CHAPTER THIRTY-TWO

Lung and Pleura

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INTRODUCTION

In the United States primary lung cancer represents about 15 per cent of all cancer cases (22 per cent in males and 8 per cent in females). Because of high fatality rates, the disease accounts for 25 per cent of all cancer deaths (34 per cent in males and 15 per cent in females). It is clear that the predominant risk factor is cigarette smoking, with industrial exposures also playing an important role, so that lung cancer is a largely preventable disease. This chapter reviews the epidemiologic and etiologic aspects of lung cancer, including the comparatively rare mesotheliomas, which arise from the pleural (or peritoneal) lining usually as a consequence of asbestos exposure.

LUNG CANCER

Demographic Factors

Geographic Variation

Lung cancer is the leading form of cancer in many countries, particularly in western Europe and North America, with annual age-adjusted incidence rates among males exceeding 100 per 100,000 population in Great Britain, United States blacks, and Finland (Waterhouse et al, 1976) (Table 1). The incidence is comparatively low in China, India, and several Latin American and African countries, where rates are near or below 25 per 100,000; yet even in these areas lung cancer still ranks as one of the three most common cancers among males. Based on available international statistics and trends, it seems likely that lung cancer now surpasses stomach cancer as the world's most common malignant neoplasm among males. The incidence is generally 4 to 6 times higher in males than females, whose reported rates are usually under 25 per 100,000. However, the male to female ratio is much lower in some groups, including Chinese populations, some Latin American countries, and the Maoris of New Zealand. In large part the worldwide variation and male predominance can be attributed to differences in tobacco consumption.

Although less striking than the international patterns, variation in lung cancer has also been documented within countries. In the United States, lung cancer mortality during the period 1950–69 was elevated in urban areas of the north, but the highest rates were clustered in the south, particularly in seaboard communities along the Atlantic and Gulf coasts (Blot and Fraumeni, 1976). Since 1970, the excess mortality has become more pronounced in southern areas, with only slight clustering in the urban northeast (Fig. 1). Distinctive patterns are also seen in China, where mapping of mortality statistics for 1973–77 has revealed high lung cancer rates around the industrialized centers of Shanghai, Tientsien, and Peking (Li and Shiang, 1980). Surveys in Japan, Norway, Italy, and several other nations also have indicated siz-

TABLE 1. Lung Cancer Incidence Among Males in Selected Countries, 1970*

Annual Age-Adjusted Rate (European Standard) Per 100,000 Population				
<25	*25–49*	*50–74*	*75–99*	*100+*
Puerto Rico	Israel	Poland	U S (white)	United Kingdom
Iceland	U S (Hispanic)	Cuba	New Zealand (Maori)	Finland
India	U S (Utah)	Yugoslavia	Germany	U S (black)
Singapore (Malay, Indian)	Spain	Hungary	Switzerland	
China	Norway	Canada	Singapore (Chinese)	
Nigeria	Sweden			
	Japan			
	Brazil			
	Colombia			

*From *Cancer Incidence in Five Continents*, Vol. 3 (Waterhouse et al, 1976). The data were often derived from selected areas within the countries and do not necessarily represent national rates. The time periods covered varied among the reporting registries, but usually centered about 1970.

able variations within countries, with generally higher rates in urban areas and coastal communities.

Time Trends and Age Curves

Lung cancer is rapidly increasing in most areas of the world, following by about 20 years a parallel trend in cigarette smoking. In Great Britain, lung cancer increased 50-fold in men, from an age-standardized death rate of about $2/10^5$ in 1911–15 to over $100/10^5$ in 1970 (Doll and Peto, 1976). The mortality trends for the United States during the period 1950–75 are shown in Figure 2. The age-adjusted rates for white males increased steadily from $24.6/10^5$ during 1950–54 to $58.6/10^5$ during 1970–75, with an even steeper incline among nonwhites. In recent years the rate of increase has been greater in females than in males, reflecting the growing popularity of cigarettes among females over the past 20 to 30 years. If present trends persist, in a few years lung cancer will become the leading cause of cancer death among women.

