SMALL CELL CARCINOMA OF THE LUNG

Epidemiology and Etiology

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Introduction

Epidemiology is defined as the study of the distribution of disease and of its determinants in whole populations. In the absence of human experimentation, the etiology of disease in mankind must be investigated epidemiologically and we are interested in etiology because it often provides a mechanism for the prevention of disease. For a problem like lung cancer whose current therapy is disappointing, prevention is of considerable importance and this is particularly true of small cell carcinoma (SCC).

Etiological purists insist that cause and effect relationships can only be proved by direct experimentation. Since proof of causation of a disease as serious as lung cancer cannot be obtained in humans for ethical reasons, the search for causality depends on circumstantial evidence. Decisions must be made on the basis of judgment and for this purpose we need a set of criteria. Sir Bradford Hill described such a set in 1965.[1] It includes the following:

1. strength of the association: the disease is more common after exposure to the agent than in its absence — the bigger the difference, the greater is the strength.
2. consistency of the association refers to the degree to which repeated studies, especially those that use different methods, arrive at the same conclusion.
3. specificity of the association refers to the degree of limitation

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between agent and disease; thus, an agent which is associated with only one disease is highly specific.

4. temporality requires that exposure to the agent precede the occurrence of disease.
5. dose-response relationship: increasing response with increasing exposure.
6. plausibility, a criterion which depends on the current state of biologic knowledge.
7. coherence between the association and other information about the disease.
8. experiment of an ethical nature: prevention of disease after cessation of exposure.
9. analogy: similarity of the association to others in which cause and effect relationships are accepted.

In the past three decades the study of cause and effect relationships has been particularly productive in lung cancer, perhaps because it is the single cancer which has endowed the twentieth century with a major epidemic. The various histologic types of lung cancer show enough epidemiological differences to suggest that this illness is a group of diseases rather than a single entity. Unfortunately, interest in the individual types has developed only recently and the data are rather limited. The epidemiology and etiology of SCC will be examined in the light of available information. Whenever it seems reasonable to do so, the gaps will be filled in by assuming that SCC has the same characteristics as lung cancer in general.

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Descriptive Epidemiology

There are several difficulties in any attempt to describe the epidemiology of SCC with respect to the basic variables of place, time, age, race, and sex. Firstly, an important problem has been the lack of histological standardization. It was not until 1967 that the World Health Organization (WHO) published an international classification of lung tumors.[2]

Secondly, although Kreyberg was the Head of the WHO International Reference Center and was instrumental in developing the details of the classification, he had previously published a number of papers in which he lumped types into two broad categories, Group I including epidermoid and small cell carcinomas and Group II including all other types (predominantly adenocarcinomas), on the hypothesis that Group I tumors accounted for most of the increase in lung cancer in large areas of the world.[3] Unfortunately, many investigators have since followed suit so that information on SCC has been lost in a larger category.

Thirdly, tumor typing is not an exact science. Pathologists disagree with each other[4] and the effect of such disagreement on the limited epidemiologic data has not been adequately studied.

Fourthly, there has been some suggestion that, just as the incidence of all lung cancer has been changing, so has the distribution of types.[5]

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However, there is no agreement on this.[6,7] Differences in method and material may account for the disagreement.

Fifthly, not all cases of lung cancer are confirmed histologically. The proportion may be less than 75% in some series, especially in elderly people who often refuse investigation. This may introduce some bias into the statistics.[8]

Lastly, but perhaps most importantly, the information may lack a population base. Risks can only be evaluated reliably by incidence, defined as the number of new cases per unit population per unit time. Thus, incidence is described by a fraction, the numerator being the number of cases and the denominator the population at risk so rates or probabilities can be calculated. To assess the determinants of risk, i.e. etiologic factors, both the numerator and denominator must be broken down into various categories. Even the few population-based studies of lung cancer with information on histologic types do not provide all the desired data.

Annegers et al[7] reported the incidence of lung cancer by histologic type in Olmstead County, Minnesota, over the period 1935-74. Only in men was the number of cases large enough to establish rates with some stability. The results are shown in Table 1. Small cell carcinoma and adenocarcinoma rates were equal and second only to that of squamous cell carcinoma in the first 30 years but SCC had the lowest rate of the four types in the most recent decade. Unfortunately the rates are not age-adjusted and

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age-specific rates are not provided. The area is largely rural.

In the metropolitan area of Portland unpublished data (William E. Morton, personal communication) for 1968-72 showed mean annual age-adjusted (to the U.S. 1970 census) rates per 100,000 for SCC of 13 in males and 4 in females. The rates were higher in the urban than in the rural part of the area and tended to be higher among males in the lower socioeconomic areas.

SCC rates among Singapore Chinese in 1968-72 were 16.9 in males and 2.6 in females.[9] These rates were age-adjusted to the 1970 World Population and inflated to approximate the actual figures, since only one-third of the cases were typed, by assuming that distributions by cell type were the same in unproved cases as in those with histologic proof.

