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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 multicenter 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 O_2 pressure was 80.2 mmHg (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 1. Characteristics of the study population

Variable	*n* (%)	
	Cases (*n* = 102)	Controls (*n* = 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)

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)		

[a]Adjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).
[b]Eight 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

[a]Adjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).
[b]Overall, 22 cases and 13 controls were exposed to moulds in two or more places.
[c]Overall, 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 (Malinauskiene *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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