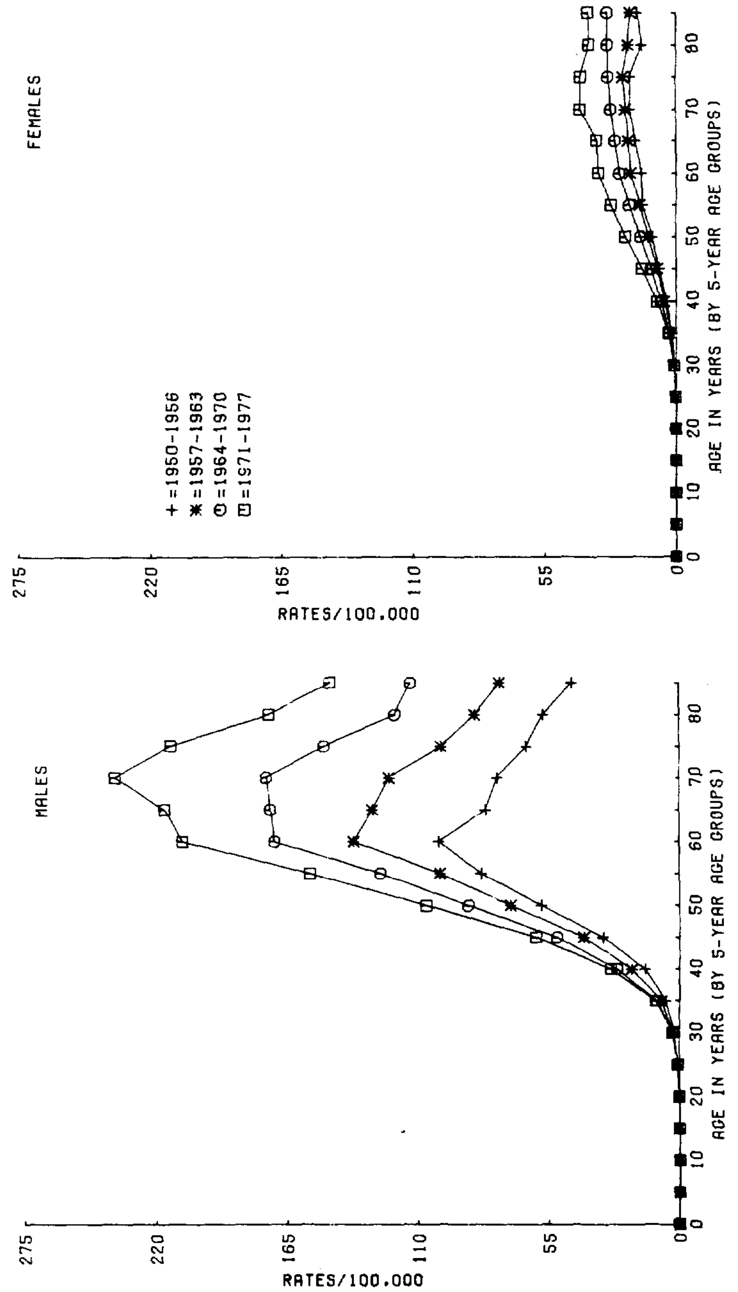
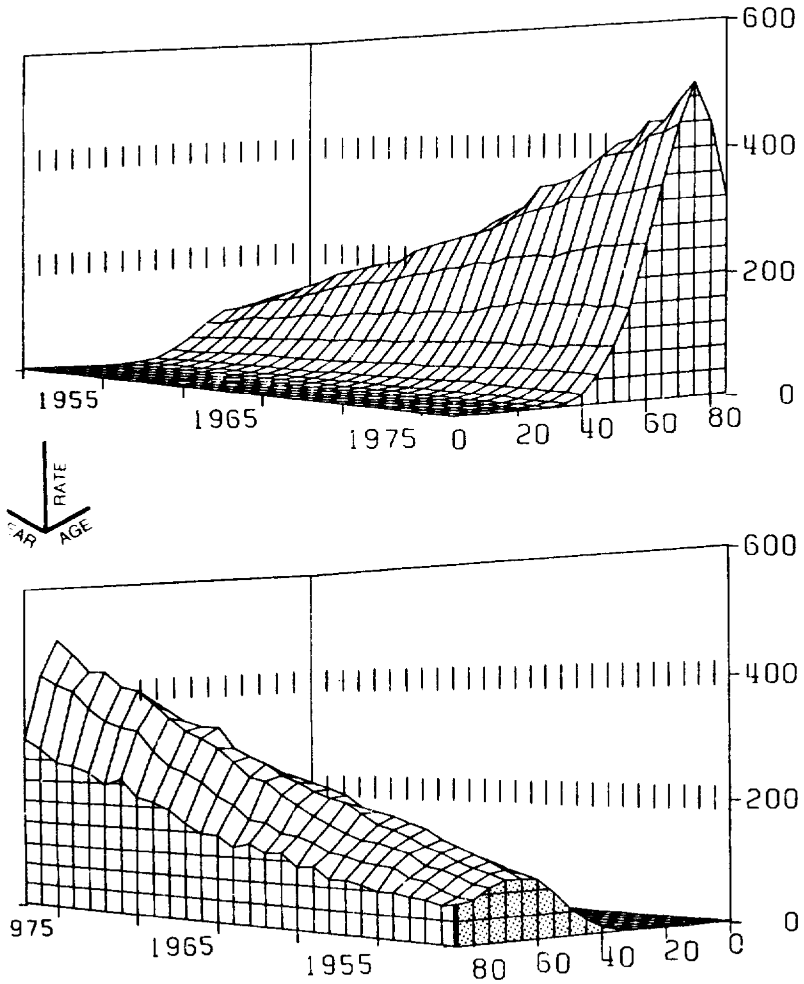


