Cryptogenic fibrosing alveolitis and lung cancer: the BTS Study
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ABSTRACT

Introduction: Risk of lung cancer is often reported as elevated for patients with cryptogenic fibrosing alveolitis (CFA).

Methods: Vital status was sought for all 588 members of the British Thoracic Society (BTS) cryptogenic fibrosing alveolitis (CFA) study eleven years after entry to the cohort. Observed deaths due to lung cancer were compared to expected, using age-, sex- and period-adjusted national rates. The roles of reported asbestos exposure and smoking were also investigated.

Results: 488 (83%) cohort members had died; 46 (9%) were certified to lung cancer (ICD9 162). The standardised mortality ratio (SMR) was 7.4 (95% ci [5.4, 9.9]). Stratified analysis demonstrated increased lung cancer mortality amongst younger subjects, males and ever smokers. Using an independent expert panel, 25 (4%) cohort members were considered to have at least moderate exposure to asbestos; lung cancer risk was elevated for these subjects (SMR 13.1 [3.6, 33.6]) versus 7.2 (5.2, 9.7) for those with less, or no, asbestos exposure. Ever smoking was reported by 448 (73%) of the cohort and was considerably higher in males (92%) than females (49%); p<0.001. Most (87%) lung cancer decedents were male and all but two (96%) lung cancer decedents ever smoked. Ever smokers presented at a younger age (mean 67 versus 70 years; p<0.001) and with less breathlessness (12% smokers reported no breathlessness versus 5% never smokers; p=0.02).

Discussion: These findings confirm an association between CFA and lung cancer although this relationship may not be causal. The high rate of smoking, and evidence that smokers present for medical attention earlier than non-smokers, suggest that smoking could be confounding this association.

INTRODUCTION

Increased lung cancer mortality amongst patients with cryptogenic fibrosing alveolitis (CFA) or idiopathic pulmonary fibrosis (IPF) has been reported in numerous studies, with prevalences as high as 48.2% ¹. Fourteen reports of lung cancer mortality in series of patients with this disease are detailed in Table 1, with a pooled estimate of 17.3% (95% confidence interval 11.2%, 25.9%). Dependent on the era of publication these studies include a variable mixture of patients with CFA and IPF; although there is no clear evidence that this has had any bearing on the reported associations with lung cancer.
Table 1  Lung cancer mortality amongst CFA/IPF patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No. of deaths</th>
<th>No. deaths with lung cancer</th>
<th>Prevalence of lung cancer (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer and Liebow (1965)</td>
<td>Necropsy series</td>
<td>19</td>
<td>4</td>
<td>21.1 (6.1, 45.6)</td>
</tr>
<tr>
<td>Turner-Warwick et al. (1980)</td>
<td>Case series</td>
<td>155</td>
<td>20</td>
<td>12.9 (8.1, 19.2)</td>
</tr>
<tr>
<td>Wright et al. (1981)</td>
<td>Case series</td>
<td>31</td>
<td>7</td>
<td>22.6 (9.6, 41.1)</td>
</tr>
<tr>
<td>Tukiainen et al. (1983)</td>
<td>Case series</td>
<td>44</td>
<td>2</td>
<td>4.5 (0.6, 15.3)</td>
</tr>
<tr>
<td>Kawai et al. (1987)</td>
<td>Autopsy case series</td>
<td>47</td>
<td>8</td>
<td>17.0 (7.6, 30.8)</td>
</tr>
<tr>
<td>Wells et al. (1994)</td>
<td>Case series</td>
<td>127</td>
<td>6</td>
<td>4.7 (1.0, 8.4)</td>
</tr>
<tr>
<td>Matsushita et al. (1995)</td>
<td>Autopsy case series</td>
<td>83</td>
<td>40</td>
<td>48.2 (37.1, 59.4)</td>
</tr>
<tr>
<td>Johnston et al. (1997)</td>
<td>Case series</td>
<td>231</td>
<td>29</td>
<td>12.6 (8.6, 17.5)</td>
</tr>
<tr>
<td>Hironaka and Fukayama (1999)</td>
<td>Autopsy case series</td>
<td>70</td>
<td>32</td>
<td>45.7 (33.7, 58.1)</td>
</tr>
<tr>
<td>Quinn (2001)</td>
<td>Autopsy case series</td>
<td>72</td>
<td>31</td>
<td>43.1 (31.4, 55.3)</td>
</tr>
<tr>
<td>Araki (2003)</td>
<td>Autopsy case series</td>
<td>86</td>
<td>15</td>
<td>17.4 (10.1, 27.1)</td>
</tr>
<tr>
<td>Jeon (2006)</td>
<td>Case series</td>
<td>50</td>
<td>4</td>
<td>8.0 (2.0, 19.2)</td>
</tr>
<tr>
<td>Okamoto (2006)</td>
<td>Case series</td>
<td>56</td>
<td>12</td>
<td>21.4 (11.6, 34.4)</td>
</tr>
<tr>
<td>Daniels (2008)</td>
<td>Autopsy series</td>
<td>42</td>
<td>0</td>
<td>0 (0, 8.4*)</td>
</tr>
</tbody>
</table>

