Scand J Work Environ Health 1993;19(2):102-107

<https://doi.org/10.5271/sjweh.1490>

Issue date: 01 Apr 1993

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by [Karjalainen A](#), [Anttila S](#), [Heikkilä L](#), [Kyyrönen P](#), [Vainio H](#)

Affiliation: Institute of Occupational Health, Helsinki, Finland.

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/8391162

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Lobe of origin of lung cancer among asbestos-exposed patients with or without diffuse interstitial fibrosis

by Antti Karjalainen, MD,¹ Sisko Anttila, MD,¹ Lasse Heikkilä, MD,² Pentti Kyyrönen, MSc,¹ Harri Vainio, MD¹

KARJALAINEN A, ANTTILA S, HEIKKILÄ L, KYRÖNEN P, VAINIO H. Lobe of origin of lung cancer among asbestos-exposed patients with or without diffuse interstitial fibrosis. *Scand J Work Environ Health* 1993;19:102-7. The effect of asbestos exposure and asbestos-associated fibrosis on the lobe of origin of lung cancer was studied among 108 lung cancer patients. The asbestos-exposed patients had significantly more lower lobe tumors than the unexposed patients. Similar results were obtained when occupational history or lung fiber concentration was used as an indicator of past occupational exposure to asbestos. The predominance of lower lobe tumors occurred even among exposed patients with no histological signs of asbestosis in their lung specimens. Both bronchial and peripheral cancers showed a lower lobe predominance among the exposed patients. Smoking history did not affect the lobar distribution of the tumors. No significant differences occurred for the histological cell types of the tumors between the exposed and unexposed patients. Patients with asbestosis had, however, more adenocarcinomas than the unexposed patients. The results indicate that asbestos may increase the risk of lung cancer even in the absence of asbestosis.

Key terms: asbestosis, electron microscopy, histological cell type, mineral fibers, smoking.

There is widespread agreement that lung cancer in the general population is the most common in the upper lobes, less common in the lower lobes, and least common in the middle lobes. Some lung cancers, however, appear in the main bronchi, and some are so advanced when diagnosed that their site of origin cannot be determined. Direct comparison of reports concerning the lobar distribution of lung cancers in the general population is difficult because of methodological differences in determining the lobe of origin. There is also great variation (10-67%) between reports regarding the proportion of cancers classified as having a central or unknown site. If only the cancers for which the lobe of origin has been determined are considered, the proportion of lower lobe tumors varies from 25 to 40% in the general population (1-5).

Several studies have indicated that the lower lobes are the predominant site of origin of lung cancer among workers exposed to asbestos. Whitwell and his colleagues (6) reported that 78% of the 65 cases of lung cancer among patients with asbestosis originated in the lower lobes. Kannerstein & Churg (7) studied 36 lung cancer patients, most of whom had asbestosis, and found the ratio of upper lobe tumors to lower lobe tumors to be 1.0:1.47. Jacob & Ans-

pach (8) and Hueper (9) also reported a predominance of lower lobe tumors among workers exposed to asbestos.

Two more recent studies investigated the lobar distribution of lung cancer in asbestos-exposed populations in which clinical manifestations of asbestosis had been less frequent than in the aforementioned studies. Among North American insulators 47% had lower lobe cancers versus 15% of the referents (10). Nearly all of the insulators had at least mild histological diffuse interstitial fibrosis. In a Swedish study of 346 consecutively diagnosed lung cancer cases among male patients, the proportion of lower lobe tumors was elevated among those exposed to asbestos as compared with those unexposed (42 versus 30%). The difference was, however, not statistically significant (11). Only three of the patients had radiological pulmonary fibrosis.

In two other studies, a predominance of upper lobe tumors among asbestos-exposed workers has been reported (12, 13).

The predominance of lower lobe tumors among patients with asbestosis, and the fact that asbestosis is the most severe in the lower zones of the lungs, has raised the question of whether the fibrogenic and carcinogenic effect of asbestos fibers are linked. The aim of our study was to investigate whether the predominance of lower lobe tumors among asbestos-exposed workers could be found in a population in which clinical manifestations of asbestosis are rare, and, if so, to determine whether the predominance of lower lobe tumors is restricted only to asbestos-exposed patients with histological diffuse interstitial fibrosis.

