Lung Cancer in the Lower Lobe Is Associated with Pulmonary Asbestos Fiber Count and Fiber Size

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We studied exposure to asbestos, pulmonary fibrosis, fiber count, and fiber size in relation to the lobar origin of lung cancer in 90 consecutive patients. Among the 32 patients with a history of occupational exposure to asbestos, 22 were construction workers. The proportion of lower-lobe tumors increased with the duration of exposure from 45% in those working less than 15 years to 82% in those working 15 years or more in the construction trade, as compared with 25% in patients who were probably not exposed. The location of the tumor in the lower lobe was explained by the high number of total fibers [odds ratio (OR) = 9.0, CI = 2.3–34.6), of fibers 3 μm and longer (OR = 22.1, CI = 3.9–125), and fibers of anthophyllite (OR = 14.6, CI = 2.4–83.4) and crocidolite (OR = 7.0, CI = 1.2–41.2) when the effect of smoking and fibrosis was adjusted in the logistic regression analysis. The location of the tumor did not correlate with fibrosis, pack-years smoked, or the number of short (<3 μm) fibers. Our findings suggest that asbestos causes an excess of lower-lobe tumors at a relatively low exposure level, independently of pulmonary fibrosis. **Key words:** anthophyllite, asbestosis, crocidolite, pulmonary fibrosis, tobacco smoking. *Environ Health Perspect* 101:166–170(1993)

Exposure to asbestos is considered the second most important cause of lung cancer after tobacco smoking. The mechanisms by which asbestos causes lung cancer are not fully understood, but the multiplicative synergism between tobacco smoking and asbestos exposure in lung carcinogenesis is well described in epidemiological studies (*1,2*). Asbestos also causes pulmonary fibrosis (i.e., asbestosis), and the question of whether asbestos fibers directly cause cancer or whether they cause cancer through the process of fibrogenesis remains controversial (*3–5*).

Many of the characteristics of occupational asbestos exposure, including a considerable duration and intensity of exposure and a latency period preceding manifestation of the disease, are conditions common to both asbestosis and asbestos-associated lung cancer. Also, the most fibrogenic asbestos types and fiber sizes differ little from the most carcinogenic fibers in animal experiments (*6–8*). In humans, the association of fibrogenesis and carcinogenesis is not so well known. According to recent investigations, short fibers in human fibrogenesis may not be as innocuous as previously thought (*9,10*). Short fibers are also thought to have less carcinogenic potency than long ones, but on an epidemiological basis this is difficult to establish because asbestos workers are often exposed to a mixture of asbestos fiber types and sizes during different periods of time.

Several studies have demonstrated that the majority of lung tumors in asbestos-exposed patients arise from the lower lobes (*11–13*), whereas upper-lobe tumors dominate in the general population (*14*). The causal factors for the predisposition to lower-lobe tumors due to asbestos exposure are not known, although increased retention of fibers in the lower lobes due to fibrosis and the origin of tumors as "scar cancers" from the fibrotic areas have been suggested. Both of these assumptions are based on the occurrence of fibrotic changes predominantly in the lower lobes in asbestosis. We report here our study of exposure to asbestos, pulmonary fibrosis, asbestos fiber count, and fiber size in relation to the lobar origin of lung cancer.

Methods

Patients

The patients operated on for a pulmonary tumor in the Departments of Thoracic and Cardiovascular Surgery of the Helsinki University Hospital from August 1988 to January 1992 were included in the study. We interviewed all patients personally about their smoking habits and chronological occupational history, as described in detail elsewhere (*15*).

The probability of past occupational exposure to asbestos was evaluated without any knowledge of the histological findings, tumor location, or pulmonary fiber counts and was classified as follows:

Definite exposure: persons employed in the mining of asbestos, the manufacture of asbestos products, asbestos insulation, or demolition of old buildings
Probable exposure: persons employed in shipyards, the construction industry, or in metal workshops
Possible exposure: persons employed in various trades with exposure to dust, such as mining, power plants, transportation, or the pulp and paper industry
Unlikely exposure: persons employed in occupations with no known exposure to asbestos.

