

Occupational and Environmental Risk Factors for Idiopathic Pulmonary Fibrosis in Egypt: A Multicenter Case-Control Study

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Abstract

Background: Despite the advances in medical therapy and technology, the prognosis of idiopathic pulmonary fibrosis (IPF) remains poor and the need for disease prevention based on identifying the risk factors becomes mandatory. Occupational and environmental exposures were studied in several countries and found to play important role in the disease development. However, in Egypt, a little attention has been paid to study the effect of these factors in the disease development.

Objective: To identify the occupational and environmental risk factors associated with the development of IPF in Egypt.

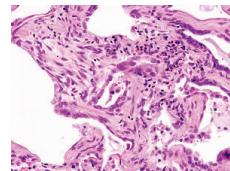
Methods: A multicenter hospital-based case-control study was carried out in chest hospitals affiliated to three Egyptian cities—Cairo, Tanta and Mansoura. Subjects were 201 patients with confirmed IPF (cases) and 205 age-, sex- and residence-matched controls. Data on occupational and environmental factors were obtained from a questionnaire. Multiple logistic regression analysis was used to determine the independent risk factors of IPF in both sexes for single factors with adjustment for age, residence and smoking status.

Results: Compared with the controls, the risk of IPF in male workers was observed to increase significantly in chemical and petrochemical industries and carpentry and wood working ($OR=2.56$, 95% CI: 1.02–7.01), and with occupational exposures to wood dust and wood preservatives. Among female workers, a significant increase was observed in farming ($OR=3.34$, 95% CI: 1.17–10.12), raising birds and occupational exposures to animal feeds, products and dusts and pesticides. Risk of IPF decreased significantly in male workers and insignificantly among female workers in sales and clerical related activities. The environmental exposures to birds and cats were significantly associated with elevated risk of IPF development in both sexes.

Conclusion: In Egypt, farming, raising birds and wood working are important risk factors for the development of IPF.

Keywords: Case-control studies; Egypt; Environment; Idiopathic pulmonary fibrosis; Occupations

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibroproliferative disorder, which consists of the progressive fibrosis of the interstitial spaces of the lung with subsequent loss of the normal parenchymal architecture that leads to respiratory failure and death.¹ In various populations, the estimated prevalence ratios for IPF, mostly based on case series and case reports, ranged from 6 to 32 per 100 000.² However, more recent studies have provided prevalence ratios of 20 per 100 000 adult males and 13 per 100 000 adult females which translates to incidence rates of 10.7 and 7.4 per 100 000 people per year for males and females, respectively.³

IPF is clinically characterized by persistent dyspnea, reduced lung volumes, impaired gas exchange, and a histological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy.^{4,5}

The etiology of IPF is still unknown; it is considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, so far suspected genes and environmental factors that consistently increase the risk of IPF have not been identified.⁶ Some studies reported several potential etiologic factors of IPF including chronic exposure to domestic wood burning,⁷ atopy,⁸ Epstein-Barr virus,^{9,10} hepatitis C virus,^{11,12} adenovirus,¹³ and genetic factors.¹⁴ Some case-control studies have focused on potential risk factors including cigarette smoking,¹⁵⁻¹⁸ atopy,^{16,18} and occupational and environmental exposures related to activities associated with a high probability of dust or vapor inhalation including wood dusts, metal dusts and dusts related to farming activities and raising birds.^{15,16,18}

Because epidemiologic information about the risk factors associated with the

development of IPF in Egypt is limited, we conducted this multicenter hospital-based case-control study to identify occupational and environmental risk factors associated with the development of IPF in Egypt.

Patients and Methods

A multicenter hospital-based case-control study was carried out in chest hospitals and departments affiliated to three Egyptian cities—Cairo, Tanta and Mansoura—between January 2010 and January 2011.

All patients with confirmed IPF admitted during the study period to one of the collaborated hospitals in the previously mentioned cities and who agreed to participate in the research were included in this study. The diagnosis of IPF by the collaborating respiratory disease specialists was made based on the diagnostic criteria of American Thoracic Society and the European Respiratory Society⁵ by history taking, clinical examination, high-resolution computerized tomography (HRCT) of the chest and pulmonary function testing (PFT). None of the cases accepted to confirm the diagnosis by either thoracoscopic lung biopsy or transbronchial lung biopsy. The presence of typical clinical and HRCT features of IPF, when identified by expert clinicians and radiologists, is sufficiently characteristic to allow a confident diagnosis and eliminate the need for surgical lung biopsy.⁵ All cases had basal fine crackles in auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis on HRCT. All cases had also abnormal pulmonary function studies including evidence of restriction—reduced vital capacity with increased FEV₁/FVC ratio. There was no evidence of either coexisting collagen-vascular disease or history of known occupational expo-

sure to agents that might produce a clinical picture similar to that of IPF in any of the cases. All eligible patients were asked to participate in this study; while 201 patients accepted to participate and were cooperative in answering the questions, 19 patients refused.

One control was selected to match each case for age (± 3 years), sex, residence and smoking habits. These controls were selected from those patients admitted to the same wards of cases during the same period and who were treated for respiratory diseases other than interstitial pulmonary fibrosis. They were diagnosed as having chest infection (25%), bronchial asthma (28%), chronic obstructive pulmonary disease (26%), bronchiectasis (13%), pulmonary embolism (5%), and bronchogenic carcinoma (3%). Out of the 220 controls selected, only 205 accepted to participate in this study.

The study was approved by the Research Ethics Committee of Mansoura Faculty of Medicine. Written informed consent was taken from all studied participants.

All data were collected by interviewing through two questionnaires. One of the questionnaires elicited information from both cases and controls about personal information including age, sex, marital status, residence, educational level, smoking habits, type of job and exposure to 11 specific occupational agents and environmental exposures as moulds in the house and indoor domestic pets. Occupational data focused on type of job held for the longest period of time during the subject's work life and years of exposure. Occupational agents were considered "present" if the subject reported >10 h of exposure per week. The other questionnaire was to collect the clinical criteria of IPF, results of chest radiography (plain and HRCT), PFT, bronchoalveolar lavage and biopsy, whenever done, and investigations done

TAKE-HOME MESSAGE

- Genetic background and environmental factors such as chronic exposure to domestic wood burning, atopy, Epstein-Barr virus, hepatitis C virus, adenovirus, may be the most etiologic factor of IPF.
- Wood and metal dusts, and dusts related to farming activities and raising birds are the most environmental and work-related exposure risk factors for IPF.
- The risk of IPF increased among male workers in carpentry or woodworking and chemical and petrochemical industry. Farming and raising birds were significant risk factors for the development of IPF among female workers.
- The environmental exposure to domestic birds and cats was positively associated with IPF development in both genders.

to exclude collagen-vascular diseases.

Statistical Analysis

Data were analyzed using SPSS® ver 11 for Windows® (SPSS Inc., Chicago, IL, USA). Both study groups were compared using the χ^2 test for qualitative variables and Student's *t* test for quantitative variables. Multiple logistic regression analysis was used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, residence and smoking for both males and females. The reference category for job title, occupational and environmental factors was based on the comparison of those exposed to a single agent with all those unexposed, including potential subjects who were exposed to

Table 1: Sociodemographic criteria of studied groups

Parameter	Cases (n=201)	Controls (n=205)	p value
Mean±SD age	51.0±10.5	50.3±10.4	0.45
<30	7 (3.5%)	6 (2.9%)	
30–44	54 (26.9%)	62 (30.2%)	
45–59	104 (51.7%)	105 (51.2%)	0.84
≥60	36 (17.9%)	32 (15.6%)	
Sex			
Male	95 (47.3%)	114 (55.6%)	
Female	106 (52.7%)	91 (44.4%)	0.11
Marital status			
Married	186 (92.5%)	178 (86.8%)	
Single	15 (7.5%)	27 (13.2%)	0.07
Residence			
Urban	77 (38.3%)	64 (31.2%)	
Suburban	41 (20.4%)	49 (23.9%)	
Rural	83 (41.3%)	92 (44.9%)	0.31
Smoking			
Current smoker	52 (25.9%)	64 (31.20%)	
Former smoker	8 (4.0%)	3 (1.5%)	
Never smoker	141 (70.1%)	138 (67.3%)	0.17
Types of smoking			
Cigarette	52 (89.70%)	51 (76.10%)	
Goza/Shesha	6 (10.30%)	16 (23.90%)	0.06
Mean±SD Packs/year	380.06±186.98	331.65±195.48	0.19
Mean±SD duration (yrs)	23.27±9.41	23.95±9.64	0.69
Educational level			
Low	102 (50.7%)	98 (47.8%)	
Moderate	73 (36.3%)	90 (43.9%)	
High	26 (12.9%)	17 (8.3%)	0.15

other etiologic factors.

Results

Table 1 summarizes the demographic data of the studied groups. Both groups were matched for sociodemographic variables. Patients with IPF had an age range of 22 to 78 years; more than half of the patients belonged to the 45–59 year age group. The disease was reported more frequently

in female (52.7%), residents of rural areas (41.3%), never smokers (70.1%), and those with low educational level (50.7%).

Clinical and laboratory characteristics of patients with IPF are demonstrated in Table 2. The mean±SD disease duration was 30.5±26.3 months. At the time of admission in the chest department, most of patients had grade IV dyspnea (53.2%), and grade I clubbing (69.2%); all of them had central cyanosis and bibasilar dry

Table 2: Clinical and laboratory characteristics of patients with IPF

Characteristics	Cases (n=201)
Mean±SD duration (month)	30.5±26.3
Grade of dyspnea	
I	3 (1.5%)
II	45 (22.4%)
III	46 (22.9%)
IV	107 (53.2%)
Grade of clubbing	
I	127 (63.2%)
II	62 (30.9%)
III	12 (6.0%)
Central cyanosis	201 (100%)
Bibasilar dry crackles	201 (100%)
Ground glass appearance on chest x-ray	201 (100%)
PFTs (% of predicted)	
FVC	62.4±13.0
FEV ₁	66.2±14.0
FEV ₁ /FVC	102.7±11.2
Arterial blood gas	
pH	7.35±0.05
PaCO ₂ (mm Hg)	40.7±12.1
Bicarbonate (mmol/L)	24.1±9.0
PaO ₂ (mm Hg)	72.8±10.5
O ₂ sat (%)	85.2±13.4

crackles. Ground glass appearance on chest CT was also observed in all patients. Reduction in the percentage of predicted FVC was found in all patients. Normal or high FEV₁/FVC ratio was observed in all patients (Table 2). Additionally, the mean arterial PO₂ and O₂ saturation was lower than normal.

Table 3 presents the adjusted risks associated with studied factors for development of IPF. Among male workers, the risk of IPF increased significantly in chemical and petrochemical industries (OR=6.47, 95% CI: 1.66–25.1) as well as carpentry and wood working (OR=2.56,

95% CI: 1.02–7.01); the risk decreased significantly in activities related to sales (OR=0.11, 95% CI: 0.02–0.54) and clericals (OR=0.21, 95% CI: 0.02–0.52). Among female workers, the risk increased significantly in farming (OR=3.34, 95% CI: 1.17–10.12) as well as raising birds (OR=1.82, 95% CI: 1.03–3.85).

The risk of occupational exposures associated with the development of IPF after controlling for age, residence and smoking are shown in Table 4. For male workers, occupational exposures to wood dust and wood preservatives significantly increased the risk of development of IPF

Table 3: Associations of various occupations with development of IPF in studied men and women

Occupational groups	Men			Women		
	Control (%) (n=114)	Cases (%) (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Clerical	11 (0.9)	3 (3)	0.21 (0.02–0.52)	9 (10)	0 (0.0)	—
Sales	17 (14.9)	2 (2)	0.11 (0.02–0.54)	7 (8)	3 (2.8)	0.35 (0.07–2.78)
Farming	28 (24.6)	20 (21)	1.00 (0.44–2.28)	7 (8)	22 (20.8)	3.34 (1.17–10.12)
Fishing	4 (3.5)	3 (3)	1.11 (0.22–5.60)	5 (5)	3 (2.8)	0.52 (0.11–2.33)
Hairdressing	1 (0.9)	2 (2)	1.89 (0.15–22.87)	10 (11)	11 (10.4)	1.01 (0.37–2.70)
Construction and Building demolition	14 (12.3)	11 (12)	0.96 (0.39–2.37)	—	—	—
Mechanics	12 (10.5)	10 (11)	0.96 (0.37–2.47)	—	—	—
Carpentry or woodworking	7 (6.1)	14 (15)	2.56 (1.02–7.01)	2 (2)	8 (7.5)	3.48 (0.67–18.16)
Chemical/petrochemical	3 (2.6)	12 (13)	6.47 (1.66–25.12)	1 (1)	2 (1.9)	2.06 (0.17–23.89)
Painting	12 (10.5)	6 (6)	0.57 (0.20–1.62)	—	—	—
Raising birds	1 (0.9)	3 (3)	3.37 (0.31–36.16)	18 (20)	35 (33.0)	1.82 (1.03–3.85)
Textile making	2 (1.8)	5 (5)	2.76 (0.45–15.57)	7 (8)	4 (3.8)	0.63 (0.17–2.35)
Housewife	—	—	—	23 (25)	28 (29.4)	0.77 (0.38–1.57)
Others	2 (1.80)	6 (6)	2.39 (0.40–14.30)	4 (4)	3 (2.7)	0.23 (0.02–2.13)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval

(OR=2.71, 95% CI: 1.01–7.37). In female workers, on the other hand, the risk of IPF development significantly increased with occupational exposures to animal feeds, products and dust (OR=1.78, 95% CI: 1.01–3.13) as well as pesticides (OR=8.68, 95% CI: 1.04–72.17).

The environmental exposures to birds and cats were significantly associated

with elevated risk of IPF development in both men and women after controlling for age, residence and smoking (Table 5). The presence of home place moulds was not associated with development of IPF.

Discussion

The present study demonstrated the as-

Table 4: Associations of occupational exposures with development of IPF in studied men and women

Occupational expo-sures	Men			Women		
	Control (n=114)	Cases (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Animal feeds, prod- ucts and dust	27 (23.7)	16 (17)	0.65 (0.32–1.30)	42 (46)	64 (60.4)	1.78 (1.01–3.13)
Foods (vegetables, fruits, meat, fishes, seafood...)	4 (3.5)	2 (2)	0.48 (0.08–2.82)	2 (2)	1 (0.9)	1.01 (0.06–16.96)
Wood dust , wood preservatives	7 (6.1)	15 (16)	2.71 (1.01–7.37)	2 (2)	8 (7.5)	4.32 (0.84–22.12)
Insecticides/pesticide	6 (5.3)	8 (8)	2.24 (0.72–7.28)	1 (1)	9 (8.5)	8.68 (1.04–72.17)
Stone, clay, glass, concrete...	14 (12.3)	12 (13)	1.11 (0.45–2.72)	0 (0)	2 (1.9)	—
Metal dust/welding fumes	15 (13.2)	17 (18)	1.58 (0.69–3.61)	—	—	—
Solvents	12 (10.5)	12 (13)	1.06 (0.44–2.59)	0 (0)	1 (0.9)	—
Hair dyes	1 (0.9)	2 (2)	1.89 (0.15–22.87)	11 (12)	11 (10.4)	0.89 (0.34–2.31)
Textile dust	2 (1.8)	6 (6)	3.25 (0.60–17.56)	10 (11)	4 (3.8)	0.40 (0.11–1.38)
Others	2 (1.8)	6 (6)	3.15 (0.56–17.61)	3 (3)	2 (1.9)	0.64 (0.10–4.06)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval

sociations of some occupational and environmental factors in the development of IPF. The risk of IPF was found to be increased among male workers in carpentry or woodworking and chemical and petrochemical industry. Several studies found chemical fumes and dusts as important risk factors for IPF.^{15-18,20} Although the mechanism is not well understood, it may be through their fibrogenic activity related to activation of oxygen species.²¹ Furthermore, genetic susceptibility^{22,23} and overwhelming of lung clearance mechanisms²⁴ are important contributing

factors. Increased chance of fibrosis and extrinsic allergic alveolitis may be attributed to the exposure to wood dust, chemicals for wood protection, wood adhesives, and mold in wood.^{16-18,25-27}

In the present study, farming and raising birds with the potential exposures to dusts of animal feeds, products and waste as well as pesticides were significant risk factors for the development of IPF among female workers. Also, the environmental exposure to domestic birds and cats was positively associated with IPF development in both genders. These findings

Table 5: Associations of environmental exposure with development of IPF in studied men and women

Environmental exposures	Men			Women		
	Control (n=114)	Cases (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Birds	12 (10.5)	22 (23)	3.49 (1.49–8.19)	25 (27)	59 (56)	3.86 (1.95–7.62)
Cats	3 (2.6)	10 (11)	6.38 (1.59–25.56)	2 (2)	15 (14)	8.24 (1.80–37.70)
Dogs	6 (5.3)	8 (8)	1.94 (0.61–6.12)	2 (2)	8 (7.5)	3.63 (0.75–17.56)
Mold‡	19 (16.6)	15 (16)	0.68 (0.30–1.45)	23 (25)	25 (23.6)	1.37 (0.71–2.36)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval, ‡Any home place mold

were in accordance with Baumgartner, *et al.*,¹⁷ Iwai¹⁵ and Gustafsson, *et al.*²⁷

Agricultural workers are exposed to very high levels of dust and aerosolized particulates from a variety of sources including feed grains, bedding, and livestock fecal material,²⁸ and tend to have a higher prevalence of lung fibrosis.²⁹

In Egypt, the poultry industry had expanded rapidly over the past 25 years to provide approximately 55% of the per capita animal protein consumption. Problems with raising birds in Egypt include widespread roof-top and back-yard raising bird, unhygienic local marketing and home slaughtering as well as the presence of approximately 40 000 poultry farms lacking biosecure and hygienic production systems and unprotected exposure to birds.^{30,31} These widespread unplanned and unprotected activities in raising birds and their environmental impacts help in magnifying the role of raising birds in IPF development. In Egypt, women were found to be more involved in raising birds than men and this may explain the elevated risk of IPF among women.³²

The risk of IPF development decreased significantly in males and insignificantly among females working as sellers and clericals. These findings were in agreement with Miyake and colleagues;²⁶ these may support the hypothesis of positive associations of IPF with dust-exposed occupations.³³

There are several limitations to our study. First, the case-control study design. Second, the study conducted in three Egyptian cities only. Third, the IPF in patients was not confirmed by lung tissue biopsy. In addition, the study did not investigate the biological mechanisms of IPF development.

Despite of these limitations, the consistency of the observed positive associations of IPF development and working in occupations with dust exposure as wood working, chemical industries farming and raising birds, and the potential occupational exposure to dusts of wood, pesticides and animals, and the environmental exposures to dusts of birds and cats, may strengthen these associations and minimize the possibility of bias related

to the case-control study design. Furthermore, the study was multicenter carried out in three Egyptian cities with different population's demographic, occupational and environmental criteria; therefore, it may be considered as a valid approach for studying occupational and environmental risk factors in Egypt.

In conclusion, the present study confirms the results from previous epidemiologic studies about the positive association of IPF development and occupational and environmental dust exposures. In Egypt, farming, raising birds and wood working are important risk factors in IPF development after adjustment for age, smoking and residence.

Conflicts of Interest: None declared.

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Occupational and Environmental Risk Factors for Idiopathic Pulmonary Fibrosis: A Multicenter Case-Control Study

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Occupational exposures were investigated in a multicenter case-control study of clinically and histologically diagnosed idiopathic pulmonary fibrosis (IPF), a chronic diffuse interstitial lung disease of unknown etiology. Results are based on 248 cases, aged 20–75 years, diagnosed at 16 referral centers between January 1989 and July 1993. There were 491 controls ascertained by random digit dialing and matched to cases on sex, age, and geographic region. Data were collected using a standard telephone questionnaire. Occupational factors were based on a detailed history of jobs lasting 6 months or more and job activity, hobby, and specific substance checklists. Several occupational factors, adjusted for age and smoking in conditional multivariate logistic regression analyses, were significantly associated with IPF: farming (odds ratio (OR) = 1.6, 95% confidence interval (CI): 1.0, 2.5); livestock (OR = 2.7, 95% CI: 1.3, 5.5); hairdressing (OR = 4.4, 95% CI: 1.2, 16.3); metal dust (OR = 2.0, 95% CI: 1.0, 4.0); raising birds (OR = 4.7, 95% CI: 1.6, 14.1); stone cutting/polishing (OR = 3.9, 95% CI: 1.2, 12.7); and vegetable dust/animal dust (OR = 4.7, 95% CI: 2.1, 10.4). Interaction was detected between smoking and exposure to livestock ($p = 0.06$) and farming ($p = 0.08$). Results confirm previous studies showing increased risk associated with dusty environments. *Am J Epidemiol* 2000;152:307–15.

case-control studies; environmental exposure; occupational exposure; pulmonary fibrosis; risk factors

Idiopathic pulmonary fibrosis (IPF), a chronic diffuse interstitial lung disease of unknown cause characterized pathologically by inflammation and fibrosis of the lung parenchyma, is usually fatal (1–3). It is one of the more frequent chronic interstitial lung diseases, although reported estimates of frequency are limited and vary. Prevalence has been estimated to range from 3 to 5 per 100,000 (4), although this is based on case series and reports. However, more recent research has provided higher estimates of 20 per 100,000 adult males and 13 per 100,000 adult females, based on an Interstitial Lung Registry in Bernalillo County,

New Mexico (5). Incidence figures based on these data are 10.7 and 7.4 per 100,000 per year for males and females, respectively (5).

The etiologic factors associated with IPF remain elusive, because there have been few investigations. The majority of studies have been case series (6–11) that have described the natural history of IPF or have identified potential etiologic factors including chronic exposure to domestic wood burning (12), atopy (13), Epstein-Barr virus (14, 15), hepatitis C virus (16, 17), adenovirus (18), and genetic factors (19). Only four case-control studies have focused on potential risk factors including cigarette smoking (20–23), atopy (21, 23), and occupational and environmental exposures related to activities associated with a high probability of dust or vapor inhalation (20, 21, 23). In the three case-control studies that focused on occupational and environmental exposures as risk factors for IPF, metal dust exposure was reported to be a significant risk factor in all three studies (20, 21, 23) and wood dust exposure in one study (21). Results based on mineralogic microanalysis of lung tissue have shown a possible association between mineral dust such as silica/silicates and IPF (24). Additional significant exposures have included farming (20), cattle or livestock (23), stone or sand dust (21), and use of wood fires (23).

In the present paper, we report results based on a multicenter epidemiologic case-control study of clinically and histologically diagnosed IPF cases and matched controls for occupational and environmental risk factors.

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Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; OR, odds ratio; SD, standard deviation; SIC, Standard Industrial Classification; SOC, Standard Occupational Classification.

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MATERIALS AND METHODS

Case ascertainment and control group selection

Cases aged between 20 and 75 years were diagnosed between January 1989 and July 1993 at 16 collaborating institutions located in 15 states. Specific details on clinical findings, case-control eligibility, and participation were provided in an earlier report on the association of IPF with cigarette smoking (22). The diagnosis of IPF by the referring centers was based on clinical history and, when available, one or more of four types of information: open lung biopsy, transbronchial biopsy, bronchoalveolar lavage, and computed tomography scan. Criteria for the diagnosis of IPF, when an open lung biopsy was available, were the same as those used in studies noted in Cherniack et al. (25). Since completion of this study, the diagnosis of IPF has become synonymous with the histologic pattern of usual interstitial pneumonia (26). Reports closest to the case's diagnosis date for lung biopsy, pulmonary function tests, chest radiographs, and computed tomography scans of the lungs were collected from the referral centers and abstracted according to a standardized protocol.

When the diagnosis of IPF was made without a review of tissue from an open lung biopsy, the available clinical data were required to document symptoms of cough or dyspnea, bilateral crackles on chest auscultation, and bilateral reticular or reticulonodular infiltrates on chest radiographic examination. A transbronchial biopsy, if taken, was required to show evidence of patchy or diffuse parenchymal involvement with alveolar and interstitial inflammation and interstitial fibrosis. In addition, referral centers excluded cases with a known occupational exposure to agents that may produce a clinical picture similar to that of IPF. Negative serum precipitin tests were necessary if a case had a history of exposure to agents associated with hypersensitivity pneumonitis.

Two controls were recruited for each case by random digit dialing (27), with matching on age, sex, and geographic region. Matching for age was within 3 years for cases younger than 50 years of age and within 5 years for those 50 years of age or older. Phone calls were made to almost 47,000 phone numbers; 43 percent ($n = 19,767$) were coded as residential and 7 percent ($n = 3,321$) could not be assigned as residential or nonresidential (answering machine, busy, no answer). The remaining phone calls were made to nonresidential (14 percent) or to nonworking (37 percent) phone numbers or to controls ($n = 0.06$ percent) matched to cases found to be ineligible during the course of the study. Nonresidential phone numbers, identified as a business or computer phone or locations not identified as either a business or a residence (hospital room, dormitory room), were considered ineligible.

Loss at the random digit dialing phase was based on a total of 23,088 phone numbers categorized as residential or with an unknown status. The total loss (25 percent) constituted the phone numbers that could not be assigned as residential or nonresidential ($n = 3,321$), the residential phone numbers that were associated with subjects who refused to provide identifying information at screening ($n = 2,185$), those subjects found to be eligible at screening but who refused to provide an address at the end of the

phone call ($n = 172$), and the eligible subjects who could not be scheduled for an interview because of such factors as illness or deafness ($n = 48$). The remaining phone numbers were associated with either those who were ineligible on the basis of screening criteria ($n = 16,751$), with interviewed controls ($n = 491$), or those who consented at screening but were not interviewed ($n = 120$) because of the reasons noted below. The study was approved by the Human Research Review Committee of the University of New Mexico School of Medicine. Written informed consent, if required, was obtained by each referral center prior to interview.

Data collection

All data for the controls and nonclinical data for the cases were collected by telephone interview. Demographic factors included ethnicity, marital status, education, employment, income, and smoking. Data were collected for checklists of 33 job activities, 14 specific occupational agents, and 12 hobbies. Activities and occupational agents that could plausibly lead to IPF were included. This was based on the disease pathogenesis and analogy with other interstitial diseases of the lung (28). This included exposures related to increased levels of dust or inhalation of potentially toxic fumes. The checklist of job activities was related to a subject's past or present job. Occupational agents were categorized on the basis of whether the exposure was for less than 10 versus 10 or more hours per week. A checklist of hobbies was included for those activities engaged in for at least 5 hours per week, including auto/truck repair, printing, welding, raising birds, stone cutting, and others related to increased dust or fume exposure such as gardening, carpentry, woodworking, or painting. Years of exposure were collected for all activities, agents, and hobbies included on the checklists.

In addition to the job activity checklist and occupational agent checklist, a complete occupational history was collected using a semistructured interview that probed for all jobs of at least 6 months' duration. Data collected included the name of the company, description of the business type, job title and job duties, the start and stop year for each job, and whether the job was full-time (≥ 35 hours per week) or part-time. Job industry and job title were coded using the Standard Industrial Classification (SIC) (29) and Standard Occupational Classification (SOC) (30), based on four-digit codes. Coding was reduced to the first three digits. The detailed descriptions recorded for industry and job duties were used to aid in the SIC and SOC coding. All coding was completed by one person, and a random sample of 33 (4.5 percent) questionnaires (12 case, 21 control) was selected for recoding by one of the authors (K. B. B.). Of the total number of 176 jobs reviewed, there was a difference in classification for 36 (20.5 percent) industries or titles by major group based on the first two digits of a code and for 18 (10.2 percent) by division based on categories of major groups. While the differences in categories may appear high, only two (1.1 percent) resulted in a change to the exposure classification.

Data analyses

Data were analyzed with conditional logistic regression (31) using a matched case-control design and the PHREG procedure in SAS (32). All logistic regression models were examined for single exposures with adjustment for age and smoking. Smoking (ever versus never) was included as a covariate, since it was previously found to be significant (22). Status of cigarette smoking (never, former, current) was substituted as an indicator for smoking, but results were comparable with those analyses based on ever versus never smoking. Age as a continuous variable was included to control for residual confounding. Although controls were matched on age, cases were on average 2 years older than controls. This residual difference was due to the difficulty in recruiting control subjects for older cases; 13 percent of control subjects, compared with 23 percent of cases, were older than 70 years. The gap in age between case and control was associated with the longer interval required to ascertain and recruit a control for an older case. Analyses were also stratified by sex. Duration of exposure (no exposure, <5 years, ≥5 years) was included for risk factors with sufficient data.

In analyses of the detailed occupational history descriptions, exposure was based on either the combination of SIC and SOC codes or the SOC code alone, as appropriate. For example, a participant was considered exposed to wood dust if the SOC code identified him/her as a carpenter or precision woodworker, regardless of type of industry, whereas a production assembler was considered exposed only if employed in an appropriate industry. These codes were aggregated into a smaller number of exposure categories based on those identified in previous studies of IPF and other respiratory diseases, including pulmonary fibrosis. These exposures included construction work, diesel exhaust, farming, metal dust, painting, the printing industry, wood dust, welding fumes, work as a mechanic, and employment in the textile industry.

The referent category for all occupational exposures was based on the comparison of those exposed to a single agent with all those unexposed and with potentially included subjects that were exposed to other etiologic factors. This issue of competing exposures among each unexposed referent group and possible collinearity was examined via correlations and cross-tabulations among the exposures. Risk factors that were significant at or below the 0.20 level or less in analysis, with adjustment for age and smoking, were entered into a multivariate model for mutual adjustment. Product terms were included to test for multiplicative interaction between smoking and the final main effect factors.

RESULTS

Of the 272 cases, 248 (91 percent) were interviewed. Reasons for noninterview included refusal (2 percent), death (4 percent), lack of controls (2 percent), and inability to contact (1 percent). Of the 611 control subjects, 491 (80 percent) were interviewed; 17 percent refused after the initial contact by letter, 2 percent could not be recontacted, and 1 percent were excluded because of the quality of the inter-

view or because of a pending interview at the time data collection was halted. Sixty percent of the cases were male. Approximately 86 percent were non-Hispanic White, and 87 percent were aged 50 years or greater. Controls tended to be slightly younger with a mean age of 59 (standard deviation (SD), 10.5) years versus 61 (SD, 10.4) years for cases. A greater proportion of controls were currently employed (47 percent vs. 33 percent) and had an educational level greater than high school (54 percent vs. 44 percent). However, distribution of income was comparable, with 37 percent of cases and 35 percent of controls reporting an income at least \$40,000 or greater. Because of their disease, cases (13 percent) were disabled more frequently than were controls (2 percent).

Job activities and occupational agents

Odds ratios obtained from the data for all subjects were increased significantly for the following job history activities: farming, hairdressing, raising birds, and stone cutting/polishing (table 1). Although the results were not statistically significant and the confidence intervals were broad, among males where there were five or more controls, there was a 50 percent increased risk of IPF for bird raising, farming, carpentry, chemical or petrochemical plant, insulation work, mining, and stone cutting/polishing. Among women, there were five or more controls for only farming, hairdressing, and asbestos or solvent exposure. An increased risk for IPF among females was associated with farming (odds ratio (OR) = 1.6, 95 percent confidence interval (CI): 0.7, 3.6) and hairdressing (OR = 3.6, 95 percent CI: 0.9, 13.9).

Odds ratios were significantly increased for exposures to vegetable/animal dust and metal dust for all subjects (table 1). Results stratified by sex for occupational agents showed a statistically significant increased risk among males for metal dust and vegetable/animal dust (table 1) and among females for vegetable/animal dust (OR = 4.8, 95 percent CI: 1.2, 19.8) (data not shown). None of the hobbies or activities outside of work with at least 5 hours per week of exposure showed a significant association with IPF, but risk of IPF among males was increased for bird raising (OR = 2.3, 95 percent CI: 0.8, 7.2) and stone cutting/polishing (OR = 1.7, 95 percent CI: 0.4, 7.0) (data not shown).

Occupational history

Only 1.5 percent of subjects (four cases, six controls) lacked occupational history. Of these, nine were females who had never held a job and were counted as unexposed. One male refused to provide specific job history information and was excluded from the occupational history analyses. There were 343 job industries and 199 job titles with a total of 1,803 unique job combinations represented. Males, both cases and controls, reported an average of six jobs compared with four for female controls and five for female cases.

Table 2 shows the results for selected occupational history exposures based on the SIC/SOC classification. Although not statistically significant, at least a 50 percent increase in risk for IPF was associated with farming, hair-

TABLE 1. Multiple logistic regression-adjusted* risk estimates based on checklists of job activities and specific occupational agents, prior to diagnosis of idiopathic pulmonary fibrosis for all subjects combined, a multicenter case-control study, 1989–1993

Occupational exposure	All subjects				Males			
	Cases (n = 248) (no.)†	Controls (n = 491) (no.)	OR‡	95% CI‡	Cases (n = 149) (no.)	Controls (n = 296) (no.)	OR	95% CI
Job activities§								
Auto/truck repair	28	59	1.1	0.6, 1.9	27	56	1.1	0.6, 2.0
Brake mechanic	14	22	1.2	0.5, 2.8	13	22	1.1	0.4, 2.6
Building demolition	10	18	1.0	0.4, 2.6	10	17	1.1	0.4, 2.7
Carpentry or woodworking	27	44	1.4	0.8, 2.6	27	41	1.7	0.9, 3.2
Chemical/petrochemical plant	15	20	2.0	0.9, 4.4	12	16	2.5	1.0, 6.2
Farming	62	95	1.6	1.0, 2.5	46	71	1.6	1.0, 2.8
Hairdressing	8	5	4.4	1.2, 16.3	1	0		
Insulation work	13	19	1.6	0.7, 3.4	13	19	1.7	0.8, 3.7
Jewelry making	4	6	2.5	0.5, 12.5	2	2	4.2	0.3, 52.0
Mining	5	7	1.7	0.4, 7.6	5	7	1.8	0.4, 8.2
Painting	28	46	1.3	0.7, 2.2	24	42	1.2	0.6, 2.1
Pipe covering/insulation	14	25	1.1	0.5, 2.2	13	25	1.1	0.5, 2.4
Printing	10	14	1.3	0.5, 3.5	9	11	1.4	0.5, 4.3
Raising birds	10	7	4.7	1.6, 14.1	6	6	3.0	0.8, 11.3
Stone cutting/polishing	8	5	3.9	1.2, 12.7	6	5	3.3	0.9, 11.9
Textile making	4	5	1.9	0.5, 7.8	1	4	0.9	0.1, 8.5
Occupational agents¶								
Asbestos	26	45	1.1	0.6, 1.9	19	28	1.4	0.7, 2.7
Fiberglass	11	16	1.3	0.6, 3.2	9	15	1.2	0.5, 3.1
Insecticides/pesticides	8	11	1.5	0.5, 4.0	6	9	1.4	0.4, 4.4
Metal dust#	25	29	2.0	1.0, 4.0	23	26	2.3	1.1, 4.8
Solvents	30	43	1.3	0.7, 2.4	25	36	1.4	0.7, 2.6
Talc	5	5	2.8	0.7, 11.2	3	5	2.6	0.6, 11.7
Vegetable/animal dust	25	15	4.7	2.1, 10.4	18	11	5.1	1.9, 13.9

* Adjusted for age (continuous) and cigarette smoking (ever/never).

† Number of cases and controls exposed; number of discordant pairs may be less.

‡ OR, odds ratio; CI, confidence interval.

§ Job activities based on checklist of past and current jobs. Jobs included if odds ratio ≥ 1.0 and total number of exposed controls ≥ 5 . Results not shown: job activities with nonsignificant ratios of <1.0 (boat/shipbuilding, boilermaking, cement manufacturing, construction, dry wall hanging, glassmaking, iron/steel manufacturing, leatherworking, pipe fitting, sandblasting, sand/gravel pit work, smelting, and welding); job activities with <5 controls (quarry work, tunnel construction, cotton ginning); or with no case response (pottery making).

¶ Occupational agents based on checklist of exposures within an occupational setting for ≥ 10 hours per week and the number of exposed controls ≥ 5 . Results not shown: occupational agents with nonsignificant odds ratios of <1.0 (aluminum, petroleum/petroleum products, silica); occupational agents with <5 controls (beryllium, cobalt, mica); or with no response (leather).

