Asbestos, asbestosis, pleural plaques and lung cancer

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Inhalation of asbestos fibers increases the risk of bronchial carcinoma. It has been claimed that asbestosis is a necessary prerequisite for the malignancy, but epidemiologic studies usually do not have enough statistical strength to prove that asbestos-exposed patients without asbestosis are without risk. Several recent studies do actually indicate that there is a risk for such patients. In addition, case-referent studies of patients with lung cancer show an attributable risk for asbestos of 6% to 23%, which is much higher than the actual occurrence of asbestosis among these patients. Thus there is an increasing body of evidence that, at low exposure levels, asbestos produces a slight increase in the relative risk of lung cancer even in the absence of asbestosis. Consequently, all exposure to asbestos must be minimized.

Key terms asbestos, lung cancer, lung fibrosis, pleural plaques.

The main cause of lung cancer is smoking. However, inhalation of asbestos fibers can increase the risk for this tumor considerably. The first reports of lung cancer in connection with exposure to asbestos all concerned patients with asbestosis (ie, pulmonary fibrosis caused by asbestos) (1—4). The German physician Nordmann was, in 1938, one of the first to suggest that lung cancer in asbestosis was an occupational disease, and he assumed that the tumor resulted from the proliferating alveolar and epithelial cells in the fibrotic lung (2). Thus, from the outset, it was assumed that the cancer was caused by the fibrosis, not the asbestos fiber in itself ("the asbestosis-cancer hypothesis"). In 1943 the German government declared lung cancer associated with asbestosis to be an occupational disease. It took another 20 years to reach the same conclusion in the United States (5).

Over the years, many researchers have remained in favor of "the asbestosis-cancer hypothesis" (6—13). Gradually, however, several papers have appeared which have shown that an increased risk for lung cancer occurs also in asbestos workers without obvious asbestosis. This finding has led to the proposition that it is the asbestos fibers, not the asbestosis, that are responsible for the tumor ("the asbestos-cancer hypothesis"). As a consequence, a linear dose-response relationship was assumed between asbestos and lung cancer (14—40). However, no consensus has yet been reached on whether lung fibrosis is an obligatory precursor to asbestos-related lung cancer or not.

The purpose of this review is to examine some of the statements made by the two factions and the findings — often statistically weak — that lie behind these claims. First, some basic facts must be remembered.

Latency time

The risk of carcinoma is very low or undetectably low for the first 10 years after exposure to asbestos, but it gradually increases and is highest after more than 30 years (17, 34, 41—43). According to some studies, exposure to low doses will not only produce fewer cancers, but also possibly longer latency times than high doses (44). Consequently, long-time follow-up is necessary, or a number of cancers can be missed and risk evaluation will be flawed (36).

Type of asbestos

The main types of asbestos are those consisting of straight fibers (amphiboles), of which the most important

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are crocidolite, amosite, tremolite and anthophyllite, and those with curly fibers, of which there is only one important type, namely, chrysotile. These fibers all differ in their diameters and lengths and also in their ability to resist breakdown in biological tissues. Chrysotile is by far the most widely used. It also has the fastest clearance from the body, probably due to its higher solubility. As a consequence, in workers' lungs at autopsy, when the exposure occurred some decades earlier, the most commonly found fibers are amphiboles, even if the exposure had been predominantly chrysotile asbestos.

Possibly for this reason, amphiboles seem to carry a greater risk for mesothelioma than does chrysotile (7, 27, 45). As for lung cancer, however, a recent review has concluded that there is little evidence to indicate lower lung cancer risk (46). To confuse matters even more, there are differences between diameters and lengths of the same type of asbestos, the result being different risks for the various diseases. For example, very long chrysotile, as was used in the textile industry, results in a considerably higher risk for cancer than does the "normal" short-fibered chrysotile (27).

