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# 5. CANCER.

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## Introduction

Cancer has been the second leading cause of death in the United States since 1937. There were an estimated 390,000 deaths from cancer in 1978 (*4*). The association between tobacco smoking and the development of lung cancer was first suggested in the 1920's and early 1930's (*159, 206*). In the early 1950's, more than a dozen retrospective studies were published which first generally alerted the medical and scientific community to the health hazards associated with cigarette smoking. The public was informed of the results of these studies, and as a consequence there was a significant, but brief, dip in the per capita consumption of cigarettes. The next decade brought an intensive worldwide investigation into the various diseases associated with cigarette smoking. The first official statement on smoking and health by the U.S. Government was contained in the Report of the Advisory Committee to the Surgeon General of the U.S. Public Health Service, which was released 15 years ago. The evidence available at that time warranted the conclusion that "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The 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" (*217*). In the 15 years since the 1964 Surgeon General's Report was published, these conclusions have been confirmed by numerous investigations in many countries. Cigarette smoking has also been implicated as a significant cause of cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas. As data concerning the relationship of smoking to the development of cancer at various sites became available, they were summarized and published in the annual issues of the Health Consequences of Smoking (*209, 210, 211, 212, 212a, 213, 214, 215, 216*).

This chapter reviews the epidemiological and experimental data for each of the cancer sites associated with cigarette smoking. Discussions of the specific cancers are presented sequentially, based on the strength of the association with cigarette smoking: cancer of the lung, larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas.

## Lung Cancer

This year more people in the United States will die from lung cancer than from any other malignant disease. In 1950, when the nation first became generally aware that there was an association between smoking and lung cancer, there were 18,313 lung cancer deaths. In 1964, there were 45,838 deaths from lung cancer. The National Center for Health Statistics reported that in 1976 there were 86,267 deaths from lung cancer in the United States (*150*). It is estimated that there

were 92,400 deaths from lung cancer in 1978 (*4*). For every preventable death from highway accidents, there were approximately two deaths from lung cancer which could have been prevented if the individual had not smoked cigarettes. There are about 280 deaths from lung cancer each day in the United States.

This epidemic increase in lung cancer is reflected in rapidly changing mortality rates in both men and women. The mortality rate for men in 1950 was 19.9/100,000/year. This rose to 41.4 in 1964, and to 63.0 in 1976. The comparable figures for white females were 4.7 in 1950 and 8.0 in 1965, and climbing rapidly to 19.5 in 1976 (Table 7).

According to results from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the mortality rates for black males and females are higher than for whites. In 1976, the lung cancer mortality rate for black males was 93.0, for black females it was 17.4 (*154*). Due to recent increases in death rates among females, the ratio of male to female mortality for lung cancer has dropped from 7:1 to less than 4:1.

While recent years have seen dramatic increases in relative survival rates for acute leukemias in children, Hodgkin's disease, multiple myeloma, and certain other malignancies, there has been little increase in survival rates for lung cancer. The 5-year survival rate for lung cancer in all states is 8 percent for males and 12 percent for females (*151*). The difference in survival rates between males and females can be explained by sex-specific differences in histology or stage of the disease.

### Trends in Lung Cancer Mortality

In the United States there has been in the past few years a significant reduction in the percent of males and females who smoke cigarettes. As yet, there has not been a decline in the age-adjusted *total* mortality rates for lung cancer. When the lung cancer mortality rates by age are examined from 1950 through 1975, there is a continuining increase in older age groups for both males and females. This is probably due to the elevated risk experienced by older persons who use nonfiltered, high tar and nicotine cigarettes and who have done so for the majority of their lives. However, for female cohorts born in 1950–54 and male cohorts born in 1935–39 and 1940–44, the *age-specific* lung cancer mortality rates are below those of previous cohorts. This probably results from the reductions in cigarette consumption which have occurred in these groups.

