Exposures and Idiopathic Lung Disease

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ABSTRACT

Of the idiopathic lung diseases, idiopathic pulmonary fibrosis (IPF) and sarcoidosis have been the focus of a growing number of epidemiological investigations on the risk of environmental and occupational exposures. To date, the consistency of epidemiological evidence is suggestive of a causal relationship between several environmental exposures and IPF, with the strongest evidence for cigarette smoking and metal dust. Current knowledge about pathogenesis provides further support for a causal link. However, scant epidemiological evidence for dose–response and temporality weaken the case for making causal inferences. In contrast to IPF, the quantity of epidemiological evidence for environmental exposures and sarcoidosis is smaller. Two studies provide consistent evidence for exposures to agricultural dust and musty odor/mold/mildew, and studies among military personnel and firefighters suggest mixed dust and fume exposures as risk factors for sarcoidosis. Although studies of the pathogenesis of sarcoidosis also provide evidence supporting environmental causation, more epidemiological studies are needed to establish consistency of associations, dose–response, and temporality. Future investigations, of gene–environment interaction offer the potential for strengthening the evidence of causation between several environmental and occupational exposures and idiopathic lung diseases.

KEYWORDS: Idiopathic pulmonary fibrosis, sarcoidosis, exposures, epidemiology, causation

Idiopathic lung diseases (ILDs) are a heterogeneous group of disorders (Table 1) without known cause, but growing evidence suggests that several environmental agents may have a causal role in selected disorders.[1,2] The available evidence linking various exposures and ILD includes studies of pathogenesis, clinical observations, and epidemiological investigations.[1,3,4] This review focuses on the most common ILDs, idiopathic pulmonary fibrosis (IPF) and sarcoidosis.

Of the available studies describing the distributions of the various ILDs, IPF and sarcoidosis have the highest occurrence.[5–11] In a 2001 report, Thomeer and coworkers[6] compared the relative incidence and prevalence of interstitial lung diseases recorded in registries from the United States, Belgium, Germany, and Italy. The distribution of diagnoses was most similar among the European registries compared with the U.S. registry, which was limited to New Mexico.[5] Overall, combining all incident cases ($n = 700$) from the registries, the four most frequent diagnoses were IPF (27%), sarcoidosis (24%), postinflammatory pulmonary fibrosis (14%), and hypersensitivity pneumonitis (9%). Because postinflammatory pulmonary fibrosis may include a substantial proportion of cases of IPF, the relative frequency of IPF is likely higher.

CAUSAL INFERENCE

The prevention of disease by eliminating exposure provides the strongest evidence for disease causation.

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Table 1 Categories of Idiopathic Lung Diseases

Idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia
Collagen vascular diseases associated with interstitial pneumonitis
Sarcoidosis
Eosinophilic pneumonia
Eosinophilic granuloma
Alveolar hemorrhage syndromes
Idiopathic pulmonary hemosiderosis
Alveolar proteinosis
Diffuse panbronchiolitis

Table 2 Classification of Levels of Evidence for Making Causal Inferences

LEVEL 1: EVIDENCE IS SUFFICIENT TO INFER A CAUSAL RELATIONSHIP
The evidence fulfills the criteria for level 2, and supports the criteria of biological plausibility, consistency, coherence, temporality, and exposure–response gradient.
LEVEL 2: EVIDENCE IS SUGGESTIVE BUT NOT SUFFICIENT TO INFER A CAUSAL RELATIONSHIP
Consistent evidence for associations from two or more high-quality studies (i.e., sufficiently free of chance, bias, or confounding), with acceptable disease and exposure measurement.
LEVEL 3: EVIDENCE IS INADEQUATE TO INFER THE PRESENCE OR ABSENCE OF A CAUSAL RELATIONSHIP
Evidence of insufficient quality, quantity, or consistency of an association.
LEVEL 4: EVIDENCE IS SUGGESTIVE OF NO CAUSAL RELATIONSHIP
Evidence from several high quality studies with acceptable disease and exposure measurement; and consistently demonstrate no association.

Adapted from U.S. Surgeon General Report 2004.[12]

However, obtaining this level of evidence is often not feasible, and multiple sources of evidence are used in the process of making causal inferences, which involves evaluating the quality of individual studies and synthesizing results from several sources.[12] The objective of this process is to estimate the level of uncertainty about the causal link between an exposure and disease (Table 2). At the level of individual studies the focus is first on evaluating the potential role of alternative explanations, other than cause and effect for an association between an exposure and disease, including bias, confounding, and chance. After establishing an association with little evidence of bias, confounding, or chance the process involves evaluating the available evidence from multiple sources, including toxicological, experimental, and observational studies. A useful framework for integrating evidence from these multiple sources was described by Hill[13] and included nine criteria: (1) experimentation, (2) plausibility, (3) coherence, (4) analogy, (5) consistency of association, (6) strength of association, (7) biological gradient, (8) temporality, and (9) specificity. Of the original criteria, specificity is no longer relevant because multiple causation of disease is a well-established concept today. This framework for evaluating evidence and making causal inferences has been described and adapted by the U.S. surgeon general (Table 2).[12]

