A Case Control Etiologic Study of Sarcoidosis
Environmental and Occupational Risk Factors

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Past research suggests that environmental factors may be associated with sarcoidosis risk. We conducted a case control study to test *a priori* hypotheses that environmental and occupational exposures are associated with sarcoidosis. Ten centers recruited 706 newly diagnosed patients with sarcoidosis and an equal number of age-, race-, and sex-matched control subjects. Interviewers administered questionnaires containing questions regarding occupational and nonoccupational exposures that we assessed in univariable and multivariable analyses. We observed positive associations between sarcoidosis and specific occupations (e.g., agricultural employment, odds ratio [OR] 1.46, confidence interval [CI] 1.13–1.89), exposures (e.g., insecticides at work, OR 1.52, CI 1.14–2.04, and work environments with mold/mildew exposures [environments with possible exposures to microbial bioaerosols], OR 1.61, CI 1.13–2.31). A history of ever smoking cigarettes was less frequent among cases than control subjects (OR 0.62, CI 0.50–0.77). In multivariable modeling, we observed elevated ORs for work in areas with musty odors (OR 1.62, CI 1.24–2.11) and with occupational exposure to insecticides (OR 1.61, CI 1.13–2.28), and a decreased OR related to ever smoking cigarettes (OR 0.65, CI 0.51–0.82). The study did not identify a single, predominant cause of sarcoidosis. We identified several exposures associated with sarcoidosis risk, including insecticides, agricultural employment, and microbial bioaerosols.

Keywords: environment; etiology; granuloma; occupation; risk factors; sarcoidosis

The etiology of the systemic granulomatous disease sarcoidosis remains obscure (1). Few comprehensive investigations of cause have been conducted, although the prevailing view suggests that sarcoidosis occurs as the consequence of exposure to one or more environmental agents interacting with genetic factors (2–5). Studies of the immunopathogenesis of sarcoidosis have shown the accumulation of oligoclonal T cells at sites of granuloma formation, suggesting an antigen-specific cell-mediated immune response (6, 7). Skin tests using either Kveim-Siltzbach spleen extract or lung extract from patients with sarcoidosis suggest a specific immune response (8, 9)**.** Clinical and pathologic features of sarcoidosis resemble other antigen-induced granulomatous disorders, including chronic beryllium disease (10) and other metal-induced granulomatoses (11), hypersensitivity pneumonitis due to inhaled organic and inorganic antigens (12), and fungal and mycobacterial antigen-induced granulomatous lung disease.

Previous investigators have suggested that environmental exposures to microbial agents may prove causative because of their infectious and/or antigenic properties (13–21). Environments that serve as reservoirs and that can both amplify and disseminate bioaerosols of bacteria, their antigens and endotoxins, as well as fungi and mycotoxins have been linked to epidemics of environmental granulomatous disease (12, 19). Epidemiologic studies documenting temporal/spatial clustering of sarcoidosis cases (22–29), and familial aggregation of this disease (30–34), raise the possibility of shared environmental exposure or of a transmissible agent. Published data suggest that a number of occupations and environmental exposures might be associated with sarcoidosis (2, 5, 27, 35–37), including employment as firefighters (38, 39), health care professionals (35, 40, 41), work in the U.S. military (42, 43), work in the lumber industry (44, 45), and coastal or rural residence (28, 29, 43–48). A recent study of African-American patients with sarcoidosis and their siblings suggests that environmental and occupational factors contribute to disease risk (5).

We report our assessment of environmental and occupational factors associated with sarcoidosis in a U.S. multicenter epidemiologic study of 706 clinically diagnosed and histologically confirmed incident patients with sarcoidosis and matched control subjects. We tested *a priori* hypotheses that environmental and occupational exposures are associated with the risk of sarcoidosis. This case control design was viewed also as a means of generating new etiologic hypotheses.

Some of the results of these studies have been previously reported in the form of abstracts (49, 50).