The histological examination of surgical specimens revealed inflammatory lesions in four cases, probable secondary carcinomas in two, and rare tumors in six cases (four carcinoid tumors, one sclerosing hemangioma, and one leiomyosarcoma). With these cases excluded, the subjects consisted of 76 male and 14 female lung cancer patients.

Histopathology

The tissue examined consisted of 49 lobectomy, 27 pulmectomy, and 14 bilo-bectomy samples. We took a sample for fiber analysis from macroscopically normal peripheral lung without pleura. The specimen was filled with 4% formaldehyde through the bronchi and immersed in formaldehyde overnight. The next day we cut the specimen sagittally into slices of 1.5 cm and inspected the slices for the size, location, and extent of the tumor, as well as for macroscopic changes of the visceral pleura and lung tissue. Histological samples representing the tumor, bronchial resection line, and lymph nodes were prepared conventionally for light microscopy and stained with hematoxylin–eosin. In

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addition, at least three lung tissue samples per lobe, including one from the central region and one with pleura, were taken according to the recommendations for the histopathological investigation of asbestos-associated diseases (*16*). We stained the lung tissue sections using the van Gieson technique to determine the grade of fibrosis, and we also stained the sections with Prussian blue to calculate asbestos bodies. The histological types of tumors were classified according to the World Health Organization classification of lung tumors (*17*). Also, their site of origin, whether in a bronchus or in a more peripheral airway, was determined macroscopically and in histological slides.

We determined the degree of fibrosis according to the grading schemes of Craighead et al. (*16*) for grading fibrosis associated with asbestosis. The score of fibrosis was assessed by this method in all cases regardless of the diagnosis. For each slide, we multiplied the maximum grade of fibrosis (0–4) by the number of affected lobules (1 = occasional, 2 = less than half, 3 = more than half). Then we calculated a mean score of fibrosis for each case. The number of slides evaluated for fibrosis in each case varied from two to seven (mean, five). The degree of fibrosis was not determined for slides with signs of obstructive pneumonia. In two cases obstructive pneumonia involved the whole surgical specimen and prevented the determination of fibrosis. We did not use the score of fibrosis as a criterion for the diagnosis of asbestosis.

Pulmonary Asbestos Fiber Content

We dried the fresh tissue sample of about 0.5 g in a vacuum and, after weighing, ashed it overnight in a low-temperature asher with oxygen plasma. To remove excess salts, we washed the ash in 1 M nitric acid and then in absolute ethanol and finally in filtrated, distilled water. The residue was sonicated for 30 sec and diluted to various concentrations (1:8, 1:16, and 1:32), which were filtered onto a Nucleopore filter of pore size 0.1 µm. The filter was coated with carbon, and a 4 × 4 mm piece was transferred onto a 150-mesh copper grid and dissolved slowly in chloroform vapor. The grid with the dust on the carbon film was coated again with carbon. We filtered all liquids used for the preparation through Teflon filters (Millipore Millex FG) with pore size 0.2 µm to avoid particle contamination. A blank sample was prepared and analyzed for each series.

Transmission electron microscopy was performed using a JEOL 100CX electron microscope, and elemental analysis was performed with a LINK AN10-25 energy dispersive spectrometer (EDS). We examined at least 20 grid squares at 10,000× magnification. Even single chrysotile fibrils could be detected, and all fibers were identified from their chemical composition by EDS or from the crystal structure by electron diffraction. We measured the length and diameter of each fiber and determined the number of fibers <3, 3–5, and >5 µm for each case. The detection limit was 100,000 ± 50,000 fibers/g dry tissue. To validate the fiber recovery and analytical techniques, we have prepared and analyzed a number of parallel lung samples in two laboratories and obtained consistent results (*18*).

