Asbestos-related cancer risk in patients with asbestosis or pleural plaques


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Summary
Introduction. — The relationships between benign asbestos-related diseases (asbestosis and pleural plaques) and thoracic cancers are still debated. The aim of this paper was to review the epidemiological data relevant to this issue.
Current knowledge. — Published studies show a significant relationship between occupational exposure to asbestos and lung cancer risk, even in the absence of abnormalities consistent with asbestosis on the postero-anterior chest x-ray. For a given cumulative asbestos exposure, the presence of radiographic evidence of asbestosis is associated with an increased risk of lung cancer. Among asbestos-exposed individuals, those having radiographic evidence of pleural plaques are at increased risk for lung cancer and pleural mesothelioma, compared to the general population. However, there is no evidence that pleural plaque confers an increased risk of lung cancer or pleural mesothelioma within a population of individuals having the same cumulative asbestos exposure.
Perspectives. — The studies identified for this review relied only on chest radiograph data. Studies involving accurate evaluations of asbestos exposure and computed tomography of the chest are needed.
Conclusion. — Currently available data indicate that patient follow-up modalities should be dictated solely by the estimated cumulative asbestos exposure and not by the existence of pleural plaques.
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**Introduction**

Asbestos is a silicate mineral whose remarkable physico-chemical properties led to many industrial uses in the past. Asbestos resists heat and chemical damage, exhibits considerable mechanical strength, and can be woven or braided. It has been estimated that about 25% of male retirees in France have been exposed to asbestos at the workplace [1]. Occupational asbestos exposure can cause several nonmalignant diseases of the pleura and lungs, including pleural plaques, pleurisy, fibrosis of the visceral pleura, rounded atelectasis, and asbestosis. Several malignancies are associated with occupational asbestos exposure, most notably lung cancer and mesothelioma [2].

Over the last two decades, data have accumulated on the epidemiology of asbestos-related diseases and on the dose-response relationships. Nevertheless, considerable uncertainty remains about the effects of low-level asbestos exposure. Another major issue is the potential link between nonmalignant asbestos-related diseases (asbestosis and pleural fibrosis) and cancer (lung cancer and mesothelioma). If non-malignant asbestos-related disease indicates an increased risk of cancer, then patient follow-up strategies should be devised accordingly, as new tools seem to hold promise for the early detection of lung cancer (e.g., low-dose computed tomography [CT] of the chest and morphometric and/or proteomics biomarkers in cells collected from the respiratory system).

Here, we review the epidemiological data that clarify potential links between radiological evidence of asbestosis or pleural plaques, on the one hand, and lung cancer or pleural mesothelioma, on the other hand. The available data are not adequate for a specific evaluation of the cancer risk in individuals having isolated fibrosis of the visceral pleura (diffuse pleural thickening). The main findings from our review are reported in Tables 1–3.

**Asbestosis and lung cancer**

Asbestosis is defined as interstitial lung disease induced by asbestos inhalation. The exposure levels required to induce asbestosis are considerably higher than those associated with non-malignant pleural diseases [3], and the preventive measures that have been taken to limit high-level exposures have diminished the incidence of asbestosis [4].

Active debate long surrounded the potential links between asbestosis and lung cancer. According to one hypothesis, asbestosis and lung cancer were two consecutive stages of the same asbestos-related disease, with the asbestos-induced lung fibrosis promoting the development of cancer cells [5–9]. Others argued, however, that asbestosis and lung cancer were two separate diseases that were related to the same cause (asbestos exposure) but involved distinct pathogenic mechanisms [10–16].

