American Journal of Epidemiology

Vol. 152, No. 4
Printed in U.S.A.

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

Kathy B. Baumgartner,[1] Jonathan M. Samet,[2] David B. Coultas,[1] Christine A. Stidley,[3] William C. Hunt,[1] Thomas V. Colby,[4] James A. Waldron,[5] and Collaborating Centers

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.

Received for publication April 20, 1998, and accepted for publication November 29, 1999.

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

[1] Epidemiology and Cancer Control Program and the New Mexico Tumor Registry, Cancer Research and Treatment Center, University of New Mexico Health Sciences Center, Albuquerque, NM.
[2] Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD.
[3] Department of Family and Community Medicine, University of New Mexico School of Medicine, Albuquerque, NM.
[4] Laboratory Medicine and Pathology, Mayo Clinic Scottsdale, Scottsdale, AZ.
[5] Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR.
Reprint requests to Dr. Jonathan M. Samet, Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, 615 N. Wolfe St., Suite W6041, Baltimore, MD 21205-2179 (jsamet@jhsph.edu).

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 interview 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 numbers. 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	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	2.3, 52.4
Smoking	1.6	1.1, 2.4	1.6	1.0, 2.4	2.9	1.4, 6.3	1.1	0.1, 1.4
Stone/sand dust§	3.9	1.2, 12.7	1.8	1.0, 3.1			1.6	0.5, 4.8
Textile dust¶	1.9	0.8, 4.4	1.8	1.1, 3.0			0.9	0.2, 3.4
Wood dust¶	1.6	0.8, 3.3	1.7	1.0, 2.9			2.9	0.9, 9.9
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.

ACKNOWLEDGMENTS

This research was supported by grants HL43153 and HL40587 from the Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health.

Participating collaborating centers and researchers were as follows. *Pulmonary and Critical Care Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio*: Dr. Robert Baughman; *Pulmonary Disease and Critical Care Medicine, University of Vermont, Burlington, Vermont*: Dr. Gerald S. Davis; *Occupational Lung Center, Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, Indiana*: Dr. Joe G. N. Garcia; *Pulmonary Division, University of Iowa Hospitals and Clinics, Iowa City, Iowa*: Dr. Gary W. Hunninghake; *Pulmonary Disease Unit, Highland Hospital, Rochester, New York*: Dr. Michael C. Kallay; *National Jewish Medical and Research Center, University of Colorado, Denver, Colorado*: Dr. Talmadge E. King, Jr.; *Mayo Medical School, Mayo Clinic Jacksonville, Jacksonville, Florida*: Dr. Michael J. Krowka; *Pulmonary and Critical Care Medicine Section, University of Nebraska Medical Center, Omaha, Nebraska*: Dr. Stephen I. Rennard; *Mayo Medical School, Mayo Clinic, Division of Pulmonary and Critical Care Medicine, Rochester, Minnesota*: Dr. Jay H. Ryu; *Pulmonary Division, The Miriam Hospital, and Brown Medical University, East Providence, Rhode Island*: Dr. Charles B. Sherman; *Pulmonary Division, Department of Medicine, Pulmonary and Critical Care Division, Northwestern University Medical School, Chicago, Illinois*: Dr. Lewis J. Smith; *Division of Pulmonary and Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, Michigan*: Dr. Galen Toews; and *Virginia Mason Medical Center, Section of Pulmonary and Critical Care Medicine, Seattle, Washington*: Dr. Richard H. Winterbauer.

