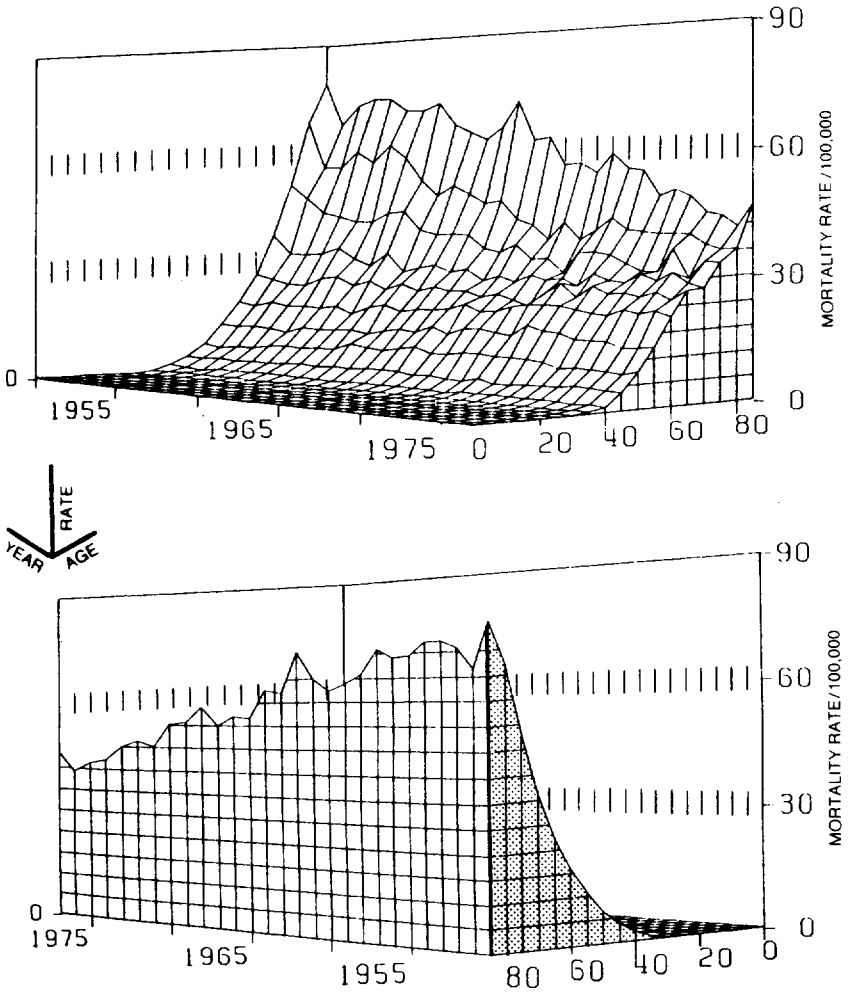

FIGURE 29.—Age-specific mortality rates by 5-year age groups for cancer of the buccal cavity and pharynx for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

in risk for cancer of the buccal cavity and pharynx among smokers of lower tar and nicotine cigarettes, but the reduction was not statistically significant. Wynder and Hoffmann (*316*) reported similar findings in a retrospective study of smokers of filter cigarettes versus smokers of nonfilter cigarettes.

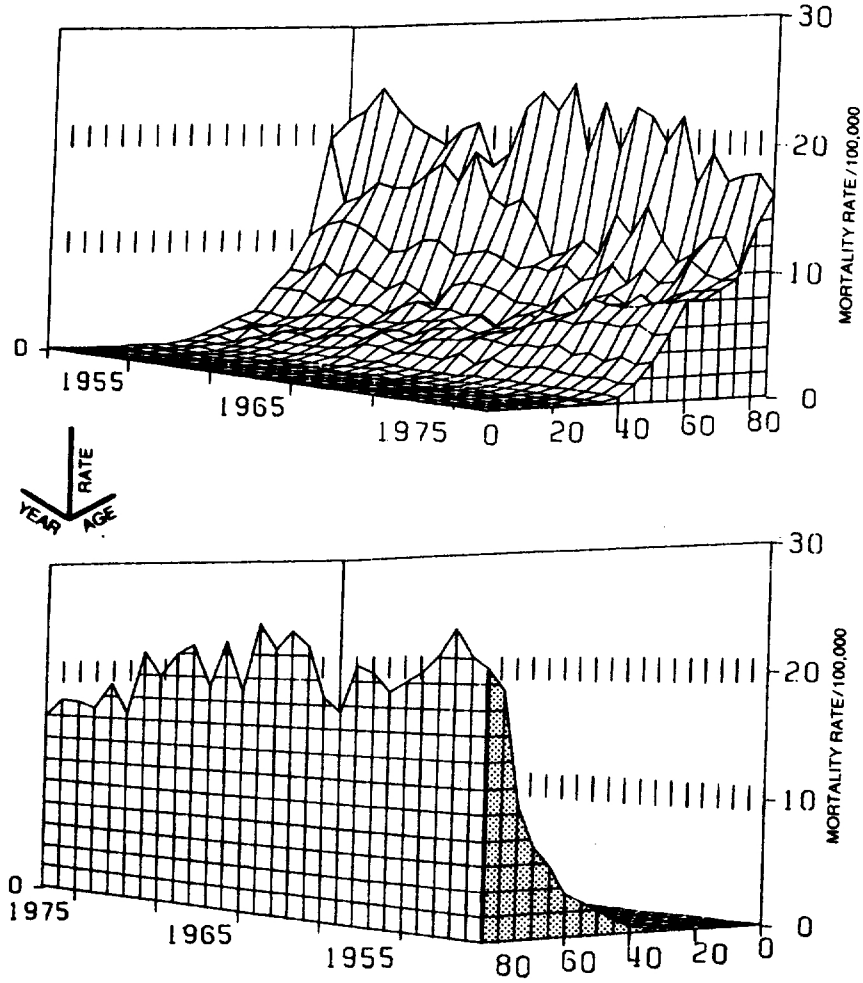

FIGURE 30.—Age-specific mortality rates by 5-year age groups for cancer of the buccal cavity and pharynx for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

Specificity of the Association

The prospective studies have reported mortality data for a large number of diseases. Specificity, which is related to the magnitude of the association between smoking and oral cancer, is evidenced by the differences in the mortality ratios (smokers versus nonsmokers) of oral cancer and other cancers (Appendix Tables A and B). These

TABLE 24.—Mortality ratios for cancer of the oral cavity—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
ACS 9-State Study	188,000 males	55	1.00	5.06	Only 3 deaths among nonsmokers
British Physicians	34,000 males	38	1.00	13.00	Includes lip, tongue, mouth, pharynx, larynx, and trachea
U.S. Veterans	290,000	61	1.00	4.22	Buccal cavity
			1.00	14.05	Pharynx
ACS 25-State Study	358,000 males	167	1.00	6.52	Buccal cavity and pharynx
	483,000 females	65	1.00	3.25	
California males in 9 occupations	68,000 males	19	1.00	2.76	
Japanese Study	122,200 males	43	1.00	2.88 males	Data for mouth only
	142,800 females	11	1.00	1.22 females	
Swedish Study	55,000 males and females	15	Mortality ratios not published		5 deaths in nonsmoking males; 10 deaths in smoking males

differences are even greater when comparisons are made with the mortality ratios of heavy smokers.

Temporal Relationship of the Association

Evidence for a temporal relationship of this association is provided by the prospective studies in which populations of apparently disease-free smokers and nonsmokers were followed over time for oral cancer mortality. In addition, the finding of premalignant oral mucosal changes in greater proportions of smokers than nonsmokers provides evidence for the temporality of the association (see below).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship between smoking and oral cancer mortality in both retrospective and prospective studies lends support to the causal nature of the association.

TABLE 25.—Oral cancer mortality ratios by amount smoked—prospective studies

Study	Population	Amount Smoked per Day				Comments
		Males		Females		
British Physicians	40,000	NS	1.00	NS	1.00	Male data by grams of tobacco per day
		1–14	5.00	1–14	—	
		15–24	7.00	15–24	4.00	
		25 +	33.00	25 +	6.50	
U.S. Veterans	290,000	NS	1.00			*Based on fewer than 20 deaths.
		1–9	2.92*			
		10–20	2.87			
		21–39	6.15			
		40 +	12.40*			
Japanese in 29 Health Districts	265,000	NS	1.00			Hypopharynx only
		1–19	1.20			
		20–29	5.50			
		30 +	9.10			
ACS 9-State Study	188,000 males	NS	1.00			Includes larynx and esophagus
		1–9	7.00			
		10–20	6.00			
		20 +	7.67			
California males in 9 occupations	68,000 males	NS	1.00			
		< ½ pack	3.69			
		1 pack	1.17			
		1½ pack	5.52			

NOTE: NS: Nonsmoker.

Correlation of Sex Differences in Oral Cancer With Different Smoking Habits

Oral cancer is predominantly a disease of males, but the difference between male and female rates of disease is narrowing. This finding is consistent with the differences in the smoking trends of males and females noted above. As with laryngeal and esophageal cancer, there is a strong association between oral cancer and alcohol consumption. This must be considered as contributing to the excess ratio of male to female oral cancer mortality (see below).

Correlation of Oral Cancer Mortality Rates Among Populations With Different Tobacco Consumption

In populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the incidence and mortality rates of cancer of the gum, mouth, tongue, and pharynx are substantially reduced (*79, 165, 166, 211, 294*).

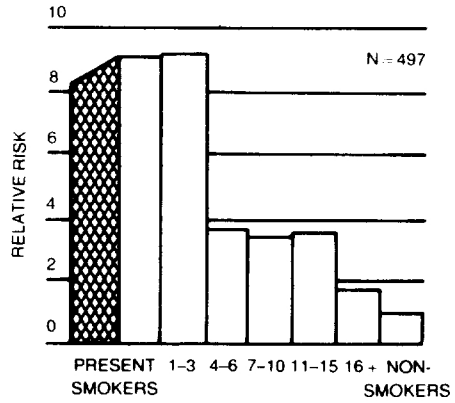

FIGURE 31.—Relative risk of male ex-smokers for cancer of the oral cavity by years since quitting smoking

SOURCE: Wynder and Stellman (*326*).

Oral Cancer Mortality and Cessation of Smoking

In the U.S. Veterans Study (*224*), ex-smokers had approximately 40 percent of the risk for oral cancers of current smokers. Data from the American Health Foundation study found that the risk of cancer of the oral cavity among former smokers declined with the number of years off cigarettes when compared to the risk of continuing smokers. After 16 or more years of cessation, the risk of oral cancer approaches that of nonsmokers (Figure 31). This is consistent with the causal nature of the association.

Smoking and Histological Changes in the Oral Mucosa

Leukoplakia is an abnormal thickening and keratinization of oral mucosa and is recognized as a precursor of malignancy of the oral cavity (*124*). A few studies have established a relationship between smoking in various forms and leukoplakia (*269*).

Oral Cancer and Non-Cigarette Tobacco Use

The oral cavity and pharynx are the sites most consistently exposed to tobacco smoke. A summary of the data from the prospective epidemiological studies is presented in Table 26. They demonstrate that cigar and pipe smokers experience a significant risk of developing cancer of the oral cavity compared with nonsmokers. This risk is approximately equal for all smokers whether an individual uses a pipe, cigar, or cigarette.

Several authors have reported a relationship between chewing tobacco and/or snuff dipping (the placement and retention of fine

TABLE 26.—Mortality ratios for oral cancer in cigar and pipe smokers. A summary of prospective epidemiological studies

Study	Smoking Type					
	Non-Smoker	Cigar Only	Pipe Only	Total Pipe and Cigar	Cigarette Only	Mixed
ACS 9-State Study [1]	1.00	5.00	3.50	—	5.06	—
British Physicians [2]	1.00	—	—	[3]9.00	13.00	11.00
ACS 25-State Study	1.00	—	—	4.94	M 6.52	—
					F 3.75	—
U.S. Veterans Study						
Oral [4]	1.00	4.11	3.12	4.20	4.22	3.79
Pharynx	1.00	—	1.98	7.76	14.05	7.75

[1] Combines data for oral, larynx, and esophagus.
[2] Figures for all non-lung respiratory cancers.
[3] Mortality ratios for ages 45 to 64 only as presented.
[4] Excludes pharynx.

ground or powdered tobacco in the oral vestibule between the gums and cheek) and oral cancer (*36, 186, 207, 234, 299, 301, 310*). A recent report found a fourfold increase in risk for oral cancer among female snuff dippers compared to nontobacco users (*301*). The excess risk for cancers of the cheek and gum was nearly fiftyfold among long-term users. The authors estimated 87 percent of these tumors were related to snuff use. In the Third National Cancer Survey, Williams and Horm (*299*) noted an excess relative risk for cancers of the gum and mouth in male and female users of chewing tobacco or snuff. However, this risk was only statistically significant for males.

A few epidemiological investigations have demonstrated an association between the combined use of alcohol and pipe or cigar smoking and the development of oral cancer (*135, 172, 173, 310*). Heavy pipe and/or cigar smoking and heavy drinking are associated with higher rates of oral cancer than are seen with either habit alone.

Synergistic Role of Alcohol and Cigarettes for Oral Cancer

Oral cancer occurs more commonly in heavier users of alcohol (*37, 88, 136, 227, 283, 301, 310*). A recent study (*179*) noted an interaction (Figure 32) for oral cavity cancer in white males who use both alcohol and cigarettes. Nonsmokers who consumed 7 ounces or more of alcohol per day had a relative risk of 2.5. Those cigarette smokers who consumed 7 ounces or more of alcohol per day had a relative risk of 5.1 if they smoked one-half a pack or less daily, 20.5 if they smoked 11 to 20 cigarettes per day, and 24.0 if they smoked more than one pack of cigarettes per day. A distinct synergy (a multiplicative effect) of alcohol and cigarette smoking has been described elsewhere (*271*). The mechanism by which these two factors interact is unclear.

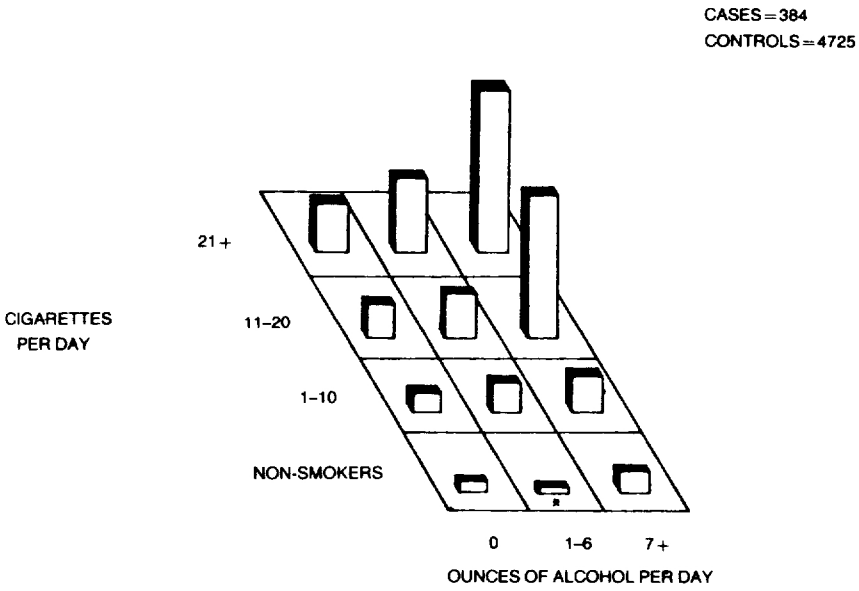

FIGURE 32.—Relative risks of oral cavity cancer by daily consumption of alcohol and cigarettes for males

* Not significant.
SOURCE: McCoy et al. (*179*).

Experimental Studies

A useful animal model for the experimental study of oral carcinogenesis has not been found. Cigarette smoke and cigarette smoke condensates generally fail to produce malignancies when applied to the oral cavity of mice, rabbits, or hamsters. Mechanical factors, such as secretion of saliva, interfere with the retention of carcinogenic agents. However, positive results have been obtained with benzo[a]pyrene, 20-methyl-cholanthrene, 9,10-dimethyl-1,2 benzanthracene, and other tobacco smoke carcinogens when applied to the cheek pouch of hamsters. The cheek pouch, however, lacks salivary glands, and its structure and function differ from those of the oral mucosa. These studies have been reviewed in previous reports of the U.S. Public Health Service (*272, 276*).

Conclusion

1. Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker.

2. Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking.
3. Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers.
4. Long term use of snuff appears to be a factor factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum.

Carcinoma of the Esophagus

Introduction

Carcinoma of the esophagus is a rapidly fatal neoplasm; there is a median survival of less than 6 months following diagnosis and a 5-year survival rate of 3 percent.

The number of deaths caused by esophageal cancer rose from 3,866 in 1950 to 7,283 in 1977. The age-adjusted death rate increased from 2.3 to 2.6 over this period (Figure 33).

In the United States in 1977, 3,924 white males and 1,520 white females died from esophageal cancer; in the other than white population, 1,404 males and 435 females died from this disease. While these figures represent only a slight increase in age-adjusted mortality in the white population, they do reflect nearly a twofold increase in the other than white population from 1950 to 1977.

The ratio of the age-adjusted death rate of the other than white population to that of the white population increased over the study period. In 1977, the death rate from this cause among other than white males between the ages of 35 and 44 years was eight times that among white males of the same age. The death rate of other than white females in this age group was 13 times the corresponding rate of white females. Mortality ratios by race (white/other-than-white) decreased with age in both males and females.

Among whites, the mortality sex ratio (male/female) declined slightly between 1968 and 1977. In the other than white group, there was also a greater relative increase in the age-adjusted death rate of females than in those of males.

Among white males and females, age-specific death rates from cancer of the esophagus (Figure 34) increased in each succeeding 10-year age group to the end of the lifespan. In other than white males, mortality peaked between ages 65 and 74 (Figure 35). The pattern was irregular in other than white females, varying with age group and time span over the 1950–1977 period.

A three-dimensional graph of age-specific death rates for white males and females for cancer of the esophagus over the period 1950–1977 is shown in Figures 36 and 37.

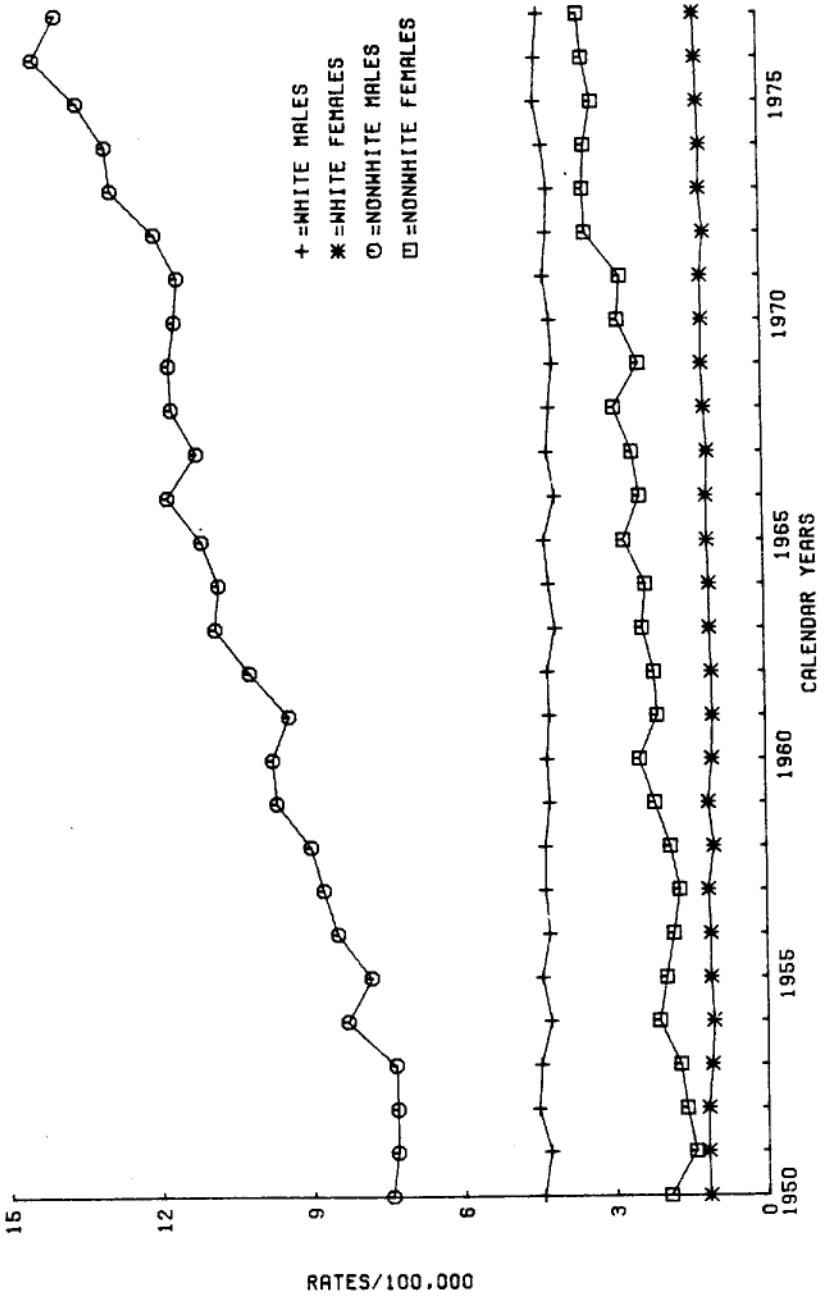

FIGURE 33.—Age-adjusted* mortality rates for cancer of the esophagus, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

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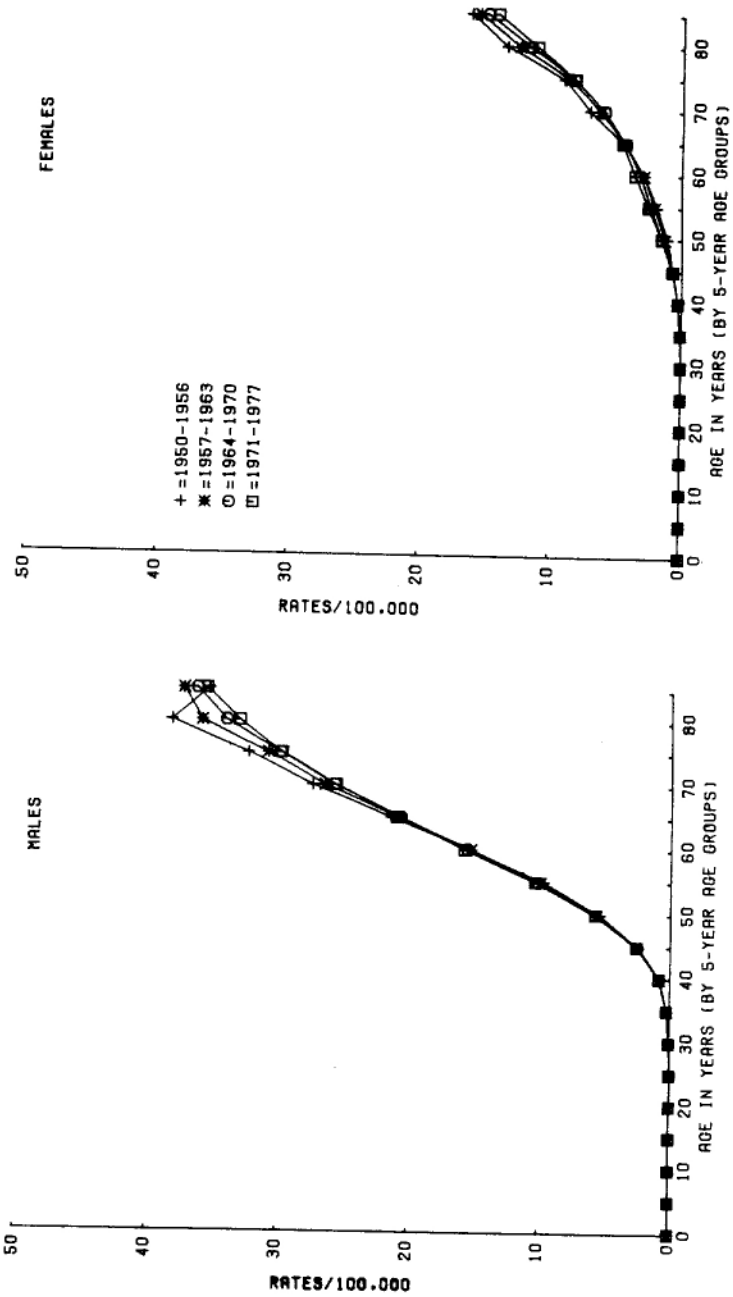

FIGURE 34.—Age-specific mortality rates for whites in the United States for cancer of the esophagus

SOURCE: National Cancer Institute (*198*).

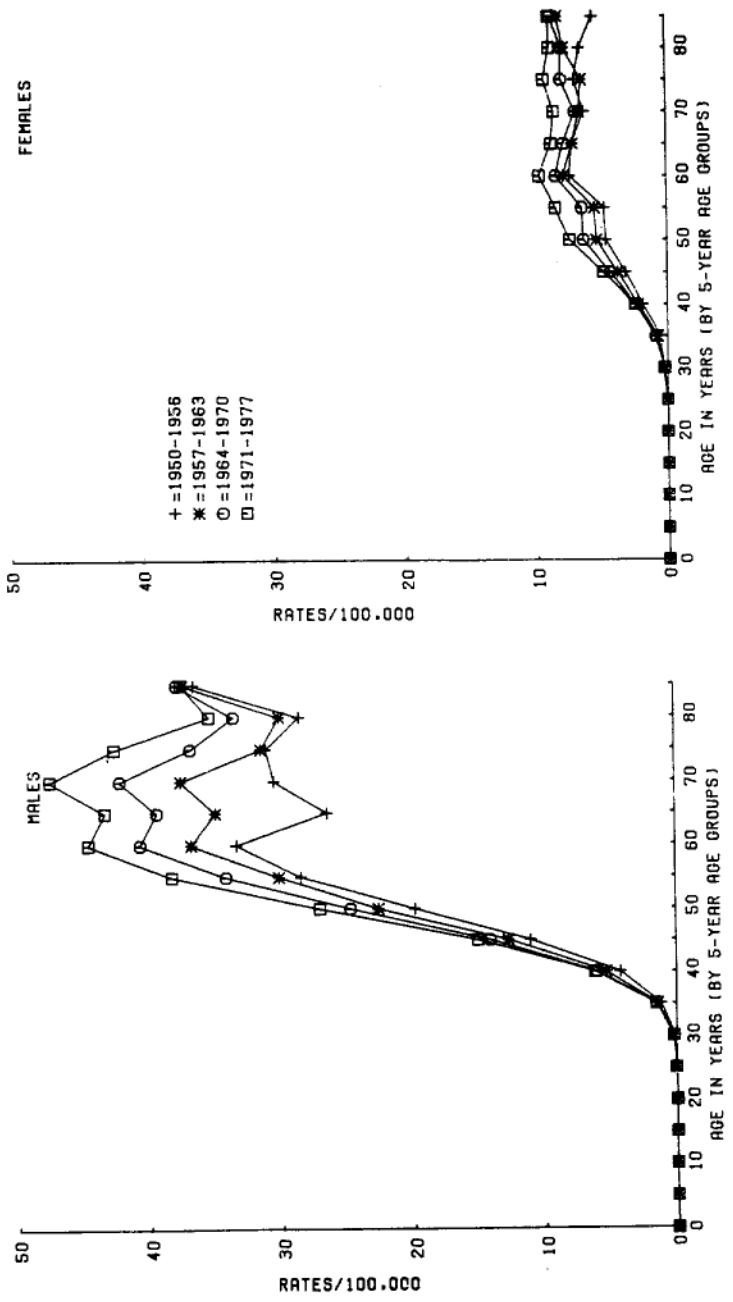

FIGURE 35.—Age-specific mortality rates for nonwhites in the United States for cancer of the esophagus

SOURCE: National Cancer Institute (*198*).

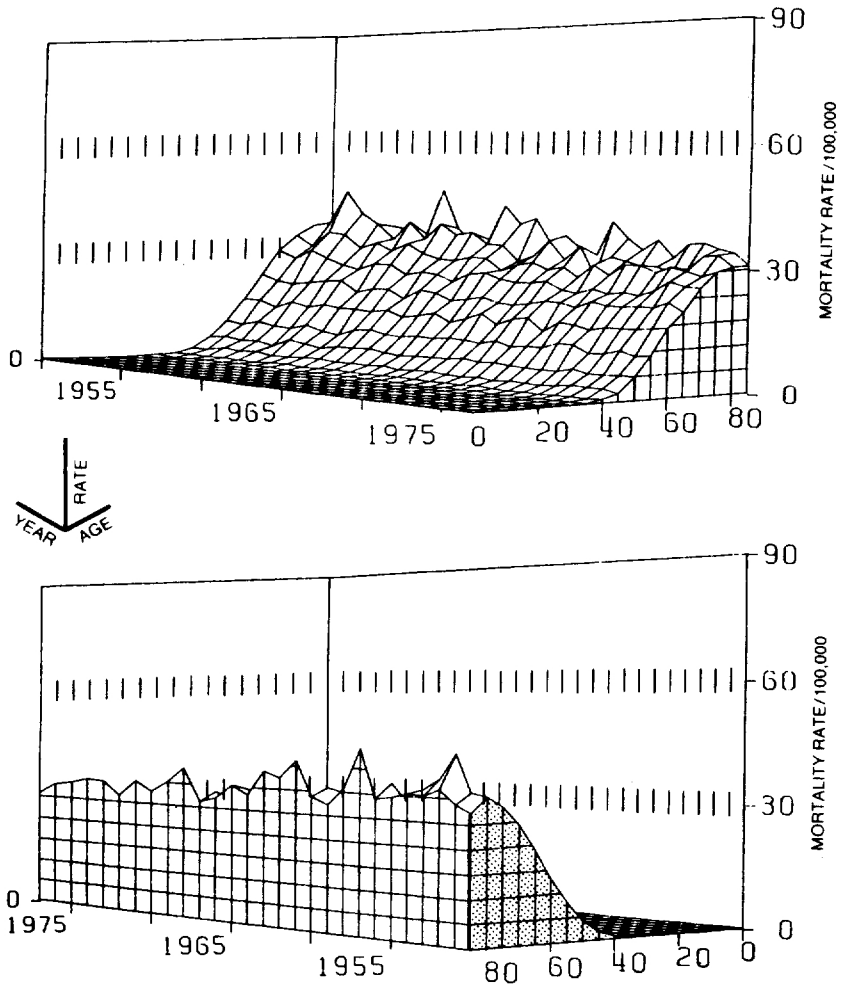

FIGURE 36.—Age-specific mortality rates by 5-year age groups for cancer of the esophagus for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

It is estimated that in 1982 in the United States there will be 8,900 new cases and 8,300 deaths from this disease (*2*).

A number of epidemiological and experimental studies have established an association between smoking and esophageal cancer.

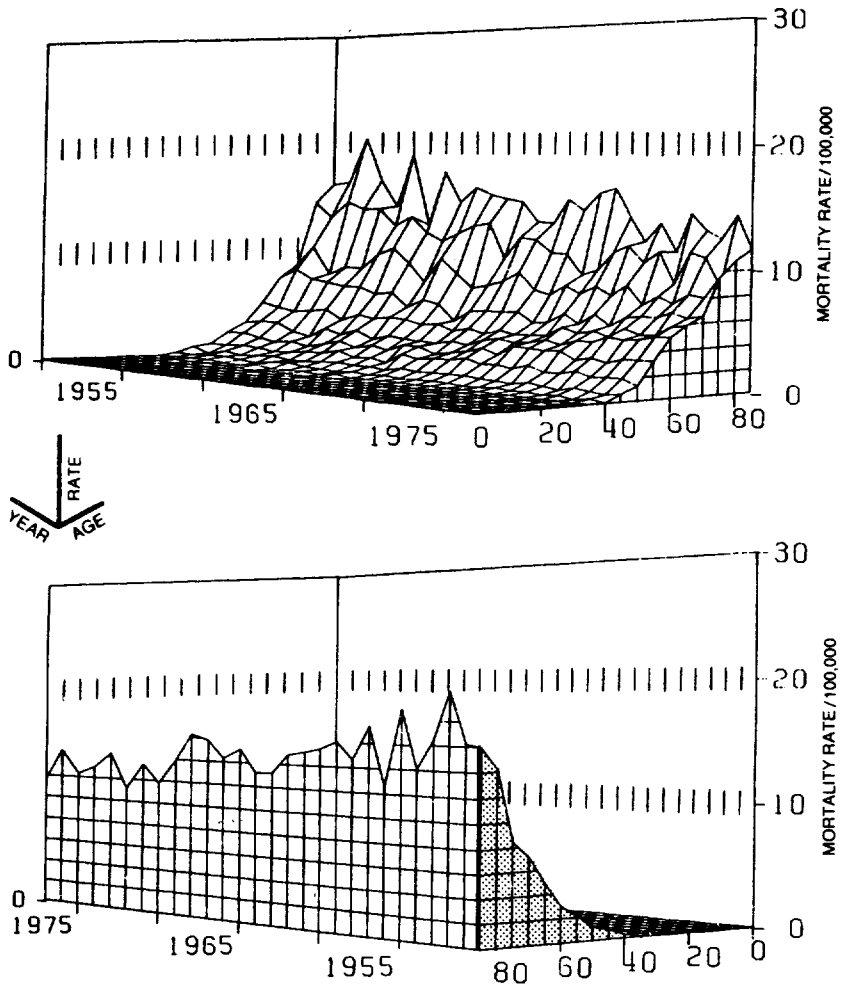

FIGURE 37.—Age-specific mortality rates by 5-year age groups for cancer of the esophagus for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

Causal Significance of the Association

Consistency of the Association

At least 10 retrospective studies have examined the relationship between smoking and esophageal cancer (*276*). Regardless of methodology, risk ratios were consistently increased. Data from the major prospective studies (Table 27) also demonstrate consistently increased mortality ratios for male smokers as compared with non-

TABLE 27.—Mortality ratios for cancer of the esophagus—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
ACS 9-State Study	188,000	1 nonsmoker 33 smokers	1.00	5.06	Esophagus and other respiratory sites
British Physicians	34,000 males	65	1.00	4.70	Esophagus and other respiratory sites
U.S. Veterans	290,000	119	1.00	6.43	
ACS 25-State Study	398,000 males 483,000 females	116 48	1.00 1.00	3.96 4.89	
California males in 9 occupations	68,000 males	32	1.00	1.82	
Japanese Study	122,200 males	215	1.00	2.35	
Swedish Study	55,000 males and females	1 nonsmoker 12 smokers	1.00	—	

smokers. The ACS 25-State Study showed similar results for female smokers and cancer of the esophagus.

Strength of the Association

Mortality ratios in the retrospective studies ranged from 1.3 to 11.1 among heavy smokers; mortality ratios in the prospective studies ranged from 1.8 to 6.4. In four of the large prospective studies, a dose-response relationship was demonstrated (Table 28). A reduced risk for esophageal cancer among female but not male smokers of lower tar and nicotine cigarettes has also been reported (*155*).

Specificity of the Association

Specificity of the association between smoking and esophageal cancer is evidenced by substantial differences in the mortality ratios (smokers versus nonsmokers) for esophageal cancer compared to other smoking-related cancers (Appendix Tables A and B).

Temporal Relationship of the Association

The temporal relationship of this association is supported by the prospective studies in which populations of initially disease-free subjects were followed for the development of esophageal carcinoma. In addition, there are histological data suggesting that smoking

TABLE 28.—Mortality ratios for cancer of the esophagus by amount smoked—prospective studies

Study	Population Size	Cigarettes/Day	Ratio	Comments
British Physicians	34,000 males	Nonsmoker	1.00	Grams of tobacco per day
		1–14	4.00	
		15–24	4.33	
		25 +	10.00	
U.S. Veterans	290,000	Nonsmoker	1.00	*Based on fewer than 20 deaths
		1–9	3.06*	
		10–20	4.34	
		21–39	12.42	
		40 +	9.20*	
Japanese in 29 Health Districts	122,200 males	Nonsmoker	1.00	
		1–19	2.20	
		20–29	2.80	
		30 +	3.20	
California males in 9 occupations	68,000	Nonsmoker	1.00	
		about ½ pk	1.27	
		about 1 pk	1.69	
		about 1½ pk	1.82	

antedates premalignant and malignant transformation of esophageal epithelium (*13, 16*).

Coherence of the Association

Dose-Response Relationship

There is a dose-response relationship between smoking and esophageal cancer mortality in retrospective and prospective studies (*276*).

Esophageal Cancer Mortality and Cessation of Smoking

Several of the prospective studies noted reduced risks for cancer of the esophagus after quitting smoking. The U.S. Veterans Study found that the mortality ratio for ex-smokers decreased to 2.41 compared to 6.43 for continuing smokers. For the British Physicians Study, the corresponding ratios were 1.66 and 5.33, respectively. Thus, ex-smokers had only about one-third the risk for esophageal cancer of current smokers.

Figure 38 presents data from the American Health Foundation study for esophageal cancer mortality risk by the number of years off cigarettes. After quitting smoking for 4 years or more, former smoker rates were not substantially above those of nonsmokers.

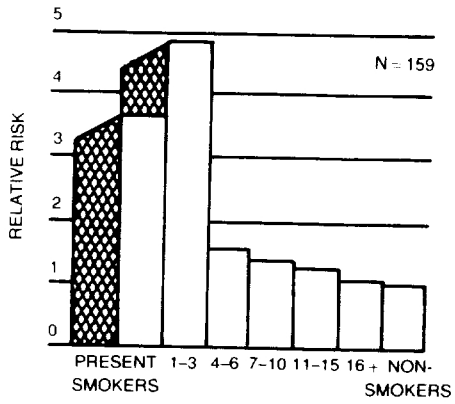

FIGURE 38.—Relative risk of male ex-smokers for cancer of the esophagus by years since quitting smoking

SOURCE: Wynder and Stellman (*326*).

Correlation of Sex Differences in Esophageal Cancer With Different Smoking Habits

Esophageal cancer is predominantly a disease of males. The sex differences observed for esophageal cancer mortality are compatible with the sex differences in smoking patterns. As with oral and laryngeal cancer, esophageal cancer has also been related to excessive alcohol consumption. This must be considered as contributing to the excess ratios of male to female esophageal cancer mortality (see page 101).

Correlation of Esophageal Cancer Mortality Among Populations With Different Tobacco Consumption

In populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the mortality rates from esophageal cancer are substantially reduced (*79, 165, 166, 211, 294*).

TABLE 29.—Mortality ratios for cancer of the esophagus in cigar and pipe smokers—a summary of prospective epidemiological studies

Study	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
ACS 9-State Study[1]	1.00	5.00	3.50	—	5.06	—
British Physicians	1.00	—	—	3.70	4.70	9.0
ACS 25-State Study	1.00	—	—	3.97	males 3.96[2] females 4.89[2]	— —
U.S. Veterans	1.00	5.33	1.99	4.05	6.43	—

[1] Combines data for oral, larynx, and esophagus.
[2] Mortality ratio for ages 45 to 64.

Smoking and Histologic Changes in the Esophagus

Examination of 12,598 histologic sections of esophageal autopsy tissue from 1,268 men showed histologic findings which were similar to the abnormalities generally accepted as being premalignant in respiratory tract epithelium (*16*). Only 2.5 percent of the slides from current smokers exhibited no atypical cells, compared with 93.5 percent of slides from nonsmokers. The finding of 60 percent or more atypical cells was rare in the tissue of nonsmokers (0.3 percent), but much more common in tissue of smokers (17.7 percent).

Esophageal Cancer and Non-Cigarette Tobacco Use

The esophagus is not directly exposed to inhaled tobacco smoke, but tobacco smoke constituents condense on the mucous membranes of the mouth and pharynx and are swallowed, thus contacting esophageal cells. The esophagus also receives mucous cleared from the lungs by the ciliary mechanism or by coughing which is also swallowed. Variations in the inhalation of the smoke of different tobacco products may not appreciably alter the degree of exposure of the esophagus. This possibility is suggested by the prospective and retrospective epidemiological studies which demonstrate similar mortality rates for cancer of the esophagus in smokers of cigars, pipes, and cigarettes. These data are presented in Table 29.

Several retrospective investigations have examined the association between smoking in various forms and cancer of the esophagus (Table 30). These studies suggest that cigar, pipe, and cigarette smokers develop cancer of the esophagus at rates substantially higher than do nonsmokers and that little difference exists between these rates observed in smokers of pipes, cigars, or cigarettes. Histologic changes in the esophagus have been related to smoking of

cigarettes and other forms of tobacco (*16*). Several retrospective studies conducted in the United States and other countries have examined the synergistic role of tobacco use and heavy alcohol intake and the risk of mortality from cancer of the esophagus. At least four of these investigations contain data on pipe and cigar smoking (*33, 172, 173, 307*). It appears that smoking in any form in combination with heavy drinking results in especially high rates of cancer of the esophagus.

TABLE 30.—Relative risk of cancer of the esophagus for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Sadowsky (*236*):		Relative risk	1.0	4.8	3.8	5.1	3.8	3.3
Cases	104	Percent cases	4	5	8	6	69	18
Controls	615	Percent controls	13	3	7	4	53	19
Wynder (*317*):		Relative risk	1.0	3.1	2.1	....	2.6	.4
Cases	39	Percent cases	13	15	18	....	51	3
Controls	115	Percent controls	24	9	16	....	36	13
Pernu (*209*):		Relative risk	1.0	....	3.0	....	2.7	5.9
Cases	202	Percent cases	17	....	7	....	59	18
Controls	713	Percent controls	39	....	5	....	50	7
Schwartz (*247*):		Relative risk	1.0	....	2.6	....	11.7	8.6
Cases	249	Percent cases	2	....	2	....	88	7
Controls	249	Percent controls	18	....	7	....	67	7
Wynder and Bross (*307*):		Relative risk	1.0	3.6	9.0	6.0	2.8	3.7
Cases	150	Percent cases	5	19	9	4	51	11
Controls	150	Percent controls	15	16	3	2	55	9
Bradshaw and Schonland (*33*):		Relative risk	1.0	....	4.8	....	2.3	....
Cases	117	Percent cases	15	....	41	....	63	....
Controls	366	Percent controls	32	....	18	....	58	....
Martinez (*172*):		Relative risk	1.0	2.0	....	....	1.5	2.2
Cases	120	Percent cases	8	9	....	....	31	43
Controls	360	Percent controls	14	8	....	....	34	34
Martinez[1] (*173*):		Relative risk	1.0	2.0	2.8	....	1.7	2.5
Cases	346	Percent cases	21	10	15	....	34	34
Controls	346	Percent controls	22	9	1	....	36	25

[1]This study combines data for oral cancer and cancer of the esophagus.

Synergistic Role of Alcohol for Esophageal Cancer

Numerous investigators have found a synergistic relationship between the use of tobacco in various forms, alcohol consumption, and the development of cancer of the esophagus (*119, 132, 143, 241, 243, 263, 299, 307, 323*). Some investigators report that tobacco is a more important carcinogen than alcohol, but others report that the reverse is true. Most of the studies report a synergism with the combined use of tobacco and alcohol, resulting in higher rates of cancer of the esophagus than would be observed by the addition of the two exposures. The mechanisms by which these two factors interact are not known. Alcohol may act as a solvent for carcinogenic hydrocarbons in the tobacco smoke or may alter microsomal enzymes in the mucosal cells of the esophagus (*306*). This hypothesis has received support from experimental observations (*150*). It has been noted, however, that alcoholism may be accompanied by severe nutritional deficiencies, which also may predispose an individual to certain diseases (*271*).

Experimental Studies

There is experimental evidence that benzo[a]pyrene is able to penetrate the cell membranes of the esophageal epithelium, producing papillomas and squamous cell carcinoma. These studies and others are presented in the Part of this Report on mechanisms of carcinogenesis.

Conclusion

1. Cigarette smoking is a major cause of esophageal cancer in the United States. Cigar and pipe smokers experience a risk of esophageal cancer similar to that of cigarette smokers.
2. The risk of esophageal cancer increases with increased smoke exposure, as measured by the number of cigarettes smoked daily, and is diminished by discontinuing the habit.
3. The use of alcohol in combination with smoking acts synergistically to greatly increase the risk for esophageal cancer mortality.

Cancer of the Urinary Bladder

Introduction

It is estimated that in 1982 in the United States there will be 37,100 new cases and 10,600 deaths from cancer of the bladder (*2*). The average annual incidence for males is almost three times that for females.

Cancer of the bladder resulted in 6,401 deaths in 1950 and 9,812 deaths in 1977 in the United States. The age-adjusted rate fell from 3.7 to 2.9 per 100,000.

The age-adjusted mortality rate fell in all four color-sex groups (Figure 39). The rate for white males, who had the highest mortality from this disease, decreased by 5.7 percent between 1950 and 1977. Among other than white males, who had the second highest mortality rate from this disease, mortality declined by 2.6 percent. In contrast, the age-adjusted death rate for white females decreased by 36.4 percent, and that of other than white females fell 25.9 percent.

White males between 45 and 74 years of age had lower death rates from cancer of the bladder in 1977 than in 1960, but older males had higher mortality. Among white females 45 years of age and older, mortality decreased over the study period. The death rate increased in other than white males 65 years of age or older and in other than white females 75 years of age or older (Figures 40 and 41).

The age-specific death rates show no significant increases in either white males or white females when plotted on a three-dimensional graph for the period 1950–1977 (Figures 42 and 43).

Most cancers of the bladder are transitional or squamous cell carcinomas. Unless these produce hematuria or obstruct the bladder outlet, they remain undiagnosed until quite late, making cure less likely. Five-year survival rates range from 4 percent for individuals with distant metastasis, to 21 percent for individuals with regional involvement, and to 72 percent with localized disease (*2*). For patients diagnosed with bladder cancer from 1960 to 1973, the overall 5-year survival rate was approximately 60 percent for whites and 30 percent for other than white (*313*).

Certain occupational exposures are associated with an elevated risk for bladder cancer. Many of these are related to the exposure to certain aromatic amines in the work place. The first report of an association between cigarette smoking and human bladder cancer in the United States was based on a retrospective study of 321 men with bladder cancer (*157*). In the ensuing 35 years, other epidemiological and experimental data have established an association between cigarette smoking and bladder cancer.

Several authors have conservatively calculated the percentage of bladder cancers that can be attributed to cigarette smoking. One study (*313*) estimated that 40 percent of male bladder cancers and 31 percent of female bladder cancers in the United States may be attributed to smoking cigarettes. This is in agreement with the estimate by Cole et al. (*48*) of 39 percent in males and 29 percent in females. A Canadian study reported a population-attributable risk of bladder cancer due to cigarette smoking of 61 percent in males and 26 percent in females (*129*).