Excludes aluminum, beryllium, and cobalt.

dressing, painting, printing, textile work, welding, and wood dust for all subjects combined. The definition of several of these exposures was evaluated on the basis of selected subsamples of industries and occupations considered to represent more or less intense exposure. The odds ratios for farming, textile, and wood dust were generally unchanged when the definition was restricted to SOC code (data not shown). However, there was a difference in the odds ratios for farming activities reported as primarily crops versus primarily livestock and for metal mining versus mining as one group. The odds ratios for exposures among males were generally lower than for those among females, but these estimates were unstable because of small numbers (table 2).

Duration of exposures

Occupational and environmental exposures were stratified by duration of exposure, but results were based on small num-

bers. Statistically significant results for <5 and ≥ 5 years of exposures are shown in table 3; in general, risk increased with years of exposure. Although not shown, we also examined time since exposure. In general, the exposure for the majority of subjects predated the diagnosis date by at least 5 years.

Multivariate analysis

Risk factors for mutual adjustment included those shown in table 4, as well as jobs related to chemical/petrochemical, printing, textile, and wood dust exposures. Removal of the latter four variables caused a negligible decrease in the remaining estimates. Stone-cutting activity and talc dust exposure were included, because the odds ratios showed at least a threefold risk and appeared to be independent risk factors (table 4). Agricultural exposure was defined in three ways: as exposure to only livestock, as specific exposure to vegetable/animal dust, or more generically as farming. Only

TABLE 2. Multiple logistic regression-adjusted* risk estimates based on occupational history of all jobs reported to be held for 6 months or more and categorized by the Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes, prior to diagnosis of idiopathic pulmonary fibrosis, a multicenter case-control study, 1989–1993

Occupational exposure	All subjects				Males				Females			
	Cases (no.)†	Controls (no.)	OR‡	95% CI‡	Cases (no.)	Controls (no.)	OR	95% CI	Cases (no.)	Controls (no.)	OR	95% CI
Odds ratio ≥ 1.5 for at least one comparison												
Diesel exhaust	63	111	1.4	0.9, 2.2	58	104	1.2	0.8, 2.0	5	7	3.4	0.9, 12.8
Farming	44	70	1.5	0.9, 2.5	37	60	1.4	0.8, 2.5	7	10	2.1	0.7, 6.8
Crop§	7	17	0.8	0.3, 2.4	7	15	1.1	0.4, 3.3	0	2		
Livestock§	25	27	2.7	1.3, 5.5	20	22	2.1	0.9, 4.7	5	5	7.1	1.4, 35.3
Hairdressing	5	3	4.3	0.8, 22.1	0	0			5	3	4.1	0.8, 20.7
Mechanic work	36	68	1.0	0.6, 1.7	32	66	0.8	0.5, 1.5	4	2	4.3	0.7, 25.0
Painting	3	4	1.6	0.3, 8.2	3	3	1.9	0.3, 10.5	0	1		
Printing	9	10	2.2	0.7, 6.5	6	7	2.0	0.6, 6.7	3	3	3.9	0.3, 45.2
Stone, clay, glass, concrete	3	10	0.9	0.2, 4.1	1	6	0.3	0.0, 2.9	2	4	2.9	0.3, 25.5
Textile	20	25	1.5	0.8, 3.1	4	9	0.7	0.2, 2.7	16	16	2.2	0.9, 5.3
Welding	8	12	1.6	0.6, 4.5	5	11	1.1	0.3, 3.9	3	1	4.4	0.4, 43.2
Wood dust	20	29	1.6	0.8, 3.3	15	26	1.4	0.7, 3.1	5	3	2.9	0.6, 14.2
Odds ratio < 1.5 for all comparisons												
Construction	34	82	0.9	0.5, 1.5	33	81	0.8	0.5, 1.4	0	1		
Metal dust	34	66	0.9	0.6, 1.6	25	52	0.8	0.5, 1.5	9	14	1.3	0.5, 3.5
Mining	2	16	0.3	0.1, 1.6	2	15	0.4	0.1, 2.1	0	1		
Metal	1	3	1.2	0.1, 14.3	1	3	1.4	0.1, 17.9	0	0		
Other	1	15	0.2	0.02, 1.3	1	14	0.2	0.0, 1.7	0	1		

* Adjusted for age (continuous) and cigarette smoking (ever/never).

† Number of cases and controls exposed; number of discordant pairs may be less.

‡ OR, odds ratio; CI, confidence interval.

§ Coded as “primarily crops” or “primarily livestock/animal specialties,” based on SIC code in conjunction with SOC code; mutually exclusive, except for two cases.

the results based on exposure to livestock are shown in table 4; estimates based on either vegetable/animal dust or on the more generic “farming” variable did not differ greatly from those that are shown.

In models exploring smoking and occupational exposure interactions, none of the interaction terms was statistically significant. However, there was evidence suggestive of an

interaction between smoking and agricultural work defined as exposure to either livestock or farming in general. For example, using those not exposed to either livestock or smoking as the referent group, the odds ratios were 0.8 (95 percent CI: 0.2, 3.1) for exposure to livestock alone, 1.7 (95 percent CI: 1.1, 2.5) for smoking alone, but 6.1 (95 percent CI: 2.1, 17.6) for exposure to both smoking and livestock.

TABLE 3. Multiple logistic regression-adjusted* risk estimates for statistically significant occupational exposures, prior to diagnosis of idiopathic pulmonary fibrosis by duration of exposure, a multicenter case-control study, 1989–1993

Occupational exposure	Duration (years)	Cases (no.)†	Controls (no.)	OR‡	95% CI‡
Livestock§	<5	10	9	2.1	0.7, 6.1
	≥5	15	17	3.3	1.3, 8.3
Raising birds¶	<5	2	3	1.4	0.2, 12.4
	≥5	8	4	7.5	2.0, 28.6
Metal dust#	<5	6	9	1.4	0.4, 4.9
	≥5	19	20	2.2	1.1, 4.7
Vegetable/animal dust#	<5	7	1	5.8	0.7, 50.8
	≥5	18	14	4.5	1.9, 10.8

* Adjusted for age (continuous) and cigarette smoking (ever/never).

† Number of cases and controls exposed; number of discordant pairs may be less.

‡ OR, odds ratio; CI, confidence interval.

§ Based on occupational history of all jobs reported to be held for 6 months or more and categorized by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes.

¶ Based on job activity checklist.

Based on occupational agent checklist with exposure ≥10 hours per week (excludes aluminum, beryllium, cobalt).

TABLE 4. Risk estimates adjusted for age and cigarette smoking compared with multivariate-adjusted odds ratios, all subjects combined, a multicenter case-control study, 1989–1993

Occupational/environmental exposure	OR*,†	95% CI*	OR‡	95% CI
Cigarette smoking	1.6	1.1, 2.4	1.8	1.2, 2.7
Hairdressing§	4.4	1.2, 16.3	4.8	1.2, 19.0
Raising birds§	4.7	1.6, 14.1*	4.1	1.3, 13.4
Stone cutting/polishing§	3.9	1.2, 12.7	3.2	1.0, 10.8
Metal dust	2.0	1.0, 4.0	2.0	1.0, 4.0
Talc	2.8	0.7, 11.2	3.3	0.8, 13.3
Livestock#	2.7	1.3, 5.5	2.2	1.0, 4.7

* OR, odds ratio; CI, confidence interval.

† Adjusted for age (continuous) and cigarette smoking. Cigarette smoking adjusted for age.

‡ Adjusted for age and all other variables listed in table.

§ Based on job activity checklist.

|| Based on occupational agent checklist.

Based on occupational history of all jobs reported to be held for 6 months or more as defined by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes.

DISCUSSION

Our results support and expand those of previous case-control studies (20, 21, 23) reporting increased risks for IPF associated with a consistent set of occupational and environmental dust exposures (table 5). There is increasing evidence that such exposures to particular dusts and fumes are associated with interstitial lung disease (33–35) and that chronic lung injury is related to diffuse pulmonary inflammation, which may promote interstitial pulmonary fibrotic diseases such as IPF (28). Associations have been reported between interstitial lung fibrosis and exposure to amorphous

silica (36) and aluminum (37–39). Several reports have documented the association between cobalt and hard metals with pulmonary fibrosis (40–42). Although the pathogenesis is not well understood (43, 44), in vitro and in vivo studies of inorganic dusts, such as cobalt, tungsten carbide, and hard metal (tungsten carbide-cobalt), demonstrate that the inflammatory and fibrotic response may be dependent on dust type (44) and that toxic activation of oxygen species due to the tungsten carbide-cobalt interaction may be an important mechanism (45). Agricultural workers are exposed to very high levels of dust and aerosolized particulates from a variety of sources, including feed grains, bedding, and fecal material (34), and tend to have an increase in the prevalence of respiratory symptoms, decreased lung function (46), and lung fibrosis (47). Wood dust, as well as chemicals for wood protection, wood adhesives, and mold present in wood, may contribute to an increase in fibrosis or extrinsic allergic alveolitis (48). Exposure to textile dust associated with the manufacturing of nylon flock and flocked fabrics also has been reported to be associated with interstitial lung disease (49).

Epidemiologic studies of occupational and environmental risk factors are subject to a variety of biases and limitations. In this study, cases were drawn from major referral centers, possibly resulting in a sample of more severely affected cases, although they appeared to be clinically similar to cases in other studies (9, 21, 50). However, cases in this study compared with those from a population-based registry were younger at diagnosis (61 vs. 72 years), more frequently had an open lung biopsy (54 vs. 10 percent), and had a different survival experience (3), but this may not be relevant to risk. It is difficult to determine whether selection bias operated with regard to the risk factors studied in this popu-

TABLE 5. Risk factors for idiopathic pulmonary fibrosis based on four international case-control studies, United States (22), United Kingdom (21), Japan (20), and England/Wales (23)*

Occupational/environmental exposure	United States, January 1989–July 1993 (n = 248)†		United Kingdom, October 1992–March 1994 (n = 218)		Japan (n = 86)	England/Wales, 1988–1989 (n = 40)	
	OR‡	95% CI‡	OR	95% CI		OR	95% CI
Farming/agricultural area§	1.6	1.0, 2.5			3.0	1.3, 7.4	
Cattle or livestock	2.7	1.3, 5.5				10.9	1.2, 96.0
Metal dust#	2.0	1.0, 4.0	1.7	1.1, 2.7	1.3	1.1, 1.6	11.0
Smoking	1.6	1.1, 2.4	1.6	1.0, 2.4	2.9	1.4, 6.3	1.1
Stone/sand dust§	3.9	1.2, 12.7	1.8	1.0, 3.1			1.6
Textile dust	1.9	0.8, 4.4	1.8	1.1, 3.0			0.9
Wood dust	1.6	0.8, 3.3	1.7	1.0, 2.9			2.9
Wood fires	0.8	0.4, 1.6				12.6	1.4, 114.0

* United States: odds ratios adjusted for age (continuous) and smoking (ever/never); United Kingdom: odds ratio for metal dust and wood dust adjusted for smoking and each other; Japan and England/Wales: no adjustment.

† Number of cases in study. UK controls (n = 569) matched for age, sex, and community; Japan controls (n = 172) matched for age (± 5 years), sex, and residential area; England/Wales controls (n = 106) matched for age (± 5 years) and sex.

‡ OR, odds ratio; CI, confidence interval.

§ Based on job activity checklist.

|| Based on occupational history of all jobs reported to be held for 6 months or more, as defined by Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) codes; textile dust based on SOC-defined exposure only.

Based on occupational agent checklist with exposure ≥ 10 hours per week for 6 months or more. Definition of metal dust in studies: in US study, as exposure excluding aluminum, beryllium, and cobalt dusts; in UK study, as exposure to a list of 15 possible metal dusts (increased risk due primarily to steel, brass, and lead); in Japanese study, as exposure to cadmium, chromium, and lead in metal production and mining; in England and Wales study, as exposure to occupational metal dust.

lation. However, this should not be a major issue, because cases were not referred due to the presence of specific risk factors, since the etiology of IPF is unknown. Referral to a specialty center is more frequently related to the need for a diagnostic biopsy and younger age. Cases were diagnosed by specialists in interstitial lung disease and had physiologic, radiologic, and histopathologic features consistent with the conventional clinical criteria for IPF, thereby reducing the possibility of misclassification. Additionally, approximately half ($n = 133$) of the cases were diagnosed by open lung biopsy, a larger percentage than found in other epidemiologic studies of IPF. When possible, the hematoxylin-eosin-stained slides were reviewed by two independent pathologists (T. V. C., J. A. W.), using a standardized quantitative histopathology assessment (25). This was done for 71 percent of the cases having an open lung biopsy. Misdiagnosis for some cases is possible given the positive association with raising birds. Two cases were excluded prior to analysis, based on a histology compatible with extrinsic allergic alveolitis due to exposure to avian proteins (51).

Differential misclassification could occur if cases were more likely than controls to remember specific occupations or exposures included in the checklists, but this difference in recall is unlikely because, again, the etiology of IPF is unknown. In the case of the occupational agents, we attempted to reduce this by restricting analyses to those subjects who reported 10 or more exposure hours per week for 6 months or more within an occupational setting. Additionally, we tried to reduce recall bias by collecting the detailed occupational history data prior to the checklists of job activities and occupational agents. Although job histories relying on occupational titles and industries are indirect exposure markers, they provide more specific information and may be less subject to recall bias than exposure-based checklists (52). However, this may be primarily true for jobs held most recently or for the longest time (53). We attempted to reduce some of these biases by collecting data using several classifications.

Although the occupational history provides a valid approach for collecting past job histories in detail, exposures defined on the basis of industry and occupation are based on a heterogeneous group of jobs. Job activities may include complex mixtures of exposures that are multiple in occurrence and difficult to quantify (54). Relevant exposure categories were based on more than one set of criteria when feasible, in order to evaluate any difference between reliance on only SOC codes versus a combination of SIC and SOC codes, and for the most part, there was no difference. We were unable to separate out more specific exposures associated with job activities (i.e., detailed list of metal or wood type).

Confounding exposures such as cigarette smoking may significantly affect risk estimates. The risk estimates for stone cutting/polishing as a job activity, adjusted for age and smoking, were at least 50 percent higher than unadjusted odds ratios. The adjusted estimates for several other exposures including insulation work, textile making, bird raising, mining, quarry work, work in a chemical/petrochemical plant, tunnel construction, and hairdressing were

10–20 percent higher than unadjusted estimates. These differences were greater when the analysis was restricted to males. Our finding of an interaction between smoking and agriculture-related factors is consistent with previous evidence for the inflammatory response of both smoking and dust inhalation (28), although this may be a spurious finding.

There is reasonable evidence to suggest that IPF is a heterogeneous disorder linked to a variety of exposures including occupation, cigarette smoking, and viral infections. A larger case-control study with an in-depth focus on the exposures consistently identified across studies would seem to be the next best step. IPF as a cause of death is increasing in several countries (55, 56), and it has been demonstrated that death certificate records underestimate the number of deaths (56), especially in the United States (57). Current corticosteroid therapy is ineffective (58), and survival is very poor with a median survival of approximately 4–5 years (3, 9, 11, 48). A better understanding of the risk factors for IPF is needed to prevent its occurrence.

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BMJ Open Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study

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ABSTRACT

Objectives: To estimate the effects of smoking, gender and occupational exposure on the risk of developing severe pulmonary fibrosis (PF), including dose-response and interaction effects.

Methods: National case-control study of 171 patients (cases) who had started a long-term oxygen therapy for PF in Sweden between February 1997 and April 2000, and 719 random control participants from the general population. Of these cases, 137 had probable idiopathic PF (IPF). The ORs for smoking, gender and occupational exposure were estimated using Mantel-Haenszel analysis and conditional logistic regression, controlling for age and year of diagnosis.

Results: The adverse effect of smoking was amplified by male gender and occupational exposure, OR 4.6 (95% CI 2.1 to 10.3) for PF, and OR 3.0 (1.3 to 6.5) for IPF, compared with non-exposed women. Higher cumulative smoking exposure was linearly associated with increased risks. Compared with smoking less than 10 pack-years, smoking ≥20 pack-years was associated with increased risk of PF and IPF, OR 2.6 (1.4 to 4.9) and OR 2.5 (1.3 to 5.0), respectively.

Conclusions: Smoking has a dose-related association with increased risk of severe PF. Men with a history of smoking and occupational exposure is a particular risk group for developing severe PF.

Strengths and limitations of this study

- Population-based case-control study of participants developing oxygen-dependent pulmonary fibrosis in Sweden with randomly selected controls from the general population.
- Analysis of detailed exposure data, accounting for confounders and lag time between exposure and disease.
- As the underlying aetiology may be difficult to ascertain in patients with oxygen-dependent pulmonary fibrosis, idiopathic pulmonary fibrosis was defined through review of national administrative register data and individual medical records.

The aetiology of IPF remains unknown.² The majority of patients with IPF are men with a history of current or past smoking.² Most case-control studies have suggested an association between smoking and an increased risk of IPF,^{4–7} although one study reported no such association.⁸ This inconsistency is most likely due to differences in study settings, the included covariates and, in some studies, the use of hospital patients as control participants, which might have biased the smoking estimates.^{4–7,9–11} Occupational exposures, including metal, stone and wood dust, have been linked to higher risks of developing IPF.¹²

It is unknown whether there are interactions between smoking, gender, and occupational exposure and the risk of developing IPF. The only two studies which analysed interactions reported a tendency towards an amplified IPF risk in patients with a history of smoking and occupational exposure, but the studies failed to establish statistically significant interactions.^{6,13} Moreover, it is unclear whether smoking really is an aetiological factor for IPF, as studies included low



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numbers of patients, and data on whether there is a dose-dependent relation between smoking and the risk of IPF are limited.

The aim of the present nationwide case-control study was, therefore, to estimate the associations between smoking, gender, occupational exposure and the risk of developing severe PF.

METHODS

This was a national, register-based case-control study. The patients who had started a long-term oxygen therapy (LTOT) for PF between 1 February 1997 and 4 April 2000 in the national Swedevox register were eligible for inclusion as cases. The Swedevox register covers 85% of all patients starting LTOT in Sweden.¹³ Details of the study design and a previous analysis using the same dataset have been published.¹⁴ Data were collected through an extensive postal questionnaire on smoking, occupational exposure (including fibres, fumes, gas, mineral dust, organic dust and vapours) and diagnosis of PF. The questionnaire has been described in detail elsewhere.¹⁵ Smoking data included the year of starting smoking, date of stopping smoking and the mean number of smoked cigarettes per day during each 10-year period between ages 15 and 65 years, and the mean exposure after age 65.¹⁵ Occupational data included the presence, start year, stop year and intensity (h/week) for any occupational exposure and exposure to birds (at work and at home), metal dust and wood dust. Occupational exposure was defined as any exposure 10 or more years before the date of the PF diagnosis, allowing for a 10-year time lag between exposures and developing the disease.

After exclusion of patients who were incorrectly registered ($n=12$; 5%) or did not respond to the questionnaire ($n=58$; 24%), 171 PF cases were included in the analysis.

Patients with probable IPF (IPF cases, $n=137$) were identified through a review of each patient's medical record performed independently by specialists in respiratory medicine (KN, TG).¹⁴ High-resolution CT was performed in 41% of patients with PF, CT in an additional 10% and transbronchial and open lung biopsy was performed in 6% of the patients. The IPF cohort excluded patients with an identifiable or probable cause of PF: rheumatic or systemic inflammatory diseases (20% of PF cases), pneumoconiosis (6%), and medications or irradiation (2%).¹⁴

Control participants were selected as a random sample ($n=1000$) from the general population of the same age range as the patients with PF. Of the control participants, 719 (72%) returned complete exposure data and were included in the analysis. All participants gave their informed consent to participate.

Statistical analysis

Cases and control participants were categorised according to year of birth (1906–1923, 1924–1936 or 1937–

1969) and cases according to the year they received their PF diagnosis (1968–1986, 1987–1993 or 1994–1999). Control participants were assigned a time point corresponding to the year the patients received their PF diagnosis, using a method described previously.^{14 15} First, control participants within each birth year group were assigned a random diagnosis year group, weighted by the number of cases in each diagnosis year group. Then, the year of PF diagnosis of each control participant was set to the mid-year of the corresponding year of the patient group. Characteristics at baseline (the date the questionnaire was filled in) were presented using frequencies and percentages for categorical variables. Continuous data were presented using mean with SD and median with range or IQR for variables with normal and skewed distribution, respectively.

Smoking status and cumulative smoking exposure, calculated as pack-years ((mean number of cigarettes per day)/20×(years of exposure)), were recorded up to 10 years prior to the date of the PF diagnosis (a 10-year time lag), allowing for time between smoke exposure and the development of oxygen-dependent PF.

Associations between smoking and the risk of developing oxygen-dependent PF and IPF, and the interactions between smoking, occupational exposure and gender, were estimated and reported using Mantel-Haenszel analysis, controlling for year of birth, year of diagnosis and gender, as applicable. Interactions were also analysed using conditional logistic regression, stratified for year of birth, year of diagnosis, gender, with adjustment for age and pack-years of smoking. All estimates were consistent between Mantel-Haenszel analysis and the conditional logistic models.

Associations were expressed as ORs with 95% CIs. Statistical significance was defined as a double-sided $p<0.05$. Statistical analyses were performed using Stata V.11.1 (StataCorp LP; College Station, Texas, USA) and SAS V.9.2 (SAS Institute, Inc, Cary, North Carolina, USA).

RESULTS

We included 171 patients with PF, of whom 137 were classified as having IPF, and 719 control participants. Baseline characteristics are shown in table 1. Among PF cases, the rate of any occupational exposure was higher in men than in women (80% vs 52%; $p<0.001$). Men also had higher smoking exposure. Ten years before the PF diagnosis, 90 (84%) men were ever-smokers with a median of 10 (IQR, 3–23) pack-years, compared with 29 (45%) women with a median of 8 (IQR, 3–15) pack-years. A similar difference was seen in IPF cases.

Interactions

There was a significant interaction between smoking, occupational exposure and gender and the risk of developing oxygen-dependent PF (test of homogeneity, $p=0.028$). The interaction was similar in the IPF cohort

Table 1 Patient characteristics

Characteristics	PF cases (n=171)	IPF cases (n=137)	Controls (n=719)
Age	73.7±9.5	74.2±9.8	64.3±13.7
Males, n (%)	107 (63)	86 (63)	337 (47)
Never-smokers, n (%)	52 (30)	44 (32)	344 (48)
Ex-smokers, n (%)	114 (67)	89 (65)	251 (35)
Current smokers, n (%)	5 (3)	4 (3)	124 (17)
Smoking exposure, n (%)*	119 (70)	93 (68)	375 (52)
1–9 pack-years	29 (17)	22 (16)	176 (24)
10–19 pack-years	34 (20)	27 (20)	91 (13)
≥20 pack-years	36 (21)	27 (20)	62 (9)
Occupational exposure, n (%)*	119 (70)	93 (68)	397 (55)
Birds	16 (9)	11 (8)	33 (5)
Inorganic dust	55 (32)	40 (29)	164 (23)
Metal dust	35 (20)	27 (19)	119 (17)
Organic dust	67 (39)	52 (38)	182 (25)
Wood dust	32 (18)	25 (18)	57 (8)

Data presented as mean±SD unless otherwise specified.

*Exposure earlier than 10 years before PF diagnosis (10-year time lag).

IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

(table 2). Men with current or past smoking and occupational exposure had markedly increased risk of PF, OR 4.6 (2.1 to 10.3), and IPF, OR 3.0 (1.3 to 6.5), compared with non-exposed women (table 2). Adjustment for differences in pack-years between men and women, in addition to the other covariates, did not affect the estimates.

Dose-response effect

There was a linear association between higher cumulative smoking exposure (up to 10 years before diagnosis) and increased risk of PF and IPF, OR 1.03 (95% CI 1.01 to 1.04) per pack-year and OR 1.02 (95% CI 1.01 to 1.04) per pack-year, respectively. Compared with lower levels of smoking (1–9 pack-years), heavy smoking (≥20 pack-years) was associated with an increased risk of PF, OR 2.6 (95% CI 1.4 to 4.9) and IPF, OR 2.5 (95% CI 1.3 to 5.0), as shown in table 3. Using a 5-year time lag for smoking exposure instead of 10 years resulted in similar estimates.

Subtypes of occupational exposure

The effect of occupational exposure seemed to be mediated partly through exposure to birds and wood dust. The risk of PF was increased by exposure to birds (OR 1.9; 95% CI 1.0 to 3.7) and wood dust (OR 1.7;

95% CI 1.0 to 3.0), controlling for age, gender, year of diagnosis and smoking. There were no evidence of effects of inorganic dust (OR 1.3; 95% CI 0.8 to 2.0) or metal dust (OR 1.1; 95% CI 0.6 to 1.8). There were signs of interactions with smoking and gender for exposure to birds ($p=0.021$) and wood dust ($p=0.023$), respectively. Estimates were similar for the IPF cohort, except for a lower effect of bird exposure (OR 1.3; 95% CI 0.6 to 2.8).

DISCUSSION

The main findings are that (1) smoking was a risk determinant in the development of oxygen-dependent PF and that this risk was amplified by male gender and occupational exposure; (2) the association with smoking was dose-dependent, which may support the theory of the causative role of smoking in the pathogenesis of severe PF.

Our findings are consistent with reports of increased risk of IPF associated with smoking^{4–6 10 12 16} and occupational exposures.^{4–7 9 12 14 16} A previous analysis using the present dataset showed that specific occupational factors associated with an increased risk of PF included exposure to birds and wood dust.¹⁴ Studies of a possible

Table 2 Effect of smoking on the adjusted risk of pulmonary fibrosis, according to gender and occupational exposure

	PF OR (95% CI)		IPF OR (95% CI)	
	Women	Men	Women	Men
No occupational exposure	1.10 (0.50 to 2.42)	1.97 (0.64 to 6.13)	1.12 (0.49 to 2.59)	1.44 (0.43 to 4.83)
Occupational exposure	1.10 (0.52 to 2.34)	4.63 (2.08 to 10.33)	1.32 (0.58 to 3.03)	2.96 (1.34 to 6.52)

OR (95% CI) for the effect of smoking versus no smoking on the risk of developing PF and IPF, estimated using Mantel-Haenszel analysis controlled for year of birth and year of diagnosis. Smoking was defined as the presence of ever-smoking earlier than 10 years before the diagnosis.

IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

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Table 3 Dose-response effect of smoking on the risk of severe pulmonary fibrosis

Smoking, pack-years*	PF OR (95% CI)	IPF OR (95% CI)
0	1	1
1–9	1.03 (0.62 to 1.70)	0.90 (0.52 to 1.57)
10–19	2.26 (1.35 to 3.80)	2.10 (1.20 to 3.68)
≥20	2.66 (1.56 to 4.55)	2.25 (1.26 to 4.02)

ORs for levels of smoking estimated using conditional logistic regression adjusted for age and stratified for year of birth, year of diagnosis, gender and occupational exposure.

*Pack-years of smoking up to 10 years before the year of PF diagnosis.

IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis.

dose-response correlation between smoking and IPF have shown conflicting results, with two studies indicating a dose-dependent effect^{5 6} and one study showing no dose correlation.¹⁷ The latter study, however, analysed only smoking status and the current smoking dose (cigarettes per day) and not cumulative smoking exposure such as pack-years.¹⁷ The present study extends the previous observations by demonstrating that the association between smoking and severe PF is dose-dependent and is modified by gender and occupational exposure.

The strength of the present study is that it included cases from a population-based prospective register of patients starting LTOT in Sweden. Control participants were randomly selected from the general population. Previous studies using control participants in hospitals may have yielded biased estimates, as the risk of hospitalisation is likely to be related to occupational factors and smoking.^{4 7 9–11} We had detailed data on the temporality, dose and duration of smoking. In contrast with previous studies, only exposure data up to 10 years before the year of the PF diagnosis was included in the analysis to avoid reverse causation and to allow for the time lag between exposure to risk factors and the manifestation of clinical disease.

A possible limitation is that the self-reported exposure data could be influenced by recall bias. The validity of the exposure classification was, however, supported by a high degree of consistency between reported employment histories and occupational exposure to specific agents.¹⁴ Second, the association between smoking and starting LTOT could be affected by survivor bias, as smokers are likely to be at high risk of dying of other smoke-related disease, such as cancer and cardiovascular disease, before they can develop severe IPF. Also, stopping smoking is a mandatory criterion for starting LTOT. Both these potential biases would tend to lower the number of smokers starting LTOT and to underestimate the association between smoking and oxygen-dependent PF. Third, the IPF diagnosis could be misclassified in some patients, especially as the cohort was collected prior to the publication of main consensus definition of IPF.¹ The validity of the PF and IPF diagnoses was checked by respiratory physicians using medical records, including available radiographic and histological data.¹⁴ Among idiopathic interstitial pneumonias, IPF is the

most common condition and it is associated with a high risk of progression to hypoxic respiratory failure and death.^{1 18} Thus, the prevalence of IPF is most likely to be high in oxygen-dependent PF. It is possible that we included patients with combined PF and emphysema, which may be present in up to one-third of patients with IPF.¹⁹ Concurrent emphysema may constitute a smoking-related comorbidity or a distinct IPF phenotype,¹⁹ and could explain, at least partly, the association between smoking, male gender and the development of severe IPF in the present study. We included the PF cohort in the analysis, as it may be difficult to obtain a specific diagnosis in patients with advanced PF in the clinic. Findings were similar in the PF and IPF cohorts, which supports the validity of the analysis. Using national population-based cases and controls, the present findings most likely have high applicability to severe PF in Swedish clinical practice. The validity to other settings may be lower owing to differences in sociodemographic factors, healthcare organisation and pattern of exposure.

Mechanisms governing the relationship between smoking, gender, occupational exposure and the development of severe PF are unknown but likely involve complex interactions between different environmental factors in genetically predisposed individuals.²⁰ The adverse effect of smoking could in part be attributable to the development of concurrent emphysema, which has been associated with hypoxaemia and earlier death in IPF.²¹

For the clinicians, this study identifies a group of male, heavy smokers with occupational exposure to harmful substances, who have a greatly increased risk of developing severe PF. In this group, interventions to help people reduce or stop smoking are a top priority.

In conclusion, smoking is associated with a dose-dependent increase in oxygen-dependent PF. The adverse effects of smoking are stronger in men and in people with occupational exposure.

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Contributors ME had full access to all the data in the study and took full responsibility for the integrity of the data and the accuracy of the data analysis. KB, KN, GT and KT were involved in conception and design. TG, KB, KN, GT and KT were involved in the acquisition of the data. ME, TG, NM and KT were involved in analysis and interpretation of data. ME, TG and KT were involved in drafting the article. ME, TG, KB, KN, GT, NM and KT were responsible for revising the article for important intellectual content and approval of the version to be published.

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Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study

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Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis

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Summary

Idiopathic pulmonary fibrosis (IPF) is a lethal lung disorder of unknown etiology. The disease is likely the result of complex interactions between genetic and environmental factors. Evidence suggests that certain environmental factors, such as cigarette smoking and metal dust exposures, or comorbidities like gastroesophageal reflux, and type 2 diabetes mellitus (DM2) may increase risk to develop IPF. Substantial uncertainty remains, however, regarding these and other putative risk factors for IPF. In this study we performed a case-control analysis including 100 patients with IPF and 263 controls matched for age sex and place of residence. We used a structured questionnaire to identify potential risk factors for IPF, including environmental and occupational exposures as well as the relevance of family history of pulmonary fibrosis. The multivariate analysis revealed that family history of pulmonary fibrosis [OR = 6.1, CI95% 2.3–15.9; $p < 0.0001$] was strongly associated with increased risk of IPF. Actually, 20% of the cases reported a parent or sibling with pulmonary fibrosis. Gastroesophageal reflux [OR = 2.9, CI: 1.3–6.6; $p = 0.007$], former cigarette smoking [OR = 2.5, CI: 1.4–4.6, $p = 0.003$], and past or current occupational exposure to dusts, smokes, gases or chemicals [OR = 2.8, CI: 1.5–5.5; $p = 0.002$] were also associated with the disease. Despite being a significant risk factor on univariate analysis DM2 was not significant in multivariate analysis. These

Abbreviation: ATS, American Thoracic Society; 95% CI, 95% confidence intervals; DLD, Division of Lung Diseases; DM2, Type 2 diabetes mellitus; ECRHS, European Community Respiratory Survey; ERS, European Respiratory Society; IIP, Idiopathic interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; LHSQ, Lung Health Study Questionnaire; OR, Odds ratio; SD, Standard deviation; SF-12, Short Form survey-12; TSR, telomere repeat copy number to single gene copy number.

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findings indicate that family history of pulmonary fibrosis is a strong risk factor for IPF. Also, we confirmed that occupational exposures, gastroesophageal reflux and former smoking increase the risk for this disease.
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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and lethal lung disorder of unknown etiology. The disease occurs predominantly in older adults, although the mechanisms for the association of aging with IPF have not been elucidated.¹ IPF is considered a complex disease where both genetic and environmental factors are believed to contribute to disease susceptibility. In the last decade a number of studies have tried to understand the genetic bases of this disease and to identify risk factors, but there are few large studies with conclusive results.

To date, smoking has consistently been associated with IPF in a number of case-control studies evaluating sporadic IPF and in one study of familial pulmonary fibrosis.^{2,3} Also, several occupational factors, adjusted for age and smoking have been found significantly associated with IPF, including metal and wood dust exposure.^{4,5} A meta-analysis supported that significant increased risk for IPF is associated with cigarette smoking and exposures to agriculture and farming, livestock, wood and metal dust, and stone and silica.² Likewise, some studies provide evidence of an association between IPF and type 2 diabetes mellitus (DM2) and gastroesophageal reflux.⁶⁻¹⁰

Familial IPF, which is virtually indistinguishable from sporadic IPF, is identified when two or more members of a family have the disease. Some studies suggest that 0.5–3.7% of IPF is familial.^{11,12} However, a remarkably higher frequency was reported in a small cohort of IPF patients from a lung transplant program where 19% had a positive family history¹³; this retrospective decade-long analysis probably had higher detection due to subsequent cases occurring in the family of patients who reported a negative family history. More recently, 10% were identified as familial within a single-center cohort of 229 patients with idiopathic interstitial pneumonias.¹⁴

In this context, we designed a questionnaire-based, case-control study to identify potential environmental risk factors in our population as well as the relevance of family history of pulmonary fibrosis in a cohort of IPF patients.

Methods

Study design

A case-control study was carried out at the National Institute of Respiratory Diseases during 2007–2009. The research protocol was approved by the institutional Scientific and Bioethics Committee (*Comité de Ciencia y Bioética en Investigación; Protocol #E05-07*). Population studied was comprised of newly-diagnosed IPF patients

(cases) consecutively seen at our institution, and healthy subjects (controls) paired by age, gender and residential area. Diagnosis of IPF was established according to ATS/ERS criteria.¹⁵ In 35% of the patients the diagnosis was confirmed by surgical biopsy showing changes of usual interstitial pneumonia.¹⁶ Healthy controls were randomly selected from the same patients' neighborhoods, at a ratio of 1–3 controls per IPF patient. In general, matching controls were living in houses located in the same block than the patients. A trained interviewer visited every household and asked if some person living there had the same age and gender than the case patient. After explaining the purpose of the study, potential control subjects were asked to participate and, if agreed, the questionnaire was applied. Control subjects were included in the study if they were no relatives of the patients and if they denied chronic pulmonary diseases or acute respiratory symptoms in the last three weeks prior to the interview. Patients and controls were individuals with the same ethnic origin and with at least two generations born in Mexico. Patients and controls have similar access and utilization to the same quality health care. A signed consent letter was obtained from all patients and controls.

Exposure assessment

Evaluation of exposures was performed with the same questionnaire used in the PLATINO study,^{17,18} which in turn derives from an already validated questionnaire (ATS-DLD-78, ECRHS, LHSQ, SF-12). The PLATINO survey was enlarged by adding questions about chronic respiratory conditions in interviewed subjects' relatives. This questionnaire was applied to all cases and controls by two trained interviewers. Among other variables, characteristics of personal (tobacco, alcohol), occupational (dusts, smokes, gases, chemicals, dairy and poultry farms), and household (ventilation, wood smoke, tobacco smoke) exposures were investigated. The questionnaire also explores the presence of current or past presence of medical conditions such as gastroesophageal reflux, gastritis, hepatitis, heart diseases, and depression. Finally, chronic pulmonary diseases in parents and siblings were also assessed. This last question included the following specific diagnoses: chronic obstructive pulmonary disease, emphysema, asthma, lung cancer, tuberculosis and pulmonary fibrosis. A diagnosis of diabetes mellitus type 2 (DM2) was established through the questionnaire, evaluating whether it was diagnosed by a physician, type of medication (oral hypoglycemic agents or insulin), and duration. Additionally, in IPF patients, diagnosis of DM2 was confirmed by pre-prandial glucose >126 mg/dl without previous corticosteroid use.

