Occupational and Environmental Risk Factors for Chronic Fibrosing idiopathic Interstitial Pneumonia in South Korea

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Objective: We studied the association of occupational and environmental agents with chronic fibrosing idiopathic interstitial pneumonia (IIP) in South Korea. **Methods:** We recruited 92 patients with chronic fibrosing IIP and 92 matched controls who had normal chest radiograph findings by age and gender. We used a structured exposure questionnaire to evaluate potential occupational and environmental risk factors for chronic fibrosing IIP, with adjustments for age, smoking, and clinical risk factors. **Results:** We used conditional logistic regression models to analyze associations with chronic fibrosing IIP adjusted for age, smoking and clinical risk factors. Exposure to stone, sand, or silica significantly increased the risk of chronic fibrosing IIP (odds ratio = 5.01; 95% confidence interval, 1.07–24.21) **Conclusions:** Our findings indicate that exposure to stone, sand, and silica might constitute a risk factor for developing chronic fibrosing IIP in the Korean population.

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of diffuse parenchymal lung diseases and non-neoplastic disorders of unknown cause that result from injury to the lung parenchyma and involve varying patterns of inflammation and fibrosis.[1] According to the current 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) update on IIP classification, the major IIPs are grouped into chronic fibrosing IIPs, which include idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (INSIP), smoking-related IIPs, and acute/subacute IIPs. Chronic fibrosing IIPs are by far the most common entities in this group of diseases. The diagnostic criteria are well established, but it is often difficult to distinguish between IPF and INSIP.[2]

Although the precise incidence and prevalence of IIPs are not known, recent studies in the United States[3,4] and United Kingdom[5,6] have shown an increase in the incidence of IPF. In addition, a review article has suggested an increasing prevalence of IPF in Western countries.[7] Moreover, IPF-related mortality seems to have increased over time.[8,9] The Korean Interstitial Lung Disease Research Group carried out a national, multicenter survey to evaluate prognostic factors in 1311 Korean patients with IPF and reported that occupational dust exposure was associated with mortality.[10] Therefore, the various occupational and environmental risk factors associated with IPF are of current interest.

Previous studies have suggested significant associations between IPF and particular occupational and environmental exposures, including agriculture/farming,[11] wood dust,[12] metal dust,[13,14] stone/sand/silica,[14–16] and tobacco smoking.[14,16] More recently, case-control studies have found associations for men with occupations related to woodworking, the chemical/petrochemical industry, and birch and hardwood dust exposure; associations for women with bird-raising and farm work,[17,18] and associations with metal mining and fabricated structural metal products.[19] Elemental analysis of the pulmonary hilar lymph nodes of patients affected by IPF has shown higher concentrations of inorganic particles (such as silicon and aluminum) than in controls.[20]

Thus far, previous case-control studies have suggested occupational and environmental agents that may contribute to the etiology of IPF, but their association with INSIP has not been evaluated. However, chronic pulmonary fibrosis results not only from IPF, but also from INSIP. In the assessment of chronic pulmonary fibrosis patients, it is important to determine their occupational and environmental history. It is also important to exclude environmental and occupational factors as secondary factors when diagnosing INSIP as a cause of chronic pulmonary fibrosis.[21] Studies have proposed several potential clinical etiologic risk factors for IPF, including diabetes mellitus (DM),[22,23] gastroesophageal reflux disease (GERD),[24] Epstein-Barr virus,[25] hepatitis C virus,[26] adenovirus,[27] and genetic factors.[28] But no study has yet been conducted adjusting for clinical risk factors to identify the influence of occupational and environmental risk factors on IPF. Therefore, the purpose of our research was to evaluate occupational and environmental factors that may contribute to the etiology of chronic fibrosing IIP, with adjustments for clinical risk factors.

We conducted a single-center, hospital-based, case-control study of clinically, radiologically, and histologically diagnosed chronic fibrosing IIP cases and matched controls to identify possible occupational and environmental risk factors of chronic fibrosing IIPs in South Korea. In this study, we focused on suggested clinical risk factors (eg, DM or GERD) and analyzed occupational and environmental risk factors of chronic fibrosing IIP with adjustments for these other factors.