A 1955 study gave some measure of support to the hypothesis of a disease continuum [17]. This study provided the first evidence obtained, using epidemiological methods, that lung cancer mortality was increased in asbestos-exposed workers. Of 113 asbestos textile workers, 11 died from lung cancer, compared with 0.8 expected. All 11 workers who died of lung cancer had histological evidence of lung fibrosis. Much later, in 1991, another study further supported the hypothesis of asbestosis as a required precursor to lung cancer [18]. Workers in two asbestos-cement manufacturing plants in Louisiana in 1969 were evaluated at least 20 years later. Among them, 420 had normal chest radiographs (profusion of small opacities score 0/0, using the International labour office [ILO] International classification of radiographs of pneumoconioses [19]). No excess mortality from lung cancer was seen in this group: the standardized mortality ratio (SMR) was 1.1 (10 observed deaths versus 9.5 expected); 95% confidence interval (95%CI), 0.5–1.9. In contrast, in the group of 77 workers having ILO profusion scores greater or equal to 1/0, suggesting asbestosis, the lung cancer SMR was significantly increased, to 4.3 (nine deaths versus 2.1 expected), 95% CI, 2.0–8.2. This finding was all the more remarkable that cumulative asbestos exposure was not noticeably different between the group with normal radiographs and the group with small opacities [18] consistent with asbestosis. This was a carefully designed study, with at least 20 years of exposure at the time of the radiographic evaluation, classification of the radiographs by three readers working independently, and collection of data on smoking and cumulative asbestos exposure. However, the small sample size and small number of observed deaths are important limitations.

However, data accumulated from the 1990s onward argue against a continuum from asbestosis to lung cancer. Of 1596 men from Upssala county in Sweden with pleural plaques detected by routine screening, 88.7% had a self-reported history of occupational asbestos exposure [20]. Among them, 50 had lung cancer, compared with 32.1 expected (observed/expected, 1.6; 95%CI, 1.16–2.05). Among the 1430 men without radiographic evidence of lung fibrosis, 41 had lung cancer compared to 28.2 expected, indicating a significant excess risk (observed/expected, 1.4; 95% CI, 1.04–1.97). In a British hospital-based case-control study of 271 lung cancer patients and 678 controls with nonmalignant diseases, chest radiographs were assessed independently by three readers and a detailed occupational history was obtained [21]. Occupational asbestos exposure was significantly associated with lung cancer even in patients having no radiographic evidence of lung fibrosis. In the subgroup of 211 patients who had an ILO profusion score greater or equal to 1/0, there was a significant association between definite or probable asbestos exposure and lung cancer (odds ratio [OR], 2.0; 95% CI, 1.0–4.1). However, asbestos exposure and lung cancer were also significantly linked in the subgroup of 738 patients having no radiographic evidence of fibrosis (ILO profusion score < 1/0; OR, 1.6; 95% CI, 1.0–2.4). In asbestos-cement workers in Canada, a significant excess lung-cancer risk was also found in individuals having no radiographic evidence of asbestosis [22]. Of 123 workers whose chest radiographs, taken 20 years after the first asbestos exposure showed no fibrosis (ILO profusion score < 1/0), 12 died of lung cancer, compared with 2.17 expected (SMR, 5.5; 95% CI, 2.9–9.7). Finally, in the beta-Carotene and Retinol Efficacy Trial (CARET) for lung cancer prevention done in the US, 2089 men with a history of occupational asbestos exposure and no radiographic evidence of asbestosis (ILO profusion score < 1/0) had a significant and dose-dependent increase in the relative risk for lung cancer [23]. Thus, after adjusting for confounders, the risk was increased 5-fold in the most
Table 1  Cohort studies of the lung cancer risk associated with a presumptive diagnosis of asbestosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>ILO profusion score</th>
<th>Indicator of lung cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes and Weill [18]</td>
<td>Asbestos-cement workers</td>
<td>0/0 (n = 420)</td>
<td>SMR = 1.1 (95%CI, 0.5 – 1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1/0 (n = 77)</td>
<td>SMR = 4.3 (95%CI, 2.0 – 8.2)</td>
</tr>
<tr>
<td>Hillerdal [20]</td>
<td>Males with pleural plaques</td>
<td>&lt; 1/0 (n = 1196)</td>
<td>SIR = 1.4 (95%CI, 1.0 – 2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1/0 (n = 166)</td>
<td>SIR = 1.6 (95%CI, 1.1 – 4.4)</td>
</tr>
<tr>
<td>Finkelstein [22]</td>
<td>Asbestos-cement workers</td>
<td>&lt; 1/0 (n = 123)</td>
<td>SMR = 5.5 (95%CI, 2.9 – 9.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1/0 (n = 20)</td>
<td>SMR = 9.9 (95%CI, 2.7 – 25.5)</td>
</tr>
<tr>
<td>Cullen et al. [23]</td>
<td>General population</td>
<td>&lt; 1/0 (n = 2089)</td>
<td>RR = 1.0</td>
</tr>
<tr>
<td></td>
<td>Exposure &lt; 10 years</td>
<td></td>
<td>RR = 2.07 (95%CI, 0.8 – 5.2)</td>
</tr>
<tr>
<td></td>
<td>Exposure = 11–20 years</td>
<td></td>
<td>RR = 2.50 (95%CI, 1.0 – 6.4)</td>
</tr>
<tr>
<td></td>
<td>Exposure = 21–30 years</td>
<td></td>
<td>RR = 3.15 (95%CI, 1.1 – 8.9)</td>
</tr>
<tr>
<td></td>
<td>Exposure = 31–40 years</td>
<td></td>
<td>RR = 5.17 (95%CI, 1.6 – 16.6)</td>
</tr>
</tbody>
</table>