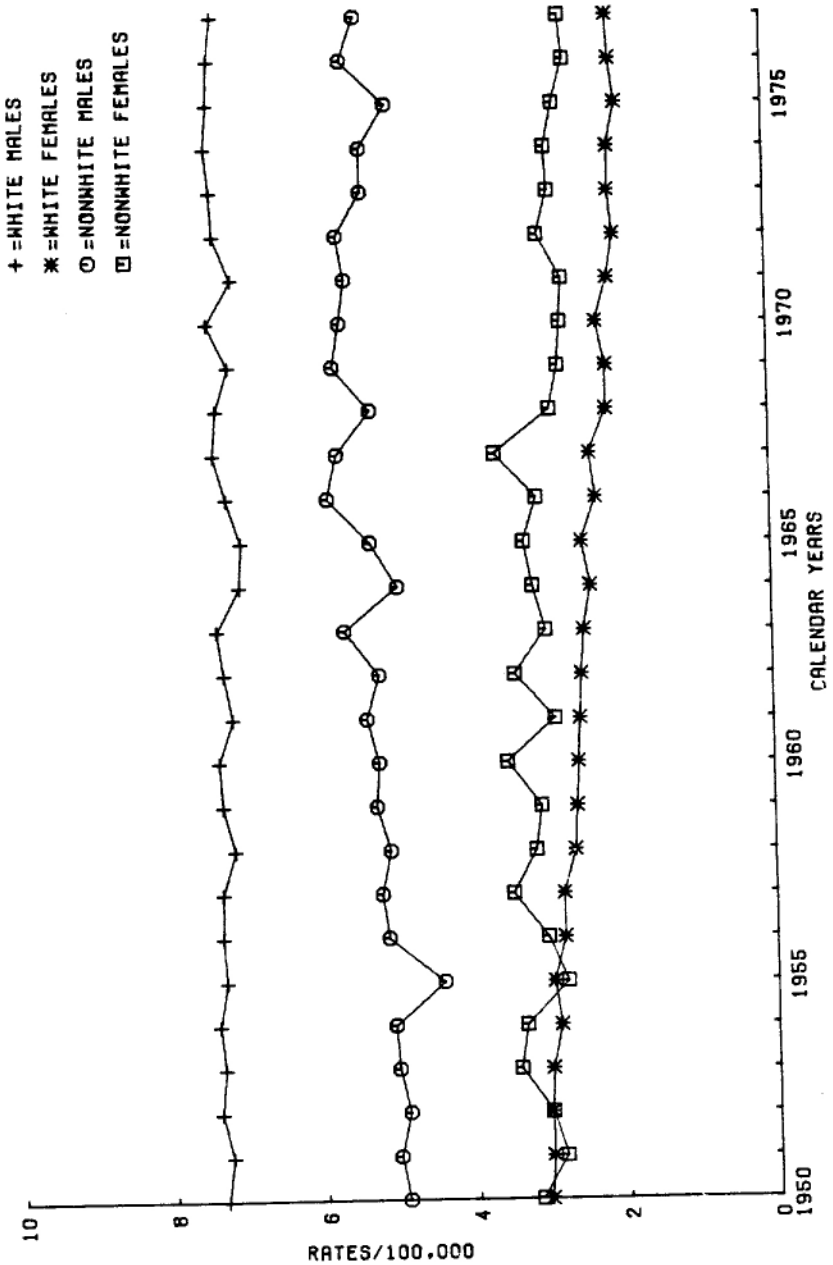

FIGURE 39.—Age-adjusted* mortality rates for cancer of the bladder and other urinary glands, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

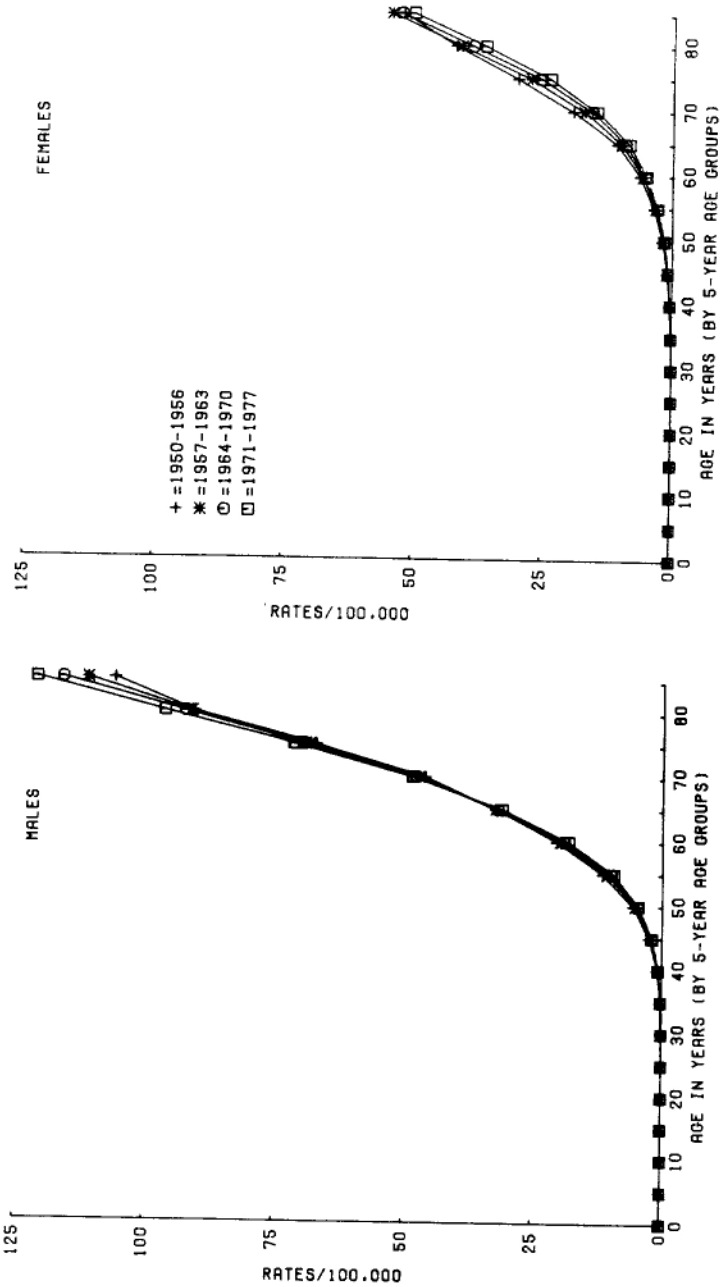

FIGURE 40.—Age-specific mortality rates for whites in the United States for cancer of the bladder and other urinary glands

SOURCE: National Cancer Institute (*198*).

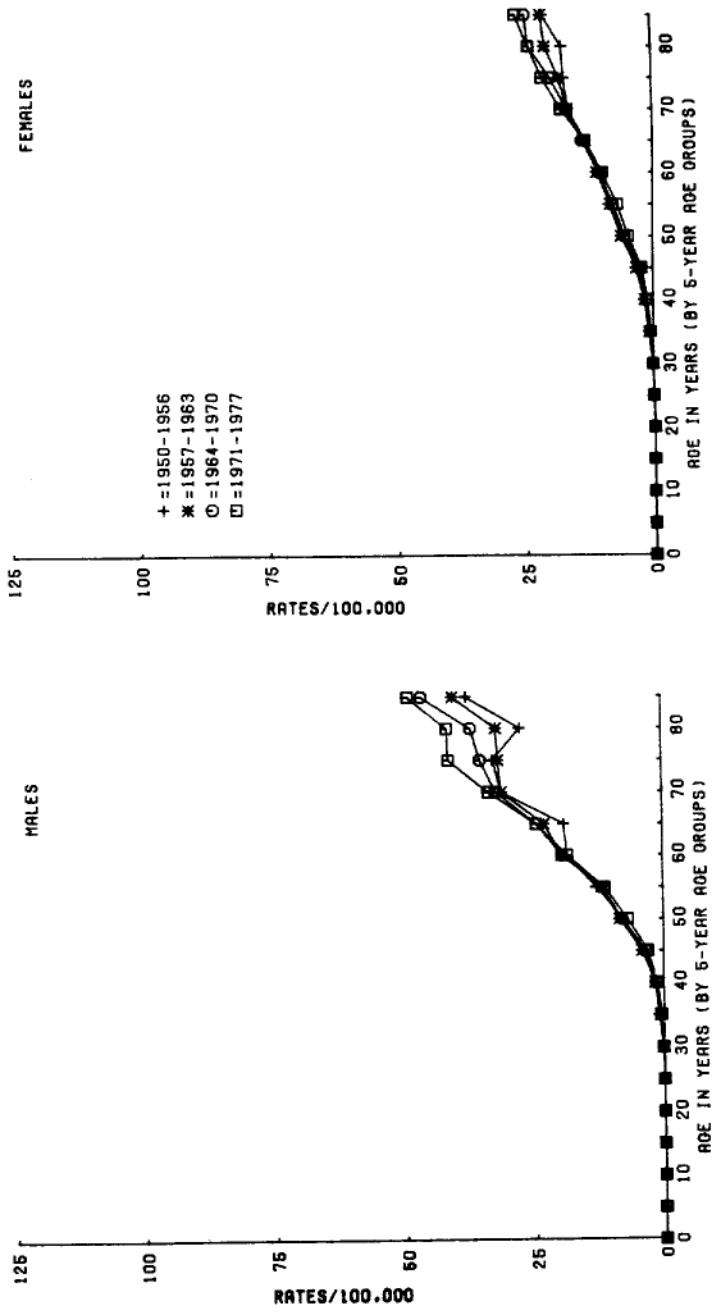

FIGURE 41.—Age-specific mortality rates for nonwhites in the United States for cancer of the bladder and other urinary glands

SOURCE: National Cancer Institute (*198*).

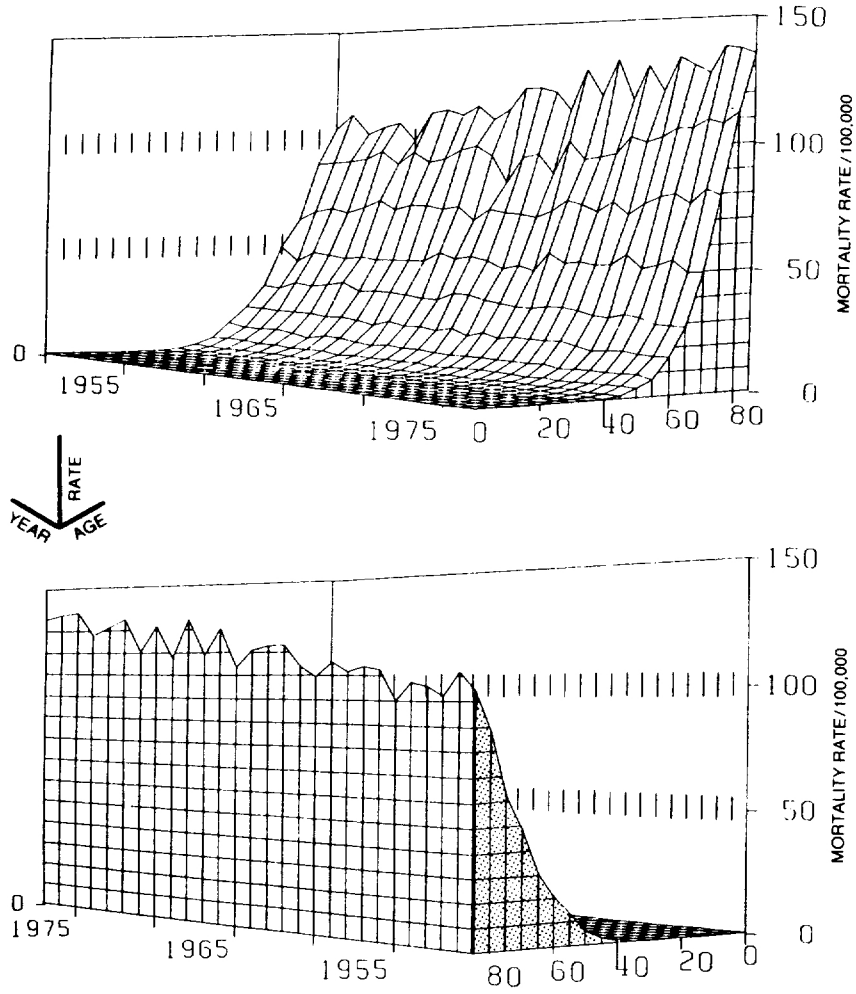

FIGURE 42.—Age-specific mortality rates by 5-year age groups for cancer of the bladder and other urinary glands for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

Causal Significance of the Association

Consistency, Strength, and Specificity of the Association

There have been numerous retrospective studies of the relationship between smoking and bladder cancer (*3, 46, 48, 55, 75, 139, 141, 157, 159, 188, 247, 253, 267, 313, 325, 327, 330*). Almost all of these studies have found an association between smoking and cancer of the

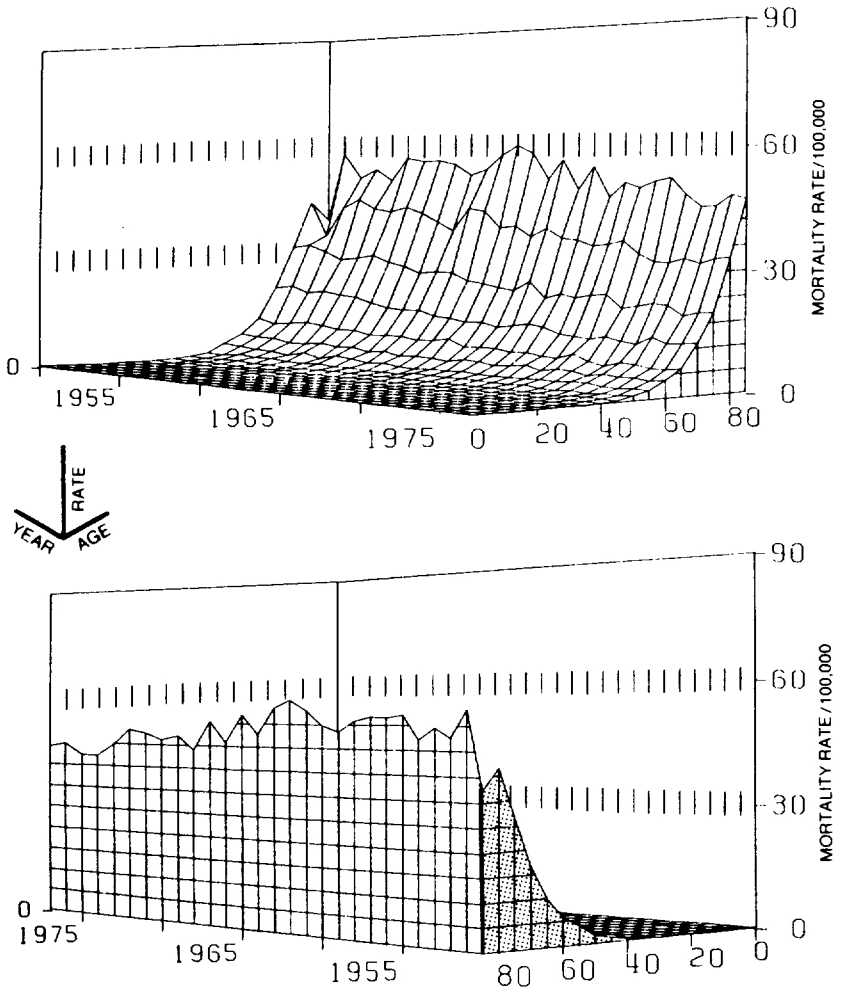

FIGURE 43.—Age-specific mortality rates by 5-year age groups for cancer of the bladder and other urinary glands for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

bladder with relative risk ratios for the smoker averaging two to three times that of the nonsmoker (Table 31). A retrospective population-based study of 470 confirmed cases of transitional cell or squamous cell cancers of the bladder found a positive relationship between cigarette smoking and bladder cancer (*48*). A dose-response

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relationship was demonstrated for both the number of cigarettes smoked per day and different degrees of inhalation.

In the TNCS study (*299*), a significant association was found between cigarette smoking and bladder cancer. The Hawaiian study of five ethnic groups (*113*) also disclosed a positive association between smoking and bladder cancer. In a Canadian population-based retrospective study of 632 case-controlled pairs (*129*), the relative risk for developing bladder cancer for those who had ever used cigarettes versus those who had never used cigarettes was 3.9 for males and 2.4 for females. A dose-response relationship was demonstrated, and reduced risk was associated with the use of filter cigarettes as compared with the use of nonfilter cigarettes. Several of the retrospective studies found a dose-response relationship of cigarette smoking for bladder cancer, with the risk increasing with increased number of cigarettes smoked per day, duration of cigarette smoking, or lifetime number of cigarettes. Further, a study of successive birth cohorts in four countries, including the United States, found increasing rates of bladder cancer with increasing smoking exposure, for both males and females (*128*).

Several of the large prospective epidemiological studies have examined the relationship between cigarette smoking and bladder cancer and are summarized in Table 32. On the average, cigarette smokers are twice as likely to die from cancer of the bladder as are nonsmokers. Several of these studies also show a moderate dose-response relationship; however, this relationship is not as strong as that noted between smoking and lung, laryngeal, oral, and esophageal cancers (Table 33). Comparisons of mortality ratios for selected causes of disease suggest that the specificity of the association is not as great as that noted for the above cancers (Appendix Tables A and B). The American Cancer Society 25-State Study (*155*) reported a reduced risk for bladder cancer among smokers of lower tar and nicotine cigarettes, a reduction which was statistically significant among females but not among males.

The lower order of strength and specificity for bladder cancer than for cancers of the lung, larynx, oral cavity, or esophagus suggests that factors other than smoking may also be associated etiologically with bladder cancer.

Bladder Cancer Mortality and Cessation of Smoking

Wynder and Stellman (*326*) reported that the risk of bladder cancer decreased almost to the level of nonsmokers after about 7 years of cessation (Figure 44). More recent data from the U.S. Veterans and British Physicians prospective studies show bladder cancer mortality ratios for ex-smokers only half those for continuing smokers (*68, 224*).

TABLE 31.—Review of literature on smoking and bladder cancer reported since 1963—retrospective studies

Country	Years of study	Authors	Relative risk smokers: nonsmokers	Number of subjects Cases	Controls	Study population
U.S.A.	1957–60	Wynder et al. (*325*)	3.5[a]	300	300	Male patients
U.S.A.	1951–61	Cobb and Ansell (*46*)	7.3[a]	131	120	Male VA hospital patients
Poland	1958–64	Staszewski (*253*)	2.7	150	750	Male patients
U.S.A.	1958–64	Dunham et al. (*75*)	1.4[a]	334	350	Male patients
			1.2[a]	159	177	Female patients
U.K.	1958–67	Anthony and Thomas (*4*)	<1	381	275	Male patients
U.S.A.	1967–68	Cole et al. (*48*)	1.9	360	381	Male patients
			2.0	108	117	Female patients
U.S.A.	1965–71	Simon et al. (*141*)	1.6	135	390	Female patients
Egypt	1966–71	Makhyoun (*157*)	1.3[a]	278	278	Bilharzial male patients
			1.7	87	87	Nonbilharzial male patients
Canada	1972–73	Morgan and Jain (*188*)	6.4[b]	158	158	Male patients
			4.4[b]	74	74	Female patients
Austria	1972–75	Flamm et al. (*84*)	1.6	150	—	Male patients; Austrian population controls
			3.0	40	—	Female patients; Austrian population controls

[a] Recalculated from author's data.

[b] Heavy smokers (≥ 25 cigarettes per day) compared with nonsmokers.

SOURCE: Wynder and Goldsmith (*313*).

TABLE 32.—Bladder cancer mortality ratios—prospective studies

Population	Study size	Non-smokers	All cigarette smokers	Comments
ACS Males in 9-State Study	187,783 White Males	1.00	2.00	Smokers of 10–20 cigarettes Includes all urinary tract cancers. Includes Prostate.
British Physicians	34,000 Male Doctors	1.00	2.11	
Canadian Veterans	78,000 Males	1.00	1.40	Genitourinary cancers considered as a group
ACS 25 State Study	358,000 Males and	1.00	2.55	
	483,000 Females	1.00	2.80	
U.S. Veterans	2,265,000 Person-Years	1.00	2.15	
California Males in 9 occupations	68,153 Males	1.00	2.89	
Japanese study	265,118 Males and	1.00	2.00 (Males)	
	Females	1.00	2.55 (Females)	
Swedish Study	55,000 Males and	1.00	1.80 (Males)	Bladder + other urinary organs
	Females	1.00	1.60 (Females)	

For male ex-smokers, the risk after 15 years of not smoking was less than one-half that of current male smokers (*129*).

Temporal Relationship of the Association

Evidence for the temporal relationship of the association is provided by the prospective studies in which populations of initially disease-free subjects were followed for the development of bladder cancer. Reliable histological studies of bladder epithelium in smokers compared with nonsmokers have not been reported.

TABLE 33.—Bladder cancer mortality ratios by amount smoked—prospective studies

Study	Population	Amount Smoked per Day	Ratio	Comments
U.S. Veterans	290,000	Nonsmoker	1.00	
		1–9	1.22	* Based on
		10–20	2.18	less than
		21–39	2.78	20 deaths
		≥40*	2.29	
British Physicians	34,000 males	Nonsmoker	1.00	Grams of
		1–14	2.20	tobacco
		15–24	2.20	per day
		25 +	1.40	
California males in 9 occupations	68,000 males	Nonsmoker	1.00	
		about ½ pk	1.52	
		about 1 pk	2.81	
		about 1½ pk	5.41	

		Males		Females	
Swedish Study	55,000 males and females	NS	1.00	NS	1.00
		1–7 gm/day	1.50	1–7	1.20
		8–15	1.60	8–15	2.10
		16 +	2.70	16 +	0.80

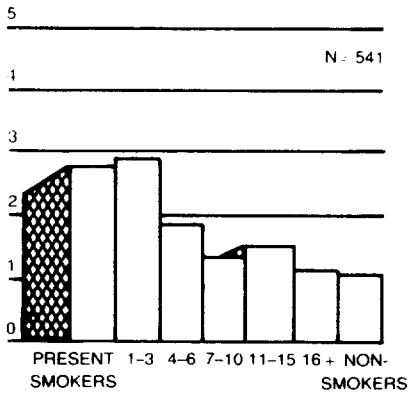

FIGURE 44.—Relative risk of male ex-smokers for cancer of the bladder by years since quitting smoking

SOURCE: Wynder and Stellman (*326*).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship in both retrospective

and prospective studies (see page 106–107) strengthens the coherence of the association of smoking and bladder cancer.

Correlation of Sex Differences in Bladder Cancer With Different Smoking Habits

Two investigators (*128, 185*), reporting 10 years apart, found an association between time trends in smoking patterns and bladder cancer mortality among both males and females. Each found an increasing risk of bladder cancer with increasing smoking exposure.

Correlation of Bladder Cancer Among Populations With Different Tobacco Consumption

Coherence of the association is also illustrated by data showing a low prevalence of this disease in groups with small proportions of smokers (e.g., Mormons and Seventh Day Adventists) (*79, 165, 166, 211, 294*).

Bladder Cancer Mortality and Cessation of Smoking

Cessation of smoking decreases the risk of bladder cancer compared to that of continuing smokers. A study of male ex-smokers (*129*) found a risk of less than one-half that of continuing smokers 15 years after quitting smoking; a similar finding was observed in two of the major prospective studies (*68, 224*).

Bladder Cancer and Non-Cigarette Tobacco Use

Two prospective studies have noted a relationship between pipe and cigar smoking and cancer of the bladder (*68, 131*). In the British Physicians Study, a mortality ratio of 1.5 was observed for the combined category of pipe/cigar smokers, whereas in the U.S. Veterans Study, a relationship was noted only for pipe smokers (ratio 1.20).

Synergistic Role of Other Substances for Bladder Cancer

The relationship between cigarette smoking and occupational exposure(s) is complex and has not been clearly elucidated. A number of carcinogens specific for the human bladder have been identified (*45*). Some of these compounds are found in cigarette smoke in very low concentrations. Cigarette smoking probably acts as an independent agent in the development of bladder cancer; however, there may also be additive or synergistic interactions between cigarette smoking and substances present in the work place.

Those who work with dye stuffs, rubber, leather, print, paint, petroleum, and other organic chemicals are at higher risk for bladder cancer than workers not exposed.

Conclusion

1. Cigarette smoking is a contributory factor in the development of bladder cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers at this site.

Cancer of the Kidney

Introduction

Over the period 1950–1977, the age-adjusted mortality rate for kidney cancer rose from 2.2 to 2.6. The annual number of deaths due to cancer of the kidney increased from 3,643 to 7,373. It is estimated that in 1982 there will be 18,100 new cases and 8,300 deaths due to kidney and other urinary tract cancers in the United States (other than bladder cancer) (*2*).

The death rate of white males was higher than that of the other three color-sex groups (Figure 45). While age-adjusted death rates increased, although at a decelerating pace, among white males throughout this period, rates among other than white males actually decreased slightly after 1967. Among white females, the age-adjusted rate increased between 1950 and 1957, when it stabilized. Among other than white females, who had the lowest age-adjusted rate of death from this disease, mortality rose from 1.2 to 1.4 per 100,000.

In the white population, the mortality sex ratio (male/female) increased from 1.75 in 1950 to 2.24 in 1977, reflecting the rise in the male death rate and the relative stability of the female rate. In the other than white populations, the mortality sex ratio was slightly lower during the 28-year period.

White males and white females were at greater risk from this disease than were their counterparts, although the white to other-than-white differential narrowed throughout the study period. In all four color-sex groups, death rates moved generally upward in the population between 45 and 84 years of age (Figures 46 and 47). In 1977, both white and other than white males had higher death rates from this disease than did white and other than white females in the 10-year age group from 35 to 44.

The age-specific death rates for cancer of the kidney show an upward trend in the older age groups, without a significant increase in the rates for the younger age groups when plotted on a three-dimensional graph for the period 1950–1977 (Figures 48 and 49).

There are four primary histological types of kidney cancer: (1) renal cell carcinoma, (2) nephroblastoma (Wilm's tumor), (3) sarco-

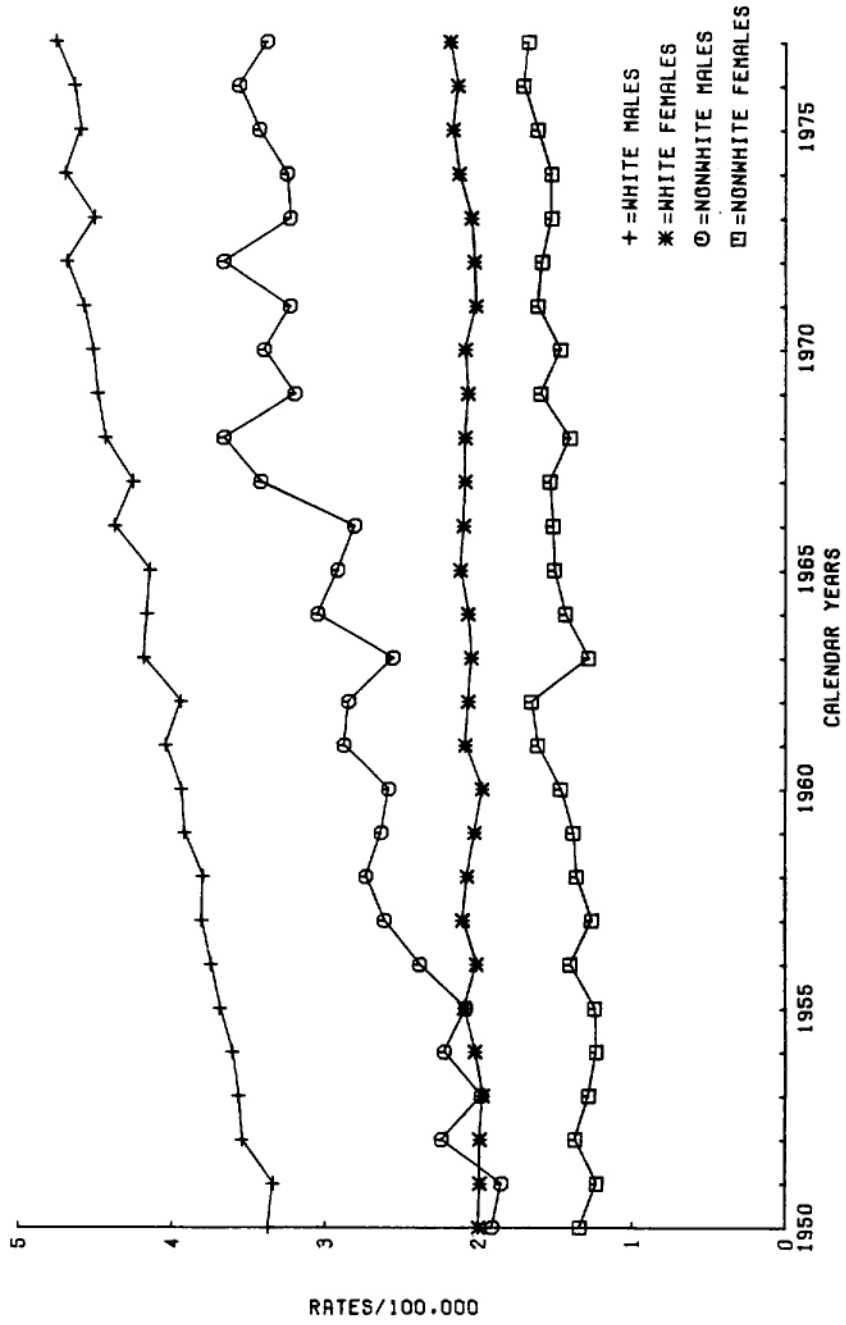

FIGURE 45.—Age-adjusted* mortality rates for cancer of the kidney, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

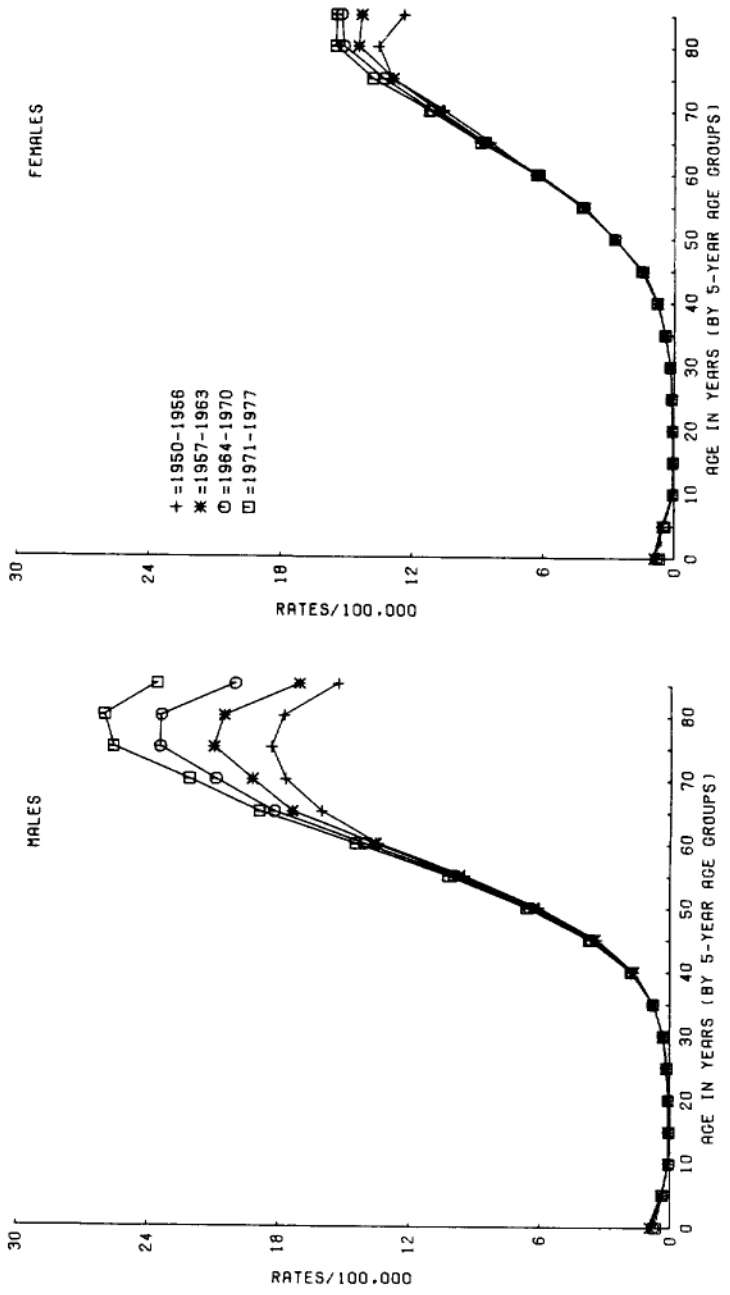

FIGURE 46.—Age-specific mortality rates for whites in the United States for cancer of the kidney

SOURCE: National Cancer Institute (*198*).

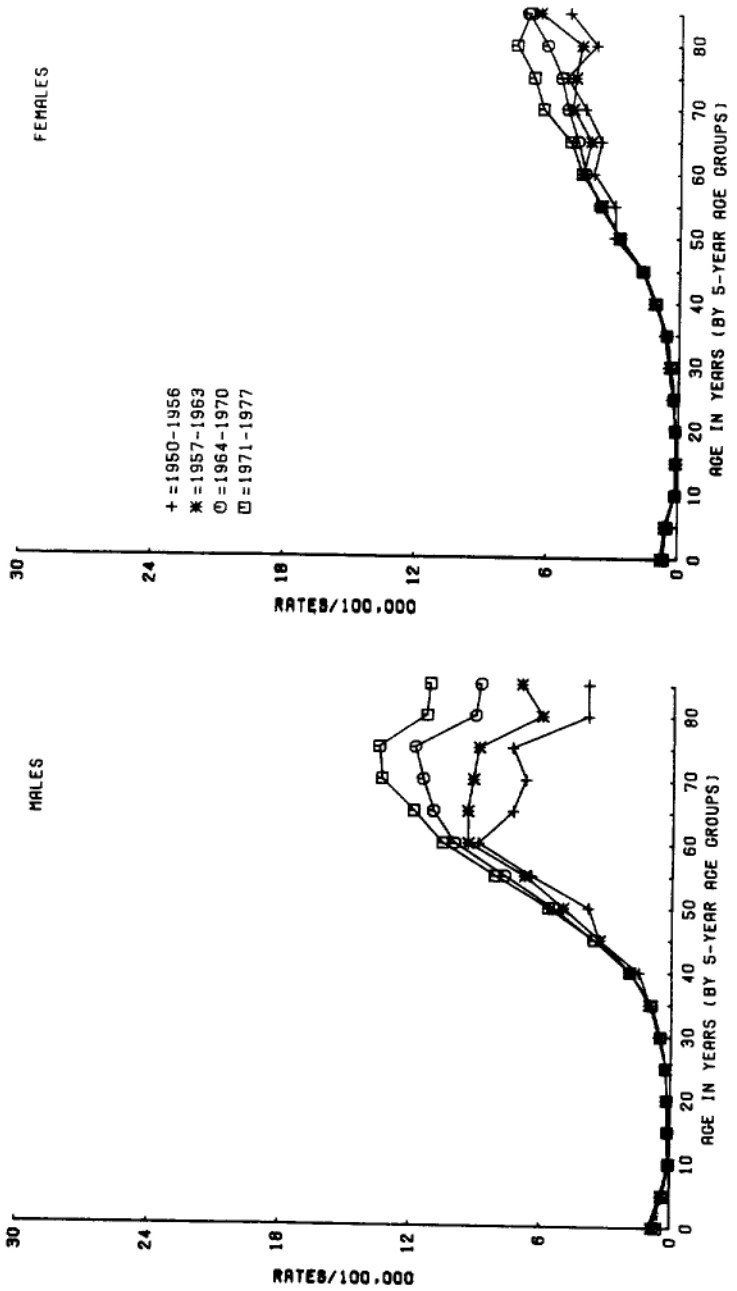

FIGURE 47.—Age-specific mortality rates for nonwhites in the United States for cancer of the kidney

SOURCE: National Cancer Institute (*196*).

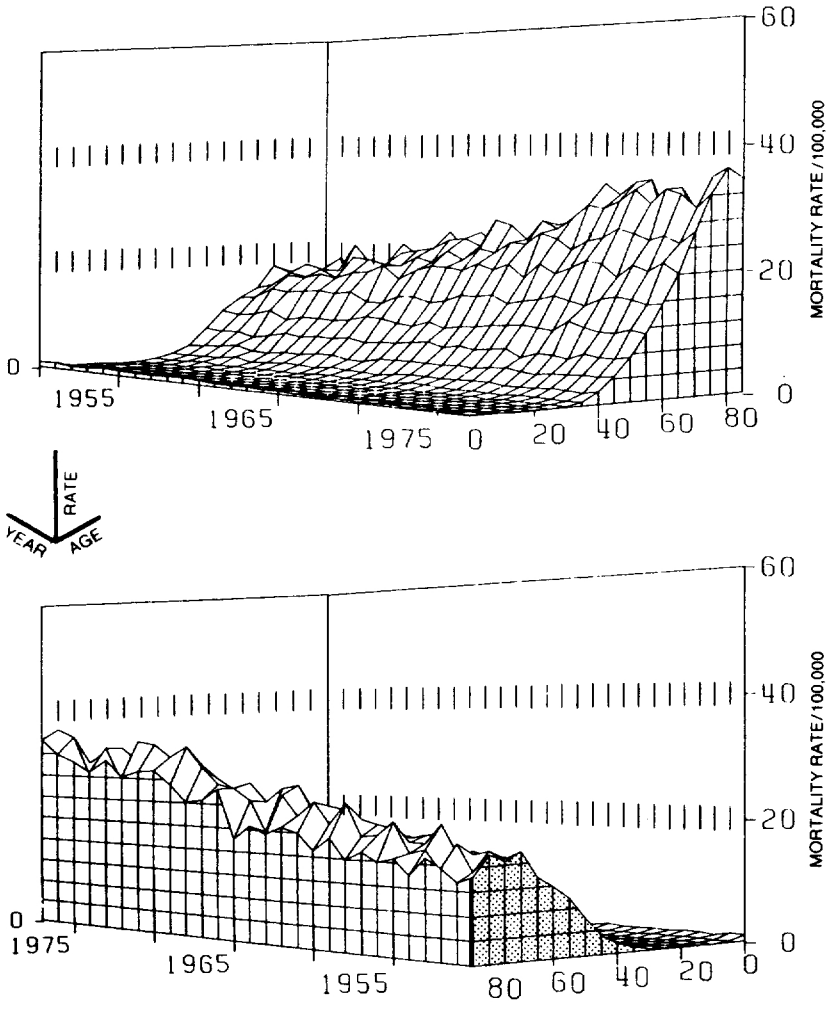

FIGURE 48.—Age-specific mortality rates by 5-year age groups for cancer of the kidney for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

ma, and (4) epithelial tumors of the renal pelvis. Renal cell carcinomas comprise about 90 percent of kidney tumors and generally affect individuals after age 40 (average 55 to 60) (*197*). This tumor may be silent until far advanced. The median survival time for kidney cancer in the adult is about 2.7 years for those aged 35 to 54 at the time of diagnosis and 1 year for those 65 or older (*197*).

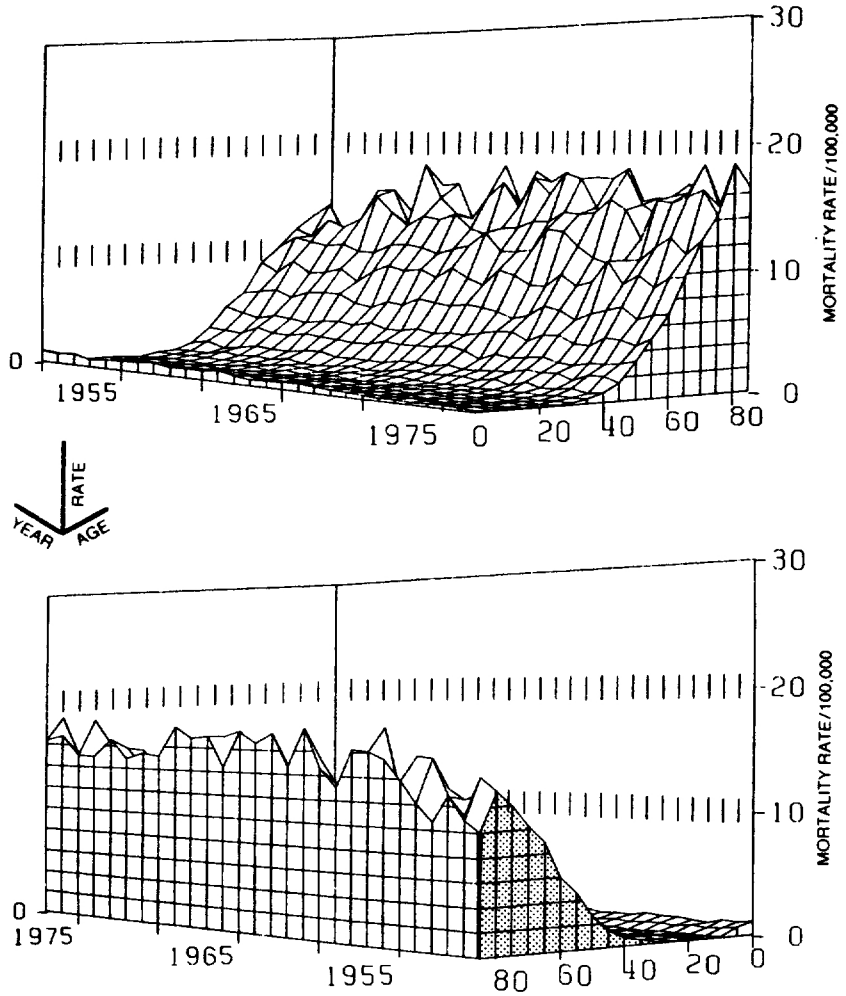

FIGURE 49.—Age-specific mortality rates by 5-year age groups for cancer of the kidney for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

Epidemiological studies have established an association between cigarette smoking and kidney cancer.

Causal Significance of the Association

Consistency, Strength, and Specificity of the Association

Several retrospective studies have examined the relationship between smoking and kidney carcinoma. Data from these studies

(Table 34) show a positive association between smoking and kidney cancer with relative risks ranging from 1.06 to over 5, with one study of renal pelvis cancer reporting a tenfold risk for heavy cigarette smokers. Other studies also reported an increasing relative risk of renal adenocarcinoma and cancer of the renal pelvis in cigarette smokers (*20, 21, 130, 238*); the increase of relative risk of renal adenocarcinoma among cigarette smokers was found for both males and females (*320*). A significant positive association between cigarette smoking and renal cancer was noted in the TNCS study (*299*) and in the Hawaiian Study of Five Ethnic Groups (*113*).

In most of the prospective studies, cancer of the kidney refers to tumors arising from the renal parenchyma as well as to tumors in the renal pelvis and ureter. In several of the large prospective studies (Table 34), an association was found between cigarette smoking and cancer of the kidney. The mortality ratios for all cigarette smokers varied from 1.20 to almost 3, compared with nonsmokers. Four of the prospective studies have noted a dose-response relationship as measured by the number of cigarettes smoked per day for kidney cancer (*68, 105, 224, 290*). Data from these studies are presented in Table 35. Generally, heavy smokers have mortality ratios two to three times greater than nonsmokers. In the U.S. Veterans Study, Rogot and Murray observed a decline in kidney cancer mortality among ex-cigarette smokers with a mortality ratio of 1.21 versus 1.41 for continuing smokers. Thus, the strength of the association of cigarette smoking related to kidney cancer risk is less marked than that for cancer of the other sites discussed above.

Chemical elements such as lead and cadmium, hormones, ionizing radiation, genetic susceptibilities, as well as tobacco smoke have each been suggested as potential etiologic factors in this disease (*322*). Several studies (*21, 32, 130, 214*) have shown that a substance present in tobacco smoke, di-methylnitrosamine, causes kidney tumors in rats.

Temporal Relationship

The prospective studies provide support for the temporal relationship of the association.

Coherence of the Association

Dose-Response Relationship

The dose-response relationship noted in four of the prospective studies lends support to the coherence of the association between smoking and cancer of the kidney.

TABLE 34.—Kidney cancer mortality, ratios and relative risks, prospective and selected retrospective studies

Population	Study size	Number of kidney cancer deaths	Mortality ratio or relative risk ratio		Comments
			Non-smokers	Cigarette smokers	
		Prospective Studies			
ACS 9-State Study	188,000 white males	54	1.00	1.58	Based on 54 microscopically proved cases
ACS 25-State Study	440,558 males	104	1.00	1.42 1.57	Age 45–64 Age 65–79
U. S. Veterans	290,000	257	1.00	1.41	
California males in 9 occupations	68,153 males	27	1.00	2.46	
Japanese Study	122,261 males	30	1.00	1.20	
British Physicians	34,000 males	46	1.00	2.66	All smokers
		Retrospective Studies			
Bennington Laubscher (*20, 21*)	renal adenocarcinoma 100 cases 190 controls	100	1.00	5.1	Risk ratio for pipe - 10.3 cigar - 12.9
Schmauz and Cole (*238*)	43 cases of renal pelvis or ureter 451 controls	18	1.00	10.0	For smokers of more than 2½ pks/day
Armstrong (*5a*)	106 adenocarcinoma of kidney	106	1.00	1.06	
	30 carcinoma of renal pelvis 139 controls	30	1.00	1.80	
Wynder et al. (*322*)	202 adenocarcinoma of kidney 394 controls		1.00	2.00	(males)
			1.00	1.50	(females)

Correlation of Sex Differences in Kidney Cancer With Different Smoking Habits

There has been an increase in the white male to female ratio of deaths from kidney cancer. This trend does not demonstrate an

TABLE 35.—Kidney cancer mortality ratios by amount smoked per day—prospective studies

Amount per Day	Study/Ratio	Comments
	U.S. Veterans	
Nonsmoker	1.00	*Less than
1–9	0.95	20 deaths
10–19	1.32	
20–39	1.63	
40+	2.59*	
All smokers	1.41	
	British Physicians**	
Nonsmoker	1.00	**Grams of
1–14	2.66	tobacco
15–24	3.00	per day
25+	3.00	
All smokers	2.66	
	ACS 9-State Study***	
Nonsmokers	1.00	***Includes
1–9	1.90	genitourinary
10–20	1.8	
21+	2.94	
All smokers	1.90	
	California Males in Various Occupations	
Nonsmoker	1.00	
about 10	0.86	
about 20	3.30	
Over 30	2.57	
All smokers	2.46	

effect of the later initiation of smoking by females as evidenced so clearly by the recent increases in female lung and laryngeal cancer risks.

Correlation of Kidney Cancer Mortality Among Populations With Different Tobacco Consumption

The relative risk of kidney cancer is reduced in populations with a low proportion of smokers (*79, 165, 166, 211, 294*), although this reduction is not as great as that observed for lung, larynx, esophageal, and oral cancer.

Smoking and Histologic Changes in the Kidney

No human autopsy studies have been published which examine histologic changes in the kidney among smokers compared to nonsmokers.

Kidney Cancer and Non-Cigarette Tobacco Use

An elevated relative risk of from tenfold to twelvefold has been reported for smokers of pipes or cigars in one study (*21*). The U.S. Veterans Study noted an association for pure pipe smokers (ratio 1.32) and for mixed smokers of pipe and cigars (ratio 1.52) and kidney cancer, but not for pure cigar smokers.

Conclusion

Cigarette smoking is a contributory factory in the development of kidney cancer in the U.S. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Carcinoma of the Pancreas

Introduction

In 1982, it is estimated that there will be 24,800 new cases and 22,300 deaths from carcinoma of the pancreas in the United States (*2*).

Pancreatic cancer caused the deaths of 8,953 persons in 1950 and 20,465 persons in 1977 (the data for 1977 include deaths coded under ICD No. 157). The age-adjusted death rate rose from 5.3 per 100,000 in 1950 to a peak of 6.8 in 1968, and has remained stable since, at about 6.7. After 1968, the age-adjusted death rate from this disease actually decreased slightly from 6.8 to 6.7 per 100,000.

Increases in the age-adjusted rate between 1950 and 1967 resulted from increases in the mortality rates of all four color-sex groups (Figure 50), with white females showing the smallest increase and other than white males showing the largest. In 1950, white males and females had higher death rates from this disease than did males and females of other races. By 1977, the age-adjusted rate for whites was 22 percent lower than the rate for others.

The age-adjusted death rate of white males increased from 6.4 to 8.3 per 100,000 over the study period, and that of white females rose slowly from 4.3 to 5.2. Rates nearly doubled in the other populations, rising from 3.4 to 6.6 in females and from 5.3 to 10.5 in males.

Among white males 25 to 84 years of age, there was an increase in mortality from 1950 until 1967 (Figure 51). Thereafter, this trend was reversed, except in males 75 or older. Among other than white males, rates rose steadily during the 1950s and early 1960s and then leveled off or declined, except among those 55 or older, whose mortality rates continued to increase through 1977 (Figure 52). Both white and other females of most ages had increasingly higher mortality rates over the entire 1950–1977 period.