METHODS

Study Design

This was a retrospective case-control study performed at a university hospital in South Korea. We extensively reviewed the medical records of patients diagnosed with IIP from January 2011 to December 2014 according to the criteria of the Korean Classification of Disease, sixth revision (KCD-6)[29] at a respiratory center at our institute. The diagnosis of chronic fibrosing IIP (including both IPF and INSIP) was made according to the established criteria of the ATS/ERS[1] and, when available, one or more of the following: surgical lung biopsy or a high-resolution computed tomography (HRCT) scan. A multidisciplinary discussion in which the clinical findings, HRCT results, and lung biopsy features with a

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This study was supported by 2014 Academic Award of The Korean Society of Occupational Asthma and Lung Diseases.

The authors report no conflict of interest.

Supplemental digital contents are available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.joem.org).

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DOI: 10.1097/JOM.0000000000001153

pulmonologist, radiologist, and pathologist is needed to diagnosis chronic fibrosing IIP with accuracy.[2] Our diagnostic process for chronic fibrosing IIP was as follows: when interstitial lung disease (ILD) was confirmed on HRCT, we identified whether it was idiopathic, and distinguished it from rheumatoid diseases such as rheumatoid arthritis, drugs, radiation, and occupational causes. We cooperated with rheumatoid physicians when necessary. If it was judged to be idiopathic, it was classified as IPF or IIP. If the HRCT findings corresponded to a typical case of IPF, the diagnosis was confirmed without a lung biopsy; however, if the findings were not definitive, a lung biopsy and consultation with a pathologist were conducted. Clinical-histological-radiological consensus was required. If a case was not IPF, the diagnosis relied on imaging findings to differentiate NSIP or other ILD, and if necessary, an attempt was made to arrive at a histological diagnosis.

All patients were over 20 years of age and consented to participate in the research. Patients with coexisting connective tissue disease (CTD) or a history of ingesting drugs or agents known to cause pulmonary fibrosis were excluded. The clinical data were collected by a thorough review of hospital charts, and non-clinical data were collected by telephone interview.

The controls were drawn from healthy subjects who were examined for an annual health check-up at the health examination center during the same period as case recruitment at our institute. Controls were randomly matched by age (±3 years) and gender, at a ratio of 5:1 controls per case. We recruited healthy controls that had normal chest radiograph findings. Three trained interviewers telephoned all subjects. The matched controls were ordered from 1 to 5. After explaining the purpose of the study, the interviewer sought consent for participation, and if the subject declined, the interviewer proceeded to call the next prospective matched control subject in the sequence. Thus, a 1:1 matching ratio of cases to controls was obtained. Data collection was approved by the institutional ethics committee of the Pusan Baik Hospital of Inje University (IRB No. 14-0106). All individuals in this study gave their informed consent before inclusion.

A total of 538 potential IIP patients were selected as cases as determined by the KCD-6 criteria.[29] A total of 297 patients were excluded due to factors such as the presence of other disease, lack of HRCT, death, or refusal to participate. A total of 141 cases along with 141 age- and sex-matched controls were interviewed by telephone, and their medical charts were reviewed. Thirty cases were excluded because of unclear diagnosis (possibility of CTD, cancer, etc) and 19 cases were excluded because of non-chronic fibrosing IIP. In total, 92 chronic fibrosing IIP cases and 92 matched controls were analyzed (Fig. 1). Of the 92 cases, 70 were IPF and 22 were INSIP. All 92 cases had HRCT. Of the 22 NSIP cases, five were diagnosed on the basis of a surgical lung biopsy (video-assisted thoracic surgery), HRCT findings, and clinical findings. The other 17 cases were diagnosed on the basis of HRCT findings and clinical consensus.

Exposure Assessment

Sociodemographic factors were assessed, including sex, age, smoking, education, marital status, income, and residential environment (flooding, pets, mold, adjacent industry). Interviews regarding occupational and environmental exposures were conducted over the telephone with a structured questionnaire by a trained industrial hygienist and industrial nurses. All collected data were reviewed and re-evaluated by an occupational and environmental medical specialist. Exposure data were collected for a checklist of 34 job activities and 22 specific occupational and environmental exposure agents that were assumed to be risk factors. Jobs were coded using the Standard Industrial Classification (SIC)[30] and the Standard Occupational Classification (SOC).[31] Exposure assessment was based on job title, job duties, and related information. Each job was assessed individually for potential exposure to harmful agents from the following categories: metal dust, stone/silica/sand, organic solvents, wood dust, organic dust, and inorganic dust. Data collected included the name of the company, a description of the job type and job sector, the start and stop years for the job, and exposure intensity, http://links.lww.com/JOM/A366. Nonetheless, it was not possible to quantify exposure precisely. Demographic factors included marital status,