Studies of pathogenic mechanisms of ILD address several of Hill's criteria, including coherence, biological plausibility, experimentation, and analogy. Coherence "implies that a cause and effect interpretation for an association does not conflict with what is known of the natural history and biology of the disease" and may be difficult to distinguish from plausibility.[14] Environmental and occupational agents cause epithelial cell injury in IPF, which may be followed by an aberrant inflammatory response in the lung parenchyma and a deranged healing process resulting in fibrosis (Fig. 1).[3,15] Whereas, development of sarcoidosis requires exposure to an antigen, which is presented by a macrophage via human leukocyte antigen (HLA) class 2 molecules to a T lymphocyte. This induces a T helper (Th)-1 T-lymphocyte response whereby cytokines are released that result in granuloma formation (Fig. 1).[4] Both responses may result in progressive impairment of gas exchange and lung mechanics. Moreover, analogy suggests that if an environmental agent may cause one diffuse parenchymal lung disease then it is reasonable that the same or other agents may also cause other parenchymal lung diseases. The obvious examples supporting this criterion for a link between exposures and ILD are asbestos causing asbestosis and beryllium causing berylliosis, each indistinguishable from IPF and sarcoidosis, respectively. The experimental evidence on pathogenic mechanisms in IPF and sarcoidosis support the criterion of biological plausibility, but the details are beyond the scope of this review and are described elsewhere.[3,4]

This review focuses on the ILD for which epidemiological evidence is available to address any of the other four criteria of consistency and strength of exposure–disease associations, biological gradient (i.e., dose–response), or temporality. There are several challenges in studying the ILD, which may affect the quality of evidence and thus the interpretation. These challenges are considered in the next section.