SMR: standardized mortality ratio; RSI: standardized incidence ratio; RR: relative risk; 95%CI: 95% confidence interval; ILO: International Labour Office.

Table 2  Cohort studies of the lung cancer risk associated with pleural plaques in the absence of asbestosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Pleural plaques or thickening (n)</th>
<th>Indicator of lung cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fletcher [35]</td>
<td>Shipyard workers</td>
<td>408</td>
<td>RR = 2.37 (P=0.004)</td>
</tr>
<tr>
<td>Edge [36]</td>
<td>Shipyard workers</td>
<td>429</td>
<td>RR = 1.88 (P&lt;0.02)</td>
</tr>
<tr>
<td>Kivi Luoto et al. [37]</td>
<td>Residence in mining area</td>
<td>700</td>
<td>RR = 0.93</td>
</tr>
<tr>
<td>Hughes et Weill [18]</td>
<td>Asbestos-cement workers</td>
<td>62</td>
<td>SMR = 1.3 (95%CI, 0.2–4.7)</td>
</tr>
<tr>
<td>Sanden et al. [38]</td>
<td>Shipyard workers</td>
<td>837</td>
<td>RR = 0.81</td>
</tr>
<tr>
<td>Partanen et al. [39]</td>
<td>Residence in mining/manufacturing area</td>
<td>604</td>
<td>RR = 1.07 (95%CI, 0.6–1.8)</td>
</tr>
<tr>
<td>Inserm [16]</td>
<td>Pooled data from [19,36–40]</td>
<td>3040</td>
<td>RR = 1.5 (95%CI, 1.2–1.9)</td>
</tr>
<tr>
<td>Hillerdal [20]</td>
<td>General population</td>
<td>1430</td>
<td>RR = 1.4 (95%CI, 1.0–2.0)</td>
</tr>
<tr>
<td>Karjalainen et al. [46]</td>
<td>Occupational diseases registry</td>
<td>4887</td>
<td>SIR = 1.3 (95%CI, 1.0–1.8)</td>
</tr>
<tr>
<td>Cullen et al. [23]</td>
<td>General population</td>
<td>764</td>
<td>RR = 1.91 (95%CI, 1.3–2.9)</td>
</tr>
</tbody>
</table>

RR: relative risk; SMR: standardized mortality ratio; RSI: standardized incidence ratio; 95%CI: 95% confidence interval.
place is significantly associated with an increased risk of lung cancer, even in the absence of radiographic evidence of asbestosis. It is worth noting, however, that none of the studies evaluating the link between asbestosis and lung cancer used CT of the chest, which is more sensitive than chest radiography for detecting lung fibrosis [28]. Neither are data available from histopathological studies.