Results

According to the personal interview, 57 of the 90 patients were current smokers, 29 were ex-smokers for at least 1 year, and 4 never smoked. On the basis of their work history, 32 patients had a definite or probable occupational exposure to asbestos. Five patients had been exposed for periods varying from 3 months to 3 years in demolition of asbestos insulation, 2 were shipyard workers, 1 was a maintenance worker, and 24 had been employed in various occupations in the construction trade for months up to 46 years (mean, 18 years). For 29 patients, including 2 foundry workers, exposure to asbestos was possible, and for 29 patients exposure was unlikely. In one case a clinical diagnosis of asbestosis had been made previously. Five additional cases of asbestos-associated pneumoconiosis were diagnosed by histological examination. Occupational, histological, and analytical data for these six cases are given in Table 1.

We classified tumors into histological types as follows: squamous cell carcinomas, 48 (53%); adenocarcinomas, 30 (33%); small cell carcinomas, 7 (8%); large cell carcinomas, 4 (4%); and adenosquamous carcinoma, 1. Of the tumors, 34 were peripheral and 50 bronchial in origin. In six cases, we could not determine tumor origin due to the large size of the tumor. There was no difference in the occurrence of various histological tumor types, nor in peripheral or bronchial tumor locations, between occupationally exposed and unexposed patients.

History of Asbestos Exposure and Fibrosis

The patients diagnosed by histological examination as having asbestos-associated pneumoconiosis had been employed in various construction occupations from 15 to 32 years (Table 1). In these occupations the intensity of asbestos exposure varied from very light to heavy depending on the job, the type of building, and years in the construction trade.

Of the 90 patients, 24 were construction workers. After exclusion of one patient, whose exact working time was not known, and of another patient, who had mainly been a stone worker and had mixed-dust pneumoconiosis, the remaining group of 22 workers was divided into 2 groups: <15 years and >15 years work time. The time from the start of exposure to cancer surgery varied from 19 to 57 years (mean, 37 years). The mean score of fibrosis was 1.4 (± 1.1) in the <15 years group and 3.0 (± 2.2) in the >15 years group (Student's t-test, $p<0.05$). The former value was not higher than the mean fibrosis in the unexposed patients. The construction workers are listed according to their work time in Table 2. Six of the patients with work time >15 years, but none of those <15 years, had asbestosis or visceral pleural fibrosis. Work times and pulmonary fiber counts are presented as complementary information in Table 2 because gradual breakdown and clearance of asbestos fibers in the lung may have taken place after the end of exposure, and higher fiber levels may have been present during the times of exposure.

Asbestos Fiber Types and Fiber Counts

Anthophyllite was the most prevalent fiber type in the lung tissue of our patients. Chrysotile fibers were found in only 23 out

Table 1. Occupational, histological, and analytical data of patients with asbestos-associated pneumoconiosis diagnosed by histological examination

Patient no.	Occupational trade	Work years	Diagnosis	Score of fibrosis	Ab/ slide	Af (million/g)	Main fiber types[a]
1	Insulator	23	Asbestosis	7.2	400	26.8	ant, cro
2	Construction	15	Asbestosis	4.4	100	49.9	cro
3	Plumber	16	Asbestosis	4.5	300	3.4	ant
4	Construction	21	Asbestosis	5.0	100	9.0	ant, cro
5	Construction Steel work	32 4	Visceral pleural fibrosis	1.4	20	4.8	cro
6	Construction	41	Asbestosis	3.5	26	1.6	ant, cro

Abbreviations: Ab, asbestos bodies; Af, asbestos fibers per gram of dry weight.
[a]Types of at least 90% of fibers; chr, chrysotile; ant, anthophyllite; cro, crocidolite.