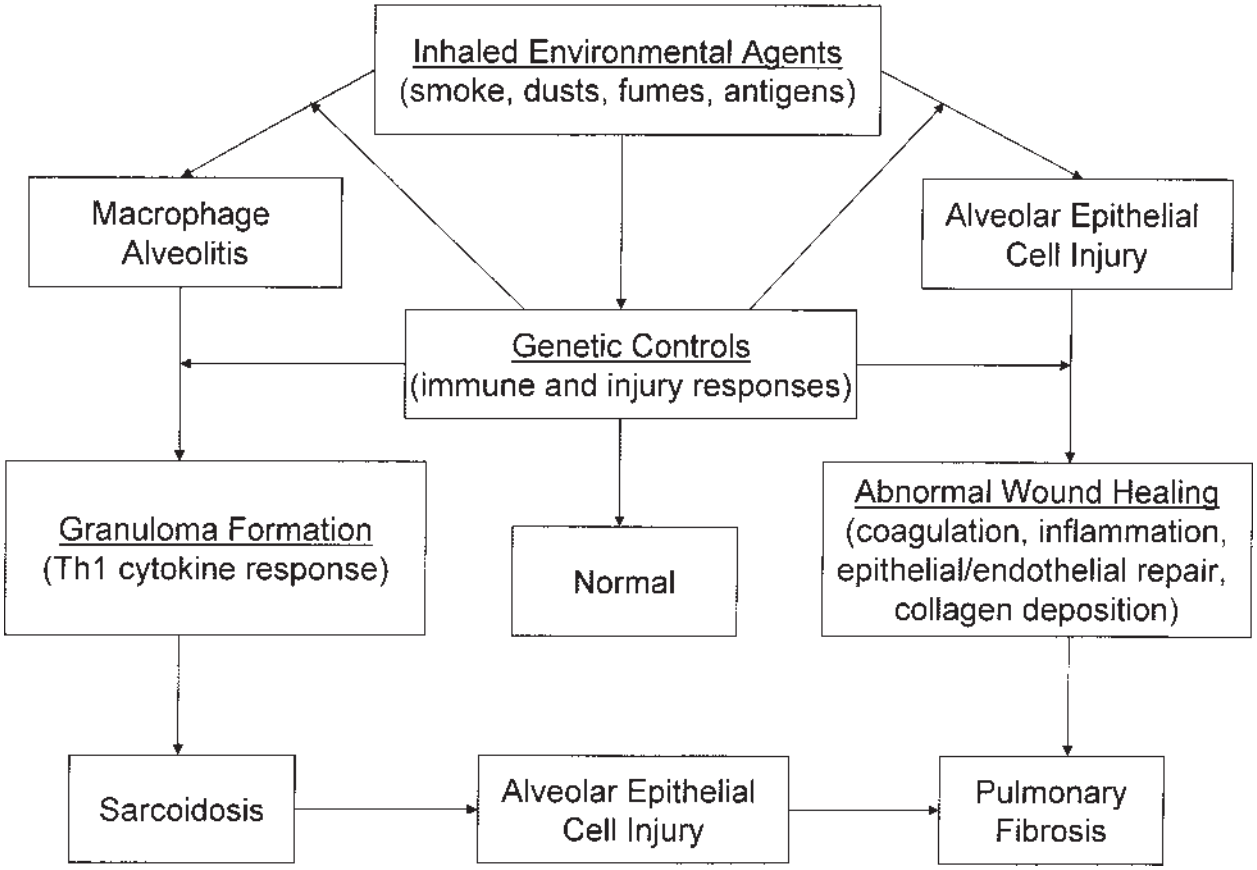

Figure 1 Proposed pathogenic mechanisms for development of pulmonary fibrosis[3,15] and granulomas[4] with exposure to environmental and occupational agents.

CHALLENGES FOR STUDYING IDIOPATHIC LUNG DISEASES

While the biological plausibility for a link between exposures and ILDs is strong, establishing a causal link in the clinical setting or through epidemiological studies presents several challenges. These challenges include (1) infrequent occurrence of ILD, (2) diagnostic misclassification, (3) exposure misclassification, and (4) variation in susceptibility to exposures. Of these challenges the relatively infrequent occurrence is a major barrier for conducting etiological studies,[5,9,10] and, although these studies have been conducted for some of the more common ILDs such as IPF and sarcoidosis, few or no data are available for many of the rarer diseases (Table 1).

Although a biopsy is the gold standard for diagnosis of IPF and sarcoidosis, few patients with IPF ever have a lung biopsy,[5,6] and there may be variation in the interpretation of the biopsy,[16] resulting in diagnostic misclassification. The advent of high-resolution computed tomography (HRCT) has enhanced the diagnosis of ILD, particularly IPF.[17] However, the available etiological studies of IPF[1] were conducted before widespread use of HRCT and before the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on the classification of the idiopathic interstitial pneumonias.[18] For sarcoidosis, a form of diagnostic misclassification may result if the different phenotypes of sarcoidosis (i.e., isolated pulmonary vs systemic) are combined when examining risk of exposures.[19] In general, the strength of an association between an exposure and disease is reduced as a consequence of diagnostic misclassification.[14]

Identifying and measuring exposures that likely occurred remotely and over many years prior to diagnosis may be difficult for the patient and clinician and may result in exposure misclassification. Furthermore, quantitative measures of dose and duration of exposure, which are important determinants of occupational and environmental lung diseases, may be virtually impossible to establish. As with diagnostic misclassification, random exposure misclassification will weaken an association between exposure and disease.[14]

Variation in susceptibility for development of lung injury and disease is also likely determined by genetic variations of the complex biological responses to inhaled environmental agents (Fig. 1).[3,4,20,21] Little is known about the genetic determinants of susceptibility for IPF[20] or sarcoidosis,[21] but this variation has the potential to limit detection of a causal link with only exposure information.

EPIDEMIOLOGICAL EVIDENCE

The available evidence linking various exposures with IPF and sarcoidosis includes studies of pathogenesis, clinical observations, and epidemiological investigations.[1,22] However, because the evidence on pathogenesis has been reviewed extensively elsewhere,[3,4] and clinical observations from case reports and case series provide weak evidence for making causal inferences, this review focuses on epidemiological evidence.

IDIOPATHIC PULMONARY FIBROSIS

IPF is one of the seven clinicopathological entities in the ATS/ERS classification of idiopathic interstitial pneumonias (IIPs) (Table 1)[18] and has been the focus of several etiological studies on occupational and environmental risk factors that have been reviewed previously.[1] The first study was published in 1990,[23] and to date, a total of six case-control studies and one cohort study[24] have been conducted in the United States, United Kingdom, and Japan. Self-reports have been the primary method for measuring the occupational and environmental exposures in these studies. Exposures associated with IPF in two or more independent studies include smoking, agriculture/farming, livestock, wood dust, metal dust, and stone/sand/silica (Table 3).[1]