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METHODS

Study Design

Between November 1996 and June 1999, ten centers enrolled 736 cases and 706 control subjects, resulting in 706 matched case and control pairs. Details of the study design are as previously published (51). (*See* online supplement for detailed methods.)

Cases

Cases met the following inclusion criteria: (*1*) tissue confirmation of noncaseating granulomas on biopsy of one or more organs within 6 months of enrollment, (*2*) clinical signs or symptoms consistent with sarcoidosis (52), and (*3*) age 18 years or greater. We excluded individuals with active tuberculosis or who were taking antituberculosis therapy. Patients with sarcoidosis with prior beryllium exposure were excluded unless they had negative blood beryllium lymphocyte proliferation tests (53). The clinical characteristics of the cases are reported elsewhere (54).

Control Subjects

Control subjects were recruited by random digit dialing methods (51, 55, 56). After a patient was enrolled, the patient's telephone exchange was used to randomly dial numbers until we located an individual who matched the case with respect to race, sex, and age (within 5 years), met inclusion criteria, and indicated that he or she was willing to participate (51). On average, 216 random phone calls were placed to recruit one control subject per case completing the protocol.

Control subjects were excluded if they had a history of sarcoidosis or medical conditions that made the determination of sarcoidosis uncertain. Because of time constraints, we were unable to enroll matching control subjects for 30 individuals before the end of the study enrollment period. Results are reported from the matched pairs analysis for 706 case and control pairs.

Data Collection

Data for cases and control subjects were collected in person by trained interviewers using a questionnaire. Cases and control subjects completed the same exposure questionnaires.

Questionnaires were designed to test the *a priori* hypotheses summarized in Appendix B in the online supplement. Based on medical literature review, activities and occupational agents that could plausibly cause sarcoidosis or other granulomatous diseases were included. The questionnaire consisted of (*1*) dichotomous questions concerning specific jobs, hobbies, and exposures both at home and at work; (*2*) a structured interview to obtain a detailed chronology of jobs held for at least 6 months; and (*3*) tobacco use (57).

If study participants affirmed exposure, the interviewer inquired systematically about the occurrence of exposure within the 3 years before the date of diagnosis, defined as the date of biopsy-proven granulomatous disease for cases. Control subjects were asked to report exposure and occupational data relative to the date of histologic diagnosis for their matching cases.

In addition to the analysis of each individual independent variable (e.g., a job title or exposure), we constructed a set of combined variables that grouped similar occupations and industries into categories.

Statistical Methods

Data analysis for matched cases and control subjects followed the methods outlined by Breslow and Day (58), using the number of informative pairs and odds ratios (ORs) with 95% binomial approximation confidence intervals and p values for each exposure. We used matched pair contingency table methods for estimating the OR and McNemar's test for significance. For continuous variables, differences in the means of control subjects versus the means of cases were compared using paired *t* tests. Point estimates of the differences in case and control means were calculated as well as 95% confidence limits. The *a priori* hypotheses shown in Appendix B in the online supplement were tested at an α level of 0.05, two-tailed. Associations identified after examination of the data were not considered to provide evidence of a significant association unless the p value was less than 0.01 in testing the null hypothesis that the OR is 1.0. (Details of statistical power analysis are presented in the Methods section of the online supplement.)

Exposures that were associated with case control status at the $p = 0.10$ level on univariable analyses were included in a conditional multiple logistic regression model for matched pairs (58) using a backward selection procedure performed at a 0.05 α level.

RESULTS

Overview of Study Group

Sixty-four percent of cases were female. By self-report, 53% of cases were white, non-Hispanic; 44% were black and non-Hispanic; 0.8% were white or black Hispanic; 0.8% Asian or Pacific Islander; 0.3% American Indian or Alaska Native; and 1.4% other. Compared with the general United States population, this study population included a relatively higher percentage of blacks and a relatively lower percentage of white or black Hispanics, in keeping with the racial prevalence of sarcoidosis in the United States. The median age of the cases was 42.1 years (range 18–83). Ninety-nine percent of cases and 99% of control subjects reported prior employment; however, patients with sarcoidosis were more likely to be currently unemployed than were matched control subjects (OR 1.83 [1.09–3.15], $p = 0.02$) (54).