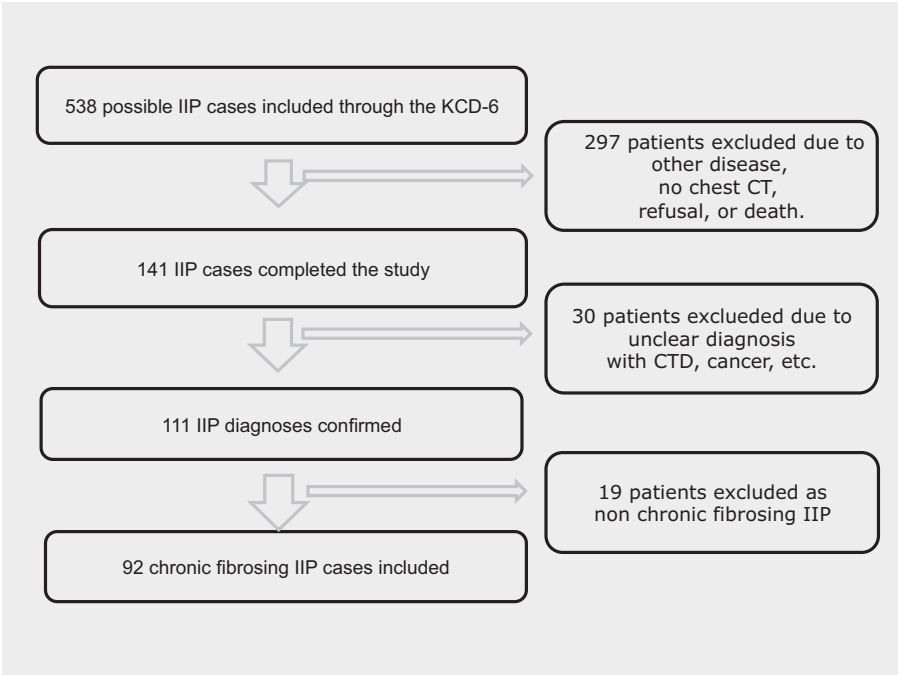

FIGURE 1. Flow diagram of case selection in this study. CT, computed tomography; CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; KCD-6, Korean Classification of Disease, 6th revision.

TABLE 1. Sociodemographic Characteristics of Subjects

	Cases (n = 92)	Controls (n = 92)	*P*	IPF (n = 70)	Controls (n = 70)	*P*	INSIP (n = 22)	Controls (n = 22)	*P*
Sex			1.000			1.000			1.000
Male	66 (71.7)	66 (71.7)		53 (75.7)	53 (75.7)		13 (59.1)	13 (59.1)	
Female	26 (28.3)	26 (28.3)		17 (24.3)	17 (24.3)		9 (40.9)	9 (40.9)	
Age			0.997			0.995			1.000
50–59	16 (17.4)	17 (18.5)		12 (17.1)	13 (18.6)		4 (18.2)	4 (18.2)	
60–69	30 (32.6)	29 (31.5)		18 (25.7)	17 (24.3)		12 (54.5)	12 (54.5)	
70–79	36 (39.1)	36 (39.1)		31 (44.3)	31 (44.3)		5 (22.7)	5 (22.7)	
80–89	10 (10.9)	10 (10.9)		9 (12.9)	9 (12.9)		1 (4.5)	1 (4.5)	
Smoking			0.000			0.000			0.372
Current smokers	8 (8.7)	19 (20.7)		6 (8.6)	15 (21.4)		2 (9.1)	4 (18.2)	
Ex-smokers	56 (60.9)	28 (30.4)		47 (67.1)	23 (32.9)		9 (40.9)	5 (22.7)	
Never smokers	28 (30.4)	45 (48.9)		17 (24.3)	32 (45.7)		11 (50.0)	13 (59.1)	
Educational level			0.001			0.004			0.030
Low	47 (68.1)	29 (37.2)		35 (63.6)	20 (35.1)		12 (85.7)	9 (42.9)	
Moderate	15 (21.7)	29 (37.2)		14 (25.5)	19 (33.3)		1 (7.1)	10 (47.6)	
High	7 (10.1)	20 (25.6)		6 (10.9)	18 (31.6)		1 (7.1)	2 (9.5)	
Diabetes mellitus history			0.254			0.825			0.132
No	72 (48.0)	78 (84.8)		57 (81.4)	58 (82.9)		15 (68.2)	20 (90.9)	
Yes	20 (21.7)	14 (15.2)		13 (18.6)	12 (17.1)		7 (31.8)	2 (9.1)	
Environmental exposure			0.044			0.718			0.048
Yes	10 (10.9)	3 (3.3)		5 (7.1)	3 (4.3)		5 (22.7)	0	
No	82 (89.1)	89 (10.9)		65 (92.9)	67 (95.7)		17 (77.3)	22 (100)	

