Cryptogenic fibrosing alveolitis and lung cancer

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ABSTRACT Lung cancer was found in 20 (9·8%) of 205 patients with cryptogenic fibrosing alveolitis (CFA) or 12·9% of the 155 patients in this series followed to death. An excess relative risk of lung cancer of 14·1 was found in patients with CFA compared to the general population of comparable age and sex, allowing for the lengths of follow-up of the CFA patients. The relative risk for male smokers was (observed/expected) 15/1·06 = 14·2, and for female smokers (O/E) 2/0·3 = 6·7. Only one male and one female non-smoker had lung cancer. These data suggest that there is an excess risk of lung cancer not wholly accounted for by age, sex, or smoking habit. The distribution of histological types was not obviously different from that found in lung cancer without pulmonary fibrosis. Large opacities suggestive of lung cancer were present at the time of first hospital attendance for symptoms relating to CFA in four of the 20 patients. Finger clubbing was present in 19 (95%) compared with 116/185 (63%) of those so far not developing cancer. There were no other clinical differences at presentation. In particular, cancer was not found especially in those with longer survival from the onset of symptoms of CFA or with a greater initial radiographic change.

Lung cancers have been observed in relation to fibrotic scarring of the lung. Some of these are identified as in situ tumours and their histological type is that of an adenocarcinoma. Hyperplastic changes in the alveolar lining cells in cryptogenic fibrosing alveolitis are also well recognised, and patients with cryptogenic fibrosing alveolitis (CFA) and bronchiol-alveolar cell carcinoma have been described.

More recently Stack et al have reported five lung cancers among 96 patients but noted that the distribution of histological types was similar to that of patients without fibrosis. Murao, reporting a national survey in Japan, also found lung cancer in 9·7% of 176 patients.

While these reports quote overall figures which strongly suggest a considerable increase in lung cancer in CFA, there has been no detailed study to assess the excess cancer risk in relation to age, smoking habit, duration of follow-up, or other clinical features of CFA. The problem is a difficult one because it requires a fairly large number of patients followed for a substantial period.

Methods

A retrospective study has been undertaken of 220 cases of CFA fulfilling the criteria used by Turner-Warwick and Haslam seen at the Brompton Hospital between 1955 and 1973 and followed for a minimum of four years to January 1977 (range 4–21 years). The clinical features including smoking habits and occupation, therapeutic response to corticosteroids, and survival data have been reported previously.

Follow-up data have been obtained either from the Brompton Hospital records or by correspondence with the physician in charge. All patients have been checked through the Register of Births and Deaths and causes of death obtained from death certificates. Histological material has been reviewed by Dr Hinson at the Brompton Hospital.

Of the 220 cases, 11 patients are believed to be alive because their deaths have not been recorded in the Births and Deaths Register and information is incomplete in four. These 15 patients have, therefore, been excluded from the present report which considers the 205 patients on whom detailed follow-up information is available.

Results

Over the follow-up period 155 of the 205 patients have died (mean survival from presentation 3·4 years ± 3·7 SD). During the period of observation 20 patients have died from lung cancer (9·8% of the population and 12·9% of...
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Table 1  Observed and expected deaths from lung cancer by age and sex

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Males</th>
<th>Females</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ob</td>
<td>Exp*</td>
<td>O/E</td>
</tr>
<tr>
<td>15-49</td>
<td>0 0-02</td>
<td>1 0-01</td>
<td>1 0-02</td>
</tr>
<tr>
<td>50-59</td>
<td>6 0-36</td>
<td>2 0-06</td>
<td>33-3</td>
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<tr>
<td>60-69</td>
<td>7 0-73</td>
<td>9 0-07</td>
<td>8 0-80</td>
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<tr>
<td>70 +</td>
<td>4 0-15</td>
<td>26 0-02</td>
<td>4 0-17</td>
</tr>
<tr>
<td>Totals</td>
<td>17 1-26</td>
<td>13-5</td>
<td>3 0-16</td>
</tr>
</tbody>
</table>

*Expected deaths calculated from the general population death rates per person years (that is, sum of years of follow-up for individuals in each age and sex group).

All relative risk ratios are significant by χ² with Yates correction with df = 1 at 1% level.