Univariable Analysis

Positive associations. Five occupations and five specific exposures identified *a priori* were more prevalent among cases than control subjects (*see* Table E1 in the online supplement). Occupations included agricultural employment, physician, job raising birds, job in automotive manufacturing, middle/secondary schoolteacher.

Patients with sarcoidosis were more likely to report exposures to insecticides and employment in pesticide-using industries, occupational exposure to mold and mildew, occupational exposure to musty odors, and use of home central air conditioning. We observed no important associations with rural, suburban, or metropolitan residence at birth, during childhood or adulthood. Other than physicians, health care occupations, such as nurses and hospital workers, were not significantly associated with sarcoidosis risk.

Negative associations. Among the hypothesized negative associations with sarcoidosis, two occupational categories and one environmental exposure (ascertained by the combination of responses to three inquiries) were found to be associated with control status (i.e., less frequent among cases than control subjects, or "protective" against sarcoidosis) (*see* Table E2 in the online supplement). Consistent with our initial hypothesis, patients with sarcoidosis were less likely to report employment in jobs that might have been relatively isolated from other workers, such as motor vehicle operator, cleaning private homes, or working as data processors, typists, or computer programmers. Compared with their matched control subjects, sarcoidosis cases were less likely to report having ever smoked tobacco, and were less likely to have current exposure to tobacco smoke in the home. Passive tobacco smoke exposure in combination with personal tobacco use was more prevalent among control subjects. A number of other occupations and exposure variables were associated with case/control status in a manner opposite to our *a priori* hypotheses, as indicated in Tables E1 and E2.

Multivariable Model

Of the hypothesized environmental and occupational factors that were associated positively with sarcoidosis in univariable analyses, seven of the ten remained significantly associated with disease in a logistic regression model (*see* Table E3 in the online supplement). The multivariable model supported our hypotheses

regarding the association of sarcoidosis with exposure to musty odors in the workplace, occupational exposure to insecticides, and air conditioning use in the home. Both occupational and nonoccupational exposures to birds were positively associated with being a case, as was employment in teaching and in automobile manufacturing. Employment as a physician did not remain significant in the multivariable model.

Several variables that we had hypothesized to be negatively associated with sarcoidosis and which were negatively associated in the univariable analysis remained in the multivariable model (Table E3). Tobacco smoke exposure at any time in the past showed the strongest negative association with sarcoidosis. Employment as data processors/typists, and programmers also remained significant in the multivariable model.

Aggregate variables with $p < 0.05$ in our univariable analysis are indicated in Tables E1 and E2. None remained in the final multivariable model.

A priori *hypotheses not confirmed.* Appendix B in the online supplement lists the *a priori* hypotheses that this study was originally designed to test. Notably, we did not confirm previous reports that have associated sarcoidosis with either occupational or nonoccupational wood dust exposure (48, 59), wood use (48, 60–63), occupational exposure to metals (11), silica, or talc (64–67). Being employed as a firefighter (38, 39) or in the U.S. Navy (28, 68, 69) have been reported as risk factors for sarcoidosis; however, we did not have adequate statistical power to test these hypotheses. The annotated questionnaire used in this study is available in an online supplement (Appendix D) and indicates those items used to test each hypothesis and those items for which there was less than 90% power to detect statistically significant associations due to low prevalence of reported exposure variable (i.e., proportion of control subjects exposed less than 0.05).

