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Occupational Risks for Idiopathic Pulmonary Fibrosis Mortality in the United States

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

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The idiopathic interstitial pneumonias are a group of diffuse parenchymal lung diseases that share many features but are sufficiently different from one another to be considered separate entities. The term idiopathic pulmonary fibrosis (IPF), formerly applied to a group of diseases, is now used to describe a distinct clinical disorder, defined by the histological pattern of usual interstitial pneumonia, as recommended by an international collaboration including the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the American College of Chest Physicians (ACCP).[1,2] In contrast, the tenth International Classification of Diseases (ICD-10) defines IPF (code J84.1) as "Other interstitial pulmonary diseases with fibrosis (diffuse pulmonary fibrosis, fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, idiopathic pulmonary fibrosis)."[3] We sought to describe patterns of IPF mortality in the United States 1999–2003 and to investigate a possible association between occupational exposure in specific industries and IPF mortality. To facilitate comparisons with previous studies, we used the terminology IPF to refer to the group of diseases classified under ICD-10.

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

The etiology of IPF is still largely unknown. The disease typically occurs in patients more than 50 years old, and mortality five years after diagnosis is estimated to be 50–70%.[7] Viruses, such as Epstein-Barr, may play a role in the development of IPF.[8] Some studies have demonstrated either serological or immunocytological evidence of infection and, in some cases, replication of Epstein-Barr virus in the lungs of patients with IPF compared with controls.[9] Other viruses also implicated in the pathogenesis of IPF include influenza,[10] cytomegalovirus,[11] and herpesvirus-6.[12] Pulmonary fibrosis may be a rare complication of exposure to certain drugs, including antidepressants, beta blockers, antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs.[13] Cigarette smoking is associated with respiratory bronchiolitis even in young asymptomatic

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

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

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

MATERIALS AND METHODS

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

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

Assessment of Occupational Risks

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

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

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

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

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RESULTS

Descriptive Statistics

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

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

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

Proportionate Mortality Ratio

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

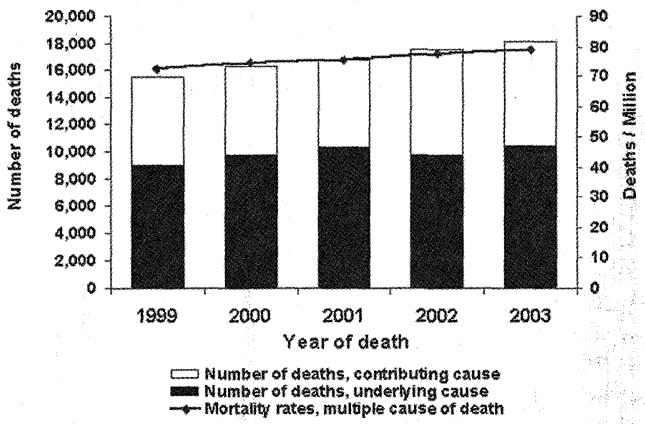

Figure 1—"Other interstitial pulmonary diseases with fibrosis": number of deaths (contributing and underlying cause of death) and age-adjusted mortality rates (multiple cause of death) by year, United States residents age 15 and over, 1999–2003.

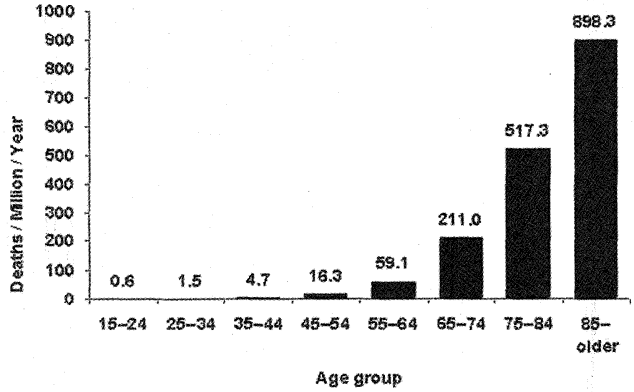

Figure 2—"Other interstitial pulmonary diseases with fibrosis": mortality rates by age group; United States residents age 15 and over, 1999–2003.