¹ Institute of Occupational Health, Helsinki, Finland.

² Helsinki University Central Hospital, Department of Thoracic and Cardiovascular Surgery, Helsinki, Finland.

Reprint requests to: Dr A Karjalainen, Institute of Occupational Health, Topeliuksenkatu 41 a A, SF-00250 Helsinki, Finland.

Subjects and methods

Subjects

The study population consisted of 108 lung cancer patients who underwent surgical lobectomy or pneumectomy in the Department of Thoracic and Cardiovascular Surgery at the Helsinki University Hospital between August 1988 and July 1992. Included were all those patients operated on in two of the three surgical units of the Department during the period in question. Histologically, there were 58 squamous-cell carcinomas, 37 adenocarcinomas, 7 small-cell carcinomas, and 6 large-cell carcinomas.

The lung cancer patients were interviewed personally about their complete, chronological occupational history, including past occupational, domestic, and environmental exposure to asbestos, and also about their smoking habits. The interview was carried out during their stay in the hospital before the operation. Standardized questionnaires were used in the interview. Special interest was focused on the detailed description, occurrence, duration, and dates (ie, what years) of jobs and tasks with definite or probable exposure to asbestos or other occupational carcinogens. The mean age of the patients was 62 (range 35–78) years, and 84% of the patients were men. About 80% of the patients came from urban areas.

Classification of asbestos exposure

The probability of past occupational exposure to asbestos was evaluated by two occupational hygienists by consensus. The exposure categorization was made without any knowledge of asbestos counts from tissue samples, the lobe of origin of the tumor, or the histological asbestos-associated findings. One month was regarded as the minimum length of exposure. The exposure was classified into four categories according to the following guidelines: (i) definite exposure (group 1): persons employed in asbestos mining, the manufacture of asbestos products, asbestos insulation, or the demolition of old buildings; (ii) probable exposure (group 2): persons employed in shipyards, the construction industry, or metal workshops; (iii) possible exposure (group 3): persons employed in various trades with exposure to dust, such as mining, power plants, transportation, or the pulp and paper industry; and (iv) unlikely or unknown exposure (group 4): persons employed in occupations with no known exposure to asbestos.

In addition to the aforementioned guidelines based on job title, also the frequency and duration of tasks with at least probable exposure to asbestos were considered in the classification. For example, residential or rural construction work without any probable contact with asbestos was classified into group 3, whereas most of the construction workers were assessed as having probable exposure (group 2). Maintenance work involving the demolition of pipe insulations was classified into group 1, whereas maintenance

work in which such exposure was not probable was classified into group 3. The duration of exposure was calculated as the sum of the work periods in occupations with definite or probable exposure to asbestos.

Samples

Fresh lung tissue, a lobe or a lung resected with a tumor, was placed on ice and brought to the Institute of Occupational Health within 45 min of the resection. Samples from 58 lobectomies, 34 pneumectomies, and 16 bilobectomies were collected. The tissue used for the electron microscopic examination was taken from macroscopically normal peripheral lung. After saturation the lobe or lung was filled with 4% formaldehyde through the bronchi and immersed in formaldehyde overnight. The next day the specimen was cut sagittally into slices of 1.5 cm and inspected for the size, location, and extension of the tumor and for macroscopic changes in the visceral pleura and lung tissue. The point of origin of the tumors, whether in cartilaginous bronchi (ie, bronchial) or in more peripheral airways (ie, peripheral) was determined both macroscopically and histologically. In ten cases, the point of origin (bronchial versus peripheral) was not distinguishable because of the large size of the tumor. In addition to histological samples representing the tumor, the bronchial resection line, and the lymph nodes, at least three lung tissue samples per lobe, including one from the central part and one with pleura, were taken according to recommendations for the histopathological investigation of asbestos-associated diseases (14).