Table 2. Asbestos exposure, fibrosis score, and tumor type and location of the 22 construction workers

No.	Work time (years)	Pack years	Af (million/g)	Fibrosis score	Tumor type[a]	Tumor location (lobe)
1	1	42	0.6	1.0	Sqcc	Upper
2	3	41	1.8	1.4	Sqcc	Lower
3	3	0	0.3	0	Ac	Upper
4	6	92	0.9	0.4	Sqcc	Upper
5	8	76	6.0	2.0	Ac	Lower
6	10	40	2.1	3.2	Sqcc	Upper
7	11	72	0.5	0.5	Sqcc	Lower
8	12	55	2.3	2.0	Sqcc	Lower
9	12	50	3.1	3.2	Ac	Upper
10	13	49	0.3	1.5	Sqcc	Lower
11	14	55	0.7	0.3	Lcc	Upper
12	15	55	49.9	4.4	Scc	Lower
13	16	10	3.4	4.5	Sqcc	Lower
14	18	27	4.8	0	Sqcc	Upper
15	21	90	9.0	5.0	Ac	Lower
16	23	33	26.8	7.2	Ac	Lower
17	24	29	2.1	1.3	Sqcc	Lower
18	26	20	1.9	2.2	Lcc	Upper
19	30	50	1.2	2.3	Ac	Lower
20	37	5	4.8	1.4	Ac	Lower
21	41	86	1.5	3.5	Ac	Lower
22	46	53	3.4	0.8	Ac	Lower

Af, asbestos fibers per gram dry weight.
[a]Tumor type: Sqcc, squamous cell carcinoma; Ac, adenocarcinoma; Lcc, large cell carcinoma; Scc, small cell carcinoma.

of 90 patients, ranging from 0.06 to 5.9 million fibers/g. The construction workers (Table 2) were exposed mainly to anthophyllite and crocidolite. In all patients, the total number of asbestos fibers analyzed consisted of 47% anthophyllite, 34% crocidolite, 10% chrysotile, and 9% others (tremolite, amosite). In patients who had an occupational exposure history of asbestos, the fiber types were 50% crocidolite, 40% anthophyllite, 6% chrysotile, and 3% amosite. In Fin-land, the common use of anthophyllite along with chrysotile in insulation is due to the mining of this asbestos in Paakkila, Finland, until 1975.

The distribution of the fiber sizes <3, 3–5, and >5 μm was 39%, 18%, and 43% in all patients and 24%, 19%, and 57% in the patients with an occupational exposure history, respectively. The fiber size categories 3–5 μm and >5 μm and longer are presented as one category (≥3 μm) in the following discussion because the two fiber lengths gave similar results with the variables studied.

The median numbers of asbestos fibers in the lung tissue of the patients classified on the basis of occupational history as definitely or probably exposed, possibly exposed, and unlikely exposed were 2.0 (range, 0.3–49.9), 0.8 (range, <0.1–58.7), and 0.6 (range, <0.1–9.2) million/g dry weight, respectively. The mean total asbestos fiber count as well as the number of short (<3 μm) and long fibers (≥3 μm) were higher in the patients classified as definitely or probably exposed compared with those considered unlikely exposed (Student's t-test, $p<0.05$).

Tumor Location, Fibrosis, and Asbestos Fibers

Fifty-two tumors (58%) were situated in the upper lobes, 3 (3%) in the middle lobe, 34 (38%) in the lower lobes, and 1 in the main bronchus. There was an excess of lower-lobe tumors among asbestos-exposed patients. Twenty of the 32 patients (63%) who were classified as definitely or probably exposed to asbestos and 14 of the 57 patients (25%) who were possibly or unlikely exposed had a lower-lobe tumor (x^2 = 10.94, p = 0.001). Correspondingly, when the patients were grouped based on the pulmonary asbestos fiber content, 16 of the 27 patients (59%) with 2 million or more fibers and 18 of the 62 patients (29%) with less than 2 million fibers/g lung tissue had a lower-lobe tumor (x^2 = 6.06, p = 0.014). Nine of the 11 patients (82%) who had been employed in the construction trade at least 15 years, compared with 5 of those (45%) who had been employed less than 15 years, had a lower-lobe tumor (Table 2). In addition, all six patients with an asbestos-associated pneumoconiosis (asbestosis or visceral pleural fibrosis) had a lower-lobe tumor: two were peripheral adenocarcinomas, one was a small cell carcinoma, and three were squamous cell carcinomas. The number of adenocarcinomas among lower-lobe tumors did not exceed that among upper-lobe tumors.

