Asbestosis and lobar site of lung cancer

William Weiss

Abstract
Objective—To assess the evidence for the hypothesis that lung cancer has a predilection for the lower lobes in workers with asbestosis.
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, 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 $\chi^2$.

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

1. Four collections of cases of lung cancer said to have asbestosis;2–5
2. Two cohorts of asbestos workers followed over a period of time;6,7
3. Six collections of cases of lung cancer stratified in five by exposure to asbestos from occupational history and in one by counts of asbestosis bodies in the lung.8–10 Group 3 was excluded because the source of material was predominantly necropsies or surgical so these studies were subject to selection bias.

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. Hueper7 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 of lung cancer derived 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 1/1.11

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 Ansbach6 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 number with asbestosis was 721 (27%) and 30 cases of lung cancer included 24 (80%) with asbestosis. Asbestosis was diagnosed with a chest radiograph classification ranging from “suspect” through three stages of increasing severity. The risk of lung cancer was increased only among workers with asbestosis compared with the general population, after adjustment for age and sex. With the sum of cancers in the upper and lower lobes as the denominator, 68.8% of cases with asbestosis originated in the lower lobes compared with 28.6% in the general population. There was no information on the method of assessing the lobar site of origin for the lung cancers.

Brodkin et al.12 published the other cohort study 32 years later with data from a double blind randomised cancer chemoprevention trial. They compared 4060 asbestos workers with 14 254 heavy cigarette smokers over the period 1985–96. Lung cancer developed in 73 asbestos workers and 167 controls. The lobe of origin was determined by review of medical records. These cases were stratified among the asbestos workers by profusion of small irregular opacities on chest x-ray film.

<table>
<thead>
<tr>
<th>Author and year</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</td>
<td>Asbestos workers</td>
</tr>
<tr>
<td>Period</td>
<td>1952–64</td>
<td>1985–96</td>
</tr>
<tr>
<td>In cohort (n)</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>
</tr>
<tr>
<td>Control group</td>
<td>Dresden population</td>
<td>&gt;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, y 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

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

Table 1 Frequency of lower lobe cancers in cohort studies

<table>
<thead>
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<th>Characteristics and results</th>
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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 epidemiological design.

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