Analysis of fiber concentration in lung tissue

The tissue for the fiber analysis was taken from the peripheral part of the fresh surgical pneumectomy or lobectomy specimens, not including pleural tissue or tumor tissue, it was stored at -70°C . For the lobectomies, the sample was taken from the lobe where the tumor was situated. For the bilobectomies or pneumectomies, the sample was taken from the lobe which appeared to be the closest to normal (with the least amount of emphysema or pneumonia).

A tissue piece of about 100 mg (wet weight) was taken for the fiber analysis. A low-temperature ashing technique was used to remove the organic tissue. The fibers were counted with a JEOL 100 CX-ASID4D electron microscope in the scanning electron microscopic mode at a magnification of 5000 $\times$. All inorganic particles having a length-to-width ratio of >3 were defined as fibers and counted. Fibers longer than 1 μm could be detected. An energy dispersive X-ray microanalyzer (Tracor TN 5500) was used to determine the type of fiber (15).

According to previous reports, with the method used, a fiber concentration of at least $1 \cdot 10^6$ fibers (f) per gram of dry tissue indicates past occupational exposure to asbestos (15–17).

Histopathology

In cases with histologically diffuse interstitial fibrosis consistent with asbestosis, the degree of fibrosis was determined according to the grading scheme of Craighead and his colleagues (14). In each slide the maximum grade of fibrosis, 0–4, was multiplied by the number of affected lobuli (1 = less than half, 2 = about half, 3 = more than half). Then a mean score of fibrosis for each case was calculated. The number of slides evaluated for fibrosis in each case ranged from two to seven, the mean being five. The score of fibrosis was not used as a criterion for the diagnosis of asbestosis.

Statistical analyses

The statistical analyses of the lobar distribution of cancers among the exposed and unexposed patients were performed with a logistic model adjusted for age and pack-years of smoking (18). The adjusted parameter estimates and their test-based confidence intervals have been given in terms of the risk ratio.

Results

Asbestos exposure and smoking habits

According to the occupational histories 12 (11%) patients had definite, 27 (25%) patients probable, 34 (31%) patients possible, and 35 (32%) patients unlikely exposure to asbestos. Groups 1 and 2 (definite or probable exposure) contained 39 (36%) patients. Four of them had been exposed in asbestos insulation work, four in shipyard work, two in maintenance work, one in the manufacture of asbestos products, and 28 in various construction jobs. The mean period between the start of exposure and the year of diagnosis (latency) for those with definite or probable exposure was 36 (range 20–54) years. The mean duration of the exposure, calculated as the sum of the work periods in occupations with definite or probable exposure to asbestos, was 18 (range 0.3–41) years.

The fiber concentration in lung tissue ranged from $<0.1 \cdot 10^6$ to $150 \cdot 10^6$ f/g dry tissue, the mean being $3.8 \cdot 10^6$ f/g dry tissue. In 34 cases (31%) the fiber concentration in the lungs exceeded $1 \cdot 10^6$ f/g dry tissue. Most of the exposed patients had mixed exposure to different types of asbestos.

Only 4% of the patients had never smoked, 66% were current smokers, and 30% were ex-smokers. The mean consumption of cigarettes among the smokers and ex-smokers was 42 pack-years. All four nonsmokers (three adenocarcinomas and one small-cell cancer) had a fiber concentration below $1 \cdot 10^6$ f/g dry tissue.

Histologically verified diffuse interstitial fibrosis

Table 1 summarizes the exposure and histopathological data of the patients with histologically verified diffuse interstitial fibrosis. Only two of the patients had previously diagnosed clinical asbestosis (patients 2 and 3 in table 1). In six additional cases histologically verified diffuse interstitial fibrosis was found that was consistent with asbestosis. In one additional case, diffuse fibrosis of the visceral pleura, associated with past exposure to asbestos, was found. In this case, however, no parenchymal diffuse interstitial fibrosis was seen. All of the cases with histologically verified diffuse interstitial fibrosis had been classified into the groups of definite or probable exposure in the evaluation of the occupational exposures. The fiber concentrations in the lungs of these patients ranged from $2.0 \cdot 10^6$ to $150 \cdot 10^6$ f/g dry tissue. All of the patients with asbestosis were either current or ex-smokers. The patient with pleural fibrosis (patient 9 in table 1) had smoked for five pack-years and had stopped smoking 40 years ago.