IPF, idiopathic pulmonary fibrosis; INSIP, idiopathic nonspecific interstitial pneumonia.

education, income, residential environment status, and smoking. The clinical data were evaluated for the presence of comorbidity in current or past medical history, including conditions such as GERD, DM, hepatitis C virus, human herpes virus, and chronic pulmonary disease, along with initial diagnostic year and dyspnea status.

Statistical Analysis

Statistical analysis was performed using the chi-square test and the Fisher exact test to evaluate differences in sociodemographic factors and between the two groups. Data were analyzed with conditional logistic regression for matched case-control groups. Associations between two variables were assessed by odds ratios (OR) and 95% confidence intervals (CIs). Conditional logistic regression models were examined for associations with specific occupations and occupational exposure agents with adjustments for age and smoking. Adjustments for clinical risk factors were also analyzed. All statistical analyses were performed using SPSS software version 21.0 (IBM Corp, Armonk, NY).

RESULTS

A total of 92 chronic fibrosing IIP patients and 92 healthy controls matched for age and sex were analyzed. The study included 70 patients with IPF and 22 patients with INSIP, out of 92 cases of fibrosing IIP. Table 1 shows the baseline demographic and clinical characteristics of the subjects. Both groups were successfully matched for sex and age, and male gender (71.7%) was predominant among the subjects. Most subjects were between 60 and 80 years of age. Regarding smoking status, ever-smoker status in patients with chronic fibrosing IIP was significantly more frequent than in controls. However, in a comparison of the IPF and INSIP groups, the proportion of females and never smokers was higher in the INSIP group than in the IPF group. A lower education level was reported more frequently in cases (68.1%) than in controls (25.6%), although 20.1% of the respondents did not provide their education level in the survey. There was no significant difference between the two groups regarding history of DM, which is considered a clinical risk factor for IPF. We interviewed the subjects regarding their

TABLE 2. Associations According to Occupation for Chronic Fibrosing Idiopathic Interstitial Pneumonia Patients and Controls

Occupations[a]	Cases (n = 92)	Controls (n = 92)	OR[b]	95% CI	IPF (n = 70)	Controls (n = 70)	OR[b]	95% CI	INSIP (n = 22)	Controls (n = 22)	*P*[c]
Metal, machinery-related trades	8	8	1	0.22–4.45	5	6	0.58	0.11–3.26	3	2	1.00
Building construction/demolition	7	4	1.37	0.34–5.53	6	3	2.55	0.51–12.85	1	1	1.00
Agriculture	18	13	1.98	0.79–4.99	16	7	4.50	1.25–16.23	2	6	0.24
Carpentry or woodworking	2	6	0.24	0.03–1.79	2	6	0.27	0.04–2.00	0	0	–
Textile making/repair	3	5	0.83	0.17–4.18	3	3	2.18	0.30–16.12	0	2	–
Hairdressing	2	1	2	0.18–22.01	1	0	–	–	1	1	1.00
Leather processing	2	1	1.18	0.05–28.90	2	1	0.73	0.02–27.14	0	0	–

CI, confidence interval; IPF, idiopathic pulmonary fibrosis; INSIP, idiopathic nonspecific interstitial pneumonia; OR, odds ratio.
[a]Occupations were based on a checklist of past and current jobs. Occupations were included if the total number of exposed controls was ≥1.
[b]OR determined using conditional logistic regression adjusted for age (continuous), smoking (ever/never).
[c]*P* value calculated by the Fisher exact test.