The lung cancer trends for American men are

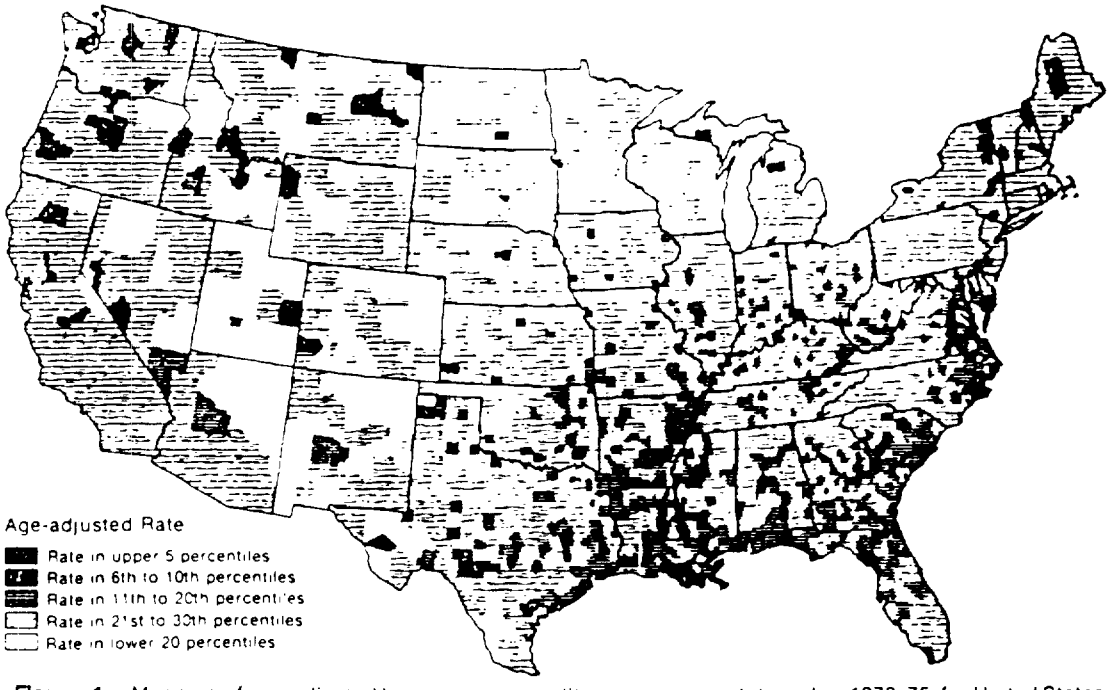

Figure 1. Mapping of age-adjusted lung cancer mortality rates among white males, 1970–75, for United States counties

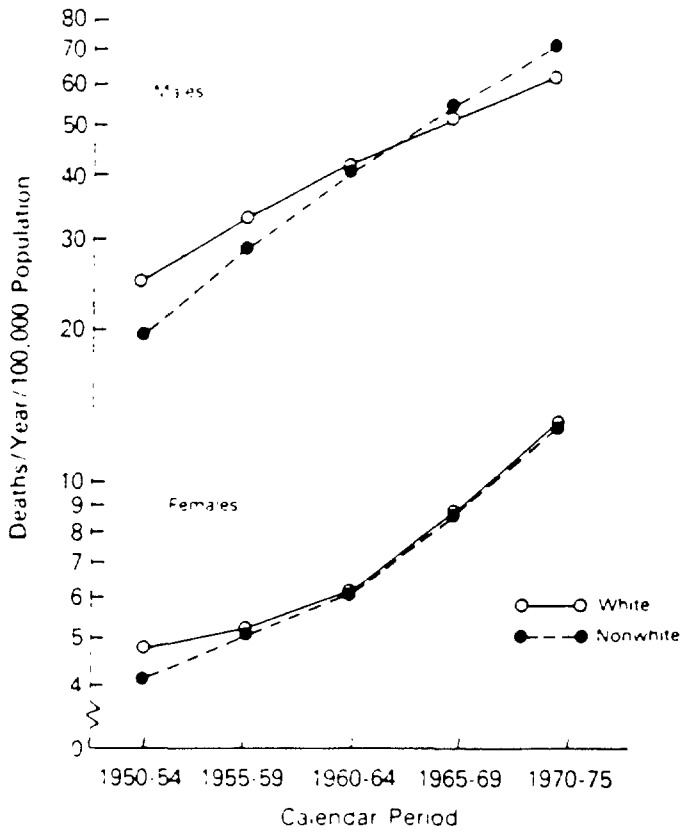

Figure 2. Age-adjusted lung cancer mortality rates, 1950–75, in the United States according to sex and race.

