ASPECTS OF ASBESTOS RELATED LUNG CANCER -

Asbestosis and lung cancer

Safe dose concept

Lung fibre burden

General considerations

A report prepared by

Dr David Douglas
MBBS MSc DIH FFOM FACOM
Consultant in Occupational and Environmental Medicine

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1. INTRODUCTION

1.1 This report addresses various aspects of asbestos-related lung cancer. First, the evidence for the importance of asbestosis in the causation of asbestos related lung cancer; second, the evidence for a safe level of asbestos exposure; third, information on asbestos fibres in the lungs, and fourth, some general considerations.

2. ASBESTOSIS AND LUNG CANCER

2.1 The following references provide strong evidence for a link between fibrosis (asbestosis) and lung cancer both in experimental animals and humans.

2.2 **Stanton M F, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Natn Cancer Inst. 1972, 48: 797-821.**

The extent of fibrosis roughly correlated with the incidence of pleural neoplasms, not only in the high and low tumour incidence groups but also in the medium tumour incidence group treated with low doses of asbestos.
In all experiments yielding few or no mesotheliomas, irrespective of the material used, fibrosis was negligible.

2.3 **Wagner J C, Berry G, Skidmore J W, Timbrell V. The effects of the inhalation of asbestos in rats. Brit J Ind Med. 1974, 29: 252-269.**

Two experiments in which SPF Wistar rats were exposed by inhalation to dust clouds of the UICC standard reference samples for periods of between one day and 2 years are described. All the samples of asbestos produced asbestosis which continued to progress after removal from exposure but only a little fibrosis was observed in control rats. Lung tumours, ranging in severity from adenomata to squamous carcinomata were produced by all samples, but in the controls there were only a few adenomata and none of the more

serious tumours. There was a positive association between asbestosis and lung tumours. Overall, the animals with lung tumours had significantly more asbestosis than without. The groups exposed for only one day provide supporting evidence of a relationship between lung tumours and asbestosis. There was very little asbestosis in these groups and restricting attention to animals which survived for at least 600 days, the mean survival times of those with and without lung tumours were very similar. There were 17 lung tumours in 201 rats; only 6 of these occurred in 157 rats without asbestosis (3.8%) while 11 occurred in the 44 rats with minimal or slight asbestosis (25%), a highly significant difference ($p<0.001$).

2.4 **Suzuki Y, Kohyama N. Malignant mesothelioma induced by asbestos and zeolite in the mouse peritoneal cavity. Environ Res. 1984, 35: 277–292.**

Fibrosis was strongly suspected to be an important precondition for the induction of the neoplasms by asbestos and fibrous erionite; all neoplasms induced by these minerals were intimately associated with fibrosis.

2.5 **Kuschner M. The effects of MMMF on animal systems: some reflections on their pathogenesis. Ann Occup Hyg 1987, 31: 791–797.**

The author reviewed animal experiments involving a variety of fibrous materials including asbestos. It thus appears that the same features of size and durability and probably physico–chemical properties that determine fibrogenicity also determine tumorogenicity in the pleural cavity and peritoneum. This is not surprising when one appreciates that fibrous proliferation precedes the development of tumours and in all likelihood is a critical event in the pathogenesis of mesothelioma.

The thesis which emerges is that fibres produce a single pathological effect, namely fibrosis. Fibrosis is a result of the release of endogeneous mediators of fibrogenesis from the macrophage; the release is dependent on the incomplete phagocytosis of long thin durable fibres; fibrosis as a consequence of the inhalation of fibres, like other forms of

diffuse interstitial scarring, renders the entrapped pulmonary epithelium more susceptible to malignant transformation (cancer).

2.6 **Newhouse M L, Berry G, Wagner J C. Mortality of factory workers in east London 1933–1980. Brit J Ind Med. 1985, 42: 4–11.**

This paper reviews the mortality of workers employed at an asbestos factory in the east end of London making asbestos textiles and other asbestos products such as prefabricated cement products and using crocidolite until the mid–1950s as well as amosite and chrysotile asbestos. In histological specimens where tumour tissue and lung tissue were available the degree of asbestosis was designated minimum, moderate or severe, using a classification outlined by the Pneumoconiosis Committee of the College of American Pathologists and the National Institute of Occupational Safety and Health in 1982. Of a total of 117 cases in which lung and tumour tissues were available, 105 (90%) had evidence of asbestosis (14% minimum, 37% moderate and 39% severe). Among the 12 who died of lung cancer without histological evidence of asbestosis, 5 were current smokers, 2 ex–smokers and in 5 the smoking history was not known.