TABLE 3. Associations According to Occupational and Environmental Exposure for Chronic Fibrosing Idiopathic Interstitial Pneumonia Patients and Controls

Occupational and Environmental Exposure Agents[a]	Cases (n = 92)	Controls (n = 92)	OR[b]	95% CI	IPF (n = 70)	Controls (n = 70)	OR[b]	95% CI	NSIP (n = 22)	Controls (n = 22)	*P*[c]
Organic dust	21	17	1.6	0.70–3.66	19	10	2.87	0.98–8.36	2	7	0.132
Textile dust	4	4	1.31	0.28–6.10	4	2	3.14	0.46–21.46	0	2	0.489
Insecticide/pesticides	17	13	1.94	0.76–4.94	15	7	4.45	1.21–16.37	2	6	0.240
Stone/sand/silica	14	3	4.98	1.05–23.63	10	1	8.84	1.07–73.49	3	2	1.000
Wood dust	8	6	1.08	0.30–3.90	7	6	1.15	0.30–4.38	1	0	1.000
Solvent	15	6	2.84	0.87–9.31	13	4	3.00	0.70–12.88	2	2	1.000
Welding fumes/metal dust	13	8	1.89	0.51–7.07	9	6	0.83	0.18–3.89	4	2	0.664

CI, confidence interval; IIP, idiopathic interstitial pneumonia; OR, odds ratio.
[a]Occupational and environmental agents were based on a checklist of past and current jobs and adjacent residential dust exposure. Occupations were included if the total number of exposed controls was ≥1.
[b]OR determined using conditional logistic regression adjusted for age (continuous) and smoking (ever/never).
[c]*P* value calculated by the Fisher exact test.

history of environmental exposure to mold, pets, past flooding in residential areas, and dust exposure from adjacent areas; environmental dust exposure was more common in cases than in controls.

Tables 2 and 3 show the occupations and occupational and environmental exposures based on the SIC/SOC classification of associated chronic fibrosing IIP risk factors adjusted for age and smoking. We present occupations and occupational exposure agents reported by more than one individual in the control group in Tables 2 and 3. ORs were greater for the following occupational categories: building construction/demolition (OR = 1.37), agriculture (OR = 1.98), hairdressing (OR = 2.00), and leather processing (OR = 1.18). However, these differences were not statistically significant. In the subgroup analysis by IPF and INSIP group, agriculture (OR = 4.50) was also significantly associated with IPF (Table 2). Only occupational and environmental exposure to stone/sand/silica was significantly associated with chronic fibrosing IIP (OR = 4.98; 95% CI, 1.05–23.63) adjusted for age and smoking. Exposure to organic dust (OR = 1.6), textile dust (OR = 1.31), pesticides (OR = 1.94), wood dust (OR = 1.08), solvents (OR = 2.84), and welding fumes/metal dust (OR = 1.89) was more common in chronic fibrosing IIP subjects, but the differences were not statistically significant. However, occupational and environmental exposure to stone/sand/silica (OR = 8.84) and insecticide/pesticides (OR = 4.45) were significantly associated with IPF (Table 3).

We used conditional logistic regression models (Table 4) to analyze the risk for chronic fibrosing IIP, adjusted for age, smoking, and clinical risk factors. Exposure to stone/sand/silica significantly increased the risk of chronic fibrosing IIP (OR = 5.01; 95% CI, 1.07–24.21). ORs were greater following occupational and environmental exposure to wood dust (OR, 1.09), welding fumes/metal dust (OR, 1.85), and organic dust (OR, 1.63). However, these differences were not statistically significant. We conducted a subgroup analysis. In the IPF group, exposure to stone/sand/silica significantly increased the risk, but not in the INSIP group (Table 5).