In the Philadelphia Pulmonary Neoplasm Research Project (PNRP),[8] a semi-annual screening study of 6,027 urban males aged 45 and over carried out in the period 1951-65, each man was observed for 10 years and 121 developed lung cancer after the start of observation. Histologic confirmation was obtained in 90 (74%).[10] The cancers were classified by a panel of pathologists according to a slight modification of the WHO schema. There were 17 SCC in 52,487.9 man-years so the rate was 32.4 per 100,000 man-years. In Olmstead County the rate was based on males of all ages while the PNRP rate was based on males aged 45 and over. Although the PNRP study group was not a random sample of all Philadelphia males aged 45 and over, the age and race distributions were quite similar.[10] Using the proportion of males younger than 45 in Philadelphia in 1955 (69.9%) to estimate the size of

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the total population of males from which the study group was recruited as 20,000, and assuming neither deaths nor lung cancers during the 10-year period among the younger males, 17 cases would have occurred in 192,228 man-years for a rate of 8.8 per 100,000 man-years. This is similar to the rate of 6.1 per 100,000 per year in Olmstead County during approximately the same period. The assumptions, of course, make the PNRP figure an underestimate. The higher rate of 13 in Portland is probably due to the later period in which the data were collected (1968-72) since lung cancer incidence has been increasing steadily. The higher rate in Philadelphia compared with that in Olmstead County may also be due partially to the well-known urban-rural gradient seen in studies of lung cancer incidence.

The SCC rates in the PNRP by age are shown in Table 2 (unpublished data). The rate increased with age up to age 55-64 (i.e. age at start of the 10-year observation period) and then fell. The decline at older ages is of uncertain significance because of the small numbers at age 65 and over but it is consistent with observations on a period basis for all lung cancers. This is probably due to a cohort effect: older people were born into earlier birth cohorts which may have been subjected to less carcinogenic exposure than younger people born into later cohorts.[11] A similar pattern may be demonstrated in age-specific rates for Portland, Oregon, in 1968-72 (William E. Morton, personal communication).

The annual incidence in Iceland for SCC by age, sex, and period can

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be calculated from data provided by Hallgrimsson (Table 3).[12] Lung cancers were typed according to the WHO classification. Because of the small numbers of cases, interpretation is somewhat restricted but, in general, the age-specific rates showed an increase with time in males, an increase with age in both sexes with a decline in the oldest age groups in the more recent period, and higher rates in males than in females in both periods. These rates for SCC were considerably higher in Iceland than in U.S. studies cited above and this is reflected in the fact that SCC contributed a much larger proportion of the lung cancers in Iceland (31 -40%) than in the U.S. (9-19%). The distribution of histologic types varies with the source of tissue, SCC being more frequent in autopsy than in surgical material,[13,14] and this may account for some of the geographic difference.

Relative Frequency of Small Cell Carcinoma

There is additional information on the frequency of SCC relative to all lung cancers, information which describes some of its predilections. It should be understood, however, that these data are not an adequate substitute for epidemiologic observations because the populations at risk, the denominators, are not defined. Still, they may provide some insights which will need to be reconciled with epidemiologic and etiologic studies if a coherent picture of the nature of SCC is to be developed.

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A group of sources (Table 4) were reviewed for the distribution of cell types in various parts of the world by sex. Those reports in which the origin of tissue was restricted (to autopsy material only, for example) were excluded. The percentage SCC contributed to all lung cancers is shown. Unfortunately, there was considerable variation of the era in which the cases were collected and this may confound the data if there has been any significant change in the relative distribution of types over the past four decades.

Table 4 shows a marked geographic variation in the percentage of SCC in both sexes. In males, it was particularly high (over 20%) in Sweden, Finland, Iceland, and in one of four U.S. studies, an investigation of lung cancer in veterans. In females the frequency was especially high in Finland, Wales, England, and Iceland. Thus, when SCC is common, it tends to be common in both sexes. This is also true in a report from New Zealand[22] not included in the table: cases collected from four hospital thoracic units during 1957-65 showed 24.2% of 2,376 male lung cancer cases and 30.2% of 301 female cases were SCC (analysis limited to the four major types).

Some additional data in the U.S. were provided by the Third National Cancer Survey,[23] 1969-71. The results were consistent with the majority of the other U.S. studies shown in Table 4: SCC was 13.4% of all lung cancers in males and 14.5% in females. The total tabulation included a

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large proportion of unspecified and rare types of tumor (32.1% of 20,234 cases). If these are excluded, then SCC)specified as oat cell in this survey) formed 19.8% of all cases (both sexes combined because the data published do not permit separation).[24]

SCC as percentage of all lung cancers varies by age, being more common in younger patients. Table 5 shows this for males in Norway.[14] This could be due to a cohort effect since older men in a particular period of time were born into earlier birth cohorts whose exposure to carcinogens might have differed from that of later birth cohorts. However, a specific age effect cannot be excluded. Supportive data were provided by several other studies. Kennedy[25] in England investigated 40 cases of lung cancer in patients less than 40 years of age and found 19 of 29 males and 7 of 11 females had SCC. Kyriakos and Webber[26] reviewed 102 male cases aged 12 to 45 in St. Louis and found 24% had SCC compared to 13% in patients of all ages. However, Putnam[27] discovered only two cases of oat cell carcinoma in 24 (both among the 18 men) patients under age 40 at Walter Reed Army Hospital.

Male:female ratios derived from data in Table 4 are shown in Table 6. These vary greatly for SCC from 1.6 in Hong Kong to 30.4 in Finland but it should be noted that the low Hong Kong ratio was recorded 18 years later than the high Finland ratio. Except for the unpublished data of W. E. Morton in Portland, Oregon (personal communication), the male: female ratios for SCC are higher than those for all other types combined.

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are scanty. Wherever there are gaps in the information for SCC, the assumption will be made that what is true for all lung cancer probably applies to SCC as well.