Although asbestosis is probably not a required preliminary to asbestos-related carcinogenesis, it increases the risk of lung cancer, compared to individuals having similar cumulative exposures but no asbestosis. That idiopathic interstitial lung disease is associated with lung cancer was established many years ago [29]. Among occupational diseases, silicosis is also associated with lung cancer [30,31]. In the above-discussed study of asbestos-cement workers, individuals with ILO profusion scores greater than 1/0 were at increased risk for lung cancer, even after adjustment for smoking history and cumulative asbestos exposure [18]. A 2005 study evaluated 1196 former workers at the crocidolite mine in Wittenoom, Australia, as well as 792 former residents of Wittenoom [32]. Cumulative asbestos exposure was significantly associated with the lung cancer risk even in patients who had no evidence of asbestosis. However, after adjustment for smoking, age, and asbestos exposure, radiographic evidence of asbestosis was associated with an increased risk of lung cancer (RR, 1.96; 95%CI, 1.09—3.46). Similarly, the CARET study showed that the lung cancer risk correlated with the radiographic ILO profusion score [23]. However, the analysis was not adjusted for asbestos exposure in this study, opening up the possibility that the risk increase was related to higher exposure levels [23].

A prospective study from Finland suggests that active asbestosis may be associated with an increased lung cancer risk, independently from the cumulative asbestos exposure [33]. Of 78 men who were receiving radiographic follow-up for asbestosis, 24 showed progressive small-opacity profusion and among these, 11 (46%) were diagnosed with lung cancer, compared to 5 (9%) of the 54 men with no radiographic evidence of asbestosis progression [33].

### Table 3 Cohort studies of pleural mesothelioma risk associated with pleural plaques.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Pleural plaques or thickening</th>
<th>Indicator of mesothelioma risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillerdal [20]</td>
<td>General population</td>
<td>Yes; n = 1596</td>
<td>RR = 11.25 (95%CI, 5.1—21.4)</td>
</tr>
<tr>
<td>Karjalainen et al. [46]</td>
<td>Occupational diseases registry</td>
<td>Yes; n = 4887</td>
<td>RSI = 5.5 (95%CI, 1.5—14.0)</td>
</tr>
<tr>
<td>Sanden and Jarvholm [52]</td>
<td>Shipyard workers</td>
<td>Yes; n = 835</td>
<td>4 cases (0.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No; n = 1852</td>
<td>7 cases (0.7%)</td>
</tr>
<tr>
<td>Koskinen et al. [53]</td>
<td>Construction workers</td>
<td>Yes; n = 6563</td>
<td>RR = 0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No; n = 10132</td>
<td>RSI = 1.19 (95%CI, 0.3—3.1)</td>
</tr>
<tr>
<td>Reid et al. [54]</td>
<td>Crocidolite miners and non-miner residents of same town</td>
<td>?</td>
<td>Adjusted RR = 1.12 (95%CI, 0.6—2.1)</td>
</tr>
</tbody>
</table>

RR: relative risk; RSI: standardized incidence ratio; 95%CI: 95% confidence interval.

- High levels of asbestos exposure are needed to cause asbestosis.
- Asbestos is not a prerequisite to carcinogenesis but is associated with an increased risk of lung cancer compared to asbestos-exposed individuals without asbestosis.
- The lung cancer risk is increased at cumulative asbestos doses lower than those considered necessary to cause asbestosis.