The "threshold value"

The existence of a threshold value below which no excess lung cancer occurs has been suggested (9, 11). On the other hand, there are claims that even low doses of asbestos can increase the risk (20, 30, 31, 34, 44, 47—51). In several studies, it has been shown that exposure to a low dose of pure chrysotile (less than 20 fiber-years) causes no measurable increase in lung cancer (25, 52—55).

However, it should be remembered that the effects of exposure to low doses of carcinogens are very difficult to measure and even more problematic to prove statistically, because very large cohorts are needed (40, 56, 57). Failure to prove statistically an excess of any disease with a low risk does not prove that such an excess does not exist, epidemiologic studies are simply not sensitive enough (58). This basic epidemiologic truth is too often forgotten.

Of course, if one subscribes to "the asbestosis-cancer hypothesis", a threshold is automatically implicated (since a fairly high exposure is necessary for asbestosis to develop); on the other hand, "the asbestos-cancer hypothesis" is compatible both with a threshold and without a threshold.

Smoking habits

Smoking and exposure to asbestos have synergistic effects on lung cancer risk. It seems that a multiplicative

model fits the data best (21, 31, 34, 43, 59, 60). Consequently, correction for smoking habits must be made in all comparisons concerning risks of lung cancer. However, in the real world, the differences in smoking habits between various occupational groups in the same society are not very great, and a relative risk in excess of 1.4 is unlikely to be due to such differences (61).

Increased risk of lung cancer in other types of lung fibrosis in man

Proponents of "the asbestosis-cancer hypothesis" have drawn attention to the fact that other types of fibrosis in humans (eg, idiopathic, other pneumoconioses, and those that occur in collagen diseases) also have an increased incidence of lung cancer. In fact, it is mainly in systemic sclerosis (62) and cryptogenic fibrosing alveolitis (63, 64) that any larger number of lung cancers are found. The risk of lung cancer in silicosis is also moderately increased (relative ratio 3.4 for smokers with silicosis and 1.7 for nonsmokers) (65—67). Whether this increased risk is due to the silicosis or to the silica particle itself is another problem.

The typical cancers in systemic sclerosis are peripheral adenocarcinomas or bronchioalveolar cell carcinomas (62), but those in idiopathic fibrosis are similar to the bronchial carcinomas found in smokers (63, 64, 68). Of special interest is the review by Mizushima & Kobayashi (68). They collected 154 patients with lung cancer in idiopathic pulmonary fibrosis from the literature. They found that the following factors were typical for these cancers: there was a predominance among men, almost all occurred in smokers, the tumors were of the same type as among patients without pulmonary fibrosis (except for a higher incidence of small-cell carcinoma), and the tumors were peripheral and mainly situated in the lower lobes. In other words, the tumors were similar to those reported for patients with asbestosis.

It should be remembered, however, that "idiopathic" fibrosis is more than twice as common in persons with some type of occupational exposure to solvents or particles (69). At least some of the substances which presumably caused the fibrosis might in themselves be carcinogenic also. Indeed, asbestosis can be difficult to differentiate histologically from "idiopathic" interstitial fibrosis (apart from the presence of asbestos bodies) unless the exposure history is known.

In lungs with interstitial fibrosis, squamous-cell metaplasia and atypical cell proliferation can be seen far into the small bronchi (63, 70). Thus there are data indicating that the risk of lung cancer is increased in at least some types of diffuse fibrosis other than that caused by asbestos, and thus there is a plausible pathological mechanism

to support this conclusion. These observations can be interpreted as supportive of the "asbestosis-cancer hypothesis".

Correlation between fibrosis and lung cancer in animal studies

In asbestos-exposed rats, the incidence of malignant tumors is related to the degree of fibrosis. However, as has been pointed out, the lung cancers in rats are histologically different from those in humans. The only conclusion one can draw from animal experiments is that both the fibrogenic and the carcinogenic effects are dose-related.

Mutagenicity of asbestos

Though the opposite has been claimed, asbestos is in fact a complete carcinogen (59, 71, 72). This is evident for humans from the occurrence of mesotheliomas, for which asbestos seems to be the single causative agent.