FIGURE 4.—Age-specific mortality rates for nonwhites in the United States for cancer of the bronchus, trachea, and lung

SOURCE: National Cancer Institute (*198*).



'IGURE 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 iseases involving the lungs. Several systems of classifying lung ancer have been proposed (Table 1).

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

37?-310 0 - 82 - 4

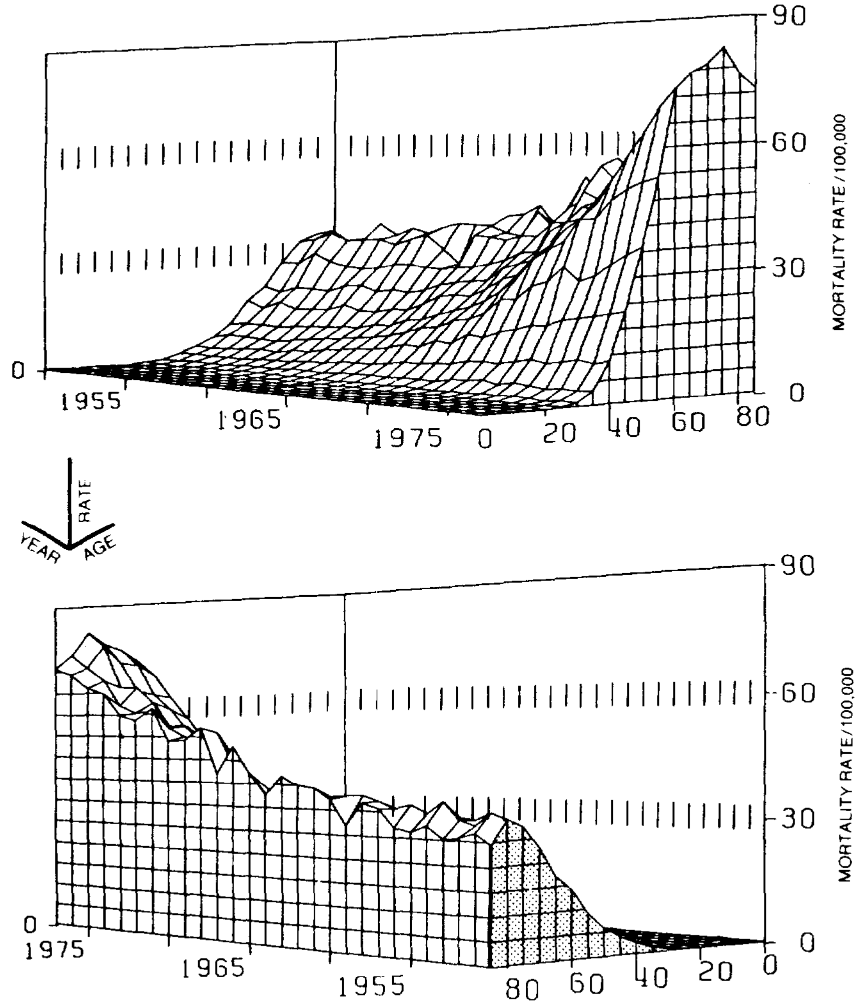


FIGURE 6.—Age-specific mortality rates by 5-year age groups for cancer of the bronchus, trachea, and lung for white females, United States, 1950–1977

SOURCE: National Cancer Institute (*1981*).

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 $8^1/_2$ 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 represented 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 Physicians	34,000 males	441	1.00	14.0
	6,194 females	27	1.00	5.0