The evidence for various agents will be evaluated in the light of the criteria for judging an association to be causal, as outlined in the introduction. The criteria for temporality, plausibility, and analogy will be taken for granted as long as the agent is inhaled some years before the cancer appears. Thus, we will be most concerned with strength, consistency, and specificity of the association, dose-response relationship, coherence, and regression of risk after cessation of exposure (human "experiment"), whenever data are available. The possibility of confounding the effect of one agent by another will be considered; for example, since smoking is the most important factor, it must be taken into account in evaluating all other factors.

Smoking

The association between the inhalation of tobacco smoke and lung cancer is a very strong one. This is shown dramatically in Figure 1 by assembling data on the proportion of current cigarette smokers by sex in U.S. adults since 1920[30,31] and age-adjusted U.S. lung cancer mortality rates by sex since 1935.[32] Mortality is a good index of incidence for this disease because 90-95% of patients die as a result of it.

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Cigarette smoking began about the turn of the century in men and reached a peak of 65% about 1940. The lung cancer rate has paralleled the increase in the proportion of cigarette smokers with a gap of about 40 years. Women began to smoke in increasing proportions in the 1930s and their lung cancer rate started to rise in the 1960s. A similar relationship has been described in England and Wales by Cairns,[33] thus demonstrating the criterion of consistency.

Many epidemiologic studies, both retrospective (case-control) and prospective, have confirmed the strength of the association. Few have provided data on the relationship between smoking and the several histologic types of bronchogenic carcinoma. Table 7 shows data from the PNRP. Seventeen of the 121 lung cancer cases were typed as SCC and all occurred among men who smoked cigarettes at the start of observation. Other types of lung cancer developed in former cigarette smokers and in pure pipe and/or cigar smokers[8] so the lack of SCC in these groups is interesting. This may be a dose-related effect as described below.

Data from the prospective study of British male physicians by Doll and Peto[18] showed only one case of SCC in 103,383 man-years of observation among those who never smoked compared to 14 in 155,708 man-years among cigarette smokers. In this study only 60% of the lung cancers were typed so the number of SCC cases is undoubtedly underestimated to a greater extent than in the PNRP.

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The data from these studies provide evidence of some specificity of the association in the sense that SCC seldom occurs in the absence of cigarette smoking but the converse is not true: cigarette smoking is not associated *only* with SCC. It has strong associations with other types of lung cancer and weaker associations with certain other diseases. This relative lack of specificity is understandable, however, when one considers the many hundreds of substances in cigarette smoke capable of inducing varied toxic effects in protoplasm.

The dose-response relationship between cigarette consumption and lung cancer incidence or mortality has been thoroughly established. This also holds for SCC in both the PNRP[34] (Figure 2) and the British physician study[18] (Figure 3). In comparing Figures 2 and 3, it may be noted that the rates are higher in the PNRP than in the British physician study.. There are several reasons for this: men in the PNRP were screened with chest films every six months so a higher proportion of cases may have come to attention, the PNRP men had a higher proportion of smokers, they were older, and a higher proportion of cases of lung cancer were histologically confirmed. Both sets of curves suggest that SCC is more characteristic of the heavier cigarette smokers and none occurred in men who smoked less than 10 cigarettes per day in contrast to other types of lung cancer. Table 8 shows the ratio of SCC to all classified lung cancers in the British physician study increases with increasing cigarette dosage. The differences are small but this relative increase is supported by data from a number of investigations without information on the populations at risk.

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Yesner et al[35] recorded an increase from 16 to 29% and Auerbach et al[6] an increase from 21 to 39% with increasing consumption of cigarettes. Although agreement is not complete on this in the limited literature,[36] Table 9 shows that among Norwegian cases of lung cancer the mean daily cigarette consumption was higher in patients of both sexes with SCC than it was in patients with epidermoid carcinoma or adenocarcinoma, especially in females.

Coherence of the association between smoking and lung cancer with other facts known about the disease is illustrated by several observations. In 1961 Auerbach et al[37] reported an extensive meticulous study of epithelial abnormalities in the human bronchial tree at autopsy and showed a close association between cellular atypia and smoking with a dose-response relationship. Recently Schlesinger and Lippmann[38] have shown a striking correlation between particle deposition in casts of the human tracheobronchial tree and lobar localization of lung cancers: both have predilections for the same parts, primarily in the upper lobes and especially the right upper lobe. Finally, cancer in animals tends to have a shorter induction-latent period from first exposure to a carcinogen to the appearance of tumor as the dose of carcinogen increases[39] and there is some evidence that, consistent with the experimental phenomenon, the mean age at diagnosis of lung cancer in humans falls with increasing cigarette consumption.[40,41]

The ultimate evidence that cigarettes cause lung cancer would come

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from a controlled concurrent randomized clinical trial. Since this is neither ethical nor feasible, we must consider uncontrolled trials that certain people elect to enter unintentionally. Thus, people who do not smoke rarely develop lung cancer. People who belong to groups that espouse opposition to smoking. such as the Seventh-Day Adventists, have a much lower risk of lung cancer than the general population and careful investigation of the smoking history in those few Adventists who do develop lung cancer is likely to yield a positive result.[42]

Smokers who stop smoking gradually experience a decline in the risk of lung cancer and the risk approaches that of nonsmokers after abstention for 10-15 years.[43,44] This lowered risk is reflected in a marked reduction of epithelial atypia in the bronchial mucosa and the appearance of cells with desintegrating nuclei.[45]

Support for the causal relationship between smoking and lung cancer has been obtained in animals. The most impressive study is that of Auerbach et al.,[46] who trained beagles to smoke through a tracheostoma with assistance. Invasive bronchiolo-alveolar carcinomas developed in 10 and invasive squamous cell carcinomas in two dogs who were heavy smokers of nonfilter cigarettes. The fact that SCC did not occur in these animals may be due to a relatively low cumulative exposure to cigarette smoke compared to humans but this is speculation. SCC rarely occurs in animals according to Berg.[47] In the discussion of Berg's paper, U. Saffiotti confirmed this and suggested that SCC may be the result of carcinogenic events taking place early in life.