*one-sided 97.5% confidence interval
In contrast, population-based co-mortality studies from the USA\textsuperscript{2} and UK\textsuperscript{3} have not confirmed an increased risk of lung cancer. In the US study, Wells et al.\textsuperscript{2} reported a lower rate of lung cancer mortality amongst decedents of pulmonary fibrosis (proportional mortality 4.8\%) than COPD decedents (10.1\%) and asbestosis decedents (26.6\%). Similar findings were reported from the UK study\textsuperscript{3}; the proportions of certificates which also mentioned lung cancer were consistently lower for certificates with mention of postinflammatory pulmonary fibrosis (3\%), other alveolar and parietoalveolar pneumopathy (6\%), silicosis (7\%) or coal workers’ pneumoconiosis (8\%) than those with a mention of asbestosis (4.3\%).

The aim of this study was to investigate the relationship between CFA and lung cancer in more detail, by consideration of death certificate details for an established UK-wide cohort of patients with CFA.

METHODS

BTS Study of CFA

On 1 December 1990, recruitment to the British Thoracic Society (BTS) CFA study began\textsuperscript{4,5}. The study concerns patients with the clinical syndrome of CFA as then diagnosed rather than patients exclusively with IPF or usual interstitial pneumonitis (UIP) according to current diagnostic criteria devised since the study started.

All respiratory physicians in England, Scotland and Wales were invited to enter prospectively all new CFA patients over the following two years. CFA was defined either on histological grounds, or according to clinical criteria. These criteria included any evidence of bilateral interstitial chest radiographic shadowing with bilateral basal inspiratory crackles and lung function parameters compatible with CFA, i.e. a restrictive and/or gas transfer effect. Open lung biopsy specimens were taken in 12\% of the study population, and transbronchial biopsies in 28\%; 60\% had no histology\textsuperscript{4,5}.

A total of 415 respiratory physicians were contacted and 330 (79.5\%) agreed to participate in the study. After two years’ enrolment period, 588 patients with definite diagnoses of CFA identified by one of 150 chest physicians were initially followed up until November 1996, or death if earlier.

Vital status

A specific code was introduced for CFA/IPF with the 9\textsuperscript{th} revision of the International Classification of Diseases in 1979 (ICD9); 516.3 Idiopathic Fibrosing Alveolitis. In version 10 the code is J84.1; Other Interstitial Pulmonary Disease with Fibrosis. Vital status as of 31 December 2001 was requested from the Office for National Statistics (ONS) for all 588 cohort members, along with all listed causes of death, coded to ICD9. By this date, 488 (83.4\%) had died, 97 (16.7\%) were not known to have died and ONS could not trace three cohort members.