**Pleural plaques and lung cancer**

Pleural plaques are well-demarcated areas of collagen-rich connective tissue lined by normal mesothelial cells and found in the parietal pleura. A review of the 1966—1992 English-language literature to assess the potential links between asbestos-related pleural plaques and lung cancer in the absence of asbestosis was published in 1993 [34]. Of 13 identified studies, six were cohort studies [18,35—39], four were case-control studies [37,40—42], and three were autopsy studies [43—45]. Only three studies, including two cohort studies in shipyard workers [35,36] and one case-control study [40], suggested an increased lung cancer risk in individuals having radiographic evidence of pleural plaques. The author concluded that pleural plaques were not associated with an increased risk of lung cancer in the absence of asbestosis [34]. However, recent data contradict this conclusion. A panel of experts convened by the Inserm in France to assess the health effects of various asbestos exposures [16] analyzed the data from the six cohort studies included in the above-mentioned review [34]. Among the individuals with radiographic evidence of pleural plaques, 83 died of lung cancer compared to 53.9 expected, producing a significantly increase in the SMR (1.5; 95%CI, 1.2—1.9). The Swedish study discussed above [20], also found an increased risk of lung cancer among individuals with a history of occupational asbestos exposure and pleural plaques, compared to the general population,
even in the absence of asbestosis. Among 4887 individuals in a Finnish registry who were monitored prospectively for pleural plaques related to occupational asbestos exposure, the standardized incidence ratio for lung cancer was significantly increased (1.3; 95%CI, 1.0—1.8) [46]. A limitation shared by all these studies is the use of radiographs instead of CT to detect the pleural plaques. Radiographs have limited sensitivity and specificity for pleural plaques detection. The postero-anterior projection does not readily visualize non-calcified plaques located anteriorly or posteriorly (seen frontally). Furthermore, opacities on the lateral chest wall that are seen tangentially are not specific and may be produced by either pleural plaques or subpleural fat.

An important question that remains unanswered is whether pleural plaques increase the lung cancer risk among individuals with similar asbestos exposures. To our knowledge, only two studies contribute to answer this question. One is a case-control study of lung-cancer patients and controls among 1500 asbestos-exposed workers receiving hospital-based screening for asbestos-related diseases [47]. The cases and controls were matched individually on ethnic origin, asbestos exposure duration, and smoking history in pack-years. No significant difference was found between the cases and controls regarding the presence of pleural plaques. However, the small number of cases (n=13) considerably limits the relevance of this study [47]. In the above-mentioned subgroup of 2089 asbestos-exposed individuals with no radiographic evidence of asbestosis who were included in the CARET program [23], individuals with radiographic evidence of pleural abnormalities (bilateral thickening or plaques) had a nearly 2-fold increase in the lung cancer risk compared to individuals whose pleura was radiographically normal (RR, 1.91; 95%CI, 1.25—2.92) after adjustment for age, smoking history, and asbestos exposure duration. However, the cumulative asbestos dose is not reported in this study. The authors acknowledge that the only specific hypothesis in their view to the increased lung cancer risk was “the likelihood that persons with plaques had more exposure on average than those without them” [23].

Thus, the evidence available as of 2008 does not support a recent statement by the American Thoracic Society [48] that pleural plaques are associated with an increased risk of lung cancer compared to individuals having similar exposures but no pleural plaques. To resolve the issue of potential links between pleural plaques and lung cancer, a prospective study in asbestos-exposed individuals free of asbestosis would be required, to compare the incidence of lung cancer in individuals with and without pleural plaques by chest CT, after adjusting on cumulative asbestos dose, age, and smoking history. A follow-up study commissioned by the French Ministry of Health and National Health Insurance Fund is being conducted as part of a pilot experiment in four regions of France (Aquitaine, Haute Normandie, Basse Normandie, and Rhône-Alpes) to evaluate consensus conference recommendations [49] for former workers with documented high- to medium-level asbestos exposures and available chest CT scans [50]. The results should help to assess the potential link between pleural plaques and lung cancer.

- Asbestos exposure increases the lung cancer risk, even in individuals who have no evidence of asbestosis.
- There is no proof that pleural plaques are associated with an increased risk of lung cancer compared to similar asbestos exposure without pleural plaques.