Lobe of origin of lung cancer

In 106 cases the lobe of origin of the lung cancer could be determined, but in two cases the determination was impossible. (In one case the cancer was situated in the bifurcation of the upper and lower lobe

Table 1. Occupation, fiber concentration in the lungs, and histopathological data of the nine lung cancer patients, all male, with histological signs of asbestosis.

Age	Occupation	Fiber concentration (fibers/g dry tissue)	Histological diagnosis	Degree of fibrosis	Tumor	
					Lobe of origin	Cell type
63	Insulator, 1949–1976	$150 \cdot 10^6$	Asbestosis	4.2	Lower	Adenocarcinoma
63	Insulator, 1950–1973	$65 \cdot 10^6$	Asbestosis	7.2	Lower	Adenocarcinoma
54	Insulator, 1960–70; plumber 1970–1991	$32 \cdot 10^6$	Asbestosis	12.0	Upper	Adenocarcinoma
61	Sheet iron worker 1948–1963; construction	$15 \cdot 10^6$	Asbestosis	4.4	Lower	Small cell
58	Construction worker 1948–1969	$15 \cdot 10^6$	Asbestosis	5.0	Lower	Adenocarcinoma
54	Demolition work 5 years in the 1950s	$6.4 \cdot 10^6$	Asbestosis	7.8	Upper	Adenocarcinoma
58	Plumber, 1952–1968; construction	$3.1 \cdot 10^6$	Asbestosis	4.5	Lower	Squamous cell
78	Carpenter, 1934–1975; construction	$2.4 \cdot 10^6$	Asbestosis	3.5	Lower	Squamous cell
73	Carpenter, 1945–1982; construction	$2.0 \cdot 10^6$	Pleural fibrosis	—	Lower	Squamous cell

bronchi, and in the other it was too widely spread for the lobe of origin to be determined.) The cancer was situated in the upper lobes in 62 (58%) cases, in the middle lobe in 3 (3%) cases, and in the lower lobes in 41 (39%) cases.

Asbestos exposure and the lobe of origin of lung cancer

Table 2 shows the distribution of lung cancers between the lower and upper-middle lobes in patients with or without exposure to asbestos. The proportion of lower lobe cancers was significantly elevated among the asbestos-exposed patients as compared with the unexposed patients. When occupational history was used as an indicator of exposure, 62% of the exposed patients' tumors occurred in a lower lobe as opposed to 25% of the unexposed patients' tumors [RR 2.6, 95% confidence interval (95% CI) 1.5–4.3, $P < 0.001$]. When the fiber concentration in the lungs was used as an indicator of exposure, 56% of the exposed patients' tumors appeared in a lower lobe as opposed to 31% of the unexposed patients' tumors (RR 1.7, 95% CI 1.1–2.5, $P = 0.017$).

Eight of our patients had histologically verified diffuse interstitial fibrosis of the lung parenchyma and one had diffuse fibrosis of the visceral pleura associated with past exposure to asbestos. Seven of these patients had a lower lobe tumor, and two had an upper lobe tumor. (See table 1.) If these cases are excluded from the groups of definite and probable exposure to asbestos, 30 exposed cases had no histologically diffuse interstitial fibrosis or pleural fibrosis in their lung specimen. Fifty-seven percent ($N = 17$) of these patients had a lower lobe tumor, the difference still being significant (RR 2.4, 95% CI 1.4–4.4, $P = 0.003$) from the percentage of lower lobe tumors (25%) among the patients with only possible or unlikely exposure to asbestos.

When the effect of smoking on the lobar distribution of tumors was analyzed, no statistically significant difference could be found between those who had smoked more than 40 pack-years and those who had smoked less than 40 pack-years (table 2).