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Ionizing Radiation

The cause and effect relationship between ionizing radiation and lung cancer has been known for many years as a result of occupational studies of miners exposed to the inhalation of radioactive substances.[48-50] External sources of radiation have also increased the incidence of lung cancer, including therapy for ankylosing spondylitis[51] and atomic bomb exposures.[52]

Lung cancers among both the miners and the Japanese exposed to the atom bomb have been studied carefully with respect to cell type. Among the uranium miners of the western U.S., as the cumulative dose of radiation increases, not only does the incidence of lung cancer rise but there seems to be a relative increase in the proportion of SCC, with a particular predilection for type 2b of the WHO classification (slightly larger polygonal cells).[53] However, squamous cell carcinoma and adenocarcinoma also show an increased incidence and all three major types of tumor show a dose-response relationship (Table 10).[54]

Further analysis by Archer et al[54] suggested that the apparent increase in the proportion of SCC with increasing radiation dose was an artifact due to dilution of the radiogenic cancers by nonradiogenic cancers at lower dose levels. At all dose levels SCC accounted for approximately 70% of the excess cases. Thus, SCC is characteristic of this carcinogen regardless of dose in U.S. uranium miners.

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These findings are not universal. In Czechoslovakian uranium miners[50] the absolute increase in lung cancer involves squamous cell carcinoma and SCC but not adenocarcinoma while in New Foundland fluorspar miners, also exposed to radon and radon daughters like the uranium miners,[49] 90% of the lung cancers have been squamous cell carcinomas.

The factors of duration of exposure and pattern of exposure in the dose-response relationship of excess risk by cell type has been recently studied in the Czechoslovakian uranium miners.[55] The dose-response curve is linear only with prolonged exposure and only with rates of exposure that remain unchanged or decrease over time. In short exposures and in those with increasing rates of exposure, the high cumulative doses are associated with plateauing or decrease in cancer frequency at the expense of SCC. These observations suggest that the SCC response to radiation is partially dependent on continuous prolonged exposure and on the dosage early in the exposure period. The implications may be similar to those of the dose-response observations described in the section on smoking above.

Periodic cytologic studies of sputum in uranium miners by Saccomanno et al[56] suggested that the pathogenesis of bronchogenic carcinoma develops through a series of identifiable stages of metaplasia and atypia. The progression appears to be orderly in many cases but sudden changes in the progression may occur, resulting in the skipping of stages or conversion from squamous cell carcinoma to SCC. Morphologically these investigators

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consider squamous cell and small cell carcinomas to be opposite ends of a continuous spectrum with no clear separation between poorly differentiated squamous cell carcinoma and SCC. The mean age at diagnosis of these two types was 52 in 18 cases of poorly differentiated squamous cell carcinoma and 53 in 81 cases of SCC while the mean age was 59 in 48 cases of well and moderately differentiated squamous cell carcinomas. This observation is consistent with the suggestion of skipped stages in the development of SCC.

Auerbach et al[57] made careful studies of the bronchial epithelium at autopsy in uranium miners with lung cancer compared to nonminers with lung cancer. The two groups were matched by age and smoking habits. They found that carcinoma *in situ* and early foci of invasive carcinoma outside the main tumor mass were more common in the uranium miners. The degree of disorganization in microscopic sections with carcinoma *in situ* was considerably greater in the miners. These facts attest to the potency of radiation in the pathogenesis of lung cancer and its widespread effects on the bronchial mucosa.

Cigarette smoke is an important cofactor in the incidence of lung cancer among uranium miners (Table 11).[58] The lung cancer rate in men who were heavy smokers and had heavy radiation exposure was 67 times the rate in nonsmokers with light radiation exposure. The induction-latent period was shorter in heavy cigarette smokers than in light smokers, exsmokers,

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and nonsmokers, an observation suggesting to the authors that cigarette smoke acts as a promoting agent rather than a synergist.[59]

The association between atomic bomb radiation and lung cancer is not as strong as that found in uranium miners. In a proportional mortality study based on the frequency of lung cancer among autopsies, all three major lung cancer types showed an elevated relative risk but only the increase of 3.9 for SCC was statistically significant.[52] The increased risk was found only in those people exposed to 200 or more rads at the time of the bomb. The proportionate mortality method is not very reliable.

Using a case-control method, a better approach, the results with respect to cell type were not the same: the relative risks were elevated for all three major types but significantly so only for squamous cell carcinoma and adenocarcinoma, not for SCC.[60] Thus, there is some doubt as to whether radiation from the atomic bomb is particularly associated with SCC. While smoking was a strong factor in the frequency of lung cancer, no evidence could be adduced that either smoking or occupation confounded the relationship between radiation and lung cancer.