2.7 **Suzuki Y, Selikoff I J. Pathology of lung cancer among asbestos insulation workers. Fedn Proc. 1986, 45: 744.**

356 cases of lung cancer in asbestos insulation workers provided material for evaluation of interstitial fibrosis. In this group, all but a single case showed mild to severe interstitial fibrosis. Ninety percent were moderate to severe fibrosis.

2.8 **Kipen H M, Lilis R, Suzuki Y, Valcinkas J A, Selikoff I J. Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation. Brit J Ind Med. 1987, 44: 96–100.**

C 3863 We have found that in the presence of lung cancer occurring in asbestos insulation

workers with occupational asbestos exposure, asbestosis was invariably present when histopathological findings were used as the criterion for diagnosis.

2.9 **Hughes J M, Weill H. Pulmonary fibrosis as a determinant of asbestos-induced lung cancer in a population of asbestos cement workers. Proceedings of VIIth International Pneumoconiosis Conference, Pittsburgh, August 1988. In Press.**

Survival and case-control analyses of the lung cancer experience of this population found that after accounting for pack-years of smoking, age, and estimated asbestos exposure, presence of small opacities was a significant determinant of lung cancer risk ($p<.03$). In this population, asbestos-induced lung cancer was restricted to workers with X-Ray evidence of asbestosis.

2.10 **Sluis-Cremer G K, Bezuidenhout B N. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. Brit J Ind Med. 1989, 46: 537-540.**

In a necropsy series of 339 amphibole asbestos miners, heavy smoking, age, and the presence of asbestosis were significantly associated with the presence of bronchial cancer. Of the 35 cases of bronchial cancer, 24 were associated with asbestosis. Eleven cases of bronchial cancer occurred in men without asbestosis; all were smokers. Standardised proportional mortality rates indicated no excess of bronchial cancer in 302 exposed men without asbestosis whereas these rates were progressively raised in men with slight or moderate/severe asbestosis. Of the four exposure variables introduced separately into a logistic regression model, "years of exposure" made a small but significant contribution; "residence time" marginally failed to achieve a 5% level of significance. Two other exposure variables tested including cumulative fibre exposure (fibre years) made no significant contribution.

In the absence of asbestosis at necropsy a bronchial cancer in a man exposed to asbestos is unlikely to be due to asbestos.

2.11 **Sluis-Cremer G K, Bezuidenhout B N. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. Brit J Ind Med. 1990, 47: 215-216.**

This was a short letter to the British Journal of Industrial Medicine in reply to a letter by R M Rudd published in the same journal. Rudd had suggested that "since the risk and severity of asbestosis are themselves dose-related much of the effect of dose on the risk of cancer had already been allowed for by the analysis of the effect of asbestosis grade. Nevertheless, years of exposure, probably the most reliable measure of dose because it is known more accurately than intensity, still had a significant effect. This is consistent with the dose of asbestos rather than asbestosis being the major determinant of the risk of cancer".

Sluis-Cremer did further statistical analyses using stepwise unconditional logistic regression analysis and concluded that "the grade of asbestosis still emerged as a highly significant risk factor for bronchial cancer".

Sluis-Cremer then did a "conditional logistic regression analysis on a matched case-referent set of subjects to assess the effect of asbestosis absent/present on risk of bronchial cancer after adjusting for the effects of age and smoking. The improvement in the fit of the model to the data with the introduction of asbestosis was significant. As in the unconditional logistic analysis in the published paper, heavy smoking emerged as a significant contributor to the risk of bronchial cancer".

2.12 **Davis J. The carcinogenicity of mineral fibres in experimental animals - an overview. NATO Advanced Research Workshop on Mechanisms in Fibre Carcinogenesis. Albuquerque, New Mexico, October 1990. In Press.**

Dr Davis reviewed several decades of work studying the mechanisms whereby asbestos and other materials affected the lungs. In summarising, Davis stated that "animal experiments support the notion that a lot of tissue damage, ie fibrosis, is necessary to cause cancer; the more fibrosis, the more tumours; and in animals, tumours were never found without fibrosis.