REFERENCES

1. King TE. Idiopathic pulmonary fibrosis. In: Schwarz MI, King TE, eds. Interstitial lung disease. St. Louis, MO: Mosby Year Book, Inc, 1993:367–403.
2. Coultas DB. Epidemiology of idiopathic pulmonary fibrosis. Semin Respir Med 1993;14:181–96.
3. Mapel DW, Hunt WC, Utton R, et al. Idiopathic pulmonary fibrosis: survival in population-based and hospital-based cohorts. Thorax 1998;53:469–76.
4. Crystal RG, Bitterman PB, Rennard SI, et al. Interstitial lung diseases of unknown cause. Disorders characterized by chronic inflammation of the lower respiratory tract (first of two parts). N Engl J Med 1984;310:154–66.
5. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 1994; 150:967–72.
6. Schwartz DA, Helmers RA, Dayton CS, et al. Determinants of bronchoalveolar lavage cellularity in idiopathic pulmonary fibrosis. J Appl Physiol 1991;71:1688–93.
7. Smith C, Feldman C, Levy H, et al. Cryptogenic fibrosing alveolitis: a study of an indigenous African population. Respiration 1990;57:364–71.
8. de Cremoux H, Bernaudin JF, Laurent P, et al. Interactions between cigarette smoking and the natural history of idiopathic pulmonary fibrosis. Chest 1990;98:71–6.
9. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980;35:171–80.
10. Carrington CB, Gaensler EA, Coutu RE, et al. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978;298:801–9.
11. Stack BHR, Choo-Kang YFJ, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972;27:535–42.
12. Ramage JE, Roggli VL, Bell DY, et al. Interstitial lung disease and domestic wood burning. Am Rev Respir Dis 1988;137: 1229–32.
13. Marsh P, Johnston I, Britton J. Atopy as a risk factor for cryptogenic fibrosing alveolitis. Respir Med 1994;88:369–71.
14. Vergnon JM, De Thé G, Weynants P, et al. Cryptogenic fibrosing alveolitis and Epstein-Barr virus: an association? Lancet 1984;2:768–71.
15. Egan JJ, Stewart JP, Hasleton PS, et al. Epstein-Barr virus replication within pulmonary epithelial cells in cryptogenic fibrosing alveolitis. Thorax 1995;50:1234–9.
16. Ueda T, Ohta K, Suzuki N, et al. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. Am Rev Respir Dis 1992;146:266–8.
17. Irving WL, Sarinder D, Johnston IDA. Idiopathic pulmonary fibrosis and hepatitis C virus infection. Am Rev Respir Dis 1993;148:1683–4.
18. Kuwano K, Nomoto Y, Kunitake R, et al. Detection of adenovirus E1A DNA in pulmonary fibrosis using nested polymerase chain reaction. Eur Respir J 1997;10:1445–9.
19. Bitterman PB, Rennard SI, Keogh BA, et al. Familial idiopathic pulmonary fibrosis: evidence of lung inflammation in unaffected family members. N Engl J Med 1986;314:1343–7.
20. Iwai K, Mori T, Yamada N, et al. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med 1994;150:670–5.
21. Hubbard R, Lewis S, Richards K, et al. Occupational exposure to metal or wood dust and aetiology of crytogenic fibrosing alveolitis. Lancet 1996;347:284–9.
22. Baumgartner KB, Samet JM, Stidley CA, et al. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997;155:242–8.
23. Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. BMJ 1990;301:1015–17.
24. Monsó E, Tura JM, Marsal M, et al. Mineralogical microanalysis of idiopathic pulmonary fibrosis. Arch Environ Health 1990;45:185–8.
25. Cherniack RM, Colby TV, Flint A, et al. Quantitative assessment of lung pathology in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1991;144:892–900.
26. Katzenstein A-LA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157:1301–15.
27. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
28. Davis GS, Calhoun WJ. Occupational and environmental causes of interstitial lung disease. In: Schwarz MI, King TE, eds. Interstitial lung disease. St. Louis, MO: Mosby Year Book, Inc, 1993:179–229.
29. Office of Management and Budget. Standard Industrial Classification manual. Springfield, VA: National Technical Information Service, 1987.
30. US Department of Commerce. Standard Occupational Classification manual. Washington, DC: US Government Printing Office, 1980.
31. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publication no. 32).
32. SAS Institute, Inc. SAS/STAT software: the PHREG procedure, version 6. Cary, NC: SAS Institute, Inc, 1991. (SAS technical report P-217).
33. Waldron HA. Non-neoplastic disorders due to metallic, chemical and physical agents. In: Parkes WR, ed. Occupational lung disorders. Oxford, UK: Butterworth-Heineman, Ltd, 1994: 593–643.
34. Craighead JE. Inorganic and organic dust pollutants. In: Craighead JE, ed. Pathology of environmental and occupational disease. St. Louis, MO: Mosby Year Book, Inc, 1995: 79–102.
35. Parkes WR. An approach to the differential diagnosis of asbestosis and nonoccupational diffuse interstitial pulmonary fibrosis. In: Parkes WR, ed. Occupational lung disorders. Oxford, UK: Butterworth-Heineman, Ltd, 1994:505–35.
36. Philippou S, Teschler H, Morgenroth K. Pulmonary fibrosis after inhalation of amorphous silicic acid. (In German). Zentralbl Pathol 1992;138:41–6.
37. Jederlinic PJ, Abraham JL, Churg A, et al. Pulmonary fibrosis in aluminum oxide workers. Am Rev Respir Dis 1990;142: 1179–84.
38. De Vuyst P, Dumortier P, Rickaert F, et al. Occupational lung fibrosis in an aluminium polisher. Eur J Respir Dis 1986;68: 131–40.
39. Vallyathan V, Bergeron WN, Robichaux PA, et al. Pulmonary fibrosis in an aluminum arc welder. Chest 1982;81:372–4.
40. Zanelli R, Barbic F, Migliori M, et al. Uncommon evolution of fibrosing alveolitis in a hard metal grinder exposed to cobalt dusts. Sci Total Environ 1994;150:225–9.
41. Figueroa S, Gerstenhaber B, Welch L, et al. Hard metal interstitial pulmonary disease associated with a form of welding in a metal parts coating plant. Am J Ind Med 1992;21:363–73.
42. Nemery B, Nagels J, Verbeken E, et al. Rapidly fatal progression of cobalt lung in a diamond polisher. Am Rev Respir Dis 1990;141:1373–8.
43. Cugell DW, Morgan WKC, Perkins DG, et al. The respiratory effects of cobalt. Arch Intern Med 1990;150:177–83.
44. Huaux F, Lasfargues G, Lauwerys R, et al. Lung toxicity of hard metal particles and production of interleukin-1, tumor necrosis factor-α, fibronectin, and cystatin-c by lung phagocytes. Toxicol Appl Pharmacol 1995;132:53–62.
45. Lison D, Lauwerys R, Demedts M, et al. Experimental research into the pathogenesis of cobalt/hard metal lung disease. Eur Respir J 1996;9:1024–8.
46. Dosman JA, Graham BL, Hall D, et al. Respiratory symptoms and pulmonary function in farmers. J Occup Med 1987;29: 38–43.
47. Liebertrau G. The occupational spectrum in alveolitis and pulmonary fibrosis. (In German). Z Gesamte Innere Medizin Ihre Grenzgebiete 1990;45:584–6.
48. Kirsten D, Liebetrau G, Meister W. Wood dust as inhalative noxious agent. (In German). Z Erkrankungen Atmungsorgane