Epidemiologic studies in humans and excess lung cancer in asbestos exposure with and without asbestosis

There is no doubt that patients with clinical and radiological asbestosis have a high risk of dying from lung cancer (table 1). At the highest exposure levels such as occurred in the early years of the industry, there may have been a lower cancer risk because the patients died from asbestosis before there was enough time to develop cancer (41, 82).

Several reports have indicated that the incidence of lung cancer is increased also for asbestos-exposed workers who lack radiological evidence of asbestosis. Some of these reports are listed in table 2.

Radiological diagnosis of asbestosis

The radiological diagnosis of asbestosis is not easy. The system developed by the International Labour Organisation (ILO) for evaluating pneumoconiosis, which has a 12-grade scale for parenchymal opacities, is used. As a general consensus, according to the ILO system, a degree of 1/0 in a worker exposed to asbestos is accepted as manifest asbestosis, while 0/1 is not. Unfortunately, the agreement between readers (or even the same reader at 2 different times) at this level is often not very good. The specificity and the sensitivity when compared with

autopsy findings is also poor, and false negative and false positive results are very common (87—89). A confounding factor is smoking, which can cause a significantly higher incidence of small irregular opacities in chest roentgenograms (90, 91). Since smoking is the main cause of lung cancer, there can be bias in that the risk for patients with radiological "asbestosis" might be overestimated.

Dose-response for asbestosis

Even if the correlation between exposure to asbestos and the occurrence of asbestosis is generally good, the lungs of some patients may be heavily burdened by asbestos without developing asbestosis (92).

Correlation between lung cancer and asbestosis according to autopsy findings

In many studies, the exposure to asbestos has been so large that most workers have some degree of asbestosis at autopsy. As proof of the "asbestosis-cancer hypothesis" some studies have been cited in which all patients with lung cancer also had asbestosis to some degree at autopsy. For instance, Kipen et al (1987) published 138 cases of lung cancer among asbestos insulation workers who all had asbestosis at autopsy; 18% of the asbestosis cases were not diagnosed from X-ray appearances (87).

In 1989 Sluis-Cremer reported autopsy findings from 339 amphibole asbestos miners (both crocidolite and amosite). Lung cancer correlated with heavy smoking, age, and asbestosis. The standardized mortality ratio for lung cancer did not show any excess for 302 exposed men without asbestosis, but it became progressively higher for those with asbestosis (93). The authors concluded that, in the absence of asbestosis at necropsy, a bronchial carcinoma in a man exposed to asbestos is unlikely to be due to asbestos. Since this study is one of the most cited in support of the "asbestosis-cancer hypothesis", it has to be realized that the study has some flaws. It is not an epidemiologic study. It was retrospective and based on the reports of different pathologists. We know nothing of the selection since only a portion of the workers came to

Table 1. Lung cancer in patients with asbestos. (SMR = standardized mortality ratio, RR = risk ratio)

Author	N	Lung cancer per cent of deaths	Ob-served	Ex-pected	SMR or RR
Couts et al, 1987 (73)	155	39	..	..	7.4
Berry, 1981 (74)	283	39	..	..	..
Huuskonen, 1978 (75)	202	32	..	..	9.0
McMillan et al, 1978 (76)		31.2	..	..	..
Buchanan, 1965 (77)	286	30.9	..	..	..
Sluis-Cremer, 1991 (78)	97		43	5.2	8.3
Hughes & Weill, 1991 (12)	77		9	2.1	4.3
Wilkinson et al, 1995 (79)	211				2.3
Hillerdal, 1994 (80)	166		9	3.9	2.3

Table 2. Relative risk of lung cancer in asbestos-exposed cohorts without asbestosis (observed/expected values). (N = number of workers, O = observed number of cases, E = expected number of cases, RR = risk ratio)