3. SAFE DOSE CONCEPT

3.1 Providing evidence for a safe dose of asbestos, ie a fibre exposure level which does not result in an increased risk of asbestos related diseases – asbestosis, lung cancer and mesothelioma – depends on having working populations exposed to low levels of asbestos for many years. It is now impossible to find such populations, outside South Africa, exposed to amphiboles because the use of crocidolite and amosite virtually stopped in the 1960s.

3.2 But chrysotile continued to be used long after the 1960s, and the following papers provide evidence to support the notion that people can be exposed to low levels of chrysotile fibres without the risk of asbestos related diseases.

3.3 **Berry G, Newhouse M L. Mortality of workers manufacturing friction materials using asbestos. Brit J Ind Med. 1983, 40: 1–7.**

A mortality (1942–80) study was carried out on 13 640 workers of a factory producing friction materials. The only type of asbestos used was chrysotile, except during two well–defined periods before 1945 when crocidolite was used. Measured and estimated fibre concentrations were available for the different jobs over the period of the study. No dose–response relationships were observed, but exposures were low with only 5% of men accumulating 100 fibre–years/mL.

The experience of this factory over a 40 year period showed that chrysotile asbestos was processed with no detectable excess mortality. The final paragraph of the paper stated: "The study reported in this paper, together with that at an asbestos cement factory (Thomas H F, Benjamin I T, Elwood P C, Sweetnam P M. A further follow–up study of workers from an asbestos cement factory. Brit J Ind Med. 1982, 39: 273–6) show that chrysotile was used in manufacturing industry with no detectable effect on mortality during a period when workers in factories processing amphiboles were experiencing high excess mortality due to lung cancer, mesothelioma and other cancers."

3.6 **Newhouse M L, Sullivan K R. A mortality study of workers manufacturing friction materials: 1941–86. Brit J Ind Med. 1989, 46: 176–179.**

The mortality of workers employed at a factory producing friction materials has been studied from 1941 to 1986, extending a previous study (para 3.3) by seven years. There was no excess of deaths from lung cancer or other asbestos related tumours, or from chronic respiratory disease. After 1950 hygienic control was progressively improved and from 1970 levels of asbestos in air have not exceeded 0.5 – 1.0 f/mL. It is concluded that with good environmental control chrysotile asbestos may be used in manufacture without causing excess mortality.

4. LUNG FIBRE BURDEN

4.1 The following papers provide examples of some of the work done on lung fibre burdens. There appear to be many problems associated with the study of asbestos fibres and asbestos bodies in the lungs, and with studying their links with the development of asbestosis, lung cancer or mesothelioma.

4.2 **Churg A M, Warnock M L. Numbers of asbestos bodies in urban patients with lung cancer and gastrointestinal cancer and in matched controls. Chest. 1979, 76: 143–149.**

The numbers of asbestos bodies extracted from the lungs of 103 patients with lung cancer and 50 patients with gastrointestinal malignant neoplasms were compared with the numbers of asbestos bodies extracted from lungs of control patients matched for age, sex, smoking habits, and, in some cases, occupation. All patients were urban dwellers over the age of 40 years, and none was a primary asbestos worker. No differences in the counts of asbestos bodies were observed between the tested and control populations. The number of asbestos bodies did not correlate well with occupation; the highest counts were found in male manual laborers. It was concluded that in the urban population studied, the

3.4 **Gardner M J, Winter P D, Parnett B, Powell C A. Follow-up study of workers manufacturing chrysotile asbestos cement products. Brit J Ind Med. 1986, 43: 726–732.**

A mortality study of workers manufacturing chrysotile asbestos cement products was conducted. Employee records of an asbestos cement facility in England for the period 1941 to 1983 were reviewed. Air monitoring data for 1968 to 1982 were reviewed and since 1970 airborne asbestos concentrations were generally below 1f/mL, most were under 0.5 f/mL. Only a few exposures above 2 f/mL were recorded.

Overall mortality was less than expected. No excess of lung cancer was observed when compared with local or national rates.

The authors note that their results are consistent with those of two other studies showing no excess cancer risk for workers exposed to low concentrations of chrysotile.