A final point to be made concerning radiation in the etiology of lung cancer stems from the observation by Radford and Hunt in 1964 that tobacco contains an emitter of alpha particles, Polonium-210.[61] They suggested that this radioactive substance inhaled in cigarette smoke may act as an

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initiator in the pathogenesis of bronchogenic carcinoma. This hypothesis is given greater credibility by the recent finding that Lead-210, with a radioactive half-life of 22 years, is also present in mainstream cigarette smoke and is highly concentrated in a small number of insoluble smoke particles,[62] thus providing a mechanism for prolonged cellular contact.

All the criteria for causality in the relationship between ionizing radiation and lung cancer, especially SCC, may be considered to have been satisfied to a marked degree except that information is lacking on regression of risk after cessation of exposure and specificity is not of a high order.

Asbestos

Beginning in the 1930s a number of case reports drew attention to an association between asbestosis and lung cancer but it was not until 1955 that a sound epidemiological study of a small cohort of asbestos workers by Doll[63] showed the risk was 14 times expected. This strong association has since been confirmed many times although it varies somewhat with the type of asbestos fiber, chrysotile being less dangerous than the amphiboles, and it also varies with the type of occupational exposure, mining being less hazardous than manufacturing which in turn seems less hazardous than insulation work.

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Close approximations to a linear dose-response relationship on arithmetic coordinates have been demonstrated among Quebec chrysotile miners and millers by McDonald and Liddell[64] and among retired asbestos manufacturing employees by Henderson and Enterline.[65]

Information on the types of lung cancer associated with asbestos is meager. The only really satisfactory study is that of Kannerstein and Churg.[66] They examined in "blind" fashion 50 cases of lung cancer in people exposed to asbestos and 50 matched control cases with no known exposure or asbestos bodies in the lung tissue. There were no significant differences in histologic type between the two groups. SCC occurred in 11 of the 50 asbestos-associated cases and 14 of the 50 control cases. The only prominent difference between the two groups noted lay in the fact that lung cancer was most common in the lower lobes among asbestos-associated cases but most common in the upper lobes of the controls, a well-known characteristic of lung cancers in the general population.[67] This predilection of asbestos-associated carcinomas for the lower lobes is coherent with the fact that asbestosis is more pronounced in the lower than in the upper lobes.

Another study by Whitwell et al[68] in England suggested an increase in the relative frequency of adenocarcinomas but this investigation suffered from the lack of a control group. Nevertheless, the facts that asbestosis is characterized by scarring and that pulmonary adenocarcinomas are associated with scar tissue[28] suggest that the British experience needs further study.

In the past 12 years cigarette smoking has been recognized as an important co factor in lung cancer among people exposed to asbestos.[69] The interaction of the two agents is synergistic but lung cancer is almost as rare in nonsmokers exposed to asbestos as in those not so exposed. This observation raises the question as to whether asbestos is merely a carrier for a carcinogen in cigarette smoke rather than a carcinogen in its own right, at least for lung tissue. If indeed asbestos-associated lung cancers, found almost entirely in smokers, have a distribution of types similar to that of unexposed smokers, then this is consistent with the hypothesis that the primary carcinogen in asbestos workers is cigarette smoke. Furthermore, the risk of lung cancer is much lower in asbestos workers who stop smoking than in those who continue to smoke.[69] There is no evidence as yet that cessation of exposure to asbestos reduces the risk of lung cancer but perhaps this should not be expected since asbestos fibers persist in the lung after inhalation.

Thus, most of the criteria for causality in the association between asbestos and lung cancer have been satisfied to a considerable degree but the data suggest the possibility that asbestos is a synergistic promoting agent rather than a primary carcinogen in the lung.

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Chemicals

A number of chemical agents have been recorded as causes of lung cancer. These have been described in occupational settings where exposures have generally been high and more or less continuous. However, there are difficulties in making a decision as to whether a suspected agent is really a human carcinogen when the relative risk is only slightly elevated, i.e. when the observed number of cases is less than twice the expected number. The reasons for these difficulties lies in the shortcomings of epidemiologic methods: (1) studies based on small populations lead to sampling errors, (2) subtle systematic bias may produce misleading results, mainly because of the lack of good control population data, and (3) confounding factors may produce spurious associations, particularly variations in smoking habits.

The chemicals for which there seems to be at least fair evidence of pulmonary carcinogenicity in humans include polycyclic aromatic hydrocarbons (PAH), certain metals or their compounds, and certain simple organic chemicals.

Exposure to PAH occurs to varying degrees in a number of occupations, involving coal, gas, coke, petroleum, coal tar, pitch, etc.[70]

Metals or their compounds implicated in lung cancer etiology include chromium, nickel, arsenic, and cadmium. People working in hematite[71,72]

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and zinc-lead mines[73] are at increased risk but this appears to be due to radiation so they are mentioned only in passing.

A few simple organic chemicals have been incriminated as lung cancer agents. These include mustard gas, the chloromethyl ethers, vinyl chloride, and recently acrylonitrile.

The relative potency of these various chemicals is difficult to assess because of variations in methods and populations, uncertainty about degrees of exposure, all of which results in variation in the relative risks among published reports. A selected comparison is illustrated in Figure 4.[74] This shows that the highest risks occurred among people exposed to chloromethyl ethers, the gas emitted by coal carbonization in Japan, and mustard gas. The data available suggested that the more potent the agent, the shorter was the induction-latent period from initial exposure to tumor appearance.

Unfortunately, information in the literature is extremely limited with respect to cell type and confounding by smoking habits. Many of the reported studies have been based on causes of death and other information gleaned only from death certificates. Particular reports with relevant data will be cited.