illustrated by the age curves for year-of-birth cohorts in Figure 3. Mortality increased almost linearly with age (on a log–log scale) except for some downward curvature in the oldest age groups, and was consistently higher in the later born cohorts. There was a remarkable shift in the rates of lung cancer according to race; for those born around 1885, the rates in whites exceeded those in nonwhites by about 50 per cent at all ages, while for those born around 1915 the situation was reversed and rates in nonwhites exceeded those in whites by about 50 per cent. The effects associated with more recent birth cohorts are diminishing, however, particularly for whites, with those born in the late 1920s and early 1930s as yet not showing rates appreciably different from those born around 1915–20. Lung cancer rates are also starting to level off in other countries. Cohort analyses in the Netherlands suggest that lung cancer mortality will peak among males born in the 1930s and then decline among those born thereafter (Van der Hoff, 1979). Lung cancer has recently decreased among British physicians, corresponding to a 60 per cent reduction in average cigarette consumption among this group over the past 20 years (Doll and Peto, 1976). It seems likely that the age-adjusted rates will reach a plateau in Western countries over the next few decades as those born in the 1920s and later constitute an increasingly larger share of the total population. Because of the fairly rapid reduction in risk following cessation of smoking, the rates may eventually drop among population groups that follow the example of British doctors.

Urbanization

Lung cancer tends to be more common in urban than rural areas in virtually all parts of the world. Table 2 shows average lung cancer mortality rates for United States counties, 1950–69, according to urbanization level and geographic sector. Regardless of region of the country, mortality tended to be higher for both sexes in the more metropolitan counties. Although people in cities tend to smoke more than those on farms, a small urban excess is still evident after controlling for smoking habits (Public Health Service, 1979).

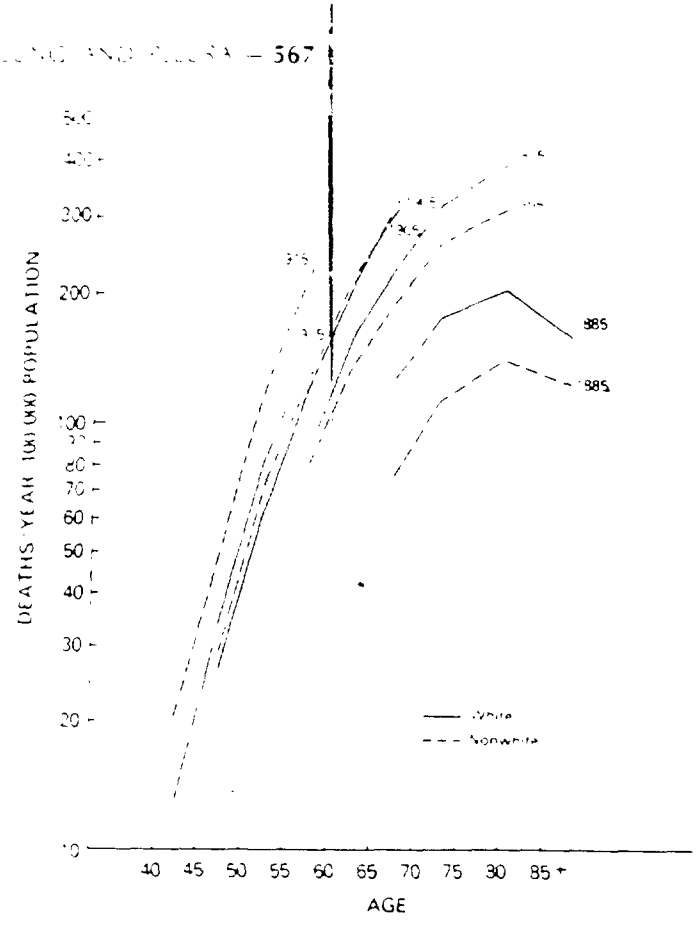

Figure 3. Age-specific lung cancer mortality rates, 1950–75, among white and nonwhite males in the United States for selected year-of-birth cohorts

