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*SELECTED REPORT*

# Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis

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*Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. R. Hubbard. ©ERS Journals Ltd 2001.*

**ABSTRACT: Cryptogenic fibrosing alveolitis (CFA), synonymous with idiopathic pulmonary fibrosis, is probably a disease entity of increasing frequency.**

**Epidemiological investigations into the aetiology of CFA are at an early age; yet there are several indications that exposures associated with traditionally male manufacturing occupations may be a cause of CFA.**

**Specifically, metal exposure, and to a lesser extent wood dust exposure, was increased in patients with CFA and may explain some cases of CFA. Indeed, the four case-control studies in the literature, to date, have all found an identical occupational exposure to metal or working with metal as a risk factor for CFA and there is now further evidence confirming this association from a case-control study nested within an occupational cohort. There is also evidence from three of the case-control studies that working with wood may be a risk factor for CFA.**

**However, these exposures clearly only explain a minority of cases of cryptogenic fibrosing alveolitis. Further studies amongst different populations with different occupational demographics are required to fully assess the impact of several exposures on the occurrence of cryptogenic fibrosing alveolitis.**

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Cryptogenic fibrosing alveolitis (CFA), or idiopathic pulmonary fibrosis (IPF), is the commonest interstitial lung disease (ILD) seen in clinical practice [1]. Data from two separate primary care sources in the UK suggest that the incidence of the disease is ~5 per 100,000 person-yrs [2]. If correct, this means that there are in excess of 2,500 new cases of CFA each year in the UK. The median survival from diagnosis of patients with CFA is <3 yrs, and on average, patients lose 7 yrs of life [3]. During the 1980s and 1990s, there have been marked increases in registered mortality from CFA in the UK and other countries [4]. Since the clinical presentation of CFA is readily recognizable [5], it is unlikely that the disease was consistently overlooked before it was first described in the 1930s [6]. Therefore, CFA is probably a disease entity of increasing frequency.

## Occupational dust exposure as an aetiological factor

Exposure to a number of occupational dusts leads to a variety of ILDs [7] and so it is perhaps unsurprising that occupation has been examined as a potential cause of CFA. The tendency for CFA to affect males more than females, together with the higher mortality rates from CFA in the central industrialized regions of the UK, suggest that exposures associated with traditionally male manufacturing occupations may be important [8].

The first study to formally examine the role of occupation in the aetiology of CFA was a case-control study carried out in Nottingham, UK [9]. The study recruited 40 prevalent cases of CFA and 106 age-, sex- and community-matched controls and used a postal questionnaire to collect details of lifetime occupational history and dust exposure. Cases were marginally more likely to report exposure to any occupational dust than controls (odds ratio (OR) 1.32, 95% confidence interval (CI) 0.84–2.04), but within the reported dust exposures there was a marked increase in metal dust exposure (OR 10.97, 95% CI 2.30–52.4). Other interesting findings were a possible association with occupational wood dust exposure, working with cattle and exposure to wood fires.

A more extensive case-control study of occupational exposure to metal and wood dust was carried out as a follow-up to this pilot study. A total of 218 cases of CFA and 569 community-matched controls were recruited from the East Midlands area of the UK [10]. Information on occupational dust exposure by both self-completed questionnaire and telephone interview was collected. Evidence of increased exposure to metal dust and wood dust amongst cases, compared to controls, was found. In general, there was good agreement between exposure status defined on the basis of the two methods of data collection ($\kappa$ statistics 0.46–0.67) and the results from the two approaches were broadly similar (table 1). There was evidence of a dose-response relationship between

Table 1. – Case control odds ratios (ORs) of occupational exposure in cryptogenic fibrosing alveolitis

| | OR | 95% CI |
|---|---|---|
| **Metal dust** | | |
| Questionnaire data | 1.71 | 1.01–2.92 |
| Interview data | 2.58 | 1.17–5.64 |
| **Wood dust** | | |
| Questionnaire data | 1.68 | 1.07–2.65 |
| Interview data | 2.22 | 1.26–3.91 |

CI: confidence interval. Adapted from [10].

disease and exposure to both metal and wood dust in terms of number of hours of exposure each day and number of years of exposure. Specific metal exposures that were increased in patients with CFA included brass, lead and steel, whilst the only wood exposure that was increased was pine. Textile and sand dusts were also implicated, although not as consistently independent risk factors.

An alternative methodological approach was reported in a paper containing a collection of epidemiological studies from Japan [11]. The first study used autopsy records and compared the occupation recorded at the time of death for 1,311 patients with CFA to a systematic sample of 393,000 patients without CFA. Occupations found to be more common in patients with CFA than controls included metalworkers, woodworkers, painters and barbers/beauticians (all $p<0.001$). The paper also included a live case-control study of 86 cases matched to two control groups; one of healthy community controls and one of patients with other respiratory conditions. The findings suggested a small increased risk resulting from jobs involving working with metals, particularly lead, zinc, chromium and cadmium.