Statistical analysis

Statistical analysis included Student's *t*-test and chi square test to evaluate differences between interval and categorical variables, respectively. Association between two variables was assessed through odds ratio (OR) and 95% confidence intervals (95%CI). Finally, multivariate models were generated by means of conditional logistic regression for matched case-control groups and included the variables that were confounders as those that were considered to be indispensable in explaining the study event. In this analysis, the following predictive variables were included: having a parent/sibling with pulmonary fibrosis, being a former cigarette smoker, past or current occupational exposure to dusts, smokes, gases or chemicals, past gastroesophageal reflux history, and DM2. Probability criteria for a variable entering to or removing from the model were 0.05 and 0.10, respectively. The analysis was performed using Stata software, Release 9.0.

Results

From January 2007 through December 2009 a total of 100 IPF patients and 263 healthy controls paired by age, gender and geographical region were studied. Average age was 67.8 ± 9.5 years (mean \pm SD) in IPF patients and 67.9 ± 9.1 years in the control subjects ($p = 0.9$). Male predominance was comparable among cases and controls (71.0% versus 69.9%, respectively, $p = 0.8$). The similar age and gender between the cases and controls indicate that matching was successful. The majority of the study population (75.2%) lived in the residential areas of the two nearest political demarcations, *Distrito Federal* and *Estado de México*.

Educational characteristics and tobacco smoke and other exposures of the study subjects are shown in Table 1. In the bivariate analysis, the IPF group had a marginal but significantly higher proportion of individuals with 6 or more education years [44.0 vs 32.3% from controls, OR = 1.6 (95% CI, 1.02–2.6), $p = 0.039$]. Occupational exposure to dusts, smokes, gases or chemicals was more frequently found among cases than in controls [77.0 vs 58.6%, respectively, OR = 2.4 (95% CI, 1.4–4.0), $p = 0.001$]. Regarding tobacco smoke exposure, former cigarette smokers also showed significant excess risk for IPF [58.0% vs 33.5%, OR = 2.7 (95% CI, 1.7–4.4), $p < 0.0001$].

As shown in Table 2, significantly more IPF patients answered affirmatively to the question about the presence of pulmonary fibrosis in a parent (father or mother) or sibling (brother or sister) [20.0% vs 2.7%, OR = 9.1 (95% CI

3.7–22.4), $p < 0.0001$]. Three of the 20 patients reported two relatives with the disease. We were able to corroborate the diagnosis of pulmonary fibrosis in the relatives of 8 of these 20 patients because the remaining 12 parents or siblings had died several years ago when we contacted the families. Diagnosis of pulmonary fibrosis in the 7 of the 8 familial cases was corroborated in our Institute using HRCT and pulmonary function tests. The last familial case was evaluated in another Hospital and diagnosis included HRCT and lung biopsy. However, even if we consider only these 8 patients, the odds ratio continued to be significantly increased [OR: 2.8 (95% CI 1.01–7.9), $p < 0.05$]. On the other hand, due to the potential existence of a recall bias (with IPF cases more prone to recall pulmonary disease in their relatives), we estimated the impact of a misdiagnosis among control group's relatives. Thus, cases and control subjects declared that 6 and 29 relatives, respectively, had chronic bronchitis, pulmonary emphysema, or chronic obstructive pulmonary disease. In this context, even if we consider that the 23 exceeding relatives of control subjects were in fact IPF patients, familial pulmonary fibrosis would remain significantly associated to IPF (20/100 and 30/263 in cases and controls, respectively) with OR: 1.9 (95% CI 1.04–3.6), $p = 0.04$.

As previously suggested in several studies on familial IPF,^{11,12,14} our IPF patients with family history of pulmonary fibrosis were significantly younger than those with negative family history (61.8 ± 7.1 versus 69.3 ± 9.4 years old, $p < 0.001$). No other variable reached a significant difference between these two subgroups of IPF patients.

Some diseases were more often observed in IPF patients, as compared with controls. Significant increased risk for IPF was associated with past gastroesophageal reflux [OR = 3.1 (95% CI, 1.7–5.9) $p < 0.0001$], and gastritis [OR = 1.9 (95% CI 1.2–3.2) $p = 0.006$]. Type 2 diabetes mellitus was also more frequent among cases than controls [30.0 vs 19.0%, OR = 1.8 (95% CI, 1.1–3.1), $p = 0.02$]. Past or current cardiac disease was marginally associated with IPF (Table 2).

Concerning household characteristics, the only feature that was more frequently seen among cases was the presence of earthen floor [9.0 vs 3.4%, respectively, OR = 2.8 (95% CI, 1.1–7.2), $p = 0.035$]. Some other variables such as working in crop cultivation or as a stockbreeder, carpenter or hairdresser, household nearness to a dairy farm, birds at home, dampness at home, and indoor use of insecticides were not different between cases and controls (data not shown).

In the multivariate analysis, having a parent or sibling with pulmonary fibrosis was the strongest variable

Table 1 Education and exposures of cases and controls.

Characteristic	IPF cases ^a (n = 100)	Control subjects ^a (n = 263)	OR (CI95%)
Formal education \geq 6 years	44 (44)	85 (32.3)	1.6 (1.02–2.6) $p = 0.039$
Occupational exposure to dusts, smokes, gases or chemicals	77 (77)	154 (58.6)	2.4 (1.4–4.0) $p = 0.001$
Former cigarette smoker	58 (58)	88 (33.5)	2.7 (1.7–4.4) $p < 0.0001$

^a Data correspond to n(%).

Table 2 Family history of pulmonary fibrosis and comorbidities of cases and controls.

Characteristic	IPF cases ^a (n = 100)	Control subjects ^a (n = 263)	OR (CI95%)
Familial IPF (parent and/or sibling)	20 (20.0)	7 (2.7)	9.1 (3.7–22.4) p < 0.0001
Past gastroesophageal reflux	23 (23.0)	23 (8.7)	3.1 (1.7–5.9) p < 0.0001
Past gastritis	40 (40.0)	66 (25.1)	1.9 (1.2–3.2) p = 0.006
Type 2 diabetes mellitus	30 (30.0)	50 (19.0)	1.8 (1.1–3.1) p = 0.02
Past or current cardiac disease	13 (13.0)	17 (6.5)	2.2 (1–4.6) p = 0.05

^a Data correspond to n (%).

associated with the disease [OR = 6.1 (95% CI, 2.3–15.9) p < 0.0001] (Table 3). Being a former cigarette smoker, having past or current occupational exposure to dusts, smokes, gases or chemicals, and past gastroesophageal reflux were also associated with increased risk of IPF. By contrast, in this multivariate analysis, DM2, showed a tendency but it was not an independent predictor of IPF.

Discussion

Idiopathic pulmonary fibrosis is a progressive, life-threatening, lung disorder that likely arises from the interplay between genetic and environmental factors. In this context, individualization of host and environmental factors responsible for IPF predisposition and onset could play an important role for disease prevention and for devising novel therapies.

Regarding exposures, cigarette smoking has formerly been associated with sporadic IPF.² Furthermore, in a family-based case-control study of familial interstitial pneumonia, Steele et al³ evaluated 111 families, with 309 affected and 360 unaffected individuals. After adjusting for age and sex, smoking was strongly related with pulmonary fibrosis. The results of the present study corroborate this association since 58% of the IPF patients were former smokers. Taken together, the evidence increasingly indicates that cigarette smoking, which among other effects generates a cumulative oxidative stress, may contribute to the pathogenesis of IPF. Interestingly, it has been shown that tobacco smoking enhances telomere shortening,^{19,20} a process recently reported in most sporadic IPF patients and in a few families.^{21,22} Telomeres are DNA-protein structures that protect chromosome ends from erosion and end-to-end fusion and that shorten successively with each cell division.²³ Importantly, a link between telomere length and aging-associated diseases and mortality has been suggested.^{24,25} In addition, numerous associations

between chronic degenerative diseases and telomere length have been reported.

Intriguingly, a putative relationship between telomere length shortening and type 2 diabetes mellitus has been recently reported.²⁶ Using a case-control study from a community-based population sample the association of leukocyte telomere repeat mean copy number to single gene copy number (TSR) and DM2 was examined. In a multivariable logistic regression analysis, it was found that decreased TSR [log(e)-transformed] was significantly associated with the disease. Shortened telomeres have been associated with DM2 in previous but generally small studies. DM2 has been associated with IPF in several studies involving different ethnic populations.^{6–8} In this study, a tendency was also noted. However, given the high prevalence of DM2 in our adult population, a much larger study population would be necessary to provide definitive results.

As previously described, several exposures (dusts, smokes, gases or chemicals) were also associated with IPF supporting that the disease is more frequent in individuals exposed to dusty environments.^{2,4,5,27} Recently, the accumulation of inorganic dusts in lung tissues of patients with IPF, chronic hypersensitivity pneumonitis, and collagen vascular diseases was analyzed by polarizing light microscopy, scanning electron microscopy and energy dispersive X-ray spectroscopy.²⁸ IPF lung tissues showed greater numbers of birefringent particles, even in patients without occupational exposure. The silicon/sulfur ratio and aluminium/sulfur ratio were increased in IPF independent of occupational exposure. A point elemental analysis showed that the major compound of the particles was aluminium-silicate. How tissue exposure to environmental toxicants predisposes or participates in the pathogenesis of IPF is largely unknown. However, chronic damage to alveolar/bronchiolar epithelial cells may play a role in genetically susceptible individuals.

The multivariate analysis also confirmed that gastroesophageal reflux is associated with a risk for IPF.

Table 3 Crude and adjusted odds ratios for IPF.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
Parent or sibling with IPF	9.1 (3.7–22.4) p < 0.0001	6.1 (2.3–15.9) p < 0.0001
Former smoker	2.7 (1.7–4.4) p < 0.0001	2.5 (1.4–4.6) p = 0.003
Past or current occupational exposure to dusts, smokes, gases or chemicals	2.4 (1.4–4.0) p = 0.001	2.8 (1.5–5.5) p = 0.002
Past or current gastroesophageal reflux	3.1 (1.7–5.9) p < 0.0001	2.9 (1.3–6.6) p = 0.007
Type 2 diabetes	1.8 (1.1–3.1) p = 0.02	1.6 (0.9–3.0) p = 0.1

Gastroesophageal reflux and silent microaspiration have been related with several lung diseases and is common among those who have had lung transplantation.²⁹ Also, a higher incidence of gastroesophageal reflux has been reported in patients with IPF compared with normal individuals suggesting that microaspiration may be a factor for IPF.^{7–10} Interestingly, it has been suggested that acute exacerbation of IPF, a devastating diffuse alveolar damage manifested by some patients may be also related to microaspiration.³⁰

The most remarkable finding in our study was the high prevalence of close relatives of our patients affected by pulmonary fibrosis. Thus, 20 percent of the patients had a parent and/or a sibling previously diagnosed with pulmonary fibrosis. In eight of these cases we were able to confirm the presence of pulmonary fibrosis in the family. Previous studies had estimated a significantly lower frequency of positive family history, e.g., between 0.5 and 3.7%.^{11,12} However, this percentage may represent an underestimation, as evidenced by a 13 year retrospective review of the Vanderbilt Lung Transplant Program, in which 9 of 47 patients (19%) transplanted for IPF had a family history significant for interstitial lung disease.¹³ Likewise, around 10% of familial IPF were recently identified within a single-center cohort of 229 patients with idiopathic interstitial pneumonias indicating that the percent of familial disease is higher than we formerly believed.¹⁴ The majority of pedigrees indicate an autosomal dominant vertical transmission pattern of inheritance with reduced penetrance.³¹ In the largest collection of familial interstitial pneumonias, 20 multigenerational pedigrees were consistent with autosomal dominant inheritance.³

Clinical features of familial IPF are indistinguishable from those of the sporadic form, except for an earlier age of onset.^{11,12,14} This observation was confirmed in our study, with the cases with familial history presenting on average 7 years earlier than sporadic patients. Nevertheless, a potential lead time bias (in which subjects with a parent or sibling with IPF are more prone to be submitted to earlier screening and hence to have an earlier diagnosis of IPF than subjects without IPF in the family) can not be ruled-out.

Certainly, an important limitation of this study was the fact that familial history of pulmonary fibrosis was self-reported. We were able to confirm the diagnosis of IPF/IIP in only 8 of 20 patient's relatives, because the remaining parents and siblings had died when we contacted the families. However, we have no reason to suspect that the accuracy of self report of disease would be different for the other 12 patients. Also, the magnitude of the odds ratio when compared to healthy controls may be subject to some bias through over-reporting among the cases and under-reporting among controls.

In summary, we found that the presence of a familial history of pulmonary fibrosis showed the strongest association with IPF. This finding supports the notion that it is crucial to carefully evaluate and if possible corroborate the presence of family history in these patients. Exposure to tobacco smoke and other environmental smokes and dusts as well as the presence of gastroesophageal reflux also were risks to develop IPF. Although the environmental associations are not a proof of causation, our findings

provide evidence that gene-environment associations are likely playing a role to trigger IPF.

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Conflict of interest

None.

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Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study

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Summary

The etiology of idiopathic pulmonary fibrosis (IPF) remains poorly understood, but some studies have suggested that cigarette smoking or other occupational or environmental exposures, diabetes mellitus, or gastroesophageal reflux may play a role. In this study we evaluated the clinical records of a group of 97 consecutive patients with IPF, and 560 patients suffering 5 different respiratory disorders that were examined as controls: asthma ($n = 111$), chronic obstructive pulmonary disease ($n = 132$), squamous cell lung carcinoma ($n = 118$), lung adenocarcinoma ($n = 101$) and patients with otorhinolaryngology problems but without lung disease ($n = 98$). In bivariate analyses male sex, diabetes mellitus and being former cigarette smoker were associated with IPF. After adjusting by these variables, multivariate analysis revealed that type 2 diabetes mellitus [11.3% in IPF patients vs 2.9% in controls, OR = 4.3 (95% CI: 1.9–9.8), $p < 0.0001$] was an independent risk factor associated to IPF. Our results provide additional evidence of a putative relationship between DM2 and idiopathic pulmonary fibrosis. Experimental research is necessary for thorough assessment of the pathogenic mechanisms involved in this association.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive scarring lung disease that leads to respiratory failure and death.¹ Although the etiology of IPF is still unknown, it is considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, up to now putative genes and environmental factors that consistently increase the risk of IPF have not been identified. Smoking presents the most

Abbreviations: COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; DM2, type 2 diabetes mellitus; ORL, patients with otorhinolaryngologic problems; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society.

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striking association with both the sporadic and the familial forms of IPF.^{2,3} Likewise, some occupational and environmental exposures, primarily to wood and metal dusts, have shown to be associated to increased risk of IPF.² Chronic viral infection (Epstein-Barr virus) and gastroesophageal reflux have been also considered as possible risk factors for this disease.^{4,5} The incidence of IPF increases with age, and aging contributes to some lifestyle-related diseases. Therefore, it is possible that lifestyle-related disorders such as type 2 diabetes mellitus (DM2) may affect either the initiation or progression of IPF. Actually, in two studies performed in different ethnic populations DM2 was found to be associated with IPF.^{6,7}

In this context, the aim of the present study was to identify possible risk factors associated to IPF in a Mexican population. Our results indicated that DM2 is a major predictor of the disease.

Patients and methods

This was a retrospective case-control, hospital-based study performed at the National Institute of Respiratory Diseases (INER), México. Clinical records of consecutive IPF patients seen at this institute from 2000 through 2005 were reviewed. Diagnosis of IPF was made according to established criteria, and confirmed by lung biopsy in 35% of subjects.⁸

The control group was integrated by patients who were seen as outpatients or were hospitalized at the INER due to selected pulmonary diseases [asthma ($n = 111$), chronic obstructive pulmonary disease (COPD, $n = 132$), squamous cell lung carcinoma ($n = 118$), or lung adenocarcinoma ($n = 100$)] and by patients with otorhinolaryngologic (ORL, $n = 98$) problems but without lung disease. Diagnosis of asthma or COPD were done according to the Global Initiative for Asthma [GINA⁹] and the Global Initiative for Chronic Obstructive Lung Disease [GOLD¹⁰], respectively. Both types of lung cancer were confirmed by histopathology. Regarding ORL patients, individuals included in the analysis were randomly selected from patients assisting to the ORL department during the study period. Cases and controls

were evaluated simultaneously. To confirm specific diagnoses of cases and controls, the clinical records were examined twice through standardized methods. Diagnosis of DM2 was done if the patient had a fasting glucose level higher than 126 mg/dl (7 mmol/l) in the absence of corticosteroids treatment, or the accomplishment of one of the following criteria: a) the patient knew that he or she had DM2 diagnosed by a clinician; b) diagnosis of DM2 was done at INER during the first consult; c) the patient was taking oral drugs for DM2; d) the patient had used insulin. The protocol was accepted by the Bioethics and Science Committee of INER.

Environmental exposures

Information concerning environmental exposures was obtained from a standardized questionnaire dealing with risk factors for respiratory diseases. This questionnaire was systematically applied by the Social Work Department to any patient admitted to the INER from 1999 onward. The questionnaire was created and validated by one of the authors (RPP) and assesses the following risk factors: age, gender, DM2, smoking habit (current, former, ever); alcoholism (current, former, ever); occupational exposure to dusts, smoke or chemicals; location and characteristics of the home (rural or urban area, construction materials, number of windows and number of hours they remain open, number of individuals living with the patient, presence of children <5 years old, home nearness to a gas station, high-traffic roads, landfills, dairy or poultry farms, and manufacturing plants); home exposure to wood smoke, coal, side-stream tobacco smoke, birds, carpets, dampness and insecticides.

Statistical analysis

Categorical variables were analyzed through the chi-square test. Interval variables were expressed as mean and standard deviation and were compared by the Student's *t*-test. Odds ratios (OR) were calculated through unconditional

Table 1 Sociodemographic characteristics of cases and controls ($n = 657$).

	IPF cases ($n = 97$)	Controls ($n = 560$)	OR (95%CI)
Age (years)	62.6 ± 11.0	62.3 ± 12.2	1.002 (0.9–1.02)
Male sex	71/97 (73.2)	347/560 (62.0)	1.7 (1.03–2.7)
Type 2 diabetes	11/97 (11.3)	16/560 (2.9)	4.3 (1.95–9.7)
Past or current occupational exposure to dust	55/97 (56.7)	292/560 (52.1)	1.2 (0.8–1.9)
Past or current occupational exposure to smoke	64/97 (66.0)	388/560 (69.3)	0.9 (0.5–1.4)
Past or current occupational exposure to chemicals	28/97 (28.9)	120/560 (21.4)	1.5 (0.9–2.4)
Tobacco smoke exposure			
Non-smoker	53/97 (54.6)	320/560 (57.1)	0.9 (0.6–1.4)
Ever smoker	44/97 (45.4)	240/560 (42.9)	1.1 (0.7–1.7)
Former smoker	39/97 (40.2)	168/560 (30.0)	1.6 (1.006–2.5)
Current smoker	5/97 (5.2)	82/560 (14.6)	0.3 (0.1–0.8)
Past passive smoker	36/95 (37.9)	213/544 (39.2)	0.9 (0.6–1.5)
Current passive smoker	9/96 (9.4)	129/542 (23.8)	0.3 (0.2–0.7)
Past or current alcohol use	39/97 (40.2)	221/560 (39.3)	1.03 (0.7–1.6)

Data correspond to mean \pm SD or to frequencies (%).

logistic regression. Variables introduced into regression models were selected according to a $p < 0.20$ or its biological relevance.

Results

Ninety seven patients with IPF and 560 controls with different lung or ORL diseases were included in the study. Demographic characteristics are shown in Table 1. As can be seen in this table, both groups did not differ regarding age, occupational exposure to dusts, smoke or chemicals, or alcohol intake. Male gender was slightly more frequent among IPF patients. The most striking difference was related to DM2 and exposure to tobacco smoke. Thus, a higher proportion of subjects with DM2 was found among cases (11.3%) as compared with controls (2.9%, $p < 0.0001$), yielding over a four-fold risk of IPF among DM2 subjects. The increased frequency of DM was even higher in the subgroup of IPF patients who had undergone surgical lung biopsy to confirm diagnosis biopsied: OR 6.8 (2.0–22.6); non-biopsied: OR 3.6 (1.2–9.6). A more in-depth analysis showed that IPF patients had such increased risk compared with almost all of the five subgroups of control patients. Thus, odds ratios (95% confidence intervals) were 4.6 (1.2–26.3) for asthma, 2.7 (0.9–9.2) for COPD, 3.7 (1.03–16.3) for squamous cell cancer, 6.3 (1.3–59.3) for lung adenocarcinoma, and 6.2 (1.3–58.7) for ORL control subgroups. Likewise, IPF patients showed a higher frequency of former smokers (40.2 vs 30.0%, $p = 0.04$), and less current active or passive smokers (5.2 vs 14.6%, $p = 0.01$, and 9.4 vs 23.8%, $p = 0.002$, respectively). The increased percentage of current active and passive smokers in the control group was mainly due to a higher proportion of smokers among COPD and squamous cell cancer patients (data not shown).

Odds ratios and 95% confidence intervals for household characteristics are shown in Fig. 1. All variables lacked statistically significant differences between both groups.

After adjusting by sex, former smoker, current active and passive smoker, multivariate analysis shown that DM2 was the most important independent predictor associated to IPF risk [OR = 4.3 (1.9–9.8) $p < 0.0001$, Table 2].

Discussion

IPF is the most common idiopathic interstitial pneumonia and the one with the worst prognosis. Thus, despite intensive research an effective therapy for this disease remains elusive. Etiology of IPF is unknown but several epidemiological observations associate the risk of developing this disease to an environmental injury to the lungs. Recognition of these and other risk factors may be crucial to prevent the development of the disease.

In this study, we approached the question about risk factors through a case-control study using a questionnaire administered by social workers to collect information regarding household characteristics, environmental exposures and other pertinent data.

Our results showed that DM2 was significantly associated to a higher risk for IPF. Thus, after adjusting for confounding factors, there was a more than 4-fold increase in odds for developing IPF among diabetics. Similar results

HOUSEHOLD CHARACTERISTICS

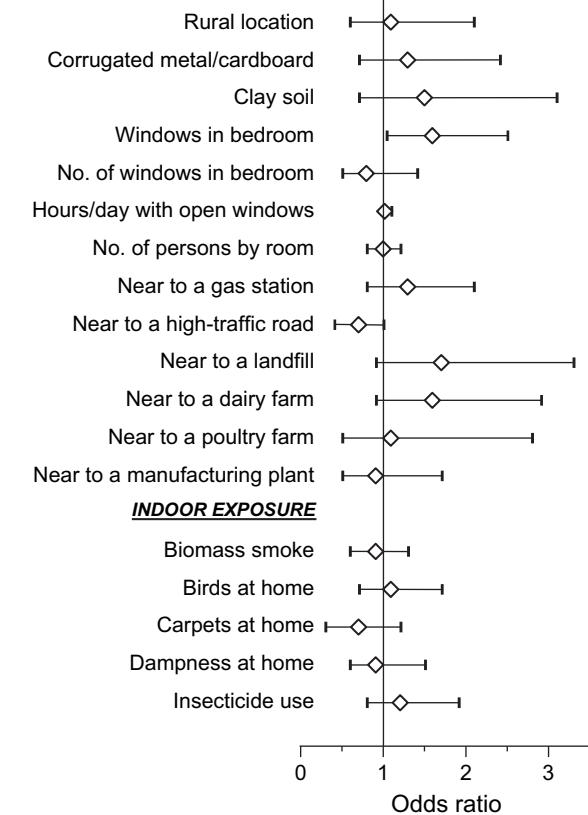


Figure 1 Odds ratios for developing IPF according to selected variables, as compared with controls.

have been reported in two previous studies involving different ethnic populations.^{6,7} In one of them, a case-control study performed in the setting of a longitudinal primary-care database in the United Kingdom showed that IPF was significantly associated to diabetes-related conditions, being insulin use the factor with the strongest association.⁷ Interestingly, in this study no association with the smoking status was found. Similar results were reported in a Japanese population, where 64 IPF patients were compared with 184 control subjects without evidence of lung disease in their chest radiographs.⁶ In this case-control study, the prevalence of DM2 was 3-fold higher in the IPF group. On the contrary, in a more recent study also performed in Japanese population, IPF patients were

Table 2 Adjusted odds ratios obtained through conditional logistic regression^a for characteristics associated to IPF ($n = 657$).

	Standardized β -coefficient	Adjusted OR (95% CI) for IPF
Male sex	0.55	1.7 (1.04–2.9)
Type 2 diabetes	1.46	4.3 (1.9–9.8)
Former smoker	1.15	3.2 (1.2–8.5)

^a Additional independent variables evaluated in (and excluded from) the logistic regression model were ever smoker and current passive smoker.

compared with unmatched controls (inpatients with acute bacterial pneumonia and outpatients with common cold), concluding that diabetes was no associated to IPF.¹¹

Studies regarding fibrosis in organs other than the lungs have also found some association with DM2. For example, history of diabetes was an independent clinical parameter associated with advanced fibrosis in patients with chronic hepatitis C.¹² Likewise, the incidence of chronic nonalcoholic liver disease is significantly higher among patients with diabetes.¹³ Furthermore, fibrosis is a frequent pathological reaction in tissues affected by diabetic complications.¹⁴ The pathogenic mechanisms implicated in the association of diabetes and IPF are presently unknown. High extracellular and intracellular glucose environment may activate several pathways related to the production of cytokines, growth factors, and reactive oxidative species, which can mediate tissue damage and fibrosis in diabetes. For example, it has been recently shown that connective tissue growth factor (CTGF) mediates high glucose and palmitate induced cardiac myocyte hypertrophy and dysfunction as well as cardiac fibrosis.¹⁵ Interestingly, CTGF has been recently implicated in the epithelial to mesenchymal transition (EMT) of renal tubular epithelial cells which contributes to the renal fibrosis associated with diabetic nephropathy.¹⁶ EMT is also involved in the expansion of the population of fibroblasts/myofibroblasts in IPF lungs, although a putative relationship with diabetes has not been evaluated.^{17,18} Many other factors play roles in the pathogenesis of diabetic nephropathy and fibrosis; for instance, both TGF- β 1 and angiotensin II are important factors to promote the development of renal fibrosis.¹⁹ These mediators are also implicated in the pathogenesis of IPF.²⁰ Furthermore, elevated circulating levels of TGF- β 1 may be part of the molecular link between diabetes, and diseases resulting in organ fibrosis.²¹

A high prevalence of current or former smokers has been reported in several series of IPF patients. In a recent meta-analysis of observational studies examining environmental and occupational risk factors for IPF, a significant increased risk for IPF was associated with cigarette smoking.² In a large study including 248 cases and 491 control subjects identified through random-digit dialing, matched by gender, age and geographic region, a history of ever or former smoking was associated with increased risk for the development of IPF.²² Also, evidence suggestive of an interaction between smoking and agricultural work has been found.²³ However, some contradictory results have also been reported, which may be partially related to the utilization of different control groups (i.e., community or hospitalized controls), small size samples, and uncertainty of IPF diagnosis since several studies were performed before the 2000 year when a consensus diagnosis was published.^{2,8,22–24}

In our study, we found by bivariate and multivariate analyses a higher proportion of former smokers in the IPF group. Interestingly however, an increased proportion of current smokers was found among control patients that is explained by the high proportion of them in the COPD and squamous lung cancer subgroups, two diseases strongly associated to cigarette smoking.

Exposure to biomass smoke was explored because in developing countries many households in rural areas or in

the periphery of urban areas depend on biomass for cooking and heating, and this exposure has been associated to pulmonary fibrosis in one study and some case reports.^{24,25} However, no association was found, probably because the high prevalence of exposure in all subgroups of patients with chronic respiratory disorders. Likewise, none of the other studied factors showed statistical significance.

This study has several potential weaknesses that restrict the power of the results. Among them, the retrospective collection of data and the relatively small sample size limit the statistical power to detect other putative associations between exposures and the disease. This is primarily due to the low prevalence of IPF that makes the number of patients available for conducting etiologic studies usually small. The main strength of our study is the validity of the diagnosis of IPF (ATS consensus) and of the other diseases that constituted the control group.

In summary, our findings indicate that DM2 might constitute a risk factor for developing IPF in Mexican population. The pathogenic mechanisms implicated in this association remain to be elucidated. Further studies are needed to confirm the putative relationship of IPF with smoking.

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Conflict of interest

Authors have no conflicts of interest to declare.

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Occupational exposure and severe pulmonary fibrosis

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Respiratory failure

Summary

Background: External agents, especially metal and wood dust, are believed to be risk factors for development of idiopathic pulmonary fibrosis (IPF). The aim of this case-control study was to investigate which occupational exposure types are associated with development of severe pulmonary fibrosis (PF), and especially IPF.

Methods: An extensive postal questionnaire including 30 specific items regarding occupational exposure was completed by 181 patients with severe PF and respiratory failure reported to the Swedish Oxygen Register, among whom 140 were judged as having IPF. The questionnaire was also completed by 757 control subjects. We stratified data for age, sex and smoking and calculated odds ratios (ORs).

Results: We found increased risk for IPF in men with exposure to birch dust (OR 2.7, 95% confidence interval (95% CI) 1.30–5.65) and hardwood dust (OR 2.7, 95% CI 1.14–6.52). Men also had slightly increased ORs associated with birds. We did not find any increased risk in association with metal dust exposure.

Conclusion: Exposure for birch and hardwood dust may contribute to the risk for IPF in men.

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Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; LTOT, long-term oxygen therapy; OR, odds ratio; PF, pulmonary fibrosis

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Introduction

Pulmonary fibrosis (PF) and in particular idiopathic pulmonary fibrosis (IPF) is increasing as a cause of death in the Western world.^{1–3} In Sweden PF, mainly IPF, has increased as

a cause of chronic hypoxemia treated with long-term oxygen therapy (LTOT).⁴

The cause of IPF, the most common of the idiopathic interstitial pneumonias,⁵ is multi-factorial and includes external factors.⁶ A mineralogical micro-analysis of lung tissue from IPF patients showed deposits of silica/silicate,⁷ and mineral dusts have been found to directly induce fibrosis in the airway wall.⁸ Five case-control studies have demonstrated increased occupational risk for IPF,⁹⁻¹³ especially with exposure to metal dust, although not supported by a study on standardised mortality ratios.¹⁴ In three of these studies, wood dust exposure was increased among the IPF cases.⁹⁻¹¹ The association between IPF and metal was further confirmed in a case-control study nested in an occupational cohort.¹⁵ Farming,^{9,10,12} stone or sand dust^{11,12} as well as smoking¹⁶ also seem to be risk factors for IPF. Most studies are from the US, UK or Japan, and there is a lack of studies from northern Europe, where exposure to soft wood and metals for instance may be more frequent.

Hence, we have performed a case-control study on a national sample of patients diagnosed with PF and starting LTOT. The specific aim of the study was to further elucidate types of occupational exposure that increase the risk for this lethal disease, with the long-term intention to prevent new cases.

Materials and methods

The Swedish Oxygen Register was started in 1987 with the purpose of assessing quality of LTOT in Sweden in terms of access to therapy, adherence to national guidelines and performance.¹⁷

The cases in the present study were recruited from the patients with chronic hypoxemia caused by PF, and came from 23 out of 29 general hospitals in Sweden covering 88% of the population in Sweden. All registered patients ($n = 241$) receiving LTOT between 1 February 1997 and 4 April 2000 were included as cases. In the subsequent analysis, the cases were divided into two groups, viz. all cases (the PF sample), and a restricted sample of cases (the IPF sample), from which all subjects with known aetiology of their fibrosis were excluded.

As controls we selected a random sample ($n = 1000$) from the general population of Sweden with the same age range as the cases (Fig. 1).

Cases and controls received an extensive postal questionnaire with items about their occupation, specific occupational exposure, drugs used and smoking habits. The questionnaire and wording of the items have been described elsewhere.¹⁸

The classification of the subjects' occupational exposure was based upon their self-reports. The questions about occupational exposure were worded as follows: "In your work, have you ever been exposed to ...?". Such items covered 29 different types of occupational exposure.

The questionnaire was completed by 193 PF patients (cases). Twelve were excluded due to erroneous diagnosis in the Oxygen Register. Hence, 181 subjects were included in the PF sample. From this sample, we excluded 27 subjects because of rheumatoid arthritis ($n = 14$), scleroderma ($n = 4$), Sjögren's syndrome ($n = 2$) and other diseases such

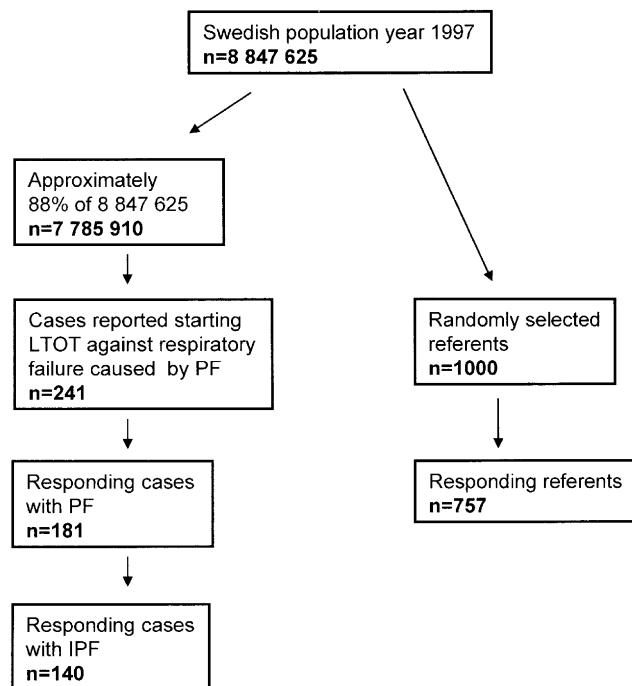


Figure 1 Flow chart showing the selection of cases and referents for the study. IPF: idiopathic pulmonary fibrosis; LTOT: long-term oxygen therapy; PF: pulmonary fibrosis.

as systemic sclerosis and systemic lupus erythematosus ($n = 7$). An additional 14 cases were excluded because of known aetiology, viz. asbestosis ($n = 6$), silicosis ($n = 5$), and irradiation or drug-induced PF ($n = 3$). Hence, 140 cases were included in the IPF sample.

The data from the Oxygen Register and the questionnaires did not allow verification of IPF according to accepted major and minor criteria.¹⁹ When identifying the IPF patients we therefore excluded all patients with host susceptibility or known external agents. We then assumed that the remaining patients had IPF, being the largest group of the idiopathic interstitial pneumonias and serious enough to cause chronic respiratory failure.

Of the 1000 controls being sent the questionnaire, 757 responded. Table 1 shows baseline data for the cases and controls with regard to age and smoking status.

Every regional ethics committee in Sweden, the National Board of Health and Welfare and the Data Inspection Board approved the study. All patients and controls gave their informed consent.

Statistical analyses

For all analyses, the Statistical Analysis System (SAS) statistical package, version 8.1 (SAS Institute, Inc., Cary, NC, US), was used. The cases and controls were divided into the following three groups according to year of birth: 1906–1923, 1924–1936 and 1937–1969. The cases were diagnosed in the years 1968–1999, and they were further divided into three groups according to their year of diagnosis, as follows: 1968–1986 (41%), 1987–1993 (28%) and 1994–1999 (31%).

Relevant exposure was exposure that had occurred before the onset of PF, approximated as the year of diagnosis. It was also necessary to define an anchor point in time for each control. Hence, in each birth year group, the controls were randomly assigned to a year of diagnosis group. The number of controls allocated to each year of diagnosis group was weighted by the number of actual cases. Each control was then assigned the mid-year in his or her year of diagnosis group as its anchor year.

To be classified as exposed, subjects had to report exposure 5 years or more before diagnosis. This means that exposure occurring during the 5-year period preceding the diagnosis was not included in the analysis. In the final analysis, the exposures were merged into five categories: occupational exposure, organic dust, wood dust, inorganic dust, and metal dust.

Two groups of cases were analysed, the whole group of cases (the PF sample) and the restricted sample (the IPF sample). The cases and controls were stratified for sex, age group and birth year group, and odds ratios (ORs) were calculated according to Mantel-Haenszel. Only exposure categories with five or more exposed cases were considered in the final analysis. Ninety-five per cent confidence intervals (95% CIs) were calculated with the test-based method.²⁰ Logistic regression modelling was also used to

adjust for overlapping exposures, and ORs with 95% CIs were estimated.

