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 <u>all</u> 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.

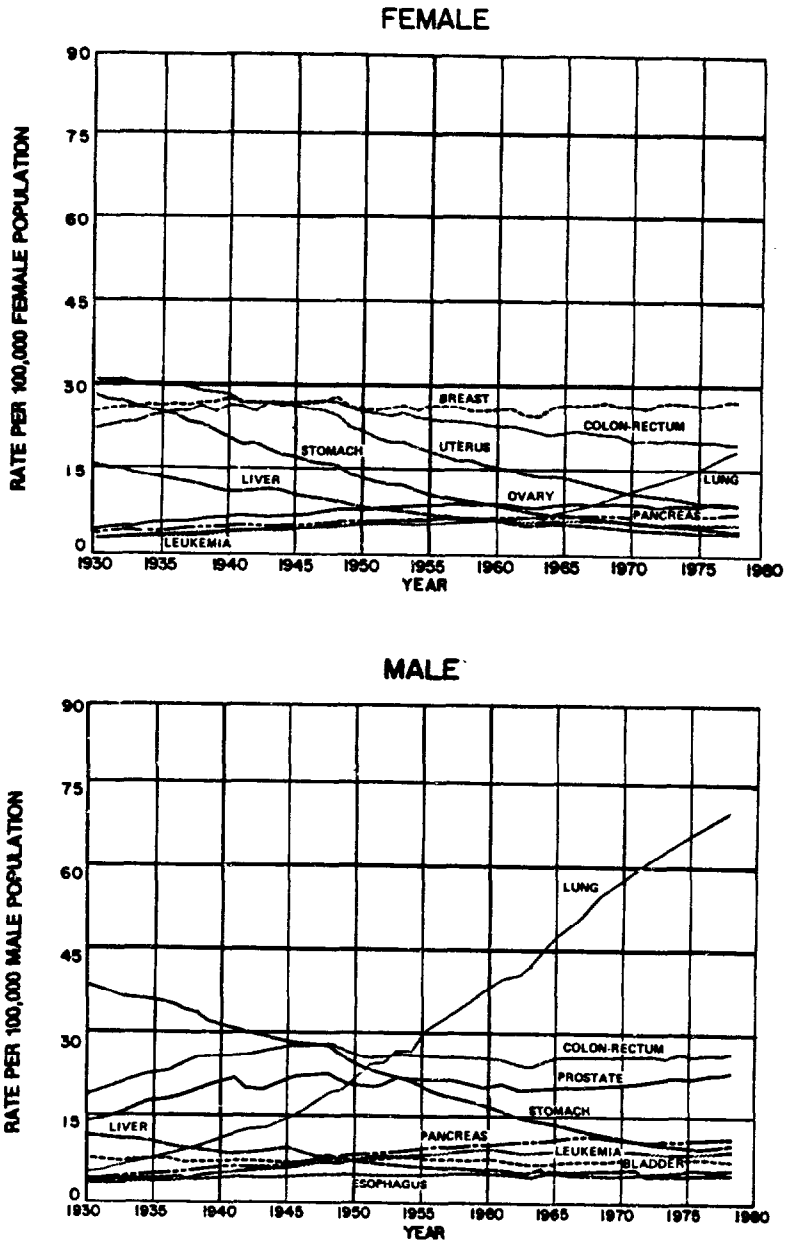

FIGURE 1.—Male and female cancer death rates* by site, United States, 1930–1978

* 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*).