Social Class

An inverse association between lung cancer and socioeconomic status has been observed in several studies. A more than twofold difference in mortality between low and high social class, as measured primarily by occupation, is seen in recent British mortality data (Registrar General, 1978) (Fig. 4). Similar results are seen in surveys measuring income or education (Graham et al, 1960; Seidman, 1970; Williams and Horm, 1977). Smoking habits contribute to at least part of the socioeconomic differential of lung cancer (Wynder and Stellman, 1977).

TABLE 2. Average Annual Age-Adjusted Lung Cancer Mortality Rates Among Whites Per 100,000 Population, 1950–69, for U.S. Counties According to Urbanization, Geographic Sector, and Sex*

Sex	*Geographic Sector*	*Urbanization (Per Cent)*			
		0–24.9	*25–49.9*	*50–74.9*	*75+*
Males	Northeast	33	35	38	44
	Southeast	29	32	39	46
	Midwest	26	29	33	40
	South Central	31	34	36	40
	North Central	22	24	27	35
	Mountain	23	24	27	30
	Far West	32	33	34	41
Females	Northeast	5.9	5.6	5.6	6.7
	Southeast	5.1	5.1	6.0	6.8
	Midwest	4.9	5.0	5.4	6.3
	South Central	5.4	5.3	5.9	6.9
	North Central	4.2	4.7	4.8	5.4
	Mountain	4.3	4.6	5.1	5.6
	Far West	5.7	6.2	6.2	7.7

*From Blot and Fraumeni (1976).

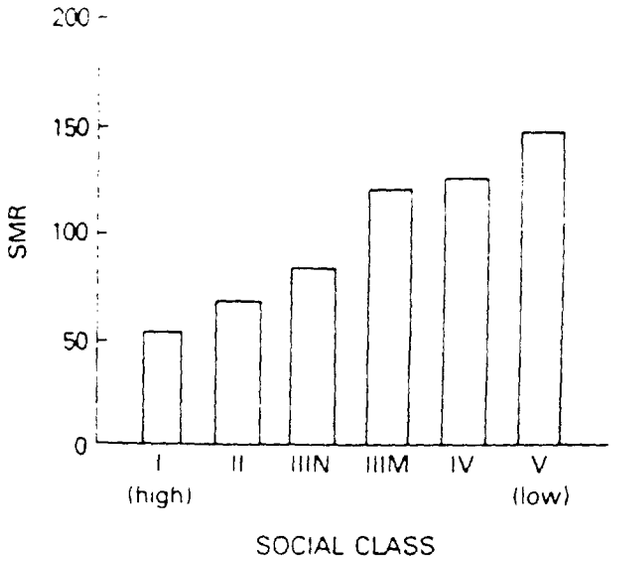

Figure 4. Standardized mortality ratios for lung cancer, according to social class, among males age 15–64, Great Britain, 1970–72 (from Registrar General, 1978).

Religion

In surveys in New York, Pittsburgh, and Montreal, a 20 to 50 per cent reduction in risk was found among Jewish males, although some excess has been noted among Jewish females (Horowitz and Enterline, 1970). The deficit in males has been attributed mostly to lower cigarette consumption, but the excess in females remains unexplained. In Israel, incidence among males is low by western standards, but not among females whose tumors are mostly adenocarcinomas (Modan, 1978). At even lower risk are Mormons and Seventh-Day Adventists, whose religious dictates proscribe the use of tobacco products (Lyon et al, 1976; Phillips et al, 1980).