Results

Subjects with any occupational exposure had an increased risk for PF (OR 1.6, 95% CI 1.06–2.37), but not for IPF (Table 2). Exposure to wood dust increased the risk for PF (OR 1.7, 95% CI 1.03–2.95).

When stratifying the analyses according to sex, we observed the highest risks for PF among men (Table 2). Exposure to wood dust among men doubled the risk for PF (OR 2.1, 95% CI 1.18–3.65).

In Table 3, the risks for all the exposures are shown for PF and IPF, and in men and women together. The analyses were restricted to exposures affecting five or more cases. An increased risk for PF was associated with exposure to mineral dust, birds, flour dust, dust from fur or fir, birch dust, hardwood dust and fire fumes. In cases with IPF, the exposures with increased risk were only birch dust (OR 2.4, 95% CI 1.18–4.92) and hardwood dust (OR 2.5, 95% CI 1.06–5.89). The OR for flour dust and IPF was just below the significance level (OR 1.9, 95% CI 0.98–3.74).

When separately analysing men and women with five or more exposed subjects to a group, risks remained increased for IPF in men exposed to birch dust (OR 2.7, 95% CI 1.30–5.65) and hardwood dust (OR 2.7, 95% CI 1.14–6.52). Men also had an increased OR associated with birds (OR 2.7, 95% CI 1.00–7.06) (not shown in the table). There was no increased risk for any of the detailed exposures in the women.

There were 10 PF cases reporting occupational exposure to hardwood dust. In the questionnaire, there was also information about occupations. Their longest held occupation was wood-products machine operator, forester, cabinet-makers, machine operator, telephone servicers and a blacksmith. There were also two carpenters and two subjects not reporting their occupation.

We also analysed the material using a latency period of 10 years instead of 5 years with similar results. The same exposures were associated with increased risks,

Table 1 Description of the study population (the cases were the subjects in the pulmonary fibrosis sample*).

	Men		Women	
	Cases (n = 114)	Referents (n = 349)	Cases (n = 67)	Referents (n = 408)
Age (years)	74.4	64.2	72.0	63.4
Never-smokers (%)	15.7	38.7	54.5	52.6
Ex-smokers (%)	80.6	46.2	43.8	27.4
Current smokers (%)	3.7	15.1	1.7	20.0

*The IPF sample (n = 140) was included in the PF sample (n = 181).

Table 2 Odds ratio* according to occupational exposure, for the pulmonary fibrosis sample and the idiopathic pulmonary fibrosis sample, stratified by sex, year of diagnosis, birth year and smoking, and for the pulmonary fibrosis sample divided into men and women, stratified by year of diagnosis, birth year and smoking.

	PF sample (n = 181)			IPF sample (n = 140)			Men with PF (n = 114)			Women with PF (n = 67)		
	n [†]	OR	95% CI	n [†]	OR	95% CI	n [†]	OR	95% CI	n [†]	OR	95% CI
Any occupational exposure	123	1.6	1.06–2.37	86	1.1	0.71–1.72	89	1.7	0.95–3.12	34	1.5	0.84–2.55
Organic dust	69	1.4	0.98–2.12	49	1.1	0.74–1.76	54	1.7	1.04–2.70	15	1.1	0.56–2.10
Wood dust	34	1.7	1.03–2.95	22	1.2	0.65–2.23	33	2.1	1.18–3.65	–	n.a.	–
Inorganic dust	57	1.2	0.79–1.97	35	0.9	0.53–1.49	54	1.4	0.84–2.23	–	n.a.	–
Metal dust	37	1.0	0.62–1.69	25	0.9	0.51–1.59	34	1.1	0.62–1.79	–	n.a.	–

*Determined using Mantel-Haenszel. Note that only exposures with 10 or more exposed cases were considered. PF: pulmonary fibrosis; IPF: idiopathic pulmonary fibrosis; 95% CI: 95% confidence interval; n.a.: not applicable.

[†]n: number of exposed cases; OR: odds ratio.

Table 3 Odds ratio* for the pulmonary fibrosis sample and the idiopathic pulmonary fibrosis sample according to occupational exposure, stratified by sex. Number of controls exposed for each occupational exposure, divided into men and women.

Exposure	PF (<i>n</i> = 181)			IPF (<i>n</i> = 140)			Controls, men (<i>n</i> = 349) <i>n</i> †	Controls, women (<i>n</i> = 408) <i>n</i> †
	<i>n</i> †	OR	95% CI	<i>n</i> †	OR	95% CI		
Welding fumes	24	1.1	0.64–1.78	15	0.8	0.42–1.42	70	1
Grinding, polishing, milling or turning or other processing of metals	22	1.0	0.57–1.64	15	0.8	0.43–1.44	62	13
Soldering	13	0.9	0.47–1.65	9	0.7	0.31–1.38	44	8
Blasting	7	3.2	1.10–9.32	—	n.a.	—	7	0
Mineral dust	27	2.4	1.39–4.06	14	1.4	0.74–2.72	39	2
Coal dust or graphite dust	11	1.8	0.83–3.82	9	1.8	0.80–4.07	18	3
Artificial mineral fibres	22	1.2	0.67–2.00	14	0.8	0.45–1.57	60	4
Asbestos	26	1.2	0.72–2.00	15	0.8	0.44–1.47	66	6
Birds	16	2.3	1.22–4.34	10	1.7	0.82–3.62	11	22
Mouldy hay or straw	12	1.4	0.68–2.68	8	1.1	0.50–2.48	23	10
Grain dust	17	1.3	0.70–2.21	12	1.1	0.57–2.15	32	22
Flour dust	18	2.1	1.14–3.76	13	1.9	0.98–3.74	19	18
Fur or fir dust	32	2.1	1.31–3.47	20	1.4	0.82–2.52	48	9
Birch dust	16	2.6	1.32–5.18	13	2.4	1.18–4.92	18	4
Hardwood dust	10	2.4	1.05–5.69	9	2.5	1.06–5.89	12	2
Paper dust	9	1.3	0.60–2.91	6	1.1	0.43–2.70	17	8
Textile dust	13	1.4	0.74–2.72	10	1.3	0.64–2.70	12	33
Radiation	6	0.9	0.36–2.28	5	0.9	0.32–2.28	16	8
Solvents	28	1.3	0.79–2.05	19	1.0	0.60–1.77	64	14
Fire fumes	8	2.9	1.10–7.58	5	2.3	0.74–6.97	9	0
Engine exhausts	24	0.9	0.54–1.50	15	0.7	0.39–1.27	74	11
Irritating gases (ammonia, chlorine dioxide, chlorine gas, sulphur dioxide)	13	1.5	0.79–3.00	10	1.5	0.71–3.06	22	10
Environmental tobacco smoke	53	1.0	0.71–1.45	40	0.9	0.61–1.36	117	90
Cutting oils/fluids	8	1.0	0.43–2.23	5	0.8	0.28–2.01	25	0
Rapid glues (Loctite®, cyanoacrylates or Omnitif®)	6	1.0	0.37–2.45	6	1.9	0.38–2.37	18	2

*Determined using Mantel–Haenszel. Note that the exposure categories are not mutually exclusive. Only exposures with five or more exposed cases were considered. IPF: idiopathic pulmonary fibrosis; PF: pulmonary fibrosis; 95% CI: 95% confidence interval; n.a.: not applicable.

†*n*: number of exposed cases and controls respectively; OR: odds ratio.

Table 4 Logistic regression models for the pulmonary fibrosis sample giving odds ratios (and 95% confidence intervals) adjusted for sex, smoking, year of birth and year of diagnosis.

Predictor	PF			
		All (<i>n</i> = 181)	Women	Men
Inorganic dust	1.1 (0.70–1.68)		0.55 (0.12–2.53)	1.1 (0.70–1.83)
Organic dust	1.5 (1.00–2.15)		1.2 (0.60–2.22)	1.7 (1.06–2.8)
Metal dust	0.98 (0.61–1.58)		0.82 (0.17–3.82)	0.97 (0.58–1.63)
Wood dust	1.9 (1.12–3.15)		0.50 (0.06–4.11)	2.1 (1.22–3.75)

PF: pulmonary fibrosis.

but the risks were slightly higher. In order to explore a cohort effect, we ran the analyses with the population divided into two groups according to the mean birth year, 1930. We found no clear indication of cohort effect.

We obtained similar results with the logistic regression models (Table 4). Exposure to organic dust (and wood dust) increased the risk for PF, especially among men. When we modelled IPF as the dependent outcome, we found no significant associations.

Discussion

The main findings of this study were increased risks for IPF among men exposed to birch dust and hardwood dust. There were no associations with these exposures in the women, probably because much fewer women work with these materials.

The study included two different samples, PF and IPF subjects. The PF group included all patients with PF reported to the Swedish Oxygen Register. This means that it included patients with different pneumoconiosis and lung fibrosis due to other known diseases. Consequently, exposure to both mineral dust and blasting was associated with increased risk for PF. This broad case selection gives us the opportunity to assess the importance of all types of occupational exposure as risk factors for severe PF. We chose to analyse the risk of occupational exposure not only in the IPF group as previous authors^{9–13} but also in the larger sample, since the known aetiology might be only one of several risk factors in those patients.

As a cohort we chose the patients with severe PF in the Swedish Oxygen Register, a national register for assessment of quality of care in LTOT for chronic hypoxemia. In 14% of LTOT patients PF is the responsible disease, but in the whole population of patients with ongoing LTOT only 8–9% have PF. The reason for this discrepancy is higher mortality compared with other patient groups receiving LTOT, such as patients with chronic obstructive pulmonary disease and sequels of pulmonary tuberculosis.⁴ The cases included in the present study were around 88% of the Swedish patients with advanced-stage PF as the cause of chronic hypoxemia. According to our findings, the most common cause of severe PF with chronic hypoxemia in Sweden is IPF, which here accounted for 77% of the patients. In 8% known external agents could explain the fibrosis and in another 15% various known host susceptibility factors were found.

In the Swedish Cause of Death Register of the Swedish National Board of Health and Welfare, there is a clear dominance of men in the diagnostic group "other interstitial pneumonias". A large percentage of this group have PF with unknown aetiology. This may indicate a strong relationship with occupational exposure. As previously mentioned, this study was performed in a large part of the Swedish population as a recruitment base, with data from the Oxygen Register of the Swedish Society of Respiratory Medicine.¹⁷ The aim was to investigate whether occupational and environmental exposure is a risk factor in Sweden for severe PF, especially IPF. In the five other case-control studies demonstrating increased occupational risk for IPF, the cases were taken from various selected hospitals^{9,11–13} and from a national autopsy register, together with live controls from 12 prefectures.¹⁰

We chose to use a random sample from the general population of Sweden as the control group rather than using patients from the Swedish Oxygen Register, since the majority of them have chronic obstructive pulmonary disease (COPD). Smoking is the dominating cause of their disease but around 15% of them may have occupational exposure as a risk factor.²¹ We would fail to demonstrate the increased risk for pulmonary fibrosis, if the same exposures can increase both the risk of COPD and pulmonary fibrosis.

The exposure assessment in this study was based on self-reporting of certain types of exposure. The exposures were

selected because of an *a priori* hypothesis of increased risk for PF. The wording of the items was as specific as possible, and we avoided questions about general classes of substances such as "dust". This probably increased the specificity and decreased the sensitivity of our exposure assessment.²² Self-reported occupational exposure data could be differentially misclassified by disease status. In a Norwegian study, the sensitivity of the question on exposure to dust and gas was biased by respiratory symptoms but hardly at all by physician-diagnosed asthma.²³ Bias in sensitivity is more important than is bias in specificity for the effect of misclassification of exposure to a common exposure, as in the present study.²⁴ The details about occupations in the 10 cases exposed to hardwood dust support the validity of self-reported occupational exposure, as there seems to be a relation between occupational title and self-reported exposure.

In the PF sample, there was an increased risk associated with wood dust as a whole, which in contrast to three of the earlier case control studies did not remain when narrowed to IPF, in men and women together.^{9–11} However, exposure to dust from birch and hardwood was associated with an increased risk for both PF and IPF in men. The risks were generally high, which probably was an effect of using specific exposure items. Pulmonary fibrosis was also associated with exposure to organic dust, fire fumes, blasting and mineral dust in men. The two latter exposures probably reflect undiagnosed silicosis. Therefore, in Sweden, severe PF appears to be associated with occupational exposure in addition to silica dust. The lack of association between PF, IPF and occupational exposure in women might be due to the fact that few women have had these occupations.

We found, as Harris et al.¹⁴ in a study from death certificates, no association with exposure to metal dust, in contrast to the findings of all other five case-control studies mentioned.^{9–13} We can think of three reasons for the difference between our results and those of other investigators. There may be less exposure to hard metal and working environments may be less harmful in Sweden than in the other study populations. There may also be differences in patient selection. In our study, the study population was the whole country, not a specific region, as was the case in two of the other studies.^{9,11} In further studies, there is a need for more detailed description of the exposure, methods that have been used in other occupational respiratory epidemiological studies.²⁵

In conclusion, exposure to wood dust, especially dust from birch and hardwood, may contribute to the risk for IPF in men.

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Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis

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Summary

Background We have previously suggested that cryptogenic fibrosing alveolitis (CFA) may be caused by occupational exposures, particularly to metal or wood dust. We have specifically investigated this hypothesis in a case-control study of patients with CFA.

Methods We obtained lifetime occupational histories by postal questionnaire from 218 patients with CFA and 569 controls matched for age, sex, and community, living in the Trent region of the UK. Information was subsequently verified by telephone interview in 165 cases and 408 controls. Serum IgE, rheumatoid factor, and antinuclear antibodies and skin sensitivity to common allergens were measured in cases and in one matched control for each.

Findings The relative risk of CFA, after adjustment for smoking, was significantly increased in relation to questionnaire-reported exposure to metal dust (odds ratio 1·68 [95% CI 1·07–2·65], p=0·024) or to wood dust (1·71 [1·01–2·92], p=0·048). Similar results were obtained with the telephone interview data. Significant exposure-response effects were found for both metal-dust and wood-dust exposure. CFA was also associated with the presence of rheumatoid factor or antinuclear antibodies, but not with positive allergen skin tests or raised IgE concentrations. There was no evidence of interaction between the effects of rheumatoid factor, antinuclear antibodies, positive skin allergen tests, or IgE concentrations and exposure to metal or wood dust. The combined aetiological fraction

attributable to exposure to metal or wood dust was of the order of 20%.

Interpretation Occupational exposures to metal or wood dust are independent risk factors for CFA. Avoidance or limitation of these exposures may provide an opportunity to prevent the disease.

Lancet 1996; **347**: 284–89

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Introduction

Cryptogenic fibrosing alveolitis (CFA) is an interstitial lung disease that affects up to 20 adults per 100 000.¹ The disease is characterised by progressive dyspnoea, dry cough, inspiratory crackles on auscultation of the chest, and restrictive lung function. It is more common in men than in women and in older than in younger people.¹ The median survival time from diagnosis is about 5 years.² The causes are as yet unknown.

We have previously shown that mortality from CFA in the UK is increasing and tends to be higher in areas of the country that traditionally had high levels of employment in manufacturing industries.³ We presented preliminary evidence that occupational exposure to metal or wood dust may be a cause,⁴ and also suggested atopy as a risk factor for the disease.^{4,5} We have tested these hypotheses in a case-control study specifically designed to investigate the role of occupational exposure to metal, wood, and other dusts as risk factors for CFA, and whether susceptibility to occupational causes of CFA is influenced by atopy, cigarette smoking, and autoimmune status.

Patients and methods

Cases and controls

We identified all potential cases of CFA seen in four teaching hospitals and five district general hospitals (total catchment

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Data-set	Number reporting exposure		Unadjusted analysis		Adjusted* analysis	
	Cases	Controls	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Questionnaire	54 (24.8%)	95 (16.7%)	1.92 (1.25-2.94)	0.003	1.68 (1.07-2.65)	0.024
Interview	46 (27.9%)	53 (13.0%)	2.32 (1.36-3.94)	0.002	2.22 (1.26-3.91)	0.006
Combined†	32 (22.2%)	32 (8.9%)	2.93 (1.39-6.17)	0.005	2.59 (1.13-5.90)	0.024

*Adjusted for smoking status and exposure to wood dust. †Participants who reported exposure both on questionnaire and in interview vs those who reported exposure in neither.

Table 1: Odds ratio for exposure to metal dust

population about 3.5 million) in the Trent Region between October, 1992, and March, 1994, by regular inspection of lung function results, local diagnostic registers, and inpatient coding data. Clinical records for each potential case were inspected. A case of CFA was defined by a histological diagnosis from an open lung biopsy or by the following diagnostic criteria: basal inspiratory pulmonary crackles; bilateral interstitial lung shadowing on chest radiograph; no documented history of exposure to asbestos or other recognised fibrogens, including birds; no clinical evidence of coexisting collagen-vascular disease; no other coexisting cause of interstitial lung disease; restrictive lung function (forced expiratory volume in 1 s as a percentage of forced vital capacity [% FEV₁/FVC] >70% together with FVC or transfer factor for carbon monoxide [TLCO] <80% of predicted). In the absence of restrictive lung function patients were included if there were pathognomonic changes of CFA on a high-resolution computed tomography scan.

All patients alive at the start of the study (prevalent cases) and all new cases identified during the 18 months of the study period (incident cases) were eligible. Information on characteristics at presentation (date of diagnosis, duration of dyspnoea, presence of clubbing, and pulmonary function results) were extracted from the clinical records. Cases from our previous pilot study⁴ and those diagnosed by the authors were not included.

Controls living in the same communities were identified from the local Family Health Service Authority (FHSA) lists of patients registered with the same general practitioner as the case; four same-sex individuals closest in age to the case were selected. If no controls responded, the next four closest in age to the case were selected from the list.

Occupational exposure

We asked the family practitioner for consent to approach each case and control. We sent each potential participant a questionnaire asking for details of lifetime occupational history, and in particular details of exposure to metal or wood dust and of the types of metal or wood involved. We included questions about other occupational dust exposures, lifetime history of smoking, and symptoms consistent with asthma, rhinitis, or conjunctivitis after exposure to pollen or household dust. Cases and controls were not told the hypothesis being tested. After return of the questionnaire we attempted to interview each case and control by telephone to verify data on occupational dust exposure. The initial part of the interview was structured and designed to produce a full occupational history with details of any dust exposure. After these structured questions, open questions were asked to elucidate further details about any dust exposures, however brief. At the outset of the interview the interviewer was unaware of the disease status of the subject, but it was not possible to maintain this unawareness throughout the interview. All telephone interviews were tape-recorded.

Cases and controls who did not return questionnaires were sent reminders. Since the accuracy of FHSA data lists has been reported to be limited,⁶ 100 control non-respondents were randomly selected for checking. We checked the names and addresses against the local electoral register and then telephoned the individuals to confirm their address and to ask for details of dust exposure.

Autoimmunity status

Each case and the control closest in age were visited at home so that a venous blood sample could be taken and skin-prick tests for *Dermatophagoides pteronyssinus*, grass pollen, cat fur, and *Aspergillus fumigatus* (Bencard UK) could be done. Skin tests

were taken to be positive if any allergen weal exceeded the saline response by 1 mm or more. Serum was separated and stored at -70°C until assay for rheumatoid factor and antinuclear, smooth-muscle, thyroid, and parietal-cell antibodies. Rheumatoid factor was assayed initially by latex agglutination and positive results were confirmed if the reciprocal titre was 40 or more, by gelatin agglutination. Autoimmune screening was by immunofluorescence with sections of rat liver, kidney, stomach, and oesophagus and human thyroid. IgE concentrations were measured by a kinetic ELISA technique (Melenia Immunoassay Systems, EURO/DPC Ltd, Llanberis, Wales).

Ethics approval for the study was granted by the Nottingham City Hospital Medical Ethics Committee and by the local medical ethics committee for each participating centre.

Analysis

Data from the questionnaires and telephone interviews were coded and entered on a micro-computer by one research assistant who was unaware of disease status of participants or the hypothesis being tested. Lung function was expressed as mean percentage of predicted values from the summary equations according to the European Community for Steel and Coal.⁷ For both the questionnaire and interview data-sets, dust exposures were defined from self-reported occupational histories as ever having been exposed to metal dust or wood dust, and agreement for dust exposures between the two data sources was assessed with the kappa statistic. The questionnaire and interview data-sets were then combined to produce a third data-set, made up of only individuals who reported dust exposure in both questionnaire and the telephone interview, and those who denied dust exposure in both. Similar analyses were carried out for asbestos and for other occupational dust exposures reported by more than 2% of cases or controls. We chose the 2% cut-off point since the study had insufficient statistical power to assess the effects of exposures with prevalence lower than this. Social class was assigned on the basis of occupation for the greatest number of years, according to the guidelines of the Registrar-General.⁸ Smoking histories were defined from self-reported smoking histories as ever-smoker if the subject had smoked one or more cigarettes per day for a year and never-smoker if otherwise, and quantified into pack-years (1 pack-year is equivalent to smoking 20 cigarettes a day for a year). Symptoms consistent with allergy to household dust or pollen were defined as ever allergy if the subject responded positively to questions about symptoms consistent with asthma, rhinitis, or conjunctivitis after exposure to household dust or pollen.

Matched case-control analysis was carried out by conditional logistic regression. For each of the three data-sets, the effects of each occupational dust exposure, smoking, atopy, and autoimmunity variables on disease status were first assessed by univariate analysis. The effects of those exposures significantly associated with CFA were then analysed together in a multivariate model. Multiplicative terms were included to test for interactions between the effects of allergen skin sensitivity, IgE concentrations, autoantibodies, and occupational exposures. IgE data were not normally distributed and were log transformed before analysis. To look for exposure-response relations for occupational exposures significantly associated with CFA, total dust exposures were calculated from questionnaire responses as work-years of exposure (one work-year of exposure was equivalent to 8 h of dust exposure per day for a year). The time between the end of dust exposures and diagnosis of disease was also assessed, and the attributable risk for each dust exposure calculated.⁹ Occupational exposures were then compared

Data-set	Number reporting exposure		Unadjusted analysis		Adjusted* analysis	
	Cases	Controls	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Questionnaire	30 (13.8%)	45 (7.9%)	1.92 (1.15–3.23)	0.013	1.71 (1.01–2.92)	0.048
Interview	24 (14.5%)	32 (7.8%)	2.55 (1.26–5.15)	0.009	2.58 (1.17–5.64)	0.018
Combined†	18 (11.9%)	16 (4.3%)	3.39 (1.30–8.83)	0.013	3.81 (1.11–13.1)	0.034

*Adjusted for smoking status and exposure to metal dust. †Participants who reported exposure both on questionnaire and in interview vs those who reported exposure in neither.

Table 2: Odds ratio for exposure to wood dust

between incident and prevalent cases by logistic regression with adjustment for age at diagnosis and sex.

The study was designed to include 225 cases of CFA and an average of four controls per case matched for age, sex, and community to provide more than 90% power to detect an odds ratio of 3.0, assuming an exposure prevalence in the control group of 3.0%.

Results

Participants

From the nine centres 244 cases of CFA that met the specified diagnostic criteria were identified. 225 (92%) returned completed questionnaires. 569 of a potential 1066 eligible controls returned completed questionnaires. From a random sample of 100 control non-respondents we established contact with 40, identified 21 who had either died or moved (not listed in the electoral register or their telephone numbers had been disconnected), and were unable to account for the remaining 39. Since at least 21% of potential cases identified in the FHSA lists were not available, our participating controls represented about 68% of those eligible. For seven cases (three male) we were unable to obtain a control response. Thus, 218 matched case-control sets provided questionnaire data for analysis, with an average of 2.6 controls per case. Telephone interviews were completed for 165 cases (76%); of the remainder 22 had died since returning the questionnaire, 11 reported themselves too unwell, four were deaf, seven had no telephone, one could not speak English, two refused, and six could not be contacted. Telephone interviews were completed for an average of 2.5 controls per case.

The mean age of the 218 cases was 66.6 (SD 11.3) years. 149 (68%) were men and 69 women (ratio 2.16/1). For 31 (14%) cases, a histological diagnosis from an open lung biopsy was available. All but one of the cases diagnosed histologically also met the clinical diagnostic criteria; the remaining case had obstructive lung function due to coexisting airways disease. There were 151 (69%) prevalent cases and 67 (31%) incident cases. Incident cases tended to be older than prevalent cases (mean age 69.8 [9.7] vs 65.2 [11.8] years, p=0.006) and included a higher proportion of men (78 vs 64%, p=0.072). There was no difference in mean age or sex distribution between the 218 cases who provided questionnaire data and the 165 cases interviewed or between either of these populations and the initial sample of 244 patients. The presence or absence of finger clubbing at presentation was recorded for 184 of the 218 cases; of these 93 (51%) had clubbing. This sign was more common in men than women (56 vs 39%, p=0.044). The mean percentage predicted FVC was 78.4% (21.0), total lung capacity (TLC) 69.6% (18.1), and TLCO 51.2% (18.0).

Smoking history

77% of cases and 71% of controls were ever smokers. Univariate analysis showed that a history of ever smoking was significantly associated with CFA (odds ratio 1.57 [95% CI 1.01–2.43], p=0.043). The odds of CFA

increased with pack-years of smoking but this effect was not significant (odds ratio for each additional 10 pack-years of smoking 1.05 [0.99–1.12], p=0.117).

Metal and wood dust exposure

Exposure to metal dust (table 1) and wood dust (table 2) was reported by more cases than controls, both in the questionnaire and telephone interview. The kappa values for agreement between the two data sets for history of metal dust exposure were 0.67 for cases and 0.50 for controls and for history of wood dust exposure were 0.67 for cases and 0.46 for controls. Univariate analysis of questionnaire data revealed significant associations between CFA and a history of exposure to metal or wood dust. Analysis of data from telephone interviews produced slightly stronger estimates of such associations, and analysis of the combined data-set produced the highest odds ratios for metal or wood dust exposures. No association was found between social class and CFA. Analysis of work-years of exposure revealed evidence of exposure-response relations for both metal dust (odds ratios per work-year of exposure 1.11 [1.06–1.16], p<0.001) and wood dust (1.12 [1.02–1.24], p=0.020).

Metal-dust and wood-dust exposures were reported from a variety of occupations. For metal dust the commonest job among cases was machine operator, including lathe turners and metal polishers (n=31, 57%) and for wood dust the commonest job was woodworker, including carpenters and French polishers/cabinet makers (n=14, 47%). The particular types of metal and wood dust exposure involved and their relation with CFA are listed in table 3.

In all cases, dust exposures had started at least 5 years before diagnosis. The median time between the start of exposure and diagnosis of disease was 47.5 years for metal

	Number reporting exposure		Univariate odds ratio (95% CI)	p
	Cases	Controls		
Metal dusts				
Aluminium	14 (6.4%)	26 (4.6%)	1.61 (0.82–3.16)	0.167
Brass	21 (9.6%)	32 (5.6%)	1.97 (1.10–3.52)	0.022
Bronze	4 (1.8%)	6 (1.1%)	2.09 (0.57–7.61)	0.266
Cobalt	1 (0.5%)	0	..	
Copper	15 (6.9%)	28 (4.9%)	1.56 (0.81–3.02)	0.185
Chrome	1 (0.5%)	4 (0.7%)	0.72 (0.08–6.52)	0.772
Gold	1 (0.5%)	0	..	
Iron	17 (7.8%)	39 (6.9%)	1.22 (0.65–2.29)	0.537
Lead	8 (3.7%)	4 (0.7%)	5.54 (1.63–18.8)	0.006
Manganese	0	1 (0.2%)	..	
Silver	0	3 (0.5%)	..	
Steel	40 (18.3%)	75 (13.2%)	1.72 (1.09–2.70)	0.019
Tin	1 (0.5%)	3 (0.5%)	0.90 (0.09–8.68)	0.925
Tungsten carbide	2 (0.9%)	0	..	
Zinc	3 (1.4%)	4 (0.7%)	2.02 (0.43–9.41)	0.372
Wood dusts				
Chipboard	2 (0.9%)	3 (0.5%)	1.89 (0.31–11.6)	0.491
Pine	8 (3.7%)	6 (1.1%)	3.37 (1.14–9.96)	0.028
Beech	1 (0.5%)	4 (0.7%)	0.79 (0.09–7.10)	0.834
Birch	1 (0.5%)	2 (0.4%)	1.00 (0.08–11.9)	1.000
Larch	1 (0.5%)	1 (0.2%)	2.45 (0.15–39.7)	0.529
Mahogany	6 (2.8%)	7 (1.2%)	2.07 (0.68–6.30)	0.202

Table 3: Odds ratios for exposure to specific metal dust or wood dust

	Cases (n=205)	Controls (n=192)	Odds ratio* (95% CI)	p
Rheumatoid factor	26 (12.6%)	10 (5.2%)	2.44 (1.13-5.31)	0.024
Antinuclear antibodies	77 (37.6%)	50 (26.0%)	1.70 (1.10-2.61)	0.016
Smooth-muscle antibodies	19 (9.2%)	13 (6.8%)	1.50 (0.72-3.11)	0.277
Parietal cell antibodies	5 (2.4%)	11 (5.7%)	0.30 (0.08-1.09)	0.067
Reticulum antibodies	3 (1.5%)	3 (1.6%)	1.00 (0.20-4.96)	1.000

*Based on analysis of 192 case control sets.

Table 4: Presence of autoantibodies and rheumatoid factor in cases and controls

dust and 45.5 years for wood dust. More prevalent cases than incident cases reported metal-dust exposure, though the difference was not significant (odds ratio adjusted for age, sex, and smoking 2.16 [0.97-4.81], p=0.059). There was little difference in reported wood-dust exposure between the prevalent and incident cases (1.04 [0.44-2.50], p=0.929).

The estimated attributable risks for metal-dust exposure from the questionnaire, interview, and combined data-sets, respectively, were 10.3%, 13.4%, and 12.5%; the corresponding risks for wood-dust exposure were 5.3%, 10.8%, and 7.1%.

We were able to assess occupational exposure by telephone interview in 32 of the sample of 100 control non-respondents. The proportions who reported metal-dust exposure (four, 13%) and wood-dust exposure (two, 6%) were similar to those for controls included in the study.

Other occupational dust exposures

No significant association was found between CFA and asbestos exposure (adjusted odds ratio 1.00 [0.41-2.40], p=0.997). Other occupational dusts reported by 2% or more of cases included dusts from textiles, coal, building sites, and tobacco, as well as sand. Questionnaire data suggested a significant association with exposure to textile dust (1.80 [1.10-2.96], p=0.019) and sand (1.76 [1.01-3.07], p=0.047) but not to other dusts. However, the effect of sand exposure was lost after adjustment for smoking, and neither effect of sand nor textile dust was significant in the telephone interview data-set.

Autoimmunity and atopy

Cases were significantly more likely than controls to report symptoms of allergy to household dust (1.51 [1.01-2.26], p=0.044) but there was no difference for symptoms of allergy to pollen (1.20 [0.75-1.91], p=0.440). 205 cases and 192 controls gave a venous blood sample and 194 cases and 187 controls had allergen skin tests. The frequency of positive tests was similar for cases and controls (15.5 vs 19.2%; odds ratio 0.81 [0.45-1.44], p=0.467). The geometric mean IgE concentration was also similar in cases and controls (29.6 vs 29.2 kU/L; 1.00 [0.89-1.14], p=0.917). Significantly more cases than controls had rheumatoid factor and antinuclear antibodies in their serum (table 4). There was no relation between presence of rheumatoid factor, antinuclear antibodies, positive skin-prick tests, or IgE concentration and a history of dust exposure, and no interaction or effect modification between these variables.

Discussion

This study has confirmed our earlier preliminary evidence that metal and wood dusts are independent risk factors for CFA, as well as the findings of Iwai et al,¹⁰ which also suggested that CFA is more common among workers in

some occupations believed to involve metal-dust exposure. We also found evidence of an exposure-response effect between dust exposure and disease. The estimates of attributable risk for metal and wood dust suggest that these dusts may be the cause of 10-13% and 5-10% of cases of CFA, respectively, in our local population. CFA was significantly associated with smoking, but adjustment for the effects of smoking did not greatly affect the associations with metal-dust or wood-dust exposure. By contrast with our previous study,⁵ however, we found no evidence of an association between atopy and CFA, and although rheumatoid factor and antinuclear antibodies were more common among cases than controls, the presence of these antibodies was not associated with susceptibility to the effects of dust exposure.

We used a case-control design to test our hypothesis because CFA is not common and because the duration of any lead time from exposure to presentation is likely to be long.⁹ We tried to minimise selection bias for the cases by attempting to identify and recruit all cases seen at each participating centre during the specified study period, and by setting clear diagnostic criteria relevant to usual diagnostic practice.¹¹ Since only about 10% of cases in the UK¹¹ undergo an open lung biopsy, this procedure was not required for eligibility, though the use of open lung biopsy in this series was commoner than expected. We did not include cases from our previous study,⁴ or cases we diagnosed ourselves, to avoid any possible diagnostic bias resulting from our previous findings. The participation rate among potential cases was high, and this, together with the fact that our cases were similar to those described previously^{1,2} in terms of age distribution, male/female ratio, presence of clubbing, results of lung function tests, and presence of autoantibodies, suggests that our cases were indeed generally representative.

We used individual matching of controls to avoid confounding by age and sex, and also by area of residence, since this factor will affect accessibility to particular occupations, and diagnostic and referral characteristics of the family practitioner. We cannot calculate our true control response rate precisely because of inaccuracies in the FHSA registers, but we estimated the rate to be at least 68%. The prevalence of reported dust exposures in the sample of control non-respondents whom we subsequently interviewed was similar to that for controls who responded to our questionnaire, so it is unlikely that there was much bias in control participation in relation to dust exposure. We also ensured that as far as possible our cases and controls remained unaware of the hypothesis being tested. The telephone interview to confirm the occupational histories was carried out after the questionnaires had been returned to assess possible recall bias in the questionnaire data, a particular objective being to provide controls with a further opportunity to recall dust exposures. In the event, agreement between the two data-sets was good; a smaller proportion of controls reported dust exposure during the telephone interview than on the questionnaire which suggests that controls may have tended to overestimate, rather than underestimate, dust exposure when completing the questionnaire.

Since smoking was associated with CFA, we adjusted for the effect of smoking in the analysis. This adjustment did not greatly affect the estimated effects of metal-dust or wood-dust exposure. Occupation-defined social class

was not associated with CFA and did not confound the effects of metal-dust or wood-dust exposure. No consistent associations were found with other reported occupational exposures, although the associations with textile dust and sand dust in the questionnaire data raise the possibility that other exposures are important and warrant further investigation. Our findings therefore indicate that the occupational dust exposure associations observed are specific to the exposures investigated and are unlikely to have arisen through bias or confounding in our study methods.

We found that exposure to steel, brass, and lead was specifically associated with CFA. However, we still do not know whether CFA results from exposure to these particular metals, or to other related exposures that occur in the industries involved. Exposure to certain metals can cause a wide range of respiratory diseases including asthma, bronchitis, emphysema, and acute or chronic interstitial lung diseases.^{12,13} Case reports have suggested that several metals may cause an interstitial lung disease that clinically resembles CFA.^{12,13} For example, diamond polishers exposed to cobalt dust¹⁴ and workers who polish tungsten carbide (which contains cobalt as a binding agent) may develop fibrosing alveolitis,¹⁵ and interstitial lung fibrosis has been reported in potroom workers exposed to aluminium dust¹⁶ and in aluminium welders and polishers.^{17,18} Other metals for which there are case reports of diffuse interstitial lung diseases or pulmonary fibrosis occurring as a long-term consequence of exposure include zinc,¹⁹ cadmium,²⁰ and mercury.²¹ We did not find evidence of association with these specific metal exposures, but low level exposure in the form of constituents of steel may have occurred for aluminium and cobalt.

Exposure to wood dust causes both airflow obstruction²² and extrinsic allergic alveolitis due either to exposure to fungi and moulds contained within the wood²³ or to exposure to isocyanates during the processing of wood.²⁴ There has been one case report of an interstitial lung disease resembling CFA in an individual with heavy exposure to a wood-burning stove²⁵ and a report of acute extrinsic allergic alveolitis in two subjects resulting from penicillium species contained in wood fuel chips.²⁶ In our study only pine wood exposure was significantly associated with CFA. Although exposure to pine dust may be a cause of CFA, it is also possible that this exposure may be merely a marker for other exposures encountered while working with wood. For example, carpenters may also work with asbestos sheeting, and French polishers are exposed to many solvents. Although exposure to asbestos was specifically sought, residual effects of unreported exposures cannot be excluded.