The score of fibrosis did not differ among the patients with different histological tumor types or between those with different tumor location (peripheral or bronchial). In the lower-lobe tumor patients, the mean score of fibrosis was not elevated compared with the upper-lobe tumor patients.

There was a greater number of 3 μm and longer fibers in the lung tissue of patients who had a lower-lobe tumor as compared with those who had an upper-lobe tumor (Student's t-test, $p<0.01$). This difference was not observed with the fibers shorter than 3 μm. The finding was not explained by sampling because the samples taken from the lower lobes did not contain any fiber size in larger numbers than the samples taken from the upper lobes.

The relation of the tumor location to the fibrosis score, the number of pack-years, pulmonary fiber count, fiber size, and asbestos type was analyzed with a logistic regression by simultaneously modeling fiber parameter, pack-years, and fibrosis. The factor studied was always adjusted for the other two factors in the model. The location of the tumor in the lower lobe was explained by the high number of total fibers, fibers 3 μm and longer, and fibers of anthophyllite and crocidolite, but it was not explained by the fibrosis score, pack-years, or the number of fibers shorter than 3 μm (Table 3). The odds ratio (OR) for a total fiber count of 3 million or more was 9.0. The odds ratio was also high for long (≥3 μm) fibers (OR = 22.1, CI = 3.9–125) and for anthophyllite (OR = 14.6, CI = 2.4–83.4), when similar fiber levels as for total fiber count were used (<1, 1–<3, and ≥3 million fibers) and for crocidolite (OR = 7.0, CI = 1.2–41.2), which was analyzed using two fiber levels (<2 and ≥2 million fibers) because of the smaller number of patients exposed to crocidolite. When long fibers and anthophyllite were simultaneously included in the model, the effect of both diminished, whereas the odds ratio of long fibers remained the same and that of crocidolite became nonsignificant. Because antho-

Table 3. Adjusted odds ratios (OR) of the selected factors for the location of tumor in the lower lobe (logistic regression)

Factor	No.	Unadjusted OR	Adjusted OR	95% CI
Pack-years				
<10	6	1.0	1.0	RL
10–<40	40	0.6	1.0	0.1-6.5
≥40	40	1.2	2.1	0.3–14.7
Fibrosis score				
<1	19	1.0	1.0	RL
1–<3	37	1.1	1.0	0.3–3.4
≥3	30	0.5	0.3	0.1–1.2
Asbestos fibers (million/g by TEM)				
<1	41	1.0	1.0	RL
1–<3	28	1.2	1.4	0.5–4.3
≥3	17	7.6*	9.0*	2.3–34.6

TEM, transmission electron microscopy.
*$p<0.001$ as compared to the reference level (RL) of the factor.

phyllite consisted mainly of long fibers and crocidolite of both long and short fibers, our observation suggests that the fiber size is more important than asbestos type in the lower-lobe tumors of asbestos-exposed patients. However, it was not possible to completely distinguish the effect of anthophyllite and crocidolite because the construction workers, especially, were exposed to both asbestos species.

Discussion

The proportion of lower-lobe tumors among asbestos-exposed patients was significantly increased in our study, being 60% as compared with 25% among those regarded as unlikely exposed according to their occupational history. When the effect of the duration of exposure on tumor location was examined separately in a group of 22 construction workers, an excess of 20% was found in the lower exposure group (less than 15 work years), and an excess of 57% was found in the higher exposure group (at least 15 work years), as compared with the proportion of lower-lobe tumors in the unlikely exposed patients. In the group of construction workers with lower exposure, no excess fibrosis was found, but asbestosis was diagnosed in 5 of the 11 patients in the group with higher exposure. The lower-lobe tumors of the asbestos-exposed patients represented all histological cell types, but there was a slight predominance of adenocarcinomas among the construction workers with at least 15 years of work time. However, six out of nine lower-lobe tumors in this group were bronchial in origin, and only one of the cancers of asbestosis patients was peripheral adenocarcinoma.