Author	Cohort	No asbestosis				Plaques only			
		N	O	E	RR	N	O	E	RR
Sluis-Cremer, 1991 (78)	Amphibole miners	..	..	..	..	302	11	12.4	..
Edge, 1976 (82)	Shipyard workers	..	..	..	..	235	13	5.4****	2.4
Fletcher, 1972 (83)	Shipyard workers	404	7	5.61	1.2	408	16	6.7***	2.4
Loomis et al, 1989 (84)	Normal population		–			59	..	..	3.0
Sluis-Cremer, 1991 (78)	Normal population	738	..	..	1.56*	..	..	..	..
Lidelle McDonald, 1980 (42)	Chrysotile miners (N = 4559)	..	..	..	..	286[a]	..	..	3.7[a]
						190[b]	..	..	2.8[b]
Hillerdal, 1994 (80)	Plaque carriers	..	..	..	..	1430	41	28.2*	1.4
Sandén & Järnholm, 1987 (85)	Shipyard workers	1095	6	4.3	..	626	3	2.9	..
Hughes & Weill, 1991 (12) workers	Asbestos cement	..[c]	10	8.1	1.2	62	2	1.5	1.3
Loomis et al, 1988 (86)	Plaque carriers	..	..	..	..	83[e]	11	3.3	3.3

[a] Uncalcified, calculated from article and might contain some with asbestosis (not clear from article).
[b] Calcified, calculated from article and might contain some with asbestosis (not clear from article).
[c] Only workers with ≤ 20 years of latency from first exposure.
[d] Estimated value from text.
[e] A few of these patients probably had asbestosis, not clear from text.
* P < 0.05; ** P < 0.01; *** P < 0.005; **** P < 0.001.

autopsy, and there was also bias, because the pathologists knew at an early stage whether the patient had cancer or not.

However, most autopsy findings do support the "asbestosis-cancer" theory. There are exceptions however. For instance, there is 1 study in which more than half the patients exposed to asbestos had lung cancer but no asbestosis at autopsy (88).

Correlation between lung cancer and asbestosis according to radiological findings

Some epidemiologic studies have been made concerning radiological findings and subsequent development of lung cancer. The study of Hughes & Weill (12) is of special interest since it has been cited by many reviewers and by the authors themselves as support for the "asbestosis-cancer hypothesis" and "proof" that cancer is no more common than expected in asbestos-exposed persons without asbestosis. As seen from table 2, the relative risk for lung cancer in men without asbestosis in this group is in fact 1.2 (ie, a 20% increase), and, though this is of course not statistically significant, it is statistical speciousness to claim that a lack of excess tumors has been proved in this study. In addition, the authors collected data from 2 factories. In 1 of the 2 crocidolite was used to some extent, and this factor was the only 1 of the 2 factories in which there was an excess of lung cancer

(94). Thus crocidolite seems to be the main risk factor rather than the occurrence of asbestosis.

Some studies on asbestos-related lung cancer have also been published in which some of the patients did not have any fibrosis (76, 95—97). Thus, in many instances, the risk of asbestosis does not parallel the risk of lung cancer (25).

Asbestos fibers or bodies and lung cancer

In several studies, the occurrence of asbestos fibers or bodies or both in the lungs of lung cancer patients — either in rejected lung tissue or at autopsy — have been compared with findings from referents. Some such studies are summarized in table 3. The fiber levels are increased in patients with lung cancer even if there is no asbestosis present. For example, in the Karjalainen study (98), only 2 of the 113 cancers had radiological asbestosis, and another 7 had slight histological fibrosis.

Pleural plaques and risk of lung cancer

In most investigations, pleural plaques are the most common radiological finding in persons exposed to asbestos.

Table 3. Asbestos fibers and bodies and lung cancer.