DISCUSSION

The relevance of occupational and environmental risk factors to IPF is already well known from a number of previous studies. However, no reports have been published on associations between occupational and environmental risk factors and chronic fibrosing IIP that explicitly include patients with INSIP. In the 2013 ATS/ERS update on IIPs, INSIP lost the label ''provisional'' and is now acknowledged as a distinct clinical entity, no longer viewed as a potential ''wastebasket'' for unclassified ILD.[2] It is difficult to accurately distinguish IPF and INSIP in diagnosis. Thus, there is a high probability that cases of IPF and cases of INSIP have been included among patients in previous case-control studies on the contribution of occupational and environmental risk factors to IPF. Cases of NSIP associated with curry powder and ground-pepper factory work in Japan have been reported,[32] and the possibility of other occupation-related substances as triggering factors for INSIP was discussed in a study conducted in Spain.[33] Accordingly, this study shows that occupational and environmental risk factors may contribute to the etiology of chronic fibrosing IIP.

The main finding of our study was a statistically significantly increased risk for chronic fibrosing IIP from exposure to stone, sand, or silica dust. Taskar and Coultas[14] reported a significant association between an increased risk for IPF and sand/stone/silica exposure

TABLE 4. Conditional Logistic Regression Models for the Risk of Chronic Fibrosing Idiopathic Interstitial Pneumonia According to Occupations and Occupational and Environmental Exposure, Adjusted for Various Variables

			Model I		Model II	
	Cases (n = 92)	Controls (n = 92)	OR	95% CI	OR	95% CI
Stone/sand/silica	14	3	4.98	1.05–23.63	5.01	1.07–24.21
Wood dust	8	6	1.08	0.30–3.90	1.09	0.30–3.93
Welding fumes/metal dust	13	8	1.89	0.51–7.07	1.85	0.50–6.88
Organic dust	21	17	1.6	0.70–3.66	1.63	0.71–3.73

CI, confidence interval; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HCV, hepatitis C virus; IIP, idiopathic interstitial pneumonia; OR, odds ratio.
Model I was adjusted by age (continuous) and smoking (ever/never).
Model II was adjusted by age (continuous), smoking (ever/never), and clinical risk factors (DM, GERD, HCV, herpes virus).

TABLE 5. Conditional Logistic Regression Models for the Risk Among Subgroups (Idiopathic Pulmonary Fibrosis/Nonspecific Interstitial Pneumonia) of Chronic Fibrosing Idiopathic Interstitial Pneumonia According to Occupations and Occupational and Environmental Exposure, Adjusted for Various Variables

			Model I		Model II				Model I		Model II	
	IPF (n = 92)	Contros (n = 92)	OR	95% CI	OR	95% CI	INSIP (n = 92)	Controls (n = 92)	OR	95% CI	OR	95% CI
Stone/sand/silica	10	1	8.84	1.07–73.49	8.75	1.05–72.96	3	2	1.00	0.06–15.81	1.00	0.06–15.80
Wood dust	7	6	1.15	0.30–4.38	1.16	0.30–4.44	1	0	–	–	–	–
Welding fumes/metal dust	9	6	0.83	0.18–3.89	0.82	0.18–3.84	4	2	–	–	–	–
Organic dust	19	10	2.87	0.98–8.36	2.83	0.97–8.26	2	7	0.37	0.36–3.69	0.21	0.13–3.51

CI, confidence interval; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; HCV, hepatitis C virus; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; INSIP, idiopathic nonspecific interstitial pneumonia; OR, odds ratio.

Model I was adjusted by age (continuous) and smoking (ever/never).

Model II was adjusted by age (continuous), smoking (ever/never), and clinical risk factors (DM, GERD, HCV, herpes virus).

Some agents were not included in the calculations due to the small number in the NSIP category (wood dust, welding fume/metal dust).

(OR = 1.97; 95% CI, 1.09–3.55) from a meta-analysis of four articles in 2006. In Japan, it has been shown that cases presented with silicon in the lymph nodes more often than controls, and these deposits were statistically significantly associated with an increased risk of IPF or usual interstitial pneumonia (OR = 2.99; 95% CI, 1.29–6.85).[20] Our study showed that the OR of stone/sand/silica risk was 4.98 when adjusted for age and smoking, and became 5.01 when adjusted for age, smoking, and clinical risk factors. Thus, we report higher ORs than previous studies. This may be due to differences in the study region, the number of subjects, the matching conditions for selected subjects, or the inclusion of the INSIP group. In one study, 22 miners in an underground iron ore mine demonstrated an airway inflammatory response in induced sputum, with increased levels of macrophages, neutrophils, fibronectin, and matrix metalloprotein-9. The macrophages are thought to be the main source of fibronectin.[34]