Table 2  Observed and expected deaths from lung cancer in CFA by smoking and sex

<table>
<thead>
<tr>
<th>Males</th>
<th>Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
<th>Females</th>
<th>Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
<th>Totals</th>
<th>Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
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</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>14</td>
<td>62-3</td>
<td>1</td>
<td>0-1</td>
<td>10</td>
<td>38</td>
<td>229-3</td>
<td>1</td>
<td>0-6</td>
<td>1-7</td>
<td></td>
<td>52</td>
<td>291-6</td>
<td>2</td>
<td>0-7</td>
<td>2-9</td>
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<tr>
<td>Smokers</td>
<td>116</td>
<td>508-3</td>
<td>15</td>
<td>1-06</td>
<td>14-2</td>
<td>29</td>
<td>161-5</td>
<td>2</td>
<td>0-3</td>
<td>6-7</td>
<td></td>
<td>145</td>
<td>669-5</td>
<td>17</td>
<td>1-76</td>
<td>9-7</td>
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<tr>
<td>Grand total</td>
<td>197*</td>
<td></td>
<td>961-1</td>
<td>19</td>
<td>2-46</td>
<td>7-7</td>
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*Smoking history unknown in eight cases
†Smoking history unknown in one case

The frequency of deaths from lung cancer in our series (12-9%) is similar to that found by Murao (9-7%). The excess risk of death from lung cancer in CFA is of particular interest in view of the relatively short survival from first symptoms in so many of the cases. In a recent large series the mean duration of symptoms...
until presentation at hospital was two years and the median survival from this time was 47 months. Thus a substantial proportion of cases run a rapidly progressive course and it is even more significant that an excess death rate from cancer can be demonstrated. It is of course possible that the onset of fibrosing changes antedates the onset of symptoms by many years and that changes in the lung relevant to the development of cancer are of much longer duration than suggested by the history alone. This is unlikely to be the only explanation because a substantial proportion of our series had relatively slight radiographic changes on first attendance. Although the natural history of the condition is very varied, cases developing cancer were not found especially among those having a prolonged survival from the onset of symptoms of CFA.

Too few non-smokers have been studied to obtain accurate information but the evidence as it stands suggests that there is an excess risk (×10) of cancer in males with CFA that cannot be accounted for by cigarette smoking alone (p<0.01).

Excess lung cancer has been reported in other types of pulmonary fibrosis. In patients with asbestosis it has been calculated that at least 30% develop lung cancer and that there is at least an additive and possibly a multiplicative influence of cigarette smoking. Although the relative risk of cancer in patients with asbestosis—that is, pulmonary fibrosis—compared to those with equivalent exposure but without fibrosis is incomplete, it appears that cases without fibrosis may also have an excess incidence but to a much lesser extent. If this is so, it raises fundamental questions as to the relationship between exuberant collagen deposition in the lung and neoplastic change. That such an association might exist is further supported by the reports of cases of lung cancer in patients with systemic sclerosis. In situ neoplastic change in the vicinity of fibrotic scars in the lung have been well described but are most frequently adenocarcinomas. The hyperplasia of alveolar lining cells observed in CFA might lead to a prediction of an increased incidence of alveolar cell carcinoma and although this has occasionally been reported, it was only seen in one of our cases. In general, however, the distribution of histological types was similar to that of lung cancer without fibrosis. The fundamental reason for predisposition to neoplastic change is obviously unknown. Alterations in the function of cells controlling the inflammatory response must be considered. If defective surveillance mechanisms are important, the finding of autoantibodies in a high proportion of cases with CFA—for example, antinuclear antibody occurred in 45% of our series of 220 cases—is of interest. However, in the 18 patients with lung cancer, antinuclear antibody was only found in five. A reduction of normal delayed hypersensitivity responses in lung cancer has been used as further evidence of a surveillance defect. However, the delayed skin type reactions are not in general reduced in CFA. Whether they are reduced in those cases developing lung cancer is unknown. More detailed work on subpopulations of different functional types of T cells is needed before such a defect can be excluded. Macrophage/lymphocyte interactions may be important in surveillance mechanisms. Recent studies have shown that alveolar macrophages in CFA are activated and appear to contain less lysosomal enzymes than controls. It is conceivable that such continuous stimulation of macrophages perhaps by immune complexes alters their capacity to maintain a normal surveillance function.

Finally, the explanation of finger clubbing in relation to CFA, asbestososis, and lung cancer is of interest. The cause of this phenomenon is quite unknown but the observation that finger clubbing was almost invariably present (19/20) in cases having or subsequently developing cancer, at the time of presentation, and often before there was clinical evidence of tumour, is of interest and contrasts with the overall prevalence of finger clubbing in our series of 63% of patients who did not develop and die from lung cancer.

References

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8 Selikoff IJ, Churg J, Hammond EC. Asbestos exposure and neoplasia. JAMA 1964; 188:22.


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M Turner-Warwick, M Lebowitz, B Burrows and A Johnson

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