In series of lung cancers representing the general population, the upper-lobe tumors compose, as a rule, two-thirds of all tumors (*14*). Several authors have reported an increase in lower-lobe tumors among lung cancer patients with asbestosis (*11–13*). Auerbach et al. (*19*) did not find any difference in the lobar origin between asbestos-exposed and unexposed patients, whereas Ruffie et al. (*20*) found a predominance of lower-lobe tumors in an asbestos-exposed subgroup of patients. Neither of these two studies report the presence or absence of cases with asbestosis. In the study of Johansson et al. (*21*) on asbestos cement workers, the distribution of the lobe of origin did not differ between the cases and controls. Their study reports an excess of adenocarcinomas in asbestos cement workers, but in the control population the number of adenocarcinomas was much lower than the usual proportion in the general population. Kannerstein and Churg (*12*) observed similar proportions of central and peripheral tumors among upper- and lower-lobe tumors, and Whittwell et al. (*13*) reported almost the same frequencies of adenocarcinomas and other cell types among lower-lobe tumors. The lack of increased occurrence of peripheral adenocarcinomas in these studies and in our study indicates that the additional lower-lobe tumors of asbestos-exposed patients are not "scar cancers."

The strongest evidence for the association of pulmonary fibrogenesis and carcinogenesis comes from animal experiments. In mice and rats exposed to asbestos, carcinomas arise as scar cancers from the center of areas with advanced fibrosis (*8*). In these rodents lung carcinomas are peripheral adenocarcinomas, whereas bronchial and squamous cell carcinomas usually do not occur (*22*). In contrast, a proportion of only 30–50% of human lung carcinomas are of this type both in the normal population and in asbestos-exposed patients. The mechanism of asbestos-induced bronchial carcinogenesis in humans may differ from that observed in animal experiments.

When we analyzed the effect of the total fiber count, fiber size, and asbestos type on the tumor location in the lower lobe with a linear logistic regression adjusting the effect of smoking and fibrosis, the fiber count proved to have an independent effect on tumor location. The highest odds ratios were observed for the count of 3 million or more long fibers (≥3 μm) and for anthophyllite fibers. Cancer in the lower lobe was often resected within a lobectomy specimen, and the sample for fiber analysis was taken from the same lobe. In a few studies long fibers have been shown to be more numerous in the lower than in the upper lobes, although the total fiber count has not differed between the lobes (*23,24*). We did not, however, detect any difference in the counts of short and long fibers between the upper- and lower-lobe samples.

The association of asbestos exposure with lower-lobe tumors at a relatively low exposure level and without asbestosis may be unique for Finnish patients because the fiber types found in the Finnish population differ considerably from those reported in Britain and North America both in normal populations and in lung cancer patients (*25–27*), where chrysotile forms a large part of the pulmonary fiber burden, whereas anthophyllite is of little importance. On the basis of fiber dimensions (mean diameter of 0.5 μm and length of about 10 μm in lung tissue)(*18*), anthophyllite may deposit extensively in the tracheobronchial region (*7,28*) and thus may be a stronger bronchial carcinogen than expected from the rarity of mesotheliomas in anthophyllite miners (*29,30*). Although we could not detect a higher number of asbestos fibers in the lower-lobe samples as a whole, it is possible that a fiber type or size that is critical in relation to lung carcinogenesis in our patient population is deposited more in the lower- than in the upper-lobe region. The bronchial and parenchymal deposition of short and long amphibole fibers in humans is worth further investigations in regard to asbestos-associated lung cancer.

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