There has been a change in the epidemic of lung cancer in England and Wales, as summarized by the International Union Against Cancer (UICC) workshop on the biology of cancer (*243*):

> In England and Wales, lung cancer mortality stopped increasing in men under the age of 50 years during the 1950's and more recently has fallen in men under the age of 60 years. The death rate from

lung cancer in women ages 40 years and over has continued to rise, but has leveled, or fallen in younger women since the 1960's...The fall in lung cancer mortality among men under the age of 60 years is likely to be due to their reduced consumption since the end of the Second World War, and to the reduction in the tar yield of cigarettes since 1955; particularly with the change to filter cigarettes.

Although lung cancer mortality in women over 40 years has continued to increase along with their cigarette consumption, it is unlikely that the incidence of lung cancer will ever reach the high levels recorded in men, because the increasing cigarette consumption by women has been, and is continuing to be compensated for by a decrease in tar yield.

**Epidemiological Studies**

The first comprehensive reviews of the effects of smoking on lung cancer were published in 1962 and 1964 by the Royal College of Surgeons of London and the Surgeon General of the United States, respectively (*171, 217*). They included data from studies on epidemiology, profiles of the consumption of tobacco, the composition and carcinogenicity of components of tobacco smoke, the effects of smoke on experimental animals, and the pathological changes observed in humans and animals. The conclusions reached in these assessments and by all of the periodic reviews that have followed at regular intervals (*209, 210, 211, 212, 212a, 213, 214, 215, 216*) are impressively uniform and consistent. So much so that it has been observed that the results of any one of the major studies might be taken to represent all of them.

There have been at least nine major prospective epidemiological studies which have examined the relationship between cigarette smoking and mortality from various causes. The results of eight of these studies are related to cigarette smoking and lung cancer and are presented in Table 1. The lowest mortality ratios are experienced by female smokers. The mortality ratios for male cigarette smokers are as low as 3.85 for Japanese males and as high as 14.0 for British doctors and Canadian veterans. Combining the data from the largest studies allows the conclusion that cigarette smokers on the average are 10 times as likely to develop lung cancer as nonsmokers. The mortality ratios are much higher for heavy cigarette smokers. This will be detailed in the section on dose-response relationships.

In the past 30 years, more than 50 retrospective studies on the relationship between cigarette smoking and lung cancer have been published. These data are too extensive for convenient summarization; they have been reviewed in recent issues of the Health Consequences of Smoking (*212, 212a, 213, 214, 215*).

**TABLE 1.—Lung cancer mortality ratios—prospective studies**

| Population | Size | Number of deaths | Nonsmokers | Cigarette smokers |
|---|---|---|---|---|
| British doctors(*47a*) | 34,000 males | 441 | 1.00 | 14.0 |
| Swedish study(*32*) | 27,000 males | 55 | 1.00 | 8.2 |
| | 28,000 females | 8 | 1.00 | 4.5 |
| Japanese study(*77a,78*) | 122,000 males | 590 | 1.00 | 3.76 |
| | 143,000 females | 148 | 1.00 | 2.08 |
| A.C.S. 25-State Study(*65*) | 440,000 males | 1,159 | 1.00 | 9.20 |
| | 562,000 females | 183 | 1.00 | 2.20 |
| U.S. veterans(*90*) | 239,000 males | 1,256 | 1.00 | 12.14 |
| Canadian veterans(*20*) | 78,000 males | 331 | 1.00 | 14.2 |
| A.C.S. 9-State Study(*68*) | 188,000 males | 448 | 1.00 | 10.73 |
| California males in 9 occupations(*228*) | 68,000 males | 368 | 1.00 | 7.61 |

## Dose-Response Relationships

An important factor in the causal relationship between smoking and lung cancer is the demonstration of dose-response relationships. In most epidemiological studies, dosage has been measured by the number of cigarettes smoked per day at the time of entry into the study. Other dose variables which have been examined include the maximum number of cigarettes smoked per day, the age an individual began smoking, the degree of inhalation of tobacco smoke, the total number of years an individual has smoked, the total lifetime number of cigarettes smoked, tar and nicotine levels of the brand of cigarettes used, the number of puffs per cigarette, the length of the unburned portion of the cigarette, and combinations of these variables into "dosage" scores. All of these variables have been shown in one study or another to contribute to the risk of developing lung cancer. Only a few representative samples of dosage variables as related to lung cancer mortality are examined in this section.