One other case-control study has been completed in the USA but this has only been published as an abstract and so it is difficult to assess in detail [12]. The study included 248 cases of CFA and 491 age- and sex-matched controls recruited using random digit dialling. The findings suggested an increase in disease with exposure to metal dust (OR 2.0, 95% CI 1.0–4.0). Other occupational exposures that were increased included farming (OR 1.6), hairdressing (OR 4.4), stone cutting (OR 3.9) and exposure to vegetable/animal dust (OR 4.7).

All of the four case-control studies reported to date have thus found some evidence of an association between metal dust exposure and/or working with metal and CFA. The consistency of these findings is reassuring, but the case-control design does have potential drawbacks, particularly problems of recall bias. This occurs because exposure status is defined on the basis of personal recall after the disease has arisen. It seems likely that patients with symptoms will ruminate on the possible cause for their disease and so may be more likely to report environmental exposures than healthy people. This problem is likely to be particularly marked when trying to estimate the impact of occupational dust exposure on respiratory disease. In order to get unbiased estimates of occupational exposure, independent records made before the onset of disease are required. Such records are usually only available for specific occupational cohorts. The problems with this approach are that there may not be enough outcomes to analyse, and it is possible that the whole cohort may be exposed to the causative agent and so there is insufficient heterogeneity of exposure.

Despite these problems, an occupational cohort using the pension fund archives held by a major metal engineering company, Rolls-Royce PLC (Derby, UK), has recently been established [13]. This cohort contains a total of 20,526 deaths between 1968–1997 and within this cohort there were 55 deaths from CFA. On the basis of national mortality data, the authors expected to find 39.5 deaths and so the proportional mortality from CFA was increased amongst employees compared to the general population (proportional mortality ratio 1.39, 95% CI 1.07–1.82). Lifetime occupational records for 22 of the cases and a random sample of 238 controls were obtained. These records were coded as "working with metal or not" by a company hygienist who was blind to case/control status. Thirteen (59%) of the cases were classified as having worked with metal and this proportion was similar to that for controls (n=125, 53%, age- and sex-adjusted OR 1.08, 95% CI 0.44–2.65). However, amongst employees exposed to metals there was evidence of a linear increase in the risk of CFA with duration of exposure (OR per 10 yrs of exposure 1.71, 95% CI 1.09–2.68, p=0.02). There was no evidence of an association between duration of employment and CFA for Rolls-Royce employees who were not metal workers. The authors also looked to see whether specific job titles increased the risk of disease amongst metal workers and although this involved subgroup analysis of very small numbers, there was a suggestion of heterogeneity of risk, with sheet metal workers being at great risk (table 2). The numbers in this study are small but it was designed specifically to remove problems of differential misclassification of exposure status. The finding of a dose-response relationship between years of working with metal and risk of disease provides further evidence that exposure related to these occupations may be important in the aetiology of some cases of CFA.

Although the epidemiological studies in the literature, to date, have all identified working with metal as a risk factor for CFA, this exposure clearly only explains a minority of cases. Estimates from the local population in the East Midlands, which has a high proportion of metal workers, suggest that ~10% of

Table 2. – Risk of cryptogenic fibrosing alveolitis in metal workers at Rolls-Royce PLC

| Occupation | OR | 95% CI |
|---|---|---|
| Engineers | 1.76 | 0.19–16.5 |
| Furnace men | 0.51 | 0.06–4.23 |
| Machinists | 0.72 | 0.23–2.27 |
| Fitters | 0.93 | 0.19–4.68 |
| Electricians | 5.50 | 0.38–79.9 |
| Sheet metal workers | 21.0 | 3.47–141.9 |

OR: odds ratio; CI: confidence interval. Adapted from [13].

cases may be explained by this occupational exposure and ~5% by wood dust exposure [10]. Obviously, a number of other aetiological factors must be important, some of which may also be occupations perhaps not represented in the study population. To investigate this problem further, one approach would be to look for associations with occupations that have been reported as serendipitous findings in the previous case-control studies on more than one occasion, which include farming [9, 12], hairdressing [11, 12] and stone cutting or polishing [10, 12]. An alternative approach would be to study small epidemics of more acute ILD believed to be due to an occupational or environmental exposure. Perhaps the two best documented of these in the literature are the outbreak of a "scleroderma-like" illness following exposure to contaminated cooking oil [14] and the outbreak of an acute alveolitis in the textile spraying industry [15].

## Conclusion

The study of the epidemiology of uncommon diseases is not simple and the epidemiological investigations into the aetiology of cryptogenic fibrosing alveolitis are at an early stage. The four case-control studies in the literature, to date, have all found an identified occupational exposure to metal or working with metal as a risk factor for cryptogenic fibrosing alveolitis and there is now further evidence confirming this association from a case-control study nested within an occupational cohort. There is also evidence from three of the case-control studies that working with wood may be a risk factor for cryptogenic fibrosing alveolitis. In order to fully assess the impact of occupational exposure, further studies are required amongst different populations with different occupational demographics.

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