Generally, the mortality sex ratio decreased with advancing age in both the white and the other than white populations. The age-specific death rates over time show an increase in the older age

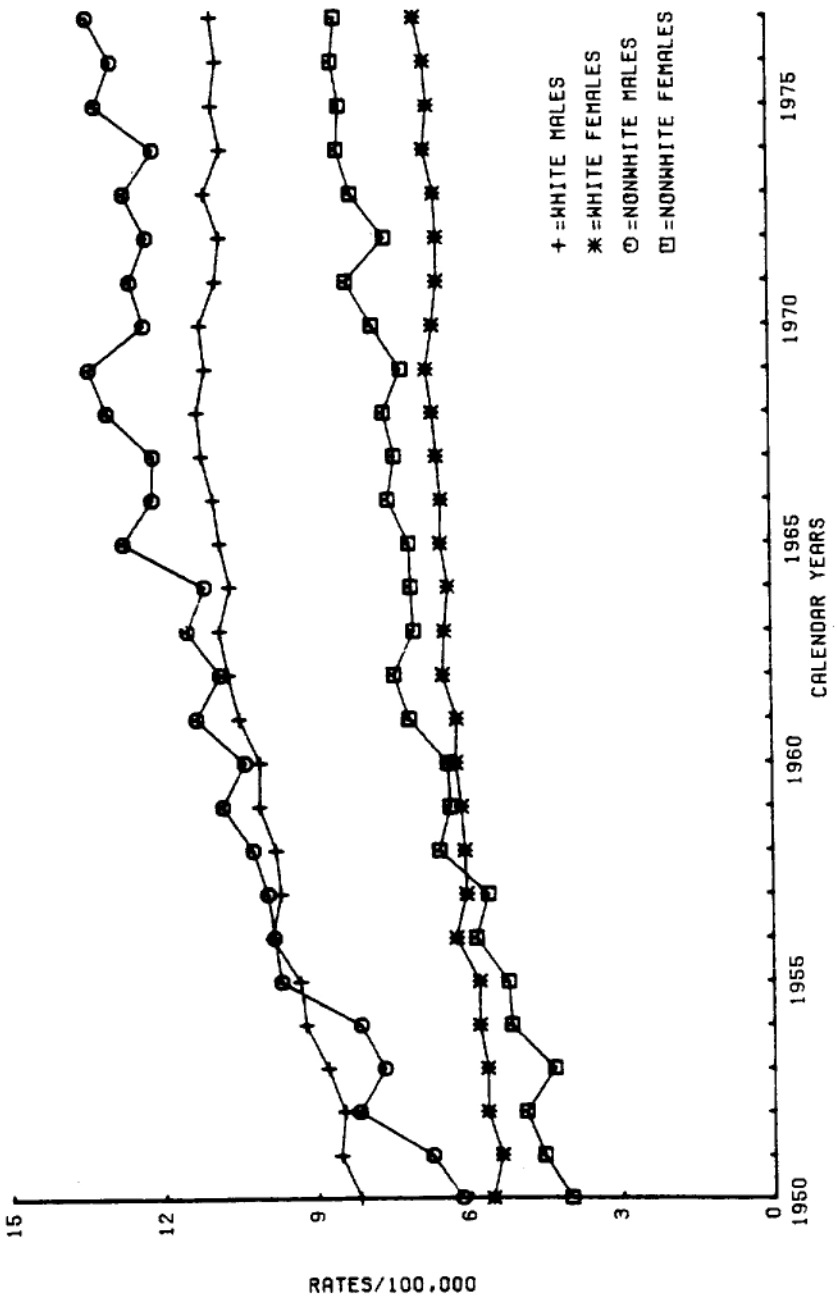

FIGURE 50.—Age-adjusted* mortality rates for cancer of the pancreas, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

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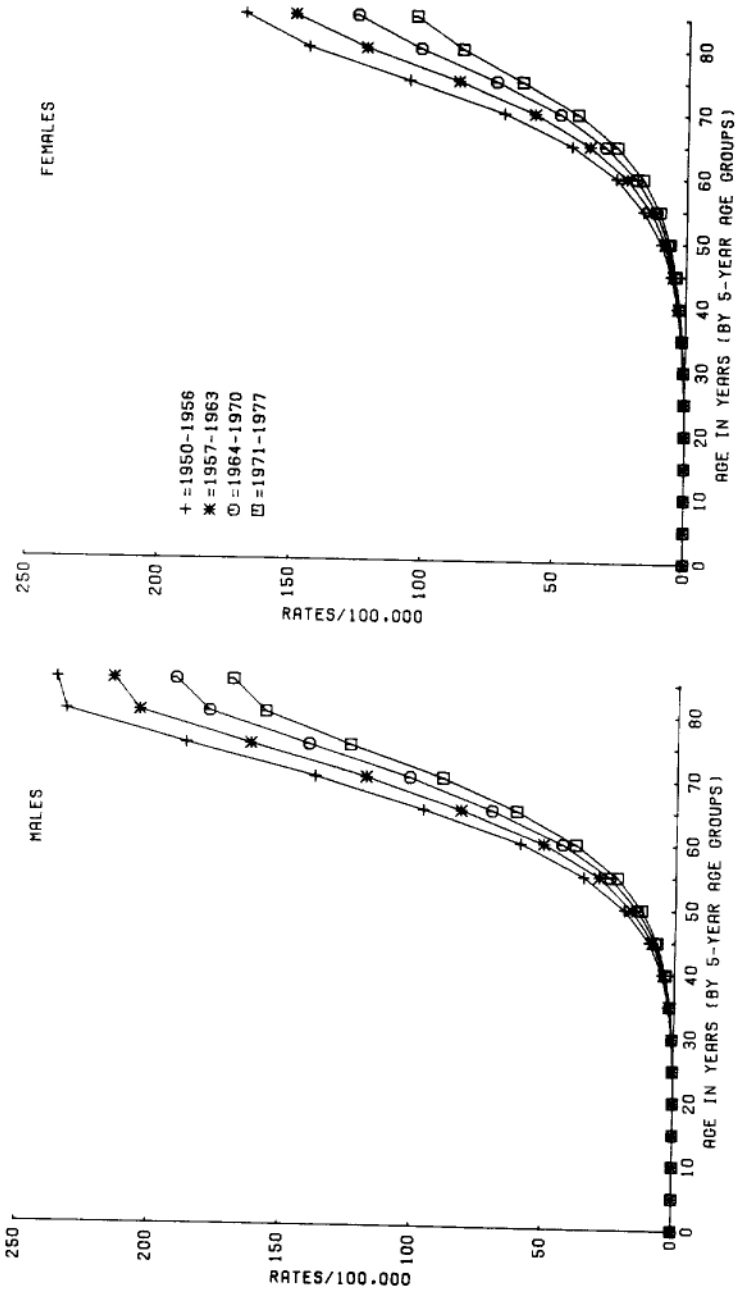

FIGURE 51.—Age-specific mortality rates for whites in the United States for cancer of the pancreas

SOURCE: National Cancer Institute (*198*).

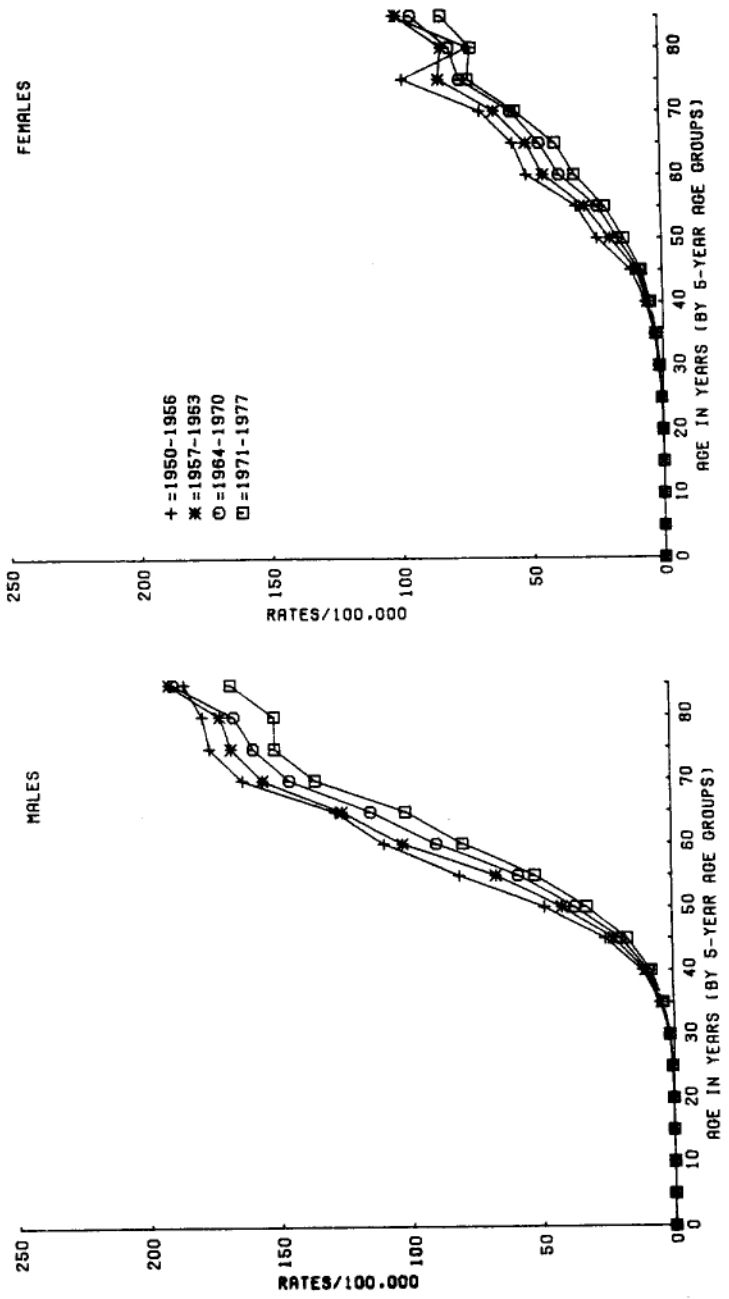

FIGURE 52.—Age-specific mortality rates for nonwhites in the United States for cancer of the pancreas

SOURCE: National Cancer Institute (*198*).

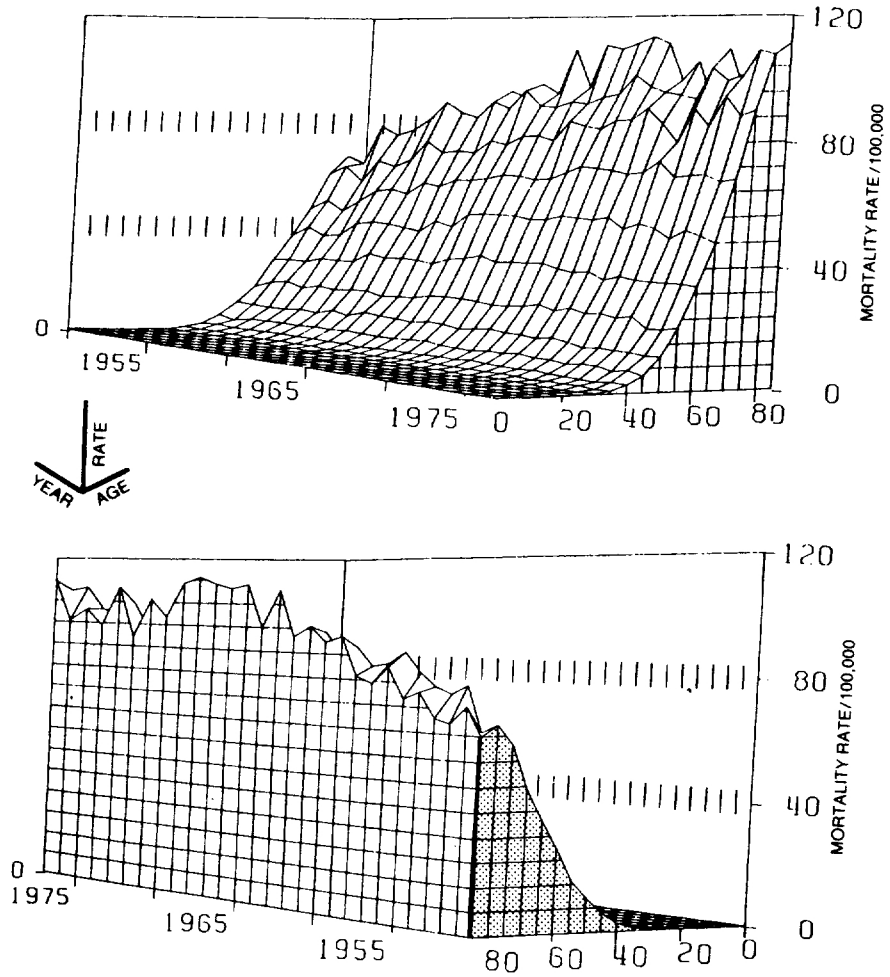

FIGURE 53.—Age-specific mortality rates by 5-year age groups for cancer of the pancreas for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

groups without significant increases in the rates of the younger age groups, as is readily apparent when age-specific death rates for white males and females are plotted on a three-dimensional graph (Figures 53 and 54).

Pancreatic carcinoma is generally undetected until late in its course, due to difficulties in diagnosis and the nonspecific nature of the presenting symptoms. Metastasis occurs relatively early in the

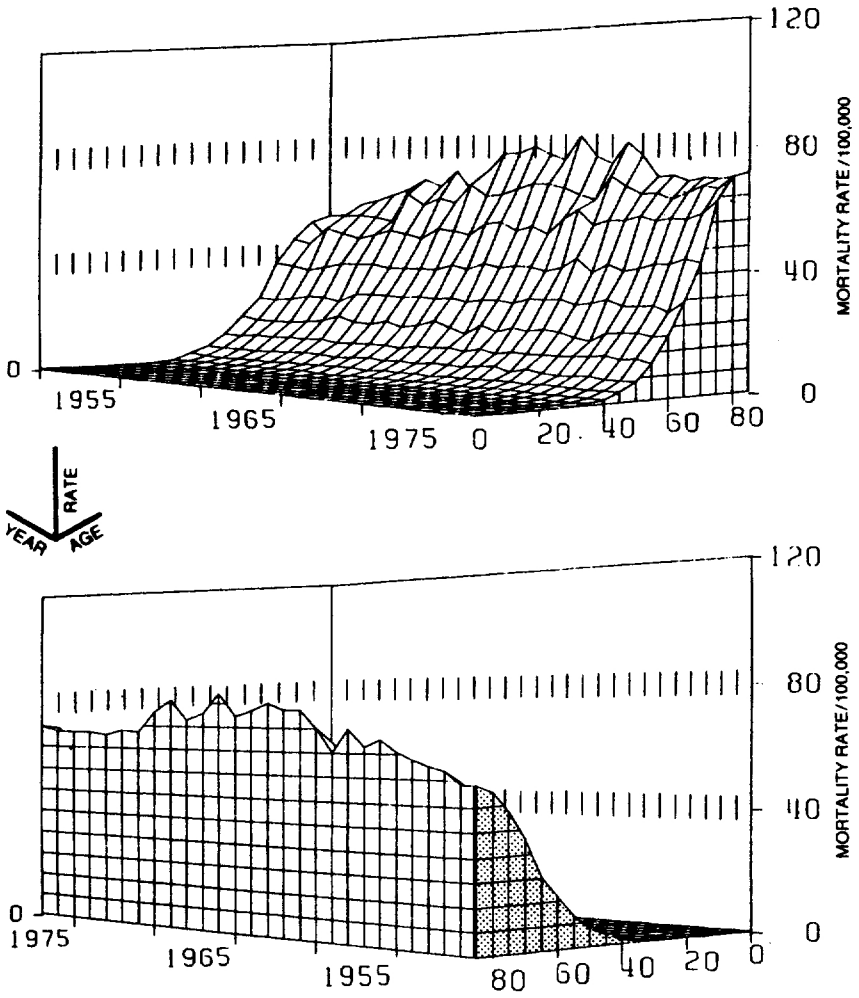

FIGURE 54.—Age-specific mortality rates by 5-year age groups for cancer of the pancreas for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

course of this disease, contributing to the poor 3-year survival rate of 2 percent (*194*) and a mean survival time after diagnosis of less than 6 months (*187*). The most common form of pancreatic cancer is adenocarcinoma. Pancreatic cancer is more common among men than among women in the United States, but the male to female ratio has been decreasing steadily from 1.6:1 during the period of 1940–1949 to 1.2:1 estimated in 1980 (*270*).

Several epidemiological studies have established an association between cigarette smoking and pancreatic cancer.

Causal Significance of the Association

Consistency, Strength, and Specificity of the Association

A number of retrospective studies have examined the relationship between smoking and pancreatic cancer. In the Third National Cancer Survey (*299*) and in the Hawaiian Study of Five Ethnic Groups (*113*), there was a significant positive relationship between smoking and pancreatic cancer. An earlier retrospective case control study of 81 cases of pancreatic cancer (*320*) found a dose-response relationship with a relative risk of 5.0 for males smoking more than two packs of cigarettes per day (Figure 55). A recent report found a positive association for both males and females who had ever smoked and cancer of the pancreas (relative risk of 1.4), but not for pipe or cigar smokers. They also reported a significant dose-response relationship for females. A similar but not significant dose-response relationship was noted for males (*169*).

Several of the large prospective investigations have reported mortality ratios of approximately 2.0 for smokers as compared with nonsmokers. These data are presented in Table 36. The dose-response relationships from four of the major prospective studies are presented in Table 37. Smokers consuming more than one pack of cigarettes per day had mortality ratios two to three times greater than those of nonsmokers.

These data consistently support an association between smoking and pancreatic cancer, although the strength of the association is less than that noted for smoking and cancer of the lung, larynx, oral cavity, and esophagus.

Temporal Relationship of the Association

Support for the temporal relationship of the association is provided by the prospective studies that observed subjects over varying periods of time for the development of pancreatic cancer. Support for the temporality of the association is advanced by a histological study showing a greater frequency of premalignant changes in pancreatic tissue of smokers when compared with tissue of nonsmokers (*162*), and by cohort analysis showing correlation between trends in smoking patterns and pancreatic cancer mortality (*22, 128*).

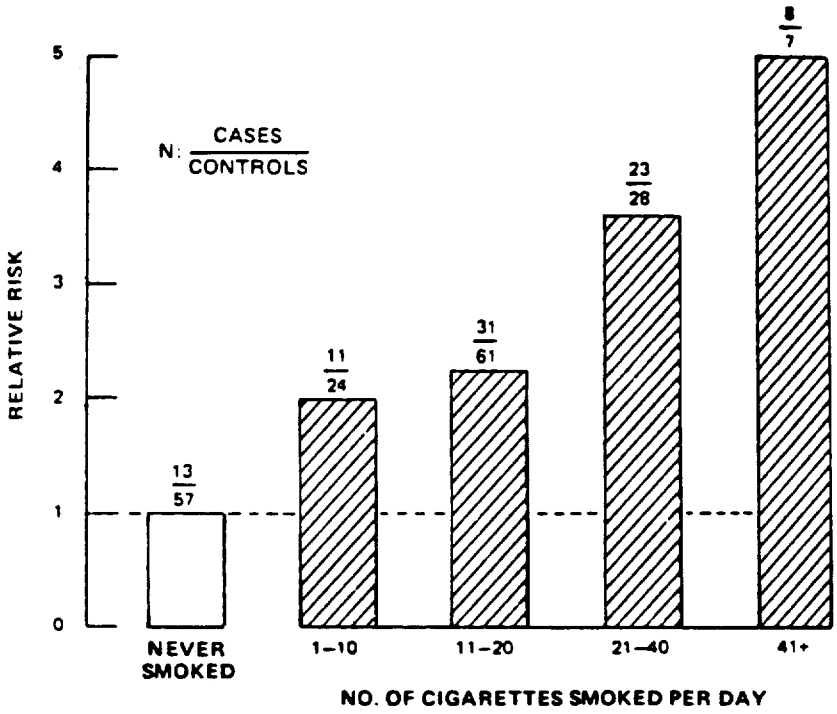

FIGURE 55.—Relative risk of pancreatic cancer in males, by number of cigarettes smoked

SOURCE: Wynder (*320*).

Coherence of the Association

Dose-Response Relationship

The coherence of the association is supported by the dose-response relationship noted above, although it is not as marked as those noted for smoking and other cancers.

Correlation of Pancreatic Cancer Among Populations With Different Tobacco Consumption

The finding of a low incidence of pancreatic cancer in special groups (e.g., Mormons and Seventh Day Adventists) with a small proportion of smokers (*79, 165, 166, 211, 294*) is consistent with a causal relationship.

TABLE 36.—Pancreatic cancer mortality ratios—prospective studies

Study	Size of Population	Nonsmokers	All Cigarette Smokers	Comments
ACS 9-State Study	188,000 white males	1.00	1.50	Based on 117 microscopically proved cases
Canadian Veterans	78,000 males	1.00	1.96	
ACS 25-State Study	358,000 males 483,000 females	1.00 1.00	2.14 1.42	
U.S. Veterans	290,000 males	1.00	1.79	
Japanese Study	122,000 males 143,000 females	1.00 1.00	1.57 males 1.94 females	
California occupations	68,000 males	1.00	2.43	
Swedish Study	55,000 males and females	1.00 1.00	3.1 males 2.5 females	
British Physicians	34,000 males	1.00	1.60	

TABLE 37.—Mortality ratios for cancer of the pancreas by amount smoked—prospective studies

Study	Population	Amount Smoked per Day				Comments
		Males		Females		
Swedish Study	55,000 males and females	NS	1.00	NS	1.00	
		1–7	1.60	1–7	2.40	
		8–15	3.40	8–15	2.50	
		15 +	5.90	15 +	3.00	
British Physicians	40,000	NS	1.00	NS	1.00	Males based on grams of tobacco per day
		1–14	1.35	1–14	0.44	
		15–24	1.42	15–24	2.66	
		25 +	2.07	25 +	1.77	
Japanese Study	265,000 males and females	NS	1.00	NS	1.00	
		1–19	1.42	1–19	1.00	
		20–39	1.57	20–29	1.60	
		40 +	0.69	30 +	1.90	
U.S. Veterans	290,000 males	NS	1.00			
		1–9	1.60			
		10–20	1.71			
		21–39	2.00			
		40 +	2.20			

NOTE: NS: Nonsmoker.

Correlation of Sex Differences in Pancreatic Cancer With Different Smoking Habits

The declining male to female mortality ratio discussed above is consistent with the delayed initiation of cigarette smoking by women as compared to men.

Two studies have performed cohort analyses of the relationship of time trends in smoking patterns among males and females and mortality rates from carcinoma of the pancreas. Bernard and Weiss (*22*) examined the relationship in the United States for the period of 1939 to 1969; Moolgavkar and Stevens (*185*) examined these relationships in England and Wales for the period of 1941 to 1975. Both studies found a positive association between changes in smoking habits in males and females and pancreatic cancer death rates.

Smoking and Histologic Changes in the Pancreas

A recently reported study (*162*) found evidence for premalignant changes in pancreatic tissue of smokers. The authors collected 108 specimens of pancreatic tissue. In 44 percent of the series, there were some focal acinar cell abnormalities, which the authors state were similar to atypical acinar cell nodules in carcinogen-treated animals. These findings were more common in tissue from patients with a history of smoking as compared with tissue from nonsmokers. Tissue from heavy smokers (67 to 100 pack-years) showed a 1.8 times higher incidence of such nodules than tissue from all smokers.

Pancreatic Cancer and Non-Cigarette Tobacco Use

The U.S. Veterans Study found an elevated risk of 1.5 for pancreatic cancer in cigar, but not pipe, smokers.

Experimental Studies

Dietary factors, the presence of underlying diseases, such as chronic pancreatitis and diabetes mellitus, and chemical exposures have been suggested as potential determinants for this disease (*187*).

The pathogenic mechanisms by which tobacco smoking influences the development of pancreatic cancer are obscure. It has been suggested that a carcinogen derived from tobacco smoke (either directly or after metabolism by the liver) is excreted into the bile (*321*). It is then refluxed into pancreatic ducts and induces cancer. One group of investigators (*145*) has reported that nicotine inhibits pancreatic bicarbonate secretion in the dog by direct action on the organ. This has led to speculation that inhibition of duct cell secretion of bicarbonate could lead to intracellular pH changes and subsequently play a role in carcinogenesis. It has also been suggested that a protease-antiprotease imbalance may be capable of promoting carcinogenesis. Cigarette smoke is known to affect the protease-

antiprotease balance *in vivo* and *in vitro*. In a study of beagle dogs smoking 12 cigarettes per day for 600 days, the authors reported significant changes in pancreatic proteases as compared with their sham-exposed controls (*189*).

Conclusion

Cigarette smoking is a contributory factor in the development of pancreatic cancer in the U.S. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Stomach Cancer

It is estimated that in the United States there will be 24,200 new cases of stomach cancer and 13,800 deaths in 1982 (*2*). For unknown reasons, mortality rates and the number of deaths have fallen dramatically over the last 28 years.

The age-adjusted mortality rate for stomach cancer has continued to decline for both males and females. Since the period of 1951–1953 through 1976–1978, the age-adjusted rate has decreased by 59 percent in males and 65 percent in females. Rates for both males and females adjusted to the 1970 population are presented in Figure 56. Figures 57 and 58 give age-specific death rates for cancer of the stomach for four separate time periods by race and sex.

In 1950, cancer of the stomach was fatal to 24,257 persons; in 1977, 14,440 died from this cancer in the United States. Death rates are higher for races other than white than for whites; other males have higher death rates than any of the other color sex groups.

The age-adjusted rate for other than white males was 31.16 in 1950 compared to 23.86 for white males. The corresponding rates for females were 16.05 and 13.13, respectively. By 1977, the rate for other than white males had decreased to 15.18; the corresponding rate for white males was 8.25. The age-adjusted rate for females other than white was 7.46 in 1977 compared to 3.83 for white females.

These differences may represent variations in exposure to undetermined dietary and other environmental factors or genetic differences.

A limited number of epidemiological studies have examined the relationship between smoking and stomach cancer. The data are not consistent, but overall, the evidence points to a possible association between cigarette smoking and stomach cancer. Olearchyk (*204*) noted that alcoholism (26.7 percent) and smoking (26 percent) were common habits of 243 patients with stomach cancer. In the population-based Third National Cancer Survey (*299*), there was a significant positive association between smoking and stomach cancer. A few other retrospective studies have also reported a statistical association between smoking and stomach cancer (*122, 151, 302*).

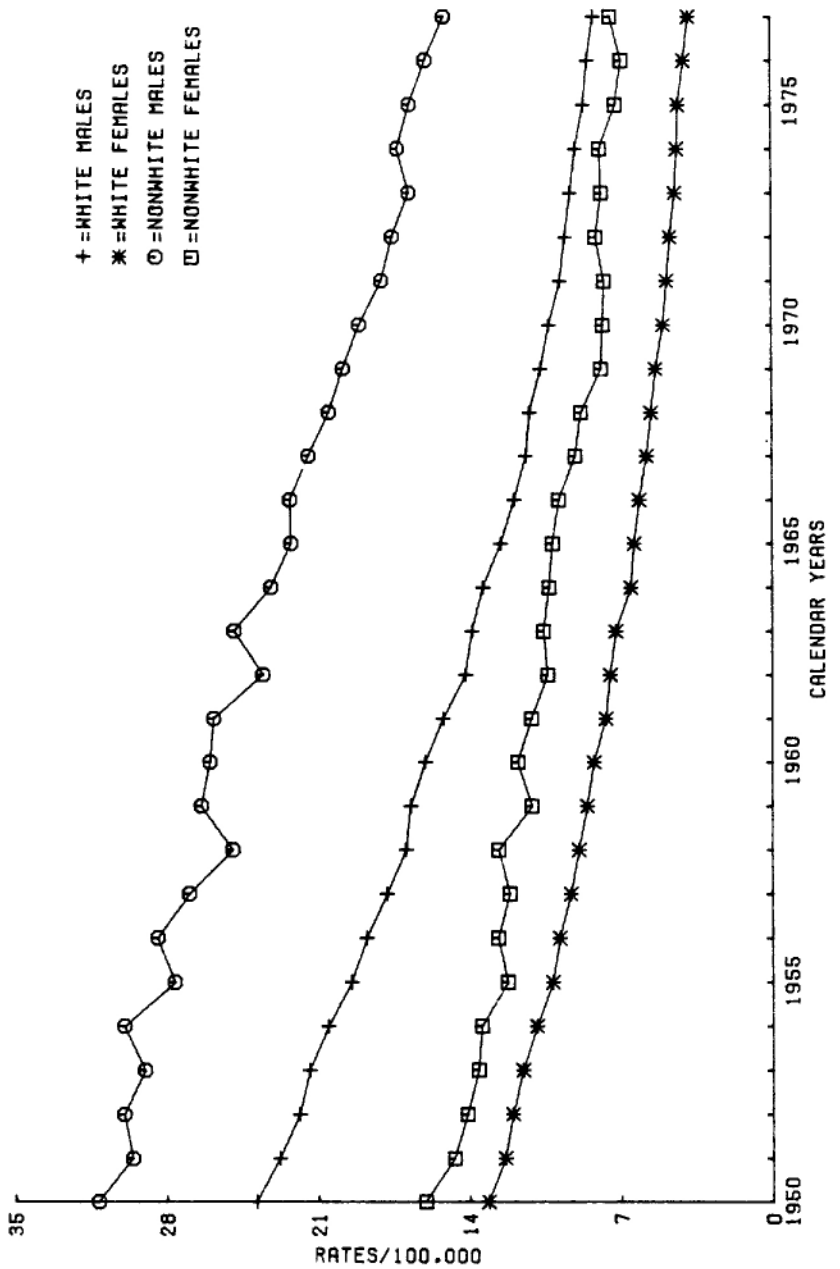

FIGURE 56.—Age-adjusted* mortality rates for cancer of the stomach, by race and sex, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of this Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

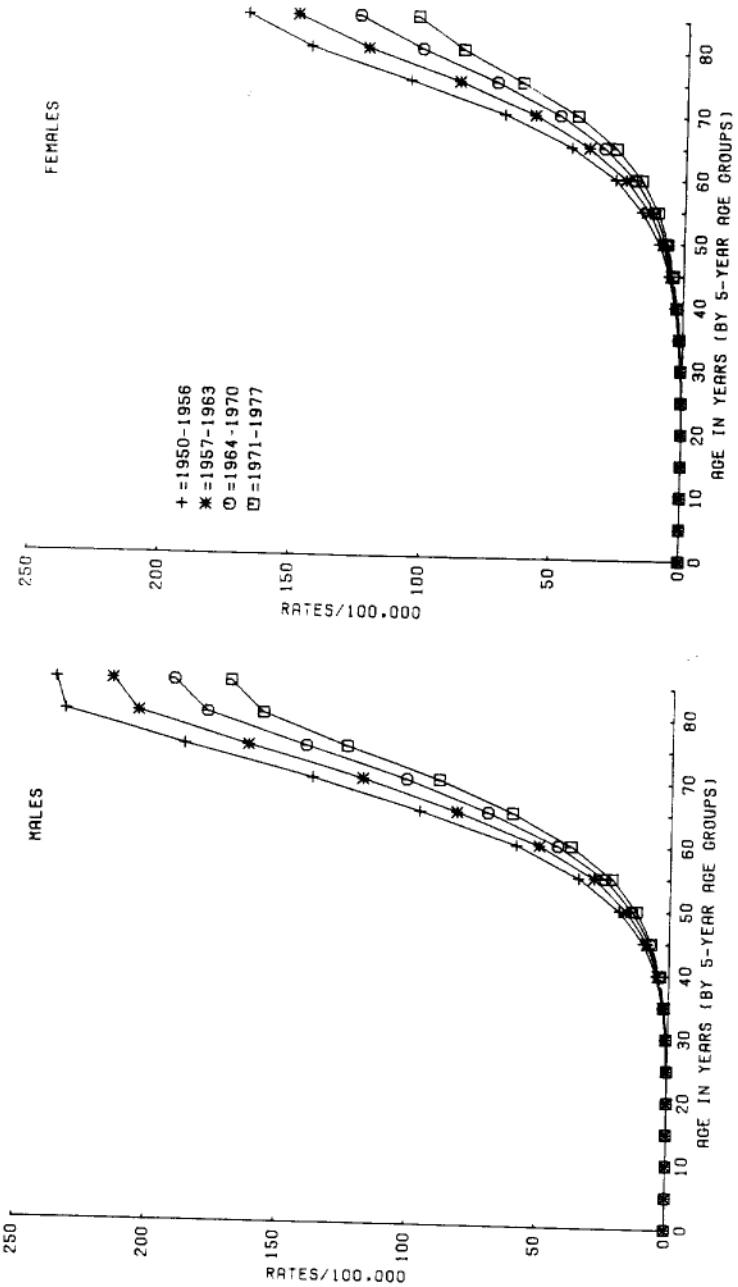

FIGURE 57.—Age-specific mortality rates for whites in the United States for cancer of the stomach

SOURCE: National Cancer Institute (*198*).

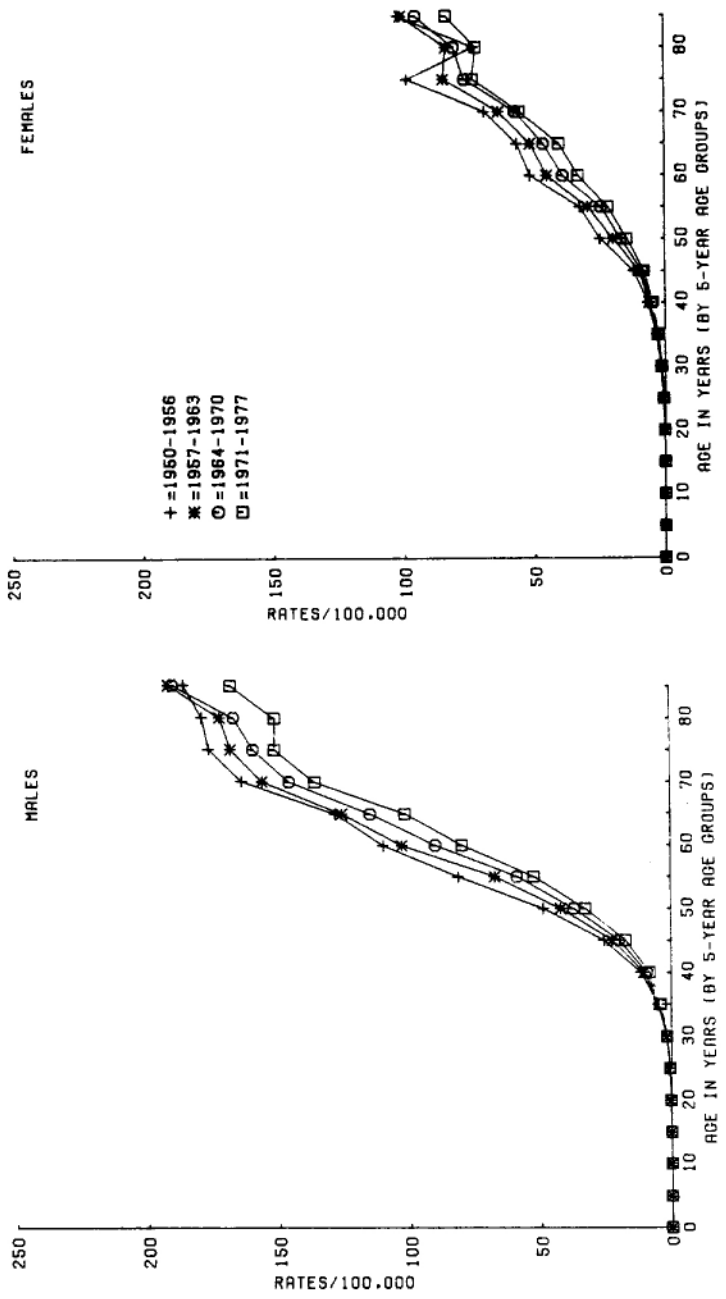

FIGURE 58.—Age-specific mortality rates for nonwhites in the United States for cancer of the stomach

SOURCE: National Cancer Institute (*198*).

TABLE 38.—Stomach cancer mortality ratios—prospective studies

Population	Study size		Non-smokers	All cigarette smokers	Comments
ACS 9-State Study	188,000 white males		1.00	1.61	Based on 176 microscopically proved cases
U.S. Veterans	290,000		1.00	1.52	
Swedish Study	55,000 males and females	(men)	1.00	1.80	Cigarette and pipe smokers
		(women)	1.00	2.30	
Japanese Study	265,000 males and females	(men)	1.00	1.59	
		(women)	1.00	1.31	
California males in 9 occupations	68,000		1.00	1.04	
ACS 25-State Study	358,400 males	45–64	1.00	1.42	
		65–79	1.00	1.26	
British Physicians	34,000		1.00	1.39	All current smokers

TABLE 39.—Stomach cancer mortality ratios by amount smoked—prospective studies

Study	Population size	Amount smoked per day	Mortality ratio	Comment
U.S. Veterans	290,000 males	Nonsmoker	1.00	
		1–9	1.47	
		10–20	1.49	
		21–39	1.55	
		40+	1.83	
British Physicians	34,000 males	Nonsmoker	1.00	Based on grams of tobacco per day
		1–14	1.20	
		15–24	1.65	
		25+	1.39	
California males in 9 occupations		Nonsmoker	1.00	
		about ½ pk	1.09	
		about 1 pk	0.94	
		about 1 ½ pk	1.25	
Japanese Study	122,000 males	Nonsmoker	1.00	
		1–19	1.46	
		20–39	1.53	
		40+	1.78	

In contrast with the above investigations, the Hawaiian Study of Five Ethnic Groups failed to show a statistically significant association between smoking and stomach cancer (*113*). Haenszel et al. (*91*)

reported an increased relative risk for stomach cancer among smokers in a series of 783 patients living in the Hiroshima and Miyagi prefectures of Japan; however, these findings were not statistically significant. In a similar study of Japanese living in Hawaii, these same authors (*92*) found a statistically significant increased risk among Issei smokers but not among Nissei. The absence of a significant association between cigarette smoking and gastric cancer has been reported by other authors (*236, 318*).

The relationship between smoking and stomach cancer was examined in several prospective studies (Table 38). Although mortality ratios were increased for smokers as compared with nonsmokers, these increases were small. Three of the four major prospective studies noted a consistent dose-response relationship as measured by the number of cigarettes smoked per day. However, the magnitude of these relationships was moderate compared to that between smoking and other cancer sites (Appendix Tables A and B).

Conclusion

1. Epidemiological studies have noted an association between cigarette smoking and stomach cancer. The association is small in comparison with that noted for smoking and some other cancers.

Cancer of the Uterine Cervix

Slightly over 8,300 women died of cancer of the uterine cervix in 1950. By 1977, the total number of deaths attributed to this site had decreased to 5,165. The age-adjusted rate for white females is only about one-third that observed for races other than white (3.53 versus 9.63) (Figure 59).

The age-specific rate for races other than white was 17.92 in 1950 and decreased to 7.99 by 1977. The age-specific rate for white females decreased from 10.12 to 4.12 over the same time period (Figure 60). Squamous cell carcinoma is the major cell type. The overall 5-year survival for patients with carcinoma of the cervix is 60 percent, but survival ranges from 86 percent for those with localized disease, to 50 percent for those with regional involvement, and to 22 percent for those with distant metastases (*2*).

Cervical cancer appears to be more common among women who have early and frequent coitus, who have early or multiple marriages or partners, and who become pregnant at an early age or frequently (*140, 264*). In addition, a number of other variables have been studied that may affect the risk for cervical cancer, including

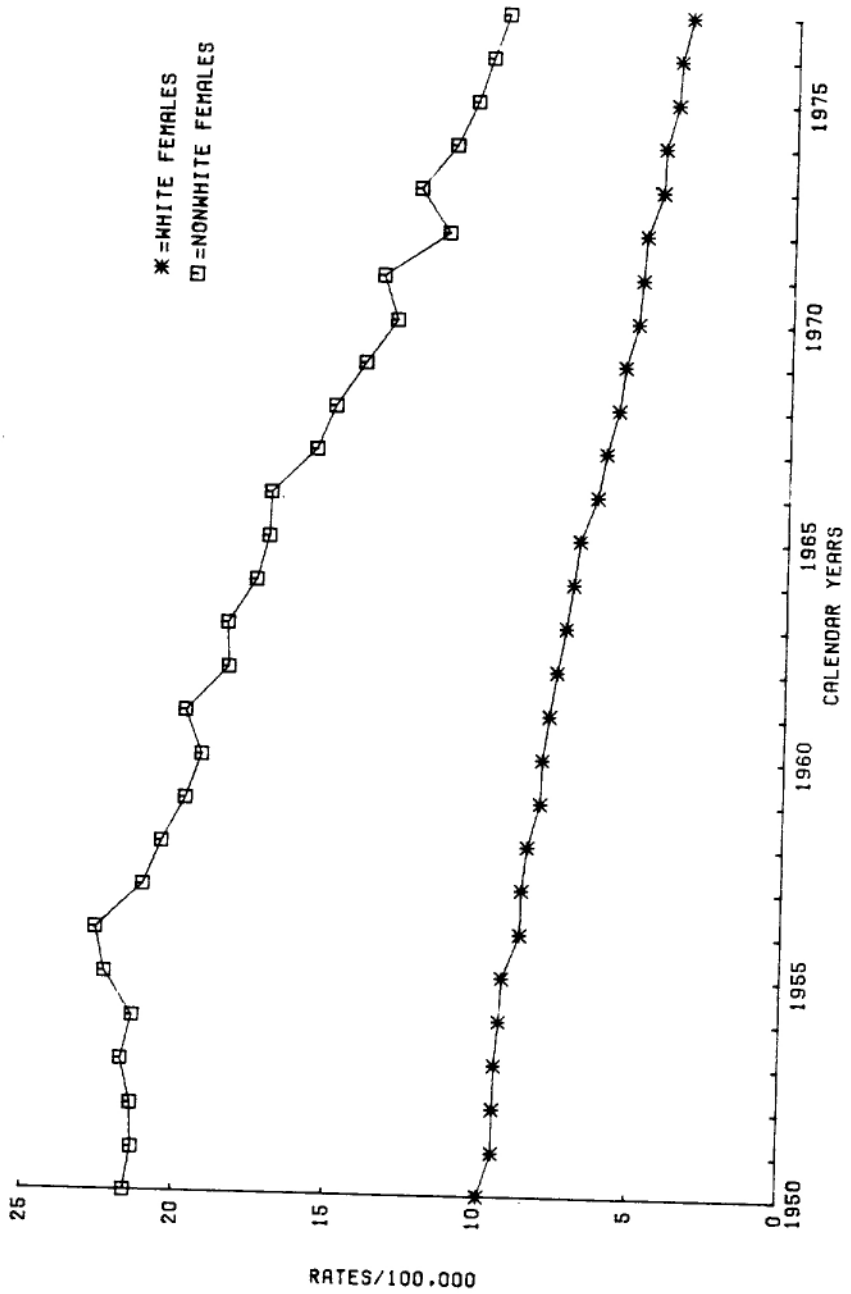

FIGURE 59.—Age-adjusted* mortality rates for cancer of the uterine cervix, by race, United States, 1950–1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.

SOURCE: National Cancer Institute (*198*).

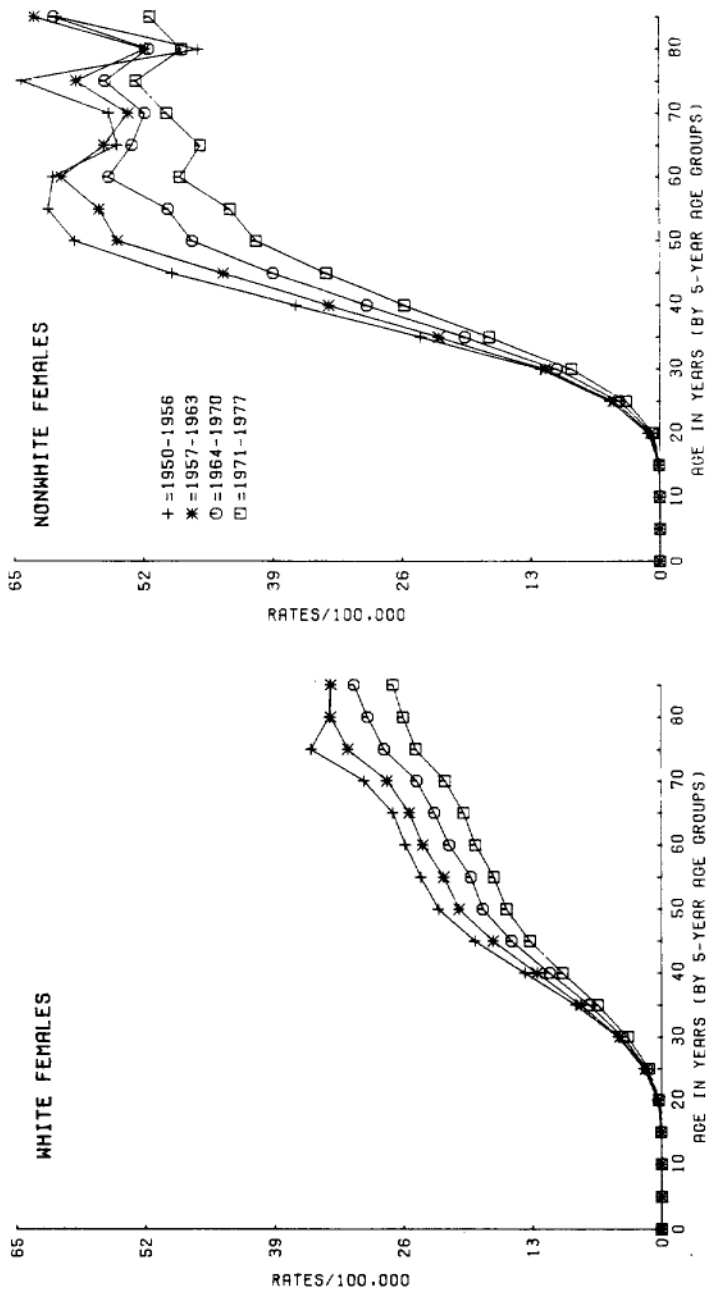

FIGURE 60.—Age-specific mortality rates for whites and nonwhites in the United States for cancer of the uterine cervix

SOURCE: National Cancer Institute (*198*).

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venereal infections, circumcision status of consort, and exogenous hormones (*264*).

A limited number of studies have attempted to identify an association between cigarette smoking and cervical cancer. One study (*192*) reported a relationship between smoking status (never smoked, ex-smokers, present smokers) and suspicious or positive cervical cytology. Thomas (*264*) administered a home questionnaire to 324 females with abnormal cervical cytology and reported that the prevalence of smoking was 70 percent in cases with carcinoma *in situ* and 58 percent in controls ($0.02 \leq p \leq 0.05$). When adjusted for thirteen other variables (including ≥ 3 births, first pregnancy prior to age 20, husband's circumcision and prior marriage history, and marital instability, among others), he reported a "borderline" significant relative risk ($0.02 \leq p \leq 0.05$) for carcinoma *in situ*, and non-significant differences for dysplasia. A case-control study among 350 Moslems and non-Moslems in Yugoslavia found that cervical cancer patients were more likely to smoke and to smoke more than one pack per day; the differences were statistically significant ($p < 0.01$) for Moslems (*140*). Subsequently, three other retrospective studies in Germany (*201*), England (*38, 305*), and Canada (*297*) have reported that smoking was a risk factor for cervical cancer. The English study (*108*) examined 31 women with dysplasia, carcinoma *in situ*, or invasive carcinoma, and attempted to control for known risk factors such as age at first intercourse and number of sexual partners of both wife and husband. They reported no effect of husband's smoking habit on the relative risk of cervical abnormalities, but a statistically significant excess risk among wives who were current smokers (RR 7.9), and an elevated risk for women who were former smokers (RR 3.7) over that for women nonsmokers (RR 1.0). Conversely, however, the Canadian study reported age-adjusted relative risks for *in situ* and invasive cancers for current smokers of 3.8 and 2.0, but no adjustment was made for other known risk factors for the disease. In the Third National Cancer Study (*299*), Williams and Horm have reported a significant positive association between cigarette smoking and both invasive and *in situ* cervical cancer, as well as between nonsmoking tobacco use (snuff and chewing tobacco) and invasive cervical cancer. A dose-response relationship was evident. The Swedish (*42*) and the Japanese (*119, 120*) prospective studies included data on smoking and cervical cancer. Cigarette smokers had increased mortality ratios, and a dose-response relationship was noted (Table 40). None of these studies controlled for other known risk factors.