DISCUSSION

ACCESS did not identify a single predominant environmental or occupational "cause" of sarcoidosis. Indeed, this large case–control data study, with concurrent data collection from cases and control subjects, leads us to suspect that multiple environmental sources of exposure initiate the granulomatous response in sarcoidosis. Alternatively, there may be a single cause that we did not recognize as a commonality across occupations and environments. Although it is conceivable that sarcoidosis has no environmental etiology, we consider it more likely that host factors such as genetics and personal habits may modify the individual's response to exposures.

Design Considerations

There are a number of important reasons why this study potentially missed risk factors for sarcoidosis or, alternatively, may have spuriously identified other risk factors that are simply chance associations. There may be environmental or occupational risk factors that we failed to consider in designing our questionnaire (*see* questionnaire in the online supplement). Conversely, we examined a large number of *a priori* hypotheses (Appendix B in the online supplement). As such, we made multiple comparisons. We cannot exclude the possibility that some of the statistically significant results may have occurred due to chance alone. As reflected in the tables, a number of other factors were statistically significantly associated with case control status but have not been emphasized in this discussion, because of wide confidence intervals, small numbers of informative pairs, because they were solitary findings, or because they were not part of our *a priori* hypothesis testing.

Cases were recruited by pulmonologists at academic medical referral centers and without nationwide geographical distribution. Although the cases appear similar to those in other studies in the United States (39, 70, 71), we cannot fully exclude ascertainment bias. The cases were not enrolled in an attempt to represent the expected clinical spectrum of disease, and thus the results might not be generalizable to all cases or to all forms of sarcoidosis by severity or acuity (54). Perhaps more importantly, our control recruitment procedure relied on the use of random digit telephone dialing techniques to find a willing, unaffected age-, sex-, and race-matched control. Many potential control subjects did not participate in the study, although our level of control enrollment was comparable to other studies (56). It is difficult to determine the extent to which either case or control ascertainment bias may have affected our findings, but in general should be considered a significant hazard in studies of this design. Cases and control subjects differed in method of ascertainment, which may have affected who enrolled and how subjects responded to questions. For example, the number of cases who were physicians was small (Table E1), and it is possible that when unaffected physicians are contacted at home by random digit dialing, they may be unlikely to enroll as control subjects.

Differential information bias is a potential concern in case–control studies of occupational and environmental agents (72). Cases and control subjects might also differ in their ability to recall and classify their exposures. Patients with disease might have spent more time considering their past exposures. Because cases were not referred due to the presence of particular exposure risk factors, differential misclassification of exposure and occupation is unlikely to be as important in our study as in some workplace investigations.

Sarcoidosis is considered to be a hypersensitivity disorder, in which an antigen induces a T cell–mediated cellular immune response. As a result, it is possible that the etiologic agent or agents may initiate disease at very low doses of exposure. By analogy, very small exposures to beryllium across a widely variable latency period can induce the granulomas of chronic beryllium disease (53, 73). Both a wide latency between cause and effect, and the potential for low doses of exposure to induce the immune response, may impair our ability to determine the sarcoidosis causative agent or agents.

There may be environmental or occupational risk factors that are important in a particular subset of patients with sarcoidosis, but were not observed in the overall group analysis. Further analyses are planned to investigate the interaction of exposures with age, sex, race, and other characteristics of cases and control subjects. Data presented here are based on the overall comparison of cases and control subjects. In addition, several previously reported risk factors for sarcoidosis were not adequately tested in our study due to small numbers. Specifically, we did not have adequate statistical power to test hypotheses concerning employment as a firefighter or in the U.S. Navy.

Environmental Factors Positively Associated with Sarcoidosis

Our data suggest that several environmental factors should be examined for their relationship to sarcoidosis, including several that have not previously been considered. In particular, we observed notable positive associations with occupational exposure to insecticides, agricultural employment, and moldy, musty environments typically associated with bioaerosol exposure. Interestingly, another study of 31 patients with sarcoidosis found that patients with sarcoidosis were more likely than control subjects to report having been exposed to workplace inorganic dusts, molds, and solvent or oils. The cases also more often reported moldy home environments (74). Similar results were recently reported in a study of African-American siblings (5).