Asbestos exposure

Information on reported asbestos exposure, other organic dust and inorganic dust exposure was collected by questionnaire administered at enrolment. Details on duration, era and intensity of exposure, along with the specific job, industry or hobby involved were recorded. The BTS CFA study eligibility criteria excluded any individual who, in the opinion of the participating chest physician, had occupational exposures which would be accepted as a sufficient basis for a diagnosis of pneumoconiosis for the purposes of state compensation\textsuperscript{4}. However, a number of the occupational histories identified possible exposure to these dusts, especially asbestos exposure (n=87; 15.0\%). In the present study six consultant Respiratory Physicians were independently asked to grade each
subject as having had no, mild, moderate or heavy exposure to asbestos, based on the reported job/industry, along with era and duration of exposure. Any cohort member who was considered by at least four physicians to have had “moderate” exposure was classified as such (n=25). The risk of mortality from lung cancer was calculated separately for these categories and in each case compared with those with lesser, or no, reported asbestos exposure. A stratified analysis of increased duration of reported asbestos exposure (>10 years) was also conducted.

Smoking

Information on smoking was also collected in the BTS questionnaire. Subjects were defined as current, ex-smokers or non-smokers.

Statistical methods

Chi-squared tests, t-tests, Mann-Whitney tests and chi-squared tests for trend were used to compare lung cancer decedents with all other decedents. Comparisons between the observed deaths due to lung cancer (ICD9 162) and the expected number of deaths were made. Expected deaths were calculated by the application of age- and sex-specific rates for the years 1990 to 2001, for England and Wales, and Scotland. Results were then expressed as Standardized Mortality Ratios (SMR; observed/expected deaths) with exact 95% confidence intervals calculated using the Poisson distribution. Five subjects were excluded from the cohort analysis as the vital status was unknown (n=3) or the recorded date of exit from the cohort was before the entry date (n=2). Analyses were stratified by severity at presentation measured by exercise grade (normal exercise grade, breathless uphill and normal pace on level or breathless at normal pace on level versus breathless when walking 100 yards slowly or breathless at rest), age, sex, smoking history and reported asbestos exposure. In order to attempt to examine the increased probability of lung cancer being diagnosed amongst subjects with CFA, for example through increased investigations, and also to investigate the latency of these diseases, univariate and stratified results were repeated after excluding individuals who died with one year of entry to the cohort, and then those who died within two, three, four of five years of entry to the cohort. Analysis was conducted using SAS (SAS Institute Inc, Cary, NC, USA) and Stata (Stata Corporation, TX, USA) software.

Risk of other cancer

In order to assess the specificity of any lung cancer association, the methodology was repeated for all cancer deaths excluding respiratory cancer, i.e. ICD9 codes 140 – 239, excluding 162, and ICD10 codes C00 - D48, excluding C34.

RESULTS

Vital status

By 31 December 2001, 488 (83.4%) had died, 333 (68.4%) with idiopathic fibrosing alveolitis (ICD9 516.3) listed as a mentioned cause, and 46 (9.4%) with lung cancer (ICD9 162). A total of 23 decedents had both idiopathic fibrosing alveolitis and lung cancer mentioned on the death certificates; 6.9% of all deaths which mentioned idiopathic fibrosing alveolitis.

Median survival was 2.56 years (95% ci 2.17, 3.06). This was significantly less for those who died from lung cancer (2.05 years [1.39, 3.18]) than for the remaining members of the cohort (2.61 years [2.20, 3.13]); p=0.01. Thirteen of the 46 lung cancer deaths (28.3%) occurred within one year of presentation, 21 (47.8%) within two years and 29 (63.0%) within three years.

Those who died from lung cancer were more likely to be male, and were younger than other decedents (Table 2). Less breathlessness and cough was reported by lung cancer decedents and the
A higher proportion of lung cancer decedents reported exposure to asbestos [23.9% versus 14.6%; p=0.09] and other inorganic dust exposure [43.5% versus 27.1%; p=0.02].