Stellman et al. (*256*) examined the records of 332 patients with cervical cancer (stages not identified) who were controls for another study of smoking and health at different hospitals in several cities. The controls were patients hospitalized for non-smoking-related

TABLE 40.—Cervical cancer mortality ratios for women by current number of cigarettes smoked per day—prospective studies

Population	Cigarettes/day	Mortality ratio
Japanese Study	Nonsmokers	1.00
	1–19	1.00
	20–29	1.85
	30+	3.50
	All smokers	1.72
Swedish Study	Nonsmokers	1.00
	1–7	2.80
	8–15	3.00
	≥16	3.40
	All smokers	3.00

diseases and matched for age, race, hospital, and hospital status (semi-private versus ward). Socioeconomic status was determined by the subject's education and occupation and by the husband's occupation. Their analysis showed an overall positive association between cigarette smoking and cervical cancer. However, after Mantzel-Haenszel adjustment for age and socioeconomic status, the authors did not find a statistically significant association. The authors suggest that the association between smoking and cervical cancer is highly confounded and not consistent with a causal hypothesis. This study also, however, failed to include direct measures of potential confounding variables, such as sexual activity. It should be noted that in the Swedish (*42*) and German (*201*) studies, differences in socioeconomic status did not affect cervical cancer incidence.

The associations described between cervical cancer and many other variables, in addition to the variation in results of studies of the possible association of cigarette smoking and cervical cancer, do not permit a conclusion on the character of this relationship at this time.

Conclusion

1. There are conflicting results in studies published to date on the existence of a relationship between smoking and cervical cancer; further research is necessary to define whether an association exists and, if so, whether that association is direct or indirect.

Smoking and Overall Cancer Mortality

Introduction

Several investigators have estimated the proportion of all cancer deaths attributable to tobacco use in the United States to range from 22 percent to 38 percent of all cancer deaths (*70, 78, 106*). The authors of a recent review of cancer causes (*70*), commissioned by the Congressional Office of Technology Assessment, concluded that 30 percent of all U.S. cancer deaths are attributable to tobacco use (Appendix Table C). These estimates reflect a growing consensus that smoking is the single largest contributor to cancer mortality in the United States.

Overall Cancer Mortality

As early as 1928, Lombard and Doering (*160*), in a study of 217 cancer patients and 217 controls in Massachusetts, identified an association between heavy smoking (defined as all types of smokers) and cancer in general. This study is of historical significance in light of our present day knowledge about the relationship between smoking and specific cancer sites. Over the last two decades, four of the eight major prospective studies have examined the relationships between smoking to overall and site-specific cancer mortality. Two of these studies (*98, 120*) included observations on females as well as males.

Male smokers, regardless of the amount smoked, have approximately twice the risk of dying from cancer than do their nonsmoking counterparts (Table 41). Data from these studies also showed a gradient increase in overall cancer mortality with the amount smoked. These data are presented in Table 42. Males who consumed more than one pack of cigarettes daily had overall cancer mortality rates almost three times greater than did nonsmokers. Mortality

TABLE 41.—Smoking and overall cancer mortality ratios—prospective studies

Study	Nonsmokers	Smokers	
		Male	Female
ACS 25-State Study	1.00	1.79 1.18 pipe and cigar	1.21
U.S. Veterans	1.00	2.12 1.32 cigars 1.29 pipes	
Japanese Study	1.00	1.62	1.41
ACS 9-State Study	1.00	1.97 cigarettes 1.44 pipe 1.34 cigar	

TABLE 42.—Smoking and overall cancer mortality ratios in males by amount smoked

Study	Amount smoked per day	Mortality ratio
ACS 9-State Study	Nonsmoker	1.00
	1–9	1.87
	10–20	1.92
	20+	2.94
	All smokers	1.97
U.S. Veterans	Nonsmoker	1.00
	1–9	1.42
	10–20	1.95
	21–39	2.66
	40+	3.31
	All smokers	2.12
Japanese Study	Nonsmoker	1.00
	1–19	1.53
	20–39	1.81
	40+	2.06
	All smokers	1.62

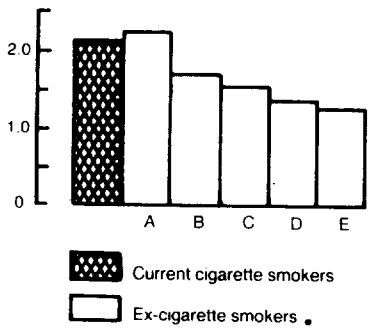

FIGURE 61.—Mortality ratios for all cancer sites for ex-cigarette smokers by number of years of smoking cessation, U.S. Veterans Study

NOTE: A: Stopped less than 5 years.
B: Stopped 5–9 years.
C: Stopped 10–14 years.
D: Stopped 15–19 years.
E: Stopped 20 or more years.
SOURCE: Rogot and Murray (*224*).

ratios for male pipe smokers and male cigar smokers were 1.44 and 1.34, respectively (*224*). Female smokers had overall cancer mortality rates 20 to 40 percent greater than female nonsmokers. Hammond (*106*) calculated that 34.5 percent of all cancer deaths in males were smoking related. These are in close agreement with estimates made by other investigators (*70, 216*).

Rogot and Murray (*224*) examined overall cancer mortality in ex-cigarette smokers compared to continuing cigarette smokers and

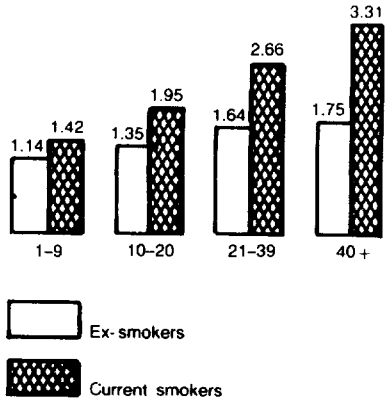

FIGURE 62.—Mortality ratios for all cancer sites for current and ex-smokers by number of cigarettes smoked daily, U.S. Veterans Study

SOURCE: Rogot and Murray (224).

found declining cancer mortality ratios for ex-smokers by the number of years off cigarettes. For those former smokers who had quit for 20 years or more, the overall cancer mortality rate was approximately 25 percent above those of nonsmokers but substantially below those of continuing smokers (1.27 versus 2.12) (Figure 61). These investigators also noted that cancer mortality among former cigarette smokers was correlated to the number of cigarettes smoked per day. A clear gradient by the amount smoked is evident for ex-smokers as well as continuing smokers for overall cancer mortality (Figure 62). Overall cancer mortality rates for former cigarette smokers were 40 percent greater than for nonsmokers.

Conclusion

1. Cigarette smokers have overall mortality rates substantially greater than those of nonsmokers. Overall cancer death rates of male smokers are approximately double those of nonsmokers; overall cancer death rates of female smokers are approximately 30 percent higher than nonsmokers, and are increasing.

2. Overall cancer mortality rates among smokers are dose-related as measured by the number of cigarettes smoked per day. Heavy smokers (over one pack per day) have more than three times the overall cancer death rate of nonsmokers.
3. With increasing duration of smoking cessation, overall cancer death rates decline, approaching the death rate of nonsmokers.

Summary

1. Cigarette smoking is the major cause of lung cancer in the United States.
2. Lung cancer mortality increases with increasing dosage of smoke exposure (as measured by the number of cigarettes smoked daily, the duration of smoking, and inhalation patterns) and is inversely related to age of initiation. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than nonsmokers.
3. Cigar and pipe smoking are also causal factors for lung cancer. However, the majority of lung cancer mortality in the United States is due to cigarette smoking.
4. Cessation of smoking reduces the risk of lung cancer mortality compared to that of the continuing smoker. Former smokers who have quit 15 or more years have lung cancer mortality rates only slightly above those for nonsmokers (about two times greater). The residual risk of developing lung cancer is directly proportional to overall life-time exposure to cigarette smoke.
5. Filtered lower tar cigarette smokers have a lower lung cancer risk compared to nonfiltered, higher tar cigarette smokers. However, the risk for these smokers is still substantially elevated above the risk of nonsmokers.
6. Since the early 1950s, lung cancer has been the leading cause of cancer death among males in the United States. Among females, the lung cancer death rate is accelerating and will likely surpass that of breast cancer in the 1980s.
7. The economic impact of lung cancer to the nation is considerable. It is estimated that in 1975, lung cancer cost $3.8 billion in lost earnings, $379.5 million in short-term hospital costs, and $78 million in physician fees.
8. Lung cancer is largely a preventable disease. It is estimated that 85 percent of lung cancer mortality could have been avoided if individuals never took up smoking. Furthermore, substantial reductions in the number of deaths from lung cancer could be achieved if a major portion of the smoking population (particularly young persons) could be persuaded not to smoke.
9. Cigarette smoking is the major cause of laryngeal cancer in the United States. Cigar and pipe smokers experience a risk for laryngeal cancer similar to that of a cigarette smoker.
10. The risk of developing laryngeal cancer increases with increased exposure as measured by the number of cigarettes smoked daily as well as other dose measurements. Heavy smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers.

11. Cessation of smoking reduces the risk of laryngeal cancer mortality compared to that of the continuing smoker. The longer a former smoker is off cigarettes the lower the risk.
12. Smokers who use filtered lower tar cigarettes have lower laryngeal cancer risks than those who use unfiltered higher tar cigarettes.
13. The use of alcohol in combination with cigarette smoking appears to act synergistically to greatly increase the risk for cancer of the larynx.
14. Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker.
15. Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking.
16. Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers.
17. Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum.
18. Cigarette smoking is a major cause of esophageal cancer in the United States. Cigar and pipe smokers experience a risk of esophageal cancer similar to that of cigarette smokers.
19. The risk of esophageal cancer increases with increased smoke exposure, as measured by the number of cigarettes smoked daily, and is diminished by discontinuing the habit.
20. The use of alcohol in combination with smoking acts synergistically to greatly increase the risk for esophageal cancer mortality.
21. Cigarette smoking is a contributory factor in the development of bladder, kidney, and pancreatic cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of these sites.
22. In epidemiological studies, an association between cigarette smoking and stomach cancer has been noted. The association is small in comparison with that noted for smoking and some other cancers.
23. There are conflicting results in studies published to date on the existence of a relationship between smoking and cervical cancer; further research is necessary to define whether an association exists and, if so, whether that association is direct or indirect.

24. Cigarette smokers have overall mortality rates substantially greater than those of nonsmokers. Overall cancer death rates of male smokers are approximately double those of nonsmokers; overall cancer death rates of female smokers are approximately 30 percent higher than nonsmokers, and are increasing.
25. Overall cancer mortality rates among smokers are dose-related as measured by the number of cigarettes smoked per day. Heavy smokers (over one pack per day) have more than three times the overall cancer death rate of nonsmokers.
26. With increasing duration of smoking cessation, overall cancer death rates decline, approaching the death rate of nonsmokers.

Technical Notes

Age-Adjusted Death Rates

Age-adjusted death rates show what the level of mortality would be if there were no changes in the age composition of the population from year to year. The age-adjusted death rates for the U.S. as a whole presented in this Report were computed by the Direct Method, that is, by applying the age-specific death rates for all causes of death or for deaths for a given cause to the standard population distributed by age. The total U.S. population as enumerated in 1940 is used as the standard population by the National Center for Health Statistics for presentation of mortality statistics. Standard populations other than 1940 have been used by other agencies, organizations, and researchers in presenting mortality data. This introduces some problems of comparability in the presentation of the statistical findings drawn from a variety of sources.

Cause-of-Death Classification

National mortality statistics from the National Center for Health Statistics for the U.S. presented in this Report are classified in accordance with the World Health Organization (WHO) Regulations, which specify that member nations classify causes of death in accordance with the International Statistical Classification of Diseases, Injuries, and Causes of Death. The deaths are tabulated and presented in *Vital Statistics of the United States, Volume II, Mortality* by cause-of-death categories that are consistent with WHO recommendations. Other organizations and researchers whose work is cited in this Report may use different cause-of-death categories. This introduces some problems of comparability in the presentation of the statistical findings drawn from a variety of sources.

Another problem of comparability in mortality rates is introduced when comparisons are made over time for specific causes of death. This is because of the practice to periodically revise the International Classification of Diseases (ICD) by which causes of death are

classified and tabulated. The ICD has been revised approximately every 10 years since 1900 to keep abreast of medical knowledge. Each decennial revision has produced breaks in the comparability of cause-of-death statistics. For many of the causes of death described in this Report, the reader may refer to the NCHS report (*199*) for information about comparability in cause of death statistics due to revisions in the ICD during 1950–1977.

Appendix Tables

APPENDIX TABLE A.—Mortality ratios (smokers vs. never smoked regularly) for smoking-related cancers among females—ACS 25-State Study and Japanese Study

Underlying cause of death	Mortality ratios	
	ACS	*Japanese*
Cancer (total)	1.21	1.41
Lung (excl. trachea, pleura)	3.58	2.03
Buccal cavity, pharynx, larynx, and esophagus	3.25	6.52
Pancreas	1.42	—
Uterus	1.18	—
Uterine cervix	—	1.72
Esophagus	4.89	—
Stomach	1.21	1.31
Bladder	2.58	2.00

APPENDIX TABLE B.—Mortality ratios (smoker vs. never smoked regularly) for smoking-related cancers among males—ACS 25-State Study and U.S. Veterans Study

Underlying cause of death	Mortality ratios		
	ACS		*U.S. Veterans*
	Age 45–64	Age 65–79	All
Cancer (total)	2.14	1.76	2.12
Lung (excl. trachea, pleura)	7.84	11.59	11.28
Buccal cavity, pharynx	9.90	2.93	4.22
Larynx	6.09	8.99	11.49
Esophagus	4.17	1.74	6.43
Bladder and other urinary	2.00	2.96	2.16
Kidney	1.42	1.57	1.41
Prostate	1.04	1.01	1.31
Pancreas	2.69	2.17	1.79
Liver, biliary passages	2.84	1.34	—
Stomach	1.42	1.26	1.52

APPENDIX TABLE C.—Cancer deaths caused by tobacco: United States, 1978

Certified cause of death[a]	Number of deaths			
	Observed	Estimated, had Americans not smoked	Approximate excess number and percent of deaths attributed to tobacco (percent in parentheses)	
Cancer, males				
Lung	71,006	6,439[b]	64,567	(90.9)
Mouth, pharynx, larynx, or esophagus	14,282	1,792 × 2[c]	10,698	(74.9)
Bladder	6,771	2,960[b]	3,811	(56.3)
Pancreas	11,010	6,585[b]	4,425	(40.2)
Other specified sites	100,799	—	5,000[d]	(5.0)
Unspecified sites	14,469	8,188[e]	6,281	(43.4)
Total, males	218,337		94,782[f]	(43.4)
Cancer, females				
Lung	24,080	5,454[b]	18,626	(77.4)
Mouth, pharynx, larynx, or esophagus	5,100	1,458 × 2[c]	2,184	(42.8)
Bladder	3,078	2,170[b]	908	(29.5)
Pancreas	9,767	7,291[b]	2,476	(25.4)
Other specified sites	127,642	—	1,000[d]	—
Unspecified sites	13,951	11,879[e]	2,072	(14.9)
Total, females	183,618		27,266[f]	(14.8)
Total, males and females	401,955		122,048[f]	(30.4)

[a] Site of origin of cancer.

[b] Number estimated by applying the nonsmoker mortality rates reported by Garfinkel (86) to the U.S. population of 1978.

[c] Double the number estimated by the procedure described in footnote b. This number was doubled to allow for the possibility that the subjects in the ACS prospective study were less exposed to alcohol or to some other cause(s) of cancer of the upper respiratory or digestive tracts than were average people in the United States. [Some evidence that this was indeed the case is that even the cigarette smokers in the ACS study had mortality rates for these types of cancer that were somewhat below the national U.S. rates (98).] However, it makes little difference to our grand totals whether the small number of cancers of the mouth and throat "expected" from the ACS nonsmoker experience are left unaltered, are doubled, or are trebled.

[d] Other specified sites include some, such as kidney, that may truly be affected by tobacco, and some, such as stomach or liver, that include a proportion of misdiagnosed cases of cigarette-induced cancer of the lung, pancreas, and other organs. Some fraction of the cancers certified as being of other specified sites is thus due to smoking, which in part explains the excess mortality among smokers in the aggregate of all such cancers that is found in the American prospective studies (Appendix Tables A and B). We have suggested, without firm evidence, that of these other cancers, perhaps 5,000 male and 1,000 female cases may have been due to tobacco. These suggested figures, totaling 6,000, may slightly underestimate the actual figures, but readers may substitute any estimate that they consider more plausible, e.g., some other estimate between 1,000 and 20,000, leading to an estimate of 29 to 34 percent of 1978 cancer deaths ascribable to tobacco.

[e] Estimated to match the proportions (43 percent male, 15 percent female) of specified sites attributed to tobacco.

[f] The percentage ascribable to tobacco is gradually increasing as lung cancer death rates are increasing among older Americans.

SOURCE: Doll and Peto (70).

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PART III. MECHANISMS OF CARCINOGENESIS

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METHODOLOGY OF EXPERIMENTAL CHEMICAL CARCINOGENESIS

Experimental Assessment of Carcinogenicity

In order to determine the possible carcinogenicity of tobacco smoke constituents, the same procedures should be employed as are used for other substances. Various criteria and guidelines for carcinogenicity tests have been advocated by several governmental and international agencies and by various advisory groups. For example, the World Health Organization (WHO) (*29*), the International Agency for Research on Cancer (IARC) (*8*), the Environmental Protection Agency (*3*), the Food and Drug Administration (*4*), the National Cancer Institute – National Toxicology Program (*22*), Health and Welfare of Canada (*2*), and the Health Council of the Netherlands (*13*), as well as others, have issued guidelines for the testing of compounds for different aspects of acute and chronic toxicity.

Chemicals

As a first step in the testing of any material for possible carcinogenicity, the researcher should obtain a complete physicochemical characterization of the material. Examinations by such techniques as thin-layer, gas-liquid, or high performance liquid chromotography should afford some idea of whether the material is homogeneous or a mixture of components. If the last is the case, identification of the individual components and determination of the level of each in the mixture are highly desirable. Otherwise, the validity and significance of the results may be questioned.

Factors Influencing Carcinogenicity

In tests for possible carcinogenicity, several factors influence the outcome of any study. Those relevant to the compound are the route of administration and the dose and frequency of administration. Factors relating to the animal are the species, strain, sex, age, diet, spontaneous tumor incidence, and immunological status.

Route of Administration

Oral administration

In addition to being a logical technique for testing compounds that may be ingested by humans, oral administration is also useful for compounds that may be inhaled as dusts, cleared from the airways by ciliary action, and then swallowed. Compounds may be mixed in the feed, given as aqueous solutions instead of normal drinking water, given by gavage at appropriate intervals, or even given in capsules. If the compound is mixed with the feed, the uniformity of

mixing, the stability in the diet, and the nonreactivity with the feed are factors of concern. Volatile compounds should not be given in the diet, for the resultant loss will lead to inaccuracies in dose levels. If given in the drinking water, solubility and stability must be considered.

Dermal

The dermal route simulates exposure of the skin as it occurs in occupational situations or in the use of cosmetics, and has been used as a standardized carcinogenicity assay. Application of a solution of the test material by means of a pipet should be made in an area that cannot be reached by the animal. Otherwise, the animal will lick the treated area so that oral ingestion occurs. To avoid the animals' licking each other, single caging is desirable. In this type of test, mice, hamsters, rabbits, and sometimes rats are used. For cutaneous application, mice of the BALB/c, C3Hf, or DBA strains or the non-inbred Swiss strain are most responsive. SENCAR mice have been especially bred for sensitivity in initiation-promotion assays. The skin should be clipped before application of the test compound, but abrasion or mechanical injury of the skin should be avoided.

Implantation: Subcutaneous and Intramuscular

Although subcutaneous injection of polycyclic aromatic hydrocarbons in mice has proved to be quite reliable as a test system, the use of this test in other species has led to controversial results. The induction of tumors at the implantation site, especially in rats, by inert materials of the proper size, by saline solutions, or by oily solvents has indicated the limitation of this test.

Injection: Intraperitoneal and Intravenous

Intraperitoneal and intravenous injections may be used to test drugs, but for various reasons are not suitable for repeated dosing. They are useful for administering a single dose or a few doses of potent carcinogens for model experiments. With this technique, exposure of personnel to carcinogens is minimized.

Inhalation

Inhalation is the major route by which persons are exposed to cigarette smoke. For laboratory study, complex installations, such as pumps or metering devices, are needed to allow uniform delivery of the test material to the experimental animals. Scrubbers and other devices are required to prevent exposure of any personnel working in the area. A test by the inhalation route usually costs much more than studies using other routes of administration.

In lieu of using large inhalation chambers in which animals are exposed, it is possible to use chambers into which the head and nose of individual animals are fitted. The test material is then forced into the chamber, resulting in an inhalation exposure. Relatively few animals can be treated with a given chamber by this method, however.

Factors that should be considered in evaluating the results of the test are effects on secretion of mucous, alteration of pulmonary ventilation, and possible toxicity to the cilia in the respiratory tract.

The dilemma is that in rodents the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ from that of humans and that animals anatomically resembling the human most closely are too expensive and have lifespans too long to permit their use in routine tests.

For inhalation tests of the carcinogenicity of tobacco smoke and various fractions of tobacco smoke, hamsters are preferable to rats and mice because they respond with a higher incidence of airway tumors (*6*).

Higher dose levels, greater frequency of administration, and longer periods of observation are required for weak carcinogens than are needed for potent ones. For example, potent carcinogens such as 7,12-dimethylbenz[a]anthracene or nitrosomethylurea can induce cancers in certain animals after a single dose. On the other hand, a single or very low dose of compounds such as N-2-fluorenylacetamide, safrole, and dioxane may not lead to tumors within the lifespan of the animal.

Animal Factors

Species

The choice of species rests on several factors, including lifespan, size, sensitivity to a specific class of compound, and availability. Early studies on skin painting of benzo[a]pyrene showed that mice and rabbits were responsive, while the few other species tested were less responsive. Guinea pigs are not suitable for testing aromatic amides and amines or their precursors. They either lack the enzyme system that activates aromatic amines or degrade the activated metabolite so rapidly that there is no effect. Overall, mice are the most useful animals for skin painting bioassays; rats are useful for test material that might be fed, especially with nitroso compounds or aromatic amines; and hamsters seem better suited for inhalation studies on tobacco smoke or its components.

Larger species including the rabbit, dog, and primate require a longer time to obtain results; they are expensive to purchase, to maintain, and to test; and they are not always readily available.

Strain

Within a given species, there are likely to be sizable strain variations in response to any specific carcinogen. In the more than 10 strains of rats that have been tested with N-2-fluorenylacetamide, the response in a given target organ varied from zero to almost 100 percent, depending on the strain. Similarly, ethionine causes liver tumors in some strains of rats but not in others; a single oral dose of 7, 12-dimethylbenz[a]anthracene leads to a high incidence of mammary tumors in Sprague-Dawley-derived virgin female rats and none in some other strains. Mouse strains also exhibit considerable variation in their response to ethyl carbamate and other carcinogens (*28*).

The spontaneous incidence of tumors of particular organs varies with the strain of animal used for the test. This factor will determine the number of animals required for a meaningful assay. Strains with a high spontaneous incidence of tumors may be particularly sensitive to exposure to test compounds, a characteristic that will also affect the numbers of animals needed for the assay. Species variation in spontaneous tumor incidence does not, however, predict sensitivity to a specific agent.

Before initiating any bioassay, thorough study of the literature is needed to select the proper strain of animal for the types of compounds under test.

Sex

There are appreciable differences in the response of male and female animals to some known carcinogens. Examples are the higher incidence of skin tumors in male mice after painting with 7, 12-dimethylbenz[a]anthracene and the greater number of liver tumors in male rats after feeding 2-diacetylaminofluorene. With *o*-aminoazotoluene, however, female mice were affected more than males. The differences may reside in the role sex hormones play in determining the levels of certain activating enzymes.

Male mice of many strains fight among themselves, causing skin wounds and deaths. The males of such strains should not be used for dermal assays unless they are individually housed or acclimated to each other when young.

Age

In routine tests, animals that are a few weeks' post-weaning are preferred so that they may be exposed to the test agent for the major part of the life span. If the animals are too old when the tests begin, they may die of other causes before tumors have time to develop.

Neonatal animals are more susceptible to many carcinogens than are young adults. A striking example is the induction of liver tumors

in mice treated on day 1–7 of life by aflatoxin B_1(AFB_1); much larger doses of AFB_1 administered to weanlings or young adult mice did not induce liver tumors (*25*). Similar results were noted with vinyl chloride (*12*). However, the difficulties in using neonatal animals are such that this method is hardly used for routine testing of compounds.

Diet

Both the total calories available from the diet and the type of diet influence the outcome of carcinogenicity studies. Restriction in calories may decrease not only the incidence of spontaneous tumors in animals but also the response to a carcinogen (*20, 24*). Diets deficient in protein, vitamins, or other essential factors may enhance the action of certain carcinogens (*11*). On the other hand, high levels of some vitamins increase the activity of detoxifying enzymes, thus depressing or inhibiting a carcinogenic effect. High levels of fats enhance the action of certain carcinogens (*14, 19*); indications are that high fat levels lead to production of bile acids (*17*), which may have a cocarcinogenic effect.

Adventitious dietary factors that may affect carcinogenesis assays include traces of nitrosamines, mycotoxins, and pesticides. Many nitrosamines and some mycotoxins are highly active carcinogens. Traces of pesticides may induce enzymes that activate or detoxify carcinogens. Similarly, vegetable material, usually a component of the processed rodent diets sold in pellet form, and antioxidants act as enzyme inducers and may influence the outcome of carcinogenicity trials.

Spontaneous Tumor Incidence

Since many experiments will extend over most of the lifespan of the experimental animals, it is necessary to know what spontaneous tumors might be expected. The many literature references on tumors in various rat or mouse strains should be consulted (*5, 7, 16, 21, 27*). These furnish background information on spontaneous tumor incidence that allows the researcher to avoid a strain with a very high tumor incidence that may complicate the interpretation and evaluation of bioassay data. However, tumor incidence in an inbred strain may shift over a period of years. Furthermore, specific laboratory conditions such as feed, water, lighting, housing, and handling procedures may affect the "spontaneous" tumor incidence. Adequate numbers of untreated control animals must be included in the experimental design.

Immune Status

The immune status of animals influences their response to the carcinogenic action of viruses or ultraviolet radiation (*1, 10, 18, 23*). The same may be true for chemical carcinogens. Although immunosuppression increases the likelihood of tumor development or successful transplantation (*9*), even from allogeneic tumors, few carcinogenicity studies have been done on immunosuppressed animals.

Procedures

Planning

Any long-term bioassay must be thoroughly planned. Consideration should be given to delineating responsible personnel and their specific duties, obtaining and analyzing the test substance, selecting the animal species and strain, and deciding on dose, route of administration, length of exposure, animal group size, randomization, what observations should be made, animal husbandry, data acquisition, processing, storage and retrieval, data analysis or statistical methods, diet, safety measures, working protocol, and quality control measures (*8, 15, 26*).

Conduct of Experiments

During the actual conduct of the experiment, the following points should be considered: quarantine of newly received animals; surveillance for disease; proper caging, general environment, lighting, temperature, ventilation, and handling; health monitoring of test animals; clinical examination; biochemical studies of blood, urine, and feces; proper necropsy procedures; histopathological techniques, diagnosis, and statistical analysis; and report preparation (*3,8*).

Such attention to detail, although costly, is necessary to avoid discrepancies that may compromise or invalidate the results of the study.

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EXPERIMENTAL CARCINOGENESIS WITH TOBACCO SMOKE

Introduction

Tobacco carcinogenesis exemplifies a meaningful and successful interaction between epidemiology and laboratory studies. The impetus for the development of experimental tobacco carcinogenesis came from large-scale epidemiologic studies between 1950 and 1960 (*2, 46, 64, 120, 201*) that indicated a causal association between cigarette smoking and cancer (see the Part in this Report on biomedical evidence).

The Physicochemical Nature of Tobacco Smoke

During the last three decades, major progress has been achieved in our knowledge about tobacco smoke, its formation, its physicochemical nature, and its composition. This new knowledge has contributed significantly to biologists in their study of the pharmacology, toxicity, and carcinogenicity of tobacco smoke.

The composition of tobacco smoke is a function of the physical and chemical properties of the leaf or of the tobacco blend, the wrapper, and the filter, as well as the way the tobacco is burned. A variety of chemical and physical processes occur in the oxygen-deficient, hydrogen-rich environment of the burning cone of the cigarette at temperatures up to 950°C. The majority of the more than 3,600 smoke components are formed in a pyrolysis-distillation zone just behind the heat-generating combustion zone (*6, 61*). The smoke is called mainstream smoke if it is generated during a puff and exits from the butt end and is called sidestream smoke if it arises mainly from the passive burning of the tobacco product and is released into the environment.

Smoking Conditions

The composition of the mainstream and sidestream smoke depends greatly on the smoking conditions and the methods of collection and analysis. This has long been realized; more than 20 years ago, standardized smoking conditions were established for machine measurements of cigarette smoke (*199*). Since then, the Federal Trade Commission (FTC), research institutions, and the U.S. cigarette industry have used the same standardized parameters for cigarette smoking (*9, 152*): one 2-second puff per minute with a volume of 35 ml and a butt length of 23 mm. For filter cigarettes, the butt length is given by the length of the filter tip plus overwrap plus 3 mm. For the analysis of sidestream smoke, a cigarette is placed in a water-cooled glass vessel with a free inner volume of 250 ml. The cigarette is smoked under the standard conditions applied for the

analysis of the mainstream smoke, but for the collection of the sidestream smoke, an air flow of 1.5 liters per minute is sent through the glass vessel (*28*).

The standard cigarette smoking conditions reflect the average smoking habits of a male smoker of nonfilter cigarettes as determined 25 years ago (*32*). Today, however, fewer than 10 percent of all U.S. smokers appear to follow this pattern (*130*). The average smoking parameters recently recorded for filter cigarette smokers were one puff of 1.94 to 2.06 seconds duration, repeated every 26.9 to 30.0 seconds, with a puff volume of 35.9 to 47.8 ml (*75*). Nevertheless, FTC-standard cigarette smoking conditions continue to be used for comparisons of tar and nicotine yields in the smoke of present cigarettes and for comparisons between present cigarettes and those made years and even decades ago. The values discussed in this introduction were obtained under the standard smoking conditions, except where otherwise noted.

For cigar smoking, the following conditions have been widely used: a 1.5-second puff every 40 seconds, a puff volume of 20 ml, and a butt length of 33 mm (*99a*). The conditions used for sidestream smoke collection of cigars are the same as those for cigarettes (*28*). Conditions for pipe smoking have not been standardized, although conditions of a 2-second puff every 18 seconds and a puff volume of 50 ml have been repeatedly used (*134*).

Temperature Profiles

The temperature profiles of the burning cigarette are affected by the length and circumference of the cigarette, the nature of the tobacco type or blend, the amount and nature of the processed tobacco "stems," the width of the tobacco shreds, the packing density and the moisture content of the tobacco, the porosity and ingredients of the cigarette paper, and the design of the filter (including the filter material and plasticizer, draw resistance, construction, and perforation). During smoking, the temperature of the burning cone reaches up to 950°C; hot spots on the periphery of the burning zone may reach 1050°C (*148, 202*). In a cigarette with paper of medium porosity, the temperature falls from 800°C to 40°C over the 30 mm of the tobacco column adjacent to the burning cone (*185*). The highest temperatures of cigars may reach slightly above 900°C and those of pipes may go slightly above 800°C; however, the temperature gradient away from the burning cone is not as steep as that in cigarettes, primarily because of the larger diameter of the burning cone and the very low porosity of the cigar wrapper and of the pipe bowl (*202*).

On the basis of the temperature profiles, three zones are defined in a burning cigarette during puffing: the high temperature zone (900–600°C), which is very low in free oxygen and contains up to 8 volume

percent of hydrogen and 15 volume percent of carbon monoxide; the oxygen-depleted pyrolysis-distillation zone (600–100°C); and the low temperature zone (<100°C), with up to 12 volume percent of oxygen. The actual generation of mainstream smoke occurs in these three zones by hydrogenation, pyrolysis, oxidation, decarboxylation, dehydration, reactions between freshly generated chemical species, distillation, and sublimation. The exit temperature of the mainstream smoke ranges from 25° to 50°C, depending on the butt length. The previously cited temperature profiles do not apply to cigarettes with perforated filters. In this case, the smoke is diluted by air drawn through the filter wrapper. This lowers the velocity of the air drawn through the burning cone. The result is a more complete combustion of the tobacco.

Smoke Analyses

About 30 percent of the total weight of the mainstream smoke originates from the tobacco; the remainder comes from the air drawn into the cigarette. Five to eight percent by weight of the total effluent from a nonfilter cigarette is made up of moist particulate matter; about 55 to 65 percent are nitrogen, 8 to 14 percent are oxygen, and the remainder consists of other gas phase components generated during smoking (*107*). Undiluted cigarette smoke, as it leaves the mouthpiece, contains up to 5×10^9 heterogeneous particles per ml, with round and spheric forms ranging in diameter between 0.2 and 1.0 μ and a median particle size of about 0.4 μ (*36, 107*). In the case of filter cigarettes, the median particle size of the smoke is somewhat smaller (between 0.35–0.4 μ). For cigarettes with perforated filter tips, the number of particles generated is significantly lower than for unfiltered cigarettes (*36*).

The smoke particles that are inhaled are slightly charged with about 10^{12} electrons per gram of smoke (equivalent to two or three cigarettes). Since the smoke is partially generated in the oxygen deficient zone, the aerosol leaving the mouthpiece has reducing activity that increases with the number of puffs drawn and that disappears completely only minutes after smoke generation (*166*). Thus, freshly generated tobacco smoke as inhaled may affect the redox balance of respiratory tract tissues.

The pH of tobacco smoke is of major significance since it influences its inhalability by the smoker and the availability of unprotonated nicotine (*3*). Figure 1 depicts the percentage of diprotonated, monoprotonated, and unprotonated nicotine in aqueous solution at various pH. For a blended U.S. cigarette, the pH of the mainstream smoke varies between 5.5 and 6.2; cigarettes made exclusively from Burley or black tobacco, and cigars yield mainstream smoke with pH ranges between 6.5 and 8.5, reaching the highest pH with the last

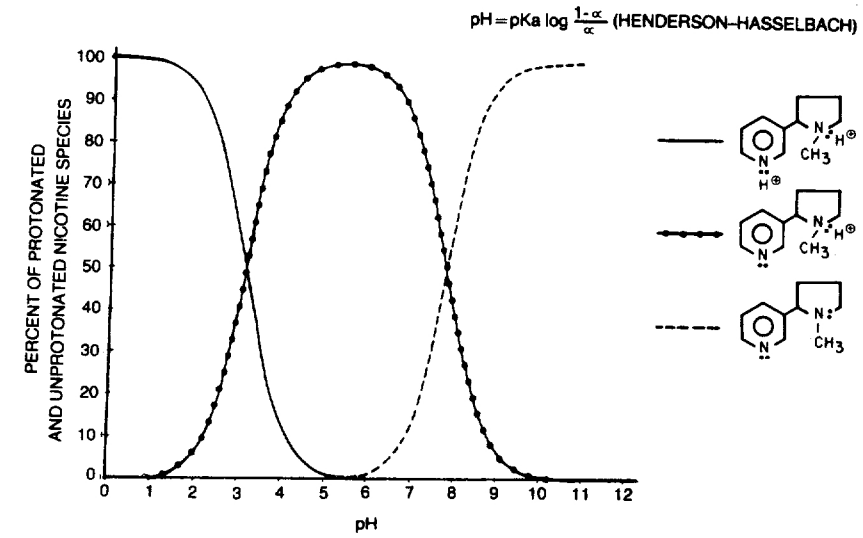

FIGURE 1.—Protonation of nicotine
SOURCE: Brunnemann and Hoffmann (*28*).

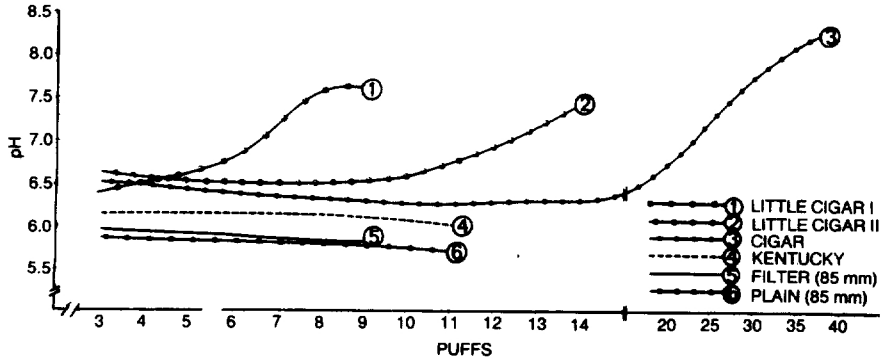

FIGURE 2.—pH of individual puffs of total mainstream smoke of various tobacco products
SOURCE: Brunnemann and Hoffmann (*28*).

puffs (*28*). Figure 2 shows the pH of individual puffs of the mainstream smoke of some tobacco products (*6*).

Bioassays

Inhalation Studies

Ideally, a suspected carcinogen should be tested using the route of administration corresponding to the exposure of humans. The experimental induction of respiratory cancer with tobacco smoke is

beset with major difficulties because of toxicity introduced by high carbon monoxide concentrations (generally 3.5 to 5 volume percent), and high levels of nicotine. Furthermore, laboratory animals are not willing to inhale aerosols very deeply and are especially reluctant to inhale tobacco smoke. Inhalation studies have been explored by training Rhesus monkeys and baboons to smoke cigarettes. This approach does not produce respiratory neoplasms because of insufficient exposure time and because of the tendency of the animals merely to puff rather than to inhale (*102, 156a*).

Invasive and noninvasive bronchoalveolar tumors developed in several of 78 dogs that were trained to smoke through a tracheostoma and that smoked cigarettes daily for about $2^1/_2$ years. In a group of 24 dogs that smoked nonfilter cigarettes, 2 animals developed early invasive squamous cell carcinoma in the bronchi (*4*). However, this observation has not been repeated so far (*137*).

A number of inhalation studies have been conducted with rats. Recently they have yielded tumors of the respiratory tract (*43, 137*). In 1980, investigators at the Oak Ridge National Laboratory succeeded in obtaining tumors of the respiratory tract of rats using a highly developed smoke inhalation device (*43, 126*). On 5 days each week over their entire lifespan, 80 rats were exposed to air-diluted smoke (10 percent) of seven cigarettes (one cigarette per hour). At the end of the experiment, a large number of rats had developed hyperplasia or metaplasia in the epithelium of the nasal system, the larynx, or the trachea. Seven of the eighty smoke-exposed rats had tumors of the respiratory tract, including five animals with pulmonary adenomas, two with alveologenic carcinomas, one with a squamous carcinoma of the lung, and one with adenocarcinoma and squamous cell carcinoma in the nasal cavity. One alveologenic carcinoma was observed in 30 sham-exposed control rats; no respiratory tract tumors were seen in 63 untreated control rats (*43*).

At present, the most promising animal for tobacco smoke inhalation studies appears to be the Syrian golden hamster. This animal is more resistant to respiratory infections than are mice and rats and is also more tolerant of cigarette smoke (*52*). Dontenwill et al. developed the first smoke inhalation device and bioassay methodology for the chronic exposure of hamsters to cigarette smoke (*51*). For 5 days per week and for the duration of their lifetime, the hamsters were exposed once, twice, or three times daily for 10 minutes to air-diluted cigarette smoke (1:15). In the 3 groups of 80 hamsters, 11.3, 30, and 30.6 percent of the animals developed pre-invasive carcinoma, and 0.6, 10.6, and 6.9 percent had invasive carcinoma of the upper larynx (*51*). Laryngeal tumors were not observed in the control group nor in the animals exposed only to the gas phase of cigarette smoke. Trachea and bronchi of all animals were free of neoplastic growth. Tumors that developed in other organs of the exposed

hamsters were not different from those in the control group. This inhalation assay represents the first reproducible method for the induction of tumors in the respiratory tract of animals exposed to tobacco smoke. Dontenwill and his group have successfully applied this method to the evaluation of the carcinogenic potential of experimental cigarettes with and without reduced activity as measured in mouse skin bioassays (*48*).

Bernfeld et al. (*11*) improved the inhalation model primarily by using an inbred hamster strain that is susceptible to carcinogenic inhalants. The smoking schedule called for exposure for 59 to 80 weeks to a 22 percent cigarette smoke aerosol twice daily for 12 minutes with cigarettes made entirely from flue-cured tobacco, such as those used in the United Kingdom. This induced carcinoma of the larynx in 27 out of 57 hamsters at risk (≅47 percent). Three of the animals developed papilloma of the trachea; none had tumors of the lung. In tests with an 11 percent smoke aerosol, only 3 out of 44 hamsters at risk (7 percent) developed laryngeal carcinoma, indicating a possible dose-response for the induction of carcinoma of the larynx with cigarette smoke. Thus, it appears that this hamster inhalation model is a promising bioassay system for estimating the relative carcinogenic potential of total, unaged smoke of various cigarettes.

Why these inhalation experiments with hamsters did not induce carcinoma of the lung remains to be elucidated. Two investigations have examined this question using tracer studies with decachlorobiphenyl (DCBP) (*11,86*). In one study, DCBP was added to cigarettes and the concentration of the tracer in the mainstream smoke was determined for the appropriate exposure for each animal. DCBP is not volatile and is, therefore, not found in the gas phase, but rather is an integral part of the smoke particulate phase. Bernfeld et al. (*11*) determined that 160 μg tar[3] reached the lung of a hamster and that 15 μg tar were deposited in the larynx after each exposure of a hamster to DCBP-spiked mainstream cigarette smoke. In another study with a different smoke inhalation device, 88 μg tar were found to reach the lungs and 2.8 μg tar were traced to be deposited in the larynx (*86*). Considering the relative surface area of both larynx (0.1 to 3.0) and lung (1,000), Bernfeld et al. calculated that, per surface area unit, 300 to 900 times more tar is deposited in the larynx than in the lungs. In the other study (*86*), the relative deposition per surface area unit was calculated to range from 110:1 to 320:1. This high density of tar deposits in the larynx suggests an explanation of the occurrence of a high yield of laryngeal cancers in hamsters exposed to cigarette smoke but a lack of lung tumors in the same experiments.

[3]Throughout this section the term "tar" is used as a descriptive noun only; it is realized that the terms "smoke particulates" or "smoke condensates" are often more correct.

Assays With Smoke Particulates

The gaseous phase of tobacco smoke does not induce tumors of the respiratory tract in laboratory animals (*51, 202*), except for lung adenomas in certain sensitive strains of mice (*119*). This suggests that the carcinogenic activity of smoke requires the particulate phase. Benign and malignant tumors have been induced with tobacco tar in the skin and ear of rabbits, in the connective tissue of rats, and by intratracheal instillation, in the bronchi of rats (*137, 202*). However, the most widely used methodology for the induction of tumors in epithelial tissues has been topical application to mouse skin. Detailed studies have shown that the effect of a tumor initiator is irreversible, but promoter activity will cease upon termination of treatment (*193, 195*). It appears likely that the metabolically activated form of a tumor initiator is bound to the DNA of a target cell, but the promoter effect is not directly linked with cellular DNA damage and can, therefore, be repaired. Single applications of a low dose of 7,12-dimethylbenz[a]anthracene (DMBA) or benzo[a]pyrene (BaP) have served as initiators in chemical carcinogenesis studies that demonstrate initiation and promotion as two successive stages. Most model experiments utilize repeated application of 2.5 μg or lower doses of tetradecanoyl phorbol acetate (TPA) as a promoter (*192*). In another setting, mouse skin is treated 10 times with a very low dose of BaP or another tumor initiator and is subsequently treated with TPA (*72, 116*). A cocarcinogen is defined as an agent that potentiates the activity of a carcinogen when both substances are coadministered. The cocarcinogen by itself may exert little or no carcinogenic activity.

The merit of the mouse skin assay lies in its sensitivity and reproducibility as a method for the identification of tumor initiators, tumor promoters, and cocarcinogens in tobacco smoke. By definition, a tumor initiator is an agent that does not elicit a significant tumor response in mouse skin or in other epithelial tissue, but suffices to bring about benign and malignant tumors when its application is followed by repeated treatments with a tumor promoter. Reversal of the order of application produces few tumors. The mouse skin assay has been employed to establish a clear dose response for carcinogenicity of tars. It has been most useful in evaluating the relative potential for the induction of benign and malignant tumors by contact carcinogens. The relative activity of the smoke particulate matter of commercial and experimental cigarettes has been compared on mouse skin (*50, 202*), and the response was found to be in good agreement with results from the bioassays in which inhalation of tobacco smoke led to carcinoma of the larynx in hamsters (*48, 49*).

The mouse skin assay has been helpful in evaluating the relative tumorigenic potential of the smoke particulates of cigarettes made from different tobacco varieties, reconstituted tobacco sheets, lami-

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na, stems, and tobacco substitutes (*88, 143*). Bioassays conducted with standardized methods on the same strain of mice have indicated a gradual decline of the carcinogenic potential of the smoke particulates of a leading U.S. cigarette brand during the last 20 years. This reflects the changes in the makeup of commercial cigarettes (*188*).

Fractionation Experiments

Assessments have been made for the materials derived primarily from two major separation schemes employed for the identification of tumorigenic agents. One system begins with fractionation of the smoke particulates into neutral, acidic, basic, and insoluble portions, followed by column chromatographic subfractionation schemes for further delineation of tumorigenic constituents (*17, 90*). The other system consists of the partitioning of the particulates with solvent systems and of the subsequent chromatographic separations (*59*). Both methods have clearly established that the tar subfractions, which contain the bulk of polynuclear aromatic hydrocarbons (PAH), are the only portions that elicit carcinoma on mouse skin when applied in high concentrations. These subfractions harbor the majority of the tumor initiators. Intratracheal instillation in rats also led to carcinomas only with those subfractions that were highly enriched in PAH. However, the PAH subfractions also contain neutral cocarcinogens. These are non-carcinogenic PAH, which nevertheless potentiate the activity of carcinogenic PAH. The chemical identification of still other cocarcinogens in these neutral subfractions points to nonvolatile ketones and tobacco terpenes (*165*).

The weakly acidic portion of smoke particulates and its subfractions have also been shown to contain tumor promoters as well as important cocarcinogens, including phenolic compounds and catechols (*18, 67*).

Transplacental Carcinogenesis

In the 1979 report *Smoking and Health: A Report of the Surgeon General,* several questions were raised in respect to transplacental effects of cigarette smoking (*189*). Activation of enzymes that induce metabolic activation of benzo[a]pyrene (BaP) in the foreskin of human newborns of smoking mothers has been interpreted as one indication of possible transplacental migration of smoke constituents (*41, 123*).