Smoking

Cigarette smoking has consistently been associated with an increased risk for IPF with odds ratios (ORs) of 1.11 to 3.23 (Table 3) among ever smokers.[23,25–29] Of five case-control studies that have examined smoking (Table 3), the increased risk was statistically significant in four, and the summary OR combining the results of all of the studies is 1.58 [95% confidence interval (CI) 1.27 to 1.97].[1] The increased risk was largely isolated to former smokers.[26,28] However, there is little evidence for a dose–response relationship between smoking and IPF.[26,28] In a separate family-based case-control study of familial interstitial pneumonia, Steele and coworkers[29] identified 111 families, with 309 affected and 360 unaffected family members. After adjusting for age and gender, ever smoking was a strong risk factor (OR = 3.6, 95% CI 1.3 to 9.8). The overall increased risk of ever smoking and the high prevalence among cases (66.3%) and controls (56.1%) (Table 3) translate into a population-attributable risk of 49%, suggesting that 49% of IPF may be prevented with the elimination of cigarette smoking.[1]

Agriculture/Farming

Exposure to agriculture and farming were examined in two of the case-control studies[27,30] with statistically significant ORs of 1.6 and 3.0 (Table 3). The overall prevalence of exposure among cases and controls was 25.7% and 17.3%, respectively, and the estimated population-attributable risk was 21%.[1]

Livestock

In two studies,[23,30] exposure to livestock was examined with statistically significant ORs of 2.7 and 10.9 (Table 3). Moreover, using multiple logistic regression adjusting for age and ever smoking, Baumgartner and coworkers[30] found limited evidence for a dose–response effect with an adjusted OR of 2.1 (95% CI 0.7 to 6.1) for < 5 years of exposure compared with 3.3 (95% CI 1.3 to 8.3) with 5 or more years of exposure.

Combining results from Scott and coworkers[23] and Baumgartner and coworkers[30] the overall prevalence of exposure to livestock among cases and controls was 10.4% and 5.0%, respectively, and because of the lower

Table 3 Case-Control Studies of Occupational and Environmental Risk Factors for Idiopathic Pulmonary Fibrosis[a]

Exposure	England/Wales Scott et al[23] (40/106)[b]	Trent region, UK Hubbard et al[25] (218/569)	United States Mullen et al[31] (17/94)	United States Baumgartner et al[30] (248/491)	Japan Iwai et al[27] (86/172)	Japan Miyake et al[28] (102/59)
Agriculture/ Farming				1.60 (1.0–2.5)	3.01 (1.29–7.43)	
Livestock	10.89 (1.24–96.0)			2.70 (1.30–5.50)		
Wood dust	2.94 (0.87–9.9)	1.71 (1.01–2.92)	3.3 (0.42–25.8)	1.60 (0.80–3.30)		6.71 (0.37–123.59)
Textile dust	0.9 (0.24–3.44)	1.80 (1.10–2.96)		1.90 (0.80–4.40)		
Mold			16.0 (1.62–158)			0.98 (0.48–2.01)
Metal dust	10.97 (2.34–52.4)	1.68 (1.07–2.65)		2.00 (1.00–4.00)	1.34 (1.14–1.59)	9.55 (1.68–181.12)
Stone/sand/ silica	1.59 (0.52–4.79)	1.76 (1.01–3.07)	11.0 (1.05–115)	3.90 (1.20–12.70)		
Wood fires	12.55 (1.40–114.0)			0.80 (0.40–1.60)		
Smoking	1.11 (0.13–1.40)	1.57 (1.01–2.43)		1.60 (1.10–2.40)	2.94 (1.37–6.3)	3.23 (1.01–10.84)

[a]Odds ratio (95% confidence interval).
[b]Number of cases/number of controls. Adapted from Taskar and Coultas 2006.[1]

prevalence of exposure compared with smoking and other agricultural and farming exposures, the estimated population-attributable risk was low at 4%.[1]

Wood Dust

Exposure to wood dust was examined in five studies,[23,25,28,30,31] with a statistically significant OR in only one of the five studies (Table 3). The overall prevalence of exposure among cases and controls was 9.3% and 4.9%, respectively, and because of the lower prevalence of exposure, the estimated population attributable risk was low at 5%.[1]

Metal Dust

In five studies,[23,25,27,28,30] exposure to metal dust was examined with statistically significant ORs in all five (Table 3). Two studies provide evidence of a dose–response relationship.[24,30] Using multiple logistic regression adjusting for age and ever smoking, Baumgartner and coworkers[30] found limited evidence for a dose response effect with an adjusted OR of 1.4 (95% CI 0.4 to 4.9) for < 5 years of exposure compared with 2.2 (95% CI 1.1 to 4.7) with 5 or more years of exposure. In a cohort study of workers at a metal engineering company in the United Kingdom, Hubbard and coworkers[24] found a dose–response increase in risk of IPF with an OR of 1.71 (95% CI 1.09 to 2.68) per 10 years of exposure.