In our study, exposure to metal dust and wood dust did not result in a statistically significant increased risk for chronic fibrosing IIP. However, other case-control studies have reported that exposure to metal dust,[13,14] or wood dust,[12,18] resulted in a significantly increased risk for IPF. According to the aforementioned meta-analysis, a significant association was found between risk for IPF and exposure to wood dust (OR = 1.94; 95% CI, 1.34–2.81) or metal dust (OR = 2.44; 95% CI, 1.74–3.40).[14] Exposure to stone/silica, wood, or metal dust is thought to induce chronic pulmonary inflammation and lead to IPF.[10] Our negative results may be due to selection bias and a small number of subjects.

We also divided the subjects into the IPF and INSIP categories and analyzed them accordingly. No significant occupational and environmental risk factors were found to be associated with the INSIP category. However, we cannot conclude that cases in the INSIP group was not related to occupational and environmental risks, because the INSIP group was so small in our study, with only 22 subjects. Therefore, in future long-term prospective studies, it will be necessary to establish larger INSIP groups and to conduct INSIP case-control studies.

Although a relationship of causation has not been established between clinical risk factors and IPF, previous studies have proposed a relation between GERD and the presence and progression of IPF.[24] GERD is hypothesized to lead to chronic microaspiration of gastric contents, both acidic and non-acidic, causing repetitive lung injury and resulting in pulmonary fibrosis in susceptible individuals.[35] In addition, type 2 DM has been assumed to be significantly associated with a higher risk for IPF.[22,36] However, our study showed no significant difference in comorbidity with DM between cases (21.7%) and controls (15.2%). After adjusting by sex and smoking status, type 2 DM was the most important independent predictor associated with IPF risk (OR = 4.3; 95% CI, 1.9–9.8) in a study conducted in Mexico.[23] High glucose levels may serve as a pathogenic mechanism by activating several pathways related to the production of cytokines, growth factors, and reactive oxygen species, which can mediate tissue damage and fibrosis in DM.[37] Thus, we conducted a conditional logistic regression adjusting for clinical risk factors to analyze the effect of occupational and environmental risk factors on chronic fibrosing IIP, while excluding the effect of clinical risk factors. Stone/sand/silica exposure was the only significant risk factor for chronic fibrosing IIP, even adjusting for clinical risk factors.

There are several limitations to our study. Recall bias was present in the case-control study design due to retrospective data collection by telephone interview, as well as selection bias due to the relatively small sample size, with subjects drawn from a single university hospital in South Korea, which limited the statistical power of the results. IPF and INSIP diagnoses in patients were rarely confirmed by lung tissue biopsy. Thus, misdiagnosis of cases may have occurred. Despite these limitations, the main strength of our study is the validity of the diagnosis of chronic fibrosing IIP (ATS/ERS consensus, and particularly the fact that diagnoses of CTD were excluded), and the comparison of cases with a healthy control group that is close to the general community group. Previous case-control studies were conducted prior to 2013.[11,18,23] At that time, the diagnostic criteria for IPF and INSIP were not clear or consistent, and occupational and environmental surveys may have been conducted without the input of an occupational and environmental specialist in the construction of the structured questionnaire; in addition, some studies included patients with other pulmonary disease among the controls.[17,23] Thus, it was possible that occupational and environmental dust effects were underestimated. An additional strength of this study is that we ensured the quality of the systematic survey by utilizing a structured questionnaire designed with the input of industrial hygienists and industrial nurses before the interview. Finally, our results may better identify occupational and environmental risk factors because we adjusted for clinical risk factors in our analysis. No epidemiologic study of the occupational and environmental risk factors associated with the development of chronic fibrosing IIP has previously been conducted. Thus, our study makes a meaningful new contribution.

CONCLUSION

Our findings indicate that exposure to stone, sand, and silica may constitute a risk factor for developing chronic fibrosing IIP in the Korean population. Further study is needed to identify how the

inhalation of stone, silica, or sand may stimulate lung epithelial cells and macrophages, induce an inflammatory reaction, and result in chronic pulmonary fibrosis. In order to determine whether INSIP is associated with any important occupational and environmental risks, further prospective, large-scale studies are needed.

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