Author	Material	Cases (N)	Asbestosis	Results
Karjalainen et al, 1993 (98)	Operated	113	9	OR $2.8 \geq 5 \times 10^6$/g per gram OR $1.5 \geq 1 \times 10^6$/g per gram
Martischnig, 1977 (47)	Autopsy	30	—	Significant higher levels of ferruginous bodies in patients with lung cancer
Smith, 1968 (99)	Autopsy	107	—	More asbestos bodies in patients with lung cancer
Kishimoto, 1992 (100)	Autopsy	92	..	More asbestos bodies in patients with lung cancer ($P < 0.01$)
Hiraoka et al, 1990 (101)	Autopsy Operated	337 139	10	More asbestos bodies in patients with lung cancer; high counts $P < 0.01$; low counts $P < 0.05$

They are in themselves harmless and can be regarded as an objective sign of previous asbestos inhalation. If there is a linear dose-response relationship between lung cancer and asbestos, the logical consequence would be that persons with plaques should have an increased incidence of bronchial carcinoma. On the other hand, if the "asbestosis-cancer hypothesis" is correct, there should be no increased risk unless the plaques are combined with asbestosis.

Radiological diagnosis of plaques

The ILO system for diagnosing plaques has a low specificity and sensitivity. At autopsy less than half of the plaques seen radiologically actually exist, but despite this fact more than twice as many remain undiagnosed (102—105). Thus, to reach an acceptable level of specificity, strict criteria are necessary (102, 106). Unfortunately, the sensitivity will then be low — and the majority of the genuine plaques will never be diagnosed (102—105). It is difficult to evaluate any study using unspecified or ILO criteria.

Degree of exposure and plaques

In the general population in a society in which there are no "endemic plaques", 80—90% of strictly defined pleural plaques discovered in chest roentgenograms are due to occupational exposure to asbestos (80). A good correlation between pleural plaques and asbestos fibers or bodies in the lung has been shown by many researchers (22, 99, 107— 115). Asbestos bodies in sputum are also correlated with pleural and parenchymal changes (116). There is also a fair correlation between the number of asbestos fibers in the lung parenchyma and the size of the plaques (113, 115, 117). This correlation supports the finding that the average or cumulative dust exposure is a significant determinant for the progression of pleural abnormalities (118—120). Since definite criteria would single out those with the largest plaques, they would tend to select those with the heaviest exposure.

However, even if the mean of asbestos fibers or bodies in persons with plaques is higher than in the normal population, there is a fairly large variation, and some persons with plaques will have values that are little or no different from those of the general population (111, 114).

Ten percent of the persons with nonmalignant asbestos-related pleural lesions without signs of parenchymal fibrosis will develop radiological and clinical evidence of it in a 10-year period (76, 80, 121). Slightly restrictive lung function has been reported for groups with asbestos-induced pleural lesions; the principal determinant of this restrictive lung function is probably parenchymal inflammation or fibrosis (122). In careful pathological investigations, small lesions in the bronchioles and surrounding parenchyma can be found in most patients with pleural plaques (123, 124). Thus the followers of the "asbestosis-cancer hypothesis" might accept the fact that persons with plaques do have an increased risk of cancer — and attribute this to subradiological asbestosis, which may be present in some these patients.

Plaques and risk of cancer

Whether patients with plaques have an increased risk of bronchial carcinoma or not has been hotly debated. A strong opinion argues that there is no excess cancer for carriers of simple plaques compared with those without (13, 125, 126) or that, if there is such an excess, it is explicable by more prevalent smoking among patients with plaques (127). However, in some studies, the incidence of bronchial carcinoma has been reported to be increased for those with plaques (table 3).

Many studies indicate that plaques are more than twice as common in chest X rays of lung cancer patients as in X rays of the general population (128—132). The same holds true for plaques at autopsy or determined during operation (table 4), but these studies could be biased by the investigator's knowledge of a tumor.

There are also reports in which no excess has been found in patients with plaques. Harper et al compared 13 patients with bronchial carcinoma from 1500 workers exposed to asbestos and found no trend toward an association of pleural plaques with subsequent malignancy (133).