1985;165:235–41.
49. Chronic interstitial lung disease in nylon flocking industry workers—Rhode Island, 1992–1996. MMWR Morb Mortal Wkly Rep 1997;46:897–901.
50. Schwartz DA, van Fossen DS, Davis CS, et al. Determinants of progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994;149:444–9.
51. Seaton A, Morgan WKC. Hypersensitivity pneumonitis. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. Philadelphia, PA: WB Saunders Company, 1984:564–608.
52. Axelson O. A note on observational bias in case-referent studies in occupational health epidemiology. Scand J Work Environ Health 1980;6:80–2.
53. Bourbonnais R, Meyer F, Theriault G. Validity of self-reported work history. Br J Ind Med 1988;45:29–32.
54. Samet JM. What can we expect from epidemiologic studies of chemical mixtures? Toxicology 1995;105:307–14.
55. Hubbard R, Johnston I, Coultas DB, et al. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. Thorax 1996;51:711–16.
56. Johnston I, Britton J, Kinnear W, et al. Rising mortality from cryptogenic fibrosing alveolitis. BMJ 1990;301:1017–21.
57. Coultas DB, Hughes MP. Accuracy of mortality data for interstitial lung diseases in New Mexico, USA. Thorax 1996;51:717–20.
58. Mapel DW, Samet JM, Coultas DB. Corticosteroids and the treatment of idiopathic pulmonary fibrosis: past, present, and future. Chest 1996;110:1058–67.