3.5 **Neuberger M, Kunki M, Friedl H P, Haider M. Exposure to asbestos, smoking and lung cancer. Proceedings of the Annual Meeting of the Austrian Society of Occupational Medicine, Baumgartner E (Ed), Gentner Verlag, Stuttgart. 1988, 223–226.**

A historic prospective epidemiological study is being carried out at the world's oldest asbestos–cement factory in Austria. All workers who had worked at least 3 years at the Vocklabruck factory between 1950 and 1981 have been studied. So far the results up to 1977 are presented. At that point, 2155 workers lived and 540 had died. Fifty of them died of lung cancer against 28.5 expected in Upper Austria (SMR = 172), but if adjusted with respect of smoking history (SMR = 104) was no more significant. The excess mortality from lung cancer, according to authors, was almost totally due to smoking and not due to asbestos. They calculate that in exposures to chrysotile below 50 fibre-years/mL in the asbestos cement industry there is no measurable excess risk of lung cancer.

numbers of asbestos bodies alone do not correlate with the presence of pulmonary or gastrointestinal carcinoma; however, uncoated asbestos fibres are also known to be present in the lung, and the possibility that such tumours may be related to the numbers of such fibres in lungs remains to be explored.

[Preparation of pulmonary tissue: Lung fixed in formaldehyde solution was digested with bleach and the digest was collected on membrane filters with a pore size of 0.45 u according to the method of Smith and Naylor as modified by Churg et al. Three samples with a wet weight of approximately 4g each were taken from each lung at autopsy or from resected lungs. Samples were taken from parenchyma away from large bronchi, tumour, consolidation, scar or pleura. The results for wet lung may be roughly converted to bodies per gram of dry weight by multiplying by a factor of 10.]

The authors did find an association between occupation and counts of asbestos bodies; 60% of the construction workers; 41% of the steel workers; and 25% of the other male manual labourers had more than 100 asbestos bodies per gram of lung, whereas only 7% of men and women with white collar occupations had more than 100 asbestos bodies per gram. But their review of the literature led to the conclusion that levels of exposure to asbestos that do not cause asbestosis are not etiologically related to lung cancer.

4.3 **Churg A. Lung asbestos content in long-term residents of a chrysotlie mining town. Am Rev Respir Dis. 1986, 134: 125-127.**

The effects of long-term exposure to very small amounts of chrysotile asbestos are controversial. To examine this problem, the lung asbestos content from 7 long-term (25 year and greater) residents of Thetford Mines, Quebec, who were never employed in the chrysotile mining and milling industry, was analysed. Thetford Mines is a chrysotile mining town with a demonstrated ambient atmospheric concentration of chrysotile asbestos approximately 200 to 500 times that in urban areas of North America. Data on the residents' lungs were compared with those obtained from 20 long term (25 yr and greater) chrysotile industry workers from Thetford Mines and 20 members of the general population of Vancouver. The median concentrations of chrysotile and tremolite in the

Thetford residents were only about one fiftieth of those of the chrysotile workers, but about 10 times that of the population of Vancouver. Because long fibres of asbestos are generally thought to be more dangerous than short ones are, the sizes of fibres from these 3 groups were also examined. The fibre size distribution of the asbestos from the Thetford residents was significantly longer than that of the Vancouver population, and resembled that of the chrysotile workers. Because epidemiologic studies have consistently failed to find an increased respiratory disease incidence in lifelong residents of Quebec chrysotile mining towns who were never employed in the chrysotile industry, these findings imply that even asbestos burdens much higher, and fibre size distributions much longer, than those of the general population of most North American cities, are not associated with demonstrable pathologic effects.

FIBER CONCENTRATIONS (x 10^6/g dry lung)

Group	Mean	Median	Range
Chrysotile			
Vancouver residents	0.3	0.2	0–1.3
Thetford residents	1.7	1.2	0.3–2.7
Workers	65	46	3.3–470
Tremolite			
Vancouver residents	0.4	0.2	0–1.2
Thetford residents	5.3	1.2	0.2–20
Workers	218	85	4–2,300

4.4 **Warnock M L, Isenberg B S. Asbestos burden and the pathology of lung cancer. Chest. 1986, 1: 20-26.**