### Pleural plaques and mesothelioma

Several published studies point to a significant association between pleural plaques and mesothelioma. In an autopsy study done in Monfalcone, Italy, where asbestos-cement was produced for many years, the prevalence of pleural plaques was significantly higher in patients who died of pleural mesothelioma (n=92) than in patients who died of other causes [51]. In the above-mentioned Swedish cohort [20], mesothelioma occurred in nine individuals with pleural plaques; compared to 0.8 expected (observed/expected, 11.25; 95%CI, 5.13—21.39). A significant increase in the mesothelioma risk was found in the Finnish cohort of 4887 individuals with occupational asbestos-related non-malignant pleural disease (standardized incidence ratio, 5.5; 95%CI, 1.5—14.0) [46].

As pleural plaques often indicate a history of occupational or environmental asbestos exposure, and mesothelioma is also associated with asbestos exposure, a link between the two would be unsurprising. However, there is no proof that pleural plaques are associated with an increased risk of mesothelioma compared to individuals without pleural plaques who have similar levels of asbestos exposure. Two studies from Sweden in asbestos-exposed shipyard [52] or construction [53] workers found no increase in the risk of mesothelioma among individuals having pleural plaques, compared to those having no radiographic pleural abnormalities. However, these results should be viewed with circumspection, as neither study adjusted for cumulative asbestos exposure and only 11 and 13 workers, respectively, were diagnosed with mesothelioma. A more informative study is the evaluation of 1988 former workers of a crocidolite mine in Wittenoom, Australia and of former residents of this town [54]. After adjustment on time since exposure onset, cumulative exposure, and age, no significant association was found between radiographic pleural thickening and the risk of pleural mesothelioma. Neither was asbestos (ILO profusion score ≥1/0) associated with the risk of pleural mesothelioma [54]. The long follow-up and collection of quantitative exposure data on each participant make this study particularly valuable. In addition, the chest radiographs were read using a standardized classification scheme. The results support a common cause to pleural plaques and mesothelioma, with no interaction between the two conditions [55]. However, after adjustment on cumulative asbestos exposure, pleural plaques were associated with an unexplained increase in the risk of peritoneal mesothelioma [54].
Conclusions

The main findings from published studies, which relied on chest radiographs, are as follows:

• Asbestosis is not a prerequisite to asbestos-related lung carcinogenesis but, in individuals having similar cumulative asbestos exposures, asbestosis is associated with an increased risk of lung cancer;
• Pleural plaques are associated with increased risks of lung cancer and pleural mesothelioma compared to the general population but, for a given cumulative asbestos exposure, there is no proof that pleural plaques are associated with an increased risk of lung or pleural malignancies.

These data are important to bear in mind, because new imaging and molecular biology techniques are being evaluated as tools for detecting early-stage lung cancer and malignant mesothelioma. Low-dose CT of the chest has been found effective in detecting very early stage lung cancer that is amenable to surgical treatment [56]. Several international studies are under way to evaluate whether annual CT screening diminishes lung cancer mortality in smokers older than 50 years of age. Should this screening strategy prove effective, then closely spaced CT monitoring would deserve consideration for workers exposed to high asbestos doses, most notably those having radiological evidence of lung fibrosis.

For individuals with isolated pleural plaques, the available evidence does not support a need for intensifying the monitoring strategy compared to the level appropriate according to the cumulative asbestos exposure. However, this evidence comes from an insufficient amount of research. There is a need for epidemiological studies relying on CT for the diagnosis of pleural plaques, instead of on chest radiographs, which are not sufficiently sensitive or specific.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


KEY POINTS

• Among male retirees in France, 25% have been exposed to asbestos at the workplace.
• The effects of low-level asbestos exposure remain incompletely understood.
• Asbestosis is not a prerequisite to asbestos-related lung carcinogenesis but, in individuals having similar cumulative asbestos exposures, asbestosis is associated with an increased risk of lung cancer.
• Pleural plaques are associated with an increased risk of lung cancer, even in individuals having no radiographic evidence of asbestosis, but whether pleural plaques confer an additional risk of lung cancer compared to individuals having similar asbestos exposures remains unclear.
• The risk of mesothelioma is increased in individuals who have pleural plaques but only because pleural plaques reflect asbestos exposure.