Several experimental studies suggest that tobacco smoke has transplacental carcinogenic effects. Intraperitoneal injections of tobacco tar in olive oil during the 10th to 14th day of gestation of Syrian golden hamsters led to tumors in 2 of 58 females and to benign and malignant tumors in 17 of 51 transplacentally exposed offspring, within 15 to 25 months of observation. The tumors in the

offspring were primarily located in the adrenal glands, pancreas, female sex organs, and liver. Untreated control animals, or those whose mothers were injected with olive oil alone, did not develop any tumors during the course of this experiment.

This experiment should be repeated, in order to establish the reproducibility of the transplacental effects. Its results are in line with general observations of transplacental carcinogenesis. These include pronounced prenatal susceptibility, expressed in a far higher lifetime tumor yield in the offspring, as compared with their mothers (*156*).

In that direct-acting alkylating agents are generally the most effective transplacental carcinogens, the high tumor incidence in the offspring of hamsters treated with tobacco tar is remarkable. Compounds requiring metabolic activation to ultimate active forms of carcinogenic species, however, are also transplacental carcinogens, though of a lesser potency than direct alkylating carcinogens. Enzymes necessary for activation are known to exist in the fetus only at low levels, if at all, until just prior to birth (*110*). A number of tobacco smoke constituents, which need metabolic activation in order to acquire carcinogenic properties, are known transplacental carcinogens. Among these are volatile N-nitrosamines, BaP, o-toluidine, ethyl carbamate, and vinyl chloride (*156*).

The role of nicotine in regard to possible transplacental effects of tobacco smoke also requires further elucidation, since its transplacental migration into the animal fetus has long been known (*184*). A smoker of 20 cigarettes daily is exposed to 20 to 30 mg of nicotine, and in a pregnant woman it is to be expected that some of this nicotine reaches the fetus. Enzymatic oxidation to cotinine in the fetus is very slow, because of low enzyme activities. Thus, nitrosamine formation from the unmetabolized nicotine may occur. Such considerations suggest the need for further experimental studies of the transplacental effects of tobacco products.

Syncarcinogenesis: Occupational Carcinogens and Smoking

In the United States, cigarette smoking is generally more prevalent among blue-collar workers than among the white-collar work force (*42*). Thus, smokers are more likely to be in occupational environments with chemicals, dusts, and fumes than are their nonsmoking counterparts (*56*). This indicates the need to examine the role of smoking as a confounding variable to occupational exposure and raises the question whether tobacco smoke acts synergistically with other factors in respiratory tract carcinogenesis.

In 1979, Hammond et al. (*65*) evaluated the smoking history relating to 276 deaths from lung cancer among asbestos workers. The calculated mortality ratios (the ratio of death rates in smokers compared with death rates in nonsmoking men of a similar age

distribution) for lung cancer were 87.36 for workers who smoked more than 20 cigarettes per day, 50.82 for those who smoked less than 20 cigarettes per day, and 5.33 for asbestos workers who had never smoked regularly. The authors also reported that exposure to asbestos dust in the absence of smoking may have little or no influence on death rates from cancer of the esophagus, larynx, pharynx, or buccal cavity.

Several carcinogenesis experiments were designed to measure the combined effects of tobacco smoke and the various types of asbestos fibers (*189*). In one such study, 500 μg of asbestos were instilled in the trachea of hamsters, prior to exposure to diluted cigarette smoke, 10 times weekly over a period of 18 months. Since no more than about 1 percent of the smoke particulates reached the hamsters' lungs in such experiments, the smoke exposure alone did not produce tumors in the lower respiratory tract, nor did it potentiate the subthreshold dose of the carcinogenic asbestos (*51*). In contrast, synergistic action of tobacco smoke and asbestos were indicated when asbestos fibers were first incubated with cigarette tar and then added to human lymphocyte cultures. This resulted in significantly increased induction of aryl hydrocarbon hydroxylase (AHH) compared with the enzyme induction in the lymphocyte cultures with either agent alone (*171*). This finding suggests that a surface (and chemical) interaction between asbestos and cigarette smoke may have occurred with formation of a product having higher carcinogenic activity than is inherent in either agent alone. An elucidation of the mechanisms involved in syncarcinogenic effects of tobacco smoke and asbestos fibers requires further experimental studies.

A substantial excess of lung cancer has been reported among uranium miners who smoke cigarettes (*189*). Archer et al. (*2*) calculated that the lung cancer rate for U.S. uranium miners who smoked was 42.2 per 10,000 persons/years compared with 4.4 for nonminers who smoked two or more packs of cigarettes a day. There is also some evidence that cigarette smoking may change the latent period for lung cancer development following radiation exposure among uranium miners (*2*). As will be discussed later, polonium 210 (^{210}PO) is present in tobacco and cigarette smoke (0.03 to 1.0 pCi/cigarette); however, it is unlikely that these traces represent a major risk for the smoker.

Beagle dogs were exposed to radon daughters in uranium ore dust (group 1) or to the same uranium ore dust, together with cigarette smoke (group 2). After more than 40 months, all dogs showed areas of epithelial changes, including large areas of adenomatosis, and squamous metaplasia of the alveolar epithelium with atypical cells. After more than 50 months of exposure, lungs from 50 percent of the dogs in groups 1 and 2 contained large cavities within the parenchyma surrounded by bands of hyperplastic adenomatous epithelial

cells. These changes were not seen in dogs exposed only to cigarette smoke (*178*).

Little and his group (*124*) tested the hypothesis that ^{210}Po α-radiation acts synergistically with polynuclear aromatic hydrocarbons (PAH) present in cigarette smoke. Syrian golden hamsters were given intratracheal instillations of low levels of both ^{210}Po and BaP simultaneously or in sequence. Upon simultaneous intratracheal instillation of ^{210}Po and BaP on ferric oxide, the induction of peripheral lung tumors was simply additive. Sequential application of a single dose of ^{210}Po (0.04 μCi) and repeated dosage of BaP (0.3 mg x 7 weeks), however, produced syncarcinogenic effects. Among 139 animals at risk in the group receiving a single dose of ^{210}Po, only 1 animal (0.7 percent) had a lung tumor. The sequential application of ^{210}Po and BaP to 135 animals induced lung tumors in 23 of them (17 percent), and BaP alone gave tumors in less than 4 percent of the hamsters (*132*).

Although other occupational environments may provide additional cancer risk factors for workers who smoke, epidemiological and experimental studies have not documented such occurrences to date. It has been suggested that synergistic carcinogenic effects may occur in cigarette smokers who work in factories producing or handling chloromethyl ether (*59*), vinyl chloride (*34*), nickel (*47*), or 2-naphthylamine (*189*).

Alcohol and Tobacco Products

Epidemiological data have indicated that the combination of chronic alcohol and tobacco consumption greatly increases the risk for cancer of the oral cavity, esophagus, and larynx, but not of the lung (*157, 189*). Several possible mechanisms have been proposed in regard to synergistic effects of tobacco smoke and alcohol. Alcohol serves as a solvent for tobacco carcinogens, or it alters the liver metabolism of tobacco carcinogens and, thus, has an indirect influence on tobacco carcinogenesis at distant organs. Chronic alcohol consumption sometimes leads to deficiencies in essential micronutrients, making the target cells more susceptible to carcinogens. Also, alcohol induces changes in metabolism of the tobacco carcinogens in target tissues.

It has been shown in the experimental setting that alcohol, as a solvent, increases the carcinogenic effect of PAH, which are the major tumor initiators in smoke (*177*) and of the distillation residues of alcoholic spirits that contain carcinogens (*114*). Chronic alcohol consumption, among other effects, enhances the drug metabolism capabilities of liver microsomes in both men and animals (*136*). The metabolism in the liver of the tobacco carcinogen N-nitrosopyrrolidine (NPYR), for example, was enhanced in ethanol-consuming

hamsters (*137*). Excessive alcohol consumption is also known to lead to various other cellular injuries that influence carcinogenesis (*136*).

Vitamin A deficiency, which frequently accompanies alcohol abuse, increases susceptibility to carcinogens of the PAH type in laboratory animals (*175*). Vitamin B_2 deficiency has been shown to potentiate effects of carcinogens in mouse skin (*37*). Rats on a zinc-deficient diet are more susceptible to the esophageal carcinogen, N-nitrosobenzylmethylamine (*55*). The carcinogenicity of NPYR in Syrian golden hamsters is enhanced when the animals are on a high alcohol diet, yet this enhancement has not been observed for the tobacco-specific N'-nitrosonornicotine (*131*). Further studies of biochemical changes and bioassays with coadministration of alcohol and tobacco smoke or its constituents may provide a better understanding of the increased cancer risk of consumers who use both alcohol and tobacco.

Tumorigenic Agents In Tobacco Products

Vapor Phase Components

The definition of the vapor phase components is arbitrary and does not represent the true physicochemical conditions prevailing in tobacco smoke. In carcinogenesis, the tobacco chemist's definition has been widely accepted. For the purposes of this discussion the term "vapor phase component" includes all smoke constituents of which more than 50 percent pass through a Cambridge glass fiber filter. Collecting smoke from a single cigarette on a filter pad yields fairly reproducible data. More than 90 percent of the total weight of mainstream smoke is made up of vapor phase components, of which nitrogen and oxygen constitute more than 70 percent. Carbon dioxide and carbon monoxide make up 15 to 20 percent by weight of the total effluents of most cigarettes, unless the cigarette filter tip contains unblocked perforations that reduce this percentage.

Carbon monoxide in cigarette smoke, although not a carcinogen, may contribute to respiratory carcinogenesis because of its inhibiting effect on the mucus clearance mechanism of the respiratory tract (*10*). Its most important toxic effect, however, lies in its burden on the circulatory system because it combines with hemoglobin of the blood to form carboxyhemoglobin.

The plain cigarette and the conventional filter cigarette contain 2 to 7 volume percent of carbon monoxide per puff, with the concentration increasing with the later puffs. The total carbon monoxide in the smoke of these cigarettes in the United States in 1980–1981 amounts to 3 to 5 volume percent or 13 to 26 mg/cigarette. However, air dilution of the smoke from cigarettes with a perforated filter tip reduces carbon monoxide to 0.5 to 13 mg/cigarette (*27,191*). It is estimated that more than 50 percent of

the cigarettes currently sold on the U.S. market have perforated filter tips. The smoke of cigars and little cigars contains carbon monoxide values up to 11 volume percent (*27*).

In the 1979 report *Smoking and Health: A Report of the Surgeon General,* carbon dioxide, nitrogen oxide, ammonia, hydrogen cyanide, and volatile sulfur compounds and nitriles have been discussed in addition to carbon monoxide (*189*). Since that time no significant new information has been published in respect to the contribution of these vapor phase components to the overall toxicity and carcinogenicity of tobacco smoke. It should be noted that the gradual reduction of tar and nicotine was accompanied by a gradual decrease of most vapor phase components in the smoke of the sales-weighted average U.S. cigarette (*89*). This reduction does not apply to the level of nitrogen oxides (NO_x), of which more than 95 percent are nitric oxide (NO). The NO_x content of the smoke of the sales-weighted average U.S. cigarette has remained at a level of 270 to 280 μg per cigarette (*89*). One reason for this appears to be the use of increasing percentages of Burley tobacco and of "stems" in the cigarette blend. Burley tobacco and "stems" are richer than Bright tobacco in nitrate, a main precursor for NO_x in the smoke. A major reduction in smoke NO_x can be achieved by high smoke dilution (*146*). As discussed before, these observations apply to the smoke generated by standard machine smoking schedules and do not allow for the fact that many smokers of low tar cigarettes smoke more intensely.

It has been demonstrated that a high percentage of the ciliatoxic agents, which inhibit the lung clearance, are present in the vapor phase (*10,44*). These are chiefly hydrogen cyanide (280 to 550 μg/cig), acrolein (10 to 140 μg/cig), ammonia (10 to 150 μg/cig), nitrogen dioxide (0 to 30 μg/cig), and formaldehyde (20 to 90 μg/cig). Squamous cell carcinomas were induced in the nasal cavities of rats exposed in chambers for 30 hours a week to 15 ppm of formaldehyde for 18 months (*182*). The mechanism of its action is unknown; metabolically, it is rapidly oxidized further to formic acid.

The vapor phase, i.e., that portion of the smoke passing through a glass fiber filter, does not by itself induce tumors in laboratory animals, except in certain strains of mice (*119*). The carcinogenic effects of low levels of volatile smoke constituents may currently escape detection by means of bioassays because of the low doses used and the low sensitivity of models available at present (*100*). Table 1 lists the major components of the vapor phase and whether the agent is reported to be toxic or tumorigenic. The volatile N-nitrosamines are largely retained by the smoke particulates in the glass fiber filters and will be discussed in the section on organ-specific carcinogens. In general, our understanding of the mechanisms of carcinogenesis by other volatile smoke components is scanty.

TABLE 1.—Major toxic and tumorigenic agents in the vapor phase* of cigarette smoke (unaged)**

Agent	Biologic activity[a]	Concentration/cigarette Range reported	U.S. cigarettes[b]
Carbon monoxide	T	0.5 - 25 μg	17 μg
Nitrogen oxides (NO_x)[c]	T	16 - 600 μg	350 μg
Hydrogen cyanide	CT, T	28 - 550 μg	110 μg
Formaldehyde	CT, C	20 - 90 μg	30 μg
Acrolein	CT	10 - 140 μg	70 μg
Acetaldehyde	CT	18 -1,400 μg	800 μg
Ammonia	T?[d]	2.5 - 250 μg	10 μg
Hydrazine	C	24 - 43 ng	32 μg
Vinyl chloride	C	1 - 16 ng	12 μg
Urethane	C	10 - 35 μg	30 μg
2-Nitropropane	C	0.73 - 120 μg	1.2 μg
Quinoline	C	0.8 - 2.0 μg	1.7 μg

*Volatile nitrosamines are listed in Table 4.

**Cigarettes contain most likely also carcinogens such as nickel carbonyl and possibly arsine, volatile chlorinated olefins and nitro-olefins.

[a] T notes toxic agent; CT, cilia toxic agent; and C, carcinogenic agent.

[b] 85 mm cigarettes without filter tips.

[c] NO_x >95% NO; rst NO_2.

[d] Not toxic in smoke of blended U.S. cigarettes because pH >6.5, therefore ammonia and pyridines are present in protonated form.

SOURCE: Hoffmann et al. (*87,90*).

Hydrazine or its salts are most effective as carcinogens in mice. Metabolic transformation of hydrazine in some animals yields acetyl and diacetyl derivatives, although ammonia is formed in dogs (*40*). Numerous studies on the toxicity and carcinogenicity of hydrazine have been reported (*125*), but few on its metabolic transformation and the mechanism of its action. Indications are that hydrazine may disrupt normal methylation processes in the organism, since methylated guanines were noted in liver DNA after exposure.

The cytochrome P-450 enzyme system forms a halogenated epoxide from vinyl chloride (*8, 205*). In turn, this epoxide may yield halogenated aldehydes or alcohols through rearrangement. Contrary to the situation with the nucleic acid adducts of most other activated carcinogenic intermediates, the epoxide from vinyl chloride ethylenates or adds across the N-1 and N-6 of adenosine or the N-3 and N-4 of cytidine, forming new rings in these particular bases (*21*). The presence of these additional structures would probably interfere in the normal base pairing between adenosine-thymidine and guanosine-cytidine.

Urethane is not a potent carcinogen, in terms of dose, except in neonatal mice. Although it is metabolized to N-hydroxyurethane, which acylates cytosine (*144*), there still remains a question whether urethane or N-hydroxyurethane is the active material (*135*).

Tumor Initiators

The carcinogenic activity of the particulate matter of tobacco smoke in epithelial tissues of laboratory animals is greater than the sum of the effects of the known carcinogens present. Large scale fractionation studies in a number of laboratories have shown that the total carcinogenic activity also results from the effects of tumor initiators, tumor promoters, and cocarcinogens in the tar.

Large-scale tar fractionation studies in a number of U.S. and foreign laboratories have shown that the tumor initiators reside in those neutral subfractions in which the polynuclear aromatic hydrocarbons (PAH) are enriched (*87*). So far, at least two dozen PAH and a few neutral aza-arenes have been identified to serve as tumor initiators at the dose levels found in tobacco tar. It is likely that the PAH concentrates of smoke particulates contain additional tumor initiators that may yet be identified by detailed capillary GC-MS analysis (*172*). All of these PAH tumor initiators are formed during smoking by similar pyrosynthetic mechanisms (*5, 87*). More recent observations showed, surprisingly, that tumor initiators are also found among dimethylated or polymethylated three-ring aromatic hydrocarbons in which the formation of bay region dihydrodiol epoxides is favored, but the detoxification to phenols is reduced. An example is 1,4-dimethylphenanthrene (*117*). These methylated three-ring aromatic hydrocarbons may be present in tobacco smoke in much higher concentrations than the corresponding parent PAH. Table 2 lists tumor-initiating PAH and aza-arenes identified in tobacco smoke.

These compounds are secondary or procarcinogens since they require metabolism to show an effect. Metabolic activation is generally mediated through the mixed-function oxidase system of enzymes. The metabolic activation of polycyclic aromatic hydrocarbons, as typified by benzo[a]pyrene (BaP), has been reviewed within the past 2 years (*58*). In brief, BaP is metabolized by means of the mixed-function oxidase system to the 2,3-, 4,5-, 7,8-, and 9,10-epoxides, of which only the 4,5-epoxide is stable enough to permit isolation and thus to exist in the environment. The various epoxides can be converted to phenols, which in turn may be conjugated through glucuronyl transferase or sulfotransferase to water-soluble glucuronides or sulfates.

The phenols may also be oxidized to quinones such as the 1,6-, 3,6-, and 6,12-quinones derived from BaP. The original epoxides are good substrates for the glutathione-S-transferase system that forms glutathione conjugates and premercapturic and mercapturic acids from the epoxides. In addition, the epoxide hydrolase system converts the epoxides to dihydrodiols with the (-)-*trans* configuration.

However, an additional activation step is required, i.e., the further oxidation of the dihydrodiols, also mediated by the mixed-function

TABLE 2.—Tumor-initiating agents in the particulate phase of tobacco smoke[1]

Compound	Relative activity as complete carcinogen[2]	ng/cig
Benzo(a)pyrene	+++	10–50
5-Methylchrysene	+++	0.6
Dibenz(a,h)anthracene	++	40
Benzo(b)fluoranthene	++	30
Benzo(j)fluoranthene	++	60
Dibenzo(a,h)pyrene	++	pr[3]
Dibenzo(a,i)pyrene	++	pr[3]
Dibenz(a,j)acridine	++	3–10
Indeno(1,2,3-cd)pyrene	+	4
Benzo(c)phenanthrene	+	pr[3]
Benz(a)anthracene	+	40–70
Chrysene	+ ?	40–60
Benzo(e)pyrene	+ ?	5–40
2- and 3-Methylchrysene	+ ?	7
1- and 6-Methylchrysene	-	10
2-Methylfluoranthene	+	34
3-Methylfluoranthene	?	40
Dibenz(a,c)anthracene	(+)	pr[3]
Dibenz(a,h)acridine	(+)	0.1
Dibenzo(c,g)carbazole	(+)	0.7

[1] Incomplete list; all listed compounds are active as tumor initiators on mouse skin.

[2] Relative carcinogenic activity on mouse skin as measured in our laboratory on Swiss albino (Ha/ICR/Mil) mice;

?: Carcinogenicity unknown; (+): not tested in own laboratory.

[3] pr: present, but no quantitative data given.

SOURCE: Hoffmann et al. (*88*).

oxidase system. For BaP, the *trans* isomer of the 8,8-dihydrodiol-9,10-expoxide thus formed appears to be the active intermediate, capable of reacting with nucleic acids, proteins, and other cellular constituents. In the nucleic acid adducts, the 10-position of the diol epoxide was linked to the amino group in the 2-position of guanosine, although some reaction with the phosphates of the DNA backbone also occurred.

Various enzymatic and radioimmunoassays have been devised to measure the level of the BaP-DNA adduct in biological materials (*93*). Although the actual biological consequences resulting from the BaP-DNA adduct have not been exactly delineated, there are indications that the adduct can interfere in elongation of the nucleic acid during replicative processes.

No studies on the mechanism of carcinogenesis by metabolic products of polycyclic heterocyclics have been reported. On the premise that they may be activated through a similar mechanism as the polycyclic aromatic hydrocarbons, some of the dihydrodiols of benz[a]- and [c]acridine have been synthesized as model compounds (*161*). The possible metabolic transformation to N-oxides should also be considered.

Tumor Promoters

The water extract of processed tobacco and the particulate matter of tobacco smoke contain tumor-promoting agents (*16, 20*). Pretreating mouse skin with 125 μg of DMBA, Bock and collaborators (*19*) found that the tumor-promoting activity of tobacco extracts requires the concurrent presence of two agents, one of large molecular weight (LM), insoluble in organic solvents, and the other of small molecular weight (SM), soluble in organic solvents. They suggest that the SM agent could be nicotine (*20*). Bock and Clausen (*15*) fractionated the portion with the LM agent by dialysis. A subfraction with a presumptive molecular weight greater than 13,000 exhibited the highest copromoting activity when tested together with nicotine. It appears likely that the LM fraction with the highest activity consists of tobacco leaf pigments (*14*).

Certain compounds used or suggested as sucker control agents or pesticides were active as tumor promoters on mouse skin when tested in concentrations between 0.3 and 1.0 percent. Certain fatty acid esters and fatty alcohols proposed as agricultural chemicals were also tumor promoting agents in concentrations of 3 percent or greater. Among the active tumor promoters were a 0.3 percent solution of dodecyldimethylamine, suggested as a sucker growth inhibitor; Tween 20 and Tween 80, used as surfactants; 1 percent of the insecticides DDD and DDT; and 3 percent mixtures of fatty acid esters and fatty alcohol proposed as sucker growth inhibitors (*20*). The very small residual amounts of these agricultural chemicals found in tobacco make it unlikely that they are of consequence in the tumor-promoting activity of tobacco extract or tar.

The total smoke condensates of cigarettes, cigars, and pipes act as tumor promoters. The active agents are found primarily in the weakly acidic portion and in certain neutral subfractions. Certain fatty acids, especially oleic acid, and phenols have been identified as weakly acidic tumor promoters. Tumor promoters in the neutral subfractions were DDD, DDT and its major pyrolysis product 4,4'-dichlorostilbene, and N-methylated indoles and carbazoles (*165, 189*). The majority of the tumor promoters in tobacco tar remain to be identified. These include certain high molecular weight components in the most polaric neutral fraction or in the insoluble portion.

Cocarcinogens

Fractionation studies of tobacco smoke particulates have shown that coadministration of the neutral and weakly acidic portions raises the tumor yield in mouse skin experiments significantly above the number of tumors obtained from each fraction alone (*67, 87, 203*). Benzo[a]pyrene (BaP) at 0.005 percent concentration applied together with a 5 and 10 percent solution of the weakly acidic portion of tobacco smoke particulates also yields tumors in greater proportion

than expected on the basis of the additive effects of the individual materials. Some subfractions of the weakly acidic portion are inactive when tested alone, yet they potentiate the carcinogenic activity of 0.003 percent BaP when coadministered with the carcinogen. Van Duuren et al. (*194*) were the first to demonstrate that catechol, the major phenolic compound in tobacco smoke (20 to 460 μg/cigarette), is a powerful cocarcinogen. Systematic fractionation studies monitored with bioassays have illustrated that the catechols are in fact a major group of cocarcinogens in cigarette smoke (*67*). A considerable number of other components have been identified in the cocarcinogenic weakly acidic subfractions. None of these, however, are known cocarcinogens (*67, 163*). They are either inactive or not as yet tested. The levels of the catechols alone cannot account for the cocarcinogenic activity observed for the weakly acidic fraction, but catechol values serve as a fairly reliable indicator of the cocarcinogenic potential of this portion of the smoke particulates. The polyphenols of the leaf apparently serve as important precursors for the catechols (*35, 162*).

Subfractions of the neutral portion that contain concentrates of PAH are also active as cocarcinogens in studies on mouse skin (*165*). So far, a number of methylated naphthalenes, indoles, carbazoles, and PAH that have no tumor initiator activity have been identified as cocarcinogens in neutral subfractions (*165, 196, 200, 202*). Further fractionations and bioassays have demonstrated that both PAH-containing and PAH-free subfractions have cocarcinogenic activity (*165*). The PAH-free material was shown to contain several unsaturated hydrocarbons as well as oxygenated terpenes, which remain to be bioassayed as potential individual cocarcinogens.

In model studies, C_{10}–C_{14} paraffin hydrocarbons as vehicles for carcinogenic PAH are potent cocarcinogens (*13, 92*). However, the normal paraffinic and the iso-paraffinic hydrocarbons in tobacco and tobacco smoke are waxy solids with chain lengths of C_{25}–C_{34} and with n-$C_{31}H_{64}$ as the predominant paraffin (*174*). The neutral subfraction that consists primarily of paraffin hydrocarbons has no demonstrable cocarcinogenic activity. In mouse skin bioassays of cigarette smoke condensates mixed with BaP, increased paraffin levels of the smoke condensates apparently inhibited tumor development (*202*).

The basic fraction of cigarette tar contains 60 to 80 percent nicotine and other alkaloids. Since nicotine is highly toxic, only the nicotine-free basic portion has been assayed for tumorigenic activity and has been found to be inactive (*90, 202*). However, when nicotine is given in low doses together with TPA and BaP, it acts as a cocarcinogen. Such cocarcinogenic activity is not found for cotinine and nicotine-N′-oxide, the two major metabolites of nicotine. In fact, nicotine-N′-oxide inhibits the cocarcinogenic activity of TPA (*14, 188*). The concept of nicotine as a cocarcinogen in tobacco products is

TABLE 3.—Cocarcinogenic agents in the particulate matter of tobacco smoke[1]

	Compound[2]	Cocarcinogenic activity[3]	Ng/cig
I.	Neutral Fraction		
	Pyrene (-)	+	50–200
	Methylpyrenes (?)	?	50–300
	Fluoranthene (-)	+	100–260
	Methylfluoranthenes (+;?)	?	180
	Benzo(ghi)perylene (-)	+	60
	Benzo(e)pyrene (+)	+	30
	Other PAH (+)	?	?
	Methylnaphthalenes (-)	+	360–6300
	1-Methylindoles (-)	+	830
	9-Methylcarbazoles (-)	+	140
	4 and 4'-Dichlorostilbene (-)	+	1500 [4]
	Other or unidentified neutral compounds (?)	?	?
II.	Acidic Fraction		
	Catechol (-)	+	40,000–350,000
	3-Methylcatechol (-)	+	11,000–20,000
	4-Methylcatechol (-)	+	15,000–21,000
	4-Ethylcatechol (-)	+	10,000–24,000
	4-n-Propylcatechol (?)	?	≅ 5,000
	Other or unidentified catechols and phenols (?)	?	?
	Other or unidentified acidic agents (?)	?	?

[1] Incomplete list.

[2] In parenthesis complete carcinogenic activity on mouse skin; (?) unknown.

[3] + = active; ? = unknown.

[4] Value from 1966 U.S. cigarettes; today's values will be lower, because DDT and DDD decreased in the U.S. tobaccos.

SOURCE: Hoffmann et al. (*88*).

supported by the observation that the concentration of the alkaloids is closely correlated with the carcinogenic activity of the tested tars in four large-scale mouse skin bioassays (*14, 143*). More research is needed to elucidate the cocarcinogenic activity of nicotine, especially since it may also be correlated with the risk of tobacco chewers and snuff dippers for cancer of the oral cavity (*189, 200*).

Table 3 lists the identified cocarcinogens and their concentrations in cigarette smoke. Although certain PAH and catechols represent two major groups of tobacco cocarcinogens, others may be identified.

Organ-Specific Carcinogens

Cigarette smokers have an increased risk of cancer of the esophagus, pancreas, kidney, and urinary bladder (*189*). Since cigarette smoke does not directly come in contact with these organs, except for the esophagus, mechanisms other than contact carcinogenesis are involved in the pathogenesis of these cancers. Several hypotheses can be postulated for such mechanisms. Cigarette smoke contains organ-specific carcinogens and also agents that give rise to *in vivo* formation of carcinogens (*189*). Cigarette smoking may also

shift the metabolism of dietary components toward *in vivo* formation of carcinogenic metabolites (*109*), or may induce enzymes that convert environmental carcinogens to their ultimate active forms (*41*). Another concept relates to the presence in cigarette smoke of cocarcinogens that potentiate the activity of trace amounts of the carcinogens from environmental sources or of those formed *in vivo* (*189*).

Epidemiological and experimental studies have documented the occurrence of organ-specific carcinogens in certain occupational settings. Classic examples for these are 2-naphthylamine, 4-aminobiphenyl, and benzidine in dye factories (*149*); vinyl chloride in the chemical industry is a more recent example (*98*). Tobacco smoke, as a plant-combustion product containing more than 3,600 compounds (*61*), also contains organ-specific carcinogens which have been identified and studied by a number of groups.

N-Nitrosamines

N-Nitrosamines are formed *in vitro* and *in vivo* by nitrosation of amines. More than 50 of the approximately 100 N-nitrosamines which have been tested have various degrees of carcinogenic potency in laboratory animals (*127*). There is a lack of direct evidence that these compounds are also human carcinogens. Nonetheless, many scientists concur with the International Agency for Research on Cancer (*97*) that, for practical purposes, these nitrosamines should be regarded as carcinogenic in humans.

Tobacco and tobacco smoke contain three types of N-nitrosamines; namely, volatile nitrosamines (VNA), nitrosamines derived from residues of agricultural chemicals on tobacco, and the tobacco-specific nitrosamines (TSNA). These compounds are formed during tobacco processing and during smoking from precursors such as primary, secondary, and tertiary amines and quaternary ammonium salts (*97*), reacting with N-nitrosating agents such as nitrogen oxides, nitrite, and some C-nitro compounds (*149, 195*). It is also possible that the oxidation of certain amines can lead to nitrosamine formation (*147*).

Volatile N-Nitrosamines

A number of volatile N-nitrosamines (VNA) are present in tobacco products and tobacco smoke. Practically all of the VNA appear to be retained by the respiratory system upon inhalation of cigarette smoke (*38*). N-nitrosodimethylamine (NDMA) and N-nitrosopyrrolidine (NPYR) occur in the highest concentrations (Table 4) (*97, 158*). NDMA, N-nitrosoethylmethylamine, and N-nitrosodiethylamine (NDEA) are among the most potent environmental carcinogens in this class of compounds (*97*). Tumors of the respiratory tract were

TABLE 4.—Volatile N-nitrosamines in tobacco and tobacco products

Nitrosamine	Tobacco ppb	Chewing tobacco or snuff ppb	Cigarette smoke ng/cigarette
Nitrosodimethylamine	7–190 (*33*)	2–56 (*12a,33*)	4–180 (*33,79,130a*)
Nitrosoethylmethylamine			1–40 (*33,130a*)
Nitrosodiethylamine	0–15 (*33*)	8.6 (*12a*)	0.1–28 (*79,130a*)
Nitrosodi-n-propylamine			0–1 (*130a*)
Nitrosodi-n-butylamine			0–3 (*130a*)
Nitrosopyrrolidine		0.05–2.0 (*12a,30*)	0–110 (*33,130a*)
Nitrosopiperidine			0–9 (*30a*)
Nitrosomorpholine		20–700 (*30*)	(*130a*)

SOURCE: Hoffmann and Adams (*77*).

induced in 29 of 36 Syrian golden hamsters given only 6 mg of NDEA (*138*). The other identified VNA are strong to moderate organ-specific carcinogens (*97*). Although the hydrophilic VNA are primarily found in the vapor phase of fresh cigarette smoke, they are retained by a Cambridge filter. This glass fiber filter has been chosen arbitrarily to separate the gas phase from the smoke particulates and has been utilized for smoke gas phase inhalation studies. The selective retention of hydrophilic VNA from smoke by cellulose acetate filter tips of cigarettes can also be explained by the fact that moisture and the moist smoke particulate act as retainers. This selective retention can remove more than 80 percent of the VNA from mainstream cigarette smoke (*33, 139*).

Recent evidence has incriminated snuff dipping for an increased risk of cancer of the oral cavity (*77, 200*). Since fine cut tobacco and snuff contain high levels of VNA (Table 4) and other nitrosamines, special efforts should be made to reduce these quantities in tobaccos used for snuff dipping. The high concentration of VNA is a consequence of the high nitrate levels in these tobacco varieties, which range from 2 to 5 percent, and of long fermentation times under anaerobic conditions. N-nitrosomorpholine (NMOR) was also detected in relatively high concentrations (*30*) in several snuff samples. Protein and amino acids serve as major precursors for most VNA in processed tobacco and in smoke, but the origin of the precursor for NMOR remains unknown. NMOR is a relatively potent animal carcinogen (*97*), inducing primary liver tumors in mice and rats and tumors of the larynx, trachea, and lung in Syrian golden hamsters.

Metabolic activation of the simplest member of this group, dimethylnitrosamine (DMN), is presumed to involve α-hydroxylation of one methyl group, followed by loss of formaldehyde, to yield a monomethylnitrosamine. In turn, this unstable intermediate loses

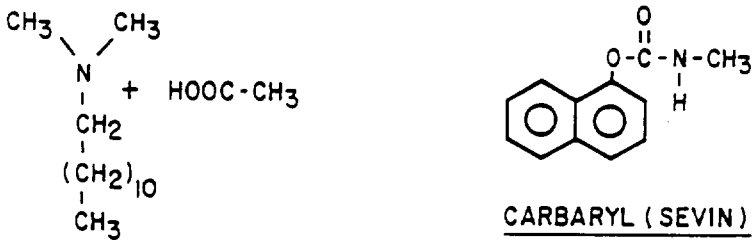
OH and nitrogen to form a methylating moiety that reacts with proteins and nucleic acids. In the latter, the N-7 and 0-6 positions are attacked. Both adducts were detected relatively soon after administration of DMN (*151*). The demethylative enzyme is a cytochrome P-450-dependent microsomal mixed-function oxidase that requires NADPH and 0_2 and can be inhibited by CO or by pretreatment of the animal with $CoCl_2$ which inhibits the synthesis of cytochrome P-450. Since ethanol is often consumed in conjunction with smoking, it is pertinent to note that in rats chronic consumption of ethanol enhanced the metabolism of DMN and the formation of mutagenic substances therefrom (*57, 131*). This observation is of special interest in view of human data showing an increased incidence of cancer of the oral cavity and esophagus in smokers who also drink large amounts of alcohol (*189*).

Diethylnitrosamine, the next higher member of the series, is also metabolized by α-oxidation to acetaldehyde and an ethylating species. In contrast, ω-oxidation of the alkyl chain of longer chain dialkylnitrosamines yielded hydroxy, keto, and carboxylic acid derivatives. Some of these metabolites, for example, N-nitroso-n-butyl-(4-hydroxybutylamine), were more active as bladder carcinogens than the parent N-nitrosodi-n-butylamine (*53*).

Like other acyclic and cyclic carcinogenic nitrosamines, NMOR undergoes metabolic α-hydroxylation to electrophilic diazohydroxide intermediates that may act as ultimate carcinogens (*73, 127*).

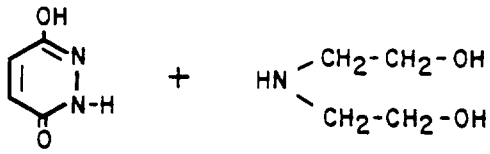
N-Nitrosodiethanolamine

Among the agricultural chemicals used for the cultivation of tobacco crops are found several amines, amides, and carbamates. These include dimethyldodecylamine (Penar), maleic hydrazide diethanolamine, and carbaryl (Sevin) as a representative of the ethyl urethanes (Figure 3) (*186, 202*). Small residual amounts of these agents were found on harvested tobacco (*169*). Diethanolamine has been studied as a possible precursor for nitrosodiethanolamine (NDELA), a carcinogen found in tobaccos (0.1 to 6.8 ppm) that were treated with the sucker growth inhibitor maleic hydrazide diethanolamine. The smoke of tobaccos thus treated contained 10 to 40 ng per cigarette of NDELA. Snuff contains especially high levels of 3.2 to 6.8 ppm of NDELA (*31*). This nitrosamine induces carcinoma of the kidney and liver of rats (*97, 123*) and carcinoma of the trachea of hamsters following subcutaneous injection, painting the skin, or swabbing the oral cavity (*83, 97*). NDELA penetrates rat (*122*) and human skin (*54*) and is primarily excreted via the urinary tract (*122, 153*).



DIMETHYLDODECYLAMINE-ACETATE (PENAR)

CARBARYL (SEVIN)



MALEIC HYDRAZIDE — DIETHANOLAMINE (MH-30)

FIGURE 3.—Agricultural chemicals for tobacco cultivation
SOURCE: Tso (*186*), and Wynder and Hoffmann (*202*).

Tobacco-Specific N-Nitrosamines

Commercial tobaccos in the United States contain 0.5 to 2.7 percent alkaloids, 85 to 95 percent of which is nicotine. Important minor alkaloids are nornicotine, anatabine, anabasine, cotinine, and N'-formylnornicotine (Figure 4). Several of these alkaloids are secondary and tertiary amines and, as such, are amenable to N-nitrosation. Tobacco and tobacco smoke were shown to contain N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanatabine (NAT), and N'-nitrosoanabasine (NAB). In model experiments, nitrosation of nicotine also yielded 4-(methylnitrosamino)-4-(3-pyridyl)butanal (NNA), which has not as yet been identified in tobacco nor in the smoke (*71, 78*).

In experiments with ^{14}C-labeled nicotine, 0.009 percent of this alkaloid is nitrosated to NNN during the curing of Burley tobacco (*68*). Of the NNN in cigarette smoke, 41 to 46 percent originates from the NNN in tobacco by transfer, and the remainder is pyrosynthesized primarily from nicotine (*80*).

Table 5 presents data for tobacco-specific N-nitrosamines (TSNA) in the tobacco and smoke of cigarettes and cigars (*80*). In addition, it must be noted that cigarette smoke contains traces of NAB (up to 0.015 μg/cig). Recent studies carried out on popular snuff tobaccos from the United States, Denmark, Germany, and Sweden revealed 5.5 to 106 ppm of TSNA in these materials, the highest levels of

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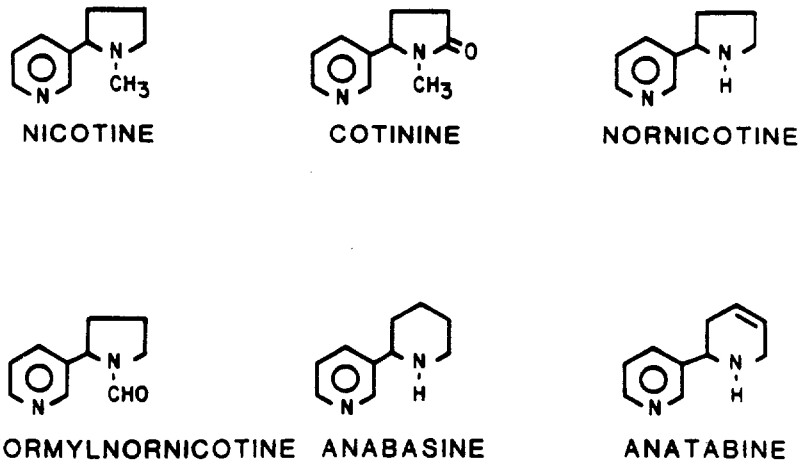


FIGURE 4.—Common tobacco alkaloids in tobacco and tobacco smoke

SOURCE: Hoffmann et al. (*80*).

TABLE 5.—Tobacco specific N-nitrosamines in tobacco products

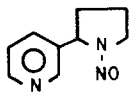
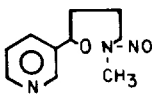
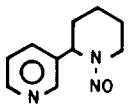
Nitrosamines	Tobacco ppm	Chewing tobacco or snuff ppm	Cigarette smoke μg/cigarette	Cigar smoke μg/cigar
N'-Nitrosonornicotine	0.2 - 45	3.5 - 77	0.2 - 3.7	3.2 - 5.5
NNK[a]	0.1 - 35	0.8 - 4.7	0.12 - 0.44	1.9 - 4.2
N'-Nitrosoanabasine	0.0 - 0.01	0.04 - 1.9	0.0 - 0.15	n.d.[b]
N'-Nitrosoanatabine	0.6 - 13	0.8 - 44	0.15 - 4.6	1.7 - 1.9

[a] NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
[b] n.d. = not determined.
SOURCE: Hoffmann et al. (*78, 79*).

carcinogenic nitrosamines reported in a consumer product that is taken into the body. The saliva of snuff dippers yielded TSNA levels at concentrations of 0.02 to 0.9 ppm (*77*). These observations are of relevance to the epidemiological findings of increased risk for cancer of the oral cavity in snuff dippers (*200*). The importance of the carcinogenic TSNA is underscored in that these compounds can also be formed within the oral cavity during snuff dipping (*68*).

At this time, there is no experimental evidence on the formation of TSNA in the lung upon inhalation of cigarette smoke. However, a smoker of one or two packs of cigarettes daily retains 20 to 60 mg of nicotine, 1 to 4 mg of nornicotine, 1.5 to 6 mg of anatabine, and 0.2 to 0.8 mg of anabasine, and inhales 0.3 to 24 mg of NO_x. Thus, *in vivo* formation of tobacco-specific N-nitrosamines is a real possibility.

TABLE 6.—Carcinogenic activity of tobacco-specific nitrosamines

Compounds	Species	Application	Principal organ affected
 NNN	Mouse	I.P.	Lung (Adenoma, Adenocarcinoma) Salivary glands (?)
	Rat	S.C. P.O. (Water)	Nasal cavity (Carcinoma) Esophagus (Papilloma, Carcinoma) Pharynx (Papilloma) Nasal cavity (Carcinoma)
	Hamster	S.C.	Trachea (Papilloma) Nasal cavity (Carcinoma)
 NNK	Mouse	I.P.	Lung (Adenoma, Adenocarcinoma)
	Rat	S.C.	Nasal cavity (Carcinoma) Liver (Hepatocarcinoma) Lung (Adenoma, Carcinoma)
	Hamster	S.C.	Lung (Adenoma, Adenocarcinoma) Trachea (Papilloma) Nasal cavity (Carcinoma)
 NAB	Rat	P.O. (Water) S.C.	Esophagus (Carcinoma) Esophagus (Papilloma) Pharynx (Papilloma)
	Hamster	S.C.	Inactive (375 mg/hamster)

The data for the carcinogenicity of NNN, NNK, and NAB are summarized in Table 6 (*23, 70, 84*); NAT assay results are not as yet reported. NNK is by far the most potent carcinogen of the TSNA. In the Syrian golden hamster, NNK has about the same carcinogenic potency as N-nitrosomorpholine and about twice the activity of N-nitrosopyrrolidine, but it has only about one-tenth of the activity of N-nitrosodiethylamine, which is the most potent carcinogenic nitrosamine in hamsters.

The influence of alcohol as a dietary component on NNN carcinogenicity was assayed in the Syrian golden hamster at two dose levels. The data did not show an accelerating effect of the alcohol on NNN carcinogenicity in the test animals whose total caloric intake was equal to that of the control animals (*131*). The metabolic pathways of NNN and NNK have been studied in rats and hamsters (*73, 74, 84*). As was seen with other acyclic and cyclic nitrosamines, the metabolic activation of these TSNA involves most likely also *via* α-hydroxylation (*73, 127*). Figures 5 and 6 depict the

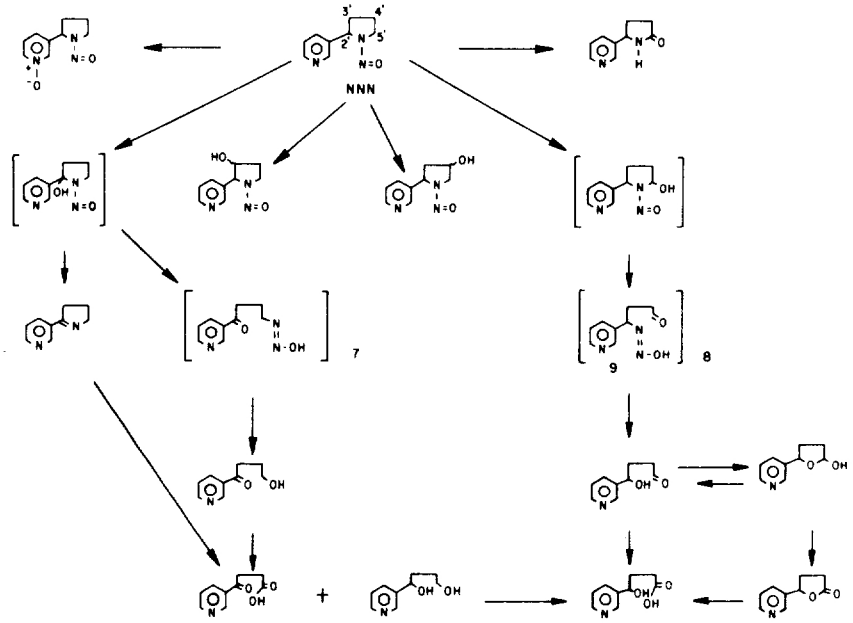


FIGURE 5.—Metabolism of NNN in rats and Syrian golden hamsters

SOURCE: Hecht et al. (*73*).

metabolic pathways of NNN and NNK (*73, 74*). Among the stable metabolites, NNN-N'-oxide and NNK-N'-oxide, as well as the secondary alcohol formed by reduction by NNK (Figure 6, formula 2), are most likely also carcinogens, based on induction of lung adenomas in strain A mice. The electrophilic diazohydroxide intermediates of NNN (Figure 5, formulas 7 and 8) and of NNK (Figure 6, formulas 7 and 9), respectively, or the resulting carbonium ions are probably the ultimate carcinogenic forms of these tobacco-specific nitrosamines. Assays of NNN metabolites obtained by incubation of the carcinogen with human liver microsomes showed that five out of six human liver specimens tested contained the enzymes that effected NNN activation by α-hydroxylation (*69*).

Two autoradiographic studies and one biochemical report on the distribution of [2'-^{14}C]NNN and [1-^{14}C]NNK in mice and hamsters, respectively, have shown that the metabolites of these labeled nitrosamines are bound to macromolecules of the tracheobronchial and nasal mucosa and to kidney, liver, sublingual and submaxillary glands, esophagus, and melanin of the eye (*25, 84, 196*). These data indicate that the binding of metabolites to the tissues of specific organs does not by itself explain the organ-specificity of the TSNA.

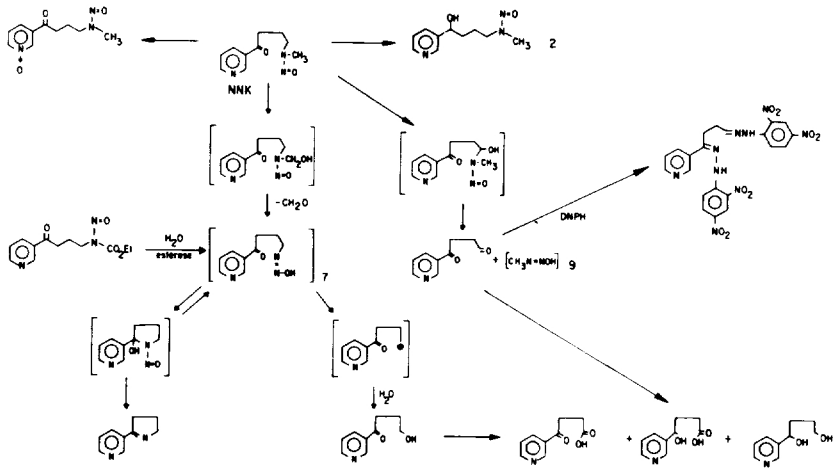


FIGURE 6.—Metabolism of NNK in rats and Syrian golden hamsters

SOURCE: Hecht et al. (*74*).

Other aspects such as the DNA repair of the affected cells must be considered.