Mortality Odds Ratio

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

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

DISCUSSION

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

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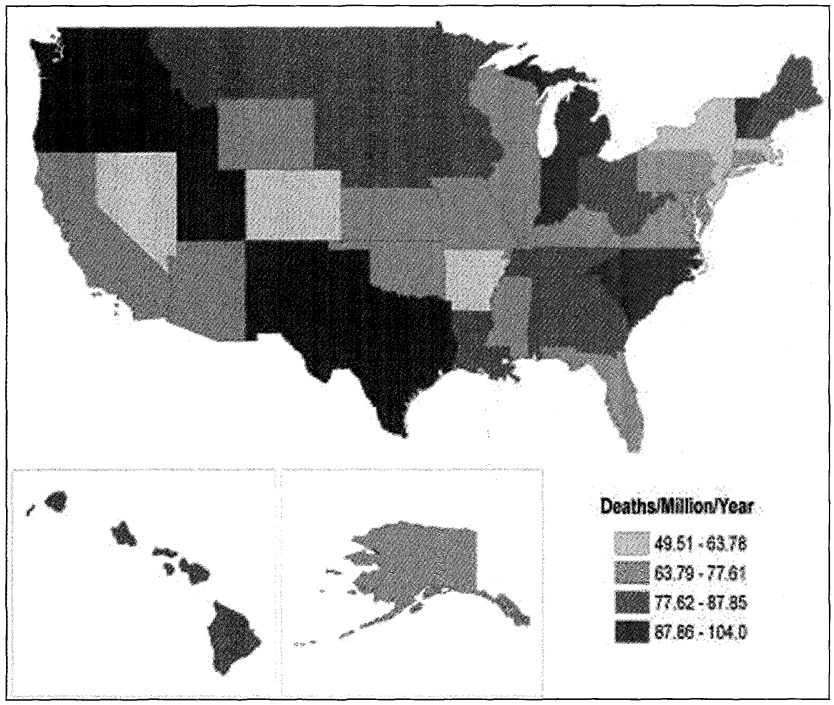

Figure 3—"Other interstitial pulmonary diseases with fibrosis": age-adjusted mortality rates by state, United States residents age 15 and over, 1999–2003.

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

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

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

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

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

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

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

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

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

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

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

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

The analysis of over 20,526 deaths registered with the pension fund of a metal engineering company in the United Kingdom between 1968–1997, demonstrated that the proportional mortality from IPF was increased compared with the general population (PMR = 1.4, 95% CI 1.1–1.8). Among employees exposed to metals there was evidence of linear increase in the risk of IPF with duration of exposure (OR per 10 years of exposure = 1.7, 95% CI 1.1–2.7). There was no evidence of an association between duration of employment and IPF for employees who were not metal workers.[17]

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

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

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

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

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

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

CONCLUSIONS

Three of the industries with likely exposure to wood or metal dust have among the highest PMRs for IPF in the United States. The MOR analysis confirmed the PMR findings. Thus, our analysis of mortality data supports previous morbidity studies about the role of occupational factors in the etiology of IPF, specifically in industries with likely wood and metal exposures. Pulmonary fibrosis represents a disorder with a potentially complex group of causes. In addition, IPF remains a heterogeneous disease, which further complicates etiology studies. Nevertheless, toxicological studies of different types of metal, wood, and other exposures in at-risk industries may assist in elucidating disease pathogenesis and draw attention to effective prevention strategies for IPF.

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Appendix 1.
International Classification of Diseases (ICD-10) Codes for Interstitial Lung Diseases Other Than Idiopathic Pulmonary Fibrosis or Causes of Pulmonary Fibrosis

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

Appendix 2.
International Classification of Diseases (ICD-10) Codes for Sudden, Injury- or Poisoning-related, and Some External Causes of Death

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

Appendix 3.
List of Industries Used to Assign Cases and Controls to the "Unexposed" Category

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

[a] Source: Bureau of the Census. 1990 Census of Population and Housing alphabetical index of industries and occupations. 1990 CPH-R-3. Washington, DC: U.S. Department of Commerce, 1992.
[b] Source: National Center for Health Statistics. 1994. Public use data tape documentation: Multiple Cause of Death for ICD-9 1992 data. Division of Vital Statistics, Hyattsville, MD.