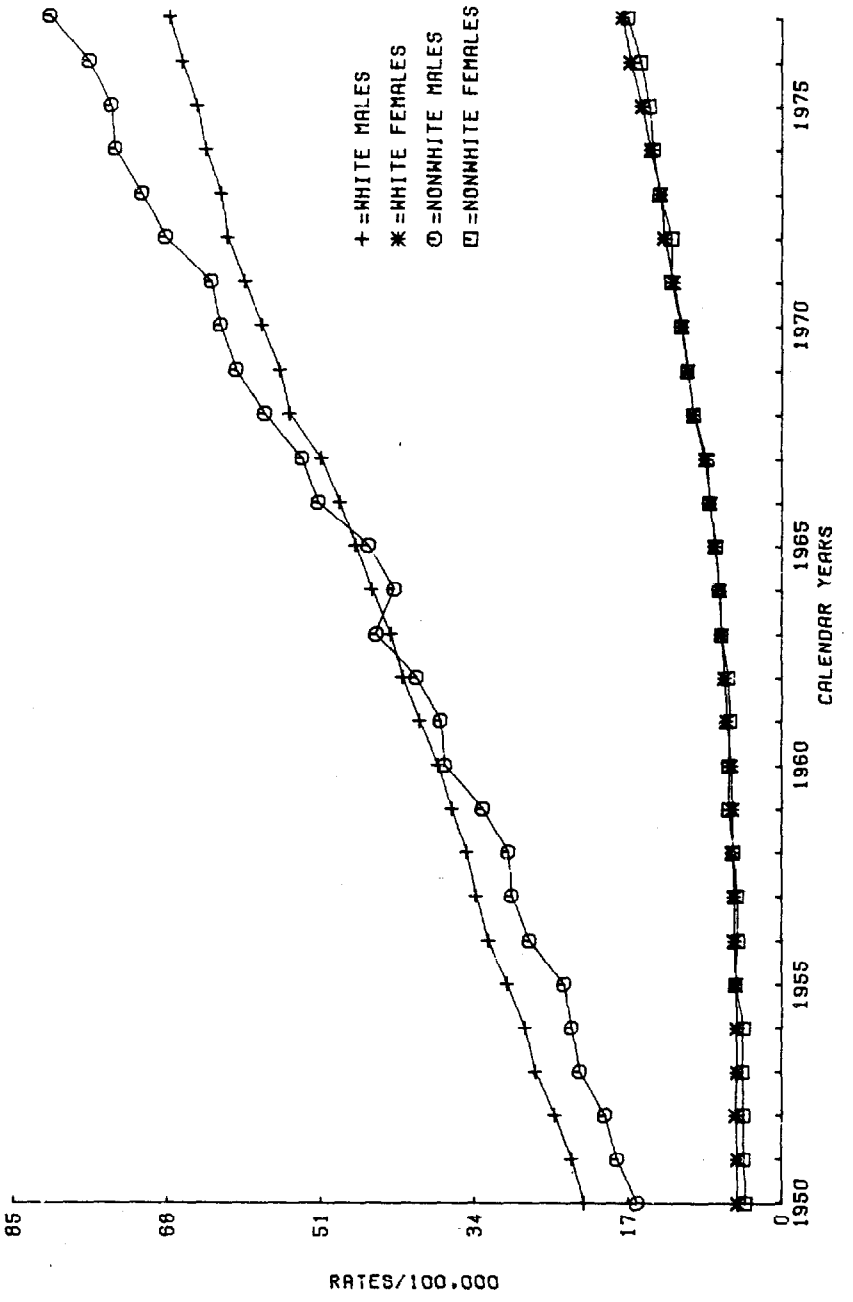

FIGURE 2.—Age-adjusted* mortality rates for cancer of the bronchus, trachea, and lung, by race and sex, United States, 1950–1977

* 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*).

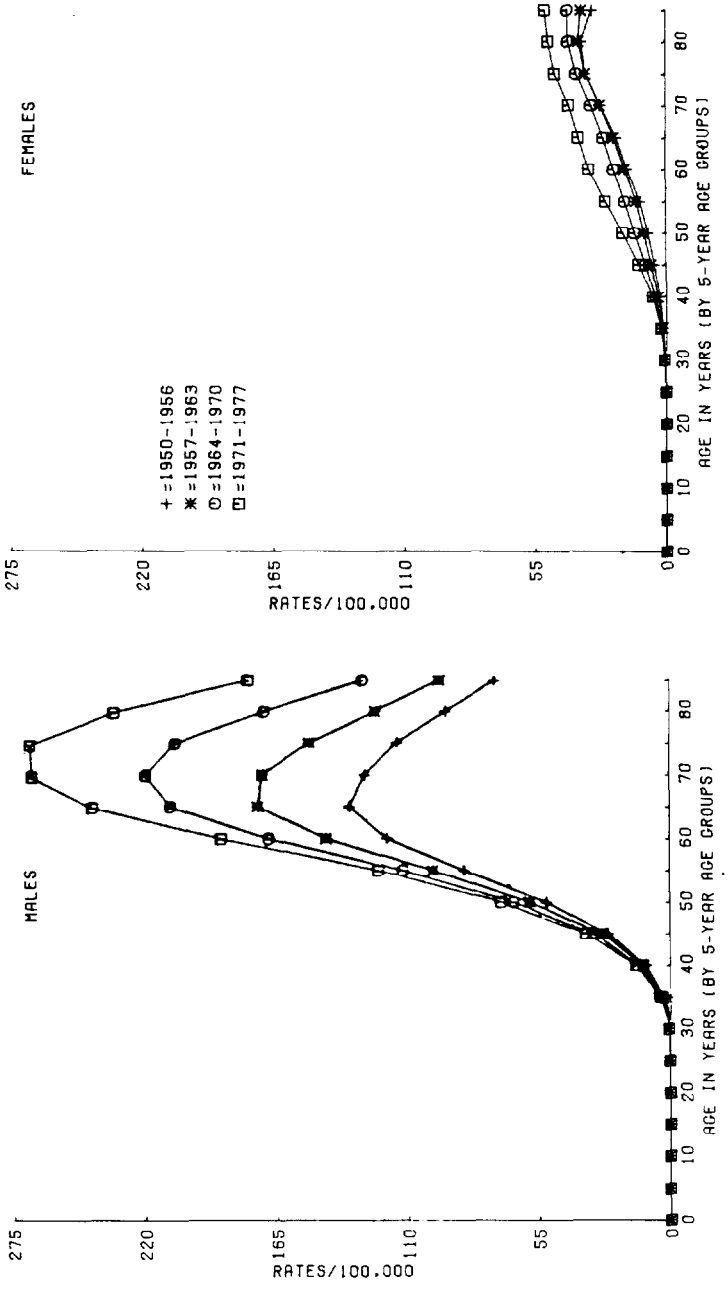

FIGURE 3.—Age-specific mortality rates for whites in the United States for cancer of the bronchus, trachea, and lung

SOURCE: National Cancer Institute (*198*).