Swedish Study	27,000 males	55	1.00	7.0
	28,000 females	8	1.00	4.5
Japanese Study	122,000 males	940	1.00	3.76
	143,000 females	304	1.00	2.03
ACS 25-State Study	358,000 males	2018	1.00	8.53
	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: Cigarettes smoked per day	Men: Mortality ratios	Women: Cigarettes smoked per day	Women: 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 1/2 pk	3.72		
	about 1 pk	9.05		
	about 1 1/2 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 based on only 9 total lung cancer deaths
	None	3.70	—	
	Light	7.80	7.20	
	Deep	9.20	·1.80	

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.

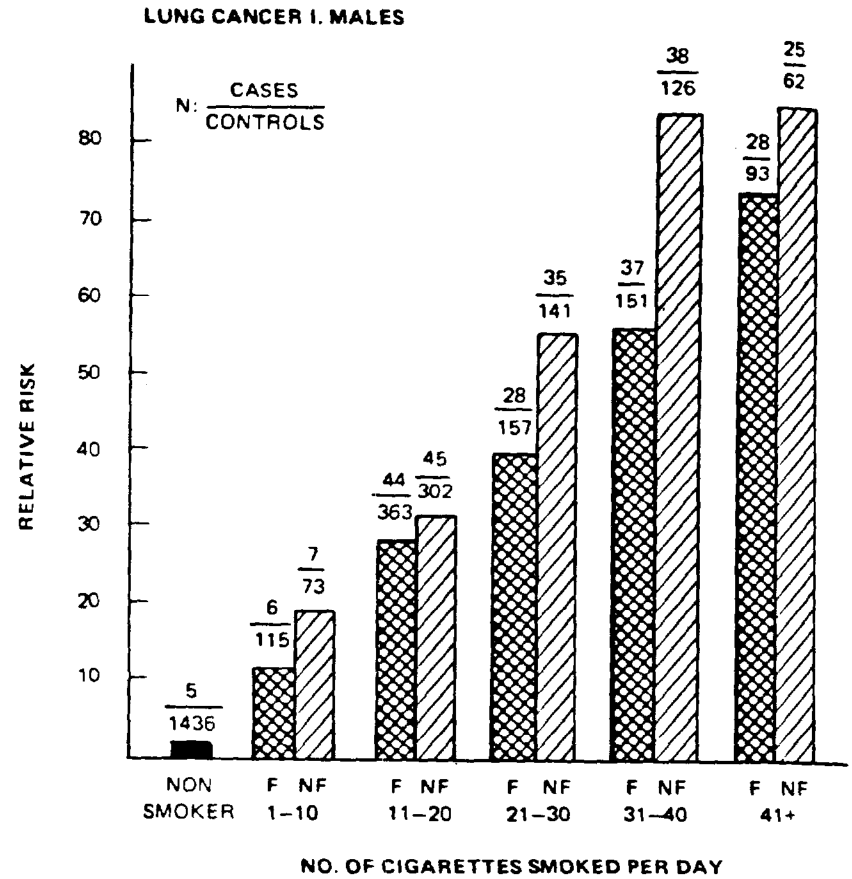


FIGURE 7.—Relative risk of lung cancer for males, by number of cigarettes smoked per day and long-term use of filter (F) or nonfilter (NF) cigarettes

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.