The finding of a significant association between CFA and smoking contrasted with the results of our pilot study⁴ but is supported by one previous report¹⁰ and by the high incidence of smoking reported from clinical case series.^{2,27} Smoking may cause alveolitis,²⁸ but it is possible that patients with CFA who smoke have worse lung function than those who do not and hence are more likely to present with symptoms of disease. One implication of the association of smoking with CFA is that in assessing the effects of an occupational exposure it is important to consider potential confounding by smoking in the analysis; no such allowance was made in the two previous case-control studies of occupation in CFA.^{4,10} In our study, however, adjustment for smoking did not influence

the effect of dust exposures appreciably, so it is likely that smoking and metal-dust or wood-dust exposures are independent.

In our pilot study we found that patients with CFA were more likely to report symptoms consistent with atopy than controls and to have higher concentrations of IgE and a higher prevalence of positive skin-prick tests. However, this study did not confirm those findings. Our results confirmed that CFA is associated with autoantibodies and rheumatoid factor,²⁹ but there was no interaction between autoantibody or rheumatoid factor status and occupational dust exposure. The presence of autoantibodies and rheumatoid factor may represent a non-specific result of lung injury, as is believed to be the case in asbestosis.³⁰

We conclude, therefore, that our findings represent new evidence that CFA occurs in association with exposure to metal or wood dust, and that these associations are independent and dose related. The combined attributable risk of these exposures in our population was about 20%, which indicates that a substantial proportion of cases of CFA, and of the approximately 1000 deaths from CFA in England and Wales each year,³ are potentially preventable through measures to control these dust exposures. Although the cause of most cases of CFA remains unexplained our findings challenge the concept that this is a disease of unknown aetiology.

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Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty

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Summary

Background In-vitro studies indicate that platelet function and the coagulation cascade are impaired by hypothermia. However, the extent to which perioperative hypothermia influences bleeding during surgery remains unknown. Accordingly, we tested the hypothesis that mild hypothermia increases blood loss and allogeneic transfusion requirements during hip arthroplasty.

Methods Blood loss and transfusion requirements were evaluated in 60 patients undergoing primary, unilateral total hip arthroplasties who were randomly assigned to normothermia (final intraoperative core temperature 36.6 [0.4]°C) or mild hypothermia (35.0 [0.5]°C). Crystallloid, colloid, scavenged red cells, and allogeneic blood were administered by strict protocol.

Findings Intra- and postoperative blood loss was significantly greater in the hypothermic patients: 2.2 (0.5) L vs 1.7 (0.3) L, $p < 0.001$. Eight units of allogeneic packed red cells were required in seven of the 30 hypothermic patients, whereas only one normothermic patient required a unit of allogeneic blood ($p < 0.05$ for administered volume). A typical decrease in core temperature in patients undergoing hip arthroplasty will thus augment blood loss by approximately 500 mL.

Interpretation The maintenance of intraoperative normothermia reduces blood loss and allogeneic blood requirements in patients undergoing total hip arthroplasty.

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Introduction

Mild perioperative hypothermia (core temperature 34–36°C) results from intraoperative heat loss and anaesthetic-induced inhibition of normal thermoregulatory control.¹ Postoperative restoration of a normal core temperature typically requires several hours,² increasing the duration of hypothermia well beyond the time in surgery. Although intraoperative hypothermia can easily be prevented,³ it remains common;⁴ no prospective randomised study has shown adverse outcomes as a result of mild hypothermia.

In-vitro studies suggest that perioperative hypothermia may aggravate surgical bleeding by impairing platelet function and directly reducing clotting factor enzyme function.^{5,6} Hypothermia increases the bleeding time, an inhibition apparently related to defective thromboxane A₂ release, upregulation of platelet surface protein GMP-140, and downregulation of platelet glycoprotein Ib-IX complex.⁵ Furthermore, hypothermia prolongs both the prothrombin (PT) and partial thromboplastin (PTT) times—most likely via direct inhibition of clotting factor enzyme function.⁶

Despite in-vitro evidence that hypothermia impairs coagulation, the extent to which mild perioperative hypothermia increases bleeding during surgery remains unknown. Accordingly we tested the hypothesis that a policy of maintaining normothermia reduces blood loss and allogeneic transfusion requirements during hip arthroplasty. This is a relatively standardised operation associated with considerable microvascular blood loss.

Methods

We evaluated blood loss and transfusion requirements in patients undergoing initial, unilateral total hip arthroplasties at the Hospital of Amstetten, Austria. The study was approved by review boards at the Hospital of Amstetten, the University of Vienna, and the University of California at San Francisco; written informed consent was obtained from participating patients. We studied 60 patients because a preliminary study indicated that this number would provide about an 80% chance of identifying a significant hypothermia-induced increase in

similar to ticlopidine, which is known to have severe adverse effects on blood cells.² Nevertheless, a loss of taste has not been described in patients given ticlopidine.²⁻⁵

A 76-year-old woman with transient vertebrobasilar ischaemia was given clopidogrel, 75 mg daily, because she had mild gastric disorders when treated with aspirin, 300 mg daily. She had a history of mammary carcinoma (1979) without radiotherapy or chemotherapy, sarcoidosis (1982), and a hyperfunctioning thyroid adenoma that was surgically removed (1983). After discontinuation of aspirin treatment the gastric disorders disappeared. About 6 weeks after the start of the clopidogrel treatment the patient observed a loss of taste. Smell was not impaired. Findings of cranial computed tomography, routine laboratory tests, and electroencephalogram were normal. 3 weeks after the taste loss was observed, clopidogrel treatment was discontinued. 20 days later, the patient recognised the taste of red and white currants. Within a few days, there was full recovery of taste.

A 64-year-old man with transient cerebral ischaemia who was receiving aspirin treatment (300 mg daily) had been given clopidogrel, 75 mg daily for 2 months, when loss of taste was observed. Smell was not impaired. The clopidogrel treatment was stopped and aspirin was resumed. Full recovery of the loss of taste was observed within 6 weeks, but another transient cerebral ischaemic attack occurred. Therefore, the clopidogrel treatment was resumed but with a different preparation (Iscover, Bristol-Myers Squibb, München, Germany, rather than Plavix, Sanofi Winthrop, München, Germany). About 2 weeks later, the patient again reported a loss of taste. Therefore, the treatment was discontinued again. 6 weeks later the loss of taste persisted.

Several mechanisms could lead to ageusia.³ Information from the manufacturer suggests that ticlopidine and clopidogrel are metabolised in the thiophene ring, which includes ring opening. The active metabolite of clopidogrel has a carboxylic group and a sulphhydryl group as a result of ring opening. In contrast, the active metabolite of ticlopidine has not been reported. Detailed information about metabolites of the two drugs is not available. Therefore, we cannot draw conclusions about the mechanistic background of this rare adverse effect.

In addition to the two cases we describe, only one unpublished case has been reported to the German regulatory authorities.

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Risk of cryptogenic fibrosing alveolitis in metal workers

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We report increased proportional mortality from cryptogenic fibrosing alveolitis in the workforce of a major UK engineering company. Measures of metal exposure from unbiased historical occupational records showed that among employees who have worked with metal, the risk of death from or with cryptogenic fibrosing alveolitis increased in relation to the duration of metal-working.

Retrospective case-control studies suggest that the risk of cryptogenic fibrosing alveolitis (CFA) may be greater in people who have worked with metal or wood.¹⁻³ To exclude the possibility that these findings have arisen from biased recall of occupational exposure, we estimated proportional mortality and the relation between death from or with CFA and metal-work exposure, by the use of unbiased archived occupational histories and pension-fund mortality data from the workforce of a major UK engineering employer.

Participants were identified from death certificates held in pension-fund records of employees working for Rolls-Royce Plc at UK sites in Derby, Coventry, Newcastle, East Kilbride, and Bristol. Cases of CFA were defined as those in which the terms cryptogenic fibrosing alveolitis, fibrosing alveolitis, or idiopathic pulmonary fibrosis were recorded anywhere on the death certificate. A random sample of controls was selected at a ratio of about ten controls per case, from deaths with no mention of fibrotic lung disease. We estimated the proportional mortality ratio (PMR) for death from or with CFA in this cohort by indirect standardisation for age and sex relative to national all-mention mortality data for 1986,⁴ the second of only 2 years for which all-mention mortality data were provided for England and Wales and the year closest to the median age at death of our cohort. To estimate indirectly whether the prevalence of smoking in our cohort was likely to be higher than the national average we also calculated the cohort PMR for lung cancer. Lifetime occupational data were obtained from individual employment records held by the company for each employee, and each job was coded according to whether it involved work with metal, by a Rolls-Royce occupational hygienist who was not aware of case or control status. The effect of ever having worked with metal on the risk of death from or with CFA was then estimated by logistic regression with adjustment for sex and age at death and analysed in relation to duration of exposure among the population of exposed cases and controls. We then carried out posthoc subgroup analyses to examine the effect of specific metal-working occupations and individual metal exposures. All analyses used STATA (version 5).

We identified 20 526 death certificates in the pension-fund archive, documenting deaths occurring between 1967 and 1997 (table 1). Median age at death was 71 years (range

Site	Years available	Total deaths	CFA deaths	CFA deaths per 1000	Occupational records located for cases	Number of controls selected	Occupational records located for controls
Derby	1969-95	4911	16	3.3	13 (81%)	156	123 (79%)
East Kilbride	1968-97	4979	5	1.0	1 (20%)	141	53 (36%)
Bristol	1973-95	3977	17	4.3	7 (41%)	124	49 (40%)
Newcastle	1967-93	3834	10	2.6	1 (10%)	109	11 (10%)
Coventry	1973-95	2825	7	2.5	0	91	0
Total	..	20 526	55	2.7	22 (40%)	621	236 (38%)

Table 1: Analysis of death certificates and occupational records

Occupation	Cases (n=13)	Controls (n=125)	Odds ratio (95% CI)
Engineers	1 (5%)	6 (3%)	1.76 (0.19–16.5)
Furnace men	1 (5%)	20 (8%)	0.51 (0.06–4.23)
Machinists	5 (23%)	73 (31%)	0.72 (0.23–2.27)
Toolmakers	0	2 (1%)	
Fitters	2 (9%)	24 (10%)	0.93 (0.19–4.68)
Electricians	1 (5%)	2 (1%)	5.50 (0.38–79.9)
Sheet-metal workers	4 (18%)	2 (1%)	21.0 (3.47–141.9)
Welders	0	5 (2%)	
Coach builders	0	14 (6%)	

Table 2: Breakdown of jobs involving metal exposure listed in lifetime occupational records

17–102) and median year of death 1988. 86% were male. There were 100 deaths for which any fibrotic lung disease was mentioned on the certificate, of which 55 (93% male, 2·7 per 1000 of the cohort) met our case definition for death from or with CFA. This number was significantly greater than the estimated 39·5 (1·9 per 1000) deaths from or with CFA expected in the cohort from national mortality rates. The PMR for death from or with CFA in the Rolls-Royce workforce was 1·39 (95% CI 1·07–1·82; p=0·02). The PMR for lung cancer was not increased (0·97 [0·93–1·02], p=0·2).

We were able to locate occupational records for 22 (40%) cases and 236 (38%) controls; the remaining records (including all those at one site) had been lost or destroyed. The median ages at death for these cases and controls were 68 and 69 years, and the median years of death 1987 and 1988, respectively. There were 13 (59%) cases who had worked with metal compared with 125 (53%) controls (odds ratio adjusted for age and sex 1·08 [0·44–2·65], p=0·9). The median duration of work with metal in cases was 9·3 years (IQR 5·7–20·2) and 5·4 years (2·4–14·4) in controls. Among employees exposed to metals there was a direct relation between duration of exposure and the risk of CFA (odds ratio per 10 years 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 analysis of specific job titles involved subgroups of very small numbers but cases were more likely to have been sheet-metal workers (table 2). There was also a non-significant increase in risk associated with having worked with lead, cadmium, or silver.

The risk of death from or with CFA in this cohort was low, but significantly higher than expected from national mortality data. This finding is unlikely to be due to confounding by cigarette smoking, since proportional mortality for lung cancer in the cohort was not increased. Although in qualitative terms there was no significant increase in the risk of death from or with CFA associated with metal-work exposure, the 95% CI for the qualitative odds ratio estimate were broad and included those reported previously.^{2,3} We did not find any significant association between CFA and individual metal exposures, but there was a non-significant association with lead exposure, which is consistent with our findings in a previous study.³ The increased risk of CFA in sheet metal workers suggests that this occupation in particular needs further investigation.

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Hirudin treatment in a breastfeeding woman

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We report on a breastfeeding woman with deep venous thrombosis treated with hirudin because of heparin-induced thrombocytopenia, in whom hirudin was not detectable in human breastmilk.

Hirudin is a direct thrombin inhibitor, recommended for anticoagulation of patients with acute coronary syndromes^{1,2} and the immunological type of heparin-induced thrombocytopenia (HIT).³ The safety of hirudin in pregnancy and during breastfeeding has not been investigated.

A 34-year-old breastfeeding woman (weight 50 kg, height 168 cm) developed a deep vein thrombosis in her calf 7 weeks after delivery and was treated with low-molecular-weight heparin (LMWH) subcutaneously (2×5000 U Fragmin P forte, Pharmacia & Upjohn, Erlangen, Germany). On day 20 of heparin treatment, her platelet count decreased from 352 000/ μ L to 239 000/ μ L and repeated heparin-PF4-antibody-assays (ELISA) were positive, indicating HIT. LMWH treatment was discontinued and 50 mg lepirudin twice daily (Refludan, Hoechst Marion Roussel, Bad Soden, Germany) was given subcutaneously. Plasma hirudin concentrations were 0·5–1·0 mg/L 3 h after injection. Because she wanted to continue breastfeeding, hirudin was measured in breastmilk 3 h after subcutaneous hirudin administration. Measurement was by use of a chromogenic substrate assay, developed to measure hirudin in plasma.⁴ To separate the fat from the breastmilk before measurement, 100 μ L hydrochloric acid was added to 2 mL breastmilk, the mixture was heated at 56°C for 15 min then centrifuged three times for 20 min each at 2000 g.

The test was calibrated with an untreated volunteer's breastmilk, to which hirudin in concentrations of 0·1–1·5 mg/L were added before separation of fat. The lower detection limit was 0·1 mg/L. After subcutaneous lepirudin administration 50 mg twice daily, no hirudin could be detected in breastmilk of the nursing mother, although her plasma hirudin level was within the therapeutic range (0·73 mg/L). Breastfeeding was continued during the period of hirudin treatment for 3 months. Platelet counts reached baseline values 6 days after discontinuation of LMWH. The heparin-PF4-antibody assay titres decreased at the same time, and the test result became negative 6 days after discontinuation of LMWH. Neither thromboembolic nor bleeding events occurred in mother or infant.

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- Topol EJ, Fuster V, Harrington RA, et al. Recombinant hirudin for unstable angina pectoris. A multicenter, randomized angiographic

Idiopathic Pulmonary Fibrosis

Epidemiologic Approaches to Occupational Exposure

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Idiopathic pulmonary fibrosis (IPF) risk-related factors were epidemiologically investigated on the basis of 1,311 Japanese IPF autopsy cases selected from the annual compilations of autopsy data records in Japan during a 12-yr period. Age and sex distribution of the subjects revealed a high peak in their seventh decade with males predominating. The IPF rate was more than two times higher ($p < 0.01$) among subjects engaged in occupations that exposed them to dust or organic solvents compared with those in other jobs. To ascertain job characteristics, an autopsy-case control study was conducted using other annual volumes of the autopsy data records and a similar tendency was observed. Then, a live-case control study was undertaken of 86 subjects with IPF. A significantly higher odds ratio was noted among metal production workers and miners compared with healthy and hospital control subjects (1.37 and 1.34, respectively, $p < 0.01$), and also a significantly lower odds ratio among subjects who frequently eat fish. Taken together with results of recent *in vitro* studies, the intrapulmonary deposition of hazardous dusts, especially metallic dusts, appears to play at least a partial role in initiating IPF. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. **Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure.** Am J Respir Crit Care Med 1994;150:670-5.

Idiopathic pulmonary fibrosis (IPF), initially described by Hamman and Rich (1) in 1944 as acute interstitial fibrosis of the lung, is now accepted as a chronic disease entity (2). Its pathologic findings are nearly identical to UIP (usual interstitial pneumonia) according to Liebow's classification (3). The term "cryptogenic fibrosing alveolitis" is also synonymous (4).

An autoimmune mechanism has been implicated in chronic IPF pathology because fibrotic changes in IPF are sometimes similar to those in collagen vascular disorders. Deposition of immune complex and neutrophil accumulation in the alveolar walls have been suspected to be followed by complement or platelet activation, causing endothelial damage through oxygen radicals of neutrophil origin, resulting in alveolar damage in the acute phase of the disease (5-8). In relation to the fibrotic process, studies have also demonstrated the activation of alveolar macrophages that regulate collagen fiber synthesis (9-11) and on the cytokine network involving agents such as transforming growth factor (TGF) and fibroblast growth factor (FGF) released from alveolar or interstitial macrophages and others (12-14).

Pathologic changes of IPF mimic lung fibrosis associated with collagen diseases in which the autoimmune mechanism is considered an important pathogenic factor. However, characteristics of IPF pathology are exclusively the development of pulmonary interstitial fibrosis with no extrapulmonary or systemic lesions.

These findings suggest that some environmental noxious agents inhaled into the lung initiate and regulate IPF pathologic processes. In our previous epidemiologic study using an X-ray population survey, a higher incidence of IPF was found in older males than in females and in rural populations than in urban (15). To investigate the involvement of environmental factors in the initiation of IPF, epidemiologic studies were conducted including three substudies: two autopsy record studies and one live-case control study.

METHODS

Substudy 1. Epidemiologic Studies by Pathologic Data Books

The *Annals of the Pathological Autopsy Cases in Japan* (APACJ), published annually since 1957 by the Japanese Society of Pathology, collect annual autopsy records from medical institutions that have more than 100 beds and with which members of the Society are affiliated. The items reported are: sex, age, job, clinical diagnosis, main and associated pathologic diagnosis, and whether treated with antibiotics, anticancer drugs, radiation, and steroid hormone, along with the code of the institution. Such information is kept in the Society's host computer (ACOS; NEC, Inc., Tokyo, Japan), using custom software written for this purpose. APACJ covers about 90% of autopsy cases in Japan, where overall autopsy rate ranges from 5 to 6%. A complete autopsy is performed on almost all of the subjects reported. Histologic examinations are usually made of one or more sections of each organ, and one or more sections of each lobe of affected lungs. The information on the computer is available only to members of the Society and to scientists introduced by a member with APACJ Committee approval.

Of 393,258 cases included in APACJ during the 12-yr period from 1974 through 1985, 2,714 cases with the main pathologic diagnosis of chronic interstitial pneumonia or pulmonary fibrosis were reported. After their records were reviewed, 1,403 cases of nonidiopathic pulmonary fibrosis were excluded according to the following criteria: (1) persons under 15 yr of age, to exclude viral pneumonia; (2) persons having pulmonary fibrosis associated with collagen disease; (3) persons treated with radiation therapy; (4) persons treated with anticancer drugs and those with suspected

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TABLE 1
NUMBER OF IPF AND TOTAL AUTOPSIES BY AGE AND SEX (1974-1985)

Age (yr)	Male			Female			Both Sexes		
	IPF Autopsy	Total Autopsy	%	IPF Autopsy	Total Autopsy	%	IPF Autopsy	Total Autopsy	%
15-19	1	2,147	0.05	0	1,223	0.00	1	3,370	0.03
20-29	8	4,996	0.16	11	3,720	0.30	19	8,716	0.22
30-39	18	10,046	0.18	25	7,751	0.32	43	17,797	0.24
40-49	43	23,535	0.18	47	14,893	0.32	90	38,428	0.23
50-59	129	43,318	0.30	71	24,673	0.29	200	67,991	0.29
60-69	236	55,902	0.42	123	33,336	0.37	359	89,238	0.40
70-79	294	53,897	0.55	157	33,162	0.47	451	87,059	0.52
80+	107	16,486	0.65	41	12,890	0.32	148	29,376	0.50
Total	836	210,327	0.40	475	131,648	0.36	1,311	341,975	0.38

drug-induced pneumonitis; (5) lung fibrosis associated with pneumoconiosis; (6) lung fibrosis associated with viral or bacterial infection; (7) lung fibrosis of localized or unilateral involvement; and (8) cases of bronchiolitis obliterans and diffuse alveolar damage (BIP), desquamative interstitial pneumonia (DIP), giant cell interstitial pneumonia (GIP), and lymphoid interstitial pneumonia (LIP) according to Liebow's classification.

The remaining 1,311 autopsy cases were assessed as IPF, and analyzed by age, sex, residence, job (according to the Japanese Standard Job Category), clinical diagnosis, and other factors. To make a random control sampling from the same APACJ used for the case selection, every 100th case was selected from all 393,258 cases in the annuals to identify their jobs. The number of jobs thus obtained from 1/100 sampling was multiplied by 100 to compare job categories between the cases and control subjects.

Substudy 2. An Autopsy Case Control Study on the APACJ Annuals

Although the APACJ reporting instructions request the longest or last job category, the following three groups were excluded because of the limited information on their actual job types: (1) unemployed older persons, because previous jobs were not available; (2) company or governmental employees, because they were a mixture of white and blue collar workers; (3) housewives, because some of them worked part-time in dusty environments. To compare job distribution in terms of occupational exposure between case and control subjects, a case control method was employed. The number of workers in each job category was so small that the following dust-related and organic solvent vapor-related jobs were combined into an occupational exposure group in reference to results of Substudy 1: metal production workers, iron production workers, miners, shipbuilding workers, lathe workers, plasterers, glassworkers, wood production workers, texture workers, boilermen, painters, leather workers, gild workers, and laundry workers. On the other hand, a nonoccupational exposure group was defined consisting of teachers, lawyers, students, doctors, and workers in 33 other job categories. These IPF cases and control subjects were obtained from more recent annuals of APACJ for the years 1986 through 1989.

In Substudy 2, the cases evaluated as interstitial pneumonia were also subjected to study with interstitial lung fibrosis (IPF). All cases were reviewed to exclude nonidiopathic cases as was done in the preceding substudy. The 615 revised cases were divided into the following three groups: Group 1, 63 cases evaluated as acute interstitial pneumonia; Group 2, 266 cases evaluated as chronic interstitial pneumonia or interstitial lung fibrosis (IPF); and Group 3, 286 cases evaluated as interstitial pneumonia without acute or chronic qualification.

Two control subjects to each case, chosen from the same APACJ annuals, were matched by sex, age (± 5 yr), and residential area. These controls consisted of persons who died from a nonrespiratory disease and those who died from non-IPF respiratory disease, mostly lung cancer. A job comparison was made between the case group and both types of controls.

Substudy 3. A Live-Case Control Study

This study was performed as a joint undertaking of two research commit-

tees. The Research Committee on Interstitial Lung Disease and the committee on Intractable Disease Epidemiology; it was sponsored by the Ministry of Health and Welfare. Eighty-six IPF cases evaluated by the committee members were collected from 12 prefectures according to the following criteria: bilateral reticulonodular shadows with honeycombing predominantly situated in the outer zone of the lower lung field on routine chest X-ray or computed tomographs, in association with three or more clinical findings of cough, dyspnea, fine crackles, accelerated blood sedimentation rate, decreased lung volume, decreased diffusion capacity or hypoxemia. Diffuse lung fibrosis of known etiology, e.g., pneumoconiosis, tuberculosis, chronic bronchitis, diffuse panbronchiolitis, hypersensitivity or drug-induced pneumonitis, and sarcoidosis or collagen disease-associated lung fibrosis were excluded.

Two healthy control subjects from the voter's list and a hospital control of non-IPF respiratory diseases from the same hospitals as the cases were chosen. These controls were matched with each case regarding sex, age (± 5 yr of age), and residential area.

A total of 344 case and control subjects (86 cases in each group) who consented to join the study were requested to be interviewed by experienced interviewers at clinic or bedside for the cases and at home or elsewhere for healthy control subjects. Questionnaire items covered 217 variables relating to food, beverage, smoking habits, hobbies, previous illness, domestic chemicals, occupational history, residential area, and so forth. These variables were analyzed by an unconditional logistic model to estimate relative risks for IPF cases. Statistical significance of the differences was evaluated by chi-square tests.

RESULTS

Statistical Analysis of IPF Cases Reported in APACJ

Initial studies were made on the 1,311 IPF cases (0.38%) over 15 yr of age selected from 341,945 autopsy cases reported in the APACJ from 1974 through 1985. IPF cases demonstrated a marked increase with age in males, peaking in the seventh decade (Table 1). Because the autopsy rate in each sex and age group of the general population differs, the number of IPF autopsy cases was adjusted by autopsy rate in each gender and age group to estimate IPF mortality in the general population. Estimated mortality increases markedly with age in both sexes, peaking in the eighth decade. Males older than 40 yr of age consistently showed higher rates than females of corresponding ages (Figure 1). IPF mortality per 100,000 population was estimated to be 3.3 in males, 2.5 in females, and 3.0 in both sexes.

The frequency of IPF cases in each job group was calculated to compare with that of control cases (equal to all cases minus specific job cases). Occupations showing significantly higher IPF frequency ($p < 0.01$) were laundry workers, barbers, beauticians, painters, production metalworkers, and production woodworkers (Table 2).

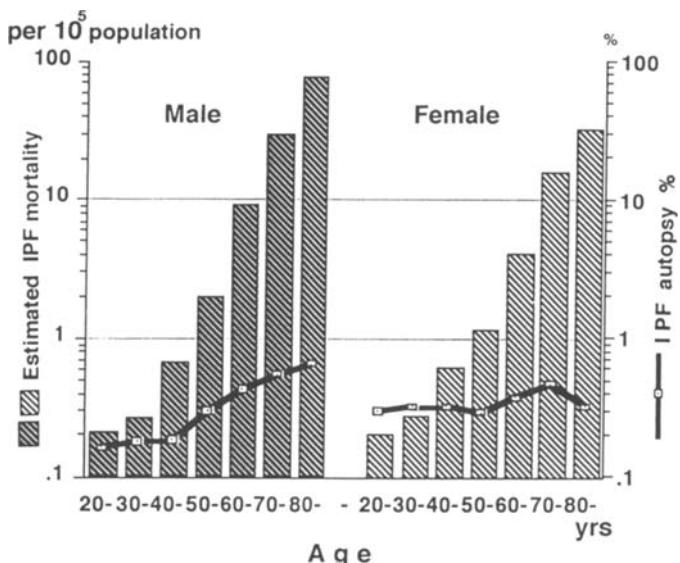


Figure 1. Estimated IPF mortality in the general population and IPF autopsy rate by age and sex. IPF mortality was estimated by adjusting the IPF autopsy number using autopsy rates of each age group and sex. After this adjustment, IPF mortality showed a markedly high rate in old people with males predominating.

Autopsy Case Control Study

The second substudy included three groups of IPF cases: acute interstitial pneumonia (Group 1), chronic IPF (Group 2), and cases of unknown course (Group 3) recorded in APACJ during the 4-yr period from 1986 through 1989.

In Group 1, composed of 63 acute cases, no difference in oc-

cupational exposure was noted between case and control groups for nonrespiratory disease. Group 2, composed of 266 subjects with chronic IPF, showed an odds ratio of 2.80 (95% confidence interval [CI]: 1.09–7.22, $p < 0.05$) to the nonrespiratory disease controls, and Group 3, composed of 286 cases of unknown course, showed a ratio of 1.86 (CI: 0.98–3.55, not significant [NS]) to the nonrespiratory disease controls. The odds ratio over the total 615 cases to the nonrespiratory disease controls was 2.0 (CI: 1.16–3.08, $p < 0.01$). The odds ratios to the respiratory disease controls showed no significant differences in any of the three groups (Table 3).

Live-Case Control Study

Sex and age distribution of the cases revealed that males predominated, especially in subjects 60 to 79 yr of age (Table 4) in both the case and control groups, as seen in the preceding autopsy cases. The results of analysis of these 53 male and 33 female sets are shown in Table 5. A statistically significant relative risk was observed in the job group of cadmium, chromium, and lead metal production and mine workers. This group produced a relative risk of 1.34 (CI: 1.14–1.59, $p < 0.01$) to the healthy control group and 1.37 (CI: 1.08–1.73, $p < 0.01$) to the hospital control group. One factor showing a significantly low relative risk to both control groups was "often eat fish." The relative risk was 0.48 (CI: 0.30–0.88, $p < 0.05$) to healthy control subjects and 0.35 (CI: 0.15–0.83, $p < 0.05$) to hospital control subjects.

Variables that showed a positive odds ratio above unity to healthy control subjects only were smoking (RR = 2.9, $p < 0.01$), previous pneumonia (RR = 3.12, $p < 0.01$), previous antibiotics intake (RR = 3.34, $p < 0.01$), residence in agricultural area (RR = 3.10, $p < 0.05$), and inhalation exposure to agricultural chemicals (RR = 3.32, $p < 0.05$). A significantly lower odds ratio below unity

TABLE 2
FREQUENCY OF IPF IN AUTOPSY CASES OF VARIOUS JOBS

Job Category	No. Jobs in Total Autopsy* (A)	No. IPF Autopsies (B)	IPF in Jobs (B/A, %)	p Value†
Company worker, teacher, lawyer, author, clergy, student, live-in renter	77,300	243	0.31	NS
Artist, sculptor, photographer	1,200	6	0.50	NS
Doctor, pharmacist, nurse, midwife, physical therapist	8,600	26	0.30	NS
Housewife, housekeeper, hotelkeeper, cook	87,900	245	0.28	NS
Shopkeeper, house-to-house salesperson	15,900	72	0.45	NS
Driver, busguide, railwayworker, ship's crew, boilerman	8,000	24	0.30	NS
Laundry worker, barber, beautician	1,300	12	0.92	< 0.001
Painter	800	10	1.25	< 0.001
Production metalworker	2,300	29	1.26	< 0.001
Production woodworker	800	8	1.00	< 0.001
Other factory production worker	15,400	56	0.36	NS
Carpenter, door-and-window fitter, plasterer	8,400	27	0.32	NS
Farmer, forestry, livestock worker	27,100	93	0.34	NS
Fishery worker	1,600	3	0.19	NS
Miner	1,500	5	0.33	NS
Physical laborer	4,300	11	0.26	NS
Occupation unknown, unemployed	130,600	441	0.26	
Total	393,000	1,311	0.33	

* Number of cases extracted from the total autopsy cases at a 1/100 extraction rate was multiplied by 100.

† p Value in chi-square test was obtained by comparison between the IPF rate in a job and that in the total job from which the objective job was excluded.

TABLE 3

ODDS RATIO ABOVE UNITY FOR OCCUPATIONAL EXPOSURES TO NONRESPIRATORY AND RESPIRATORY DISEASE CONTROL SUBJECTS IN THE THREE DISEASE GROUPS

Cases*	Nonrespiratory Disease Controls		Respiratory Disease Controls	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Group 1	1.55	0.37-6.70	1.05	0.31-3.64
Group 2	2.80	1.09-7.22†	1.22	0.68-2.20
Group 3	1.86	0.98-3.55‡	1.10	0.64-1.90
Total	2.00	1.27-3.16§	1.04	0.60-1.80

* Group 1: Acute interstitial pneumonia. Group 2: Chronic IPF cases. Group 3: Acute or chronic, indeterminable.

† p < 0.05.

‡ p < 0.10.

§ p < 0.01.

to healthy control subjects only was found for frequent intake of black tea ($RR = 0.13$, $p < 0.01$), alcohol ($RR = 0.43$, $p < 0.01$), and antihypertension drugs ($RR = 0.44$, $p < 0.05$). A significantly higher odds ratio above unity only to hospital controls was noted in subjects with a history of previous rubella infection ($RR = 11.0$, $p < 0.05$). A significantly lower odds ratio to hospital controls only was noted in previous tuberculosis ($RR = 0.22$, $p < 0.01$) and bronchiectasis ($RR = 0.16$, $p < 0.01$).

No significant difference to both control groups was noted for the following variables:

Foods: meat products, soybean products, vegetables, fruit, and green tea.

Previous illness: measles, pertussis, varicella, mumps, herpes, hepatitis, pleurisy, asthma, chronic bronchitis, and hypertension.

Medicines: antituberculous drugs, analgesics, cardiac stimulants, antidiabetic drugs, tranquilizers, and hormones.

Domestic chemicals: detergents, softeners, bleaching agents, other cleaning agents, aromatics, antimold agents, insecticides, and herbicides.

Womens' cosmetics: hair sprays, astringents, perfumes, hair dyes, lipsticks, and depilatories.

TABLE 4

AGE DISTRIBUTION OF IPF CASES AND CONTROL SUBJECTS

Age (yr)	IPF Cases	Hospital Controls	Healthy Controls
Total	86	86	172
20-29	1	1	2
30-39	1	1	4
40-49	7	5	14
50-59	20	20	37
60-69	26	33	55
70-79	26	20	51
80-	5	6	9
Male:female	53:33	53:33	106:66

Men's cosmetics: hair tonics, aftershave lotions, colognes, and hair dyes.

DISCUSSION

IPF mortality estimated from autopsy data after adjustment by autopsy rate in each age group and sex, revealed male predominance and an increase with advancing age, as seen in our previous report on IPF morbidity detected by an X-ray population survey (15). This pattern resembles that of chronic obstructive airway disease or lung carcinoma.

Occupational histories available from the autopsy records are of limited value for evaluation purposes. Some subjects might have changed jobs during their lifetime, and detailed features and doses of exposed substances are difficult to obtain. Some autopsied subjects who died at an advanced age were often reported as "no job" or "unknown." Company or government employees and even housewives who worked part-time may have worked in dusty workplaces. However, most Japanese employees rarely change jobs because of the lifetime employment system, and many craftsmen continue the same type of work because they hold an occupational license, hence the job before retirement is usually the one held the longest. Finally, taking an occupational history may result in a bias between autopsy cases and live cases.

TABLE 5
RELATIVE RISKS IN LIVE-CASE CONTROL STUDY

Variables	Hospital Controls		Healthy Controls	
	Relative Risk	95% CI	Relative Risk	95% CI
Food, beverage and smoking				
Meat	0.72	0.39-1.32	0.57	0.32-1.00
Fish	0.35	0.15-0.83*	0.48	0.26-0.88*
Shell	1.28	0.69-2.36	1.20	0.70-2.05
Milk	1.06	0.55-2.05	1.67	0.94-2.94
Vegetable	0.78	0.29-2.08	0.66	0.31-1.41
Green tea	0.67	0.19-2.36	0.70	0.26-1.91
Tobacco	1.49	0.70-3.58	2.94	1.37-6.30†
Occupational exposure				
HCN, H ₂ SO ₄	1.00		0.43	0.05-3.87
SO ₂ , CS ₂ , Cl, dye	1.00		0.86	
Cd, Cr, Pb, Zn, metal, mine	1.37	1.08-1.73†	1.34	1.14-1.59†
Spinning, paint, oil, medicine	1.28	0.97-1.67	1.61	1.06-2.42*
Residential area				
Agriculture area	2.50	0.86-6.40	3.01	1.29-7.43*
Agricultural chemicals	2.02	0.77-5.34	3.32	1.22-9.05*
Factory area	1.50	0.25-8.92	1.99	0.40-9.90
Urban and polluted area	2.18	0.74-6.48	3.33	1.26-8.79*

* p < 0.05.

† p < 0.01.

In Substudy 1, the IPF autopsy case rate was significantly high in jobs that have a probability of dust or vapor inhalation. No single job or specific substance could be identified, and exposure to mixed dust was possible in many jobs. In the group of laundry workers, barbers, and beauticians, laundry workers may be exposed to irritating vapor of organic solvents; additionally painters may be exposed to solvent vapor from painting materials. Production metal workers and woodworkers may sometimes inhale metal or wood dusts in the workplace. Although the precise exposure dose of metal or wood dusts is unknown, it is certainly higher in this group than in other job groups.