Table 2  Lung cancer mortality and all other causes of mortality in the BTS CFA cohort

<table>
<thead>
<tr>
<th></th>
<th>recorded cause of death</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lung cancer (ICD9 162) n=46</td>
<td>all other causes n=442</td>
</tr>
<tr>
<td>sex; n (%) male</td>
<td>40 (87.0%)</td>
<td>281 (63.6%)</td>
</tr>
<tr>
<td>age at entry; mean (SD)</td>
<td>65.8 (7.7)</td>
<td>69.6 (9.3)</td>
</tr>
<tr>
<td>age at death; mean (SD)</td>
<td>68.4 (7.0)</td>
<td>72.2 (9.2)</td>
</tr>
</tbody>
</table>

**Presentation:**
- breathlessness; n (%) 37 (80.4%) 403 (91.2%) 0.02
- duration of breathlessness; median (range) months 12 (1 - 60) 10 (1 - 84) 0.85
- cough; n (%) 28 (60.9%) 337 (76.2%) 0.02
- duration of cough; median (range) months 6 (1 - 60) 7 (1 - 84) 0.93
- chronic bronchitis (MRC 1); n (%) 10 (21.7%) 86 (19.5%) 0.72
- exercise grade; n (%) normal 8 (17.4%) 36 (8.1%) 0.12
  - breathless up hill 17 (37.0%) 129 (29.2%) (0.01*)
  - breathless on level 8 (17.4%) 95 (21.5%)
  - breathless walking slowly 11 (23.9%) 137 (31.0%)
  - breathless at rest 2 (4.4%) 45 (10.2%)
- clubbing; n (%) 31 (67.4%) 219 (49.7%) 0.02
- ischaemic heart disease 14 (31.3%) 77 (17.5%) 0.03

**Exposures:**
- smoking history; n (%) current 19 (41.3%) 72 (16.3%) <0.001
  - ex-smoker 25 (54.4%) 260 (58.8%) (<0.001*)
  - non-smoker 2 (4.4%) 110 (24.9%)
- ever smoked; n (%) 44 (95.7%) 332 (75.1%) 0.002

* p-value for trend test

There was also some evidence that those who died from lung cancer were more likely to present with other conditions; 37 (80.4%) of the 46 lung cancer decedents reported at least one of the specific conditions detailed within the patient’s general medical history compared to 287/442 (64.9%) of those who died from all other causes; p=0.03.

When compared to national statistics, and after taking age, sex and period into account, there were 7.40 times more deaths from lung cancer observed than expected (95% ci [5.42, 9.88]). This excess reduced to 1.79 (0.72, 3.69) once those who died within five years of presentation were excluded (Figure 1).

* Defined as “a cough productive of sputum for at least three months of two consecutive years” 39
**Stratified analyses**

Stratified analyses demonstrated increased lung cancer mortality amongst younger subjects (aged <68.75 years), males, current and ex-smokers (Figure 2), and those with reported asbestos exposure (Table 3). Few differences were observed when the data were stratified by severity on presentation. When individuals who died within specific periods of presentation were excluded, estimates of risk lung cancer mortality tended towards unity and in most cases were no longer significantly raised once subjects who died within five years of presentation were omitted (data not shown). Only amongst the 122 younger subjects and the 44 current smokers who were still alive five years after presentation were there significantly higher lung cancer deaths than expected (6 observed, 1.90 expected, SMR 3.16 [1.16, 6.87] and 5 observed, 0.82 expected, SMR 6.08 [1.97, 14.18] respectively).
Table 3  Observed and expected deaths from lung cancer for members of the BTS CFA cohort