Aromatic Amines and Aromatic Nitrohydrocarbons

The incomplete combustion of organic matter yields C,H-radicals, which serve as precursors for benzene, naphthalene, or PAH (*5*). In the burning cone of a cigarette, the aromatic hydrocarbons or their radicals react with nitrogen oxides to form nitrobenzene, nitronaphthalenes, or nitro-PAH (*85, 150*). These can be reduced to aromatic amines in the oxygen deficient zones. Aromatic amines may also be formed directly from proteins and amino acids (*129*). The presence of both aromatic nitrohydrocarbons and aromatic amines and their dependence on the nitrate concentration in the tobacco is thus not surprising (*85, 150*). Tables 7 and 8 list the data available at present on these compounds in cigarette smoke. 4-Nitrocatechol and other nitrophenols are also present in cigarette smoke. The reported values of 200 ng/cigarette of 4-nitrocatechol and also the values for other nitrophenols require verification, since they were obtained without the precautions that prevent artifacts during smoke collection and analysis (*106, 111*).

Epidemiological data from dye workers have documented that certain aromatic amines such as 2-naphthylamine and 4-aminobiphenyl are human bladder carcinogens (*149*). Some *o*-aminotoluenes induce cancer in animals (*39*). On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in human bladder cancer is

TABLE 7.—Nitroarenes and nitrophenols in cigarette smoke

Nitro compound	μg/cigarette[a]
Nitrobenzene	25.3
2-Nitrotoluene	21.4
3-Nitrotoluene	10.4
4-Nitrotoluene	19.6
2-Nitro-1,4-dimethylbenzene	
4-Nitro-1,2-dimethylbenzene	6.5
4-Nitro-1,3-dimethylbenzene	18.5
4-Nitrocumene	5.3
2-Nitrophenol	35
3-Nitrophenol	+
4-Nitrophenol	20
2-Nitro-3-methylphenol	30
2-Nitro-4-methylphenol	90
4-Nitro-3-methylphenol	+
2-Nitro-5,6-dimethylphenol	+
4-Nitrocatechol	200

[a] + = present
SOURCE: Schmeltz and Hoffmann (*164*).

questionable, even if one were to consider the total of the aromatic amines and their active metabolites, which may be formed *in vivo* from aromatic nitrohydrocarbons of the smoke. However, Doll (*45*) concluded that 2-naphthylamine (together with other aromatic amines) may suffice to explain the increased bladder cancer risk for cigarette smokers working in gasification plants.

Although the importance of traces of aromatic amines in smoke for the increased bladder cancer risk of smokers is disputed, there may be reason for concern about the increasing levels of nitrate in present-day cigarettes (1.2 to 1.5 percent). Twenty years ago, these levels were only about 0.5 percent. The increased potential for formation of aromatic amines and of N-nitrosamines should be studied carefully.

The metabolic detoxification and activation of 2-naphthylamine (2-NA) have been studied intensively (*22, 155*). Many detoxification products have been identified; most are hydroxylated derivatives that can also be excreted as sulfuric acid or glucosiduronic acid conjugates. Premercapturic and mercapturic acids have also been identified. However, the evidence points toward an N-hydroxy derivative of 2-NA as the active carcinogen rather than the parent compound. Furthermore, an N-glucuronide appeared to be the transport form. 2-NA or the N-hydroxy derivative form adducts with guanine in nucleic acids (*103*), and other adducts have also been identified (*105*). By analogy to the situation with 1-hydroxynaphthylamine, the O-6 position of guanine is arylaminated (*104*). The

TABLE 8.—Aromatic amines in cigarette smoke

Aromatic amine	ng/cigarette [a]
Aniline	100 - 1,200
2-Toluidine	32
3-Toluidine	15
4-Toluidine	14
2,3-Dimethylaniline	8
2,4-Dimethylaniline	14
2,5-Dimethylaniline	+
2,6-Dimethylaniline	15
3,4-Dimethylaniline	+
3,5-Dimethylaniline	+
2-Ethylaniline	+
3-Ethylaniline	+
4-Ethylaniline	+
2,4,6-Trimethylaniline	+
2-Methylaniline	+
3-Methylaniline	+
3-Methoxyaniline	+
4-Methoxyaniline	+
Diphenylamine	+
1-Naphthylamine	4.3 - 27
2-Naphthylamine	1.0 - 22
2-Methyl-1-naphthylamine	5.8
2-Aminobiphenyl	1.8
3-Aminobiphenyl	2.7
4-Aminobiphenyl	2.4
2-Aminostilbene	+

[a] + = present
SOURCE: Patrianakos and Hoffmann (*150*) and Schmeltz and Hoffmann (*164*).

biological significance of the different adducts has not been delineated as yet.

Although N-hydroxylation also occurs during metabolism of 2-aminostilbene (*145*), the N-hydroxy group does not participate in formation of nucleic acid adducts. Instead, the ethylenic bond of the stilbene forms adducts at the N-1 and N-6 of adenosine or similar adducts with the nitrogens in other bases (*167, 168*).

A definitive experiment on the metabolism of *o*-toluidine showed that acetylation of the amino group and hydroxylation at the 4-position of the ring were the major pathways during metabolism (*173*). Mainly sulfate and to a lesser extent glucuronide conjugates of the cresols thus formed were also excreted. There was some oxidation of the methyl group to a hydroxymethyl or carboxylic acid. Another minor pathway was oxidation of the amino group, since azoxytoluene and nitrosotoluene were identified. Whether these metabolites were derived from an N-hydroxy-*o*-toluidine was not delineated.

Polonium-210

In 1964, Radford and Hunt (*154*) suggested that bronchogenic carcinoma in cigarette smokers could be induced by the α-particle emitter polonium-210 (^{210}Po). Since then, a number of studies have reported varying quantities of ^{210}Po in the smoke (0.03 to 1.0 pCi per cigarette) (*66, 202*). Harley et al. (*66*) gathered data for ^{210}Po in cigarette tobaccos from many countries and calculated 0.45 pCi of the radioactive element per gram tobacco as a median value. Major sources for ^{210}Po in tobacco are airborne particles, taken up by the glandular hair of the tobacco leaf, as well as lead-210 (^{210}Pb) and ^{210}Po from soil that is fertilized with certain phosphates (*128, 187*). Thirty to fifty percent of ^{210}Po in the cigarette tobacco were reported to be transferred into the mainstream smoke of cigarettes; up to 90 percent of ^{210}Po can be retained by filter tips (*24*).

Upon inhalation, ^{210}Po produces tumors of the lung in rats (*204*). Tests with multiple intratracheal instillations of ^{210}Po in Syrian golden hamsters revealed a dose-response relationship in regard to bronchocarcinoma and adenocarcinoma in the peripheral lung (*108*). Simultaneous multiple instillations of benzo[a]pyrene (total dose 4.5 mg) and ^{210}Po (total dose 50,000 pCi) on the same carrier induced about twice the number of tumors expected from the additive effect of the two carcinogens (*124*).

Lead-210 (^{210}Pb), the grandparent of ^{210}Po, is found in all environmental atmospheres (0.01 pCi ^{210}Pb/m^3 and 0.003 pCi ^{210}Po/m^3). The daily exposure of a cigarette smoker to ^{210}Pb has been estimated to be 2.5 to 3.0 times greater than that of a nonsmoker (*66*). Harley et al. (*66*) reviewed 12 studies that had determined ^{210}Po in the parenchyma of the lungs and in the bronchial tissues of cigarette smokers, ex-smokers, and nonsmokers. The studies showed general agreement that ^{210}Po is stored in the parenchyma of smokers at three times higher levels than in nonsmokers and that it also persists in the bronchial mucosa of smokers in higher concentrations than in nonsmokers.

From comparisons of radon-daughter exposure of underground miners with their relative risk of lung cancer, Harley et al. deduced that ^{210}Po is a questionable risk factor for lung cancer in cigarette smokers. They recommend, nevertheless, that methods for lowering ^{210}Po levels in tobacco should be considered (*66*).

Nickel

A large number of studies from the United States and from other countries have shown that the tobacco of one cigarette contains 2 to 14 μg of nickel (*141, 202*). Analyses have determined that 10 to 20 percent of the nickel in cigarettes is transferred into the mainstream smoke (*141*). In one study, it was found that an average of 84 percent

of the nickel is present in the gas phase (*183*), indicating that cigarette smoke may contain nickel carbonyl.

The possible existence and relative stability of nickel carbonyl in cigarette smoke is indirectly supported by several observations. Sunderman et al. (*181*) found nickel carbonyl in the exhaled air as well as in the blood of man. Stähly (*176*) reported that passing carbon monoxide through an unlit cigarette column removed much of the nickel from the tobacco. Nickel has also been found in pipe tobacco 0.5 to 10 μg/cig), cigars (1.9 to 15 μg/cigar), and in U.S. snuff (2 to 3 μg/g) (*141*).

The presence of nickel in tobacco smoke is an important finding regardless of whether it is in the form of nickel carbonyl or in other forms, because nickel itself and several nickel compounds are carcinogenic in laboratory animals, inducing sarcomas by subcutaneous injection and rhabdomyosarcomas upon intramuscular injection. It appears that nickel subsulfide (Ni_3S_2) is a strongly sarcogenic agent (*96, 141*). Intrarenal injection of a single dose of 5 mg Ni_3S_2 induced a high rate of renal carcinomas in rats (*180*). Exposure of rats for 30 minutes three times weekly for 1 year to an atmosphere containing 30 to 60 μg of nickel carbonyl produced pulmonary carcinoma in two of six animals (*179*).

Workers in nickel refineries in England and Canada were reported to have excessive rates of cancer of the nasal cavity and of the lung. Studies from Japan, the U.S.S.R., and the German Democratic Republic also reported increased incidences of lung cancer among nickel workers. The International Agency for Research on Cancer (*96*) concluded on the basis of epidemiological studies that workers in nickel refineries have an increased risk for cancer of the nasal cavity and of the lung. Although it is not likely that nickel plays a significant role in the etiology of lung cancer in cigarette smokers (*141*), prudence dictates that efforts should be made to reduce the amount of this metal in tobacco and to avoid contamination of tobacco with nickel during cutting and other processes in cigarette manufacture.

Arsenic

Extensive studies have been conducted on paired soil residues in tobacco. From 1932 to 1951, arsenical pesticides were used on tobacco in the United States. During this time, the arsenic content of U.S. cigarettes rose from 12.6 to 42 μg/cigarette (*63*). In 1952, arsenicals were removed from the list of recommended insecticides for control of hornworms on tobacco. Since then, a sharp decrease in the arsenic content of cigarette tobacco has occurred. Guthrie (*62*) concluded in 1968 that arsenic residues in U.S. cigarettes do not exceed 2 ppm and are normally about 1 ppm or less and that tobacco is no greater source of arsenic for consumers than food. The last reported data for

U.S. tobacco range between 0.5 and 0.9 ppm. The arsenic now found in tobacco appears to come primarily from natural sources (*63*). Between 7 and 18 percent of the total arsenic on tobacco leaves is recovered in the mainstream smoke of cigarettes. Studies with ^{74}As-labeled cigarettes have shown that, depending on the individual's smoking pattern, 2.2 to 86 percent of the arsenic in cigarette tobacco is transferred to the respiratory tract. About 50 percent of the inhaled arsenic is eliminated within 10 days, primarily in urine, the remainder is either deposited in tissues, exhaled or otherwise eliminated (*91*).

Skin cancers have been reported to be particularly prevalent among people exposed to arsenicals through drugs, drinking water, or pesticides. The anatomic sites of these tumors suggest that they are causally associated with exposure to arsenic. Lung cancer has been associated with inhalation exposure to arsenicals in copper smelters, workers in pesticide manufacturing plants, Mosel vineyards, and Rhodesian gold mines (*99, 142*). The International Agency for Research on Cancer (*99*) concluded in its review, "There is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans." The U.S. National Academy of Sciences (*142*) arrived at a similar conclusion, but also mentioned that exposure to arsenicals or other metals and to sulfur dioxide may constitute carcinogenic cofactors for an increased risk for lung cancer of miners and metal workers. The view that inorganic arsenicals cause cancer of the skin and lung has not been widely accepted, since these compounds have not produced cancers in experimental animals (*101, 118, 142, 170*). Ivankovic et al. (*101*) reported in 1979 the induction of lung carcinomas in rats after a single intratracheal instillation of an arsenic-containing pesticide mixture, such as those formerly used by vineyard workers. Of the 15 rats exposed, 7 developed bronchogenic adenocarcinoma and 2 had bronchioalveolar carcinoma following a single instillation of 0.07 mg of arsenic as calcium arsenate.

Cadmium

Several forms of cadmium (Cd) are carcinogenic in experimental animals (*95*). Two studies indicate that occupational exposure to cadmium oxide is associated with an increased risk for prostatic cancer. It has been suggested that a heavy smoker who is exposed by inhalation to 70 to 90 ng Cd per cigarette retains 1.5 μg of Cd per day and may accumulate up to 0.5 mg (*95*).

In Table 9 is summarized the present knowledge of the presence of organ-specific carcinogens in cigarette smoke. Special importance in this group of carcinogens should be given to the tobacco-specific N-nitrosamines, since these are found only in the *Nicotiana* varieties, and appear in high concentrations in tobacco products. They are

TABLE 9.—Organ-specific carcinogens in cigarette smoke

Smoke carcinogen	Amount per cigarette
Nitrosodimethylamine	4 - 180 ng
Nitrosoethylmethylamine	1 - 40 ng
Nitrosodiethylamine	0.1 - 28 ng
Nitrosodi-n-butylamine	0 - 3 ng
Nitrosopyrrolidine	0 - 110 ng
Nitrosopiperidine	0 - 9 ng
Nitrosodiethanolamine	0 - 40 ng
N'-Nitrosonornicotine	0.2 - 3.7 μg
NNK[a]	0.12 - 0.44 μg
N'-Nitrosoanabasine	0 - 0.15 μg
N'-Nitrosoanatabine	0.15 - 4.6 μg
2-Naphthylamine	4.3 - 27 ng
4-Aminobiphenyl	2.4 - 4.6 ng
Polonium-210	0.03 - 1.0 pCi
Nickel	0 - 3 μg

[a]NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
SOURCE: Brunnemann and Hoffmann (*29*), Brunneman et al. (*33*), and Patrianakos and Hoffmann (*150*).

moderately active animal carcinogens or, as in the case of NNK, a potent animal carcinogen.

Sidestream Smoke

The sidestream smoke (SS) is a composite of effluents generated in different ways during the burning and smoking of a tobacco product. While the product smoulders in between puff taking, smoke is freely emitted into the air; during puffing a little smoke escapes from the burning cone, and vapor phase components diffuse partially through the cigarette paper. The SS, generated between puffs, originates from a hydrogen-enriched, strongly reducing atmosphere. It contains, therefore, combustion products formed by thermal cracking and compounds that result from reactions involving nitrates in greater proportions than are found in mainstream smoke (MS). These compounds include nitrogen oxides, nitrosamines, ammonia and amines, and total particulate matter. Table 10 lists the known SS/MS ratios for major toxic and tumorigenic agents.

The SS/MS ratios are especially high for volatile nitrosamines and for the nitrogen oxides, which constitute major precursors for *in vitro* and *in vivo* formation of nitrosamines. The relevance of this finding in regard to the SS exposure of nonsmokers in closed environments has been repeatedly discussed (*26, 29, 158, 189*). The SS components are diluted by air prior to being inhaled and the particulates settle rather quickly on environmental surfaces. Deep and intentional inhalation of MS delivers a far greater burden of

TABLE 10.—Toxic and tumorigenic agents of cigarette smoke; ratio of sidestream smoke (SS) to mainstream smoke (MS)

A. Gas phase	Amount/cigarette				SS/MS
Carbon dioxide	10	-	80	mg	8.1[1]
Carbon monoxide	0.5	-	26	mg	2.5[1]
Nitrogen oxides (NO_x)	16	-	600	µg	4.7 - 5.8
Ammonia	10	-	130	µg	44 - 73
Hydrogen cyanide	280	-	550	µg	0.17 - 0.37
Hydrazine			32	µg	3
Formaldehyde	20	-	90	µg	51
Acetone	100	-	940	µg	2.5 - 3.2
Acrolein	10	-	140	µg	12
Acetonitrile	60	-	160	µg	10
Pyridine			32	µg	10
3-Vinylpyridine			23	µg	28
N-Nitrosodimethylamine	4	-	180	ng	10 - 830
N-Nitrosoethylmethylamine	1.0	-	40	ng	5 - 12
N-Nitrosodiethylamine	0.1	-	28	ng	4 - 25
N-Nitrosopyrrolidine	0	-	110	ng	3 - 76

B. Particulate phase	Amount/cigarette				SS/MS
Total particulate phase	0.1	-	40	mg	1.3 - 1.9[1]
Nicotine	0.06	-	2.3	mg	2.6 - 3.3[1]
Toluene			108	µg	5.6
Phenol	20	-	150	µg	2.6
Catechol	40	-	280	µg	0.7
Stigmasterol			53	µg	0.8
Total phytosterols			130	µg	0.8
Naphthalene			2.8	µg	16
1-Methylnaphthalene			1.2	µg	26
2-Methylnaphthalene			1.0	µg	29
Phenanthrene	2.0	-	80	ng	2.1
Benz(a)anthracene	10	-	70	ng	2.7
Pyrene	15	-	90	ng	1.9 - 3.6
Benzo(a)pyrene	8	-	40	ng	2.7 - 3.4
Quinoline			1.7	µg	11
Methylquinoline			6.7	µg	11
Harmane	1.1	-	3.1	µg	0.7 - 2.7
Norharmane	3.2	-	8.1	µg	1.4 - 4.3
Aniline	100	-	1,200	ng	30
o-Toluidine			32	ng	19
1-Naphthylamine	1.0	-	22	ng	39
2-Naphthylamine	4.3	-	27	ng	39
4-Aminobiphenyl	2.4	-	4.6	ng	31
N'-Nitrosonornicotine	0.2	-	3.7	µg	1 - 5
NNK[2]	0.12	-	0.44	µg	1 - 8
N'-Nitrosoanatabine	0.15	-	4.6	µg	1 - 7
N-Nitrosodiethanolamine	0	-	40	ng	1.2

[1] In cigarettes with perforated filter tips the SS/MS ratio rises with increasing air dilution. In the case of smoke dilution with air to 17 percent, the SS/MS ratios for TPM rise to 2.14, CO_2 36.5, CO 23.5, and nicotine to 13.1

[2] NNK = 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.

SOURCE: Hoffmann et al. (82).

respiratory pollutants to the lungs than does normal breathing

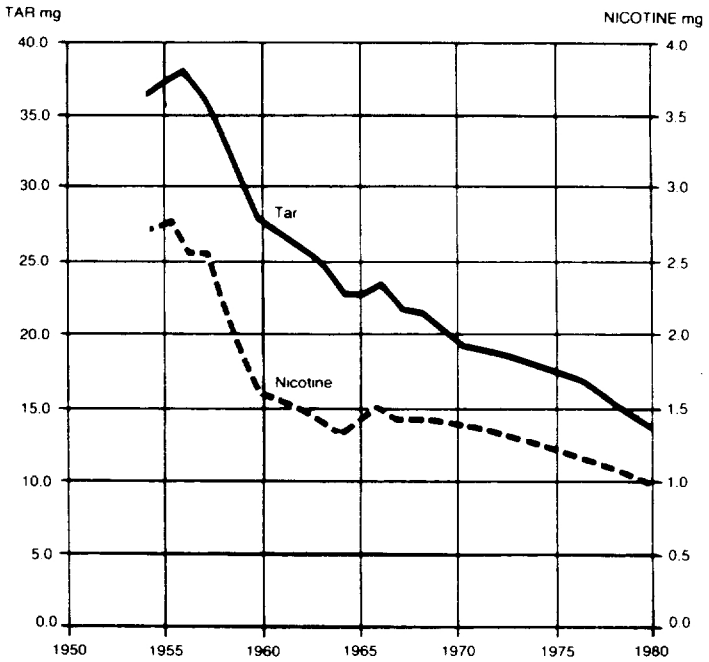


FIGURE 7.—U.S. sales-weighted average tar and nicotine yields

SOURCE: American Cancer Society (*1*).

during regular nonoccupational activities.

Reduction of Tumorigenic Potential

The trends for the sales-weighted average tar and nicotine deliveries of U.S. cigarettes since 1955 (≅37 mg tar, 2.7 mg nicotine) until 1980 (≅14 mg tar, 1.0 mg nicotine) are shown in Figure 7 (*1*). During this time, the percentage of filter-tipped cigarettes in U.S. cigarette production increased from 18.7 to 90 percent.

The agricultural aspects and methods of tobacco processing and product manufacturing leading to changes in smoke composition, toxicity, and carcinogenicity have been discussed in previous Surgeon General's Reports (*188, 189*) and elsewhere (*60, 89*). Table 11 summarizes the average machine-smoked values of selected smoke components for the cigarette before 1960 and during 1978–79, as well as the average values for a leading low-tar U.S. cigarette with a perforated filter tip (*89*).

A significant reduction of carbon monoxide in cigarette smoke did not occur until cigarettes with perforated filter tips were introduced (Table 12; *89*). A recent publication reported that the average

TABLE 11.—Changes in smoke composition of cigarettes manufactured in the United States

Smoke constituent	Average delivery per cigarette		
	Before 1960	1978/79	1978/79 (Low-tar cigarette)
Total particulate matter	43	16	8
Nicotine (mg)	3.0	1.1	0.6
CO (mg)	23	17	8.9
NO_x (μg)	270	280	100
HCN (μg)	410	200	130
Acrolein (μg)	130	80	50
Phenol (μg)	100	60	20
Benzo[a]pyrene (ng)	35	18	10

SOURCE: Hoffmann et al. (*89*).

cigarette sold in the United Kingdom between 1934 and 1940 (>99 percent plain cigarettes) delivered under standard smoking conditions 32.9 mg tar, 2.0 mg nicotine, and 18.6 mg carbon monoxide (*197*). In contrast, in 1979 the average cigarette in the United Kingdom (9 percent plain tobacco, 77 percent unventilated filter brands, and 14 percent ventilated filter cigarettes) delivered 16.8 mg tar, 1.39 mg nicotine, and 16.6 mg carbon monoxide. The authors also point out that there was a sizeable decrease since 1934 in delivery of tar (49 percent) and nicotine (31 percent), but only an 11 percent decrease in carbon monoxide delivery. The average U.K. unventilated filter cigarette of 1979 delivered 18.1 mg carbon monoxide and the average ventilated filter cigarette delivered 12.0 mg carbon monoxide (*197*). This finding and the values of Table 12 support the concept that filter perforation is the most important development for the reduction of carbon monoxide in cigarette smoke.

The reported data are based on measurements obtained by machine smoking of cigarettes under standard conditions. As discussed before, these conditions may have reflected the average smoking habits of individuals 25 years ago, but today they appear to be representative of less than 10 percent of U.S. smokers. Russell and coworkers (*160*), as well as others (*75, 76*), reported that some smokers of lower tar, lower nicotine cigarettes will intensify smoking and inhalation in order to satisfy a physiological need for nicotine and cotinine. A statistical reevaluation (*113*) of the data of Russell et al., however, showed that the nicotine blood serum levels of smokers of cigarettes with perforated filter tips were, in fact, lower than those of other cigarette smokers. On the basis of model studies, it also appears unlikely that a smoker of perforated filter cigarettes can increase his smoking intensity to such a degree that he can fully compensate for the loss in nicotine delivery without significantly

TABLE 12.—Carbon monoxide in smoke of cigarettes

Commercial product	Carbon monoxide (mg/cigarette)		
	Nonfilter	Regular filter	Perforated filter
U.K. (1975)*	9.0–16.0 (N=9)	13.0–18.0 (N=10)	—
U.K. (1979)**	10.9	18.1	12.0
Germany (1975)	16.0–21.0 (N=7)	15.5–22.5 (N=17)	—
Germany (1978)	14.5–19.9 (N=16)	8.6–18.5 (N=15)	2.2–13.8 (N=9)
U.S.A. (90% of av. 1977/78 sales)***	11.0–17.0 (N=8)	14.4–20.0 (N=23)	2.8–12.8 (N=9)
U.S.A. (FTC - 1981)	13.0–22.0 (N=18)	13.0–26.0 (N=87)	0.5–13.0 (N=82)

* Average values for nonfilter cigarettes, 12.5 mg; for filter cigarettes, 16.1 mg.

** Sales-weighted average carbon monoxide yields, average of all U.K. brands, 16.6 mg. Wald et al. (*200*)

*** Average values for nonfilter cigarettes, 14.9 mg; for regular filter cigarettes, 17.1 mg; for perforated filter cigarettes, 8.9 mg.

SOURCE: Hoffmann et al. (*89*).

increasing his daily cigarette consumption (*81*). The increase in smoking intensity by the smoker of perforated filter cigarettes may lead to an increase in the delivery of carcinogenic tar.

In addition to these changes in the pattern of smoking, smokers of lower tar and nicotine products may increase their actual dose of smoke constituents over that predicted by machine measurements through voluntary or involuntary blocking of the ventilation holes in filters. Kozlowski et al. (*112*) examined the effect of partial and total occlusion of perforations on machine measurement of tar, nicotine, and carbon monoxide in one brand of lower tar cigarettes. With full occlusion, he found that the nicotine yield increased 118 percent, the tar yield increased 186 percent, and the carbon monoxide yield increased 293 percent. He reported survey results of from 32 to 69 percent (95 percent confidence limits) of lower tar smokers had blocked holes with fingers, lips, or tape. Further research is necessary to define the actual impact of occlusion of ventilations in filters on actual smoker exposure.

The development of the low-tar cigarette required enrichment of smoke flavors in order to make the product acceptable to the consumer. The flavor is enhanced by the addition of undescribed materials that may include concentrates of flavor precursors obtained from tobacco, licorice, extracts from other plants, or semisynthetic or fully synthetic flavor components. Because these additives

have not been identified, no judgment can be made as to whether they result in new compounds or in higher concentrations of hazardous components in the smoke. The practice of flavor enrichment requires detailed toxicological studies that are not available at present for scientific evaluation of their health impact (*116a, 189*).

Research Needs and Priorities

Tobacco carcinogenesis has been intensively studied for more than 25 years by epidemiologists, chemists, biochemists, toxicologists, and pathologists. As a result, there is a much expanded knowledge of the major factors contributing to the toxicity and carcinogenicity of cigarette smoke. Nonetheless, significant gaps in that knowledge remain.

Benign and malignant tumors have been induced in the larynx of hamsters by long-term exposure to diluted cigarette smoke. Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains. Neither rats nor hamsters nor baboons inhale cigarette smoke as deeply and as intensely as the cigarette smokers who have provided the data with the consequences of their "experiment" in the form of clinical evidence gathered by epidemiologists. In view of this compelling evidence, it appears that the experimental induction of bronchogenic carcinoma should receive limited priority as a research goal.

However, major efforts should be devoted to the elucidation of the steps involved in the formation of lung tumors. Such investigations must attempt to answer the following questions: Does cigarette smoke induce enzymes that activate tumor initiators and carcinogens to their ultimate active forms? Are certain carcinogens, such as tobacco-specific N-nitrosamines, formed from smoke components in the lungs? Can the *in vivo* formation of such carcinogens in the lung be prevented? Is it feasible to inhibit metabolic activation and DNA binding of tobacco smoke carcinogens by chemopreventive measures? Both prospective and retrospective studies have indicated that cigarette smokers with low serum vitamin A levels have an increased risk for lung cancer compared with cigarette smokers with normal or high vitamin A levels (*133, 198*). Evidence from *in vivo* and *in vitro* studies in carcinogenesis has supported the protective role of vitamin A (*115*). Studies of the specific effects of vitamin A and retinoic acid on the induction of lung tumors by tobacco carcinogens are thus needed.

So far, only limited attention has been given to mechanisms of induction of cancer of the esophagus, pancreas, kidney, and urinary bladder by tobacco smoke. Initial experiments support the concept that certain nutritional deficiencies such as those of zinc and

vitamin A may increase the susceptibility of the esophageal epithelium to insults from tobacco smoke constituents. Whether tobacco smoke as an enzyme inducer may be indirectly responsible for increased metabolic activation of organ-specific carcinogens in the esophageal epithelium needs to be determined.

Only a few studies have been concerned with the effect of tobacco smoke and its nicotine level on the biochemistry and function of the pancreas in smokers and in laboratory animals (*7, 140*). It needs to be determined whether nicotine has a direct influence on the induction of pancreatic cancer in cigarette smokers or whether it gives rise to an organ-specific N-nitrosamine or a carcinogenic metabolite of the latter. The elucidation of these questions should have high priority, since pancreatic cancer is associated with cigarette smoking, and since its incidence in the United States has increased steadily between 1950 and 1970.

An earlier Part of this Report dealt with the various concepts on the correlation of cigarette smoking and bladder cancer. Currently, the most valid theory relates to the likelihood that the urine of smokers contains traces of bladder carcinogens that derive from inhaled smoke constituents either directly or via precursors. Whether urine of smokers does in fact contain precursors that lead to the formation of carcinogens in the presence of infectious agents or under the influence of other pathologic conditions or whether the urine of smokers contains cocarcinogens needs to be explored.

The identification of cocarcinogenic agents in the neutral and weakly acidic portions of tobacco smoke will also require much more detailed investigation as to chemical nature, precursors, and biological interactions of such compounds.

In view of repeatedly expressed concerns regarding the possible transplacental effects of cigarette smoke inhalation (*188, 189, 190*), intensive research in this area is urgently needed. The concern is based in part on the observation that the foreskin of newborn infants of smoking mothers contains enzymes that metabolize benzo[a]pyrene (*41, 121*). Furthermore, it is known that nicotine crosses the placenta (*184*) and may thus give rise to formation of carcinogenic nitrosamines in the fetus. The hamster appears to be a suitable model for smoke inhalation studies designed to examine various aspects of transplacental carcinogenesis (*11, 51*).

The ongoing modifications of tobacco products offer constant challenges to the analytical chemists and toxicologists who monitor the characteristics of these products. The increasing nitrate content of cigarettes raises concerns regarding the possibility of higher yields of volatile and tobacco-specific N-nitrosamines in the smoke and regarding possible formation of aromatic nitrohydrocarbons and amines.

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The changes in flavor composition or changes in tobacco that affect the "flavor bouquet" of tobacco products may conceivably be responsible for mutagenic, tumorigenic, or otherwise toxic smoke constituents. Monitoring and identifying such biological activity and associated chemical characteristics remain a constant responsibility of the tobacco health research scientist.

Although the published epidemiologic data regarding a possible effect of sidestream smoke on lung cancer induction in nonsmokers are not in total agreement (see the Part of this Report on involuntary smoking), the release of carcinogens from the burning cigarette into enclosed environments warrants a detailed study of this problem. Subsequent approaches toward a reduction of risks by inhibiting or altering the release of certain sidestream smoke components may need to be developed.

Summary

This overview presents evidence and observations on tobacco carcinogenesis primarily developed since 1978.

1. The biological activity of whole cigarette smoke and its tar and tar fractions can now be measured by improved inhalation assays in addition to tests for tumor-initiating, tumor-promoting, and cocarcinogenic activities on mouse skin.
2. Studies on smoke inhalation with the hamster now appear suitable for estimating the relative tumorigenic potential of whole smoke from commercial and experimental cigarettes. The identification of the smoke constituents that contribute to tumor induction in the respiratory tract is best achieved by fractionations of tar and by assays on mouse epidermis that determine the type and potency of the carcinogens. In combination with biochemical tests, mouse skin assays should also aid in evaluating the possible role of nicotine as a cocarcinogen.
3. The identification, formation, and metabolic activation of organ-specific carcinogens have been studied which help explain the increased risk to cigarette smokers of cancer of the esophagus, pancreas, kidney, and urinary bladder. In addition to certain aromatic amines, tobacco-specific N-nitrosamines appear to be an important group of organ specific carcinogens in tobacco and tobacco smoke. Little is known of the *in vivo* formation of organ-specific carcinogens from nicotine and other *Nicotiana* alkaloids. The modification of their enzymatic activation to ultimate carcinogenic forms needs to be explored by chemopreventive approaches.
4. Transplacental carcinogenesis as it may relate to effects of cigarette smoking should be investigated more fully. It has been known for some time that inhalation of tobacco smoke

activates enzymes in the placenta and fetus and the consequences of such changes need to be studied.

5. The continuing modification of U.S. cigarettes has led to changes in the quantitative and perhaps also the qualitative composition of the smoke. This ongoing development requires continued monitoring of the toxic and carcinogenic potential of the smoke of new cigarettes.
6. The changes in cigarette composition lead generally to reduced emission of major toxic mainstream smoke constituents as measured in analytical laboratories under machine-smoking conditions. Many smokers intensify puff volume and degree of inhalation when smoking a lower-yield cigarette. Therefore, it should be determined what effect different techniques of air dilution and filtration have in counteracting the increased smoke exposure that results from intensified smoking.
7. Snuff tobaccos are increasingly used as an alternative to cigarette smoking. More information is needed regarding the carcinogenic activity of snuff tobaccos and the presence of tumorigenic agents in these products.

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Exposure

An individual's actual smoke exposure dose is difficult to quantify, even for an acute exposure. For the longer exposure periods, as in chronic disease epidemiologic studies, the exposure quantification problems are magnified. Dosage is dependent upon the amount of smoking by those around the nonsmoker, the spatial distance between the nonsmoker and smoker, the duration and frequency of exposure, and a number of other factors that complicate the quantification of involuntary smoke exposure in either retrospective or prospective studies. Several studies have used the smoking habits of the spouse of the nonsmoker as a means of identifying two groups (nonsmokers with smoking or nonsmoking spouses). This estimate of exposure is subject to misclassification, as the nonsmoker may be a former smoker. This may be true for either the nonsmoker being followed or the nonsmoking spouse in the control group. In addition, in societies with a high rate of divorce or multiple marriages, the smoking habits of the current spouse may not approximate the actual exposure. Further, there is a demonstrable correlation between the smoking habits of spouses that decreases the proportion of couples available for study who are discordant for smoking.

Long Latency Periods

Lung cancer follows exposures experienced over decades and, therefore, it is necessary to observe nonsmokers over an extended time in order to estimate their actual exposure.

Other Carcinogenic Exposures

Exposure to cigarette smoke may occur in conjunction with exposure to other occupational or environmental carcinogens. Epidemiologic studies should control for or investigate possible interactions with other environmental exposures as far as possible, but limitations clearly exist here as well. Accurately assessing lifetime exposures and attempting to control for such exposures are difficult, if not impossible.

Current Epidemiologic Evidence

To date, three epidemiologic studies have been published that examine the lung cancer risk of involuntary smoking. Two of these studies (*19, 42*) were conducted in the relatively traditional societies of Greece and Japan; the third analysis was conducted in the United States by Garfinkel (*12*), based on data originally collected by Hammond (*14*).

Trichopoulos et al. used the case-control method of study over the period of September 1978 through June 1980. They identified 51

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PART IV. INVOLUNTARY SMOKING AND LUNG CANCER

INVOLUNTARY SMOKING AND LUNG CANCER

Introduction

The social pressure to limit smoking in public places (*6*) reflects concern for protecting nonsmokers from the annoyances of others' cigarette smoke, as well as concern about the possible adverse health effects of involuntary smoking, or secondhand exposure to others' cigarette smoke.

A recent publication presented the scientific evidence linking involuntary smoke exposure to adverse health effects (*44*). Children of smoking parents had more bronchitis and pneumonia during the first year of life (*17*); and acute respiratory disease accounted for a higher number of restricted activity days (1.1 days) and bed disability days (0.8 day) in children whose families smoked than in those whose families did not (*3*). A reduction in exercise tolerance with exposure to sidestream cigarette smoke has been demonstrated in patients with angina pectoris (*1*), and a decrease in small airway function of the lung equivalent to that observed in light smokers (1 to 10 cigarettes a day) has been reported in adults who never smoked themselves nor lived with smokers, but who were exposed to cigarette smoking in the workplace (*49*).

Only recently has attention focused on the possibility that lung cancer may be caused by involuntary inhalation of tobacco smoke. This concern is based upon: (1) the occurrence of similar chemical constituents in sidestream smoke (smoke released from the cigarette between active puffs) and mainstream smoke (smoke actively inhaled); (2) the established dose-response relationship between voluntary cigarette smoking and lung cancer, and the absence of evidence establishing a threshold for effect; and (3) the recent epidemiologic studies that examined lung cancer mortality in nonsmoking spouses of cigarette smokers.

Smoke Constituents

The average person spends most of the time indoors where there may be significant exposure to tobacco smoke generated by others (*31*). For various reasons, the exposure of nonsmokers is more difficult to quantitate than that of the smoker. The constituents of the particulate and gas (vapor) phases of tobacco smoke have been quantitatively analyzed in several studies (*8, 22, 37, 38*). As is shown in Table 1, many of the chemical constituents of mainstream smoke are also found in sidestream smoke. Some constituents occur in markedly higher concentrations in sidestream than in mainstream smoke (note SS to MS ratio); however, sidestream smoke is released into the ambient air, resulting in dilution of constituents. The resulting concentration of smoke is dependent upon the amount of

TABLE 1.—Constituents of cigarette smoke.[1] Ratio of sidestream smoke (SS) to mainstream smoke (MS)

A. GAS PHASE	MS	SS/MS		MS	SS/MS
Carbon Dioxide	20–60 mg	8.1	Nitrogen Oxides (NO_x)		
Carbon Monoxide	10–20 mg	2.5	Ammonia	80 μg	73
Methane	1.3 mg	3.1	Hydrogen cyanide	430 μg	0.25
Acetylene	27 μg	0.8	Acetonitrile	120 μg	3.9
Propane Propene	0.5 mg	4.1	Pyridine	32 μg	10
Methylchloride	0.65 mg	2.1	3-Picoline	24 μg	13
Methylfuran	20 μg	3.4	3-Vinylpyridine	23 μg	28
Propionaldehyde	40 μg	2.4	Dimethylnitrosamine	10–65 μg	52
2-Butanone	80–250 μg	2.9	Nitrospyrrolidine	10–35 μg	27
Acetone	100–600 μg				

B. PARTICULATE PHASE	MS	SS/MS		MS	SS/MS
"Tar"	1–40 mg	1.7	Quinoline	1.7 μg	11
Water	1–4 mg	2.4	Methylquinolines	0.7 μg	11
Toluene	108 μg	5.6	Aniline	360 ng	30
Stigmasterol	53 μg	0.8	2-Naphthylamine	2 ng	39
Total Phytosterols	130 μg	0.8	4-Aminobipheny!	5 ng	31
Phenol	20–150 μg	2.6	Hydrazine	32 ng	3
Catechol	130–280 μg	0.7	N'-Nitrosonornicotine	100–500 ng	5
Napthalene	2.8 μg	16	NNK[2]	80–220 ng	10
Methylnaphthalene	2.2 μg	28	Nicotine	1–2.5 mg	2.7
Pyrene	50–200 μg	3.6			
Benzo(*a*)pyrene	20–40 μg	3.4			

[1]Nonfilter cigarette

[2]NNK = 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (tobacco specific carcinogenic nitrosamine)

SOURCE: U.S. Department of Health, Education, and Welfare (*44*).

smoke generated, the volume of ambient air, and the type and amount of the ventilation of that space (*2, 4, 24, 34, 44*). In addition, the chemical composition of smoke changes with the passage of time (*24a*). Further complicating factors include the continuous low-dose exposure of involuntary smokers contrasted with the intermittent high-dose exposure of the active smoker. Thus, many factors complicate the theoretical extrapolation of machine measurements of smoke constituents to the biologic effects to be expected with exposure of nonsmokers.

The actual absorption of smoke constituents by nonsmokers in smoke-filled spaces has not been completely characterized. A few studies have examined the absorption of carbon monoxide by measuring carboxyhemoglobin levels in exposed nonsmokers (*44*); however, the absorption of most other constituents has not been studied. Furthermore, the pattern of involuntary inhalation probably differs from that of voluntary inhalation of smoke by the smoker, affecting the pattern and amount of deposition or absorption of

chemical constituents in nonsmokers compared to smokers. Differences in the carcinogenicity of sidestream and mainstream smoke may also exist; sidestream smoke condensate is more tumorigenic per unit weight in mouse skin assays than is mainstream smoke condensate (*50*).

Some evidence exists that suggests, however, that involuntary exposure to cigarette smoke does result in deposition or absorption of constitutents. Involuntary inhalation of cigarette smoke has been shown to produce tracheobronchial epithelial metaplasia and dysplasia in animals (*23*). The applicability of these data to human exposures is not clear, however, since the levels of smoke exposure used in this animal study were substantially higher than those normally encountered by humans in enclosed spaces where smoking is allowed (*38*). In a smoke-filled, unventilated, unoccupied room, the concentrations of several smoke constituents, including several volatile gases, total particulate matter, and nicotine, remained constant and were higher than when humans were present. Further, several vapor phase constituents such as nitrogen oxide, acrolein, and aldehydes were observed to decrease continuously over 3 hours when humans were placed in the room, despite fresh sidestream smoke being generated to keep the ambient carbon monoxide level stable (*24*). The difference in absolute levels and the continuing decrease in constituent concentrations despite the continuing addition of smoke to the environment suggest absorption by humans, although the actual site(s) of deposition has not been determined.

Dose-Response Relationships

Examination of the dose-response relationship for voluntary smokers suggests an increased risk with any level of regular cigarette smoking (*43*). No threshold level of exposure for the development of lung cancer has been established and, therefore, any level of exposure is of concern. Figure 1 reflects the data that led to the scientific consensus that there is no threshold level. This absence of a clear threshold level of exposure raises the issue of whether the levels of exposure reached through involuntary smoking may also produce an increased risk of lung cancer.

Epidemiologic Studies

The use of epidemiologic techniques to search for an association between involuntary smoke exposure and lung cancer has a number of methodologic difficulties.

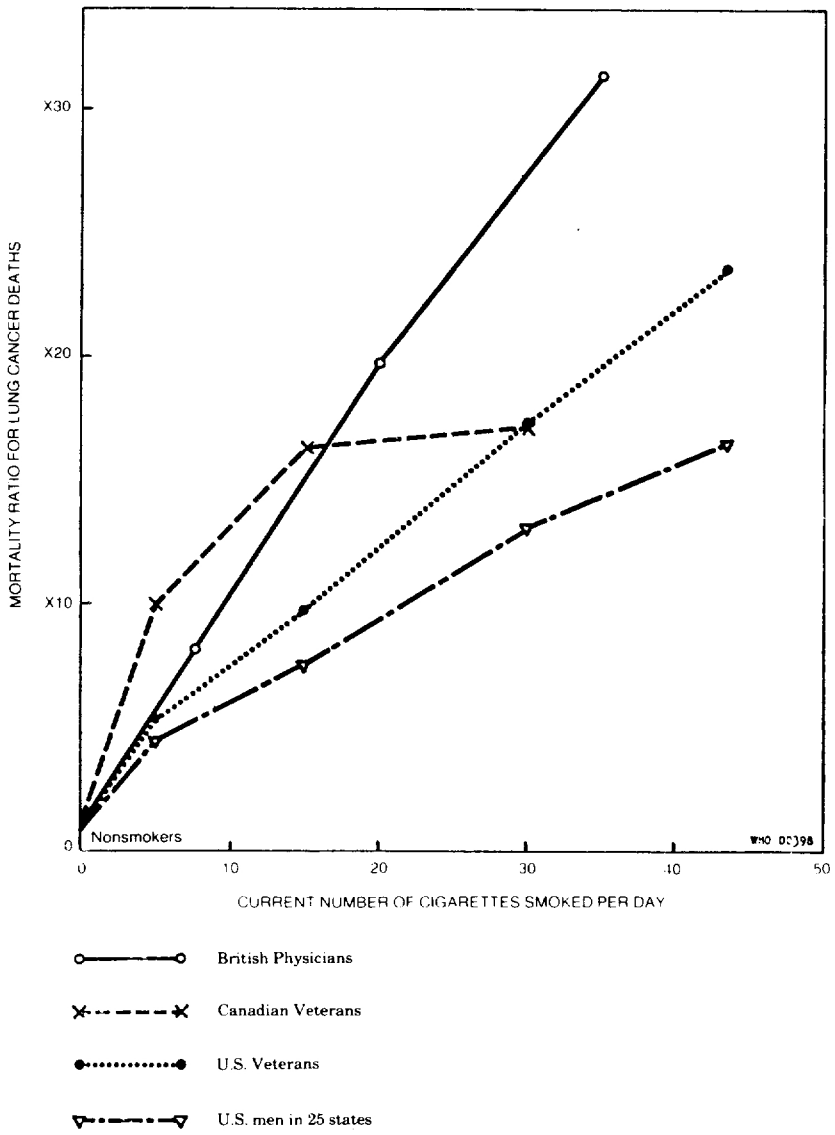

FIGURE 1.—Mortality ratios of deaths from lung cancer in men. Data from four large prospective studies

British Physicians
Canadian Veterans
U.S. Veterans
U.S. men in 25 states

SOURCE: Royal College of Physicians of London (*35*).

Caucasian female lung cancer patients and 163 adult female orthopedic patients in Athens. All subjects were questioned on their personal smoking habits, and husbands were classified as nonsmokers (never smoked or quit more than 20 years prior), ex-smokers (stopped smoking 5 to 20 years prior), and current smokers (currently smoking or smoked within 5 years prior to interview). Single women were classified with the group having nonsmoking husbands. The cases and controls did not differ in age, duration of marriage, occupation, education, or place of residence, although specific matching on these characteristics was not performed. Involuntary exposure of the wife was estimated from her husband's daily consumption, from the date of marriage until their divorce, her husband's death, or change in his smoking habits; multiple marriages were also considered.

Excluding 11 voluntary smokers from the 51 female lung cancer cases, and 14 smokers from the 163 controls, the remaining 40 nonsmoking lung cancer patients and 149 nonsmoking control women were compared by their husband's current smoking status, and estimated total cigarettes smoked by the husband by the time of interview. The results are shown in Tables 2 and 3 respectively. Compared with the control group, at interview the lung cancer cases showed 1.8-fold greater probability of being married to an ex-smoker; 2.4-fold greater odds of being married to a light or moderate smoker (20 or fewer cigarettes per day); and 3.4-fold greater odds of being married to a heavy smoker (more than 20 cigarettes per day). The trend observed in these findings was statistically significant, with a p value less than 0.02. Exclusion of single women from this analysis modified the relative risks only slightly. Table 3 shows a similar trend of increasing relative risks in nonsmoking wives with increasing (estimated) total number of cigarettes smoked by the husband prior to the interview.

Some limitations and strengths of this study were recognized and discussed by the authors. Among the limitations were: the number of cases was small; 35 percent of the tumors lacked histologic confirmation; controls were chosen from a different hospital than were the cases; a single unblinded interviewer was used for both cases and controls. On the other hand, the authors suggested that the conservative social setting for this study may be less subject to errors of misclassification resulting from the exposure of nonsmoking wives of nonsmokers to the smoke of others outside the home. The number of cases of adenocarcinoma that were excluded from the analysis is not given. Analysis including such cases would be of interest (*16*), as many investigators have found cigarette smoking to be a cause of adenocarcinoma of the lung as well as of other histologic types of lung cancer (*45*). Additional control groups for comparison to the cases might have enhanced the findings of this study.

TABLE 2.—Smoking habits of husbands of nonsmoking women with lung cancer and of nonsmoking control women

Diagnostic group	Nonsmokers	Ex-smokers	Cigarettes per day (current smokers) 1-10	11-20	21-30	31+	Total
Lung cancer	11	6	2	13	4	4	40
Controls	71	22	9	32	6	9	149
RR[a]	1.0	1.8	2.4		3.4		
RR[b]	1.0	1.5	2.0		3.0		

[a] Relative risk—the ratio of the risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are nonsmokers. $X^2 = 6.45$, p(2-tail) < 0.02.

[b] Analysis excluding single women arbitrarily classified as nonsmokers. X^2(linear trend) = 4.6, $p < 0.03$.

SOURCE: Trichopoulos et al. (*42*).