The autopsy case control study in Substudy 2, which contained more precise exposure histories, also indicated a significantly high rate of workers exposed to dusts or vapors in chronic IPF cases in comparison with control subjects with nonrespiratory disease. No difference was found in comparison with control subjects with respiratory disease, who mainly had lung cancer. It is well known from clinical observations that approximately 10% of IPF cases are associated with lung cancer (16), and our autopsy series shows an association rate of approximately 30% (unpublished data). Therefore, negative results for respiratory disease controls may be caused partly by this high proportion of lung cancer autopsy cases inevitably included with respiratory disease controls, and may be partly attributable to dust or vapor exposure related both to IPF and to non-IPF lung diseases.

Occupational exposure showed no correlation to acute cases in Substudy 2. Acute cases in this study were thought to correspond partly to Hamman-Rich syndrome, partly to acute interstitial pneumonia recently described by Katzenstein and coworkers (17), and partly to an antemortem acute exacerbation of IPF, all of which show hyaline membrane and/or cellular alveolitis as a main histologic feature with a clinical course shorter than 3 mo before death. Chronic cases are usually identified as having predominant fibrosis and honeycombing pathologically with a clinical course longer than 6 to 12 mo. The difference in occupational exposure between acute and chronic IPF cases may indicate a different pathogenicity affecting the two groups. Group 3 showed an intermediate odds ratio between Group 1 (acute) and Group 2 (chronic), probably reflecting a mixture of acute and chronic cases.

IPF cases in the live-case control study were diagnosed by using consensus clinical criteria adopted by the Japanese Committee for IPF. Sex and age distribution in this substudy resembled that reported elsewhere (4) and in the present autopsy data (Table 1). Results obtained in the present study demonstrate a significantly higher rate of metallic dust workers in IPF cases in comparison to both healthy and hospital control subjects. This result resembles that in the case-control study reported by Scott and coworkers in which a significantly higher rate of cryptogenic fibrosing alveolitis was observed in the workers exposed to metal dust, wood dust, and other workers (18). In this study, a significantly higher difference was noted between the cases and healthy control subjects than between the cases and hospital control subjects, probably because of the inclusion of many subjects with non-IPF respiratory diseases in the hospital control group. Because there is a possibility that a common pathogen or pathogens are implicated in IPF and other respiratory diseases, this may be a reason to have lowered odds ratios to hospital control subjects.

The factor of "often taking fish" showed a significantly low odds ratio regardless of the characteristics of the control groups. This unexpected result may draw some attention because there is growing consensus that the intake of polyunsaturated fatty acid, which

is abundantly present in fish oil, may reduce the risk of cardiovascular diseases (19), as well as promote metabolism and excretion of chemicals such as chlorobenzene compounds given experimentally (20). Parenteral administration of fish oil has been reported to suppress bleomycin-induced lung fibrosis in rats (21). The suppressive effect of lung fibrosis by eicosanoic acid, which is found in fish oil, is an attractive subject for further studies.

In regard to dust deposition in IPF-affected lungs, Inoue (22) and Honma and colleagues (23) found a high content of silicon in IPF-affected lung tissue by using the elementary analysis, particle-induced X-ray emission (PIXE). Monso and coworkers (24) found a high Si/S ratio in IPF-affected lung, and Ogawa and co-workers (25) demonstrated a high content of silicon, magnesium, and titanium in IPF-affected lung tissue. Hashimoto and colleagues (26) examined metal elements in the hilar and mediastinal lymph nodes using fluorescent X-ray analysis and demonstrated a significantly high content of nickel with a slightly higher content of silicon. From a histologic standpoint, typical occupational asbestos is sometimes difficult to distinguish from IPF histology. Recent pathologic observation of silicosis autopsies also demonstrated the presence of diffuse interstitial fibrosis similar to IPF in approximately 4% of the cases in addition to typical silicotic nodules (27).

It has been reported that industrial exposure to metal elements such as nickel, chromium, and cadmium might also induce lung fibrosis and/or lung cancer. The frequent association and possible shared pathogenesis of lung fibrosis and lung cancer are a recent topic of interest. Long-term inhalation studies of carbon black, diesel exhaust particles, TiO_2 , SiO_2 , talc, and asbestos fibers revealed that all kinds of particles or fibers deposited would induce fibrosis and cancer in the same lung to various extents (28). *In vitro* studies in which a mammalian cell line was cultured with a low concentration of silica particles provoked transformation of the cells which developed to sarcoma when subcutaneously injected into mice (29). Fibroblast cell lines cultured with asbestos fibers have demonstrated chromosomal aberration, depending on fiber length (30). Furthermore, cytokines such as FGF, platelet-derived growth factor (PDGF), and TGF are known to promote fibroblast growth as well as oncogenic expression and growth of the cells.

Taken together with the results in the previously cited study series and in the present study, it is possible to propose a hypothesis that in some IPF cases, hazardous dusts, especially metallic dusts deposited in the lung, or irritable vapor of organic solvents repeatedly inhaled may continuously stimulate lung cells and induce an inflammatory reaction in the lung tissue, with subsequent progressive fibrosis. The mechanisms that regulate promotion and continuous progression of the pathologic changes remain to be studied, and other factors relating to IPF pathogenesis should also be studied.

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Occupational exposure and idiopathic pulmonary fibrosis: a multicentre case-control study in Korea

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SUMMARY

SETTING: Multicentred hospital-based cases and control subjects in Korea.

OBJECTIVE: To evaluate the association between idiopathic pulmonary fibrosis (IPF) and hazardous materials to which people are occupationally exposed.

DESIGN: A multicentre, hospital-based, matched case-control study was performed. The ratio of IPF cases to controls was 1:1 ($n = 78$ in each group). IPF cases and controls were matched in terms of age group, sex and place of residence. Conditional logistic regression analysis was performed.

RESULTS: In simple logistic regression analysis, exposure to metal dust and any exposure for >1 year in an

occupational setting were significantly associated with IPF (metal dust OR 4.00, 95%CI 1.34–11.97; any exposure OR 3.67, 95%CI 1.02–13.14). After adjustment for environmental and military exposures and smoking history, the OR for metal dust exposure was 4.97 (95%CI 1.36–18.17) in multiple logistic regression analysis.

CONCLUSIONS: Metal dust was associated with incident IPF in Seoul and Gyeonggi Provinces in Korea. This information will be used to support a tailored preventive strategy in specific industries or occupations.

KEY WORDS: IPF; occupational exposure; metals; epidemiology; case-control study

IDIOPATHIC PULMONARY FIBROSIS (IPF), a form of idiopathic interstitial pneumonia, is clinically defined as progressive fibrosing interstitial pneumonia of unknown cause with a chronic clinical course.¹ Previous studies have been aimed at identifying factors associated with IPF, and occupational and environmental causes were considered as attributable risks for IPF. These studies evaluated the associations of silica,^{2–6} wood dust,^{6,7} metals^{2,3,5,7} and chemical fumes² with IPF, and were performed outside Korea, in Sweden, the United Kingdom, the United States, Mexico, Egypt and Japan. The aetiological features of occupational and environmental exposures vary because the composition of industrial materials differs among countries. IPF was associated with wood dust in Sweden⁴ and the United States,⁸ and with metal dust in the United Kingdom⁹ and Japan.¹⁰ These findings show that occupational and environmental exposures may vary according to country.

A recent Korean study has classified risk groups

according to industry or job.¹¹ Although that study attempted to identify an association between occupational exposure and IPF at the nationwide level, the industrial and job classifications used (unemployed, agriculture or fishing, sales or service, clerical or professional, and dust-exposed group) may have been too ambiguous to definitively identify materials such as wood dust, metal dust and chemical exposures as possible risk factors.¹¹

The present multicentre study was performed to evaluate the association between IPF and hazardous materials to which people are occupationally exposed in the Seoul and Gyeonggi Provinces in Korea.

METHODS

Enrolment of cases and controls

Cases were defined as patients newly diagnosed (incident cases) with IPF using chest computed tomography (CT), transbronchial lung biopsy and

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Table 1 Degree of agreement between occupational physicians in assessing exposure to potentially hazardous materials linked to idiopathic pulmonary fibrosis

Exposures	κ (95% CI)
Occupational exposure	
Silica dust	0.870 (0.782–0.957)
Wood dust	0.944 (0.835–1.000)
Asbestos fibres	0.820 (0.649–0.991)
Metal dust	0.903 (0.820–0.986)
Others*	0.711 (0.569–0.853)
Environmental exposure [†]	0.853 (0.861–0.998)
Military exposure [†]	0.926 (0.825–1.000)

* Fumes, gases, organic solvents, chemicals and cotton dust.

[†] One or more exposure.

CI = confidence interval.

video-assisted thoracoscopic lung biopsy, in line with the official American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association statement.¹ Cases were recruited from in- and out-patient clinics of the departments of respiratory medicine of four teaching hospitals, Seoul St Mary's Hospital (Seoul), Yeouido St Mary's Hospital (Seoul), Bucheon St Mary's Hospital (Bucheon, Gyeonggi Province) and Incheon St Mary's Hospital (Incheon, Gyeonggi) between 1 January and 31 December 2014. To perform a blind interview, the case list was mixed with that of controls and released to the interviewer, who was blinded to the diagnosis. Cases with collagen-vascular disease ($n = 4$), those who refused to participate in the study, those whose history was difficult to evaluate due to admission to an intensive care unit, those whose CT findings made it difficult to distinguish their condition from mycobacterial tuberculosis and/or bacterial infections and those with other types of idiopathic interstitial pneumonia besides IPF ($n = 33$) were excluded. A final total of 78 patients were eligible for inclusion in the study.

Hospital-based controls were enrolled to match each case from these hospitals over the same period of time. Patients with *Mycobacterium tuberculosis* infection, community-acquired bacterial or viral infection, pneumothorax and pleurisy were included. However, among these patients, those with work-related respiratory diseases (e.g., asthma, pneumoconiosis, chronic obstructive lung disease, lung cancer and mesothelioma) were excluded. To avoid information bias by the interviewer, the entire in- and out-patient clinic list from the respiratory physician was given to the chief occupational physician, who randomly selected eligible controls and invited two occupational physicians to perform a blinded in-depth interview. Although 123 controls were enrolled, those aged ≤ 40 years ($n = 3$) were excluded, and 120 controls were selected. After matching cases to controls, a final total of 78 controls was used for the analysis.

The study was approved by the Institutional

Review Board of the Catholic Medical Center, Seoul, Korea (ID: XC14QNNI0035K). Written informed consent was provided by the study participants.

Matching methods

The ratio of IPF cases to controls was 1:1. The age group, sex and place of residence of cases and controls were matched. Age was classified into three groups (<60, 60–79 and ≥ 80 years), and cases and controls were matched accordingly. The study population was enrolled from two hospitals in Seoul and two hospitals in Gyeonggi Province; the place of residence of cases and controls was also matched. Matching was randomised using the random matching syntax for Statistical Analysis System (Cary, NC, USA).¹²

Exposure assessment

Exposure was assessed by two trained occupational physicians (CYM and CBS) after completion of the qualitative structured questionnaire assessing environmental, occupational and military exposures. The lifetime personal history of each subject's place of residence and occupation and possible exposure to air-borne materials (silica, wood, metal, asbestos, fumes, gases, organic solvents, chemicals and cotton dust) previously linked with IPF or interstitial lung disease (ILD)^{2–7} were recorded. Duration of employment ≥ 6 months and detailed description of the tasks performed since the subject started the first job were described. Subjects exposed to potentially hazardous materials for >1 year were regarded as exposed. Detailed information about work conditions, such as use of respiratory protective equipment, hours worked per day, memory of previous work-related diseases among co-workers or themselves, exposure to hazardous materials via the respiratory tract, etc., were also recorded. Exposure to each potentially hazardous material was assessed by two independent experienced occupational physicians (MJP and CBS). Exposure probability (P) was classified into none ($P = 0\%$), low ($0\% < P \leq 25\%$), moderate ($25\% < P \leq 50\%$) and severe ($50\% < P$); those with moderate or severe exposure were considered occupationally exposed. The degree of agreement in exposure assessment by the two occupational physicians is shown in Table 1.

Environmental and military exposures were assessed using the same procedure. The history of exposure during military service was also taken at the same time as occupational exposure. Korean males undergo mandatory military service in their late teens and early twenties. Military exposures to any potential hazardous materials were recorded as yes or no (Table 1). Environmental and residential history since birth was recorded along with residential information, type of house, use of biological fuels indoors, large-scale demolition for site reconstruc-

Table 2 General and occupational characteristics after matching for age group, sex and place of residence

	Matched		
	Cases n (%)	Controls n (%)	P value
Place of residence			1.0000
Seoul	32 (41.0)	32 (41.0)	
GyeongGi	46 (59.0)	46 (59.0)	
Age, years, mean ± SD	69.6 ± 8.8	70.6 ± 9.5	0.4965
<60	11 (14.1)	12 (15.4)	0.9365
60~79	58 (74.4)	56 (71.8)	
≥80	9 (11.5)	10 (12.8)	
Sex			1.0000
Male	55 (70.5)	55 (70.5)	
Female	23 (29.5)	23 (29.5)	
Environmental exposure			0.0090
No	52 (66.7)	66 (84.6)	
Yes	26 (33.4)	12 (15.4)	
Military exposure			0.1595*
No	68 (87.2)	74 (94.9)	
Yes	10 (12.8)	4 (5.1)	
Smoking history			
Never smoker	26 (33.3)	36 (46.2)	0.1941
Ex-smoker	43 (55.1)	32 (41.0)	
Current smoker	9 (11.6)	10 (12.8)	
Pack-years, mean ± SD	34.5 ± 25.2	38.4 ± 22.9	0.4344
Occupational exposure			
Silica			
No	57 (73.1)	62 (79.5)	0.3466
Yes	21 (26.9)	16 (20.5)	
Wood dust			
No	75 (92.3)	75 (96.1)	0.4947*
Yes	6 (7.7)	3 (3.9)	
Metal dust			
No	57 (73.1)	69 (88.5)	0.0243*
Yes	21 (26.9)	9 (11.5)	
Asbestos fibres			
No	74 (94.9)	75 (96.1)	1.0000*
Yes	4 (5.1)	3 (3.9)	
Other [†]			
No	69 (88.5)	65 (83.3)	0.4909*
Yes	9 (11.5)	13 (16.7)	
Any of above			
No	35 (44.9)	43 (55.1)	0.2002
Yes	43 (55.1)	35 (44.9)	
Total	78 (100.0)	78 (100.0)	

* Fisher's exact test.

[†] Fumes, gases, organic solvents, chemicals and cotton dust.

SD = standard deviation.

tions, specific petrochemical factories or asbestos or other dust-generating factories, transporting asbestos products at railway stations, etc. Subjects exposed to hazardous materials such as silica, wood, metal, asbestos, fumes, gases, organic solvents, chemicals and cotton dust within a radius of 500 m of their house for more than 1 year were regarded as exposed.

Statistical analysis

All statistical analyses were performed using SAS 9.4 software (Statistical Analysis System, Cary, NC, USA). The degree of agreement was estimated in κ and 95% confidence intervals (CIs) calculated using the McNemar's test. The χ^2 test was used for categorical variables, and Fisher's exact test was used to calculate P values. Student's t-test was used for

continuous variables. As this was a matched case-control study, the odds ratio (OR) for any association between IPF and exposure to potentially hazardous materials was estimated using conditional logistic regression. After adjusting for environmental exposure, multiple conditional logistic regression analysis was performed (Model 1). Model 2 was fitted after adjusting for environmental and military exposure. In Model 3, multiple conditional logistic regression analysis was performed after adjusting for environmental, military and smoking exposure.

RESULTS

The characteristics of IPF cases and controls before and after matching are given in Table 2. Before matching, females were predominant in the control group ($P < 0.05$); environmental and military exposure to potentially hazardous materials and smoking history differed significantly between cases and controls. After matching, environmental exposure (cases 33.4% vs. controls 15.4%) and occupational metal exposure (cases 26.9% vs. controls 11.5%) were associated with IPF ($P < 0.05$). Twenty-five cases (vs. 10 controls) were exposed to asbestos from asbestos-containing slate roofing over a one-year period, and one case was environmentally exposed to petrochemical fumes.

The OR and 95% CIs for each hazardous material and IPF are shown in Table 3. In simple logistic regression analysis, exposure to metal dust and any exposure to occupational hazardous materials for >1 year were significantly associated with IPF (metal dust, OR 4.00, 95%CI 1.34–11.97; any exposure, OR 3.67, 95%CI 1.02–13.14). After adjusting for environmental and military exposure and smoking history, the OR for metal dust exposure was 4.97 (95%CI 1.36–18.17) in multiple logistic regression analysis.

DISCUSSION

In this multicentre case-control study conducted in Korea, metal dust was found to be associated with incident IPF. Metal dust has previously been reported to be closely associated with IPF: in a case-control study of the association between metal dust and ILD with 165 cases with cryptogenic fibrosing alveolitis and 408 local Family Health Service Authority controls in the United Kingdom, the OR of questionnaire-reported exposure to metal dust for cryptogenic fibrosing alveolitis was 1.68 (95%CI 1.07–2.65).⁷ The attributable risk for occupational metal dust exposure was estimated to be up to 13.4%. Other epidemiological studies reported ORs of metal dust exposure for IPF ranging from 1.37 to 21.00.^{3–6,9,13} These results are consistent with our findings on metal dust exposure (OR 4.97, 95%CI 1.36–18.17)

Table 3 Associations between occupational exposure and idiopathic interstitial fibrosis as determined by simple and multiple logistic regression analyses

Occupational exposure	Crude	Model 1*	Model 2†	Model 3‡
Silica				
No	Reference	Reference	Reference	Reference
Yes	1.71 (0.67–4.35)	1.62 (0.62–4.18)	1.78 (0.64–4.97)	1.24 (0.41–3.76)
Wood dust				
No	Reference	Reference	Reference	Reference
Yes	2.00 (0.50–8.00)	3.20 (0.67–15.20)	3.26 (0.66–16.02)	2.51 (0.52–12.28)
Metal dust				
No	Reference	Reference	Reference	Reference
Yes	4.00 (1.34–11.97)	3.80 (1.21–11.88)	3.36 (1.06–10.66)	4.97 (1.36–18.17)
Asbestos fibres				
No	Reference	Reference	Reference	Reference
Yes	1.50 (0.25–8.98)	1.50 (0.25–8.98)	1.50 (0.25–8.98)	1.27 (0.17–9.56)
Other				
No	Reference	Reference	Reference	Reference
Yes	0.64 (0.25–1.64)	0.70 (0.27–1.84)	0.89 (0.31–2.54)	0.89 (0.31–2.54)
Any of above				
No	Reference	Reference	Reference	Reference
Yes	3.67 (1.02–13.14)	3.67 (0.94–14.27)	3.40 (0.85–13.53)	2.67 (0.65–10.93)

* Adjusted for environmental exposure.

† Adjusted for Model 1 and military exposure.

‡ Adjusted for Model 2 and smoking history.

in multiple logistic regression analysis. Aluminum,¹⁴ cadmium¹⁵ and zinc¹⁶ may be related to pulmonary fibrosis. The underlying mechanism is unknown; however, in vitro and in vivo studies suggest that inorganic dusts and metals are related to inflammatory and fibrotic responses.¹⁷ In a study on aluminum silicates and lung fibrosis among potroom workers, aluminium particles were predominantly detected in fibrosing lung specimens.¹⁴ Another study detected aluminium dust levels 1000-fold higher than background levels among workers with diffuse interstitial fibrosis.¹⁸ In the present study, there were several incident cases with definite aluminium exposure among aluminium potroom workers, workers at a foundry for aluminium-containing materials and workers manufacturing aluminium pipes.

Wood dust and job-related exposure to birds are associated with IPF in countries other than Korea.^{2–4,7} Differences in industrial and environmental distribution as well as exposure might underlie differences among countries. In a study on occupational exposure and pulmonary fibrosis using data derived from the Swedish Oxygen Register, hardwood dust was related to pulmonary fibrosis in Swedish men (OR 2.10, 95%CI 1.22–3.75).⁴ The authors of the Swedish study suggest that wood dust exposure might be more frequent in Sweden than in other countries.⁴ In addition, a multicentre study of occupational and environmental exposure in Egypt reported that exposure to wood dust (males, OR 2.71, 95%CI 1.01–7.37) and birds (males, OR 3.49, 95%CI 1.49–8.19; females, OR 3.86, 95%CI 1.95–7.62) was associated with incident IPF cases.² Because the poultry industry, including poultry farms, has grown rapidly in Egypt, the authors concluded that a lack of appropriate

hygiene during poultry farming contributed to these results.² There are several industrial clusters related to the manufacturing of precision machinery and the electrical and electricity industry in Seoul, Incheon and Bucheon, the cities included in our study,¹⁹ and differences in baseline industrial or environmental exposure should be carefully considered.

The OR for each exposure for incidental or prevalent pulmonary fibrosis or IPF might differ according to study design and the source of cases and controls (Table 4). In a study using a factory-based registry with individual employment records, the OR for metal exposure in pulmonary fibrosis was 21.0.⁹ However, the ORs for IPF were much lower in hospital-based case-control studies.^{3,4,7,13} The probability of meeting a possibly exposed person may be higher among factory-based subjects than among the general population and hospital-based subjects. Another reason for these discordant results is the study design. Most studies on IPF used a case-control design, which is the most appropriate approach for evaluating rare diseases. However, selection bias might arise due to the low prevalence of such diseases. To overcome this problem, a multicentre case-control study^{2,3,7,10} or a national registry may be recommended.⁴ According to Table 4 and a meta-analysis,²⁰ selection bias is less likely in such cases. A multicentre study design was therefore used here to reduce selection bias. However, as there are differences in the distribution of industries among regions, studies in other regions of Korea are needed.

Exposure assessment is an important factor for introducing discordance in study results and the statistical significance of study results. Structural questionnaires are generally adapted to assess expo-

Table 4 Previous epidemiological studies of the association between occupational exposure and idiopathic pulmonary disease

Author, year, country, reference	Study design	Source of controls and cases	Matching	Adjustment	Exposure assessment	Statistically significant result
Iwai, 1994, Japan ¹³	Case-control study	Hospital controls; healthy controls	Age, sex, region		Questionnaire	
Hubbard, 1996, UK ⁷	Case-control study	Multicentre hospital (cases); community-based (controls)	Age, sex, region		Self-reported questionnaire (cases); telephone interview (controls)	Hospital controls, OR 1.37 (95%CI 1.08–1.73) Healthy controls, OR 1.34 (95%CI 1.14–1.59)
Mullen, 1998, USA ⁶	Case-control study	Hospital (cases and controls)	Age, sex		Self-reported questionnaire	Metal dust, OR 1.68 (95%CI 1.07–2.65)
Baumgartner, 2000, USA ³	Case-control study	Multicentre hospital (cases and controls)	Age, sex, region	Age, smoking	Telephone interview	Wood dust, OR 1.71 (95%CI 1.01–2.92) Silica dust, OR 11.0 (95%CI 1.05–11.1) Metal dust, OR 2.0 (95%CI 1.0–4.0) Birds, OR 4.7 (95%CI 1.6–14.1) Silica dust, OR 3.9 (95%CI 1.2–12.7) Vegetable or animal dust, OR 4.7 (95%CI 2.1–10.4)
Hubbard, 2000, UK ⁹	Case-control study	Rolls-Royce Plc. workers (cases and controls)	Age, sex, region		Individual employment record	Sheet-metal workers, OR 21.0 (95%CI 3.47–141.9)
Miyake, 2005, Japan ¹⁰	Case-control study	Multicentre hospital (cases); hospital (controls)	Age, sex	Smoking	Doctor interview; telephone interview	Metal dust, OR 9.55 (95%CI 1.68–181.12)
Gustafson, 2007, Sweden ⁴	Case-control study	Registry-based (cases and controls); Swedish Oxygen Register	Age, sex	Smoking	Swedish Oxygen Register data; questionnaire	Smoking, OR 3.23 (95%CI 1.01–10.84)
Awadalla, 2012, Egypt ²	Case-control study	Multicentre hospital (cases and controls)			Questionnaire	Organic dust, OR 1.7 (95%CI 1.06–2.80) Wood dust, OR 2.1 (95%CI 1.22–3.75) Males Wood dust, OR 2.56 (95%CI 1.02–7.01)

OR = odds ratio; CI = confidence interval.

sure. There are two principal factors, interviewer training and estimation of possible exposure, i.e., metal or wood dust, for ensuring proper assessment of exposure. As IPF is a rare disease, differential bias may arise in estimations of ORs without proper exposure assessment, which should be performed by trained, experienced occupational physicians. As the degree of agreement between occupational physicians in exposure assessment is high (Table 1), differential information bias may have been reduced.

According to the ATS/ERS statement, the most important criterion for defining IPF is the exclusion of other known causes of ILD, such as domestic, occupational, environmental and connective disorders.¹ However, as the association between occupational exposure and IPF has been widely reported (Table 4), it may be difficult to identify any specific material as the definitive cause of IPF even in IPF patients with a history of exposure to hazardous materials. It may also be difficult to make a differential diagnosis between IPF without any exposure and ILD due to specific exposure. An operational definition, and not a definite diagnosis, is therefore necessary to diagnose specific exposure-induced ILD. Definite causes of IPF have not been previously identified, and various possible candidates for IPF have been suggested. To validate the differential diagnosis, subjects with silicosis and asbestosis were excluded from the present study. However, our results indicate that occupational exposure may be associated with IPF. This suggests that clinicians should ensure that the history of occupational and environmental exposure is systematically recorded to avoid classifying these diseases as idiopathic.²¹

There are several limitations to the present study. First, the dose-response relationship was not assessed. Baumgartner et al. reported that duration of exposure to metal dust for ≥ 5 years was significantly associated with IPF.³ The authors had estimated the proper appropriate numbers of study participants with and without specific exposure for a matched case-control study. The duration of exposure was therefore not classified in the present study. More participants should be enrolled to show the dose-response relationship in future studies. Second, the location of the participating hospitals was restricted to Seoul and Kyeonggi Provinces. Selection bias due to the restricted location also existed in previous studies with a hospital-based case-control design (Table 4). To reduce information or selection bias during enrolment of IPF cases from a single centre study, a multicentre design was adopted. Third, differential misclassification may have occurred in assessing occupational exposure. In the absence of individual employment records, this misclassification is inevitable due to recall bias.⁹ Individual employment records including the frequency of exposure

intensity (i.e., an hour per day, or 8 hours/day, etc.) was not assessed as this was a hospital-based case-control study. These limitations were overcome by history of exposure and occupational exposure being recorded by two experienced occupational physicians, and showing the degree of agreement between them. Fourth, the elimination of the possible impact of excluding patients with possible occupational exposure may have resulted in selection bias. In terms of epidemiological research, if diseases such as lung cancer, chronic obstructive pulmonary disease and asthma-related occupational exposure had been included in the control group, the strength of the association between hazardous material exposure and IPF may have been underestimated. In addition, the design of the present study did not include the exploration of possible associations, as in an ecological study. The exclusion of possible occupational lung disease and the matched case-control design may have reduced potential selection bias in the study.

The present study also has several strengths. First, incident IPF cases were enrolled to follow the premise of a case-control study. Second, occupational exposure was evaluated by two occupational physicians, and the degree of agreement between them was assessed. Third, to avoid bias in the matching method for age group, sex and place of residence, a random computerised method was used.¹² Fourth, history of environmental, military and smoking exposure was adjusted for in multiple analysis.

CONCLUSIONS

Exposure to metal dust is associated with incident IPF in Seoul and Gyeonggi Provinces, Korea. There are several types of industry in Korea. A pooled analysis of IPF and occupational exposure should therefore be performed to evaluate the association between specific exposures and IPF. Such studies can be used to create preventive strategies tailored to specific industries or occupations. In future, further studies are needed of ILD or IPF induced by different occupational exposures to evaluate whether they have a different prognosis.

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R E S U M E

CONTEXTE : Etude cas témoins multicentrique en hôpital.

OBJECTIF : Evaluer l'association entre fibrose pulmonaire idiopathique (IPF) et matériaux auxquels sont exposées les personnes dans leur travail dans un endroit bien précis de Corée.

SCHÉMA : Une étude multicentrique cas-témoins appariés, basée dans des hôpitaux, a été réalisée. Le ratio de cas d'IPF aux témoins était de 1:1 ($n = 78$ dans chaque groupe). Les cas d'IPF et les témoins ont été appariés sur la tranche d'âge, le sexe et le lieu de résidence. Une analyse de régression logistique conditionnelle a été réalisée.

RÉSULTATS : En analyse de régression logistique simple, l'exposition à la poussière de métal et toute

exposition durant plus d'une année sur les lieux de travail ont été significativement associées à l'IPF (poussière de métal, OR 4,00 ; IC95% 1,34–11,97) ; toute forme d'exposition (OR 3,67 ; IC95% 1,02–13,14). Après ajustement sur les expositions environnementales et militaires et les antécédents de consommation de tabac, l'OR pour la poussière de métal a été de 4,97 (IC95% 1,36–18,17) en analyse de régression logistique multiple.

CONCLUSION : La poussière de métal a été associée aux cas d'IPF dans les provinces de Séoul et Gyeonggi en Corée. Cette information sera utilisée pour étayer une stratégie de prévention adaptée dans des industries ou des postes de travail spécifiques.

R E S U M E N

MARCO DE REFERENCIA: Un estudio hospitalario multicéntrico de casos y testigos.

OBJETIVO: Evaluar la asociación entre la fibrosis pulmonar idiopática (IPF) y los materiales responsables de exposición laboral en las personas de una región específica de Corea.

MÉTODO: Fue este un estudio hospitalario multicéntrico de casos y testigos emparejados. La proporción de casos de IPF y testigos fue 1:1 ($n = 78$ en cada grupo). Los casos y los testigos se emparejaron con respecto al grupo de edad, el sexo y la residencia. Se llevó a cabo un análisis de regresión logística condicional.

RESULTADOS: En el análisis sencillo de regresión logística se observó que la exposición al polvo metálico

y cualquier exposición en el entorno laboral durante más de 1 año se asociaba de manera significativa con la IPF (OR 4,00; IC95% 1,34–11,97) y con cualquier exposición (OR 3,67; IC95% 1,02–13,14). Tras ajustar con respecto a la exposición ambiental y militar y el antecedente de tabaquismo, la exposición al polvo de metal exhibieron un OR de 4,97 (IC95% 1,36–18,17) en el análisis de regresión logística múltiple.

CONCLUSIÓN: La exposición al polvo de metal se asoció con la aparición de casos IPF en Seúl y la provincia de Gyeonggi en Corea. Esta información se utilizará con el fin de fundamentar la elaboración de una estrategia preventiva dirigida específicamente a las industrias y las ocupaciones.

Occupational and Environmental Factors and Idiopathic Pulmonary Fibrosis in Japan

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Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease of unknown etiology. Environmental factors, especially occupational agents, may be of great importance in the manifestation of IPF. We examined the relationship between occupational and environmental factors and IPF in Japan. A multicenter hospital-based case-control study was performed in 2001. Included were 102 cases aged 40 years or over who were within 2 years of having been diagnosed in accordance with the most recent criteria. Controls, aged 40 years or over, were 55 hospitalized patients diagnosed as having acute bacterial pneumonia and four outpatients with common colds. Data on occupational and environmental factors were obtained from a questionnaire. Multiple logistic regression analysis was used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, sex and region. Compared with controls, cases were more likely to have been managers, officials or production workers and less likely to have been protective service or materials handling workers. Clerical and related work was significantly related to a decreased risk of IPF after further adjustment for pack-years of smoking (OR = 0.42; 95% CI = 0.18–0.95). Exposure to metal dust was significantly associated with an increased risk of IPF (OR = 9.55; 95% CI = 1.68–181.12). From 20.0 to 39.9 pack-years of smoking was significantly associated with an increased risk of IPF (OR = 3.23; 95% CI = 1.01–10.84). Our results appear to confirm data from previous epidemiologic studies. Metal dust exposure may be a particularly important risk factor for IPF.

Keywords: case-control studies; metal dust; occupations; pulmonary fibrosis; smoking

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease of unknown etiology (Selman *et al.*, 2001). The mortality rate appears

to be increasing in Western populations (Johnston *et al.*, 1990; Hubbard *et al.*, 1996a; Mannino *et al.*, 1996). Men are more likely than women to develop or die from IPF (Johnston *et al.*, 1990; Coultas *et al.*, 1994; Iwai *et al.*, 1994; Hubbard *et al.*, 1996a; Mannino *et al.*, 1996). A study in the UK found increased deaths due to IPF in traditionally industrialized areas (Johnston *et al.*, 1990). Thus,

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environmental factors, especially occupational agents, may be of great importance in the manifestation of IPF.

Four case-control studies demonstrated that exposure to metal dust was associated with an increased risk of IPF (Scott *et al.*, 1990; Iwai *et al.*, 1994; Hubbard *et al.*, 1996b; Baumgartner *et al.*, 2000). A historical cohort study in the workforce of a major UK engineering company found a dose-response relationship between years of working with metal and risk of IPF and a 21-fold increase in the odds ratio (OR) among sheet-metal workers (Hubbard *et al.*, 2000). Other occupational agents and job activities associated with IPF have been identified, including wood dust (Hubbard *et al.*, 1996b), textile dust (Hubbard *et al.*, 1996b), sand or stone (Hubbard *et al.*, 1996b; Baumgartner *et al.*, 2000), silica (Mullen *et al.*, 1998), mould in the workplace (Mullen *et al.*, 1998), agricultural chemicals (Iwai *et al.*, 1994), cattle or livestock (Scott *et al.*, 1990; Baumgartner *et al.*, 2000), vegetable/animal dust (Baumgartner *et al.*, 2000), farming (Baumgartner *et al.*, 2000), raising birds (Baumgartner *et al.*, 2000) and hairdressing (Baumgartner *et al.*, 2000). A study of death certificates in England and Wales showed that standardized mortality ratios were elevated among members of the armed forces, miners and quarrymen, service, sports and recreation workers, and electrical and electronic workers, but found no evidence of an increased risk among persons in occupations that potentially exposed them to wood and metal dust (Harris *et al.*, 2001). Cigarette smoking was related to an increased risk of IPF, although there was no clear exposure-response pattern with cumulative consumption of cigarettes in two case-control studies (Hubbard *et al.*, 1996b; Baumgartner *et al.*, 1997). Because epidemiologic information regarding the etiologic factors associated with IPF is sparse in Japan, the present study examined the relationship between occupational and environmental factors and the development of IPF, based on a multi-center hospital-based case-control study.

MATERIALS AND METHODS

Subjects

Eligible cases aged 40 years or over who were within 2 years of having been diagnosed with IPF were identified among 21 collaborating hospitals and their 29 affiliated hospitals during the period from 1 June to 30 November 2001. The diagnosis of IPF by the collaborating respiratory disease specialists was based on clinical history, clinical examination and high-resolution computerized tomography (HRCT) of the chest. Results of video-assisted thoracoscopic lung biopsy transbronchial lung biopsy and/or bronchoalveolar lavage, corresponding to the

international consensus statement on IPF of the American Thoracic Society and the European Respiratory Society (American Thoracic Society, 2002), were also used when available, either alone or in combination, to assist diagnosis. All cases had basal fine crackles through auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis and bronchiolectasis on HRCT. There was no evidence of either coexisting collagen-vascular disease or history of known occupational exposure to agents that might produce a clinical picture similar to that of IPF in any of the cases. The physicians in charge asked eligible patients to participate in this study, and 104 patients were cooperative in answering the questionnaires while three patients refused.

Control subjects, aged 40 years or over and without prior respiratory diseases, were prospectively selected from individuals who received treatment at the respiratory ward of the 21 collaborating hospitals and their 29 affiliated hospitals during the same time period as the cases. Potential control subjects consisted of 56 hospitalized patients diagnosed as having acute bacterial pneumonia and four outpatients with common colds. Only one eligible control subject who was asked to take part in this study by a physician refused to answer the questionnaire. Controls were not, individually or in larger groups, matched to cases. Few patients with acute infectious or common diseases receive treatment at a specialized medical institution. Of the 21 collaborating hospitals, 14 were university hospitals with doctors who exclusively treated patients with serious illnesses. Thus, 95 of the 104 cases were recruited from the 21 collaborating hospitals and 34 of the 60 controls were selected from 29 hospitals that were affiliated to the collaborating hospitals. All study subjects gave their fully informed consent in writing.

The study subjects were originally restricted to males, but included in the analysis were 10 female cases and five female controls whose treatment was provided at six of the collaborating hospitals and one affiliated hospital. Incomplete data in relation to cigarette smoking caused the exclusion of two male cases and one male control. There were 102 cases and 59 control subjects left for analysis.