### *Number of Cigarettes Smoked Per Day*

The risk of developing lung cancer increases with the number of cigarettes smoked per day. In the U.S. and British populations, the risk of developing lung cancer for individuals smoking more than two packs

**TABLE 2.—Lung cancer mortality ratios for males, by current number of cigarettes smoked per day, from selected prospective studies**

| | Cigarettes smoked per day | Mortality ratio |
|---|---|---|
| A.C.S. 25-state study(*65*) | Nonsmoker | 1.00 |
| | 1–9 | 4.62 |
| | 10–19 | 8.62 |
| | 20–39 | 14.69 |
| | 40+ | 18.77 |
| British doctors(*47a*) | Nonsmoker | 1.00 |
| | 1–14 | 7.80 |
| | 15–24 | 12.70 |
| | 25+ | 25.10 |
| Swedish males(*32*) | Nonsmoker | 1.00 |
| | 1–7 | 2.30 |
| | 8–15 | 8.80 |
| | 16+ | 13.90 |
| Japanese males(*78*) | Nonsmoker | 1.00 |
| | 1–9 | 1.90 |
| | 10–14 | 3.52 |
| | 15–24 | 4.11 |
| | 25–49 | 4.57 |
| | 50+ | 5.78 |

a day is approximately 20 times that of nonsmokers (*47a, 65, 68, 80, 228*). Data for Swedish males are of the same magnitude (*32*). Japanese males who smoke 50 or more cigarettes a day experience a risk which is 5.8 times greater than for nonsmokers. Hirayama noted that the slope of the dose-response curve for lung cancer was less in Japan than in the United States and that this was probably due to the lower percentage of regular deep inhalers, a lower level of environmental promoting conditions, and also a higher percentage of adenocarcinoma in Japan than in the United States (*78*). Table 2 presents lung cancer mortality ratios from selected prospective studies for males by the current number of cigarettes smoked per day.

*Age at which Smoking Began*

Lung cancer mortality ratios exhibit an inverse relationship with the age of initiation of the smoking habit. Lung cancer mortality ratios for males by age at which they began smoking are presented in Table 3. Most cigarette smokers began the habit while in high school and are at the greatest risk of developing lung cancer. Those who began smoking

**TABLE 3.—Lung cancer mortality ratios for males, by age began smoking, from selected prospective studies**

| | Age began smoking in years | Mortality ratio |
|---|---|---|
| A.C.S. 25-State Study(*65*) | Nonsmoker | 1.00 |
| | 25+ | 4.08 |
| | 20–24 | 10.08 |
| | 15–19 | 19.69 |
| | under 15 | 16.77 |
| Japanese study(*78*) | Nonsmoker | 1.00 |
| | 25+ | 2.87 |
| | 20–24 | 3.85 |
| | under 20 | 4.44 |
| U.S. veterans(*90*) | Nonsmoker | 1.00 |
| | 25+ | 5.20 |
| | 20–24 | 9.50 |
| | 15–19 | 14.40 |
| | under 15 | 18.70 |

after the age of 25 have mortality ratios which are only 4 to 5 times greater than those of nonsmokers.

*Inhalation of Cigarette Smoke*

Inhalation of tobacco smoke is an important dosage variable. Inhalation of smoke well into the lungs is the major mechanism whereby lung tissue is exposed to the carcinogens which ultimately produce lung cancer. Techniques for quantitating the degree of tobacco smoke inhalation have been developed using carboxyhemoglobin levels or end expiratory carbon monoxide levels as an index of smoke inhalation. These objective methods of measuring inhalation have not been applied to studies of lung cancer mortality. In most investigations, the smoker was asked to report subjectively on his own inhalation practices. This is subject to considerable variation but is not as inaccurate as might be presumed. Available data show a strong dose-response relationship between self-reported inhalation of cigarette smoke and lung cancer mortality. Representative figures from selected prospective studies are presented in Table 4. These data suggest that cigarette smokers may underestimate the degree to which they inhale cigarette smoke. Those who report that they do not inhale cigarette smoke experience lung cancer mortality ratios which are 4 to 8 times greater than for nonsmokers. Deep inhalation results in mortality ratios which are as high as 17 times greater than for nonsmokers.