To determine whether they could distinguish asbestos related lung cancers from unrelated ones, the authors typed and quantified, by electron-optical methods, the asbestos fibres in the lungs of 75 men with lung cancer. All but 8 men had some history of asbestos exposure, eg shipyard workers. They concluded that, in their subjects, neither the type nor the location of lung cancers was dependent on the degree of parenchymal fibrosis or on residual amosite/crocidolite burden. The question of the usefulness of asbestosis as a marker of asbestos-related cancer remains. They proposed that persons with an asbestos burden heavy enough to cause asbestosis in some should be considered at increased risk for lung cancer. They further concluded that in the absence of an amosite and crocidolite fibre determination, an asbestos body concentration over 1000 per gram of dry lung in a person with a history of exposure to such fibres should be used in place of asbestosis as an indication that a lung cancer may be asbestos related.
[These last two sentences are proposals which other researchers in the field have not supported, and both sentences seem to fit into the general mind-set which concludes that: any lung cancer may be due to any asbestos exposure in any person, so for the purposes of litigation, all lung cancers in all persons exposed to any asbestos are due to the asbestos.]

4.5 **Sebastien P, Armstrong B, Monchaux G, Bignon J. Asbestos bodies in broncho-alveolar lavage fluid and in lung parenchyma. Am Rev Resp Dis. 1988, 137: 75-78.**

Numerical concentrations of asbestos bodies were determined by light microscopy after digestion and filtration according to the standardised method. (Bignon J, Sebastien P, Jaurand M C, Hem B. Microfiltration method for quantitative study of fibrous particles in biological specimens. Envion Health Perspect. 1974, 9: 155-160). The parenchymal concentrations of 1000 asbestos bodies per gram has been proposed as an upper limit for

persons non-specifically exposed, the so-called "general population". Support for this proposal comes from the authors' group in Canada: parenchymal concentrations greater than 1000 asbestos bodies per gram were measured in only 4 of 67 accident cases supposed to reflect the general population; by contrast, all but 1 of 79 miners and millers from the Quebec asbestos mining industry in Thetford Mines had more than 1000 asbestos bodies per gram in their lungs at autopsy.

5. GENERAL CONSIDERATIONS

5.1 This section includes extracts from two papers which look at temporal factors in the causation of lung cancer, one paper on mechanisms of asbestos associated lung cancer, and an overview paper on asbestos-related lung cancer.

5.2 **Copes R, Thomas D, Becklake M R. Temporal patterns of exposure and non-malignant pulmonary abnormality in Quebec chrysotile workers. Arch Environ Hlth. 1985, 40: 80-87.**

Different temporal patterns of exposure appear to be responsible for parenchymal and pleural fibrosis, though both are recognised as a consequence of asbestos exposure.
For the former (asbestosis), it is the sustained inhalation of dust particles reflected in cumulative exposure that most closely relates to outcome, with less effect from dust accumulated over short periods and/or during peaks of exposure.
For the latter (pleural fibrosis) cumulative exposure is only poorly related to outcome, whereas two other features in the temporal pattern of exposure emerge as more closely related to outcome, namely, the length of time dust has been resident in the lung as well as dust inhaled during heavy or peak exposures.
These findings for parenchymal and pleural fibrosis are in keeping with published data. Somewhat surprising was the finding that for each response scale, the highest crude correlations were with variables containing only time information. This may be because temporal factors such as residual time are contained indirectly in these variables, or

because the men in this workforce with higher exposures would tend to have started work earlier and been exposed to higher levels, or simply because these variables are more strongly compounded by age. Indeed, given the inaccuracy of many post exposure intensities, it may often be appropriate to use only duration of exposure in the calculation of excess risk and/or exposure–response relationships since it can be accurately measured.

5.3 **Mossman B T, Craighead J E. Mechanims of asbestos associated bronchogenic carcinoma. In Asbestos Related Malignancy, Ed: Autman K, Aisner J. Grune and Stratton Inc, Orlando, Florida. 1987; 137–150.**

The authors conclude that these data generally confirm the description of asbestos as a classical tumour promoter, and cocarcinogen with PAH in the respiratory epithelium. The effect of asbestos on metabolic capabilities of cells of PAH may cause carcinogenic derivatives to persist in cells for protracted periods of time. Both smoking and asbestos exposure may affect lung clearance of those carcinogens adversely.