Lung cancer type-specific rates are generally not available in these studies but in some the relative distribution of lung cancer cases by

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type is given, albeit the total number of cases is usually quite small. If the relative distribution of types is similar to that among lung cancer cases in the general population, then the elevated risk in occupational groups must signify that the incidences of all major types are increased. But if the relative distribution is distorted, then the increased incidence may be largely limited to the type(s) contributing unusually high proportions to the distribution.

Table 12 shows the relative distribution of lung cancer cases by histologic type in recent reports[75-83] that distinguish instances of SCC. Data are given for 7 chemical agents and are arranged in order of increasing percentage of total cases due to SCC. The number of typed cases varied from only 6 to 39. With respect to the percentage due to SCC, one report at each extreme stands out from all the rest. At one extreme is a small number of cases in workers exposed to vinyl chloride.[75] In this study the relative risk was very low, 1.56 times the expected number, but the types of lung cancer were entirely limited to adenocarcinomas and large cell carcinomas. There is some question as to whether vinyl chloride causes lung cancer because various reports are inconsistent[84] but this distribution of cell types is rather unusual.

Reports of lung cancer due to nickel,[76,77] cadmium,[78] arsenic,[79,80] chromate,[81] and acrylonitrile[82] showed percentages due to SCC varying from 15 to 33%.

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At the other extreme is the group of cases in men exposed to chloromethyl ethers (CME) in Philadelphia: 68% of 28 cases were SCC.[83] These chemicals, chloromethyl methyl ether (CMME) and bis(chloromethyl)ether (BCME), are important because, although only a small number of cases has been attributed to them, their relationship to lung cancer has been studied rather thoroughly, because BCME is a very potent carcinogen, and because SCC seems to be a characteristic response. While CMME is a weaker carcinogen than BCME, CMME in the workplace is contaminated with BCME so workers have been exposed to both chemicals.

For most of the chemicals mentioned above, there are large gaps in the evidence supporting a judgment of causality. However, for CME all the criteria used to judge whether an association is one of cause and effect have been well satisfied. The association is strong, the overall risk being 5.42 times expected.[83] There is consistency since similar elevated risks have been reported in Japan,[85] Germany,[86] and California.[87] The effects are highly specific in that, except for evidence of chronic bronchitis,[88] no disease other than lung cancer has been associated with CME exposure.[89] There is a strong dose-response relationship between cumulative CME exposure and lung cancer incidence (Figure 5). SCC is characteristic of workers with moderate to heavy CME exposure but occurs with the same relative frequency as in lung cancers in the general population among workers with light cumulative exposure to CME (Figure 6).

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There is coherence between the CME-SCC relationship and what we know about the natural history of SCC. For example, SCC tends to contribute a larger proportion of lung cancers in the young than in the old, as discussed above in the section on relative frequency early in this chapter, and a large proportion of the lung cancers in workers with moderate to heavy CME exposure occur under the age of 50 (Figure 7). This tendency may be due to a short induction-latent period associated with potent carcinogens or large carcinogenic doses. It is possible that study of the antecedents in cases of SCC among young people may reveal previously unsuspected carcinogens.

As for the experimental criterion of causality, while BCME has been shown to be a very potent carcinogen by inhalation in wild rats,[90] there is as yet no published evidence of regression of risk after cessation of exposure to CME. In Philadelphia, exposure to CME ceased in 1971 after complete enclosure and automation of the CME process; unpublished data suggest that the microepidemic of lung cancer which began in 1960 is beginning to subside.

The influence of tobacco smoking on the relationship between chemical carcinogens and lung cancer has seldom been examined in a way that would demonstrate its effect on risk as has been done in uranium miners and asbestos workers. In these two groups, as described above, the interaction between cigarette smoke and occupational agent seems to be synergistic. The limited data for chemical agents seem to show no effect or

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actual antagonism. A small case-control study of zinc-lead miners[73] showed the risk of lung cancer was higher in nonsmokers than in smokers; since the causative agent in these workers is thought to be ionizing radiation rather than metal exposure, this observation contrasts sharply with the synergism noted in uranium miners. Pinto et al[91] studied mortality in pensioners from a copper smelter, arsenic being postulated as the likely carcinogen, and found that the risk relative to that in U.S. veterans by smoking habits was 5.07 in nonsmokers compared to only 2.45 in exsmokers and 2.87 in current smokers. The elevated risk in nonsmokers was not statistically different from that in current smokers and exsmokers combined ($Z = 0.75$, $P > 0.05$) but at least one can say there was no positive interaction between smoking and occupational exposure.

In a small 10-year prospective study of 125 chemical workers in Philadelphia, of whom 88 (later corrected to 91) were exposed to CME, Weiss[88] found that the risk of lung cancer was much lower in current cigarette smokers (3-6%) than in nonsmokers (23%) and cigar/pipe or exsmokers of cigarettes (19%). The difference between current cigarette smokers and the other two groups combined was statistically significant (chi square with Yates' correction = 4.86, d.f. = 1, $P < 0.05$). Unpublished data, calculating expected numbers of cases by smoking habit from lung cancer rates in U.S. veterans,[92] show that among 51 men with moderate to heavy cumulative CME exposure, 6 cases of lung cancer occurred among 13 men with 112 man-years of observation who were nonsmokers

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or exsmokers of cigarettes when 0.00222 case was expected. In contrast, 5 cases occurred among 38 men with 353 man-years of observation who were current cigarette smokers when 0.1409 case was expected. The relative risk in nonsmokers and exsmokers was an astounding 2,703 times expected and in the current smokers it was only 35 times expected. The difference between these relative risks was statistically significant despite the small numbers ($Z = 2.40$, $P < 0.02$). This difference could not be accounted for by a small difference in the mean cumulative dose of CME between the two groups.