**TABLE 4.—Lung cancer mortality ratios for males, by degree of inhalation, from selected prospective studies**

| | Degree of inhalation | Mortality ratio |
|---|---|---|
| A.C.S. 25-State Study(*65*) | Nonsmoker | 1.00 |
| | None | 8.00 |
| | Slight | 8.92 |
| | Moderate | 13.08 |
| | Deep | 17.00 |
| Swedish males(*32*) | Nonsmoker | 1.00 |
| | None | 3.70 |
| | Light inhalation | 7.80 |
| | Deep inhalation | 9.20 |

*Tar and Nicotine Content of Cigarettes*

The major constituents of cigarette smoke that cause lung cancer are among the more than 2,000 different compounds found in cigarette smoke. Cigarette filters, first introduced during the mid-1950's, have the effect of trapping tar. Data presented by Maxwell (*136*) show that, in 1976, more than 600 billion cigarettes were smoked and that 88.4 percent of these were filtered. It has been known that the risk of developing lung cancer increased with the tar and nicotine content of cigarettes. Until recently, however, there has not been a great deal of evidence that individuals who switch to lower tar and nicotine cigarettes experience less lung cancer mortality (*27*). It has been argued that, if the tar and nicotine content of tobacco were reduced, individuals might increase the number of cigarettes smoked per day and thereby abolish any benefit that might be gained. Alternatively, those who switch to low tar and nicotine cigarettes might inhale the smoke more deeply than smokers of high tar and nicotine cigarettes, and thereby exposure to tar and nicotine might not be reduced. In a large prospective study by Hammond, et al. (*67*), these tar and nicotine relationships were examined with respect to lung cancer. The 897,825 men and women in 23 States were divided into 3 tar and nicotine categories. The high tar and nicotine (T/N) category was defined as 2.0 to 2.7 mg of nicotine and 25.8 to 35.7 mg of tar. The medium T/N category was defined as 1.2 to 1.9 mg of nicotine and 17.6 to 25.7 mg of tar. The low T/N category included cigarettes containing less than 1.2 mg of nicotine and less than 17.6 mg of tar. A matched-group analysis, similar to age standardization, was utilized. Individuals in each group were alike with respect to age, race, number of cigarettes smoked per day, age when they began to smoke cigarettes, place of residence,

TABLE 5.—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, E.C. (67)

occupational exposure to dust fumes, chemicals, etc., education, prior history of lung cancer, and prior history of heart disease. Results of this analysis are presented in Table 5. The mortality ratio for the category with the highest risk was made 1.0 so that the relative reduction in risk with the use of lower T/N cigarettes could be visualized. For males smoking the same number of cigarettes per day, there appears to be a 20 percent reduction in risk of developing lung cancer with the use of low T/N cigarettes. For females, there was a 40 percent reduction in the risk of developing lung cancer with the use of low T/N cigarettes, keeping the number of cigarettes smoked per day constant. The amount of tar and nicotine taken into the body per day depends on the number of cigarettes smoked, as well as on the tar and nicotine content of each cigarette. Hammond conducted a second matched-group analysis comparing subjects who smoked 1 to 19 high T/N cigarettes per day and those who smoked 20 to 39 low T/N cigarettes per day. These results are presented in Table 6. The number of cigarettes smoked per day was a relatively more important variable than the tar and nicotine content of cigarettes. The mortality ratio was 1.6 for males and 2.1 for females who smoked 20 to 39 low T/N cigarettes a day, compared to individuals who smoked only 1 to 19 high T/N cigarettes per day.

Wynder and Stellman (*253*) conducted a large retrospective study of 1,034 white males and females with histologically proved cancer of the lung and larynx. Relative risks were consistently lower among long-term smokers of filter cigarettes, compared to smokers of nonfilter cigarettes. These groups were standardized for number of cigarettes smoked, duration of smoking, inhalation, and cigarette butt length. These dose-response relationships are presented in Figures 1 and 2.