5.4 **Thomas D C. Models for exposure–time response relationships with applications to cancer epidemiology. Ann Rev Public Health. 1988, 9: 451–482.**

SMOKING AND LUNG CANCER An apparently paradoxical observation is that relative risks rise slowly after start of cigarette smoking, yet fall rapidly after quitting. Among continuing smokers, the relative risk declines slowly with age at start of smoking, but is neither constant, as predicted if only the penultimate transition were affected, nor strongly declining, as predicted if only the first stage were affected. These observations have suggested to a number of authors that smoking acts on both an early and a late transition. This would imply that the absolute risks should be a quadratic function of the number of cigarettes per day and a power of the duration of smoking; Doll & Peto fitted this model to the data on British doctors and arrived at the equation:

$$0.273 \times 10^{-12} \text{ (cigarettes/day + 6)}^2 \text{ (age - 22.5)}^{4.5}$$

for the annual lung cancer incidence in the age range 40–79. Brown & Chu fitted a multistage model involving effects on both first and penultimate transitions and found that this adequately describes these patterns.

OCCUPATIONAL EXPOSURES Much of our knowledge about temporal variables comes from occupational exposures. These can be difficult to interpret, however, because the exposures are always extended over time and exposure levels usually varied considerably with calendar time, so that it is essential to control for total exposure. This is often difficult to do, however, because of problems of multicollinearity, and because the levels of exposure are unknown.

Asbestos Perhaps the most widely quoted data on the evolution of lung cancer risk following asbestos exposure comes from a cohort of workers exposed only briefly during World War II. In this group, relative risks began to rise after a lag of 10 years from first exposure and peaked after a lag of 30 years. However, Walker has pointed out that this apparently late peak is partly an artifact of the way the data were presented, pooling all years after each choice of lag; when analysed as independent intervals, the peak occurs 15–19 years after first exposure. Reviewing five studies that describe the pattern of risk following first exposure, he concluded that all show a decline in risk near the end of follow–up, presumably attributable to cessation of exposure. Data from the Quebec cohort suggest that the median latent period measured from each increment of exposure rather than from first exposure may be closer to 16 years. The relative risk was much lower after age 65 than before, but was not significantly modified by average age at exposure. These observations would suggest that a relatively early stage was affected, but fits to multistage models rejected this in favour of a relatively late–stage effect. However, the interpretation is confounded by the fact that asbestos is retained in the lung and continues to exert a carcinogenic effect for many years.

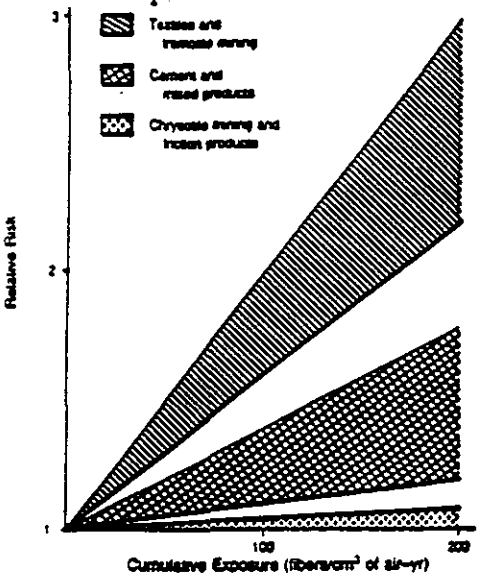
Mesothelioma rates appear to be proportional to the third or fourth power of time since first exposure but are independent of age at first exposure. These data would be consistent

with an effect of asbestos on the first transition rate. As for lung cancer, however, the data would be equally consistent with a somewhat later effect of retained asbestos.

5.5 **Mossman B T, Gee J B L. Asbestos-related diseases. New Eng J Med. 1989, 320: 1721-1730.**

The association between exposure to various types of asbestos and bronchogenic carcinoma has been demonstrated in a number of occupational settings. The average latency period of the disease from the time of first exposure to asbestos ranges from 20 to 30 years. The degree of association varies with the type of asbestos, fibre morphology, concentration, exposure regimen, and such cofactors as smoking habits or the presence of certain other chemical in the workplace, but there is usually a dose-response relation (fibres per cubic centimetre of air times the number of years of exposure). Cohorts such as textile workers have a higher relative risk of disease than others, such as chrysotile miners and workers in plants that manufacture friction products.