Air Pollution

Ambient air contains low concentrations of known carcinogens such as polycyclic aromatic hydrocarbons and an association has been reported between air pollution and lung cancer incidence or mortality by geographic area.[93-97] However, the association is weak and inconsistent, specificity is poor, dose-response data are generally lacking, there is lack of coherence since the association does not usually hold for females, there are no reliable data to show a regression of risk after decrease of exposure, and confounding of the association by other causative factors, such as cigarette smoking, is only partially ruled out. Information on lung cancer types is scanty and inconsistent.[93,94]

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Table 1

Mean Annual Male Incidence of Lung Cancer in Olmstead County, Minnesota, By Histologic Type and Period*

Type	1935-54		1955-64		1965-74	
	No.	Rate**	No.	Rate**	No.	Rate**
squamous cell	13	3.5	25	10.3	58	19.4
adenocarcinoma	8	2.2	15	6.1	27	9.2
small cell	8	2.2	15	6.1	17	6.0
large cell	5	1.4	14	5.8	25	8.4

* adapted from reference no. 7

** number/100,000/year

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Table 2

Ten-year Incidence of Small Cell Carcinoma by Age in Older Males in 1951-65*

Age at start of observation	No. of men	No. of man-years	Incidence No.	Incidence Rate**
45-54	2,304	26,418.6	6	22.7
55-64	2,169	18,530.9	9	48.6
65-74	881	6,526.5	2	30.6
75+	173	1,011.9	0	—
Total	6,027	52,487.9	17	32.4

* unpublished data from the Philadelphia Pulmonary Neoplasm Research Project[8]

** number per 100,000 man-years

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Table 3

Annual Incidence of Small Cell Carcinoma in Iceland

by Sex, Age, and Period[11]

Age	1955-61		1962-68	
	No. of cases	Rate*	No. of cases	Rate*
males				
35-44	2	19.8	0	—
45-54	7	84.9	9	98.6
55-64	7	109.0	11	153.6
65-74	0	—	7	141.6
75+	3	153.4	2	81.9
females				
35-44	2	20.6	0	—
45-54	0	—	4	44.4
55-64	3	45.4	5	69.2
65-74	3	67.1	2	36.4
75+	3	105.4	1	30.4

* number/100,000

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Table 4

Frequency of Small Cell Carcinoma as Percent of All Typed Lung Cancers* By Sex and Country

Country	Author	Era	Male			Female		
			No. typed	SCC No.	%	No. typed	SCC No.	%
Norway	Kreyberg[14]	1950-64	709	123	17.3	95	9	9.5
Sweden	Berge[15]	1958-69	561	153	27.3	149	22	14.8
Finland	Kreyberg[3]	1958-59	545	152	27.9	21	5	23.8
Wales	Harley[16]	1964-68				103	37	35.9
England	Kennedy[17]	1955-71				168	75	44.6
England	Doll[18]	1951-71	124	17	13.7			
Iceland	Hallgrimsson[12]	1941-68	144	57	39.6	79	26	31.3
Hong Kong	Chan[19]	1976-77	122	21	17.2	93	13	14.0
U.S.A.	Weiss[10]	1951-65	90	17	18.9			
U.S.A.	Annegers[7]	1935-74	240	40	16.7	64	6	9.4
U.S.A.	Beamis[20]	1957-72				201	25	12.0
U.S.A.	Herrold[21]	1954-62	1,313	368	28.0			
U.S.A.	W. E. Morton**	1968-72	1,283	185	14.4	353	63	17.8

* including the five major types: squamous cell carcinoma, small cell carcinoma, adenocarcinoma and bronchiolar carcinoma, large cell carcinoma, and mixed squamous cell and adenocarcinoma

** personal communication

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Table 5

Distribution of 709 Male Norwegian Lung Cancer Cases, 1950-64, By Histologic Type and Age[14]

Age	No. in age group	Histologic type		
		Epidermoid %	Small cell %	Adenocarcinoma %
<50	104	53.8	26.0	20.2
50-59	298	67.4	17.8	14.8
60-69	249	71.1	15.3	13.7
70+	58	67.2	8.6	24.1

* of number in each age group

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Table 6

Male:female Ratios of Small Cell Carcinomas and of Other Lung Cancer Types By Country

Country	Author	Era	SCC		Other types	
			M:F Nos.	Ratio	M:F Nos.	Ratio
Norway	Kreyberg[14]	1950-64	123:9	13.7	586:86	6.8
Sweden	Berge[15]	1958-69	153:22	7.0	408:127	3.2
Finland	Kreyberg[3]	1958-59	152:5	30.4	393:16	24.6
Iceland	Hallgrimsson[12]	1941-68	57:26	2.2	87:53	1.6
Hong Kong	Chan[19]	1976-77	21:13	1.6	101:80	1.3
U.S.A.	Annegers[7]	1935-74	40:6	6.7	200:59	3.4
U.S.A.	W. E. Morton*	1968-72	185:63	2.9	1098:290	3.8

* personal communication

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Table 7

Crude 10-year Incidence Rates for Small Cell Carcinoma in Older Men By Type of Smoking at Start of Observation