It seems that even low levels of exposure to asbestos (such as the environmental plaques in Finland) can result in plaques. These plaques do not seem to indicate a

Table 4. Pleural plaques and cancer at autopsy or operation. (RR = risk ratio)

Author	Material	Type of referents	Ob-served	Ex-pected	RR
Wain, et al 1984 (103)	409 autopsies	Compared within the group	4	3.4	1.2
Smith, 1968 (99)	109 autopsies	Age/gender matched	27	16	1.7
Mollo, et al 1985 (117)	1019 autopsies	Compared within the group			1.9
Toty, et al 1976 (132)	125 operated cancer	Operated without	30	10.4	2.9

measurably increased risk of cancer (134). This study also showed that there was no increased risk in persons with fibrosis only — but fibrosis in combination with plaques gave a relative risk of 2.8! In a later Finnish study, a rough estimate of the relative lung cancer risk for patients with these mainly environmental plaques in comparison with that of the general population gave the figure of 1.1 (136) — which is such a small risk that unrealistically large population studies would be necessary to prove it statistically (137).

Lobar distribution and histological type of lung cancer in patients with asbestos exposure

Generally, lung tumors are more common in the upper lobes than in the lower ones. In asbestos workers the reverse is true (31, 81, 95, 138). This reversal is seen also in asbestos-exposed cohorts without pulmonary fibrosis (50, 95, 139). In 1 of these studies, in patients with more

than 2 million fibers/g of dry weight of lung tissue, 59% of the cancers were situated in the lower lobes, while, in those with less, only 29% had this distribution (138).

Adenocarcinomas are reported to be relatively more common among persons exposed to asbestos than among unexposed persons (95, 75, 128, 139—141). There is, however, no consensus on this report (137), and the incidence of all the main types of bronchial carcinoma is in fact increased (96, 138, 141, 143—146). There are indications that with heavier exposure, and thus in patients with asbestosis, relatively more adenocarcinomas are seen (22, 31, 139, 142, 145). At lower exposure levels, squamous-cell carcinomas seem to be more common (47, 80, 143, 146). This phenomenon might reflect the relative importance of smoking versus asbestos; at a lower exposure level to asbestos, the "tobacco effect" predominates, creating mainly squamous carcinomas.

Relative and "attributable" risk of asbestos in lung cancer patients

Various reports have tried to outline the importance of asbestos as a cocarcinogen in lung cancer. Case-referent or similar studies of patients with lung cancer reported an attributable risk of 6% to 23% for asbestos (table 5). Occupations with exposure to asbestos are overrepresented among clinical cases of lung cancer (129, 130, 151).

The actual occurrence of asbestosis among clinical cases of lung cancer is much lower than the 6% to 23%, when asbestos played a role according to the epidemiologists. Of special interest is the study by Wilkinson et al (79), in which lung cancer cases were compared with referents, not only regarding occupational exposure and

Table 5. Percentage of "attributable risk" of asbestos in lung cancer. (RR = risk ratio)

Author	Cohort	Cases (N)	Asbes-tosis	Referents	RR	Attributable risk (%)
De Vos & Irvine et al, 1993 (146)	Men in west Scotland	..	..	—	—	6
Karjalainen et al, 1994 (115)	Surgery	65	5 (1 + 4)	297	—	19
Imbernon et al, 1995 (145)	Workers (gas, electricity)	310	..	1240	1.4	..
Kjuus et al, 1986 (143)	Surgery	176	?	176	3.0	23
Vena et al, 1985 (142)	Patients	1002	..	1119	1.7[a] 2.9[b]**	..
Stayner et al, 1996 (46)	Surgery	201	—	201	2.35***	..
Wilkinson et al, 1995 (79)	Patients	271		678	1.7*	..
Blot et al, 1978 (147)	General population	535	?	659	1.6***	..
Järvholm et al, 1993 (148)	Göteborg	147	?	111 109	1.6—1.8	16
Bovenzi et al, 1992 (149)	Trieste	756	?	756	2.0	20

[a] Exposed < 20 years.
[b] Exposed > 20 years.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.