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>person years at risk</th>
<th>observed deaths</th>
<th>expected deaths</th>
<th>SMR (95% ci)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>583</td>
<td>2296.30</td>
<td>46</td>
<td>6.21</td>
<td>7.40 (5.42, 9.88)</td>
</tr>
<tr>
<td>Younger (&lt;68.75 years)</td>
<td>293 (50.3%)</td>
<td>1423.91</td>
<td>28</td>
<td>2.61</td>
<td>10.72 (7.10, 15.45)</td>
</tr>
<tr>
<td>Older (≥68.75 years)</td>
<td>290</td>
<td>872.40</td>
<td>18</td>
<td>3.58</td>
<td>5.02 (2.98, 7.95)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>370 (63.5%)</td>
<td>1369.62</td>
<td>40</td>
<td>4.93</td>
<td>8.12 (5.80, 11.05)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>213</td>
<td>926.68</td>
<td>6</td>
<td>1.28</td>
<td>4.67 (1.72, 10.20)</td>
</tr>
<tr>
<td><strong>Non-smokers</strong></td>
<td>136 (23.3%)</td>
<td>516.82</td>
<td>2</td>
<td>0.94</td>
<td>2.13 (0.26, 7.69)</td>
</tr>
<tr>
<td><strong>Ex-smokers</strong></td>
<td>337 (57.8%)</td>
<td>1270.76</td>
<td>25</td>
<td>3.98</td>
<td>6.28 (4.06, 9.27)</td>
</tr>
<tr>
<td><strong>Current smokers</strong></td>
<td>110 (18.9%)</td>
<td>508.72</td>
<td>19</td>
<td>1.29</td>
<td>14.67 (8.83, 22.92)</td>
</tr>
<tr>
<td>Less severe symptoms on presentation†</td>
<td>375 (64.4%)</td>
<td>1786.28</td>
<td>33</td>
<td>4.75</td>
<td>6.95 (4.78, 6.96)</td>
</tr>
<tr>
<td>More severe symptoms on presentation‡</td>
<td>207</td>
<td>499.47</td>
<td>13</td>
<td>1.46</td>
<td>8.93 (4.74, 15.23)</td>
</tr>
<tr>
<td>No reported asbestos exposure</td>
<td>494 (85.0%)</td>
<td>1967.87</td>
<td>35</td>
<td>5.18</td>
<td>6.76 (4.71, 9.40)</td>
</tr>
<tr>
<td>Reported asbestos exposure</td>
<td>87</td>
<td>327.86</td>
<td>11</td>
<td>1.03</td>
<td>10.65 (5.32, 19.06)</td>
</tr>
<tr>
<td>Less than “moderate” exposure</td>
<td>557 (95.7%)</td>
<td>2193.17</td>
<td>42</td>
<td>5.88</td>
<td>7.15 (5.15, 9.66)</td>
</tr>
<tr>
<td>“Moderate” exposure or more</td>
<td>25</td>
<td>98.38</td>
<td>4</td>
<td>0.30</td>
<td>13.12 (3.57, 33.59)</td>
</tr>
<tr>
<td>Less than ten years exposure</td>
<td>543 (93.5%)</td>
<td>2168.52</td>
<td>38</td>
<td>5.78</td>
<td>6.57 (4.65, 9.02)</td>
</tr>
<tr>
<td>At least ten years exposure</td>
<td>38</td>
<td>127.21</td>
<td>8</td>
<td>0.43</td>
<td>18.58 (8.03, 36.66)</td>
</tr>
</tbody>
</table>

 † defined as normal exercise grade, breathless up hill and normal pace on level or breathless at normal pace on level
‡ defined as breathless when walking 100 yards slowly or breathless at rest
Asbestos exposure

The analyses stratified by asbestos exposure demonstrated increased risk of lung mortality amongst the higher exposed group, with ratios of observed to expected lung cancer deaths between two to three times higher amongst the exposed subjects. However, in most analyses estimates tended to be wide with confidence intervals that overlapped (Table 3). Again estimates tended towards the null when those who died soon after presentation were excluded (data not shown).

Smoking

A large majority of the cohort members were current or ex-smokers (76.2%; Table 4). This proportion was similar for those who had died by 31 December 2001 (77.0%) and those who were not known to have died by that date (73.5%; p=0.41). Of 46 lung cancer deaths, only two (4.3%) were never smokers and only six (13.0%) were female. Median survival was longer amongst current smokers (3.81 [2.75, 4.80] years) than non-smokers (2.34 [1.37, 3.54] years) or ex-smokers (2.24 [1.84, 2.95] years); p=0.26.