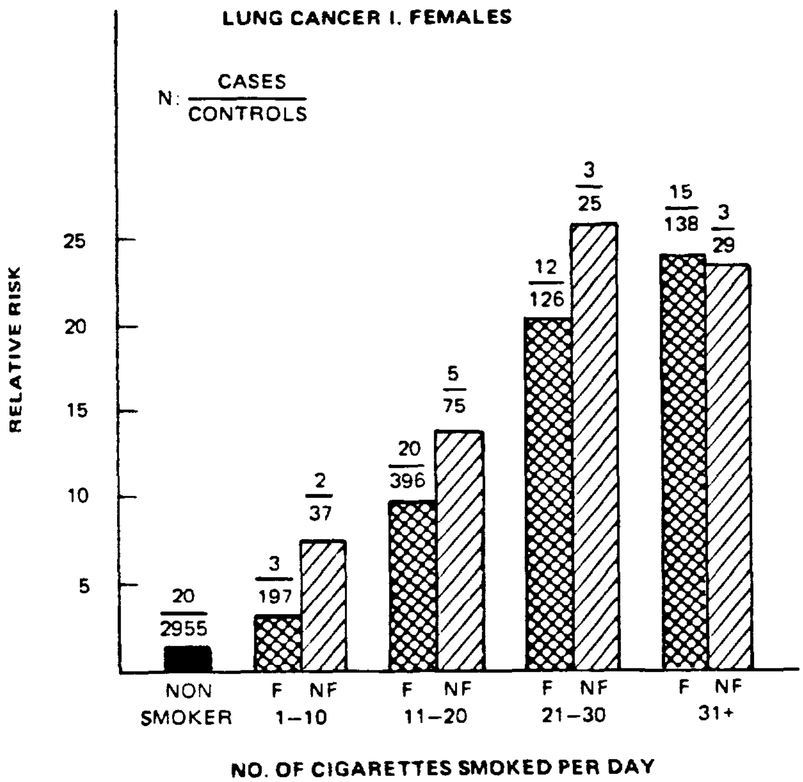


FIGURE 8.—Relative risk of lung cancer for females, by number of cigarettes smoked per day and long-term use of filter (F) and nonfilter (NF) cigarettes

