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 bronchiolar-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 habits, 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</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>0-36</td>
<td>16-7</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>0-73</td>
<td>9-6</td>
</tr>
<tr>
<td>70 +</td>
<td>4</td>
<td>0-15</td>
<td>26-7</td>
</tr>
<tr>
<td>Totals</td>
<td>17</td>
<td>1-26</td>
<td>13-5</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.

The deaths). Lung cancer occurred in 17 of 137 men (12-4%) and three of 18 women (16-7%). The mean age at presentation was 62-1±9-7 SD years and this was similar to that age of those without cancer. The mean age at death was 65-2 years ±9 SD and again this was similar to that of patients dying without clinical evidence of lung cancer. The relationship with age is set out in table 1. There was a rising prevalence of cancer with increasing age (p<0-03), and this was more marked for the men (p<0-002). By contrast, all three women with cancer were less than 59 years old. The significant increase in men compared with women persists when adjusted for age (p<0-02), but is eliminated when corrected for smoking (table 2). The difference between the prevalence of cancer in non-smokers, 2/52 (3-8%) compared with 17/145 (11-5%) of smokers (including ex-smokers) was not formally significant, (p<0-07); it became so, however, when adjusted for age (p<0-04).

The expected death rates from lung cancer in a population of men and women who do and do not smoke have been obtained from Doll. The ratio of observed cancers in CFA to the expected numbers in a sex and smoking matched “control” population, making allowance for the varying follow-up times, shows that the greatest excess of cancers occur in the smoking males (risk ratio 14-2) and smoking females (risk ratio 6-7). As lung cancer occurred in only one non-smoking male and one non-smoking female, risk ratios in these groups are unreliable.

Large opacities suggestive of lung cancer were present at the time of first hospital attendance in four of the 20 patients. In the other 16, the distribution of radiographic profusion scores at presentation was similar to that in those who did not develop lung cancer subsequently. Interestingly, 19 of the 20 cases had finger clubbing at presentation compared to 63% of the 185 cases who have not developed and died with lung cancer. The median survival from presentation to death from lung cancer was 3-1±3-1 SD years compared to 3-4±3-8 SD in those who died but did not develop cancer.

The histological type of the tumour was known in 15 instances. This was classified as squamous in nine, adenocarcinoma in two, alveolar cell carcinoma in two, undifferentiated in one, and giant cell in one.

### Discussion

The frequency of deaths from lung cancer in our series (12-9%) is similar to that found by Murao in 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

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

<table>
<thead>
<tr>
<th>Males Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>14</td>
<td>62-3</td>
<td>1</td>
<td>0-1</td>
</tr>
<tr>
<td>Smokers</td>
<td>116</td>
<td>508-3</td>
<td>15</td>
<td>1-06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>14</td>
<td>62-3</td>
<td>38</td>
<td>229-3</td>
</tr>
<tr>
<td>Smokers</td>
<td>116</td>
<td>508-3</td>
<td>29</td>
<td>161-5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Totals Number</th>
<th>Years at risk</th>
<th>Ob</th>
<th>Exp</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>52</td>
<td>291-6</td>
<td>2</td>
<td>0-7</td>
</tr>
<tr>
<td>Smokers</td>
<td>145</td>
<td>669-5</td>
<td>17</td>
<td>1-76</td>
</tr>
<tr>
<td>Grand total</td>
<td>197+</td>
<td>961-1</td>
<td>19†</td>
<td>2-46</td>
</tr>
</tbody>
</table>

*Smoking history unknown in eight cases
†Smoking history unknown in one case
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 pos-
sible 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
\((\times 10)\) 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 as-
bestosis it has been calculated that at least 30% develop lung cancer and that there is at least
an additive and possibly a multiplicative in-
fluence of cigarette smoking.\(^7\) 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.\(^8\) If this is so, it raises fundamental
questions as to the relationship between exuber-
ant collagen deposition in the lung and neo-
plastic change. That such an association might
exist is further supported by the reports of cases
of lung cancer in patients with systemic sclerosis.\(^9\)
In situ neoplastic change in the vicinity of fibrotic scars in the lung have been well
described but are most frequently adenocar-
cinomas. The hyperplasia of alveolar lining cells
observed in CFA\(^10\) might lead to a prediction of
an increased incidence of alveolar cell carcino-
ma and although this has occasionally been
reported, it was only seen in one of our cases.
In general, however, the distribution of histo-
logical tyers 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. How-
ever, in the 18 patients with lung cancer, anti-
nuclear 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. How-
ever, the delayed skin type reactions are not in
general reduced in CFA.\(^11\) Whether they are
reduced in those cases developing lung cancer
is unknown. More detailed work on subpopula-
tions of different functional types of T cells is
needed before such a defect can be excluded.
Macrophage/lymphocyte interaction 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.\(^12\) It is conceiv-
able that such continuous stimulation of macro-
phages perhaps by immune complexes\(^13\) alters
their capacity to maintain a normal surveillance
function.

Finally, the explanation of finger clubbing in
relation to CFA, asbestosis, and lung cancer is of
interest. The cause of this phenomenon is quite
unknown but the observation that finger club-
bing 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 preva-
ience of finger clubbing in our series of 63% of
patients who did not develop and die from
lung cancer.

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