<table>
<thead>
<tr>
<th>alive on 31/12/2001</th>
<th>all (n=588)</th>
<th>females (n=215)</th>
<th>males (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>died by 31/12/2001</td>
<td>71/97 (73.2%)</td>
<td>25/47 (53.2%)</td>
<td>46/50 (92.0%)</td>
</tr>
<tr>
<td>died from lung cancer</td>
<td>44/46 (95.7%)</td>
<td>5/6 (83.3%)</td>
<td>39/40 (97.5%)</td>
</tr>
<tr>
<td>died free of lung cancer</td>
<td>332/442 (75.1%)</td>
<td>76/161 (47.2%)</td>
<td>256/281 (91.1%)</td>
</tr>
<tr>
<td>all</td>
<td>448/588 (76.2%)</td>
<td>106/215 (49.3%)</td>
<td>342/373 (91.7%)</td>
</tr>
</tbody>
</table>

Reported rates of smoking were higher amongst the men (91.7%) than women (49.3%); p<0.001. Males were significantly more likely to have died than females (86.5% versus 78.0%; p=0.01). Deceased males were significantly more likely to be defined as current or ex-smokers on presentation (91.9% versus 48.5%; p<0.001) and have lung cancer recorded on their death certificates (12.5% versus 3.6%; p=0.001). Smoking rates were significantly higher for those who had died from lung cancer than those who died free from lung cancer (95.7% versus 75.1%; p=0.002).

Smokers presented at a younger age than non-smokers; mean 67.0 years (95% ci 66.1, 67.8) compared to 70.6 years (68.7, 72.5); p<0.001. There was also evidence that current or past smokers presented earlier, since less breathlessness was reported by smokers on presentation (54 [12.1%] ever smokers reported no breathless versus 7 [5.0%] never smokers; p=0.02). Ratios of observed to expected deaths for smokers stratified by exercise grade on presentation did not follow a clear trend (Table 5).

| Standardised mortality ratios stratified by severity of disease (ever smokers) |
|-----------------------------|-----------------|-----------------|-----------------|
| n                           | observed deaths | expected deaths | SMR (95% ci)    |
| normal                      | 54              | 8               | 1.01            | 7.91 (3.42, 15.61) |
| breathless up hill          | 159             | 17              | 1.95            | 8.73 (5.08, 13.96) |
| breathless on level         | 98              | 8               | 1.16            | 6.90 (2.98, 13.59) |
| breathless walking slowly    | 106             | 9               | 1.00            | 9.01 (4.12, 17.08) |
| breathless at rest          | 30              | 2               | 0.16            | 12.69 (1.51, 45.15) |
Risk of other cancer
There were 24 observed deaths due to other cancers; carcinomatosis (n=8), stomach (3), oesophagus (2), colon (2), rectum (2), pancreas (2), liver, prostate, breast, cervix, ovaries; and 17.07 expected deaths. The SMR for all cancers excluding lung cancer was 1.41 (0.90, 2.09). When respiratory cancers were included (total 70 deaths), the SMR for all cancers was 3.01 (2.34, 3.80).

DISCUSSION
The mortality analysis of the members of the BTS CFA cohort identified that there were 46 lung cancer deaths amongst 488 decedents (9.4%) and 23 (6.9%) deaths with both idiopathic fibrosing alveolitis and lung cancer mentioned on the death certificates; a figure only marginally higher than the UK co-mortality estimate (5.6%) 3.

It is plausible that the population-based co-mortality studies 2, 3 were limited by incomplete listings of pulmonary fibrosis on the death certificates, and diagnostic misclassification may have also contributed to the lack of association between IPF and lung cancer. Far higher prevalence of lung cancer was reported in other studies. The highest were those by Matsushita et al. 1, Hironaka and Fukayama 6 and Qun 7 with lung cancer prevalence of 48.2%, 45.7% and 43.1% respectively; all of these studies were autopsy studies conducted in Japan, none of which was blinded. These estimates may be elevated by the increased probability of the presence of lung cancer being detected once an autopsy has taken place. The aim in this present study was to avoid these potential limitations by investigating lung cancer mortality within a large cohort of patients with CFA/IPF.

