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Case-Control Study of Idiopathic Pulmonary Fibrosis and Environmental Exposures

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Abstract

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17 cases (37.7%) and 94 controls (32.4%) responded to the questionnaire, although many of the case addresses were no longer valid.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

Interstitial lung diseases (ILD) are thought to represent approximately 15% of clinical pulmonary practice. A population-based registry in the United States suggested a prevalence of 70 per 100,000 in the United States,1 with over half occurring without obvious cause. The mean survival for this disease is four to six years after initial diagnosis, and an estimated 8400 to 14000 Americans die of this disease annually. ILD is associated with a long list of chronic diseases, including collagen vascular and autoimmune disorders. Approximately 3% are thought to be related to occupation.1 Occupational exposures associated with diffuse interstitial fibrosis (DIF) generally lead to additional characteristics, ie, asbestosis to asbestos bodies and pleural changes, hard metal disease to giant cells, silicosis to silicotic nodules, and coal workers pneumonoconiosis to centrilobular emphysema and anthracosis. In clinical practice, the diagnosis of work-related ILD is often made simply on the basis of an abnormal chest x-ray and a pertinent occupational history. Idiopathic pulmonary fibrosis (IPF) is estimated to occur at a prevalence of approximately three to five cases per 100,000 in the United Kingdom. Johnston et al noted rising mortality from IPF with significant variations between regions of England and Wales,2 suggesting environmental exposures in the etiology of the disease. No etiologic studies of ILD have been published in the United States. In the United Kingdom, IPF was associated with metals exposure and wood dust 3,4 in two studies.

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

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

Outline

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

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Subjects and Methods

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

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

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

Data were entered by a commercial vendor using double-key entry, with an error rate of less than .02%. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) for Windows. Standard statistical tests were used. True Epistat Version 5.1 [18] was used to analyze matched case controls by logistic regression for occupational and domestic exposure to asbestos, mold/mildew, and silica.

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Results

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

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


Table 1

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

0.57 to 80.7; with *P*= 0.09) were not significantly elevated, mold or mildew (odds ratio, 16.00; 95% CI, 1.62 to 158; *P* = 0.003) and silica (odds ratio, 11.00; 95% CI, 1.05 to 115; *P* = 0.016) were significantly more frequent among cases. These exposures were reported in four (26.6%) and three (20,0%) of cases, respectively.

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

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


Table 2

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

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Discussion

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

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

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

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

A second hypothesis was that moisture sources in the home are associated with DIF. Some home risk factors approached significance, but none appeared robust. Having poor exhaust in bathroom and kitchen, mold in the bathroom, and the presence of humidifiers in the home did not reach significance. A recent report of pneumonitis in children 21 identified home moisture and growth of the mycotoxin producing fungus*Stachybotrys atra* (now called *chartarum*) as a risk factor. Such exposures are associated with pulmonary disease in animals.22 Mycotoxins affect alveolar macrophage function.23,24 Recent outbreaks of mycotoxin-associated disease in adults have been associated with building moisture.25 Other reports have indicated that*Stachybotrys atra*,26,27*Aspergillus versicolor,* and several toxigenic species of*Penicillium* are potentially hazardous, especially when the air-handling systems have become heavily contaminated.23,24 Dampness of the buildings was the primary factor of concern.28-30 At least one group of authors have argued that a component of most fungal cell walls might be the primary etiologic agent rather than mycotoxins.31

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

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Just the Facts

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

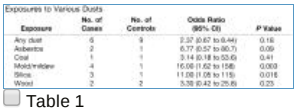
Americans declaring bankruptcy in 1996: 1 in 225 % change since 1982 of time Americans were delayed in traffic: +95

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

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

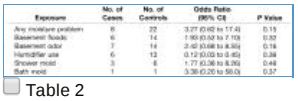
IMAGE GALLERY

Select All **Export Selected to PowerPoint**


Exposures to Various Dusts

Exposure	No. of Cases	No. of Controls	Odds Ratio (95% CI)	P Value
Any dust	6	9	2.37 (0.67 to 8.44)	0.16
Asbestos	2	1	6.77 (0.57 to 80.7)	0.09
Coal	1	1	3.14 (0.18 to 53.6)	0.41
Mold/mildew	4	1	16.08 (1.62 to 158)	0.003
Silica	3	1	11.08 (1.05 to 115)	0.016
Wood	2	2	5.38 (0.42 to 25.8)	0.23

Table 1



Exposure	No. of Cases	No. of Controls	Odds Ratio (95% CI)	P Value
Any moisture problem	8	22	3.27 (0.62 to 17.4)	0.15
Basement floods	6	14	1.90 (0.52 to 7.10)	0.32
Basement odor	7	14	2.42 (0.66 to 8.80)	0.18
Humidifier use	6	12	0.12 (0.03 to 0.45)	0.24
Shower mold	3	6	1.77 (0.36 to 8.36)	0.48
Bath mold	1	1	3.36 (0.20 to 56.0)	0.37

Table 2

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