Insecticides. One of the strongest positive associations in our study was for occupational exposure to insecticides, at any time before participation in the study and in the 3 years immediately preceding diagnosis. Cases reported insecticide exposure in both agricultural and industrial settings. Home use of insecticides was not significantly associated with sarcoidosis. We had hypothesized that insecticide use may be associated with sarcoidosis, based on previous reports linking pyrethrins with hypersensitivity pneumonitis (75, 76). We did not inquire about specific use of pyrethrins or other specific categories of insecticides, and thus consider this finding speculative. It is possible that the occupational use of insecticides is a surrogate for exposures to one or more antigens in the workplace not directly assessed in our questionnaire. In a recent study of rural exposures in sarcoidosis, insecticide use was not found to be a risk factor. However, the study lacked statistical power to test that association (48).

Agriculture. Previous studies have suggested an association between sarcoidosis and agricultural employment or other exposures in rural communities (28, 29, 44, 45, 47, 48). Our data demonstrated a positive association between sarcoidosis and employment in the agricultural industry in univariable analysis only. Agricultural workers potentially encounter a variety of high level exposures to chemicals, aerosolized particulates, including grains, bedding materials, silicates, animal proteins, insect proteins, fungi, bacteria, mycotoxins, and endotoxins. Agricultural employment dropped in its significance when entered in the multivariable model that included insecticide exposure at work.

Microbial bioaerosols. We hypothesized that environments favorable to the production of bioaerosols—whether infectious or antigenic—would be associated with sarcoidosis. As a general indicator of such exposures, we asked cases and control subjects if they had occupational exposures to musty odors. This exposure was associated with sarcoidosis in the multiple logistic regression model. In our univariable analysis, cases were more likely than control subjects to report occupational exposures to mold and mildew as well. Most fungi exude volatile organic compounds during active growth, causing the "musty" or "moldy" odor associated with fungal contamination (77, 78), and may reflect microorganism presence even when there is no visible growth (79, 80). Additionally, we observed that sarcoidosis cases were more likely to report central air conditioner use in the home. Several studies have found symptoms to be associated with central air conditioning with or without humidification (77, 81, 82).

Our results, taken in context with several previous studies, add to mounting evidence linking microbial bioaerosols to sarcoidosis risk. Many of the microbes that have been suggested as possible causes of sarcoidosis or of diseases mimicking sarcoidosis (2, 17, 20) grow readily in standing water. Opportunities to aerosolize particulate antigen and/or infectious agents may result in the inhalation, pulmonary deposition, and immune response to such particles. In a recent study (48), sarcoidosis-related hospitalizations were concentrated in proximity to the South Carolina coastline. Previous studies have shown a predilection for sarcoidosis in coastal states (28, 47, 48). In a study by Rose and coworkers, 31 lifeguards developed granulomatous pneumonitis that was histologically indistinguishable from sarcoidosis after exposure to bioaerosols in an indoor leisure swimming center (19). In a study of African-American siblings, using a questionnaire based on the ACCESS survey instrument, Kucera and colleagues observed that siblings with sarcoidosis were more likely to report indoor exposures to high humidity, water damage, or musty odors than were their unaffected siblings (5). In addition, clusters of granulomatous pneumonitis mimicking sarcoidosis have been described in relation to occupational exposure to microbially contaminated metal working fluids in the automotive/metal machining industry (83). It is interesting to note in this regard that recent employment in automobile manufacturing was associated with sarcoidosis in our study (Table E1), whereas automobile/truck repair as a hobby was not. The study by Kucera and coworkers, examining cases and control subjects in urban Detroit, similarly reported elevated sarcoidosis risk associated with metal machining and metalworking (5). Employment in cotton ginning among sarcoidosis cases may suggest the potential for organic antigen and endotoxin exposures.