Careful comparison of observed deaths to the number expected based on age-, sex- and period-specific national lung cancer mortality rates identified that the lung cancer deaths within this CFA cohort were significantly more frequent than expected, with a standardised mortality ratio of 7.40 (95% confidence interval 5.42, 9.88).

There was also an excess of deaths due to other cancers (24 deaths), although this was not statistically significant (SMR 1.41 [0.90, 2.09]). When respiratory cancers were included the SMR for all cancers was 3.01 (2.34, 3.80). This was higher than the estimate obtained by Le Jeune et al. 8 who reported a rate ratio of 1.51 (1.20, 1.90) amongst 1,064 IPF cases compared to matched controls.

Stratified lung cancer mortality analysis identified increased risk amongst younger subjects, males, smokers (in particular current smokers), and those who reported asbestos exposure. These findings largely agree with a study by Aubry et al. 8 who compared a group of 24 patients with IPF and lung cancer to 63 patients with IPF only and observed that patients with IPF and lung cancer were more likely to be male and smokers. Other studies have also demonstrated considerable excess of lung cancer amongst male CFA/IPF patients 1, 6, 10-13 far greater than the male:female ratio observed in CFA/IPF.

In a large study of CFA cases and matched controls extracted from general practice data reported by Hubbard et al. 14, the rate ratio of lung cancer amongst CFA cases was 7.31 (4.47, 11.93), similar to the standardised mortality ratio for the BTS CFA cohort. The observed increase remained when analysis was restricted to current smokers only (RR 7.36 [1.54, 35.19]) 14. When only current smokers were considered for the BTS CFA cohort, the SMR was much higher (14.67 [8.83, 22.92]) as no adjustments for smoking habits amongst the population mortality data were possible.

The simple - and most widely held - explanation for the excess of lung cancer observed in the BTS cohort is that CFA causes lung cancer. However, other explanations need to be considered. First,
non-small cell lung cancers probably start to grow from the first malignant cell approximately 10 years before clinical manifestation while for small cell cancers the interval is approximately three years \(^\text{19}\) suggesting that many of the patients who subsequently died from lung cancer would have had the disease much further back in time and almost certainly at the time of presentation. Thirteen of the lung cancer deaths occurred within a year of presentation (28.3%), 21 (47.8%) within two years and 29 (63.0%) within three years. All stratified analyses were segregated by survival time and the resulting estimates of lung cancer risk tended towards the null when those who died soon after presentation were excluded from each analysis. If CFA does cause lung cancer it might reasonably be expected that these estimates of risk would increase with survival time since those patients who survive longer theoretically experience an increased time in which to develop lung cancer. It is also likely that the first fibroblastic focus may also occur many years prior to diagnosis suggesting that it is possible that the tumour and fibrosis occur concurrently.

Second, all but two of the lung cancer deaths (95.7%) occurred amongst smokers and the prevalence of past or current smoking was high in this cohort (76.2%). A similar prevalence of smoking was reported by Hubbard et al. \(^\text{16}\) (77%), Baumgartner et al. \(^\text{17}\) (72%) and Antoniou et al. \(^\text{18}\) (75%) although other studies have reported much lower rates (between 29 and 37\%). \(^\text{8;14;19}\) Two of these three studies were based on information extracted from a large general practice database and the third study was based on data extracted from an Oxygen Registry. Smoking data may be incomplete in these studies - or in the case of the last, inaccurate since patients may have underestimated their smoking in order to get access to oxygen. Alternatively, these variations may reflect subtle differences in the use of terms such as CFA and IPF. Many studies have identified smoking as a risk factor for CFA/IPF, with a population-attributable risk of 49.1% \(^\text{20}\).