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

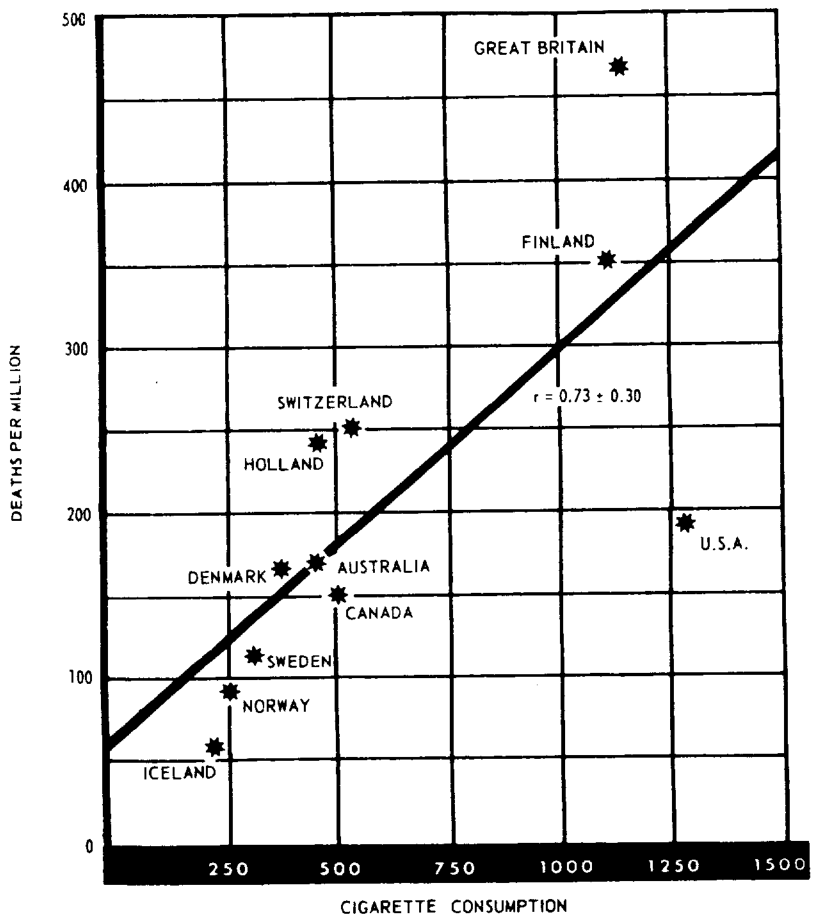


FIGURE 9.—Crude male death rate for lung cancer in 1950 and per capita consumption of cigarettes in 1930 in various countries

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

377-310 O - 82 - 5

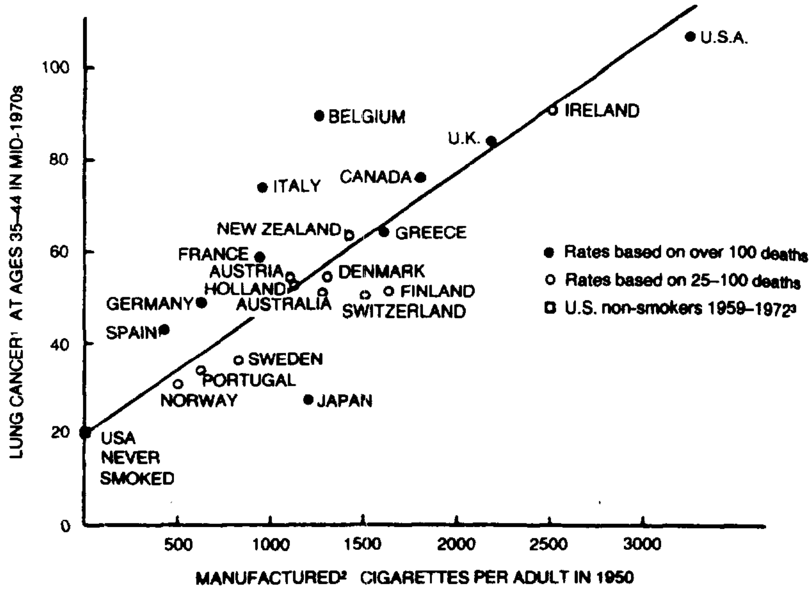


FIGURE 10.—International correlation between manufactured cigarette consumption per adult in 1950 while one particular generation was entering adult life (in 1950), and lung cancer rates in that generation as it enters middle age (in the mid-1970s)

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

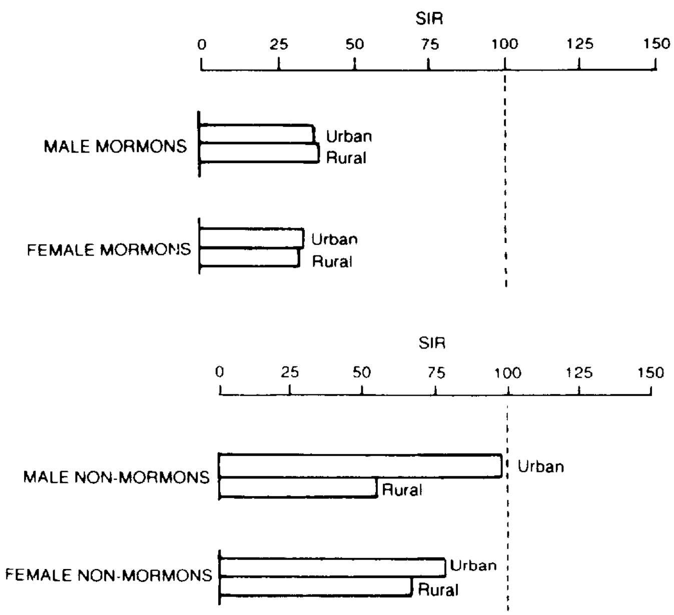


FIGURE 11.—Standard incidence ratios* (SIR) for lung cancer among Utah Mormons and non-Mormons by site of residence and sex

* 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]		Occupations[b]	Demonstrated Interaction with cigarette Smoking	Remarks
			Epidemiological	Experimental			
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.