### Lung Cancer in Women

*Trends in Cigarette Consumption Among Females*

In 1964, the Advisory Committee to the Surgeon General concluded that cigarette smoking was causally related to cancer in men, and that

**TABLE 6.—Age-adjusted lung cancer mortality ratios* for males and females, comparing those who smoked a few high T/N cigarettes with those who smoked many low T/N cigarettes**

| | 1-19 high T/N cigarettes/day | 20-39 low T/N cigarettes/day |
|---|---|---|
| Males | 1.00 | 1.6 |
| Females | 1.00 | 2.1 |

*The mortality ratio for the category with lowest risk was made 1.00 so the increase in risk with smoking more cigarettes/day could be illustrated.
SOURCE: Hammond, E. C. (*67*)

"the data for women though less extensive, point in the same direction" (*217*). Today, 15 years later, the lung cancer epidemic among women is well established. Several investigators had predicted sharp increases in lung cancer mortality among women. In 1966, Linden (*118*) examined lung cancer mortality in California women and predicted: "One can expect to see further increase in the number of lung cancer deaths and the death rates as the increasing proportions of women who smoke cigarettes reach the age when lung cancer is most likely to occur."

In 1964, lung cancer was the fifth leading cause of death from cancer in women. It became the fourth leading cause in 1967 and moved to the third leading cause of death from cancer in 1969, passing cancer of the uterus. Projections for 1979 indicate that lung cancer is approaching cancer of the colon and rectum as the second leading cause of death from cancer in women. If present trends are not reversed, during the next decade lung cancer will become the leading cause of death from cancer in women, exceeding deaths from cancer of the breast.

In 1955, there were only 4,100 deaths from lung cancer in women. In 1976, the National Center for Health Statistics reported there were 20,455 deaths from lung cancer among females in the United States (*150*); the American Cancer Society estimated that in 1978 this increased to 21,900 deaths (*4*).

These increases are not due to increases in the population. Death rates for lung cancer have been steadily rising in women, especially in the past decade. The lung cancer mortality rate for white females in 1950 was 4.7 per 100,000; by 1976 this had risen to 19.5 per 100,000. This is more than a fourfold increase (Table 7).

The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute recently reported that the lung cancer death rate for black females exceeded that of white females (16.8 blacks, 15.0 whites)(*154*). Data from this survey are collected from 10 geographic areas in the United States and therefore do not represent