Questionnaires

Sets of two self-administered questionnaires were handed to cases and controls by physicians. The subjects filled out the questionnaires and mailed them to the data management center. A telephone interview was conducted by a trained research technician to complete missing or illogical data.

One of the self-administered questionnaires elicited information on age, sex, type of job held for the longest period of time, exposure to 13 specific

occupational agents, smoking habits, moulds in the house, indoor domestic pets and residential municipality. Employment data focused on type of job held for the longest period of time during the subject's work life and years of exposure were requested regarding the job and occupational agents, respectively. Occupational agents were defined as present if the subject reported ≥ 10 h of exposure per week. Neither the questionnaire nor a telephone interview requested a full occupational history or gave any information to help responders recall possible exposures to occupational agents that they may otherwise have overlooked in relation to their particular occupation.

The other self-administered questionnaire was a validated self-administered dietary history questionnaire that was used to assess dietary habits over a period of 1 month (Sasaki *et al.*, 1998, 2000). In the present study, data obtained from the dietary history questionnaire were not used.

Statistical analysis

Jobs held for the longest period of time were coded using the Japanese Standard Occupational Classification and stratified into 11 major groups (professional and technical; managers and officials; clerical and related fields; sales; service; protective service; farming, fishing and forestry; transport and communication; production; materials handling; and construction and extraction). Included in this analysis were eight specific occupational agents to which three or more subjects had been exposed for more than a year. Age was classified into four categories (<50, 50–59, 60–69 and 70+ years); region into five (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu); cigarette smoking into three (never smoked, former smoker and current smoker); pack-years of smoking into five (none, 0–19.9, 20.0–39.9, 40.0–59.9, and 60.0+); and residential municipality into two (city and town or village). Multiple logistic regression analysis was used to estimate the adjusted ORs and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, sex and region. The reference category for all occupational factors, moulds in the house and indoor domestic pets was based on the comparison of those exposed to a single agent with all those unexposed, including potential subjects who were exposed to other etiologic factors. All computations were performed using version 8.2 of the SAS software package (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Dyspnea on exertion was present at enrollment in 83 of the 104 cases (81.4%). The median (90% central range) of arterial O₂ pressure was 80.2 mmHg

Table 1. Characteristics of the study population

Variable	<i>n</i> (%)	
	Cases (<i>n</i> = 102)	Controls (<i>n</i> = 59)
Sex (male)	92 (90.2)	54 (91.5)
Age (years)		
<50	3 (2.9)	2 (3.4)
50–59	15 (14.7)	19 (32.2)
60–69	56 (54.9)	24 (40.7)
70+	28 (27.5)	14 (23.7)
Region		
Kanto-Koshinetsu	56 (54.9)	27 (45.8)
Tokai	11 (10.8)	10 (17.0)
Kinki	14 (13.7)	5 (8.5)
Chugoku-Shikoku	4 (3.9)	6 (10.2)
Kyushu	17 (16.7)	11 (18.6)

(57.2–97.0) and that of vital capacity expressed as percentage predicted values was 77.8% (41.0–116.3) in cases. The proportions of male subjects among cases and controls were 90.2% and 91.5%, respectively (Table 1). Compared with control subjects, cases were older and had a lower prevalence of residence in Chugoku-Shikoku.

Table 2 presents adjusted ORs and 95% CIs for IPF in relation to occupational factors after controlling for age, sex and region. Because five female cases had never held a job, they were regarded as 'unexposed' in the occupational analyses. The median duration of the job held for the longest period of time was 35 years in cases and 31 years in controls. No marked difference was found in the risk of IPF among occupational groups ($P = 0.50$, Wald $\chi^2 = 9.38$ with 10 degrees of freedom for homogeneity of OR for each occupational group). None of the occupational groups was related to the risk of IPF with statistical significance, although at least a 2-fold increase in OR was observed among managers and officials and production workers, and there was a <0.5-fold decrease in OR among those in clerical and related fields, protective service and materials handling. Further adjustment for pack-years of smoking slightly strengthened associations with two major occupational groups: managers and officials, and clerical and related occupations (adjusted ORs were 6.06, 95% CI: 0.97–118.6 and 0.42, 95% CI: 0.18–0.95, respectively). Overall, 25 cases and three controls were exposed to only one of the occupational agents being studied, and four cases and two controls were exposed to two agents. Only three and one cases were exposed to three and six occupational agents, respectively. Exposure to any of the eight kinds of dust being studied was significantly associated with an increased risk of IPF. In particular, exposure to metal dust was related to an ~ 10 -fold increased risk of IPF. No association

Table 2. Adjusted odds ratios for idiopathic pulmonary fibrosis in relation to occupational factors

Factor	n (%)		Adjusted odds ratio ^a	95% confidence interval
	Cases (n = 102)	Controls (n = 59)		
Job held for the longest period of time				
Professional or technical	9 (8.8)	7 (11.9)	0.71	0.23–2.25
Manager or official	9 (8.8)	1 (1.7)	4.26	0.74–80.88
Clerical or related occupation	18 (17.7)	18 (30.5)	0.49	0.22–1.08
Sales	11 (10.8)	6 (10.2)	1.29	0.44–4.18
Service	6 (5.9)	3 (5.1)	1.02	0.23–5.46
Protective service	2 (2.0)	3 (5.1)	0.33	0.04–2.19
Farming, fishing or forestry	7 (6.9)	7 (11.9)	0.55	0.16–1.89
Transport or communication	4 (3.9)	2 (3.4)	1.10	0.19–8.73
Production	18 (17.7)	5 (8.5)	2.56	0.91–8.54
Materials handling	2 (2.0)	2 (3.4)	0.46	0.05–4.34
Construction or extraction	11 (10.8)	5 (8.5)	1.37	0.42–4.44
Occupational agents				
Any dust ^b	33 (32.4)	5 (8.5)	5.61	2.12–17.89
Metal	12 (11.8)	1 (1.7)	9.55	1.68–181.12
Wood	5 (4.9)	0 (0.0)		
Asbestos	3 (2.9)	0 (0.0)		
Coal	3 (2.9)	0 (0.0)		
Stone or sand	11 (10.8)	4 (6.8)	1.75	0.52–7.01
Solvents	4 (3.9)	0 (0.0)		
Pesticides	6 (5.9)	2 (3.4)	1.46	0.30–10.61
Chalk	4 (3.9)	0 (0.0)		

^aAdjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).

^bEight cases and two controls were exposed to two or more occupational agents.

of exposure to stone, sand or pesticides with the risk of IPF was found. None of the control subjects reported exposure to wood, asbestos, coal, solvents or chalk. Additional adjustment for pack-years of smoking did not change the association with IPF of exposure to any of the dusts being studied and metal dust. When exposures to metal dust, stone, sand and pesticides were included in the same model with age, sex and region, a positive association between metal dust exposure and IPF was slightly attenuated but remained statistically significant (adjusted OR 9.25, 95% CI: 1.59–176.7).

Results for environmental factors are shown in Table 3. More cases than control subjects were former smokers, whereas current smoking was more prevalent in controls than in cases, although differences between groups were not statistically significant. Adjusted OR for the comparison of having smoked with never having smoked was 1.91 (95% CI: 0.71–5.15). A significantly increased risk of IPF was observed for smokers with 20.0–39.9 pack-years, but there was no dose-response association with cumulative consumption of cigarettes. Although not statistically significant, moulds in the living room and the presence of indoor hamsters were

associated with a >50% decreased risk of IPF. Moulds in the bathroom, kitchen or closets and the presence of indoor birds, cats or dogs were not measurably related to the risk of IPF. There was no clear difference between cases and controls in terms of residential municipality.

DISCUSSION

The present study demonstrated that, compared with control subjects, cases were more likely to have been managers and officials or production workers and less likely to have been protective service workers or materials handling workers, although none of the effects reached significance. Workers in clerical and related fields had a significantly decreased risk of IPF independent of age, sex, region and smoking status. Exposure to metal dust was significantly associated with an increased risk of IPF, but exposure to stone, sand or pesticides was not materially related to IPF. There was no statistically significant relationship between the environmental factors under study and IPF, although 20.0–39.9 pack-years of smoking was significantly associated with an increased risk of IPF.

Table 3. Adjusted odds ratios for idiopathic pulmonary fibrosis in relation to environmental factors

Factor	n (%)		Adjusted odds ratio ^a	95% confidence interval
	Cases (n = 102)	Controls (n = 59)		
Smoking status				
Never smoked	18 (17.6)	14 (23.7)	1.00	
Former smoker	80 (78.4)	34 (57.6)	2.21	0.82–6.04
Current smoker	4 (3.9)	11 (18.6)	0.50	0.10–2.24
Pack-years of smoking				
None	18 (17.7)	14 (23.7)	1.00	
0.6–19.9	10 (9.8)	11 (18.6)	0.87	0.25–3.10
20.0–39.9	30 (29.4)	10 (17.0)	3.23	1.01–10.84
40.0–59.9	29 (28.4)	15 (25.4)	2.22	0.70–7.23
60.0+	15 (14.7)	9 (15.3)	1.59	0.46–5.64
Moulds				
Any place ^b	56 (54.9)	36 (61.0)	0.98	0.48–2.01
Living room	5 (4.9)	8 (13.6)	0.36	0.10–1.20
Bathroom	51 (50.0)	28 (47.5)	1.38	0.69–2.82
Kitchen	12 (11.8)	11 (18.6)	0.61	0.24–1.57
Closets	17 (16.7)	9 (15.3)	1.25	0.50–3.30
Indoor domestic pets				
Any pets ^c	40 (39.2)	25 (42.4)	0.94	0.47–1.86
Birds	17 (16.7)	9 (15.3)	1.16	0.47–3.03
Cats	14 (13.7)	8 (13.6)	1.24	0.45–3.58
Dogs	15 (14.7)	10 (17.0)	0.85	0.33–2.26
Hamsters	2 (2.0)	3 (5.1)	0.27	0.03–1.80
Residential municipality				
Village or town	15 (14.7)	12 (20.3)	1.00	
City	87 (85.3)	47 (79.7)	1.35	0.56–3.28

^aAdjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).

^bOverall, 22 cases and 13 controls were exposed to moulds in two or more places.

^cOverall, 8 cases and 3 controls had two or more types of indoor domestic pets.

These findings are in agreement with previous observations showing a positive relationship between exposure to metal dust and the risk of IPF (Scott *et al.*, 1990; Iwai *et al.*, 1994; Hubbard *et al.*, 1996b; Baumgartner *et al.*, 2000), but they are at variance with a case-control study that reported positive associations between farming and stone/sand dust exposure and IPF (Baumgartner *et al.*, 2000). The mechanisms underlying the positive association between metal dust exposure and the risk of IPF are still obscure. Recent experimental research has demonstrated that particulate nickel promotes pulmonary fibrosis by inhibiting the fibrinolytic cascade (Andrew and Barchowsky, 2000). Potolicchio *et al.* reported that susceptibility to hard metal lung disease is associated with binding of cobalt by HLA-DP molecules (Potolicchio *et al.*, 1997, 1999). Managers, officials and those working in clerical and related fields are not likely to be potentially exposed to metal dust. The first Whitehall study showed that mortality rates from lung cancer, chronic bronchitis and respiratory diseases were

markedly increased with a decrease in employment grade (van Rossum *et al.*, 2000). The present findings partially contradict this observation. In our current study, nine cases were managers and officials: six presidents of a company, two department managers of a company and one director of a union. One of the controls was an executive director of a company. None had been exposed to any of the occupational agents under investigation. A non-significant increased risk of IPF among managers and officials may be ascribed to unrecognized factors that are related to job grade. A case-control study in Lithuania found that the main risk factors of myocardial infarction for managers were hypertension and stress (Malinauskienė *et al.*, 2002). Their stressful work life may have contributed to the manifestation of IPF. The excess IPF risk among managers and officials was not likely to be explained by over-diagnosis in the higher employment grades. All Japanese are covered by universal medical care insurance and all are provided with completely free access to the same medical care.

A case-control study in the USA reported that being a former smoker and 21–40 pack-years of smoking were significantly related to an increased risk of IPF, whereas there was no association of current smoking and more than 40 pack-years of smoking with IPF (Baumgartner *et al.*, 1997). Our results are generally in agreement with these findings, although a positive relationship between having previously smoked and IPF was not statistically significant in this study. A history of having ever smoked was associated with a 1.6-fold increased risk of IPF in the above-cited US study (Baumgartner *et al.*, 1997) and a study in the UK (Hubbard *et al.*, 1996b). The present findings, although not statistically significant, are similar to these observations. Overall, 34 cases and 14 controls quit smoking within 3 years of data collection. It is possible that cases were more likely to quit smoking because of diagnosis or the progression of their disease. When these subjects who stopped smoking within 3 years were considered to be current smokers, adjusted ORs (95% CIs) were 2.11 (0.72–6.19) and 1.73 (0.60–5.03) for former and current smoking, respectively. Additional adjustment for pack-years of smoking slightly affected the association with IPF in managers and officials and workers in clerical and related fields, although the interaction with pack-years of smoking was not statistically significant for those occupational groups. On the other hand, adjustment for smoking did not measurably influence the effects of metal dust exposure. Thus, smoking and metal dust exposure were likely to be independent factors. A case-control study of 17 cases and 94 controls in the USA reported that patients with interstitial lung disease were 16.0 times more likely to be exposed to mould than were controls in their workplace (Mullen *et al.*, 1998). The present results are not consistent with this finding. To our knowledge, no study has assessed the relationship between domestic pets and the risk of IPF. Our findings contradict a previous epidemiologic study in Japan showing a positive association between residence in an agricultural area and the risk of IPF (Iwai *et al.*, 1994).

Selection and information bias are methodological issues that need careful consideration. We attempted to identify and recruit all eligible cases seen at each participating hospital during the specified study period according to the most recent diagnostic criteria. Only three eligible patients did not take part in this study. Thus, it was unlikely that selection bias for the cases occurred. It is difficult to ensure that control subjects are drawn from the same study population as the cases. This disadvantage is likely to be diluted by controlling for region. Almost all controls were hospitalized patients with acute bacterial pneumonia. Therefore, control subjects may not have been representative of the general population that generated the

cases. The prevalence values of having ever smoked in the present controls were not likely to differ from those reported elsewhere, although the prevalence values of current smoking were relatively low in this study. In a population-based case-control study of acute myocardial infarction in Fukuoka, Japan, the proportions of people who had never smoked, had formerly smoked and currently smoked were 25%, 23% and 52%, respectively, among 260 male controls below 65 years old, and 24%, 41% and 35%, respectively, among 212 male controls aged 65 years or over (Miyake and Fukuoka Heart Study Group, 2000). The corresponding figures in this study were 14%, 55% and 31%, respectively, among 29 male controls below 65 years old, and 24%, 68% and 8%, respectively, among 25 male controls aged 65 years or over. If acute bacterial pneumonia shared risk factors with IPF, the reported OR would have been underestimated. The ratio of controls to cases was below 1:1. Eligible control subjects with acute bacterial pneumonia were not likely to arise during the summer months because of seasonal variation in this disease. Moreover, eligible control patients who received treatment at the non-respiratory ward of 50 hospitals were not recruited. The statistical power of this study was extremely low, although a statistically significant association was observed. Cases may have been more likely than controls to remember specific exposures under study. However, subjects would not have been aware of the possible ill effects of occupational and environmental factors under investigation because the etiology of IPF is unknown. Thus, a difference in recall between cases and controls was not likely to have occurred. We did not collect data for a detailed occupational history. However, the impact of job activities, other than the job held for the longest period of time, on IPF was likely to be negligible and unlikely to differ between cases and controls because the median duration of the job held for the longest period of time was 30 years or more in both cases and controls. The consequence could be a minor underestimation of values in our results.

Despite these potential limitations, the present results appear to confirm data from previous epidemiologic studies. Exposure to metal dust is a particularly important risk factor for IPF in Japan, as well as in the UK and the USA. Larger studies with more precise and detailed exposure measurements are needed to assess the impact of occupational and environmental factors on the development of IPF. Investigations regarding biological mechanisms are also required.

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Abstract

The authors conducted a matched case-control study of interstitial lung disease (ILD) using a self-administered questionnaire. All cases in the practice of two pulmonary specialists were identified. Cases were excluded if they were thought to have occupational exposures as a contributor, hypersensitivity pneumonitis or sarcoidosis, or some other well-recognized cause. Three controls were matched by sex and age (one year) as identified through orthopedic surgeons at the same institutions. Two rounds of a questionnaire were mailed; 17 cases (37.7%) and 94 controls (32.4%) responded to the questionnaire, although many of the case addresses were no longer valid. Individuals with ILD were 16.0 times as likely to report mold exposure and 11.1 times as likely to report silica as were controls in their workplace. Odds ratios associating ILD with moisture indicators in the home were in the same range as previously published associations between such indicators and wheezing. ILD may have environmental and occupational causes that warrant more systematic exploration.

Interstitial lung diseases (ILD) are thought to represent approximately 15% of clinical pulmonary practice. A population-based registry in the United States suggested a prevalence of 70 per 100,000 in the United States,¹ with over half occurring without obvious cause. The mean survival for this disease is four to six years after initial diagnosis, and an estimated 8400 to 14000 Americans die of this disease annually. ILD is associated with a long list of chronic diseases, including

collagen vascular and autoimmune disorders. Approximately 3% are thought to be related to occupation.¹ Occupational exposures associated with diffuse interstitial fibrosis (DIF) generally lead to additional characteristics, ie, asbestosis to asbestos bodies and pleural changes, hard metal disease to giant cells, silicosis to silicotic nodules, and coal workers pneumoconiosis to centrilobular emphysema and anthracosis. In clinical practice, the diagnosis of work-related ILD is often made simply on the basis of an abnormal chest x-ray and a pertinent occupational history. Idiopathic pulmonary fibrosis (IPF) is estimated to occur at a prevalence of approximately three to five cases per 100,000 in the United Kingdom. Johnston et al noted rising mortality from IPF with significant variations between regions of England and Wales,² suggesting environmental exposures in the etiology of the disease. No etiologic studies of ILD have been published in the United States. In the United Kingdom, IPF was associated with metals exposure and wood dust^{3,4} in two studies.

As interest in environmental and occupational medicine has grown among internists and subspecialists, the high rates of underdiagnosis of occupational and environmental disease has been recognized, usually estimated in the range of 60% to 95%.⁵⁻¹⁰ Simultaneously, an association between moisture and chest symptoms has been recognized in residential environments.^{11,12} Morey et al suggested an association of moisture with respiratory disease in buildings after a series of outbreak investigations.¹³

Several patients with ILD at the Occupational and Environmental Medicine Unit at the University of Connecticut described exposure to metals either through grinding, welding, and "air-arcng, with exposure to metal dusts and fumes," or to

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molds and moisture, primarily in office buildings. None of these patients had granulomas or giant cells on biopsy, suggesting that this did not represent hypersensitivity pneumonitis or giant cell alveolitis, diseases associated with environmental exposure. Hypersensitivity pneumonitis was not suspected clinically by the pulmonary specialists who had seen the patients initially. This study was therefore developed to identify whether these two risk factors would appear in a case-control study; ie, could an elevated risk from metals exposure or moisture and mold play a role in the etiology of ILD.

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Subjects and Methods

All patients with ILD referred from two Hartford pulmonologists' offices were eligible. None of these cases had been seen in the Occupational and Environmental Medicine Unit. Cases were chosen if the diagnosis was confirmed by either lung biopsy or radiographic examination, and there were no exposures in the view of the treating physician considered adequate to explain DIF or other associated diseases. Cases were excluded if they had granulomas on biopsy. Controls were drawn from records of patients from two orthopedists in the same institutions. Six controls were identified for each patient, matching for sex and age within one year.

Cases and controls received a packet containing a letter signed by their treating physician and the investigators explaining the purpose of the study and asking them to participate. The envelope also contained a copy of the questionnaire and a self-addressed stamped envelope. If no response was received within two weeks, a second package was mailed.

The questionnaire was modified from an instrument used in a similar study in the United Kingdom addressing the same disease, kindly provided by the investigators.³ The questionnaire inquires about exposures to dusts, tobacco smoke, animals, occupational and environmental agents and urban vs suburban living. Additional questions were developed to inquire about moisture problems at home and in the workplace. [A copy is available from the authors upon request.] A physician trained in occupational and environmental medicine and blinded to case status coded exposures to individual inorganic dusts, such as silica, asbestos and coal, and to organic dusts, such as molds and wood. Exposures were coded on ordinal scales to frequency (0: none; 1: <5% of time; 2: 5-30% of time; 3: more than 30%); intensity (1: use in workplace remote from job; 2: bystander; 3: direct user or generator); and duration (in years) as described by others,^{14,15} considered to possess reasonable external validity,¹⁶ and used previously.¹⁷ Summary variables were created by transformations, including a variable for all occupational dust exposures, any moisture problems, any moisture problems in basement and bathrooms, and mold exposure.

Data were entered by a commercial vendor using double-key entry, with an error rate of less than .02%. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) for Windows. Standard statistical tests were used. True Epistat Version 5.1¹⁸ was used to analyze matched case controls by logistic regression for occupational and domestic exposure to asbestos, mold/mildew, and silica.

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Results

A total of 45 cases and 290 controls were contacted. Only 17 cases (37.7%) and 94 controls (32.4%) responded to the questionnaire. Fifteen matched triplets were assembled. No controls could be identified for two cases, because middle-aged males randomly identified as controls did not respond to the questionnaire. These two were excluded from further analyses. Cases and controls were not significantly different in age, (mean age among controls, 68.0 years; among cases, 67.3 years) and age at which they left school (controls: mean, 19.2 years; case: mean, 18.9 years). Among cases, 80.5% were non-Hispanic Caucasian, 6.7% African-American, 6.7% Asian, and 6.7% Hispanic, while all controls were non-Hispanic Caucasian. Cases and controls were equally likely to have lived in urban and rural settings.

Cases and controls were similar in their occupations, and in the intensity and duration of exposure to factors associated with DIF (cobalt, metals, etc). There was no significant difference between cases and controls in their work with animals or solvents.

Four of 15 (26.6%) described exposure to mold in the workplace, three to silica, and two each to asbestos and wood dust, the latter associated with ILD in a prior study. Occupational exposure to dust in general was more prevalent among cases (47%) than controls (27%) ($P = 0.028$) (Table 1). These dusts reported included asbestos, coal, wood, sand and stone, and must or mildew. Cases also had a higher cumulative exposure to all dusts. Only one control reported exposure to asbestos. While the odds ratio for exposure to any dust (odds ratio, 2.37; 95% confidence intervals [CI], 0.67 to 8.44; with $P = 0.18$) and asbestos (odds ratio, 6.77; 95% CI,

Table 1

0.57 to 80.7; with $P=0.09$) were not significantly elevated, mold or mildew (odds ratio, 16.00; 95% CI, 1.62 to 158; $P = 0.003$) and silica (odds ratio, 11.00; 95% CI, 1.05 to 115; $P = 0.016$) were significantly more frequent among cases. These exposures were reported in four (26.6%) and three (20.0%) of cases, respectively.

Broad descriptions of environmental variables, such as housing type, the presence or absence of carpeting in the home, or type of heating in the home were no different between cases and controls.

Interestingly, several moisture-related risk factors in the home, identified in other studies, approached significance (**Table 2**). Patients were more likely to have any moisture problem in the home (odds ratio, 3.27; 95% CI, 0.62 to 17.4; $P = 0.15$). Cases were more likely to report having a moldy basement odor (odds ratio, 2.42; 95% CI, 0.68 to 8.55; $P = 0.16$). Having no exhaust in the bathroom and kitchen, mold in the bathroom, or the presence of humidifiers in the home were not seen to be significant, although the odds ratios were above unity.

Lastly, as has been borne out in other studies, smoking history was not significantly different between cases and controls.

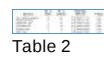
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Discussion

This study was a preliminary attempt to determine the role that occupational and environmental exposures have in the etiology of DIF, replicating a previous study in the United Kingdom. A surprisingly large number of patients chose not to respond to this survey, although their own treating physician co-signed the letter inviting them to participate. In addition, a high rate of "returned-undeliverable" packages was covered, reflecting either inaccurate records or patient moves. This left relatively few cases for examination with inadequate power to detect anything but very strong associations. The resulting relatively low response rate may lead to the introduction of biases, in that cases with some concern about an external etiology for their disease might have responded more frequently than others. As the introductory letter was "low-key" and no description of the specific hypotheses were given, so that no specific information bias is likely to have been introduced, the authors do not feel that this represents a likely concern. Nevertheless, recall bias is a fundamental problem with case control studies that rely on interviews for exposure histories.

Although the association between metals exposure and machining exposures with DIF led to this study, only two cases and one control had this risk factor. A third case with substantial exposure was excluded because no controls could be identified for a 40-year-old male among the respondents. If this subject had been included and if the associated controls followed the same frequency of metals exposure, the results would have identified "metals exposures" as an additional risk factor. Metals exposure was identified with a 10-fold relative risk in the UK study.³ Although wood, coal (even in Connecticut), and asbestos exposure approached statistical significance, these do not, in the final analysis of this data set, appear to play a substantial role. They may be related to metals exposure, as foundry work, grinding, welding, and air arcing involve some use of not only asbestos but also silica. On the other hand, some have argued for attributing interstitial fibrosis to even "trivial" quantities of asbestos or silica. Silica in this study appeared to be statistically significantly associated with ILD, even though exposure had not been considered enough to cause disease by the treating physicians. Only a larger study, with greater power to detect associations and to model interactions among variables, will answer the question of individual associations, actual exposures, and confounding. Nevertheless, recall bias is a fundamental problem with case control studies that rely on interviews for exposure histories.

Occupational exposures to mold in a variety of occupations was strongly associated with DIF. This is biologically plausible, as disease due to organic dusts is well recognized, though not considered a common occurrence in New England. Moisture is clearly associated with fungal growth, not only at home but also at work. Anecdotal reports have implicated moisture as a cause of interstitial fibrosis in the work place for many years,¹³ although most of these were thought to represent hypersensitivity pneumonitis. A first explanation is that the cases seen here represent end-stage hypersensitivity pneumonitis. The treating pulmonary specialists (T.G., C.A.D.G.) have a long-standing interest in environmental and occupational lung disease and actively sought hints of an etiology, ie, any temporal associations and traditional occupational history taking procedures. At present, no sensitive diagnostic procedures allow the early diagnosis of hypersensitivity pneumonitis in the absence of granulomata, clinical course, and history. The authors are currently examining the pulmonary biopsy material and reviewing histories more closely to examine potentially more complex relationships. The intricacies of blinded reviews, suitable "control material," and the relatively small sample size make the scientific interpretation of this work difficult. Another is that some additional form of interstitial disease may be related to mold exposures in the workplace. Several outbreaks of disease associated with organic ducts ¹⁸⁻²⁰ do not appear to resemble

 Table 2

hypersensitivity pneumonitis but may represent something similar to organic dust toxic syndrome.

A second hypothesis was that moisture sources in the home are associated with DIF. Some home risk factors approached significance, but none appeared robust. Having poor exhaust in bathroom and kitchen, mold in the bathroom, and the presence of humidifiers in the home did not reach significance. A recent report of pneumonitis in children²¹ identified home moisture and growth of the mycotoxin producing fungus *Stachybotrys atra* (now called *chartarum*) as a risk factor. Such exposures are associated with pulmonary disease in animals.²² Mycotoxins affect alveolar macrophage function.^{23,24} Recent outbreaks of mycotoxin-associated disease in adults have been associated with building moisture.²⁵ Other reports have indicated that *Stachybotrys atra*,^{26,27} *Aspergillus versicolor*, and several toxigenic species of *Penicillium* are potentially hazardous, especially when the air-handling systems have become heavily contaminated.^{23,24} Dampness of the buildings was the primary factor of concern.²⁸⁻³⁰ At least one group of authors have argued that a component of most fungal cell walls might be the primary etiologic agent rather than mycotoxins.³¹

An estimated population attributable risk may be calculated using prevalence of moisture and mold indicators in the work place (.15) and at home (.3 to .4). The relative risk seen here in the workplace (odds ratio = 15) and at home (3.5) allows the calculation of an etiologic fraction of 10% for work and 12% for home. As no systematic identification of moisture sources at work was undertaken in this study, this may represent an underestimate. Nevertheless, occupational exposure to mold or mildew and dusts may be an important factor in the etiology of diffuse interstitial fibrosis. Unwanted moisture incursion is not clearly identified as an occupational risk factor. Although this study must obviously be replicated, patients with interstitial lung disease and exposure to moisture at home and in the workplace may need to be removed from their workplace in order to determine whether their disease will resolve and to prevent it from progressing.

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Just the Facts

Human rights declarations signed by China: 17; by the US: 15 Ratio of Nixon tape hours released to those yet to be released: 1:8 Americans declaring bankruptcy in the Great Depression: 1 in 215

Americans declaring bankruptcy in 1996: 1 in 225 % change since 1982 of time
Americans were delayed in traffic: +95

% change since 1982 of car trips by Americans: +17 Minimum campaign contribution for Nixon ambassadorship: \$250,000

-Harper's Index. *Harper's*, 1998;296:1772, p 13 (sources on p 80).

IMAGE GALLERY

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Exposures to Various Dusts				
Exposure	No. of Cases	No. of Controls	Odds Ratio (95% CI)	P Value
Any dust	6	9	2.27 (0.67 to 8.44)	0.18
Asbestos	2	1	0.77 (0.20 to 3.09)	0.99
Coral	1	1	3.14 (0.18 to 53.0)	0.41
Mold/mildew	4	1	10.00 (1.02 to 156.0)	0.03
Paper	3	1	11.00 (1.02 to 110.0)	0.018
Wood	2	2	3.58 (0.42 to 25.8)	0.25

Table 1

Exposure	No. of Cases	No. of Controls	Odds Ratio (95% CI)	P Value
Any moisture problem	6	22	3.27 (0.92 to 17.4)	0.15
Basement flooding	3	14	2.40 (0.98 to 8.84)	0.19
Basement mold	3	12	0.12 (0.03 to 0.46)	0.34
Handdrier use	6	13	1.75 (0.62 to 5.10)	0.44
Household mold	3	1	3.30 (0.20 to 50.0)	0.37*
Other mold	1	1	3.30 (0.20 to 50.0)	0.37*

Table 2

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Occupational Risks for Idiopathic Pulmonary Fibrosis Mortality in the United States

**GERMANIA A. PINHEIRO, MD, MSC, PHD, VINICIUS C. ANTAO, MD, MSC, PHD,
JOHN M. WOOD, MS, JAMES T. WASSELL, PHD**

Metal and wood dust exposures have been identified as possible occupational risk factors for idiopathic pulmonary fibrosis (IPF). We analyzed mortality data using ICD-10 code J84.1—"Other interstitial pulmonary diseases with fibrosis," derived age-adjusted mortality rates for 1999–2003, and assessed occupational risks for 1999, by calculating proportionate mortality ratios (PMRs) and mortality odds ratios (MORs) using a matched case-control approach. We identified 84,010 IPF deaths, with an age-adjusted mortality rate of 75.7 deaths/million. Mortality rates were highest among males, whites, and those aged 85 and older. Three industry categories with potential occupational exposures recognized as risk factors for IPF were identified: "Wood buildings and mobile homes" (PMR = 4.5, 95% confidence interval (CI) 1.2–11.6 and MOR = 5.3, 95% CI 1.2–23.8), "Metal mining" (PMR = 2.4, 95% CI 1.3–4.0 and MOR = 2.2, 95% CI 1.1–4.4), and "Fabricated structural metal products" (PMR = 1.9, 95% CI 1.1–3.1 and MOR = 1.7, 95% CI 1.0–3.1). Workers in these industry categories may benefit from toxicological studies and improved surveillance for this disease. Key words: idiopathic pulmonary fibrosis, mortality data; industrial hazards

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The idiopathic interstitial pneumonias are a group of diffuse parenchymal lung diseases that share many features but are sufficiently different from one another to be considered separate entities. The term idiopathic pulmonary fibrosis (IPF), formerly applied to a group of diseases, is now used to describe a distinct clinical disorder, defined by the histological pattern of usual interstitial pneumonia, as recommended by an international collaboration including the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the American College of Chest Physicians (ACCP).^{1,2} In contrast, the tenth

Received from: Division of Respiratory Disease Studies (GAP, VCA, JMW) and Division of Safety Research (JTW), National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Address correspondence to: Germania Pinheiro, MD, MSc, PhD; c/o James T. Wassell, PhD; 1095 Willowdale Road—MS 1811; Morgantown, WV 26505; telephone: (304) 285-5946; e-mail: <germania.pinheiro@yahoo.com>.

Disclosures: The authors report no conflicts of interest.

International Classification of Diseases (ICD-10) defines IPF (code J84.1) as "Other interstitial pulmonary diseases with fibrosis (diffuse pulmonary fibrosis, fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, idiopathic pulmonary fibrosis)."³ We sought to describe patterns of IPF mortality in the United States 1999–2003 and to investigate a possible association between occupational exposure in specific industries and IPF mortality. To facilitate comparisons with previous studies, we used the terminology IPF to refer to the group of diseases classified under ICD-10.

There have been few studies of the prevalence and incidence of IPF in the United States. A population-based study for all interstitial lung diseases in Bernalillo County, New Mexico, for the period 1988–1990, revealed an IPF prevalence of 20.2 cases per 100,000 males and 13.2 cases per 100,000 females.⁴ A recent study based on health care claims for the period 1999–2000 estimated the incidence and prevalence of IPF in the United States using different case definitions.⁵ An annual incidence of 16.3 and a prevalence of 42.7 cases per 100,000 were found using a broad definition (i.e., presence of the ninth International Classification of Diseases (ICD-9) code 516.3—"Idiopathic fibrosing alveolitis"⁶—and absence of other types of interstitial lung disease in medical records). Using a narrower definition (i.e., broad definition criteria plus medical record evidence of diagnostic procedures such as surgical lung biopsy, transbronchial lung biopsy, and computed tomography of the thorax), the results were 6.8 and 14.0 cases per 100,000 for incidence and prevalence, respectively.⁵

The etiology of IPF is still largely unknown. The disease typically occurs in patients more than 50 years old, and mortality five years after diagnosis is estimated to be 50–70%.⁷ Viruses, such as Epstein-Barr, may play a role in the development of IPF.⁸ Some studies have demonstrated either serological or immunocytochemical evidence of infection and, in some cases, replication of Epstein-Barr virus in the lungs of patients with IPF compared with controls.⁹ Other viruses also implicated in the pathogenesis of IPF include influenza,¹⁰ cytomegalovirus,¹¹ and herpesvirus-6.¹² Pulmonary fibrosis may be a rare complication of exposure to certain drugs, including antidepressants, beta blockers, antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs.¹³ Cigarette smoking is associated with respiratory bronchiolitis even in young asymptomatic

individuals.¹⁴ A case-control study reported from the United States suggested that smoking may play a role as a risk factor for IPF.¹⁵ A study from the United Kingdom showed odds of developing IPF increased with pack-years of smoking, although this effect was not significant.¹⁶ Smoking certainly must be considered in the analysis of the etiology of this disease, and is also an important factor in predicting survival.⁷

Several studies have suggested that IPF may be linked to a variety of occupational and environmental exposures. Increased risk has been found mainly among wood and metal workers^{17,18} and among farming and livestock workers.¹⁹ In addition, existing biological evidence suggests that a succession of multiple microscopic and continuous insults to the alveolar epithelial cells from a variety of inhaled environmental agents may be the triggering event in IPF.²⁰ The investigation of possible etiologies is considered a priority for better understanding this disease.²¹

The aims of this study were to describe the patterns of IPF in the United States from 1999–2003 and to investigate a possible association between occupational exposure to wood and metal dust and IPF mortality in specific industries.

MATERIALS AND METHODS

The United States National Institute for Occupational Safety and Health (NIOSH) maintains a mortality surveillance system for respiratory diseases of occupational interest, utilizing various data sources.²² For this study, we used 1999–2003 multiple cause-of-death data compiled by the National Center for Health Statistics for United States residents aged 15 years and older.²³ Both underlying and contributing causes of death were analyzed. To facilitate comparisons between our results and previous studies, the term “IPF” refers here to the group of diseases classified under ICD-10 code J84.1, comprising “Other interstitial pulmonary diseases with fibrosis, including fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, and idiopathic pulmonary fibrosis.”