Combining results from the five studies that have examined metal dust exposure the overall prevalence of exposure among cases and controls was 11.8% and 5.4%, respectively. Because of the lower prevalence of exposure, the estimated population-attributable risk was low at 3.4%.[1]

Stone/Sand/Silica

In four studies,[23,28,30,31] exposure to stone/sand/silica was examined, with statistically significant ORs in three of the four studies (Table 3). The overall prevalence of exposure among cases and controls was 6.9% and 3.5%, respectively, and because of the lower prevalence of exposure, the estimated population-attributable risk was low at 3.5%.[1]

Other Exposures

Additional exposures have been significantly associated with IPF, but the level of risk has only been investigated in a single population of patients. In a multivariate analysis adjusting for age, ever smoking, and other exposures Baumgartner and coworkers found significant associations for hairdressing (OR 4.8, 95% CI 1.2 to 19.0) and raising birds (OR 4.1 95% CI 1.3 to 13.4).[30] The overlap between IPF and chronic hypersensitivity pneumonitis[32,33] may explain the association with raising birds.

Conclusions

Because of the relatively infrequent occurrence of IPF the case-control design offers the most feasible approach for investigating risk of environmental exposures in this disorder. While recognizing the potential for diagnostic and exposure misclassifications, which likely results in an underestimation of the magnitude of risk, the consistent, statistically significant associations in different populations provide suggestive evidence for numerous environmental exposures causing IPF (Table 3). The level of evidence, based on the number of studies with significant associations, is strongest for cigarette smoking and metal dust. However, limited evidence is available for dose–response relationships.

Using the framework for classifying evidence from available epidemiological studies in making causal inferences, the evidence is suggestive but not sufficient to infer a causal relationship between several environmental exposures and IPF (level 2) (Table 2). Although studies of pathogenesis provide evidence supporting the criteria of biological plausibility and coherence for environmental causes of IPF,[3] more data are needed on dose–response and temporality before the evidence is sufficient to infer a causal relationship. However, the feasibility of designing a study to address temporality is doubtful given numerous challenges, including infrequent occurrence, and problems of diagnostic and exposure misclassification.

SARCOIDOSIS

Compared with IPF, the available etiological studies on environmental exposures and sarcoidosis are more limited (Table 4). However, for decades ecological studies, case reports, and case series have suggested several associations between sarcoidosis and environmental factors.[34] Studies on variation in the occurrence of sarcoidosis between regions provide indirect evidence for the role of environmental exposures.[35] Although high occurrence of sarcoidosis has been reported in northern European countries and for those living in rural or coastal residences, specific exposure measures are lacking.[35] Moreover, variations between geographic regions are confounded by regional variations in racial and ethnic groups, such as high rates among African Americans.

Earlier studies have reported associations with pica, pine pollen,[36] the lumber industry,[37] and the use of wood stoves.[38] Furthermore, workers exposed to beryllium develop granulomatous disease that closely resembles sarcoidosis.[39] Granuloma formation is also induced by other inorganic dusts, including aluminum,

Table 4 Case-Control Studies of Occupational and Environmental Risk Factors for Sarcoidosis[a]

Exposure	Kucera et al[52] (273/921)[b]	Newman et al[2] (706/706)	Barnard et al[44] (706/706)
Metal machining /dusts Titanium	7.47 (1.19–47.06)		0.69 (0.48–0.98)
	3.15 (1.02–9.68)		
Exposure to welding		0.4 (0.16-.96)	
Industrial organic dust Cotton ginning		4.98 (1.19–20.89)	2.57 (1.35–5.16)
Agricultural dusts	1.82 (1.01–3.27)	1.46 (1.13–1.89)	
Work insecticide exposure		1.61 (1.13–2.28)	
Building materials			3.2 (1.12–11.17)
Air conditioning at home		1.48 (1.10–1.99)	
Raising birds		3.73 (1.10–12.59)	
Educators	2.18 (1.07–4.44)	1.80 (1.14 - 2.83)	1.42 (1.02–1.99)
Indoor high humidity	1.51 (1.13–2.02)		
Musty odor / mold/mildew	1.78 (1.32–2.4)	1.61 (1.13–2.31)	
Transportation	12.71 (1.32–122.56)		
Automobile manufacturing		13.38 (1.48–120.98)	
Smoking		0.62 (0.5–0.77)	

[a]Odds ratio (95% confidence interval).
[b]Number of cases/number of controls.

barium, cobalt, copper, gold, lanthanides, titanium, and zirconium[40] ; humanmade mineral fibers (glass fibers or rock wool); clay and crystalline silica[41]; and mixed dust exposures.[42] Based on observations of transmission of disease to organ recipients from tissue donors with sarcoidosis infectious agents have been implicated,[43] although none has been conclusively demonstrated.[22]

The major epidemiological evidence on environmental exposures and risk for sarcoidosis has been derived from a recent large case-control study of patients with sarcoidosis identified from health care settings and smaller studies that have focused on selected populations, including military personnel, fire fighters, familial sarcoidosis, and silica-exposed workers. Results of these investigations of exposures to noninfectious agents are described separately in the following sections.