Ethnic Groups

Recent incidence data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute permit a breakdown for several ethnic and racial groups within the United States (Table 3). Low rates are seen for some groups, notably Hispanic males, American Indians, and Japanese, related in part to low tobacco consumption. The highest rates are seen in native Hawaiians and blacks. Hispanic American females were once reported to have increased rates for lung cancer, but recent data suggest that the excess no longer exists (Menck et al, 1975). The high rates among Chinese females are consistent with United States mortality data (Fraumeni and Mason, 1974) and with the high incidence of lung adenocarcinoma reported in Chinese females in Singapore and Hong Kong (Chan et al, 1979; MacLennan et al, 1977). Smoking habits do not explain this pattern.

Histology

Virtually all lung cancers are derived from epithelial tissue (McDowell et al, 1978). Although there are several histologic types, squamous cell (epidermoid) carcinoma is the most common form in western nations, predominates in males, and is closely linked to smoking habits. Next most common is adenocarcinoma, which constitutes a high percentage of cases in low-risk countries and in females, and is less closely related to smoking. A disproportionate

TABLE 3. Average Annual Age-Adjusted (1970 Standard) Lung Cancer Incidence, 1973–77, in SEER Registry Areas in the United States, According to Sex, Racial and Ethnic Groups

Racial or Ethnic Group	*Incidence (Cases/Yr/10⁵)* *Male*	*Female*
White	76 4	21 8
Hispanic (New Mexico)	27 0	17 7
Black	110 0	24 3
Chinese (San Francisco Hawaii)	62 3	32 0
Japanese (San Francisco, Hawaii)	49 1	13 6
Hawaiian	116 9	50.7
American Indian (New Mexico)	10.8	3.9

recent increase in adenocarcinoma has been noted but may be related to changing diagnostic practices (Vincent et al, 1977). The third most common type is small cell anaplastic carcinoma, which is more common in males and closely related to smoking. Other cell types, such as large cell carcinoma, alveolar cell carcinoma, and malignant carcinoid, are relatively uncommon.

Survival

The National Cancer Institute has evaluated the survival experience of patients with lung cancer in the United States since 1950 (Axtell et al, 1976). Although the fraction of all cases with localized disease has remained about 20 per cent, the one-year survival rate for white patients increased from 20 per cent in 1950–54 to 31 per cent in 1970–73, and the five-year rate increased from 6 to 9 per cent over the same period. Females experienced better survival than males. Among patients with localized disease, the five-year survival rates rose from 21 to 33 per cent. Improvements occurred also for patients with regional disease, but were less pronounced. The corresponding survival patterns for black patients were less favorable. Patients with small cell carcinoma, which had the smallest proportion of localized tumors, showed the poorest survival.

Tobacco

In the 1920s and 1930s clinical observations and an alarming increase in lung cancer incidence raised some suspicion that smoking might be a causal factor. By the early 1950s case-control studies in the United States and Great Britain supported the link (Doll and Hill, 1952; Levin et al, 1950; Wynder and Graham, 1950), and the evidence became conclusive through surveys of large cohorts of smokers. The Public Health Service (1971) summarized 35 case-control and 8 cohort studies dealing with this issue. Every one, regardless of method or location, indicated an elevated relative risk (RR) of lung cancer among smokers. Table 4 shows the RR according to amount smoked based on data from the three largest cohort studies: the American Cancer Society (ACS) follow-up over six years of 1 million persons (Hammond, 1972); the 20-year assessment of mortality of 34,000 male British physicians (Doll and Peto, 1976); and the 8 1/2-year follow-up of 290,000 United States veterans (Kahn, 1966). All three investigations revealed a steady rise in lung cancer with increasing amount smoked, so that the risk for male smokers of two or more packs per day was nearly 20 times that of nonsmokers.

Similar trends were seen with other indices of cigarette consumption, including duration of smoking and total pack-years of use. The ACS survey showed a higher RR among males than females, a pattern seen in other studies as well. The male excess is generally attributed to the fact that women began smoking later in this century than men, started at older ages, and inhaled less deeply (Hoover, 1978). The studies in the United States have shown an increased risk with inhalation, but the British data indicate an inhalation effect limited to light or moderate smokers. Detailed investigations have uncovered no confounding variable or bias that might affect the association between smoking and lung cancer, so that a cause and effect relationship is beyond question. It is noteworthy that tobacco smoke contains several agents, includ-

TABLE 4. Relative Risks of Death From Lung Cancer According to Number of Cigarettes Smoked in Three Cohort Studies