We used SAS statistical software version 9.1 (SAS Institute, Cary, NC) to calculate age-adjusted and age-specific mortality rates, and to develop a linear regression model. Age-adjusted mortality rates (per million per year) were computed using the 2000 United States standard population. Age-specific mortality rates (per million per year) by gender were computed for the following age groups: 15–44, 45–54, 55–64, 65–74, 75–84, and 85 years and older. A simple linear regression model (with years 1999–2003, coded from 0 to 4, respectively), was used to estimate the overall trend in mortality rates. We used Arc View GIS version 9.1 (Environmental Systems Research Institutes, Redlands, CA) to map the geographic distribution of age-adjusted mortality rates by state.

Assessment of Occupational Risks

Proportionate Mortality Ratio. Proportionate mortality ratio (PMR) by industry was computed on a subset of the NCHS multiple cause-of-death files containing 3-digit Census Industry Codes (CIC)²⁴ from 19 states which coded this information on death certificates for 1999, the most recent year for which these codes were available.²³ The PMR was calculated by dividing the observed number of deaths with IPF in a specified industry by the expected number of deaths with that condition (i.e., total number of deaths in the CIC of interest multiplied by a proportion defined as the number of cause-specific IPF deaths in all industries, divided by the total number of deaths in all industries). The data were adjusted for age, sex, and race. Confidence intervals (CIs) were obtained assuming Poisson distribution of the data.

Mortality Odds Ratio. To improve precision in the assessment of occupational risks, we used matched case-control logistic regression to estimate mortality odds ratios (MORs), which allowed for a better ascertainment of cases and controls than the PMR approach. Cases and controls were extracted from the same subset of the 1999 NCHS data mentioned above. We excluded from the analysis all decedents whose death certificates mentioned the following CIC codes: 951 (Retired; with no other industry reported), 961 (Non-paid worker or non-worker), or 990 (Industry not reported). Cases were defined as those decedents whose death certificates mentioned ICD-10 code J84.1 (i.e., IPF) as the underlying or contributing cause of death and did not mention any other type or cause of interstitial lung disease (Appendix 1). Controls were decedents whose death certificates did not mention ICD-10 codes J84.1 (IPF), J84.8 (Other specified interstitial pulmonary diseases), J84.9 (Interstitial pulmonary disease, unspecified), or any of the codes indicating sudden, injury- or poisoning-related, or other external causes of death (Appendices 1 and 2).

Decedents whose death certificates listed one of the industries with significantly elevated PMR (i.e. those with a lower 95% CI greater than 1) and for which available literature indicated presence of potential occupational exposures were assigned to the “exposed” group. “Unexposed” were those whose death certificates mentioned industries not likely to have the exposures of interest (Appendix 3). Decedents whose death certificates mentioned an industry with potential exposures of interest but without a statistically significant PMR were excluded from the analysis.

Four controls were matched for each case based on sex, age, race, and state of residence, using the “gmatch” SAS macro.²⁵ Conditional logistic regression with the SAS PROC PHREG was used to estimate the MOR and 95% CI for each industry of interest.

RESULTS

Descriptive Statistics

There were 84,010 IPF deaths from 1999 through 2003. In the majority of cases (59%), IPF was coded as the underlying cause of death. The number of deaths and mortality rates increased over time (Figure 1). The linear regression between mortality rates and years showed an $r^2 = 0.98$ ($p < 0.001$) and a slope = 1.569. The age-adjusted mortality rate for the study period was 75.7 per million. The disease was more common among males, with age-adjusted mortality rates by sex of 98.9 per million for males and 60.7 for females. The greatest age-specific mortality rate was in the 85 years and older category (Figure 2).

The age-adjusted mortality rate was higher among whites (78.2 per million) compared with blacks (50.5 per million). The rates were slightly higher among Hispanics (83.6 per million) compared with non-Hispanics (75.2 per million).

The highest age-adjusted mortality rates (>100.0 per million) associated with IPF were found in North Carolina (104.0 per million), Vermont (100.9 per million), New Mexico (100.6 per million), and South Carolina (100.1 per million) and the lowest in Nevada (49.5 per million) (Figure 3).

Proportionate Mortality Ratio

The industries with significantly elevated PMRs for IPF in 1999 are listed in Table 1. We selected "Fabricated structural metal products," "Metal mining," and "Wood buildings and mobile homes" as industries having potential occupational exposures recognized as risk factors for IPF, such as wood and metal dust.

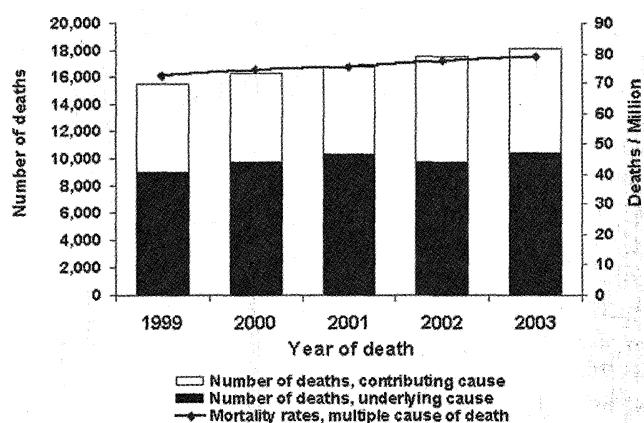


Figure 1—"Other interstitial pulmonary diseases with fibrosis": number of deaths (contributing and underlying cause of death) and age-adjusted mortality rates (multiple cause of death) by year, United States residents age 15 and over, 1999–2003.

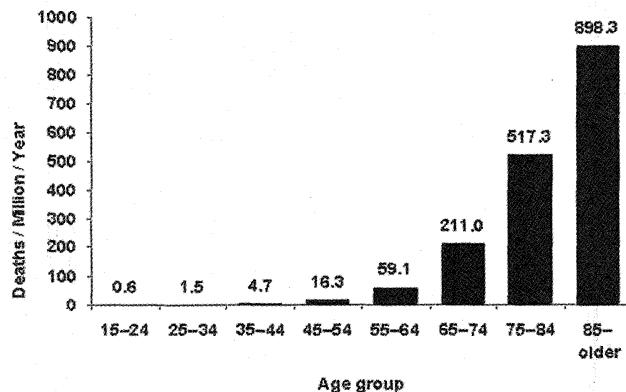


Figure 2—"Other interstitial pulmonary diseases with fibrosis": mortality rates by age group; United States residents age 15 and over, 1999–2003.

Mortality Odds Ratio

There were 598,246 death certificates available from the 19 states that reported industry codes for 1999. We excluded 208,542 death certificates from the analysis based on reporting of non-specified industry (CICs 951, 961, or 990) and 220,522 because the reported industry was not considered relevant to the analysis (i.e. had a potential risk for pulmonary fibrosis but did not have a statistically significant PMR). We excluded from the potential control group 15,892 decedents because their death certificates mentioned non-natural causes of death and 229 decedents whose death certificates mentioned "Other specified interstitial pulmonary diseases" or "Interstitial pulmonary disease, unspecified." Finally, we excluded 54 decedents whose death certificates mentioned other types or causes of interstitial lung disease in addition to IPF. The most frequently reported diseases in this group were "Systemic connective tissue disorders" ($n = 31$), "Sarcoidosis, unspecified" ($n = 9$), and "Pneumoconiosis due to asbestos and other mineral fibers" ($n = 9$). The number of cases and potential controls by each industry group for the 153,007 decedents eligible for analysis are shown in Table 2. After the matching process a total of 29 cases, which had 3 or fewer controls, were excluded from the modeling.

We found statistically significant MORs for all three industries with possible exposure to wood and metal dust: "Fabricated structural metal products," MOR = 1.7 (95% CI 1.0–3.1); "Metal mining," MOR = 2.2 (95% CI 1.1–4.4); and "Wood buildings and mobile homes," MOR = 5.3 (95% CI 1.2–23.8).

DISCUSSION

Our study demonstrates that the majority of decedents with a mention of IPF on death certificates were white males, aged 75 and older, in accordance with the demographic characteristics of the disease found in morbid-

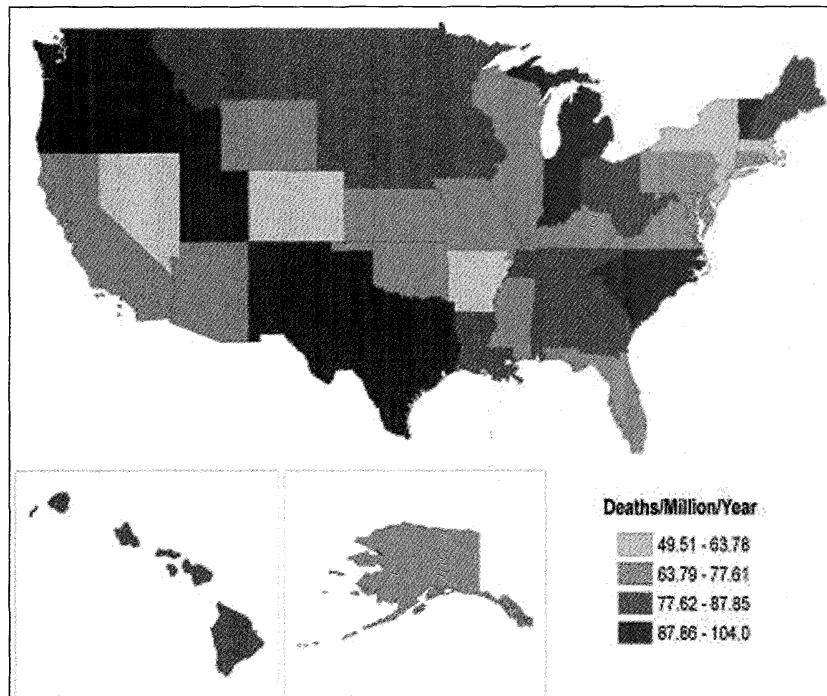


Figure 3—“Other interstitial pulmonary diseases with fibrosis”: age-adjusted mortality rates by state, United States residents age 15 and over, 1999–2003.

ity studies. In addition, mortality rates correlate well with these recent incidence estimates.⁵ It is unclear whether the geographic distribution of IPF mortality observed in this study reflects regional differences in the risk of disease or diagnostic/reporting practices among health care providers. For instance, the New Mexico Interstitial Lung Disease Registry, established in 1988,²⁶ may have contributed to increased awareness about IPF in that state, which has one of the highest mortality rates in the United States. Another explanation may be misclassification of occupational diseases, such as silicosis, asbestosis, and hypersensitivity pneumonitis (HP), which may differ by state.²⁷

We identified three industry categories with potential exposure to wood and metal dust that were associated with statistically significant risk estimates for IPF mortality. The findings from the PMR analysis were confirmed by the assessment of MOR, which is regarded as a more robust measure of relative mortality in studies of possible occupational hazards. Miettinen and Wang state that the MOR comparing the “exposed” with the “nonexposed” can be interpreted as the observed-to-expected ratio or the standardized mortality ratio, and is superior to the PMR calculations given that the mortality rate for the auxiliary causes is unrelated to exposure.²⁸

In this study, the case-control approach was useful to confirm the significance of PMR estimates by controlling for matching variables. We excluded death certificates from the analysis based on several criteria: first,

those reporting industry non-specified or not considered relevant to the analysis; second, those mentioning ICD codes that could be easily confused with IPF and those where IPF could not have been ruled out (e.g., non-natural causes of death), which could have caused misclassification of controls; third, those mentioning IPF in association with other types of pulmonary fibrosis recognized as separate entities or with conditions that can cause pulmonary fibrosis. The proportion of excluded cases and controls was similar in both the “exposed” and “nonexposed” categories. Moreover, we excluded those decedents whose death certificates mentioned an industry with potential exposures of interest but without a statistically significant PMR because they were neither unexposed nor clearly exposed to the hazards included in the exposed group. The proportion of cases and controls in this category was also comparable. Therefore, the exclusion of cases and controls is not likely to have introduced unintentional bias in the analysis. In addition, the calculation of MORs allowed better comparisons with previous case-control studies that evaluated the same type of exposure using morbidity data, and also found increased risks for IPF among subjects exposed to metal and wood dust.

Hubbard et al. obtained occupational history from 218 patients with IPF and 569 controls matched for age, sex, and community living. After adjusting the data for smoking, the relative risk for IPF was significantly increased in relation to questionnaire-reported expo-

TABLE 1 "Other Interstitial Pulmonary Diseases with Fibrosis": Significantly Elevated Proportionate Mortality Ratios (PMRs) and 95% Confidence Intervals (CIs) by Industry, Selected States,* 1999

Industry (CIC [†])	PMR	95% CI
Wood buildings and mobile homes (232)	4.5	1.2-11.6
Miscellaneous general merchandise stores (600)	2.6	1.1-5.2
Metal mining (040)	2.4	1.3-4.0
Research, development and testing services (891)	2.2	1.2-3.8
Fabricated structural metal products (282)	1.9	1.1-3.1
Offices and clinics of physicians (812)	1.8	1.2-2.7
Electric light and power (460)	1.8	1.2-2.6
Banking (700)	1.7	1.2-2.3
Colleges and universities (850)	1.5	1.1-2.0

*Includes data from 19 states: Colorado, Georgia, Hawaii, Idaho, Indiana, Kansas, Kentucky, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, North Carolina, Rhode Island, South Carolina, Utah, Vermont, West Virginia, and Wisconsin.

[†]Census Industry Code

sure to metal dust (Odds ratio [OR] = 1.7, 95% CI 1.1-2.7) and wood dust (OR = 1.7, CI 1.0-2.9).¹⁶

Scott et al., in a matched case-control study, administered questionnaires to 40 patients with confirmed IPF and 106 community controls, asking about lifetime exposure to dust, animals, and smoke at home and at work. The patients with IPF were more likely to report occupational exposure to metal dust (OR = 11.0, 95% CI 2.3-52.4) or wood dust (OR = 2.9, CI 0.8-9.9), to have worked with cattle (OR = 11.0, CI 1.2-96.0) or to have lived in a house heated by a wood fire (OR = 12.6, 95% CI 1.0-114.0). A history of smoking or social class was not significantly related to the outcome.²⁹

In a multicenter case-control study in the United States, Baumgartner et al. found 248 cases of IPF diagnosed in reference centers from 15 states.¹⁹ The diagnosis was based on clinical history and other information when available, such as: open lung biopsy, transbronchial biopsy, and computed tomography scan. Negative serum precipitin tests were required if a case had a history of exposure to agents associated with HP. All information for the controls and nonclinical data for the cases were collected by telephone interview, including activities and exposure to occupational agents that could be regarded as possible risks for IPF. Based on conditional multivariate regression analyses, cases of IPF were significantly associated with exposure to metal dust and livestock, and work in certain occupations including hairdressing, raising birds, and stone cutting or polishing.¹⁹

The analysis of over 20,526 deaths registered with the pension fund of a metal engineering company in the United Kingdom between 1968-1997, demonstrated that the proportional mortality from IPF was increased compared with the general population (PMR = 1.4, 95%

TABLE 2 Number of Cases of "Other Interstitial Pulmonary Diseases with Fibrosis" and Available Controls, by Exposure Group and Industry, 1999

Exposure Group/Industry	Cases	Controls
"Exposed"		
Fabricated structural metal products	17	1,058
Metal mining	14	614
Wood buildings and mobile homes	4	115
"Unexposed"		
Other transportation	60	8,367
Utilities and sanitary services	48	4,821
Food, bakery, and dairy stores	37	6,242
Eating and drinking places	44	10,436
Finance, insurance, and real estate	123	13,403
Other business, and repair services	46	7,546
Other personal services	40	6,886
Beauty and barber shops	22	3,127
Entertainment and recreation services	19	3,392
Health services	188	22,344
Legal, engineering, and other services	52	5,818
Educational services	211	26,027
Social services	54	6,470
Public administration	164	19,780
Military	41	5,377
Total	1,184	151,823

CI 1.1-1.8). Among employees exposed to metals there was evidence of linear increase in the risk of IPF with duration of exposure (OR per 10 years of exposure = 1.7, 95% CI 1.1-2.7). There was no evidence of an association between duration of employment and IPF for employees who were not metal workers.¹⁷

A Japanese study described an increased risk of death from IPF among metal workers. In the report, data from a live case-control study demonstrated statistically significant relative risk for IPF in mine workers and workers who were exposed to cadmium, chromium, and lead metal production.³⁰

Studies addressing the effects of smoking on the risk of developing IPF are contradictory.^{15,29} Since smoking status is not available on death certificates, we created a surrogate variable to assess these possible effects. Decedents whose death certificates mentioned "Unspecified chronic bronchitis" (ICD-10 code J42), "Emphysema" (ICD-10 code J43), or "Other chronic obstructive pulmonary disease" (ICD-10 code J44) were considered to be "possible smokers" and the remaining decedents were considered to be "possible nonsmokers." This crude "smoking status" variable was used as a covariate in the logistic regression models. However, no statistically significant effect was noted (data not shown).

Our study presents other limitations in addition to the lack of information about smoking status. Cause-of-

death information is subject to potential errors associated with disease diagnosis, recording, and coding. Nevertheless, mortality data are national, comprehensive, and represent a very important source of population-based information on the epidemiology of IPF, which can complement investigations that use different methodologies. There is limited availability of industry codes: the PMR only reflects the industrial profile of certain states and may not reflect the decedent's actual exposure. Lack of detailed information about past exposure to dusts, such as silica, asbestos, or grains, may contribute to misdiagnosis. Histopathological material to confirm the cases and differentiate among the subtypes of the disease was not available.

Despite the well known limitations of mortality data, we noticed an important change in the quality of these data for IPF, following the introduction of ICD-10. Under the ICD-9, there was a specific code for this disease, but only around 200 deaths per year were reported.²⁶ There is an impressive rise in the number of IPF deaths with the adoption of ICD-10: more than 15,000 cases were reported in 1999 and an increase in the number of deaths has also been observed in the subsequent years. A possible explanation for this changing pattern is that under ICD-9 the disease was probably misclassified as "Post-inflammatory pulmonary fibrosis," code 515, which accounted for an average of 10,000 deaths per year in the period of 1979–1999 (data not shown). However, underreporting is not so evident in England, where IPF is usually called "Cryptogenic fibrosing alveolitis."³¹ The registered mortality in that country increased substantially since 1979, the year ICD-9 was introduced, probably reflecting the similarity between the ICD code title ("Idiopathic fibrosing alveolitis") and the commonly used medical terminology.³¹

Several other industries also had statistically significant PMRs, suggesting that exposures in these industries may be associated with IPF (Table 1). However, there are no reports in the literature about these associations. Therefore, since there is probably no exposure to wood and metal dust in those industries, we considered that any discussion about potential risks would be speculative and beyond the scope of this paper. Nevertheless, these findings may be useful to raise awareness for further studies addressing possible etiologies for IPF.

CONCLUSIONS

Three of the industries with likely exposure to wood or metal dust have among the highest PMRs for IPF in the United States. The MOR analysis confirmed the PMR findings. Thus, our analysis of mortality data supports previous morbidity studies about the role of occupational factors in the etiology of IPF, specifically in industries with likely wood and metal exposures. Pulmonary fibrosis represents a disorder with a potentially complex

group of causes. In addition, IPF remains a heterogeneous disease, which further complicates etiology studies. Nevertheless, toxicological studies of different types of metal, wood, and other exposures in at-risk industries may assist in elucidating disease pathogenesis and draw attention to effective prevention strategies for IPF.

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APPENDIX 1.

International Classification of Diseases (ICD-10)
Codes for Interstitial Lung Diseases Other Than Idiopathic Pulmonary Fibrosis or Causes of Pulmonary Fibrosis

ICD-10 Code	Condition
D76	Certain diseases involving lymphoreticular tissue and reticulohistiocytic system
D86.0	Sarcoidosis of lung
D86.2	Sarcoidosis of lung with sarcoidosis of lymph nodes
D86.9	Sarcoidosis, unspecified
E75.2	Other sphingolipidosis
E77	Disorders of glycoprotein metabolism
E85	Amyloidosis
J60	Coal workers' pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibers
J62	Pneumoconiosis due to dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J65	Pneumoconiosis associated with tuberculosis
J67	Hypersensitivity pneumonitis due to organic dust
J68	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors
J70	Respiratory conditions due to other external agents
J82	Pulmonary eosinophilia, not elsewhere classified
J99	Respiratory disorders in diseases classified elsewhere
K50	Crohn's disease [regional enteritis]
M30	Polyarteritis nodosa and related conditions
M31	Other necrotizing vasculopathies
M32	Systemic lupus erythematosus
M33	Dermatomyositis
M34	Systemic sclerosis
M35	Other systemic involvement of connective tissue
M36	Systemic disorders of connective tissue in diseases classified elsewhere
Q85	Phakomatoses, not elsewhere classified

APPENDIX 2.

International Classification of Diseases (ICD-10)
Codes for Sudden, Injury- or Poisoning-related, and Some External Causes of Death

ICD-10 Code	Condition
S00-T98	Injury, poisoning and certain other consequences of external causes
V01-V99	Transport accidents
W00-X59	Other external causes of accidental injury
X60-X84	Intentional self-harm
X85-Y09	Assault
Y10-Y34	Event of undetermined intent
Y35-Y36	Legal intervention and operations of war

APPENDIX 3.

List of Industries Used to Assign Cases and Controls to the "Unexposed" Category

3-digit Census Industry Codes ^a	Corresponding Census Industry Recode Title ^b
401-402; 412-432	Other transportation
460-472	Utilities and sanitary services
601-611	Food, bakery, and dairy stores
641	Eating and drinking places
700-712	Finance, insurance, and real state
721-742; 752-760	Other business, and repair services
762-771; 781-791	Other personal services
772-780	Beauty and barber shops
800-802	Entertainment and recreation services
812-840	Health services
841; 882-892	Legal, engineering, and other services
842-860	Educational services
861-881	Social services
900-932	Public administration
942	Military

^aSource: Bureau of the Census. 1990 Census of Population and Housing alphabetical index of industries and occupations. 1990 CPH-R-3. Washington, DC: U.S. Department of Commerce, 1992.

^bSource: National Center for Health Statistics. 1994. Public use data tape documentation: Multiple Cause of Death for ICD-9 1992 data. Division of Vital Statistics, Hyattsville, MD.

What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust

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Abstract

Objective—To investigate the role of occupational and domestic exposure to dust in the aetiology of cryptogenic fibrosing alveolitis.

Design—Matched case-control study.

Subjects—40 Patients with cryptogenic fibrosing alveolitis and 106 community controls matched for age and sex who responded to a questionnaire.

Main outcome measure—Responses to self administered questionnaire asking about lifetime exposure to dust, animals, and smoke at home and at work.

Results—The patients with cryptogenic fibrosing alveolitis were more likely to report occupational exposure to metal dust (matched odds ratio 10.97 (95% confidence interval 2.30 to 52.4), $p<0.001$) or wood dust (2.94 (0.87 to 9.90), $p=0.08$), to have worked with cattle (10.89 (1.24 to 96.0), $p=0.01$), and to have lived in a house heated by a wood fire (12.55 (1.04 to 114), $p=0.009$). A history of smoking and social class based on occupation were not significantly related to disease state.

Conclusion—Environmental exposure to dust may be an important factor in the aetiology of cryptogenic fibrosing alveolitis.

Introduction

Cryptogenic fibrosing alveolitis has a prevalence of roughly five cases per 100 000,^{1,2} and patients survive for about four to five years after it is diagnosed.^{3,4} It generally develops between the ages of 40 and 70 but may occur in childhood.^{5,6} Mortality from the disease is increasing in England and Wales,⁷ with over 600 deaths each year.

The cause or causes of cryptogenic fibrosing alveolitis and the explanation for the increasing mortality are unknown. In the accompanying paper we described small but significant differences in mortality from the disease among standard regions of England and Wales.⁷ This suggests that environmental exposure to some agent(s) may have a role in the aetiology of the disease, and as mortality is highest in the traditionally industrial areas of England and Wales some of this exposure may be related to industrial occupations.⁷ We tested the hypothesis that environmental exposure to dust has a role in the aetiology of cryptogenic fibrosing alveolitis by comparing lifetime occupational and domestic exposure to various dusts in all patients with the disease known to the Nottingham hospitals and a series of community controls matched for age and sex.

Subjects and methods

We reviewed the case notes of patients on a register of all patients with cryptogenic fibrosing alveolitis seen by respiratory physicians or tested in the pulmonary

function laboratories in Nottingham in the two years before the study. The disease was confirmed if the patient had documented inspiratory basal crackles, bilateral interstitial shadowing in chest x ray films, restrictive pulmonary function, and a noted absence of appreciable exposure to known occupational or other fibrogenic agents in the past. Up to four controls matched for age and sex were obtained for each index patient. These controls were drawn from the list of the index patient's general practitioner (held by the family practitioner committee) and were selected randomly if more than four suitable subjects were available; if four controls of the same age were not listed with the general practitioner the age matching was widened to within five years.

Permission to enter an index patient and the matched controls into the study was requested from the general practitioner, and on receipt of permission a questionnaire was posted to the subject's home. The questionnaire included questions on previous areas of residence, past and present occupations and their duration, the duration of exposure to occupational dusts and their type, exposure to animals at work or at home, types of heating in current and previous housing, smoking history, and symptoms of allergy. Ethical permission for the study was granted by Nottingham City Hospital's ethics committee.

The data obtained with the questionnaire were coded and entered into the mainframe computer system at Nottingham University and were analysed descriptively with the Statistical Package for the Social Sciences—(SPSS-X).⁸ Occupations were coded by using the classification of occupations of the Office of Population Censuses and Surveys and were categorised prospectively as dirty or clean according to whether the job description in this classification implied direct exposure to atmospheric dust (table I).⁹ Matched case-control analysis of occupational and domestic exposure to dust, cigarette smoking, and other variables of primary interest was by conditional logistic regression with the statistical package EGRET¹⁰ on a micro-computer.

Results

We obtained the general practitioner's permission to contact 43 index patients and their controls. Four controls were found for 39 of the index patients and at least one control for each of the four other patients. Forty index patients (87% of the 46 originally identified) and 106 controls (60% of the original sample) returned a completed questionnaire. The proportions of men and women among all the index patients and controls identified and those who returned the questionnaire were similar, as were their mean ages (table II).

Occupational exposure to dust of any sort at any time was reported by 27 index patients and 47 controls. The

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TABLE I—*Jobs classified as dirty and their ICD codes*

Job	ICD codes
Textile worker	087
Furnaceman, smith	096, 109
Materials processor (textiles, tobacco)	098
Woodworker, sawyer	105, 106
Craftsman, labourer	107.1
Metal worker, fitter, or machinist	110, 113, 117, 126
Machine (for example, lathe) operator	097, 112
Welder or galvaniser	128, 131
Builder, construction worker, or labourer	140, 141, 142, 160
Miner, quarryman	145, 146

TABLE II—*Distributions of age and sex among all index patients and controls identified and all respondents to questionnaire*

	Men		Women		Overall mean (SD) age (years)
	No	No (%)	Mean (SD) age (years)	No (%)	
Original sample:					
Index patients	46	35 (76)	66.7 (9.2)	11 (24)	68.0 (9.1)
Controls	177	133 (75)	65.7 (8.3)	44 (25)	68.0 (8.7)
Respondents:					
Index patients	40	30 (75)	66.8 (8.9)	10 (25)	67.6 (9.4)
Controls	106	80 (75)	66.7 (8.8)	26 (25)	67.1 (9.2)
					66.9 (9.1)
					66.3 (8.5)
					66.8 (8.4)

TABLE III—*Exposure to various dusts in index patients and controls and matched odds ratios for disease*

	No of index patients	No of controls	Matched odds ratio (95% confidence interval)	p Value
Any dust	27	47	1.32 (0.84 to 2.04)	0.19
Metal	6	2	10.97 (2.30 to 52.4)	<0.001
Wood	6	5	2.94 (0.87 to 9.90)	0.08
Asbestos	4	9	1.46 (0.42 to 5.09)	0.56
Coal	8	22	1.23 (0.44 to 3.44)	0.70
Stone or sand	6	16	1.59 (0.52 to 4.79)	0.42
Tobacco	5	7	1.11 (0.13 to 1.40)	0.29
Fabric	3	10	0.90 (0.24 to 3.44)	0.88
Cows	5	3	10.89 (1.24 to 96.0)	0.01
Wood fires	4	1	12.55 (1.40 to 114.00)	0.009

dusts reported were metal, wood, coal, sand or stone, fabric, and tobacco dusts. Four index patients also reported occupational exposure to asbestos; in two of these cases the exposure had been recorded in the clinical notes and considered to be unimportant, and in two the exposure had not been recorded. The odds of disease given exposure to any of these dusts were not significantly increased (matched odds ratio 1.32 (95% confidence interval 0.85 to 2.04), p=0.19), but in relation to exposure to specific dusts more of the index patients had been exposed to metal dust (10.97 (2.30 to 52.4), p<0.001) and wood dust (2.94 (0.87 to 9.90)), though the effect of wood dust did not quite reach significance (p=0.08). Exposure to coal, asbestos, sand or stone, tobacco, or fabric dust did not differ significantly between the index patients and controls (table III). Index patients were more likely than controls, however, to have had occupations classified as dirty (3.09, 1.23 to 7.89, p<0.01), even after adjustment for exposure to wood and metal dusts (adjusted odds ratio 2.15 (0.78 to 5.95), p=0.14).

Index patients were more likely than controls to have worked with cattle (odds ratio 10.89 (1.24 to 96.0), p=0.01) and to have lived in a house heated by a wood fire (12.55 (1.40 to 114), p<0.01). There was no association between disease state and a history of having ever smoked (odds ratio 0.93 (0.37 to 2.35), p=0.88), duration of residence in any of the standard regions of the United Kingdom, social class based on occupation (manual or non-manual), age at leaving school, exposure to pets and animals other than cows, passive smoking, or domestic heating other than wood fires. Exposure to factors significantly associated with cryptogenic fibrosing alveolitis had always predated the clinical onset of the disease, in most patients by at least 10 years.

Allergic symptoms, defined as cough, wheeze, tight-

ness of the chest, shortness of breath, runny nose, or itchy eyes, were reported significantly more commonly by the index patients in association with exposure to household dust (2.60 (1.25 to 5.41), p=0.001), and tree, grass, or flower pollen (2.30 (1.09 to 4.85), p=0.03).

Discussion

In this study we identified patients with cryptogenic fibrosing alveolitis by applying clinical criteria similar to those used previously⁴⁻¹¹ and did not use histological criteria because lung biopsy is not widely used to investigate the disease in the United Kingdom.¹² We selected individually matched controls as the simplest and most efficient means of controlling for confounding by age, sex, and referral bias by the general practitioner.

Our identification of 46 patients with the disease among a local population of roughly 750 000 suggests a prevalence of about six cases per 100 000, which is slightly higher than previous estimates.¹² The higher proportion of men among our patients than in previous studies^{3,4,13} does not necessarily reflect sampling bias because previous reports have tended to be on selected patients from tertiary referral centres. A higher prevalence in men is also suggested by the fact that mortality from the disease in men is roughly double that in women.⁷ We were unable to determine, however, whether the effect of male sex is independent of occupational exposure to agents, because of the individual matching of cases and controls for sex.

We used a self administered questionnaire to collect information on exposure to dust and attempted to limit recall bias by keeping the patients and controls blinded to the hypothesis being tested. Some bias in recalling occupation is, however, inevitable because our patients had already had to provide occupational histories in the course of their clinical assessment. We were unable to validate the questionnaire responses on exposure to dust against any external standard, but responses to questions on exposure to animals and dust and on lifetime occupations were internally consistent. The data recorded with the questionnaire can therefore be considered to be reasonably valid.

The agents to which subjects reported occupational exposure in the questionnaire included a wide variety of dusts, particularly coal, sand or stone, fabric, tobacco, and asbestos dusts. Not all of these, however, would be expected to increase the risk of cryptogenic fibrosing alveolitis because some are recognised causes of other diagnostic categories of fibrotic lung disease. For example, clinically important exposure to asbestos in a patient with fibrosis of the lungs should lead to a diagnosis of asbestosis rather than cryptogenic fibrosing alveolitis and exposure to coal, sand, or stone dust may lead to a diagnosis of pneumoconiosis. In the event none of these exposures was associated with a significantly increased risk of cryptogenic fibrosing alveolitis. Whether a diagnosis of cryptogenic fibrosing alveolitis is justifiable when the patient has a history of exposure to asbestos, however minor, is unresolved; excluding the four patients with any exposure to asbestos from the analysis, however, did not substantially alter the results in relation to exposure to other dusts significantly associated with disease.

We found that exposure to metal dust was significantly increased in the patients. We also found a strong though non-significant association between cryptogenic fibrosing alveolitis and exposure to wood dust and a more general association with occupations classified as dirty. The patients were also more likely than the controls to have worked with cattle or to have been exposed to wood fires at home. Collectively these results support our hypothesis that environmental

dusts have a role in the aetiology of cryptogenic fibrosing alveolitis. Several metal dusts have been implicated as causes of pulmonary fibrosis,¹⁴ but whether in our patients metal and wood dusts were true fibrotic agents or markers of exposure to other fibogens is not clear. For example, workers exposed to metal dust are often also exposed to grinding or lubricating materials, and joiners exposed to wood dust may also work with insulation or roofing materials containing asbestos. In relation to exposure to cattle, cryptogenic fibrosing alveolitis in a dairy worker has previously been attributed to occupational exposure to hydrogen peroxide.¹⁵ Clearly, the extent of confounding by exposure to other agents needs to be explored, but the necessary detail is not available in the present study. Our finding that patients with cryptogenic fibrosing alveolitis had had a higher exposure to domestic wood fires adds support to a suggestion that wood smoke may be a cause of the disease.¹⁶ Cigarette smoke, however, had no appreciable effect in the present study despite an apparent protective effect against lung fibrosis due to extrinsic allergic alveolitis or sarcoidosis.^{17 18}

The relevance of the increased reporting of allergic symptoms by our patients is not clear as shortness of breath on exposure to allergens may be a non-specific symptom and recall bias may also have contributed. Further investigation of this is therefore indicated. Future studies should also investigate whether disease associated with inhalation of dust differs in terms of histological findings or clinical progress from the classic rapidly progressing form of the disease as cryptogenic fibrosing alveolitis might be a stereotyped end organ response to many different aetiological factors. The present evidence associating the disease with potentially avoidable exposure to environmental agents, however, raises the possibility that it may at least to some extent be preventable.

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Copies of the questionnaire are available on request.

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Rising mortality from cryptogenic fibrosing alveolitis

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Abstract

Objective—To determine the pattern of mortality ascribed to cryptogenic fibrosing alveolitis and to identify factors that might be important in the aetiology of the disease; and to assess the validity of death certification of the disease.

Design—A retrospective examination of mortality ascribed to cryptogenic fibrosing alveolitis in England and Wales between 1979 and 1988 with analysis, by multiple logistic regression, of independent effects of age, sex, region of residence, and social class as indicated by occupation on data for 1979-87; also a retrospective review of hospital records of patients certified as having died of cryptogenic fibrosing alveolitis in Nottingham and of the certified cause of death of patients known to have had the disease.

Main outcome measures—Time trends in mortality nationally; effects on mortality of age, sex, and region of residence; validity of death certification in Nottingham.

Results—The annual number of deaths ascribed to cryptogenic fibrosing alveolitis doubled from 336 in 1979 to 702 in 1988, the increase occurring mainly at ages over 65. Mortality standardised for age for both sexes likewise increased steadily over the period. Deaths due to cryptogenic fibrosing alveolitis were commoner in men (odds ratio 2.24, 95% confidence interval 2.11 to 2.33) and increased substantially with age, being 7.84 (7.24 to 8.49) times

higher in subjects aged ≥ 75 than those aged 45-64. Odds ratios of death due to cryptogenic fibrosing alveolitis adjusted for age and sex were increased in the traditionally industrialised central areas of England and Wales ($p < 0.02$, maximum odds ratio between regions 1.25), but no significant increase in odds of death was found for manual occupations. Of 23 people whose deaths were registered in Nottingham as having been due to cryptogenic fibrosing alveolitis, 19 were ascertained from clinical records to have had the disease. Only 17 of 45 patients known to have had cryptogenic fibrosing alveolitis in life were recorded as having died from the disease.

Conclusions—The diagnostic accuracy of death certification of cryptogenic fibrosing alveolitis is high, but the number of deaths recorded as being due to the disease may underestimate the number of patients dying with the disease by up to half. Mortality due to the disease is increasing, and the male predominance and regional differences in mortality suggest that environmental factors are important in its aetiology.

Introduction

The aetiology of cryptogenic (idiopathic) fibrosing alveolitis is unknown, and the mean life expectancy of a patient after presentation with the disease is only four

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