Asbestososis and lobar site of lung cancer

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Abstract
Objective—to assess the evidence for the hypothesis that lung cancer has a predilection for the lower lobes in workers with asbestiosis.

Method—a review of the available literature with relevant information.

Results—Six published reports were analysed. In four studies limited to series of cases with diagnoses of asbestosis, three showed lower lobe predominance of lung cancer whereas the fourth study included cases in which the radiographic readings did not meet the usual criterion of profusion for asbestosis. One cohort study showed lower lobe predominance; the other reported only 33% lower lobe cancers compared with 20% in unexposed controls.

Conclusion—There is some support for the hypothesis but more studies are needed.

Keywords: asbestos; asbestosis; lung cancer

The anatomical sites for the origin of lung cancer can be established in most cases. In the general population the disease originates predominantly in the upper lobes. This has been found consistently in several studies.1–5 By contrast, there have been few studies on the lobar origin of lung cancer among people with asbestosis. The results have been inconsistent.

Methods
Publications were collected through an ongoing search of Medline and bibliographies of papers published in English. Data sought included the source of material, period in which the material was collected, the number of cases of lung cancer studied, and for cohorts the population size, stratification by asbestosis, criteria for the diagnosis of asbestosis, the denominator used to calculate the percentage of lower lobe tumours, the number of control (unexposed) cases, criteria for the lack of exposure, and percentage of lower lobe cancers in the controls. Differences between percentages were evaluated by χ2.

Results
Twelve studies were found with information on lobar site of lung cancer in people exposed to asbestos. These were divided into three groups:

GROUP 1
The studies in this group were limited to subjects with lung cancer and a diagnosis of asbestosis. They were published between 1966 and 1978. There was no consistency in the source of material. Huuper7 simply collected information from publications before his publication in 1966. Hourihane and McCaughey8 presented a series from a collection of cases of lung cancer with histological confirmation at the London Hospital. Whitwell et al9 reported a series of necropsied cases of asbestosis certified by pneumoconiosis panels. The study by Huuskonen10 consisted of cases from a registry of workers with small irregular opacities on chest x-ray films in a profusion of at least 0/1 on the International Labour Organisation (ILO) classification. In all four studies, cases were collected before 1977 and the number varied from 17 to 65. The frequency of lower lobe location of the cancer ranged from 62.5% to 88.3% in the first three studies but was only 35.3% in the last study.10 This discrepancy may be due to its rather liberal inclusion of cases with a profusion of 0/1; unfortunately there was no detailed stratification by profusion in this investigation by Huuskonen. Generally asbestosis is not diagnosed by chest radiograph unless the profusion of small irregular opacities reaches 1/0 or 1/1.10

GROUP 2
Only two cohort studies have been published with information on site of lung cancer among workers exposed to asbestos (table). In 1965 Jacob and Ansbach11 reported an investigation of all workers exposed to asbestos in Dresden, Germany, covering the period 1952–64. The data base originated in a city wide registry established in 1952 for 2636 exposed workers including those with asbestosis. The entire population of Dresden in the same period provided the control data.
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The interval between the chest radiograph and the diagnosis of lung cancer: mean (range)=4 (0–10) y in the cohort of Brodkin et al.12

Other differences between the two studies may account for contrasting results but these are difficult to evaluate. For example, the radiographic systems for classifying the degree of small irregular opacities were different in the two studies and it is not possible to equate them. In the study of Jacob and Anspach11 the classification was a crude one originated by Saupe, who, according to Bohlig,21 suggested the system which evolved into the ILO classification with ongoing refinements. If we were to assume that stages II and III disease in the earlier study were equivalent to the ILO categories 2 and 3 in the later study, the frequency was 28% in the earlier study and only 11% in the later one. This would be consistent with the fact that asbestos exposures were considerably greater in workers followed up in 1952–64 than in those followed up in 1985–96.

Discussion

There are several problems in assessing the literature on this subject. There were few studies. The papers were published over a long period 1965–1998 and covered periods from before 1952 to 1996, an era during which there was a marked decline in exposure to asbestos, improved surveillance, and falling risks of relevant disease. The early reports provided less detail than the later ones. The source of material was seldom population based and often poorly defined. The method for diagnosis of asbestosis varied.

The finding that there is a tendency to increased frequency of lower lobe lung cancers in the presence of asbestosis is consistent with the fact that asbestosis predominates in the lower lobes and with the hypothesis that asbestosis is a marker for the increased risk of lung cancer among people with sufficient exposure to asbestos.22 23

Research on basic mechanisms in recent years provides some understanding for the close relation between asbestosis and excess risk of lung cancer. Macrophages attempt to ingest long asbestos fibres and as a result release lymphokines, growth factors, active oxidants, and proteases.24 25 Some of these may be genotoxic and others may cause cell proliferation.26 Cell proliferation increases

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**Table 1 Frequency of lower lobe cancers in cohort studies**

<table>
<thead>
<tr>
<th>Characteristics and results</th>
<th>Jacob and Anspach 196511</th>
<th>Brodkin et al 199712</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of material</td>
<td>Registry of all asbestos workers in Dresden 1952-64</td>
<td>Asbestos workers 1985-96</td>
</tr>
<tr>
<td>Period</td>
<td>2636</td>
<td>4060</td>
</tr>
<tr>
<td>With lung cancer (n)</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Stratification by asbestosis</td>
<td>No, 80% had asbestosis on x ray film</td>
<td>Yes, by profusion of small irregular opacities on x ray film</td>
</tr>
<tr>
<td>Cancer site denominator</td>
<td>Upper + lower lobes</td>
<td>Upper + lower lobes</td>
</tr>
<tr>
<td>Lower lobe %</td>
<td>68.8</td>
<td>32.9*</td>
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</tr>
<tr>
<td>Control group</td>
<td>Dresden population</td>
<td>14254 20 pack-year smokers</td>
</tr>
<tr>
<td>Lower lobe %</td>
<td>28.6</td>
<td>20.4*</td>
</tr>
</tbody>
</table>

*p<0.05, y2 for difference=4.34,
Odds ratio calculated by authors: 1.92 (95% CI 1.03 to 3.55).
The interval between the chest x ray film and lung cancer: mean (range)=4 (0–10) y in the cohort of Brodkin et al.12
chances for errors during DNA replication, leading to neoplasia and limiting repair of DNA damage induced by mutagens—such as those in cigarette smoke. How these mechanisms relate to bronchogenic carcinoma is unclear.

Conclusion
The published information providing data for the hypothesis that lung cancer has a predilection for the lower lobes in the presence of asbestosis is limited. Confirmation requires more detailed studies with good epidemiologic design.