TABLE 3.—Distribution of nonsmoking women with lung cancer and of nonsmoking control women according to the estimated total number of cigarettes smoked by their husbands by the time of the interview

Diagnostic group	Total number of cigarettes (in thousands) 0	1-99	100-199	200-299	300-399	400+	Total
Lung cancer	8	4	6	9	6	7	40
Controls	56	21	26	16	12	18	149
RR[a]	1.0	1.3	2.5		3.0		

[a] Relative risk—the ratio of the risk of lung cancer among women whose husbands belong to a particular smoking category to that among women whose husbands are nonsmokers. $X^2 = 6.50$, p(2-tail) < 0.02.

SOURCE: Trichopoulos et al. (*1981*).

Hirayama (*19*) used a prospective design in 29 health districts in Japan over 14 years, from 1966 to 1979, in which 91 to 99 percent of the census population was interviewed. He analyzed interview data from 265,118 adults aged 40 years and older, and found that 72.3 percent of the couples had data on the smoking habit of both spouses. Among 91,540 married women, 245 deaths from lung cancer were recorded, of which 174 were nonsmokers. He reported a statistically significant excess rate of lung cancer among nonsmoking wives of smokers as compared to nonsmoking wives of nonsmokers. Table 4 shows the standardized mortality rates for lung cancer in nonsmoking wives, adjusted for age and occupation. There is an apparent dose-response relationship in each of the analyses presented. Certain methodologic details (e.g., the definition of an ex-smoker

husband, the method of age and occupation standardization, and the technique or extent of histologic confirmation) were not presented. Hirayama also examined the effects of voluntary smoking in relationship to involuntary exposure and nonexposure. The standardized annual mortality rate for nonsmokers who were not involuntarily exposed was 8.7 per 100,000. For women who reported being exposed to cigarette smoke only involuntarily, the standardized annual mortality rate was 15.5 per 100,000. For women who voluntarily smoked, the standardized annual mortality rate was 32.8 per 100,000. He concluded that the effect of involuntary smoking was approximately one half to one third that of active or voluntary smoking.

The age and occupation standardized risk ratios in this population failed to show any statistically significant effect of spousal smoking on nonsmoking women's standardized risk ratios for deaths from other causes, including emphysema (although the trend in relative risk was in the same direction as for lung cancer mortality), cervical cancer, stomach cancer, or ischemic heart disease (Table 5); no significant role of spousal alcohol consumption was demonstrated for any of the above diseases.

The public press has reported a possible error in Hirayama's computation of the chi square test of statistical significance (*33*). However, the scientist to whom this finding was attributed has subsequently stated that he raised questions about the study but denied reaching any conclusion (*29a*).

Harris and DuMouchel (*18*) recalculated the chi square using the originally presented data of Hirayama by combining Tables 1 and 2. The calculated chi square of 8.09 yielded a statistically significant two-sided p value of 0.0004.

In a subsequent, more detailed tabular presentation, Hirayama (21a) confirmed the statistically significant excess in lung cancer death rates in wives of smokers when adjusted for husband's age, occupation and smoking habits. In this subsequent analysis, Hirayama restricted his analysis to data from one prefecture for a possible dose-response relationship of involuntary smoking and lung cancer mortality. The exposure of nonsmoking wives was calculated by multiplying the hours of the day the husband was at home by the number of cigarettes smoked per hour, assuming that the number of cigarettes smoked per hour remained constant over waking hours. There was a clear dose-response observed (Table 6) for each of three categories for length of hours and for number of cigarettes smoked per day. The risk of death from lung cancer in nonsmoking women increased with either the time of exposure or increasing daily number of cigarettes. In that set of analyses, the relative mortality risk (as measured by the standardized mortality ratio) observed

TABLE 4.—Standardized mortality for lung cancer in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)

Husband's smoking habit	Nonsmoker	Ex-smoker or 1–19/day	≥20/day
Husband's age: 40–59 years			
Population of wives	14,020	30,676	20,584
No. of deaths from lung cancer	11	40	36
Occupation-standardized mortality/100,000	5.64	9.34	13.14
Husband's age: ≥60 years			
Population of wives	7,875	13,508	4,877
No. of deaths from lung cancer	21	46	20
Occupation-standardized mortality/100,000	15.79	24.44	29.60
Standardized risk ratio for all ages	1.00	1.61	2.08
Husband working in agriculture			
Population of wives	10,406	20,044	9,391
No. of deaths from lung cancer	17	52	24
Age-standardized mortality/100,000	9.54	17.02	18.40
Husband working elsewhere			
Population of wives	11,489	24,140	16,070
No. of deaths from lung cancer	15	34	32
Age-standardized mortality/100,000	9.13	10.46	17.78
Standardized risk ratio for all occupations	1.00	1.43	1.90

SOURCE: Hirayama (*19*).

among nonsmoking wives of smoking husbands was markedly lower than that observed for women who actively smoked (Figure 2).

The observed differences between wives of smokers and wives of nonsmokers were evident for each of the four socioeconomic status classes.

Hirayama's article has stimulated much discussion, which has been published as Letters to the Editor of the *British Medical Journal* (*5, 13, 25a, 27, 27a, 30, 36, 40, 42a*). In three replies to the same journal (*20, 21, 21a*), the reader is referred to the specific issues raised and responded to in these letters.

TABLE 5.—Age-occupation standardized risk ratio for selected causes of death in women by smoking habit of the husband (patient herself a nonsmoker)

Cause of death	Husband's smoking habit			p value *
	Nonsmoker	Ex-smoker, or 1-19/day	≥20/day	
Lung cancer (n=174)	1.00	1.61	2.08	0.0001
Emphysema, asthma (n=66)	1.00	1.29	1.49	0.474
Cancer of cervix (n=250)	1.00	1.15	1.14	0.249
Stomach cancer (n=716)	1.00	1.02	0.99	0.720
Ischaemic heart disease (n=406)	1.00	0.97	1.03	0.393

* (X^2 linear trend).
SOURCE: Hirayama (*19*).

TABLE 6.—How often wives with smoking husbands inhale cigarette smoke passively in Japan (calculation based on a study in Aichi Prefecture, Japan)

No. cigarettes smoked by husband/day	Length of contact in a day					
	1.5 h		4 h		15.0 h	
	Frequency (%)	No. cigarettes to which they were exposed*	Frequency (%)	No. cigarettes to which they were exposed*	Frequency (%)	No. cigarettes to which they were exposed*
1-19 (average 10)	11.8	(0.88)	14.2	(2.55)	6.8	(8.82)
20-29 (average 25)	19.8	(2.21)	25.4	(5.88)	8.6	(22.06)
30-60 (average 45)	5.6	(3.97)	5.2	(10.59)	2.6	(39.71)

*Length of contact multiplied by number smoked in an hour (number smoked in an hour equals average number of cigarettes smoked in a day divided by total hours awake).
SOURCE: Hirayama (*21*).

Nonetheless, the applicability of such results to the U.S. population remains to be established.

Garfinkel (*12*) published an analysis of data from the American Cancer Society's prospective study conducted from 1960 through 1972. He reported results on 176,739 nonsmoking women who were then married (a) to men who never smoked, (b) to men who currently smoked less than 20 cigarettes per day, or (c) to men who currently smoked 20 or more cigarettes per day. In an analysis that did not attempt to control for possible confounding variables, the observed to expected lung cancer mortality ratio (expected numbers were derived from the lung cancer rates of women married to nonsmokers by 5-year age groups) was 1.27 for women married to smokers of less than 20 cigarettes per day and 1.10 for women married to smokers of 20 or more cigarettes per day. These increases in mortality ratios over those of wives of nonsmokers were reported to be not statistical-

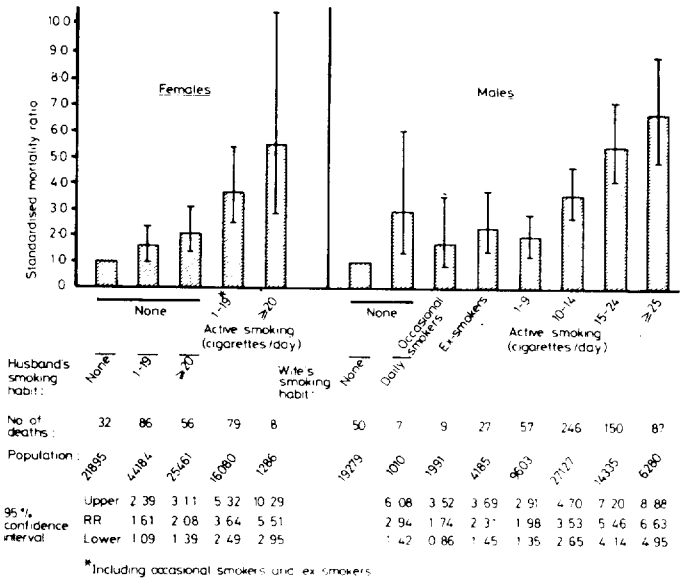

FIGURE 2.—Active and passive smoking and standardised mortality rates for lung cancer: relative risks (RR) with 95 percent confidence intervals—prospective study, 1966–1979, Japan

*Includes occasional smokers and ex-smokers
SOURCE: Hirayama (*21a*).

TABLE 7.—Observed versus expected* lung cancer deaths among nonsmoking women with cigarette-smoking husbands, ACS study, 1960–1972**

Parameter	Husband did not smoke	Husband smoked < 20 cigarettes per day	Husband smoked ≥ 20 cigarettes per day
Observed deaths	65	39	49
Expected deaths	65.00	30.67	44.67
Mortality ratio	1.00	1.27	1.10

*Expected deaths are based on the lung cancer rates by 5-year age groups in women with nonsmoking husbands applied to the person-years of women with smoking husbands.
**The 95 percent confidence limits for women with husbands smoking < 20 cigarettes/day were 0.85 and 1.89; for women with husbands smoking ≥ 20 cigarettes/day, they were 0.77 and 1.61.
SOURCE: Garfinkel (*72*).

ly significant (p value not specified) (Table 7), and no dose-response effect was evident.

The same three groups of nonsmoking women were compared in another analysis. In an attempt to eliminate possible confounding

TABLE 8.—Matched group study: Adjusted lung cancer deaths among women with nonsmoking husbands matched* with women with smoking husbands

Group	Number of adjusted lung cancer deaths	Ratio	p[a]
Nonsmoking husband	25.6	1.00	
Husband smoked <20 cigarettes/day	35.0	1.37	NS
Nonsmoking husband	34.5	1.00	
Husband smoked ≥20 cigarettes/day	35.8	1.04	NS

*Matched on the basis of (a) wife's 5-year age group, (b) husband's occupational exposure, (c) highest educational level of husband or wife, (d) race, (e) urban-rural residence, and (f) absence of serious disease at the start of the study.

[a]NS = not significant.

SOURCE: Garfinkel (*12*).

variables, pairs of women were matched on multiple factors. The number of deaths in each matched diad was "adjusted" as described in a prior publication (*15*). The results of this analysis are shown in Table 8. Neither group of nonsmoking wives of smokers showed a statistically significant difference ($p > 0.05$); there is no dose-response pattern apparent. The actual size and composition of the matched study population, however, were not shown. The author concluded that any effect passive smoking had on lung cancer mortality would be small.

The author presented the limitations of this analysis. The study was not designed to examine the question of effects of passive smoking and, therefore, there were difficulties with the accurate assessment of exposure. The appropriateness of this analysis of the ACS data has been questioned (*16*) for this reason. The difficulties include the measurement of involuntary exposure to smoke from persons other than the husband, and an inability to adjust for changes in husband's smoking subsequent to actual interview or for exposure(s) from previous husbands. A study should be specifically designed to measure exposure, as neither the Japanese (*19*) nor the ACS study met that criterion. Additionally, among 564 cases of lung cancer in nonsmoking women, the husband's smoking status was available for only 153 (27 percent).

Thus, each of the three epidemiologic studies published to date shows an increased risk of lung cancer with involuntary smoke exposure (Table 9). The results were statistically significant in two of the three studies, which also found a dose-response effect. The evidence currently available suggests that involuntary smoke exposure may increase the risk of lung cancer in nonsmokers, but

TABLE 9.—Observed and expected deaths from lung cancer in nonsmoking women with smoking husbands

	Observed	Expected	Difference	Ratio	X^2	
Japan (Hirayama)	142	85.8	+56.2	+65.5%	36.81	Significant
U.S. (Garfinkel)	88	75.3	+12.7	+16.9%	2.14	Not significant
Greece (Trichopoulos et al.)	29	12.1	+16.9	+139.7%	23.60	Significant
Total	259	173.2	+85.8	+49.5%	42.50	Significant

SOURCE: Hirayama (21).

limitations in data and study design do not allow a judgment on causality at this time.

Summary

1. Mainstream and sidestream cigarette smoke contain similar chemical constituents. (Mainstream smoke is smoke that the smoker inhales directly during puffing. Sidestream smoke is smoke emitted from a smoldering cigarette into the ambient air.) These constituents include known carcinogens, some of which are present in higher concentrations in sidestream smoke than they are in mainstream smoke. Passive or involuntary smoking differs from voluntary cigarette smoking with respect to the concentration of smoke components inhaled, the duration and frequency of smoke exposure, and the pattern of inhalation.
2. In two epidemiologic studies, an increased risk of lung cancer in nonsmoking wives of smoking husbands was found. In these studies, the nonsmoking wife's risk of lung cancer increased in relation to the extent of the husband's smoking. In a third study, the risk of lung cancer among nonsmoking wives of smoking husbands was also increased, but the difference was not statistically significant.
3. Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem.

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PART V. CESSATION OF SMOKING

PREVENTION IN ADULTHOOD: SELF-MOTIVATED QUITTING

Introduction

It has been observed that 95 percent of those who have quit smoking have done so without the aid of an organized smoking cessation program (*33*). Furthermore, most current smokers indicate a preference for quitting with a procedure they may use on their own and a disinclination to enter an organized, comprehensive program. In one survey of male smokers belonging to a prepaid medical group in California, respondents were asked to indicate in which of 10 approaches to smoking cessation they would be willing to participate (*32*). In order of popularity, subjects chose instructions (69 percent "yes" or "maybe" responses), medicine (66 percent), television programs (64 percent), and a book (53 percent). Group discussions (36 percent) and public health clinics (36 percent) were least popular. On average, the procedures that could be carried out totally alone (the book or television programs) received "yes" or "maybe" responses from 58 percent of those surveyed; those requiring the continuing, active involvement of others received "yes" or "maybe" responses from only 39 percent.

The preferences of smokers and the unaided efforts of most who have quit point clearly to the desirability of effective self-help programs in smoking cessation. Such programs would appeal to many who are unlikely to be reached by organized cessation clinics. Furthermore, self-help programs are more easily disseminated than are organized cessation clinics. With an estimated 50 million adult smokers in this country and an average of 30 participants in an organized clinic, 1.67 million clinics would be needed to treat all of the adult smokers. This staggering estimate dramatizes the desirability of a self-help approach.

Additional encouragement of self-help approaches arises from observations that comprehensive or complex interventions may be less effective in long-term behavior change than less comprehensive interventions. As noted by Franks and Wilson (*9*, p. 361), "'more' is not inevitably better—it could even be counterproductive." Several smoking cessation research reports have indicated that programs using a combination of treatments are less effective than the individual components of which the programs are comprised (e.g., *17,18*). On the other hand, researchers cannot yet designate what cessation techniques are most helpful for what individual, so that offering a smoker a comprehensive package from which she or he may self-select may still be preferable to offering only single techniques.

The following sections review self-help approaches to smoking cessation and the attempts to identify motivational factors or

personal characteristics that predict success with self-help approaches. As used in this text, the term "self-help" refers to an individual's or group of individuals' efforts to quit smoking without the continuing assistance of professionals, trained leaders, or organizations (except for materials and occasional consultation). By this definition, programs that minimize therapist involvement but include group meetings or classes organized by people other than the members themselves are not considered as self-help procedures. They are discussed in the next section of this Part of the Report, which reviews long-term maintenance of smoking cessation.

Programs that involve mass media approaches, programs with no person-to-person contact with trained leaders or professionals, and programs with merely a single informational contact are included in this discussion. Oftentimes, single informational contacts provide only an instigation to cessation or a very specific, limited aid in cessation. Essentially, the individual is left to his or her own devices in quitting. As such, then, these interventions may be understood as self-help programs, in that they instigate efforts to quit that are otherwise unaided.

Review of Self-Help Approaches

In reviews of manuals for smoking cessation published prior to 1978, little success was reported when such manuals were used without guidance or appreciable input from a clinician or group leader (*12, 13*). The one exception was a study conducted in West Germany in which subjects used on their own a behavioral treatment manual, directions for behavioral contracting, or a combination of the two. These led to a 50 percent abstinence rate at a 15-month followup, with no differences among the treatments (*20*, as cited by *12*). This report provides some optimism regarding the potential impact of self-help approaches.

In their comparison of several manuals for smoking cessation to be used either with or without therapist contact, Glasgow et al. (*14*) compared the books of Danaher and Lichtenstein (*6*) and Pomerleau and Pomerleau (*27*) with the "I Quit Kit" of the American Cancer Society (*1*). All subjects paid a $15 deposit (returnable). Half of the subjects were given the materials with no other contact and were told that the program would be most effective if used on their own. The remaining 50 percent of the subjects, who were told that working with a therapist would facilitate use of the materials, met in small groups (four to six subjects) with a therapist for eight sessions. At the conclusion of treatment, the subjects' self-reports of abstinence indicated that the two books were more effective when used with a therapist than when used alone. In contrast, the "I Quit Kit" tended to be slightly more effective when used alone than with a

therapist. Analysis of abstinence data based on carbon monoxide levels showed a parallel trend.

At a 6-month followup, those using the books still tended to do better in the therapist-administered program, whereas those with the "I Quit Kit" tended to do slightly better when using it alone. These trends were statistically significant when based on self-report data and of borderline significance ($p < 0.10$) for abstinence determined by carbon monoxide testing. Self-reported abstinence rates at the 6-month followup ranged from 0 percent with the therapist-administered "I Quit Kit" and the self-administered use of the Pomerleau and Pomerleau book to 24 percent in the therapist-administered use of the Pomerleau and Pomerleau book. For all those who used materials without therapist administration, the self-report data indicated a 7 percent abstinence rate (3 of 41 subjects) at 6-month followup.

These data of Glasgow et al. (*14*) are sobering regarding the potential of self-help approaches. However, several considerations should be kept in mind. Because some subjects were to be in therapist-administered treatments, solicitations placed little emphasis on the possibility of self-help procedures. The deposit and the failure to emphasize self-help in solicitations may have kept individuals eager for a self-help program from being encouraged to join. Furthermore, subjects were rather heavy smokers, reporting a pretreatment mean of 32 cigarettes smoked per day and an average smoking history of 19 years. Thus, selection factors may have lessened the impact of the procedures employed.

Subjects reported the extent to which they actually read the treatment manuals and the percent of five critical activities they actually completed. Therapist-administration led to higher rates of completion of the books, whereas subjects in both programs with the "I Quit Kit" read approximately equal amounts of their materials. For percent of activities completed, therapist-administration was found related to compliance with all three manuals. Subjects working with therapists reported completion of 66 percent of the activities suggested, but those working alone reported completion of only 41 percent. These measures of adherence were correlated with self-report of number of cigarettes smoked per day at posttreatment ($r = -0.42$ and -0.43 for material read and activities completed, respectively) and followup ($r = -0.42$ and -0.24). These findings are unusual in the behavioral medicine literature, as correlations between outcome and reports or observations of adherence to specific treatment recommendations have not often been noted. The indices of adherence were somewhat broad—extent of book read and percent of critical activities completed. As such, they may have been as much a behavioral measure of motivation as of the impact of any single program element. Their correlations with outcome may reflect the

importance of participant effort rather than of actual number of pages read or activities carried out.

Minimal Interventions

In addition to procedures used by individuals without assistance, two classes of minimal interventions may also be considered within the field of self-help: those including brief exhortation and advice on quitting, and those with mass media or public education approaches.

The influence of simple advice to quit was found significantly related to percentage reduction in smoking in a study reported by Raw (*28*). Forty smokers attending a chest clinic were interviewed just after seeing a physician and questioned as to whether or not the physician had advised them to quit smoking. Half of them were also provided with information regarding the risks of smoking and the benefits of cessation. A higher percentage reduction in smoking at 3-month followup was obtained among those subjects reporting physicians' directions to quit (39 percent) compared with those not so advised (17 percent). Thus, simple information or encouragement (or, perhaps, remembering such) may be instrumental in changing smoking behavior among some people. Since reductions in smoking rate may be short-lived and fluctuating, it is unfortunate that cessation rates were not reported.

Several findings from this study shed light on the issue of motivation. First, Raw found that greater percentage reduction at 3-month followup occurred when the interviewer wore a white coat at the time of his interview with patients, irrespective of whether he was advising them to quit. Thus, the authoritativeness of the whole procedure seems to mediate its impact. A questionnaire measure of subjects' motivation to quit at the time they arrived at the chest clinic was correlated with percentage reduction ($r = 0.43$). The attempt to motivate quitting through information on the health risks of smoking and benefits of quitting was ineffective, leading only to a 20 percent reduction in smoking at the 3-month followup in comparison with a 36 percent reduction among those not receiving the instructions intended to be motivating. This difference was not significant.

A more controlled version of a physician-effected minimal intervention trial was conducted in the offices of 28 general practitioners, involving 2,138 cigarette smoking patients (*31*). Self-reports of smoking status were collected via mailed anonymous questionnaires identified by numerical code. Patients received one of four treatments: group 1, none (non-intervention controls); group 2, questionnaire-only controls; group 3, physician-advice to quit smoking; and group 4, physician-advice to quit smoking, an informational leaflet, and a warning that a followup would be performed. The advice to

quit was delivered during 1 to 2 minutes of the visit in the physician's own style. At 1-month followup, a greater percentage of patients reported attempting to quit smoking in the two physician-advice groups than in the remaining two groups. Patients in group 4 demonstrated a higher rate of trying to quit (17.2 percent) compared with the combined control groups, and a slightly higher rate of quitting (7.5 percent versus 3 percent). However, the percentage of patients attempting to quit that actually succeeded was not significantly different among the four groups. Thus, physician advice, with or without the leaflet, had no effect upon the success rate of those attempting to stop. The increased motivation to quit was strongest in the first month after the visit to the physician, persisted through the 3-month followup, and was enhanced in the leaflet plus followup warning condition. A measure of the intervention's effectiveness was taken to be the percentage of patients in each group who had stopped smoking within 1 month of the physician visit, and who were still abstinent at 1-year followup. Those percentages were: group 1, 0.3 percent; group 2, 1.6 percent; group 3, 3.3 percent; and group 4, 5.1 percent ($p < 0.001$). Furthermore, physician advice resulted in a signficantly lower relapse rate 1 year later among those who had quit at 1 month. There was no differential benefit derived from the leaflets over the longer term.

This study indicates the potential for truly minimal (e.g., 1 to 2 minute) interventions by physicians. The authors point out that the collective efforts of all general practitioners (in the United Kingdom) working in this manner would produce more ex-smokers annually than would intensive smoking cessation clinics which, although obtaining much higher success rates than the 5 percent reported here, reach far fewer smokers and incur far greater costs.

Another study of a relatively minimal intervention that included screening and advice to quit smoking carried out in a medical setting was reported by Rose and Hamilton (*29*). Following screening those at high cardiorespiratory risk, those men at risk who also smoked were assigned either to "normal care" or to the intervention. The general practitioners of those in "normal care" received a full report of the screening. The men assigned to the intervention were invited by letter to an appointment with a physician to review their screening and the high risk posed for them by smoking. The 15-minute appointments included a review of the benefits of cessation as well as the risks of smoking. Subjects were scheduled for a second appointment the following week, by which time they were to decide if they wished to quit. They were given two booklets reviewing why and how to stop, but were told the decision was up to them.

At the second interview, decisions were reviewed, the importance of quitting rather than cutting down was emphasized, and the men were given a card for recording daily consumption, to be returned by

mail after 3 weeks. Further 15-minute sessions were scheduled 10 weeks and 6 months later with continued contact by record card and personal letter as needed. Thus, this intervention included more contact between physician and patient than probably meets the self-help criterion. However, the subjects were given little direct aid in quitting other than advice, two brief manuals, and a possibly highly motivating interaction with a physician.

Followup was conducted by clinic staff, and a questionnaire was completed in person or returned by mail. No objective validation of subjects' self-reports was made. The authors encouraged truthful reporting through the use of "impersonal" and "standardized" followup procedures to "avoid pressure to . . . deny or underestimate continued smoking" (*29*, p. 277). However, such an austere climate may heighten the tendency to disclose desirable outcomes, and thereby encourage over-reporting of abstinence. Response rates 1 year after the screening were 81 percent for the intervention group and 86 percent for the "normal care" subjects. Of these, 39 and 9 percent, respectively, reported no cigarette consumption. Three years after the screening, response rates were 64 and 70 percent and abstinence rates were 35.5 and 14.5 percent in the intervention and the "normal care" groups.

With regard to predictors of abstinence, smoking less than 20 cigarettes per day, non-inhaling, use of filter tips, and previous attempts to stop, increased chances of success. On the other hand, marital status of "other than married," and neuroticism as measured by the Eysenck Personality Inventory, decreased probability of success.

While not clearly within the category of self-help approaches, the interventions reported by Raw (*28*), Russell et al. (*31*), and by Rose and Hamilton (*29*) indicate the potential impact of brief contacts with physicians. Such contact is apparently enhanced by its timing as part of a visit to a chest clinic, as in Raw's study, to a general practitioner, as in the study of Russell et al., or as part of response and followup to screening for individuals at high risk, as in that of Rose and Hamilton. Similar findings are reported for myocardial infarction patients following minimal physician intervention (*5, 19*).

Public media approaches to smoking cessation have begun to achieve some popularity in recent years. Perhaps that receiving the greatest publicity is "The Great American Smokeout" sponsored each year by the American Cancer Society (ACS). A Gallup Poll survey based on personal interviews with a representative national sample of 1,551 men and women, 18 years of age and older, was sponsored by the ACS to evaluate the 1980 Great American Smokeout (*2*). The interviewing for the study was conducted 1 to 10 days after the Smokeout. The findings indicated a high degree of visibility for the program, as 83 percent of those interviewed knew of

it. Approximately 30 percent of smokers interviewed participated in the program—9.2 percent reported refraining totally from smoking and an additional 21.2 percent reported cutting down on that day. Demographic analyses showed a more pronounced impact of the Smokeout in terms of rate of participation among women, younger people, and better educated people, compared with men, medium-aged and older people, and the less well educated. Finally, the success of the program, as judged by level of familiarity with and active participation in the 1980 Smokeout, was equal to or greater than that occurring in the 1978 and 1979 programs.

The use of television in smoking cessation has been explored by several investigators. One format involved carrying out a smoking cessation program as part of a nightly news program. Each weekday evening, for 3 weeks, the regular science reporter devoted 2 minutes to the program. The program included habit-breaking and self-motivating procedures and several ways to prepare for a quit date, including gradual withdrawal. Viewers were also urged to quit before the quit date if they felt able to do so. Announcements the week prior to the program's start encouraged viewers to participate and to send a post card to the station if they were willing to be included in the evaluation of the program. Out of about 5,000 post cards received, a sample of 300 was drawn for followup. One month after the final broadcast, 8 percent of the sample reported abstinence (*7*). This sampling procedure probably included a selection bias for highly motivated individuals; however, it should be noted that subjects sent in their post cards prior to the start of the program, before they knew how much they would like the program, or whether they would succeed in it.

Working with the same televised cessation program, Dubren (*8*) explored the impact of taped telephone messages to encourage maintained abstinence. Following a broadcast invitation, 200 viewers sent in cards indicating they had quit for at least 1 day; of these, 64 were assigned to treatment or control groups. The treatment group received a telephone number to call, but the controls received no further attention except for followup. Run each weekday for 4 weeks, the 3-minute telephone messages were changed daily. Subjects were encouraged to call the telephone number to help themselves remain abstinent throughout this period. Among those offered the telephone messages, 65.5 percent reported not smoking at the end of the 4-week period. In contrast, only 34.4 percent of the control group reported abstinence. Seventy-eight percent of those offered the telephone messages reported calling at least once. Twenty-four percent reported calling for all 20 of the recorded messages. The mean number of calls among those who called at least once was 10.6. The validity of these reports is suggested by the fact that the monitor on the telephone answering machine recorded 256 calls received and

the subjects reported having made 245. The abstinence rates among this group are impressive. However, it should be recalled that the group was selected from among those who had quit for 1 day and who took the initiative of sending in a post card to report their success. For logistic reasons, the subject population was limited to those residing within New York City, but only 67 cards were received from this area. Thus, these results do not necessarily provide an accurate indication of outcome to be expected in a more general population of smokers.

Best (*3*) also reported on a television version of a smoking cessation clinic consisting of six half-hour shows broadcast weekly. The program content was developed from self-management components of a clinic program also developed by Best and his colleagues (*4*). The shows emphasized problem solving with behavioral self-management approaches. Other procedures included self-monitoring, encouragement of a buddy system, and modeling (each show included a simulated interview with a participant). A quit date was set for the day on which the fourth show was to be televised, but participants were given an alternative of gradual withdrawal between shows three and five.

A "companion self-help guide" was offered to all who wrote or called the station. The 1,403 smokers who did so were followed for program evaluation. Followup response rates varied from 64 to 87 percent due to unrelated events (e.g., a phone workers' strike). Among those responding, abstinence rates were 11.5 percent at the end of the series and 14.7 and 17.8 percent 3 and 6 months later. This suggests a "sleeper effect" of increased abstinence over time.

Best reports costs of the program to have been $8,500, apparently excluding promotion and cost of air time. This averages $48 per abstinent case at 6-month followup, higher than several others reviewed here, perhaps because of the limited population of the setting—Bellingham, Washington.

Also explored in Best's study were predictors of successful outcome. Pretreatment smoking rate was less (23.5 per day) among those who were abstinent 6 months later than among those who were not (27.2 per day). Several other predictors of outcome were previous attempts to quit unaided, reduced rate of smoking during the program but prior to quit-day, and subjects' perceived likelihood of success. All these may be viewed as measures of motivation. This, too, is consistent with the previous studies reviewed above. Subjects' ratings of the extent to which they actually used the procedures advocated in the program were also related to abstinence at 6 months. Again, such ratings are ambiguous as to whether they reflect the subjects' motivation or the specific effects of program components.

The importance of motivation is suggested by one final aspect of Best's program. It achieved an abstinence rate about twice that gained by the program reported by Dubren (*7*). Selection factors may account for this. Dubren's program was run weeknights on the news broadcast. Considerably greater commitment was required by Best's program, as it was run between 7:00 and 7:30 on Saturday evenings. Thus, it may have achieved a higher abstinence rate due to a higher motivation level of its participants.

The viability of media as a vehicle for smoking cessation programming is suggested by overall success of two well-known programs for coronary risk reduction, the Stanford Heart Disease Prevention Program and the North Karelia Project in Finland. Only the Finnish project reports population shifts in smoking, obtained from assessing different random samples over time. Both of these programs include mass media encouragement of smoking cessation along with other procedures for heart disease risk reduction. For example, as part of the Stanford project, residents of one town receiving only mass media intervention showed an 8 percent abstinence rate at a followup 3 years after the initiation of the community program. A control community showed an abstinence rate of only 3 percent. Smokers at high risk for coronary heart disease were offered counseling for smoking cessation in a third community. The overall abstinence rate was 24 percent within this community (*24*). The abstinence rate among those offered the group treatment was between 32 and 50 percent at the 3-year followup, depending on whether those smoking at the start but not available at followup are counted or not counted as smokers (*23*). This study admirably puts into perspective the contribution of a media approach relative to no treatment and to intensive treatment.

The focus of the North Karelia study was to explore the impact of a televised smoking cessation clinic (*21*). An actual clinic with a group of participants and a leader was videotaped and televised nationally. The airing of the 10 sessions was timed so that the final session would show the group members at actual 6-month followup, discussing their experiences. Within the Province of North Karelia, smokers were encouraged to watch the programs in groups. About 200 leaders volunteered to form the groups, which the authors calculated to be only about 1 leader for every 300 to 400 smokers within the Province. National surveys conducted before and 1 month after the program indicated decreases in the percentage of persons reporting smoking during the month prior to the second survey, from 45 to 43.2 percent among males and from 25.7 to 24 percent among females. However, these trends were not statistically significant. About 7 percent of the national sample watched at least four of the seven sessions. Only 10 percent of those who watched reported viewing the program in a supportive group setting.

This program was also evaluated by comparing the results in North Karelia with those in a neighboring province. These results were confined to data based on males, 30 to 64 years old. Intensive publicity efforts within North Karelia resulted in 9 percent of this sample viewing four or more of the seven programs in comparison with 4.8 percent of the sample in the neighboring province. For both samples, 27 percent of those who watched at least four programs and attempted to stop smoking reported abstinence at a 6-month followup. Although 2.3 percent of North Karelia smokers reported abstinence at the 6-month followup in comparison to 1.3 percent in the control province, this difference was not significant.

Thirteen months after the airing of the shows, a national survey was repeated and indicated a maintained abstinence rate of about 1 percent of those smoking at the original airing. Furthermore, shows were repeated 3 months prior to this final national survey. Approximately another 1 percent reported abstinence from this second airing of the shows. Thus, the two broadcasts of the program led to approximately 2 percent of smokers nationwide remaining abstinent for 3 months to 1 year. The authors estimated that this constitutes 10,000 to 30,000 individuals, an appreciable number, especially when the health and economic costs of diseases related to smoking are considered. The authors further estimated that production of the seven sessions cost only $8,000. These figures indicate a cost per abstinent smoker of less than $1.00.

Predictors of Outcome

As mentioned previously, a number of studies have attempted to identify personality patterns that typify the smoker. No underlying personality pattern responsible for smoking has been found and, therefore, no pattern-specific treatments have been developed. A somewhat more productive strategy has explored those characteristics related to success in specific cessation programs. Social support factors have been found to encourage success in maintenance of cessation (*15, 22, 34*) while a history of "negative affect" smoking (*26*) has been found to reduce maintenance success. (See the section in this Part of the Report on maintenance of smoking cessation.)

More directly pertinent to self-help approaches was a study of those who had successfully reduced smoking without assistance (*25*). Subjects were university students who had smoked 20 or more cigarettes per day for a minimum of 6 months. To be counted as successful, they had to have reduced their consumption at least 50 percent for at least 4 months; half of the 24 successful subjects were abstinent. Data were also gathered from 24 unsuccessful smokers. All subjects were identified retrospectively. Thus, the decision to quit

or cut down and the manner in which this was accomplished were not influenced by the survey.

Successful individuals reported greater use of self-reward and problem-solving or self-management procedures than did the unsuccessful persons. However, they did not report frequent use of self-monitoring procedures, a nearly universal component of behavioral self-control programs. Finally, 40 percent of the successful subjects reported use of techniques to control cues related to smoking. This study indicates that self-reward and active problem-solving strategies may be worth emphasizing both in self-help and in more organized approaches to smoking cessation. The importance of self-reward is also suggested by Rozensky and Bellack (*30*) in studies of self-rewarding tendencies for those who had quit smoking or lost weight.

Friedman et al. (*11*) also surveyed several behavioral, social, and psychological characteristics of Kaiser Permanente subscribers who had or who had not quit smoking. Smoking histories, number of cigarettes smoked per day, and reported depth of inhalation indicated less intense smoking at the time of the examination among those who remained quitters than on the part of those who persisted in smoking. The quitters reported somewhat less alcohol consumption than persistent smokers among whites and among black males. The percentage of subjects reporting consumption of more than six cups of coffee per day at the time of the index examination was also lower among quitters than among persistent smokers for all subjects. Among whites but not among blacks, a greater portion of quitters had completed at least some college.

Implications

For a decade, those studying smoking cessation have felt little encouragement from the relatively poor long-term outcome of intensive smoking cessation clinics. With few exceptions, results have stayed quite close to the 20 to 30 percent abstinence figures described by Hunt and Matarazzo (*16*). More optimism is spurred by the present assessments of self-help and mass media approaches and of brief interventions by health professionals. Such approaches have the potential to reach large numbers of smokers who find them attractive. Abstinence rates ranging from 5 to 40 percent have been obtained in selected but nevertheless large audiences (*3, 14, 29*). In entire populations, such approaches may encourage 2 percent of smokers to quit in a year's time (*21*). Their impacts may be enhanced by "sleeper effects" in which increasing numbers of persons exposed to them continue to quit as time passes (*3*). Largely unexplored is the extent to which these approaches may be combined to enhance each others' impacts (*23*).

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What determines the impact of self-help approaches? Those most likely to quit on their own or with minimal media intervention seem to be physically and psychologically healthier (*10*), have milder smoking habits, in terms of history and intensity of current smoking (*3, 10, 29*), and may be generally more skillful in controlling their own behavior, as measured by the use of self-reward and problem-solving tendencies (*25*).

The other reliable predictor of outcome seems to be motivation, as measured by participants' willingness to read manuals and to carry out activities encouraged in them (*14*). If motivation to quit smoking reflects incentives for long life, then the fact that measures of motivation predict outcome suggest that quality of life is an important factor.

A number of characteristics of the programs reviewed here may be emphasized to promote higher levels of motivation and cessation of smoking. Among these are modeling (*3, 21*), or pointing up the positive consequences of cessation in an authoritative manner (*29*). Several of the programs include buddy systems, but these apparently have not been emphasized. Supportive self-help groups (*21*) may also add to an individual's willingness to follow through with a program. All of these program elements may be combined with the range of media sampled to develop improved packages.

Summary

1. Ninety-five percent of those who have quit smoking have done so without the aid of an organized smoking cessation program, and most current smokers indicate a preference for quitting with a procedure they may use on their own, and a disinclination to enter an organized, comprehensive program.
2. Research evaluations of self-help aids have reported success rates up to 50 percent cessation at extended followups (6 to 15 months). Most estimates, however, fall below this, around 5 to 20 percent.
3. Brief and simple advice to quit smoking delivered by a physician has substantial potential for producing cessation in a cost-effective manner.
4. Televised smoking cessation clinics result in variable rates of abstinence at followup. The use of television and other mass media are a cost-effective intervention because of their large potential audiences.
5. Retrospective studies revealed greater use of self-reward and active problem-solving strategies among those who quit or reduced smoking on their own than among those who were unsuccessful in quitting or reducing smoking.

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PREVENTION IN ADULTHOOD: MAINTENANCE OF CESSATION

Introduction

In their review, Hunt and Matarazzo (*25*) plotted the temporal trend in relapse among smoking cessation clinic participants who had quit at end of treatment. They demonstrated that the proportion of participants remaining abstinent fell to about 25 percent 3 to 6 months later and remained fairly stable after that time, a trend replicated by Evans and Lane (*15*). Even less optimistic were data showing a long-term abstinence rate of 17.8 percent among 559 participants surveyed 5 years after attending smoking cessation clinics (*51*). Hunt and Matarazzo also showed similar curves for abstinence from heroin and alcohol use. With few exceptions (*8, 24, 27, 33, 39, 49*), studies published in recent years have failed to exceed 6-month abstinence rates of 30 percent. Therefore, improving the ability to maintain nonsmoking status following successful cessation would be a major advance in cessation technology.

Overview of Maintenance Procedures

Major reviews in recent years (*3, 50*) have emphasized the importance of procedures directed specifically at maintenance. Such procedures generally encourage maintenance directly by focusing on events or problems that occur following cessation, rather than encouraging maintenance indirectly by trying to develop more effective cessation procedures or by scheduling "booster" sessions that merely review cessation procedures. A number of approaches to developing distinctive maintenance procedures have been reported in recent years. Among these are reinforcement or incentive procedures, self-management procedures, attempts to find the best level of therapeutic contact, tailoring treatments to client characteristics, identifying and treating antecedents of relapse, and social support. Predictors of outcome have also been studied. Each will be reviewed in turn.

Reinforcement of Maintenance

In general, changes in behavior will be better maintained if they are supported by reinforcers that are relatively immediate and positive (*40*). The incentives for smoking cessation that are naturally occurring are negative and represent probabilities of delayed events (i.e., disease incidence). The naturally occurring consequences of cessation that are quick in developing, such as improved sense of taste, less minor respiratory distress, and monetary savings may not seem like large rewards. Unfortunately, the naturally occurring aversive consequences develop quickly and are generally profound

and highly salient (*45*). Consequently, supplementing naturally occurring reinforcers for cessation with programmed reinforcers may help maintain abstinence through periods when incentives for resumed smoking are strong.

Some research has shown beneficial effects of reinforcement on nonsmoking. A monetary reward for adherence to a gradual withdrawal scheme led to 50 percent abstinence levels in participants at 6-month followup, versus 24 percent in controls (*52*). Subjects in the United Kingdom (*36*) made a deposit of £25, which was returned at the rate of £5 per week for each of the first 4 weeks following cessation. For the second 4-week period, subjects made a further £20 deposit, which was returned at the rate of £10 for each 2 weeks of abstinence. Subjects who smoked during the periods lost the amount of money that would have been returned to them. Deposits forfeited in this way were divided among those remaining abstinent. At the end of this 2-month period, abstinence levels among participants approximated 75 percent, validated by urinary nicotine analyses. Control subjects who did not participate in the reinforcement procedure showed a 2-month abstinence level of 55 percent. However, the difference between the two groups was no longer apparent at 6-month followup.

One way in which some have attempted to build reinforcement into the real world is through programs in the workplace. Rosen and Lichtenstein (*42*) reported a reinforcement program using a salary bonus of $5 each month plus a Christmas bonus for employees who did not smoke during working hours. A questionnaire evaluation of 12 participants who had smoked prior to the program revealed a decline from an average of 33 cigarettes per day before the bonus system to 9 cigarettes per day after. Four of these individuals reported abstinence at the end of the program.

A number of anecdotal reports of smoking cessation and reinforcement programs in the workplace have also appeared. Among the procedures employed are reimbursement of the cessation clinic fee for people who maintain their abstinence until a target date, substantial salary bonuses (some on the order of $1,000), making bets against the "house" (i.e., the company) on one's chance of success, and chances in a lottery for a fishing boat. Many of the programs seem to have centered on a chief executive's enthusiastic efforts to quit and, concurrently, to encourage other employees to do so (*17*). Whether this sort of enthusiasm can be replicated in planned programs is not clear.

The National Interagency Council on Smoking and Health recently surveyed several hundred major American companies regarding their interests and current activities in smoking cessation programs for employees. Programs were already offered by 14.7 percent of these companies. Further details on approaches to smoking cessation

programs in the workplace are available in a conference report published by the Council (*35*) and in papers by Danaher (*13*) and Fisher et al. (*17*).

Another approach to reinforcement is self-reward. This was found to be more common among those who were successful than among those who were unsuccessful in attempts to quit smoking independent of any organizational program (*37*).

Self-Management

Self-management packages may include procedures for relaxation to cope with urges or the emotions likely to provoke craving, procedures for contracting with oneself regarding aversive consequences for relapse and positive consequences for maintenance, and "stimulus control" procedures in which cues for smoking are avoided or eliminated. Lando (*27*) found 76 percent abstinence rates at 6-months after cessation when a comprehensive program was added to "laboratory smoking," which alone achieved 35 percent abstinence rates.

Several studies have reported the impact of comprehensive self-management on situational control procedures without aversive components. Their results all report approximately 30 percent abstinence at followup 6 months or more after cessation. These are more striking, however, because of their validation by reports of other group members (*5*), saliva thiocyanate (*31*), or urinary nicotine (*58*).

A different assessment of the importance of self-management was reported by Hackett and Horan (*23*). They studied self-management procedures including making contracts for maintenance with peers and family members, using relaxation skills, restructuring cognitions related to smoking and the desire for cigarettes, and thought stopping. This last procedure (*8*) is designed to interrupt repetitive or troubling thoughts, as a means for coping with urges. Their program was used with and without "focussed smoking," in which participants faced a wall, received suggestions as to the aversive quality of smoking, and chain smoked for about 15 minutes for each of approximately six sessions. Individuals smoked between 3 and 3.5 cigarettes on the average in each of these 15-minute sessions. Results showed no improvement in maintenance with the addition of a self-management package. Focused smoking with or without the comprehensive program achieved abstinence rates of 40 percent from 6 to 9 months after cessation. It is important to note, however, that the content of the self-control packages used by Lando and by Hackett and Horan differed. Danaher (*12*) also failed to find any advantage of including self-control training with rapid smoking or with a normally paced "placebo" alternative.

Therapist Contact

Another approach to maintenance has been increased or varied modes of therapist contact. Schmahl et al. (*44*) found that subjects called biweekly by a research assistant to check on progress following cessation were *more* likely to relapse than were those called only monthly. Similarly, Relinger and his colleagues (*41*) found that increased therapeutic contact following cessation did not improve outcomes. A similar finding was reported by Lando (*28*), exploring both extent of therapist contact and magnitude of treatment. A two-stage treatment combined "laboratory smoking" and the comprehensive maintenance procedures reported by Lando (*27*). Subjects in a three-stage treatment received this combination plus a pre-cessation phase including films, pamphlets, and discussion of the risks of smoking. In an intensive contact program, subjects attended 13 or 15 treatment meetings, depending on whether they were in the two- or three-stage treatment. Minimal contact subjects attended only three or four sessions, again depending on whether they were in the two- or three-stage treatment. A significant interaction was found; subjects receiving the two-stage treatment did better in the intensive contact program, but the subjects in the three-stage treatment did better with less intensive contact. Lando (*28*) attributed his finding of relatively poor outcomes in the frequent therapist contact, three-stage group to possible "information overload" or to excessive complexity of treatment.

The finding that more contact may sometimes reduce treatment benefits points up a failing in the behavioral medicine and health education literatures. Reports often present only sketchy information on the manner in which curricula are presented. For instance, many devote little time to describing how meetings were run, what media were or were not used to support interventions, whether leaders used a didactic or a "self-discovery" approach to instructing participants, etc. Additionally, the scheduling of meetings to coincide with the natural progression of experiences prior to and after cessation is rarely discussed. An admirable exception to this latter point is a paper by Best (*4*).

Tailoring Treatments to Individual Characteristics

Treatment effects may be explored as interactions among treatment type, client type, and circumstances.

Best (*4*) explored interactions between treatments and client motivation and status on Rotter's (*43*) dimension of expectancy for internal versus external locus of control. The internal versus external (I–E) dimension was expected to interact with a "treatment focus," either satiation through doubling normal smoking rate or analyzing external cues for smoking. Satiation was expected to work better for internals since it provided a means of reducing desires for

cigarettes. Analyzing environmental cues for smoking, on the other hand, was expected to be better for externals since they would tend to be governed by such cues. The I–E variable was also expected to interact with whether or not subjects were told to "punish" relapses by smoking double their normal rate for 24 hours following any relapse. Internals were expected to benefit more from punishment since the punishment was self-managed and involved the satiation procedure directed toward urges to smoke.

The level of motivation was measured by several scales, including a semantic differential evaluation of smoking and subjects' estimates of their motivation to quit, desire to smoke, and probability of success. Several hypotheses were posed: (1) that motivation would interact with the timing of an attitude change manipulation related to the negative aspects of smoking; (2) that attempts to provoke attitude change would be more effective after quitting than before (before quitting, they might simply be met by client resistance); and (3) that this would be more pronounced among subjects low in motivation, since there would be greater difference between their attitudes prior to quitting and the attitudes encouraged in the change procedure. All subjects received individualized aversive conditioning, using rapid smoking and concentrated cigarette smoke in the treatment room.