	American Cancer Society (ACS)		*United States Veterans*	*British Physicians*
	MALES	FEMALES		
Nonsmokers[a]	1.0	1.0	1.0	1.0
Current cigarette smokers[b]	9.2	2.2	12.1	14.0
1–9	4.6	1.3	5.5	7.8
10–19	8.6	2.4	9.9	17.4
20–39	14.7	4.9	17.4	25.1
40+	18.8	7.5	23.9	–

[a]Did not smoke any form of tobacco.
[b]Classification refers to ACS study. The categories for United States veterans were 1–9, 10–20, 21–39, and 40+, and for British physicians were 1–14, 15–24, and 25+ cigarettes per day

ing polycyclic hydrocarbons that are carcinogenic in laboratory animals (Wynder and Hoffmann, 1976).

The risk of lung cancer is related to the type of tobacco product smoked. Although the effect of smoking low tar and nicotine cigarettes is not yet well quantified, case-control studies have shown some reduction in risk for users of filter compared to nonfilter cigarettes even after controlling for the amount smoked (Wynder and Stellman, 1977). Recent data from the ACS survey have also shown some lowering in mortality, by about 20 per cent, for male users of low compared to high tar and nicotine cigarettes (Hammond et al, 1977). The greatest reduction in risk comes from cessation of smoking (Table 5), as several studies have shown a substantial lowering of mortality among long-term ex-smokers (Public Health Service, 1979). Increased risks of lung cancer have also been associated with pipe and cigar smoking, but these are of a lower order of magnitude than the risks seen with either filter or nonfilter cigarettes (e.g., RR ~ 2 in the ACS and United States veterans studies and RR ~ 7 among British physicians). It has been suggested that cigarette smoke is less irritating and thus more easily inhaled than pipe or cigar smoke.

Smoking seems to induce lung cancers of all the major histologic types (Vincent et al, 1977; Wynder and Stellman, 1977). The strongest associations are for squamous cell and small cell carcinomas, but dose-response relationships for adenocarcinomas and other cell types have also been reported. Figure 5 shows increasing mortality ratios with amount smoked for squamous cell or small cell (undifferentiated) carcinomas and for adenocarcinoma. The data were obtained from family informants and physicians for 2,381 lung cancer deaths, representing a 10 per cent sample of all deaths in the United States during 1958 (Haenszel et al, 1962).

It is estimated that in the United States cigarette smoking may contribute to at least 80 per cent of lung cancer in males and 40 per cent in females (Hammond and Seidman, 1980). Smoking will continue to be the dominant risk factor for lung cancer in the years to come, but its relative importance may decline if recent trends toward reduced cigarette consumption and lower tar and nicotine yields are maintained (Wynder and Hoffmann, 1979). More remains to be learned about the changing risk of various diseases following alterations in smoking habits and product modification, and the extent to which smoking interacts with other environmental and host determinants of lung cancer.

Occupational Factors

Although cigarette smoking is the principal cause of lung cancer, studies of occupational groups have led to the discovery of several respiratory carcinogens (Fraumeni, 1975). There are probably other hazards that remain to be identified in the workplace, so it is difficult at present to estimate the overall contribution of occupational factors to cancers of the lung and other sites. It is also significant that the effects of some occupational carcinogens (asbestos, radon) are greatly enhanced by tobacco smoke.

Asbestos

Over the past 25 years epidemiologic evidence has accumulated indicating that the risk of lung cancer, mesothelioma, and asbestosis is substantially raised among workers in various asbestos industries, including miners and mill-

TABLE 5. Relative Risks* of Death From Lung Cancer According to Years Since Cessation of Cigarette Smoking

	Years Since Stopped Smoking				
	0	*<5*	*5–9*	*10–14*	*15+*
British physicians[a]	15 8	10.7[b]	5 9	5 3	2.0
American Cancer Society					
1–19 cigarettes/day	7 1	3.3	1 3	0.4	
20+ cigarettes/day	17 1	10.1	6 5	1.8	

*All risks relative to nonsmokers of any form of tobacco.