Smoking habit	No. of men	No. of man-years	Small cell carcinoma	
			No.	Rate*
cigarettes only	3,269	28,153.9	11	39.1
current	2,585	22,176.7	11	49.6
former	684	5,977.2	0	—
cigarettes + other	868	7,607.4	6	78.9
pipe and/or cigars	1,032	8,925.5	0	—
never smoked	830	7,551.1	0	—
incomplete information	28	250.0	0	—
Total	6,027	52,487.9	17	32.4

Source: reference no. 8 and unpublished data

* no./100,000 man-years

Note: rates are not age-adjusted but differences in age distribution between smoking habit groups are small

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Table 8

Ratio of Oat Cell Carcinoma to Total Histologically Classified Lung Cancer By Daily Cigarette Dose in British Male Physicians

No. of cigarettes smoked per day	No. of oat cell carcinomas	No. of cancers classified	Ratio
1-9	0	6	0
10-19	2	18	0.11
20-29	4	52	0.08
30-39	7	39	0.18

Source: reference no. 18

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Table 9

Mean Daily Number of Cigarettes Smoked By Patients With Various Types of Lung Cancer By Sex

Tumor type	Number of cigarettes	
	Males	Females
Epidermoid	20.9	14.0
Small cell	22.4	21.0
Adenocarcinoma	16.7	10.0

Source: reference no. 14, p. 41

Table 10

Observed and Expected Lung Cancers Among U.S. Uranium Miners, 1950-1970, By Radiation Dose and Histologic Type*

Radiation dose**	Histologic type								
	Squamous cell			Small cell			Adenocarcinoma		
	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio
1-359	4	3.06	1.31	9	0.73	12.33	2	0.69	2.90
360-1799	14	3.89	3.60	23	0.93	24.73	1	0.87	1.15
1800-3319	8	1.02	7.84	22	0.24	91.67	2	0.23	8.70
3320+	4	0.30	13.33	12	0.07	171.43	3	0.07	42.86
Total	30	8.27	3.63	66	1.97	33.50	8	1.86	4.30

* adapted from data of Archer et al[54]

** cumulative working-level months

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Table 11

Respiratory Cancer Mortality Among White Uranium Miners Five Years or More After Start of Mining By Radiation Dose and Cigarette Dose, 1950-1974[57]

Cigarettes per day	Cumulative radiation in working-level months								
	1-359			360-1799			1800+		
	Man-years	Cancer		Man-years	Cancer		Man-years	cancer	
		No.	Rate*		No.	Rate*		No.	Rate*
0	4,918	1	0.20	3,488	3	0.86	1,437	2	1.39
1-19	3,169	5	1.58	2,618	3	1.14	717	6	8.30
20	6,907	9	1.30	8,237	29	3.52	3,176	30	9.40
21+	2,944	8	2.72	3,635	17	4.68	1,127	15	13.30
Total	17,938	23	1.28	17,978	52	2.89	6,457	53	8.21

* Number per 1,000 man-years

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Table 12

Distribution of Lung Cancer Cases By Cell Type and Chemical Agent

Chemical	Total no. of cases	Cell type							
		Squamous cell		Small cell		Adenocarcinoma		Large cell or other	
		No.	%	No.	%	No.	%	No.	%
Vinyl chloride[75]	8					3		5	
Nickel[76;77]	39	26	67	6	15	7	18		
Cadmium[78]	8	3		2				3	
Arsenic[79]	25	15	60	8	32	3	12	1	4
Arsenic[80]	18	8		6	33	2		2	
Chromate[81]	12	8	67	4	33				
Acrylonitrile[82]	6	4		2					
Chloromethyl ethers[83]	28	1	4	19	68	5	18	3	11

Note: percent not calculated when denominator is less than 10

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Legends

Figure 1. Temporal trends in the estimated percentage of current cigarette smokers in the U.S. adult population by sex[30,31] and trends in the U.S. age-adjusted (to the 1950 population) lung cancer mortality rates by sex.[32]

Figure 2. Dose-response curves for lung cancer by cell type in relation to the number of cigarettes smoked per day by males aged 45 and over in the Philadelphia Pulmonary Neoplasm Research Project.[34] Cancer types: 1 = squamous cell carcinoma, 2 = small cell carcinoma, 3 = adenocarcinoma. Rates are adjusted for age and race.

Figure 3. Dose-response curves for lung cancer by cell type in relation to the number of cigarettes smoked per day by British male physicians aged 40-79.[18] Cancer types: 1 = squamous cell carcinoma, 2 = oat cell carcinoma, 3 = adenocarcinoma. Rates are not age-adjusted but the distribution of man-years by age does not differ much between smoking habit groups. Age-adjusted rates were calculated from the raw data and showed only slightly smaller values in the heaviest smoking group.

Figure 4. Relative risk of lung cancer, in comparison with unexposed or general population, among workers exposed to chemicals (Weiss[74]). The studies were selected and limited to those with a relative risk in excess of 2.

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Legends continued

Figure 5. Standardized mortality ratio (SMR) for lung cancer among chemical workers by degree of cumulative exposure to chloromethyl ethers (CME) showing a strong dose-response relationship.

Figure 6. Percentage of small cell carcinomas among lung cancers in the general population (data from the Philadelphia Pulmonary Neoplasm Research Project[10]) and in chemical workers by degree of cumulative exposure to chloromethyl ethers (CME).

Figure 7. Percentage of lung cancer cases diagnosed under age 50 in the general population (data from the Philadelphia Pulmonary Neoplasm Research Project[10]) and in chemical workers by degree of cumulative exposure to chloromethyl ethers (CME).

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