Health Care Populations

The largest and most comprehensive etiological study of sarcoidosis was A Case Control Etiologic Study of Sarcoidosis (ACCESS), which resulted in several publications on risk associated with environmental and occupational factors.[2,19,44] Patients with sarcoidosis were identified from 10 academic health centers in the United States, and a total of 706 newly diagnosed patients with sarcoidosis enrolled along with an equal number of age-, race-, and sex-matched control subjects. Newman and coworkers[2] found statistically significant positive associations for sarcoidosis after adjusting for age, sex, and race in multiple logistic regression with the use of home central air conditioning (OR = 1.48, 95% CI 1.10 to 1.99), occupational exposure to insecticides (OR = 1.61, 95% CI 1.13 to 2.28), occupational exposure to musty odors (OR = 1.62, 95% CI 1.24 to 2.11), occupation as a middle or high school teacher (OR = 1.8, 95% CI 1.14 to 2.83), involvement in raising birds (OR = 3.73, 95% CI 1.10 to 12.59), employment in cotton ginning (OR = 4.98, 95% CI 1.19 to 20.89), and automobile manufacturing (OR = 13.38, 95% CI 1.48 to 120.98). A lower risk for sarcoidosis was found with ever smoking cigarettes (OR = 0.65, 95% CI 0.51 to 0.82) and exposure to welding (OR = 0.4, 95% CI 0.16 to 0.96) (Table 4).

Barnard and coworkers[44] used standard industrial classification codes and standard occupational classification codes to evaluate the risk of sarcoidosis with various workplaces (Table 4). In univariate analyses several factors were associated with an increased risk of sarcoidosis, including retail sales (selling building materials, hardware, garden supplies, and mobile homes), industrial inorganic dusts (aerosolized raw plant material, manufacturing textiles, paper, agricultural chemicals), work in elementary/secondary schools, and employment as an educator (Table 4). A larger number of occupations were associated with a decreased risk of sarcoidosis, including personal service (OR = 0.48, 95% CI 0.29 to 0.78), electrical energy (OR = 0.5, 95% CI 0.25 to 0.96), social and rehabilitation services (OR = 0.62, 95% CI 0.44 to 0.87), child care (OR = 0.65, 95% CI 0.45–0.93), information services (OR = 0.65, 95% CI 0.42 to 1.0), and metal dust/metal fume exposures (OR = 0.69, 95% CI 0.48 to 0.98). These results are limited by the lack of control for confounding factors.

In the same publication Barnard and coworkers[44] conducted stratified analyses to examine variation in risk with race and gender. Among Caucasians but not among African Americans, they found increased risks for sarcoidosis associated with exposures to industrial organic dusts (OR = 8.7, 95% CI 2.7 to 44.7) and employment

in colleges/universities (OR = 1.74, 95% CI 1.06 to 2.91). Several other exposures were associated with increased risk among African Americans but not Caucasians, including dusty trades with crustal dust (OR = 2.57, 95% CI 1.02 to 7.28), metal working fluids (OR = 2.2, 95% CI 1.16 to 4.36), metal dust/fume (OR = 1.8, 95% CI 1.08 to 3.06), transportation equipment (OR = 2.18, 95% CI 1.03 to 4.93), and general merchandise stores (OR = 1.73, 95% CI 1.05 to 2.92). Among women, increased risk of sarcoidosis was associated with employment in real estate (OR = 3.38, 95% CI 1.49 to 8.60) and as supervisors or in sales/retail (OR = 2.41, 95% CI 1.34 to 4.53). Employment in national security was associated with a decreased risk (OR = 0.30, 95% CI 0.11 to 0.73) among women. These results should be interpreted cautiously because of multiple comparisons and lack of control of confounding.

In another analysis from ACCESS, Kreider and coworkers[19] examined how the risk of several exposures varied with different phenotypes of sarcoidosis (i.e., pulmonary-only versus systemic). In multivariate analyses adjusting for confounding factors and multiple comparisons only workplace agricultural organic dust among whites (OR = 0.33, (95% CI 0.16 to 0.71) and wood burning among blacks (OR = 0.36, 95% CI 0.23 to 0.59) were significantly associated with a lower risk of systemic disease.

Rural Residence

In a separate case-control study of 44 patients with sarcoidosis from South Carolina, risk factors associated with living in a rural environment were investigated.[38] Using multiple logistic regression adjusting for confounding factors only wood stoves (OR = 3.1, 95% CI 1.2 to 7.9) and fireplaces (OR = 5.7, 95% CI 1.8 to 18.4) were significantly associated with sarcoidosis. There was evidence for a dose–response effect, but the effect was only statistically significant for fireplaces.