Although some of our results seem to support the bioaerosol hypothesis, a number of other questions that we used to explore potential microbial bioaerosol exposures showed either no association or unexpected negative associations with sarcoidosis. Those results must be interpreted with caution. Those which did not directly test one of our *a priori* hypotheses should be considered exploratory findings.

Known Causes of Granulomatous Disease

In our study, sarcoidosis occurred more frequently in individuals who reported exposures to environments in which other forms of granulomatous lung disease are known to occur. Many known organic and inorganic antigens and microbes can initiate granulomatous reactions that histologically, and sometimes clinically, resemble sarcoidosis (4). These include various metals (11), certain pesticides, drugs, other chemicals (2), rock dusts containing talc and silica (65–67, 84), bird antigens (85), and microbial organisms, among others that may be clinically mistaken for sarcoidosis. Both occupational bird handling and nonoccupational bird exposures remained in our final multivariable model (Table E3). Although we cannot fully exclude the possibility that some of our cases had hypersensitivity pneumonitis, to reduce the possibility of misclassification we established strict diagnostic criteria, including pathology confirmation of all cases. The frequency of extrathoracic involvement in our cases (54) makes misclassification of hypersensitivity pneumonitis unlikely. Furthermore, when we did a detailed review of these bird-exposed sarcoidosis cases, most of them had patterns of disease (hilar lymphadenopathy, extrathoracic involvement) not commonly described in bird-related hypersensitivity pneumonitis. Antigens or infectious agents that cause sarcoidosis might share the same environment with antigens causing these other granulomatous disorders. Alternatively, the same bird antigens might produce a different type of reaction and pattern of illness, perhaps depending on an individual's expressed genes. We found no significant associations between sarcoidosis and other known causes of granulomatous disease. Patients with tuberculosis, chronic beryllium disease, or other known granulomatous disorders were excluded from the study.

Environmental Factors Negatively Associated with Sarcoidosis

One of the most robust findings in our study was the negative association between tobacco smoking and sarcoidosis risk. In the multivariable model, the odds ratio was 0.65 (0.51–0.82, $p < 0.001$) for ever-smokers. This result is consistent with several previous studies that have reported low prevalence of cigarette smoking among patients with sarcoidosis (35, 86–89). Studies of hypersensitivity pneumonitis and chronic beryllium disease have similarly demonstrated that these granulomatous lung disorders are less common among smokers (89–95) and have a number of biologically plausible explanations (89, 96–99).

Conclusions

In summary, we performed a case–control study of the environmental and occupational factors associated with sarcoidosis. We did not find a single, proximate cause. However our data suggest the hypotheses that insecticides, agricultural environments, and

conditions of exposure to microbial bioaerosols may be associated with sarcoidosis. Researchers may be successful in adopting a cohort approach or a "sentinel event" outbreak investigative approach similar to that used in seeking the underlying causes of other granulomatous conditions such as hypersensitivity pneumonitis and infectious granulomatous disorders. Field investigations of the home and work environment of individual cases of sarcoidosis, and of sarcoidosis case clusters, may be useful in following up on these leads. For example, cohort studies of sarcoidosis occurring in environments in which microbial bioaerosols occur may provide additional clues to etiology. Studies of the mechanisms underlying tobacco smoke's negative association may provide added insights. Efforts should be directed at integrating exposure data with our emerging understanding of other sarcoidosis risk modifiers such as tobacco use, genetics, and familial aggregation.

Conflict of Interest Statement: L.S.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.S.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.A.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.D.R. is the PI at the University of PA for a clinical trial of infliximab in active sarcoidosis and depending on patient recruitment could receive up to $6,926 in salary and extended benefits over the course of the contract with Centocor; J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.L.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.E.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.C.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.A.J. received $3,000 in 2003 to function on the medical Advisory Board of Centocor; G.L.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.W.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; H.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.J.J. deceased; D.L.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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