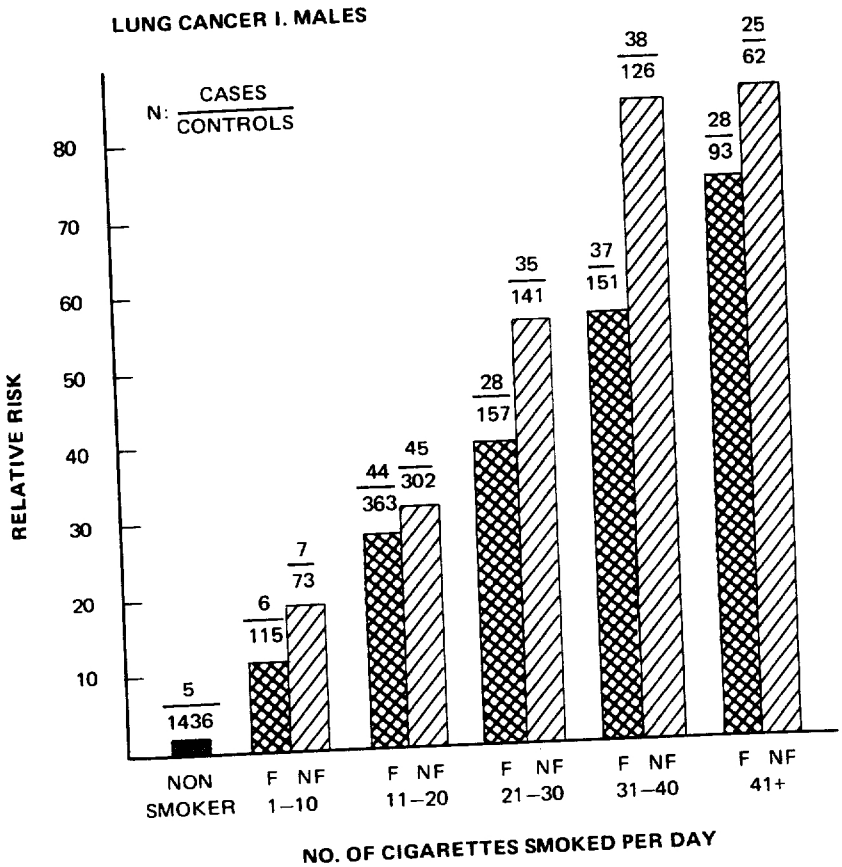


**FIGURE 1.—Relative risk of lung cancer for males, by number of cigarettes smoked per day and long-term use of filter (F) or nonfilter (NF) cigarettes**

SOURCE: Wynder, E.L. (*253*)

national trends per se. The lung cancer mortality rate (15.0 per 100,000) among black females in the general U.S. population is equal to that of whites.

Increases in lung cancer mortality among females cannot be explained by exposure to occupational carcinogens. Increases in cigarette consumption are responsible for these trends.

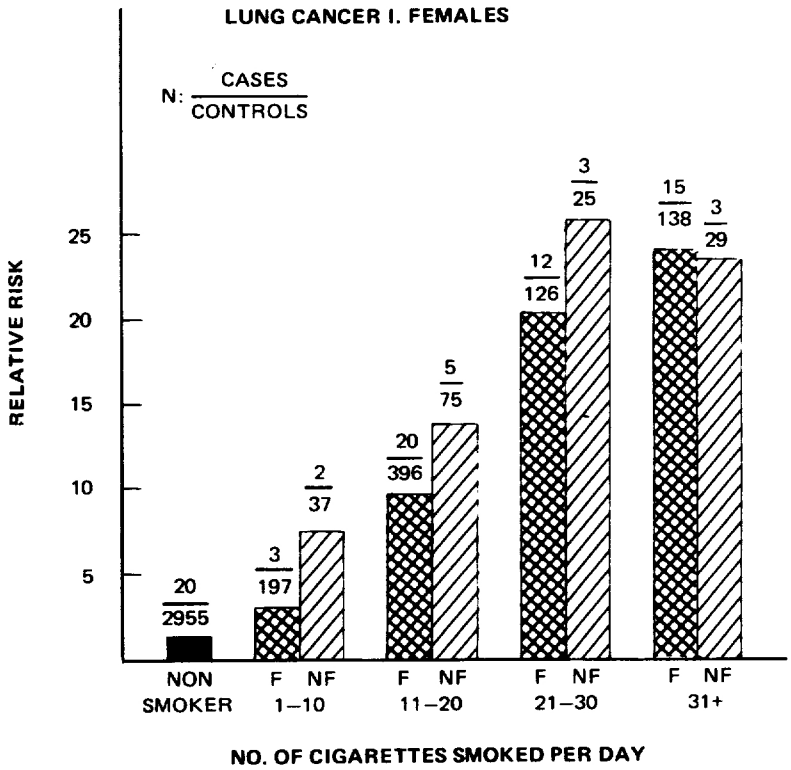


**FIGURE 2.—Relative risk of lung cancer for females, by number of cigarettes smoked per day and long-term use of filter (F) and nonfilter (NF) cigarettes**

SOURCE: Wynder, E.L. (*253*)

The epidemic of lung cancer in women has lagged behind that in men, primarily because of differences in patterns of cigarette smoking. There are fewer women smoking than men, but the gap is narrowing. Among teenagers in several age categories, girls are smoking more than boys (*155*). Table 8 shows the percentage of the U.S. adult population who are currently smoking cigarettes for selected years. In 1975, approximately 29 percent of adult females were smoking, whereas 39 percent of adult males were smoking (*155*). It should also be noted that, over the past decade, there has been a 2.6 percent