Military Population

Gentry and coworkers[45] analyzed records from 297 cases of sarcoidosis among American armed forces personnel from World War II. A high proportion was African American from the rural southeastern United States. The greatest difference in race-specific occurrence was almost 7 to 1 for the various soil areas in the Southeast. This study suggested a possible etiologic agent in the soils in the southeastern United States, but as an ecological study lacked specific exposure information.

In 1992, an enlisted serviceman developed symptomatic pulmonary sarcoidosis after his work grinding antiskid materials from aircraft carrier decks, and a lung biopsy showed mineral deposits that could be attributed to the same work exposures aboard the aircraft carrier.[46] The U.S. Navy then requested a National Institute for Occupational Safety and Health (NIOSH) investigation to evaluate any potential relationship between sarcoidosis and the navy work environment. Records from the Naval Health Research Center were reviewed for all incident cases of sarcoidosis among black and white enlisted men between 1965 and 1993, and compared with a random sample of 10,000 controls from the same population. African Americans were disproportionately represented among cases (48%) compared with controls (11%). Furthermore, men with sarcoidosis served twice as long as controls (mean 10.7 years vs 5.5 years). A statistically significant association was identified with sarcoidosis and ever having served on a U.S. aircraft carrier (RR [relative risk] = 1.5; 95% CI 1.2 to 1.9). The risk was higher among African Americans (RR = 1.7, 95% CI 1.3 to 2.3) compared with Caucasians (RR = 1.2, 95% CI 0.8 to 1.7).[46]

Risk of exposures for sarcoidosis with military service was further explored by Jajosky[47] using the same database and examining the association with clean ships (i.e., hospital, research, cargo, store, tug, or escort) versus industrial ships (i.e., repair, carriers, tenders, floating dry docks, salvage ships). Industrial ships had a higher proportion of dusty, manual jobs. Onboard activity codes were added to the database after 1973. A "clean ship" assignment was associated with decreased risk of sarcoidosis (OR = 0.33, 95% CI 0.10 to 0.84) in a multivariate logistic model adjusted for race, time period, length of service, and age at entry. The effect of clean ship assignment further reduced the risk of race on sarcoidosis incidence in full models. On the other hand, possible exposure to dust from removal of nonskid deck coating material as in aircraft carriers was associated with a higher incidence of sarcoidosis.

Using a cohort design, Gorham and coworkers[48] examined trends in diagnoses of sarcoidosis among enlisted navy personnel from 1975 to 2001. After 1975, the requirement for routine annual chest radiography was eliminated and the incidence of sarcoidosis among the enlisted African American population dropped by nearly 50%. The incidence declined further in 1989 when the requirement for chest radiography at naval enlistment and separation was eliminated. The average annual incidence of sarcoidosis from 1975 to 2000 was 21.9 per 100,000 for African American and 3.5 per 100,000 for Caucasian men. African American servicemen and aviation structural mechanics experts had a higher incidence compared with all enlisted African Americans. Furthermore, Caucasian mess management specialists had twice the incidence compared with all active-duty Caucasian personnel. Increased risk was also associated with working in humid environments such as operating dry-cleaning and laundry equipment, and barbers exposed to talc aerosols.

Fire Fighters

Several studies have found an increased risk of sarcoidosis with work as a firefighter. Kern and coworkers[49] reported a time–space cluster of three cases of sarcoidosis among 10 firefighters who had trained together. As part of a surveillance program for New York City firefighters with respiratory symptoms, Prezant and coworkers[50] found 25 firefighters with sarcoidosis between 1985 and 1998. The annual incidence among firefighters averaged 12.9 per 100,000 compared with 2.5 for white men in the U.S. Navy from 1985 to 1993. The point prevalence of sarcoidosis among the firefighters was 222 per 100,000 compared with 35 per 100,000 for emergency medical services heath care workers and 17 to 64 per 100,000 for various other populations in New York City.[50] In a separate study of firefighters 5 years after exposures at the World Trade Center disaster new-onset sarcoidosis with intrathoracic adenopathy was found in 26, and among these firefighters extrathoracic adenopathy was found in six. Moreover, compared with 15 years before the disaster the annual incidence of sarcoidosis increased from 15 per 100,000 to 22 per 100,000 after the disaster.[42]

Exposure to Silica

In Iceland the association between silica exposure and sarcoidosis was studied using a case referent design among a population cohort of 70 referents of which 13 were exposed to diatomaceous earth and cristobalite.[41] Eight cases of sarcoidosis were found, six of whom were in the exposed group. The odds ratio of cases to referents was 13.2, and the annual incidence of sarcoidosis in this cohort was 9.3 per 100,000, which is higher than that for the general population of Iceland, estimated at between 0.5 and 2.7 per 100,000. The main strength of this study was that exposure history was obtained independent of subject recall. However, the association between crystalline silica exposure and sarcoidosis was not supported by a matched case-control study of 2036 deaths from 27 U.S. states.[51]