[a]All individuals smoked cigarettes at least 5 years and began before age 25. These who stopped had smoked about 10 per cent fewer cigarettes per day than those of the same age who continued.

[b]Excluded men who quit smoking after the diagnosis of lung cancer.

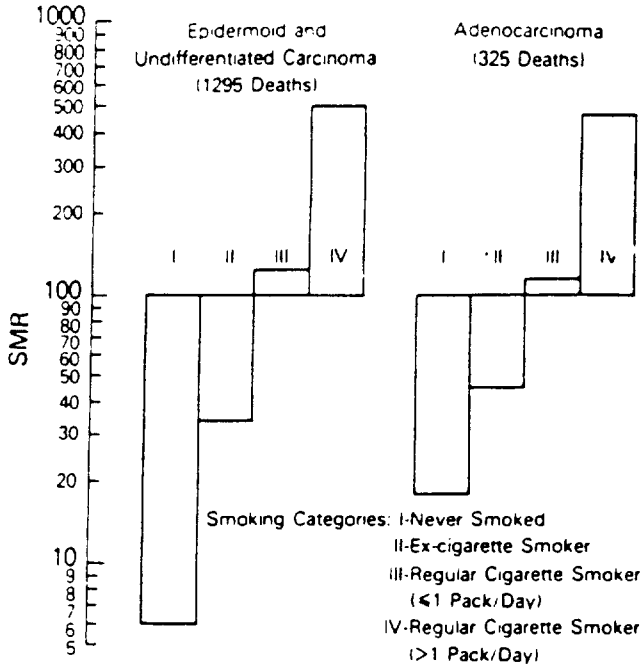

Figure 5. Standardized mortality ratios for squamous cell/undifferentiated carcinomas and adenocarcinoma of the lung by smoking category among white males in the United States, 1958 (based on data from Haenszel et al, 1962)

ers, and textile, insulation, shipyard, and cement workers (Lemen et al, 1980). Lung cancer is the major asbestos-related disease, resulting in about 20 per cent of all deaths in some exposed cohorts, with higher percentages in subgroups with greater intensity and duration of exposure (Newhouse and Berry, 1979; Selikoff et al, 1979). The length of exposure is not necessarily long, however, as indicated by the doubling of risk 20 years after working for less than nine months in a United States amosite factory (Seidman et al, 1979), and by the 60 to 70 per cent excess risk that now exists among American men who worked temporarily in shipyards during World War II (Blot et al, 1978, 1980). Because of its carcinogenic potential and widespread distribution in many industries, asbestos is the agent generally considered to pose the largest carcinogenic threat in the workplace.

Although exposures are usually to mixed forms of asbestos, all fiber types (chrysotile, amosite, crocidolite, anthophyllite) are thought to increase the risk of lung cancer (Lemen et al, 1980). The asbestos-related tumors tend to arise more often in the lower lobes, but all histologic types of lung cancer seem to be affected.

In most studies the risk of asbestos-induced lung cancer is characterized by a latent period of 20 years or longer between start of exposure and onset of the disease. In a mortality follow-up of 17,800 United States and Canadian asbestos insulation workers, the excess of lung cancer was twofold during the period of 10 to 14 years after initial employment, reached nearly sixfold between 30 to 34 years after employment, and declined at longer intervals (Selikoff et al, 1979). Another characteristic of asbestos-induced lung cancer is its synergistic relation with cigarette smoking (Saracci, 1977). A recent survey of 276 lung cancer deaths among insulation workers (Hammond et al, 1979) revealed relative risks of about 5 following asbestos exposure alone, 10 following cigarette smoking alone, and 50 following combined exposure (Table 6). Calculation of mortality ratios for this cohort according to the amount smoked showed a gradient in risk, with heavily smoking asbestos workers experiencing nearly 90 times the risk of individuals who were not exposed to tobacco or asbestos. Similar results have been seen among amosite factory employees (Selikoff

TABLE 6. Relative Risks of Lung Cancer According to Asbestos Exposure and Cigarette Smoking Status*

Asbestos	*Cigarette Smoking*	
	No	*Yes*
No	1.0	10.9
Yes	5.2	53.2

*From Hammond et al (1979).