Statistical analyses revealed significant interactions in the predicted directions between the treatment focus and the I–E variable and between the timing of the attitude change manipulation and two of the nine measures of motivation, the desire to smoke and the estimated probability of success. No significant interaction was found between the I–E measure and self-managed punishment following relapses. Using the desire for cigarettes measure of motivation and the I–E scale, subjects were coded as highly or not highly motivated and as internal or external. Depending on such status and the treatment received, they were then coded as matched or mismatched for treatment focus and for timing of attitude change. Among those matched for each, 50 percent were abstinent 6 months after treatment. Among those mismatched for each, 30 percent were abstinent 6 months later, while 25 percent of those matched on one and mismatched on the other variable were abstinent. Analyses of the percentage of pre-treatment levels still smoked at 6-month followup showed a significant difference between the matched-matched (30.4 percent) and mismatched-mismatched (75.2 percent). Several problems limit this study. First, a control condition that did not manipulate the procedures with which subjects were matched or mismatched in other conditions was not significantly less successful than the best of the other conditions. Second, in order to demonstrate the clinical utility of tailoring by individual differences, one

special emphasis on teaching skills in recognizing and resisting social pressures to smoke.

would have to show that such tailoring was more successful than simply assigning all participants to the best available treatment.

Antecedents of Relapse

Social models and pressures to smoke, drink, or take drugs and feelings of frustration, anxiety, or sadness may frequently precede relapse (*32*). In this analysis, social pressure was divided into two classes, direct and indirect. Direct social pressure involved offering or encouraging consumption. Indirect social pressure primarily included other people smoking, drinking, etc., in one's presence. For alcohol and drug groups, 14 percent and 28 percent of relapses, respectively, were in response to direct social pressure, but only 4 and 6 percent followed indirect social pressure. For smokers, this was reversed; direct social pressure preceded 6 percent of relapses, but 19 percent were preceded by indirect social pressure.

The findings of Marlatt and Gordon (*32*) have been replicated by Lichtenstein et al. (*30*). Subjects who had quit on their own and then relapsed reported that social pressure, interpersonal conflict, and negative emotional states accounted for 80 percent of the relapses. These same circumstances also accounted for 80 percent of the relapses studied by Marlatt and Gordon. The subjects interviewed by Lichtenstein et al. reported more social pressure (48 versus 25 percent) and fewer negative emotional states (20 versus 43 percent) as antecedents of relapse than did the subjects studied by Marlatt and Gordon, but the general pattern remains similar. One area of appreciable difference between the two studies concerns "urges and temptations," coded as the major antecedent of relapse for 18 percent of subjects interviewed by Lichtenstein et al., but for only 6 percent of those studied by Marlatt and Gordon.

Lichtenstein et al. (*30*) also asked subjects about the circumstances surrounding their relapses. Most took place either at home or in a bar, tavern, or restaurant. Only 7 percent took place while working. Other persons were present at 83 percent of the relapses, 59 percent occurred in small groups, but only 5 percent at parties, reflecting the setting in which indirect social pressure may occur. Sixty-two percent of relapses occurred when other people were smoking; 46 percent of relapse cigarettes were requested from others, 11 percent were offered by others, and only 27 percent were bought. Thirty-six percent of subjects said they were drinking alcohol at the time of their relapse.

An important pattern emerging from the survey of Lichtenstein et al. that describes the impact of social facilitation of relapse and the social atmosphere surrounding relapses: others are present (83 percent), they are often smoking (62 percent), and they are often the source of the relapse cigarette (57 percent). The importance of these factors is reflected indirectly in respondents' answers to a question

regarding what they thought would be "most helpful" in quitting and in remaining abstinent. Answers varied widely, but the most frequent was social support, mentioned by 25 percent.

Shiffman (*46*) studied relapse crises described by callers to a smoking cessation hotline. Relapse crises were situations threatening continued abstinence, defined by the subjects' decisions whether or not to call the hotline. Sixty-one percent of the callers had not relapsed. Callers had to have been abstinent for at least 2 days. The median number of days abstinent was 9.7, but duration of abstinence ranged up to 2 years.

Shiffman's results were similar to those of Lichtenstein et al. (*30*) and Marlatt and Gordon (*32*). Although 56 percent of the crises took place in the callers' homes, in contrast with 26 percent of relapses in the sample of Lichtenstein et al., others were present during most of the crises (61 percent). Someone else was smoking in 32 percent of the situations. Thus, social facilitation and modeling are again implicated in relapses.

Relapse crises were often preceded by consumption of food (29 percent), alcohol (19 percent), or coffee (18 percent). These data may be understood in conjunction with the withdrawal symptoms that accompanied 53 percent of the crises. It may be that food, alcohol, or coffee serve as conditioned stimuli for urges to smoke. Shiffman's sample suggests this possibility in that half of the subjects had been abstinent fewer than 10 days at the time of their crises, perhaps accentuating the role of withdrawal symptoms.

Affect and stress were also found by Shiffman to be major antecedents of relapse crises. Seventy-one percent were preceded by negative affect, 42 percent of all callers indicated their crises were preceded by anxiety, 26 percent by anger or frustration, and 22 percent by depression (callers could cite more than one antecedent of relapse).

Relapse crises were coded as to the circumstance or setting most responsible for them. Fifty-two percent were coded as negative affect or stress and 32 percent as smoking stimuli, most often the smoking of others, but also including the presence of cigarettes, ashtrays, and so forth. Together, these two categories accounted for 84 percent of the crises, almost matching the 80 percent of the relapses attributed to interpersonal conflict, negative emotional states, and social pressure found by Lichtenstein et al. (*30*) and Marlatt and Gordon (*32*).

The factors governing whether or not relapse crises actually resulted in smoking were explored in analyses of over 30 variables. Only a few were significant. The presence of another smoker, the consumption of alcohol, and the location of the occurrence were all instrumental. If another smoker was present, 54 percent of the crises led to relapse, as opposed to only 32 percent in the absence of other

smokers. When alcohol was consumed, 61 percent of crises led to relapse, as opposed to 33 percent in the absence of alcohol. Finally, being at home or at work was relatively safe; only 33 percent of crises in these settings led to relapse, as opposed to 57 percent in other settings. This replicates the findings of Lichtenstein et al. that relapses occurred less frequently when respondents were alone or at work.

Coping strategy reports differentiated crises that did and did not lead to relapse. Subjects using behavioral coping strategies (e.g., leaving the situation) relapsed in only 28 percent of crises in contrast with 58 percent of those who did not. Similarly, those who did and those who did not employ cognitive coping strategies (e.g., talking oneself out of an urge) relapsed 30 and 55 percent of the time, respectively.

Reports of types of coping used were associated with other aspects of crises. Behavioral coping was reported less often when respondents had been drinking than when they had not. Use of cognitive coping, however, was not influenced by alcohol.

Depressed mood was also related to cognitive and behavioral coping skills. A greater percentage of subjects reporting cognitive coping overcame crises centered on depressed moods than of those reporting behavioral coping strategies. Only a modest difference favoring behavioral coping was found in the success rates for subjects with crises centered on moods other than depression. Of course, associations among subjects' reports of moods, actions, and outcomes need to be interpreted cautiously. Social perception and labeling processes (*2*) may distort them. They may also reflect interactions among length of abstinence, type of crisis precipitant, and use of coping skills. For instance, after several weeks of abstinence, when negative emotion may be more related to relapse (*38*), ex-smokers may grow weary of the vigilance or effort demanded by behavioral coping strategies and either stop using them or use them with less vigor and, thus, less effect.

Differences among the findings of Marlatt and Gordon (*32*), Lichtenstein et al. (*30*), and Shiffman (*46*) may be attributed in part to differences in their samples.

In addition to the antecedents of relapse, the "abstinence violation effect" may lead some to give up the attempt to maintain abstinence or control (*32*). The abstinence violation effect is a hypothesized reaction to first relapse and entails the attribution to oneself of insufficient skill to maintain abstinence, feelings of dejection over relapse, and anticipation of positive benefits from the use of the previously denied substance. The abstinence violation effect and Shiffman's findings regarding cognitive coping skills suggest several treatment approaches. These include the correction of misattributions of relapse to immutable personal failings, as well as procedures

to teach cognitive and behavioral skills with which to cope with social pressures or with troublesome emotions leading to relapse. Several reports of such procedures used with smokers have not indicated success (*6, 20*).

Social Support

As reviewed above, many relapses take place in social circumstances and in apparent response to social facilitation by other people smoking. Furthermore, those surveyed by Lichtenstein et al. (*30*) identified social support as a potential aid in maintaining abstinence. The importance of social support is suggested further by findings, for instance, that the presence of a smoking spouse is related to smoking status (*22*) and to relapse following smoking programs (*51*). Returning to smoking following abstinence has also been found by Eisinger (*14*) to be inversely related to the proportion of former smokers among the friends of the individual.

In spite of the replication of findings linking smoking status and success in quitting with social factors, few studies have attempted to manipulate social support for abstinence. A buddy system was explored by Janis and Hoffmann (*26*), in which 30 adults in a five-session smoking cessation program were assigned to one of three treatments: "high contact" partners, who made daily phone contact with each other; "low contact" partners, who spoke to each other only at clinic meetings; and controls, who had different partners at each meeting. At followup 1 year after treatment, the high contact partners indicated smoking at only 25 percent of the levels reported at pretreatment. In contrast, subjects in the low contact group reported smoking at approximately 75 percent of pretreatment levels. Those in the control group had returned to their pretreatment levels by the time of the 1-year followup. The authors did not report abstinence data.

The role of spouses has been further explored by Mermelstein et al. (*35*) with clients of a cessation program. Respondents indicated which spouse behavior they found helpful or unhelpful. Cluster analyses of these responses identified four groups of spouse behaviors: (1) nagging or shunning, (2) policing or monitoring, (3) cooperation and advice, and (4) reinforcement and support. Cooperation and reinforcement were positively correlated with reduction or abstinence, while nagging and shunning were negatively correlated with reduction or abstinence.

Lichstein and Stalgaitis (*29*) explored "reciprocal aversion" among spouses. In this procedure, a spouse who had smoked a cigarette was responsible for telling his or her spouse of it. The spouse so informed then was also to smoke a cigarette. Six months after treatment, 5 of 10 subjects located for followup reported abstinence. If the two subjects who were unavailable for the followup are counted as still

smoking, the abstinence rate is 42 percent. The potential utility of including spouses in treatment is also suggested by the work of Brownell et al. (*7*) in weight-loss treatment administered to couples.

Powell and McCann (*39*) combined an intensive 1-week treatment program with three maintenance conditions manipulating social support: a 4-week support group in which thoughts and feelings could be discussed, a 4-week telephone contact system for group members, and a no-contact control group. All subjects received the same cessation treatment and a series of self-help maintenance messages at the final treatment session before being divided into the three maintenance programs. At the end of treatment, 100 percent of the 51 subjects completing treatment were abstinent. At 1-year followup, 63 percent of the subjects reported total abstinence. There were no significant differences among the three maintenance programs and no gender differences in abstinence. The unexpectedly high long-term abstinence rates, therefore, cannot be attibuted to either of the social support maintenance conditions. The authors suggest that the self-help maintenance message manual received by all groups may alone have been sufficient. Furthermore, self-control techniques learned during the program may have served as appropriate maintenance tools.

The power of social support as a component in cessation and maintenance strategies may be imputed from the results of the Multiple Risk Factor Intervention Trial (MRFIT) available to date (*24, 35a*). This unique study constituted a 6-year clinical trial utilizing random assignment to treatment (Special Intervention) and control (Usual Care) conditions. It investigated the effects of reducing three cardiovascular risk factors (elevated cholesterol level, hypertension, and smoking) in a large sample of asymptomatic men in the upper ranges of heart disease risk. The Usual Care (UC) condition was not a non-treatment control group. Participants knew of their elevated risk status, were contacted at 4-month intervals, and received annual examinations and testing. The Special Intervention (SI) group consisted of 4,103 smokers, aged 35 to 57, who received an intensive 10-week group intervention program for simultaneous reduction of all three risk factors, followed by continued maintenance of abstinence or extended intervention to lower CHD risks. All return visits (annual physical examinations, data collections at 4-month intervals, and more frequent visits for risk-factor management) provided opportunities for intervention. Techniques used in the 10-week cessation program excluded aversive methods such as rapid smoking, satiation smoking, and warm, smoky air because of potential health risks and to pursue the goal of maximizing subject retention in the program. A wide variety of educational and behaviorally-based cessation techniques were utilized in small groups of 6 to 10 participants and their wives, led by

professional counselors. Wives were invited to participate in the smoking cessation program, and to provide support and reinforcement for their spouses. In addition to spousal involvement, group support, utilization of group dynamics, and generalization of learning were invoked to enhance cessation efforts.

Abstinence rates for men in the SI condition were high, estimated at 47.3 percent at the end of intervention (4 months) and at 45.9 percent at 48-month screening, using both self-report and objective measures of smoking cessation (serum thiocyanate level). Conservative estimates counting missing subjects as smokers were 43.9 percent and 40.3 percent, respectively (*24*). Greater reduction of smoking occurred among UC participants than was anticipated (*35a*). Quit rates were adjusted using serum thiocyanate levels to correct for underreporting of smoking in both groups. The adjusted quit rate difference between SI and UC groups was approximately 18 percent, decreasing only slightly from 20 percent at 12 months to about 19 percent at 48 months. For third and fourth years of the study, the observed differences in overall cigarette smoking reductions between SI and UC groups exceeded predictions.

Among the many results reported for this study was the identification of subgroups of smokers: those who can quit with minimal assistance; those who can quit with the aid of a formal cessation program; those who are unable to quit with any technique provided; and those who are capable of quitting and remaining abstinent only while in contact with a formal program.

While the MRFIT program represents a special group of persons—men at high risk for cardiovascular disease—who received perhaps the most extensive intervention/maintenance program ever devised for smoking cessation, the results deserve close scrutiny for the wealth of relationships to be measured and the generalizations that can be made to smoking research and intervention as a whole.

Predictors of Outcome

Pomerleau et al. (*38*) found that a lower pre-treatment rate of smoking, fewer number of years smoked prior to quitting, lower percent overweight, and compliance with a record-keeping requirement of treatment all predicted abstinence at the end of a 2-month cessation program. These variables, however, were not related to abstinence 1 year after treatment. Rather, extended abstinence was inversely related to the extent to which subjects indicated that negative affect was a mood most likely to lead to smoking. Subjects were asked to list five moods in order of the likelihood that they would lead to smoking. Those mentioning negative moods as most likely to lead to smoking were coded as "negative affect smokers." Among them, only 26 percent were abstinent 1 year later in comparison with 50 percent of those who were not negative affect

smokers. This also supports the findings on the role of negative emotions in relapses cited above.

Results analyzed to date from the MRFIT trial show that lighter smokers were more successful in quitting than heavier smokers (*24*). At end of treatment, conservatively estimated abstinence rates for light (1 to 19 cigarettes/day), medium (20 to 39 cigarettes/day) and heavy ($\geq$40 cigarettes/day) smokers were, respectively, 66.8, 46.7 and 35.3 percent. At 48-month evaluation, these rates were 66.1, 42.8, and 31.2 percent respectively. The recidivism rate is thus also lower among the lighter smokers. Relationships between success in quitting and psychosocial or demographic variables are not yet available.

Emerging from several findings reviewed here is the distinction between smoking as a habit and smoking as a response to negative moods. The results of Pomerleau et al. (*38*) suggest that initial success in quitting is closely related to the extent to which smoking has been an overlearned habit, as gauged by number of years of smoking and number of cigarettes smoked per day. However, having quit, the likelihood of remaining abstinent may be more closely related to the extent to which smoking is cued by negative moods. This pattern suggests that cessation strategies should concentrate on breaking habits and that maintenance strategies should concentrate on coping with negative moods.

Contradictory findings were reported in a recent study by Flaxman (*19*). She explored relationships among factors derived from the subjects' scores on Horn's Reasons for Smoking Scale and the subjects' reports of self-control techniques used to prolong abstinence following a smoking cessation clinic. Flaxman reasoned that, if self-control techniques varied in their effectiveness for different types of smokers, they should be more closely related to measures of type of smoker among successful quitters than among the unsuccessful. This expectation was confirmed. Reports of use of relaxation and thought stopping were more highly correlated with measures of smoker types among those abstinent than among those nonabstinent at a followup 1 or 6 months after cessation. However, the use of these two procedures was more closely related to a factor representing the extent to which smoking is a firm habit than to factors measuring emotional causes of smoking. It had been expected that reported use of relaxation, especially, would be more related to the measure of emotional causes of smoking. The import of Flaxman's paper is limited by a design problem. The outcome data for 65 percent of the subjects were gathered at a 6-month followup, but data for the other 35 percent were based on 1-month followup. Pomerleau et al. (*38*) found smoking habit and history to predict abstinence at the earlier followup, but status as a negative affect smoker was found to predict the later outcome. The failure of Flaxman's paper to replicate these

latter findings may be due to combining data from different followup intervals for which the findings would be expected to vary.

A final predictor of outcome is self-perception, the extent to which subjects see themselves as responsible for changes they make or as having a good chance of maintaining them. Bandura's concept of perceived self-efficacy (*1*) has drawn attention to such factors in many areas of psychology.

Colletti and Kopel (*9*) and Fisher et al. (*16*) found abstinence at followups positively related to measures of the extent to which subjects attributed their cessation to their own efforts, skills, or changes in attitudes. Such self-attribution was contrasted with attribution to external factors such as luck and the skill of the group leader.

Finding self-attribution of change related to positive outcomes suggests more recent concepts of self-efficacy (*1*). Self-efficacy refers to the extent that one feels he or she has the skills or abilities necessary to accomplish a goal. Cooney and Kopel (*11*) increased self-efficacy by giving group participants a "controlled relapse" in which they gained experience at handling a slip. Contrary to the hypothesis, those with self-efficacy most enhanced by this procedure were most likely to relapse. Shiffman et al. (*47*) also found this pattern among callers to a relapse prevention hotline. Reported levels of self-efficacy prior to a relapse crisis were greater among those who had returned to smoking than among those who had not. However, Condiotte and Lichtenstein (*10*) found general levels of self-efficacy regarding outcomes related to observed outcomes. Resolution of this is suggested by Gottlieb et al. (*21*) showing that general confidence regarding long-term abstinence and low confidence for dealing with "slips" both predicted reduction in smoking 1 and 4 months after cessation. The findings of Cooney and Kopel (*11*) and Shiffman et al. (*47*) both pertain to self-efficacy for dealing with a slip while those of Condiotte and Lichtenstein (*10*) pertain to more generalized confidence in outcomes.

Implications

There are a number of promising approaches to encouraging continued nonsmoking that go beyond strong cessation procedures and focus on maintenance itself. These approaches may be divided into those that try to make smoking cessation clinics better, and those that look for alternatives to smoking cessation clinics.

A number of ways to improve cessation clinics may be extracted from the papers reviewed. Perhaps most current is the focus on antecedents of relapse: the emotions of frustration, anxiety, anger, and perhaps sadness, as well as the social models and cues and settings that seem to bring on relapses (*30, 32, 46*). Skills for dealing

with the emotional antecedents may be developed, perhaps sharpening the focus of previous successful self-management approaches to maintenance (*27*). Clarifying cognitive coping skills (*46*) and finding ways to teach them may be helpful. They may be more versatile or simply more acceptable to people than the more overt behavioral coping approaches. While most smoking programs are conducted in groups, it may be that those groups can be made stronger counterforces to the social cues that seem to encourage relapse.

Outcomes are sometimes better with less rather than more therapeutic contact. This and the improvements observed through tailoring treatments to individual characteristics suggest another dimension for improving cessation programs. In the review of Best's (*4*) findings regarding results of tailoring treatment to subjects' levels of motivation and internality versus externality, the findings did not seem strong enough to provide a basis for individual clinical decisions. Nevertheless, the findings do suggest the importance of packaging treatment components so that they will be well accepted by target audiences. The timing of manipulations, especially those intended to shape or alter attitudes, needs to be considered carefully. Satiation or aversion procedures may be best presented in a way that offers the individual whom they do not suit a way to decline their use without taking the role of a noncompliant deviant within the program.

The findings of Condiotte and Lichtenstein (*10*) that subjects can predict the situations in which they relapse further support the possible utility of self-tailoring. So, too, does the finding of 6-month abstinence rates of 33 percent and 29 percent in two separate studies (validated by saliva thiocyanate) using no aversive procedures but a self-control package in which subjects develop their own specific self-control strategies based on their own needs as they judge them (*31*). More generally, these results suggest that participant's subjective evaluations of program components need to be considered.

Programs conducted through institutions may hold much promise as alternatives to cessation clinics. Including incentives or reinforcements for nonsmoking may prove beneficial. While cessation clinics may be part of such programs, use of the institution's organizational features to support, encourage, and reinforce nonsmoking should extend far beyond a cessation clinic meeting held once a week. The social and organizational factors that may be harnessed to encourage nonsmoking appear to have only begun to be identified. Some social support interventions have been effective (*26, 29*). Reliable findings link social cues, smoking friends, and smoking spouses to relapses and smoking (*14, 22, 30, 32, 46, 51*). These findings suggest that harnessing social forces to encourage nonsmoking will be productive.

Summary

1. Until recently, the long-term outcome of intensive smoking cessation clinics has remained at 25 to 30 percent abstinence. New emphasis on techniques to improve the maintenance phase of cessation promises to improve these rates, with several reports of greater than 50 percent abstinence at followups of 6 months or longer.
2. To improve maintenance of nonsmoking after intensive treatment programs have ended, reinforcement should be built into the natural environment. Smoking cessation programs in the workplace may offer an opportunity for this.
3. Comprehensive self-management packages that have been shown to boost maintenance rates include a wide variety of techniques.
4. Treatment outcome may be improved by focusing on the antecedents of relapse. These include feelings of frustration, anxiety, anger, and depression as well as social models and smoking-related cues and settings. Behavioral and cognitive skills for dealing with such antecedents should be developed.
5. Social support interventions are promising. Reliable findings link social cues, smoking friends, and smoking spouses to relapse, whereas the presence of group support, nonsmoking spouses, and professional contact decreases recidivism.

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PREVENTION IN ADOLESCENCE: INITIATION AND CESSATION

Introduction

In this section, what is known about spontaneous cessation rates in adolescence and the predictors of spontaneous cessation in adolescence will be considered.

Spontaneous Cessation Rates

Spontaneous cessation rates in adolescence may be estimated from several data sources. However, comparisons between studies are difficult to make because of the variety of ways the cessation question has been asked. Often the "quit" category is in reality a residual category without precise meaning. A distinction probably should be made between cessation from regular use and cessation from occasional or experimental use (*17*). Also, the way data usually are reported, the totality of cessation can only be implied. All persons who perceive themselves as having quit are grouped together, whether the last cigarette was smoked years before or only days earlier. Most studies reporting cessation rates are retrospective, although there are exceptions (most notably *14*).

With these data limitations in mind, four sources of data on smoking cessation in adolescence are considered. It has been necessary to conduct secondary analyses on published data found typically in tabular form in order to estimate spontaneous cessation rates, since cessation was not the focus in any of these studies.

Johnston, Bachman, and O'Malley (*23, 24*) conducted annual national surveys of high school seniors to study trends in the prevalence and frequency of recent drug use and, retrospectively, when several types of drugs were first used. The numbers of persons reporting having smoked "regularly in the past" (but not now) has remained stable from 1975 to 1978 (the last year reported to date). The proportion of high school seniors reporting regular smoking (half a pack per day or more) in the past but not now was 8.6 percent, 9.2 percent, 8.8 percent, and 9.1 percent for 1975, 1976, 1977, and 1978, respectively. By summing the use categories, "regularly in the past" and "regularly now," it is possible to estimate the proportion of one-time regular smokers who have stopped. For 1975, 1976, 1977, and 1978 the proportion of regular smokers who had quit was 28.2, 35.3, 27.0, and 28.5 percent, respectively, an average of 29.8 percent, with no apparent temporal trend.

In the only study to date reporting a prospective analysis of smoking cessation in adolescence, Green (*14*) reinterviewed by telephone 1,194 of 2,553 respondents (ages 17 to 23) who had been interviewed 5 years earlier as part of a national survey of smoking

behavior in youth. She found that 27 percent of the original "current regular smokers," those smoking one or more cigarettes per week, had stopped smoking and continue not to smoke. These figures, although they include less frequent smoking as part of the "regular" smoking category, are similar to the cessation rates of the Johnston (*24*) respondents.

In a longitudinal study of junior high school students in suburban Minneapolis, Luepker et al. (*26*) enhanced the validity of cessation estimates by collecting saliva samples for thiocyanate analysis (*27*). If only those persons who report smoking twice or more monthly are counted as smokers, the proportion of quitters by ninth grade was 26.5 percent, a figure that is comparable to the cessation rates for high school students reported by Johnston et al. (*23*).

A study of drug use among 13- to 19-year-old Vancouver, British Columbia secondary school students reports cessation rates for less frequent users (*16*). In 1974, 63.9 percent of all respondents reported having smoked at some time in their lives. Forty-three percent of these "ever smokers" were still smoking, and 57 percent had stopped. Of the 1978 cohort, 72.1 percent reported having ever smoked. Of these, 40.4 percent said they were still smoking and 59.6 percent said they had quit.

The Chilton survey data as presented by Green (*14*) were reanalyzed for reports of duration since last cigarette to help interpret the meaning of cessation for these adolescent groups. Only 1 percent said they had quit within the last month, giving some assurance that the "quitter" category did not contain a high proportion of wishful thinkers. Still, 28.9 percent said they quit between 1 and 5 months before the followup survey, and 13.4 percent said they quit 6 to 11 months before. Expected quit rates for those periods (based on 1.67 percent per month for 60 months) were 7.3 and 10.0 percent, respectively, suggesting that a substantial proportion of recent "quitters" would remain abstinent for a relatively short duration. If 6 months' abstinence is taken as a criterion for cessation, 70.1 percent of self-proclaimed quitters qualify. At an average monthly quit rate of 1.30 percent for 54 months, we would expect about 78 percent of "quitters" would be enduring quitters, or a stable quit rate of about 21 percent instead of the 27 percent reported by Green. This does not represent a substantial difference and may even somewhat underestimate true cessation. Nevertheless, the bias from reports of recent quitting should be kept in mind in estimating the range of possible adolescent cessation rates.

In the Chilton survey, 91.8 percent expressed interest, either by cessation attempts or by positive responses to a questionnaire item, in stopping smoking. This compares favorably with results found among adults surveyed in 1975 with 86.2 percent of males and 84.8 percent of females not wanting to continue to smoke (*7*).

In summary, the spontaneous smoking cessation rate among adolescent regular smokers (those who smoke once a week or more often) appears to be between 20 and 30 percent. Cessation rates are higher if experimental and occasional smokers are considered as well.

Predictors of Spontaneous Cessation

In 1979, Green (*14*) reported the results of a followup interview of two national samples interviewed as adolescents 5 years earlier. At the time of the followup interview, respondents ranged in age from 17 to 23 years, and 47 percent of the original 2,553 were successfully reinterviewed. Older groups (who tend to smoke more) and smokers within each age cohort, especially female smokers, were underrepresented in the followup interviews, resulting in a possible overestimation of spontaneous cessation (reported to be 27 percent for the 5 years).

Retrospective Predictions

Green reported the retrospective associations between various "predictor" variables measured in 1979 and smoking transitions between 1974 and 1979.

Reported cessation rates were the same for both sexes, which were 28.0 percent for males and 25.7 percent for females. Age was a significant factor. The highest cessation rates (31.5 percent) were found in the 20- to 21-year-old cohort (15 or 16 at time of the original survey). The 17- to 19-year old cohort (12 to 14 at original survey) had the lowest cessation rate: 18.2 percent. The oldest cohort, age 22 to 23 (17 or 18 originally), had a moderate spontaneous cessation rate: 26.3 percent.

Prospective Attitudinal Predictors

Green (*14*) explored changes in smoking behavior prospectively by creating 8 factors from 24 questions about smoking attitudes. Two of the eight factors were significant prospective predictors of cessation. Those who had given up smoking by 1979 were less likely in 1974 to have held to "stereotypes of smoking." That is, those who continued as smokers were more likely than those who became quitters to agree with the statements, "Most girls start smoking cigarettes to attract boys," "Most boys start smoking cigarettes to try to become popular," and "If you don't smoke cigarettes other teenagers put you down." This may represent a greater sensitivity to or belief in social influences to smoke and may have motivated continued smoking. Quitters were also less likely to adhere to "stereotypes of smokers." Those still smoking in 1979 were more likely than quitters to have agreed in 1974 with the statements, "Kids who smoke are showoffs,"

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"Teenage smokers think they are grown up but they really aren't," and "Teenage smokers think they look cool, but they don't really." There is some irony in the way that nonquitters perceived the social plight of smokers. Whereas they saw smokers as more responsive to what they believed to be social benefits of smoking, they seemed to perceive the actual social consequences in a more negative light (e.g., "...think they look cool, but they don't really"). The original nonsmokers were the group with the strongest stereotypic beliefs about smokers and those who continued to smoke, more than those who quit, shared this somewhat negative view of smokers. This pattern is consistent with findings that adults who fail in cessation programs tend to have lower self-esteem than those who succeed (*35*).

Social Influences

Smoking by parents, older siblings, and peers all have been shown consistently to predict the *onset* of smoking in adolescents, both by retrospective and prospective association (*3, 32, 33, 35*). Flay et al. (*13*) found that parental smoking had a different effect on cessation than on smoking onset. The probability of experimental or regular (one or more weekly) smoking was 9.7 percent for 6th graders if neither parent smoked, 18.0 percent if one parent smoked, and 21.9 percent if both smoked. Cessation probability (denominator includes experimenters) was 35.5 percent if neither parent smoked, but 44.8 percent if one parent smoked, and 47.9 if both smoked. Given that both current regular and experimental smokers were included in the denominator when these figures were computed, this unexpected finding could be taken to mean that although children of smoking parents are more likely than others to try smoking by sixth grade, this greater tendency is expressed largely in experimentation, from which experimenters typically revert quickly to nonsmoking status.

Secondary analyses of the published Chilton survey data (*14*) reveals that, by retrospective association, smoking by older siblings was associated with cessation probability. Among respondents with older siblings, the probability of quitting was 25.3 percent if no older sibling was smoking at the time of the followup interview, and 32.4 percent if one or more siblings smoked; the probability was 27.3 percent for those who had no older siblings. This finding is consistent with that reported by Flay et al. (*13*), and suggests that a large portion of the excess smoking due to family influences was experimental smoking that was likely to be given up.

Spielberger et al. (*41*) recently reported a study of smoking habits in 955 college students with a median age of 19. They examined differences in family smoking patterns among current smokers, occasional smokers, and ex-smokers in this sample. Overall, it appeared that neither parental nor sibling smoking habits differentiated these groups. This conclusion may obscure important sex

differences. In males, more ex-smokers come from families in which neither parent smokes, as expected. Among females, ex-smokers are more likely to come from families in which at least one parent smokes. In the NIE survey, boys whose siblings do not smoke are least likely to be ex-smokers; the highest quit rates were reported among boys who came from families where one, but not both, siblings smoked (*14*).

Cessation probability was even more closely related to the smoking practices of close friends. The likelihood of a smoker's quitting was 50 percent if none of his or her four closest friends smoked regularly, and was 23.4 percent if one or more smoked regularly.

Previous research has shown consistently that level of education is inversely associated with cigarette smoking behavior (*42, 43, 44*). This relationship also occurs with adolescent cessation rates (*14*). The probability of cessation was 42.0 percent for 1974 adolescent smokers who had at least started college by 1979 and 24.6 percent for smokers who did not go to college. For those who failed to complete high school, the cessation probability was only 10.3 percent. Smoking onset rates after 1974 were 14.8 percent for those who started college, 25.6 percent for those who did not, and 35.9 percent for those who did not complete high school (*14*).

The probability of quitting decreased linearly with the duration of the smoking practice (Figure 1). There was a 64.5 percent probability of quitting in the first year of smoking, declining to 30.8 percent by the third year, and to 14.3 percent after 7 years. This finding is consistent with the results reported by Pomerleau et al. (*38*) that adults in a cessation clinic were less successful the longer they had smoked. However, Hansen (*15*) found no relationship between spontaneous cessation of adolescence and duration of the smoking practice.

Age of onset, surprisingly, was earlier for ex-smokers than for those who still smoked. Cessation probability was 49.4 percent for those who began regular smoking at age 13 or 14 and 37.2 percent for those who began at age 15 or 16, 32.5 percent for those who began at age 17 or 18, and 30.1 percent for those who began at age 19 or older.

Studies have shown that quitting "cold turkey" is a more effective cessation strategy for adults than is trying to cut back gradually (*35*). The Chilton survey suggests as much for adolescents as well. Of those who said they had tried to cut down without trying to stop entirely, eventually 24.0 percent went on to quit. Of those who said they had never tried just cutting back, 38.6 percent successfully quit smoking (*14*).

Quitting appears to have been the result of persistence more than anything else, since 73.4 percent of smokers who kept trying to stop eventually were successful. Figure 2 reveals the cumulative probability of stopping smoking at each successive try. Whereas only 24.7

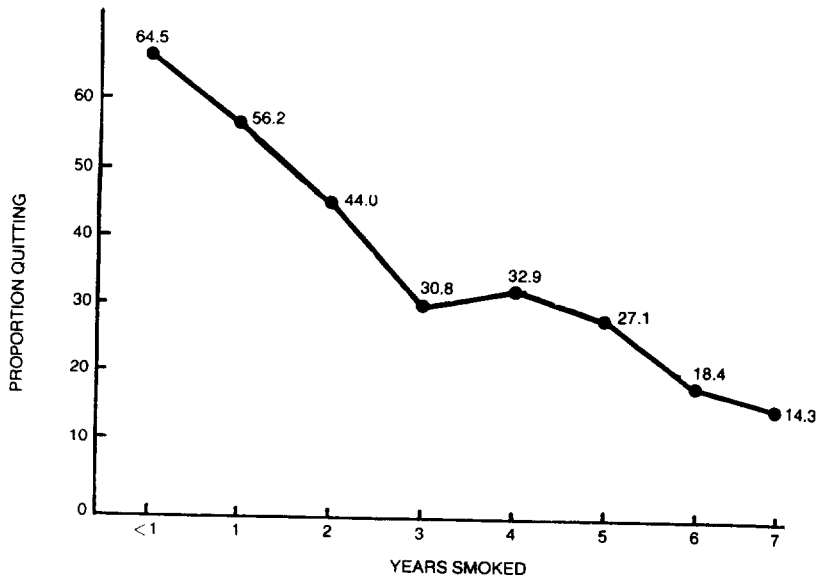

FIGURE 1.—Probability of quitting smoking in adolescence and duration of smoking practice

SOURCE: Green (*14*).

percent were successful the first time they tried, 38.4 percent were successful by the second attempt, 58.6 percent by the third attempt, and 73.4 percent by the fourth or more try. One can conclude that persistence pays off. Still, only 27 percent of original smokers had quit by the time of the 5-year followup interview, presumably because more than a third (37.8 percent) of those still smoking had never tried to stop, and 35.6 percent of those who had tried only tried once. Repeated cessation attempts may indicate stronger motivation to stop. In addition, coping skills may be learned with conscientious repeated attempts to stop smoking, increasing the possibility of success. At the same time, repeated failures probably reduce expectations of self-efficacy (*2*), decreasing the likelihood that one will try again.

The intensity by which the practice of smoking occurs ought to be a predictor of cessation probability. Studies with adults have shown that the number of cigarettes smoked (*3*) and cigarette nicotine/tar content (*39*) are related to cessation probability. The number of cigarettes smoked per day was associated with cessation probability (Table 1) (*14*). Cessation probabilities declined in a roughly linear fashion from 65.8 percent for those who never smoked more than one cigarette per day to 22.2 percent for those who had advanced as far as 25 to 34 per day. Cessation probability for those smoking more

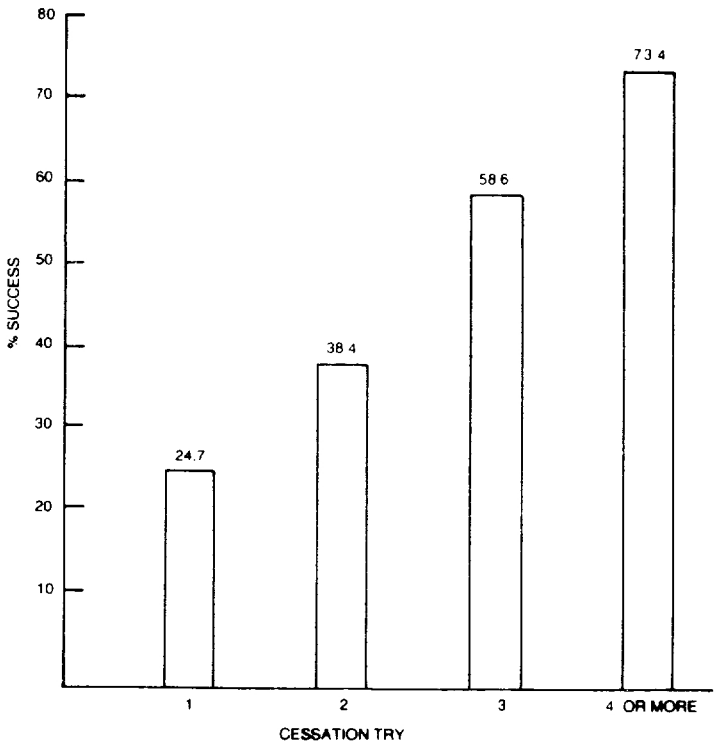

FIGURE 2.—Cumulative probability of quitting smoking in adolescence and number of tries

SOURCE: Green (*14*).

than 34 per day was 48.4 percent. Whether this means that reaching higher smoking levels provides an extra impetus to stop, or whether the results are a chance finding perhaps due to sample bias, is unknown. Excluding the heavy use category, the pattern is similar to the association between frequency of smoking and cessation probability for adults reported elswehwere (*38*). The findings are also similar to other findings reported for adolescents (*15*).

In a study of 76 high school smokers, age 16 to 18, Hansen (*15*) found that regularity of smoking pattern was signficantly associated with cessation probability ($r = -0.40$). Those who smoked in a more regular and predictable fashion were less likely to stop smoking than those who smoked without apparent pattern. This effect still held when controlling for amount smoked per unit time. It may be that "pattern" smokers were maintaining or achieving what was for them an optimal dosage level upon which they became dependent, or it may be that smoking was in response to predictable environmental

TABLE 1.—Frequency of smoking and probability of cessation in adolescence

Number of cigarettes	Cessation probability (%)
Less than everyday	65.8
1–4/day	50.0
5–9/day	45.5
10–14/day	27.1
15–24/day	29.5
25–34/day	22.2
≥35/day	48.4

SOURCE: From the NIE-sponsored Chilton Survey; Green (*14*).

demands or stressors (*38*). Either would predict greater cessation difficulty for "pattern" smokers.

Recent Developments in Smoking Prevention Programs

Smoking prevention has been espoused as a desirable alternative to cessation programs aimed at youth. This position is based on the arguments that (1) more young people can be reached in prevention than in cessation programs, (2) preventing the onset of smoking is easier than eliciting and maintaining cessation, (3) smoking of even short duration may be harmful to some, and (4) even if programs only delay rather than truly prevent the onset of smoking, there will be substantial health benefits to the population for whom the delay has occurred.

Recently a number of researchers have developed and tested adolescent smoking prevention programs (*4, 5, 11, 12, 13, 18, 20, 21, 28, 29, 40*). Critical reviews of these recent prevention programs are Johnson (*19*), Flay et al. (*13*), and Evans (*9*). The programs that have met with consistent success share a number of features in common. All have been based on social-psychological theory and research, most notably on attitude change theory (*31*), social learning theory (*2*), and attribution theory (*25*). All have been school-based programs targeted for the most part at seventh grade students.

Evans (*8*) developed the first of several recently tested social-psychological strategies for deterrence of cigarette smoking in youth. Although the original study (*12*) did not show experimental interventions to be superior to just monitoring smoking behavior periodically, it did establish the rationale and feasibility of several social-psychological principles for an adolescent prevention program. Emphasis was on the short-term consequences of smoking; films were used extensively to demonstrate typical pressures to smoke from peers, parents, and media, and to depict role models resisting smoking pressures. Students were encouraged to develop counter-

arguments against smoking in order to strengthen themselves against future persuasion attempts (*30*). Evans (*9*) has been especially interested in developing social modeling films that would provide a standard and easily transportable medium for the prevention message. Although the effectiveness of standard films used alone is not yet established (*19*), the general approach to role model presentation employed by Evans has been used in other social-psychological prevention research efforts of this type. A methodological contribution was the use of saliva sample collection (for nicotine analysis) to augment the validity of self-reports about smoking. Evans et al. (*10*) found that persons were twice as likely to report smoking when self-reports were preceded by saliva collection for analysis than when not.

McAlister and others (*28, 29, 36, 37*) of Stanford and Harvard also used role models to teach smoking resistance skills. Their role models were live, rather than on film, and consisted of a team of five to seven students from a nearby high school recruited and trained to conduct six sessions in seventh grade classrooms. Skills training was more active as well, employing role-playing of resistance techniques. Although at the start of the sessions in the fall more persons in the treatment school (2 percent) than in the control school (0.9 percent) said "yes" to the question "Have you smoked in the last week?," by spring, 10.3 percent in the control condition and 5.3 percent in the treatment condition reported smoking in the previous week. In May 1980, 2 years after termination of the program, 15.1 percent and 5.2 percent, respectively, said they had smoked in the previous week (*36*). Program effects seem to have endured for at least 2 years beyond the end of the program.

McAlister et al. (*28*), report an extension of the smoking prevention model to prevent alcohol and marijuana abuse as well. There was a 4.7 percent increase and a 0.1 percent decrease in regular or experimental smoking by end of year among sixth and seventh grade students in the five control schools and five experimental schools, respectively. Finally, Perry et al. (*37*) have reported a successful replication of the 7th grade smoking program for 10th grade students, with college students acting as peer leaders. The authors report a 21 percent overall reduction in the number of self-reports of smoking in the last week, compared with the baseline number.

Johnson and Luepker at the University of Minnesota developed a similar strategy for smoking prevention in adolescents (*1, 18, 22*). Experimental adaptations of social-psychological theory were based on systematic interviews with Twin Cities seventh and eighth grade students, and scenarios for role model films and for active role playing were distilled from these interactions. As a result, the emphasis on immediate negative consequences took on a decidedly social aspect (e.g., yellow teeth, bad breath). This research program,

which was developing independent of the research at Stanford, also used peer leaders, but with two important differences. First, peer leaders were defined as same-age persons already in the classroom who are "natural" opinion leaders. Leaders were selected by peer nomination, recruited into prevention leadership status, and brought to the university for leadership training. Second, the peer leader component was tested quasi-experimentally with the prevention program implemented in one school without peer leader recruitment and in another school with peer leader recruitment. Each school was then compared with a control school in which traditional health-oriented smoking prevention was taught in compulsory health education classes by school health educators. Approximately an equal number of class sessions (five) were devoted to all three curricula. As in the Houston and Stanford programs, all sessions in the experimental schools were supervised by nonschool personnel who were members of the research team. Finally, public commitment was tested experimentally by having students in a random number of classrooms in the peer-led school give a public speech on why they would not smoke. In the fall of 1977, baseline measure students in the three schools did not differ in mean number of cigarettes smoked in the past week: 0.89, 0.46, and 0.29 in the control, social consequences curriculum, and peer-led social curriculum, respectively. By May, the average number of cigarettes smoked in the past week were 2.50, 1.47, and 0.40, respectively. By May of the following year, controls were smoking five times as many cigarettes per week as were students in the peer-led school—5.8¢ versus 1.02. By this time, smoking in the social consequences school (5.71) had ceased to differ from the control school. Two years after program termination, the mean number of cigaretttes smoked in the previous week were 10.97, 10.60, and 4.61 in the control, social consequences, and peer-led schools, respectively (*26*). As in the Stanford study, the effects of a peer-led prevention program endured for at least 2 years. An important finding from the Minnesota study was that prevention effects of an equivalent program led by adults rather than peers were weak in the short run and not measurable at 1 year. The preventive advantage of a peer-led program was particularly great for females; only with peer leader involvement was the experimental program effective with females, both in the short and long run (*22*).

A conceptual replication of the initial Minnesota smoking prevention study was begun by the Minnesota researchers in 1979. All seventh grade students in two schools were assigned to a peer-led, short-term consequences treatment, and a standard media package was used in conjunction with other activities. Students in two other schools received the same peer-led, short-term consequences program without the media package. Students in two additional schools

received the media-augmented social program taught by health educators rather than by peer leaders. Students in the final two schools received an equivalent health-oriented curriculum taught by the health educators brought in for that purpose. End-of-year data (*1*) indicate that all four programs were effective compared with an external control group consisting of seventh grade students not receiving a program in the previous year. By spring of the following year, the peer-led program with media appeared to be most effective, and the teacher-led health program was least effective in preventing onset of regular (weekly or more) cigarette smoking. Currently, a replication is underway with school health educators teaching or supervising in the various schools.

In addition to theory-based experimental tests of program effects, the Minnesota group has developed biochemical assays for independent validation of self-reports (*27*). The Minnesota group has found that post-treatment saliva thiocyanate levels are greater in control groups than in treatment groups and, like Evans et al. (*10*), that self-reports of smoking are twice as likely when saliva samples are collected prior to self-reports.

Botvin et al. (*4, 5*) have reported a more general approach to life-skills training for prevention of cigarette smoking. This program consists of 10 weekly sessions designed to teach skills necessary to resist social pressures to smoke, to develop students' autonomy and thereby reduce their susceptibility to indirect social pressures to smoke, to develop self-esteem and self-confidence, and to provide a means of coping with anxiety. Hence, the approach begun by Botvin at the American Health Foundation and continued at Cornell goes beyond teaching the skills specific to smoking avoidance. The original program was implemented by allied health professionals and a followup program was implemented by older peer leaders. Three-month followup data in the original study and 6-month followup data in the second study indicate that significantly fewer students began smoking in the experimental group compared with the nontreatment control group (6 versus 18 percent onset at 6-month followup in the second study). Botvin is replicating these studies with a program conducted by classroom teachers.

Flay et al. (*13*) have filled a large methodological gap created by the quasi-experimental methodology employed in each of the previously reported prevention research programs. In each of these programs, researchers opted to devote whole schools to interventions, with the number of schools per group ranging from one to five. Consequently, random assignment of participants was not possible, raising questions about what one can infer from any one study (*6*). Strictly speaking, the unit of analysis in these studies ought to be school, a practical impossibility because of limited degrees of freedom. Flay et al. (*13*) were able to find multiple schools in the

Waterloo (Ontario, Canada) area, each with a single classroom per grade. Eleven schools were randomly assigned to either program or control conditions. The strength of this methodology is that it permits random assignment of classrooms and, appropriately, the use of the classroom as the unit of analysis. The Waterloo program was administered in sixth grades, except for two booster sessions given in seventh and eighth grades. The program is similar to those at Stanford and Minnesota. Smoking-related information is elicited from students rather than told to them; there is a focus on social influences; decision-making skills are taught; and a public commitment is obtained. By seventh grade, differences in experimental smoking were beginning to emerge between treatment and control groups. If these trends continue, this methodologically tight study will lend experimental support for the consistent pattern of findings to date.

The weight of data available to date consistently supports the finding that smoking prevention programs with certain identifiable components can be successful in preventing the onset of smoking in adolescence.

Summary

1. Spontaneous smoking cessation among regular users (approximately once a week or more often) is estimated to be on the order of 25 percent during adolescence.
2. Probability of quitting was greater for those adolescent smokers first interviewed in 1974 who had at least started to attend college by 1979 than for those smokers who did not attend college (42.0 percent vs. 24.6 percent).
3. Probability of quitting decreases linearly with duration of the smoking practice, changing from 64.5 percent in the first year of smoking to 14.3 percent after 7 years.
4. Quitting "cold turkey" appears to be a more effective cessation strategy than cutting down without trying to stop entirely.
5. Success at quitting increased with the number of efforts made: about 73.4 percent of adolescents who kept trying eventually succeeded.
6. Smoking prevention programs are desirable alternatives to cessation programs aimed at youth. Successful programs have been based on social psychological theory and research, and are school based. Results have shown a 50 percent or more reduction in smoking onset.
7. The most successful programs were those emphasizing the social and immediate consequences of smoking rather than long-term health consequences. These programs have placed

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