Familial Studies

Kucera and coworkers[52] examined the role of occupational exposures in familial sarcoidosis. A detailed job history was obtained from 921 African Americans with 273 index cases of sarcoidosis and 648 siblings, of whom 30 (4.6%) also had sarcoidosis. After adjusting for age, sex, total number of jobs, having a usual occupation in education (OR = 2.18, 95% CI 1.07 to 4.44) and in metal machining (OR = 7.47, 95% CI 1.19 to 47.06), and ever holding a job in metal working (OR = 2.05, 95% CI 1.14 to 3.7) were associated with an increased risk of sarcoidosis. Other exposures in the workplace that were associated with sarcoidosis included indoor exposure to high humidity in the area for >1 year (OR = 1.51, 95% CI 1.13 to 2.02), water damage for >1 year (OR = 1.50, 95% CI 1.11 to 2.03), ever seeing mold or mildew (OR = 1.50, 95% CI 1.11 to 2.03), and ever smelling a musty odor in the workplace (OR = 1.78, 95% CI 1.32 to 2.4). Exposures to titanium, beryllium, silica, and vegetable dust were associated with elevated risks, but only titanium and vegetable dust were statistically significant (Table 4). In another publication[53] from this familial study data regarding photocopier exposure were examined, and in a matched pair analysis ever using a photocopier was associated with an increased risk of sarcoidosis (OR = 1.74, 95% CI 1.23 to 2.46), and a higher risk associated with ever changing toner or photocopier maintenance (OR = 2.88, 95% CI 1.83 to 4.54).

Conclusions

Of the available epidemiological evidence on risk factors for sarcoidosis, consistent statistically significant increased risk has been found in two studies[2,52] for exposures to agricultural dust and musty odor/mold/mildew (Table 4). Moreover, an increased risk with humid indoor workplace was also supported among military personnel.[48] Furthermore, cigarette smoking has been consistently associated with a lower risk of sarcoidosis and other granulomatous lung diseases.[2] Although several other exposures were associated with an increased risk in the ACCESS study (Table 4), these exposures have either not been examined in other populations or the results have not been consistently demonstrated. Evidence from military personnel[46–48] and firefighters[42,50] suggest that exposure to mixed dusts and fumes increases the risk for sarcoidosis. Finally, limited evidence suggests that the risk for sarcoidosis from several exposures may be modified by race and gender, and the sarcoid phenotype may vary with different exposures.

Because of the relatively small number of epidemiological studies of environmental risk factors for sarcoidosis the evidence is inadequate to infer the presence or absence of a causal relationship between environmental exposures and sarcoidosis (Table 2). Although studies of pathogenesis provide evidence supporting the criteria of biological plausibility and coherence for environmental causes of sarcoidosis,[4,54] further well-designed etiological studies are needed to establish consistency of associations and to fulfill the other criteria needed to infer a causal relationship.

SUMMARY

Of the idiopathic lung diseases, IPF and sarcoidosis have been the focus of a growing number of epidemiological investigations on the risk of environmental and

occupational exposures. To date, the consistency of epidemiological evidence is suggestive but not sufficient to infer a causal relationship between several environmental exposures and IPF (level 2) (Table 3). The level of evidence, based on the number of studies with significant associations, is strongest for cigarette smoking and metal dust. Moreover, current knowledge about pathogenesis and the causal link between other exposures (e.g., asbestos) and pulmonary fibrosis provide strong evidence supporting causation between other exposures and IPF. However, scant epidemiological evidence for dose–response and temporality weaken the case for making causal inferences.

In contrast to IPF, to date the quantity of epidemiological evidence for environmental exposures and sarcoidosis is smaller, making it inadequate to infer the presence or absence of a causal relationship (level 3) (Table 2). Two studies provide consistent evidence for exposures to agricultural dust and musty odor/mold/mildew, and studies among military personnel and firefighters suggest mixed dust and fume exposures as risk factors for sarcoidosis. Although studies of pathogenesis and the causal link between other exposures (e.g., beryllium) and granulomatous disease provide strong evidence supporting causation, more epidemiological studies are needed to establish consistency of associations, dose–response, and temporality.

For both IPF and sarcoidosis there are several methodological challenges for conducting etiological studies. Although minimizing diagnostic and exposure misclassification is essential in any future investigations, studies of gene–environment interaction offer the potential for strengthening the causal link between several environmental and occupational exposures and idiopathic lung diseases.

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