Lung tumours are rare among asbestos workers who do not smoke. Although early epidemiologic studies indicated that the effects of asbestos and smoking combine in a multiplicative fashion to produce lung cancer, several recent surveys have suggested that this model is inapplicable in some cohorts. For example, there is a weak interaction between the effects of asbestos and smoking in Canadian chrysotile miners and millers, as well as in British factory workers.



Estimated Risks of Lung Cancer in Various Occupational Cohorts.

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The risk of lung cancer in nonsmokers with asbestos exposure can be assessed only in a

very large cohort, because male asbestos workers are frequently heavy smokers. The inaccurate classification of smokers as nonsmokers may disproportionately inflate the calculated risk of lung cancer among nonsmokers. Workers' estimates of their own cigarette smoking are also questionable, subject to faulty recall, and not always verifiable by independent questionning of friends and relatives. Moreover, a high incidence of passive smoking in the presence of other workers whose smoking rates were higher than those of the general population could enhance the risk among nonsmokers. The data on asbestos workers who are nonsmokers have been summarised recently. But, for the reasons we have mentioned, it remains uncertain whether any type of asbestos acting alone can cause lung cancer in non-smokers.

Several considerations are relevant to the question of a possible contribution of environmental asbestos to lung cancer among members of the general population. First, the numbers of coated asbestos fibres (feruginous bodies) in the lungs of persons with and without lung cancer are comparable. Second, the correlation between the incidence of placques - an indicator of asbestos exposure - and the increased risk of lung cancer is variable, weak, and inconclusive. Third, recent epidemiological studies of persons with low exposure to asbestos either occupationally or environmentally provide little support for the concept that there is an increased risk of lung cancer when asbestos concentrations are at levels several hundred or thousand times lower than those found in workplace situations in the past. In a recent British paper analysing two very large cohorts, one working before and the other after the introduction of a new standard of asbestos regulation, the workers studied after the standard was imposed had no clear evidence of increased cases of lung cancer or asbestosis. As the authors point out, however, the follow-up period was short (12 years), and the latency period established for these diseases is far from over.

A current controversy with important medicolegal ramifications concerns the possible causal role of asbestosis in the development of lung cancer. That scar cancers can occur at sites of fibrotic postinflammatory disease (eg tuberculosis) has long been recognised.

There is also evidence for the concurrence of fibrogenicity and tumorigenicity with various fibre types and clinical forms of pulmonary fibrosis in humans. Several difficulties are inherent in dissociating asbesotosis from exposure to asbestos without asbestosis as a cause of lung cancer in asbestos workers. First, since the development of both diseases is related to the amount of exposure to asbestos, the appearance together of lung cancer and asbestosis cannot be distinguished directly from the requirement for asbestosis as a precondition for the development of lung cancer. Second, by impairing the lung's ability to clear fibres, smoking may magnify the extent of fibrogenesis due to asbestos. Third, at levels of exposure that cause no detectable fibrosis, the epidemiologic difficulties in detecting small increases in the risk of lung cancer are considerable, particularly when smoking is both prevalent and heavy. A study of Quebec miners and millers suggests that "most, but not necessarily all, [patients with] lung cancer "attributable" to chrysotile have small (radiologic) parenchymal opacities before death". This study addresses indirectly the issue of distinguishing asbestosis-associated lung cancer from lung cancer in asbestos workers who smoke and who have little or no "clinical" asbestosis.

In West Germany and the United Kingdom, lung cancer is attributed to asbestos if there is evidence of asbestosis on either chest films or pathological examination. Somer reports have indicated that adenocarcinomas occur more frequently and more peripherally in patients with lung cancer who have asbestosis. Others stress that the histologic types of the tumours are similar in patients with lung cancer with and without fibrosis. Many asbestos workers with lung cancer have histopathological evidence of asbestosis on in-depth examination, though some have questioned this view. The diagnosis of asbestosis is made in living patients when radiological and functional features associated with respiratory symptoms and clinical changes are present. There is no doubt that pathologically evident asbestosis can precede these diagnostic features, as is also true of idiopathic pulmonary fibrosis. Thus, asbestos workers with lung cancer can also have occult minor asbestosis. However, without an autopsy, one must still rely on the clinical evidence of asbestosis in assigning a statistical probability to the relative contribution of asbestos and smoking.