No significant differences were found in the histological cell types of tumors between the exposed and unexposed patients. Among the patients with definite or probable exposure there were 23 (59%) squamous-cell carcinomas, 12 (31%) adenocarcinomas, 2 small-cell carcinomas, and 2 large-cell carcinomas. Among the patients with possible or unlikely exposure there were 35 (51%) squamous-cell carcinomas, 25 (36%) adenocarcinomas, 5 small-cell carcinomas, and 4 large-cell carcinomas. The adenocarcinomas showed a lobar distribution pattern similar to that observed for all cancers taken together (5 in the upper or middle lobes and 7 in the lower lobes among the exposed patients and 19 in the upper or middle lobes and 5 in the lower lobes among the unexposed patients). Among the eight patients

Table 2. Lobe of origin of lung cancer in 106 of the 108 lung cancer patients according to asbestos exposure and smoking.

	Lobe of origin			
	Lower		Upper or middle	
	N	% ^a	N	% ^a
Asbestos exposure				
Occupational history				
Probable or definite exposure (N = 39)	24	61.5	15	38.5
Possible or unlikely exposure (N = 67)	17	25.4	50	74.6
Fiber concentration in the lungs				
$\geq 1 \cdot 10^6$ fibers/g dry tissue (N = 34)	19	55.9	15	44.1
$< 1 \cdot 10^6$ fibers/g dry tissue (N = 72)	22	30.6	50	69.4
Smoking				
≥ 40 pack-years (N = 43)	19	44.2	24	55.8
< 40 pack-years (N = 63)	22	34.9	41	65.1

^a Percentage of the patients in the corresponding asbestos exposure or smoking category.

Table 3. Distribution of peripheral and bronchial tumors in 98 of the 108 lung cancer patients according to exposure category and lobe of origin.

	Lower lobe (N)	Upper or middle lobe (N)
Peripheral tumors		
Definite or probable exposure	8	4
Possible or unlikely exposure	6	26
All exposure categories	14	30
Bronchial tumors		
Definite or probable exposure	16	6
Possible or unlikely exposure	10	22
All exposure categories	26	28

with asbestosis there were, however, five adenocarcinomas (table 1).

Table 3 presents the distribution of peripheral and bronchial tumors by lobar origin and exposure category. The lower lobe predominance among the exposed lung cancer patients can be seen for both types of tumor.

Discussion

We found a significant predominance of lower lobe tumors among the asbestos-exposed lung cancer patients as compared with the unexposed patients. The exposure to asbestos was assessed by two methods, namely, by an evaluation of the occupational history and by analysis with scanning electron microscopy for the fiber concentration in lung tissue. The difference in the lobar distribution pattern between the exposed and unexposed patients was similar with both of these methods. Although the sample site for the fiber analysis depended on which lobe or lobes

were resected, we assume that the fiber concentrations are comparable and equally representative of cumulative exposure to asbestos. In previous electron microscopic studies, no systematic differences between different lobes have been found in the concentration of fibers of all sizes taken together (15, 19, 20), and our recent studies have shown agreement between the exposure categorization and the fiber concentration in lung tissue (17, 21). It must be emphasized that the fiber concentration was used only as an indicator of past exposure to asbestos. How this total concentration of fibers, not regarding fiber size, reflects the carcinogenic or fibrogenic effect of asbestos remains unknown.

It is noteworthy that, in our study, a significant predominance of lower lobe tumors was found among the patients exposed to asbestos at a level at which clinical manifestations of asbestosis are rare.

Even more interesting was the finding that, among the exposed patients without any histologically diffuse interstitial fibrosis consistent with asbestosis, most of the tumors originated in the lower lobes. In our study the evaluation of histological changes was restricted to the part of the lungs removed in the operation. Therefore the 17 cases of lower lobe tumors among the exposed patients without histologically diffuse interstitial fibrosis are the most important. In seven of these cases only one lobe was available, three lobes were available in two cases, and the entire lung was available in seven cases. Since these were cases with lower lobe tumors, the lower lobe was always examined. Given the typical distribution pattern of asbestosis, one would assume that, if histological fibrosis were present, it would have been evidenced in the histological examination of the lower lobe. Nevertheless, the complete exclusion of histologically diffuse interstitial fibrosis in the parts of the lungs that were not resected cannot be confirmed in these cases.