There was also some evidence from this cohort that ever smokers present earlier, based on less reported breathlessness. Smokers were also younger at presentation. It is possible that smokers are more likely to receive an X-ray, and this may lead to CFA being systematically and preferentially being diagnosed amongst subjects who smoke, or who have ever smoked, introducing ascertainment bias. There was some evidence of survival amongst current smokers being longer than for never or past smokers, an observation reported earlier by King et al. \(^\text{21}\) where survival was significantly higher for current smokers and by Antoniou et al. \(^\text{18}\) where lower mortality was observed for current smokers when compared to former smokers. In this latter paper, the investigators examined survival after adjustment for severity and concluded that this improved outcome suggested that current smokers present with less severe CFA. Smoking may play two distinct roles in pulmonary fibrosis: by increasing the patient’s probability of presenting for medical attention, and by directly increasing the risk of CFA patients developing lung cancer.

The third possibility is that the observed excess of lung cancer deaths is due in part to misclassification of asbestosis; the associations between asbestosis and lung cancer are well established. \(^\text{22;23}\) Recorded occupational data highlight that some patients (14.9%) reported exposure to asbestos. Lung cancer mortality was between two and four times higher for those with asbestos exposure.

The final consideration, which arises in part from the observation of increased smoking amongst these CFA patients and from the observation of fewer symptoms on presentation amongst past or current smokers, may explain the excess of lung cancer mortality observed within this and other CFA/IPF series, including notable studies by Turner-Warwick \(^\text{24}\) and Hubbard \(^\text{14}\). This increased risk of lung cancer may be driven by an inherent ascertainment bias (an example of Berkson’s bias \(^\text{25}\)). Berkson recognised that hospitalized patients are not representative of the general population, and that people with two or more conditions are more likely to attend hospital than those with only one condition with the potential for producing false associations. Within the BTS CFA cohort it is
plausible that the increased observation of lung cancer may have arisen by increased ascertainment amongst smokers, or amongst those already with lung cancer. Certainly the high rates of smoking, especially amongst the men who accounted for the majority of lung cancer deaths, would support this hypothesis.

The associations between lung cancer and other fibrotic diseases are more established; many studies have reported increased lung cancer risk amongst patients with asbestosis. Increased risk of lung cancer has also been reported amongst patients with silicosis and scleroderma. These studies of asbestosis and silicosis are based upon population data, arguably providing an improved setting in which to examine the pathogenesis of these fibrotic diseases. Most studies of CFA/IPF which have reported increased risks of lung cancer have findings based upon hospital case series, where inherent ascertainment bias is more probable.

In summary, evidence from this and other studies suggest an association between CFA and lung cancer. However, in the light of the questionable temporality of this association, the confounding effects of smoking, the high rate of asbestos exposure amongst this cohort and the possibility of inherent ascertainment bias highlighted by Berkson, the causal relationship of CFA and lung cancer remains questionable.

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What is already known on this subject

Many studies have demonstrated increased lung cancer risk for patients with CFA/IPF.

What this study adds

By comparison of observed to expected deaths, we found an increased risk of lung cancer (SMR 7.4) amongst patients enrolled onto a large UK-wide CFA study. However, this risk tended towards the null once those who had died soon after presentation were excluded. All but two subjects were ever smokers, and smokers appeared to present sooner than non-smokers. We believe that the causal relationship between CFA and lung cancer remains uncertain.

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Legends for Figures

Figure 1: Standardised mortality ratios and 95% confidence intervals for lung cancer mortality within complete and restricted datasets

Footnote: Results are based upon the whole dataset (n=583) along with restrictive datasets after excluding those who died within specific periods (n=412, 328, 270, 227, 186 respectively).

Figure 2: Standardised mortality ratios and 95% confidence intervals for lung cancer mortality within complete and restricted datasets, stratified by smoking

Footnote: Black lines (with squares) represent non-smokers; mid grey lines (diamonds) represent ex-smokers; light grey lines (squares) represent current smokers. Results are based upon the whole dataset (n=136 non-smokers, 337 ex-smokers and 110 current smokers) along with restrictive datasets after excluding those who died within specific periods (n=88, 72, 62, 54, 40 [non-smokers]; 236, 182, 147, 118, 102 [ex-smokers]; 88, 75, 61, 55, 44 [current smokers]).
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all data

excluding those who died within 1 year

excluding those who died within 2 years

excluding those who died within 3 years

excluding those who died within 4 years

excluding those who died within 5 years
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