The question arises of whether the selection of only operable lung cancer patients may have affected the lobar distribution of tumors among the exposed and unexposed patients in this study. The decision to operate is based on the histological cell type of the tumor, the clinical stage, and the cardiorespiratory function of the patient. In a Swedish study there were no significant differences in the percentage of operable tumors of the upper and lower lobes (22). Nor do we have evidence that the tumors of asbestos-exposed patients would be more often operable than those of unexposed patients (23). Actually they are probably somewhat more often inoperable, since asbestosis is associated with a decrease in ventilatory function. The bronchial versus peripheral distribution of tumors between the exposed and unexposed patients did not show any significant differences that may have influenced the decision to operate. Therefore it is not likely that the selection of operable lung cancer patients in this study would ex-

plain the observed predominance of lower lobe tumors among the asbestos-exposed patients.

Some studies have found a predominance of adenocarcinomas among asbestos-exposed patients (24). We observed no differences in the histological cell types of lung cancer between our exposed and unexposed patients. Among the eight patients with asbestosis there were, however, five adenocarcinomas. Surgically treated lung cancer patients are not very suitable for histological cell type analyses, however, since operability is partly based on the histological cell type of the tumor and small-cell cancers are only occasionally treated surgically. It has also been pointed out that the frequencies of various histological cell types vary depending on whether the series is derived from biopsies, operations, or autopsies (6, 25).

Our study comprised lung cancer patients operated on consecutively in two surgical units, and they represented the general population of southern Finland. The proportion of lower lobe cancers (39%) of all of the cancers in our study was at the upper limit of that reported for the general population (25–40%). (See the Introduction.) The high percentage of lower lobe tumors might reflect the greater number of asbestos-exposed patients with an adequate latency time in our study as compared with the corresponding number in the studies conducted in the 1960s and 1970s. About 36% of our patients were evaluated as having definite or probable past exposure to asbestos with a mean latency time of 36 (range 20–54) years. Most of the exposed patients had been of working age in the 1960s and 1970s when the annual use of asbestos was highest in Finland (12). In as many as 31% of the cases the fiber concentration in lung tissue exceeded $1 \cdot 10^6$ f/g dry tissue, a finding indicating past occupational exposure to asbestos. Our study focused on the most industrialized area of Finland, and about 80% of our patients were from urban areas. This fact may have contributed to the relatively high percentage of occupationally exposed persons among our patients.

Since lower lobe tumors are more frequent among asbestos-exposed patients, it is an interesting question whether the lobe of origin of lung cancer can be used in attributing the cancer to past exposure to asbestos. It is a reasonable assumption that lower lobe cancers are likely to be attributable to asbestos at a lower level of exposure than upper lobe cancers are (26).

The mechanisms of carcinogenicity and fibrogenicity of asbestos fibers are poorly understood. As asbestosis and lung cancer among exposed patients are the most frequent in the lower lobes, one would assume that the distribution of asbestos fibers would display a similar pattern. As already mentioned, no systematic distribution pattern has been found for the total concentration of fibers of all sizes. There is evidence that long fibers are both more carcinogenic and fibrogenic than short fibers in animals (27–29), but the relative roles of long and short fibers in hu-

mans are unclear. There is some evidence that the fibers found retained in the lower lobes of humans would be longer than in other parts of the lungs, both in patients with asbestosis and in healthy asbestos-exposed patients (19, 30). The local differences are so small, however, that the role in the pathogenesis of asbestos-related diseases remains unclear.

The relative roles of different types of asbestos in carcinogenesis and fibrogenesis are also unclear. In this study, most of the patients had mixed exposure to several types of asbestos. The most frequent types of asbestos found in the lungs are anthophyllite, crocidolite, and chrysotile, and in a few cases also amosite and tremolite fibers have been found (31).

Acknowledgments

The authors express their thanks to T Tuomi, DSc, who helped in classifying the occupational exposure, to Ms M Mönkkönen and Ms S-L Sarpola, who helped in preparing the samples, and T Kaustia, MA, who did the linguistic revision of the manuscript.

This work was supported by the Finnish Work Environment Fund.

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Received for publication: 27 August 1992