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Occupational Silica and Solvent Exposures and Risk of Systemic Lupus Erythematosus in Urban Women

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Objective. **To assess the risk of systemic lupus erythematosus (SLE) associated with occupational exposure to silica dust and organic solvents in an urban population.**

Methods. **Women with SLE were identified through both community screening and hospital databases in 4 predominantly African American neighborhoods in Boston. Female control patients were volunteers from the same communities and were screened for the absence of connective tissue disease. Demographic factors, smoking history, and a detailed occupational history, including exposures to specific chemicals, were obtained by in-person interviews. The exposure assessment was based on independent evaluation of the occupational history by 2 reviewers who were blinded to each subject's disease status. The risks associated with exposure to silica and solvents were analyzed using multivariate conditional logistic regression models, adjusted for potential confounders.**

Results. **Ninety-five patients and 191 age- and race-matched controls were included in this analysis. Exposure to silica for longer than 1 year was associated with SLE (odds ratio [OR] 4.3, 95% confidence interval [95% CI] 1.7–11.2). An exposure-response effect was seen for longer duration of exposures to silica (*P* for trend = 0.01). The association between occupational exposure to organic solvents and SLE was not statistically significant (OR 1.04, 95% CI 0.34–3.2).**

Conclusion. **Silica exposure from a variety of industrial occupations in urban areas is associated with an increased risk of SLE. A longer duration of exposure to silica dust is associated with greater risks. This study provides further impetus for additional research into the influence of modifiable exposures on the pathogenesis of SLE.**

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organ systems. It is characterized by humoral and cellular immunity to self antigens, but its exact pathophysiology is unknown. Approximately 90% of patients with SLE are female, and the incidence of SLE among African Americans is increased 3–4-fold compared with the incidence among Caucasians (1,2). The source of the racial disparity in the risk of SLE is not clear. A variety of susceptibility genes have been identified (3), but none of the genes identified to date adequately explain the excess risk of SLE observed in persons of African descent. The relatively low penetrance of the disease suggests that environmental factors and gene–environment interactions play important roles in the etiology of SLE (4). The prevalence of SLE in persons of African descent in industrialized

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countries is thought to be much higher than the prevalence of SLE in West African countries (5). It has been hypothesized that this "gradient in prevalence" is related to environmental factors associated with migration to industrialized countries, as well as gene–environment interactions.

Environmental risk factors are important, because they are modifiable. Various environmental exposures have been hypothesized to contribute to the risk of SLE. A 1989 study focused on exposure to aromatic amines in hair dyes and other sources (6), but subsequent studies (7,8) did not confirm the strong association observed in this initial investigation. More recent studies have examined occupational exposure to silica dust, mercury, pesticides, and solvents (8–10). Other potential environmental influences on the risk of SLE include infectious agents such as the Epstein-Barr virus, ultraviolet radiation, dietary constituents, smoking, and exogenous sex hormones (11).

The aim of this study was to assess the risk of SLE associated with occupational exposure to silica dust and organic solvents in an urban, predominantly African American population. Our research hypothesis was that in this population, occupational exposures to silica and organic solvents increased the risk of SLE.

PATIENTS AND METHODS

Study population. The participants in this study were women enrolled in the Roxbury Lupus Project, which has been described in detail elsewhere (12,13). Briefly, the project was started in response to community concerns about a perceived increase in the incidence of SLE in the Boston neighborhoods of Roxbury, North Dorchester, and Mattapan, which are economically disadvantaged communities in comparison with citywide economic indices of Boston. More than 75% of the 88,000 adult female residents in these neighborhoods are of African American descent (14). With the aid of partners including the Massachusetts Department of Public Health, the National Institute of Environmental Health Sciences, and the SLE patient advocacy group Women of Courage, the study team developed an organized system for identifying all current and new patients with SLE in the study area. The specific aims were to identify all diagnosed cases of SLE in the study area, recruit a healthy control group from the same communities, and assess several environmental exposures.

Study design. In a population-based case–control study, we examined the association between work history and the risk of SLE in these predominantly African American neighborhoods of Boston. Cases of SLE were identified through hospital database screening and community screening. Hospital cases of SLE were identified through the billing databases, which were screened for SLE diagnosis codes among female patients with zip codes from the study area, at each major teaching hospital in Boston (Brigham and Women's Hospital, Boston Medical Center, New England Medical Center, Massachusetts General Hospital, and Beth Israel Deaconess Hospital) and a local community hospital (Carney Hospital).

After obtaining approval by the institutional review board at each hospital, a rheumatologist screened the medical records for American College of Rheumatology (ACR) criteria for SLE (15). Patients were classified as having definite SLE on the basis of fulfilling $\geq$4 of the ACR criteria (15). Each potential patient identified was invited to participate in the study and to complete a structured questionnaire (by interview) regarding environmental and occupational exposure. To obtain a more complete ascertainment of SLE in this population and include patients who were not followed up in hospitals, community screening was performed at health fairs, neighborhood events, lupus support groups, educational seminars, churches, and community health clinics in the study area, using a short symptom questionnaire (the Connective Tissue Disease Screening Questionnaire [CSQ]) (12,16) and a fingerstick blood sample for antinuclear antibody (ANA) determination. Participants who reported at least 4 symptoms of SLE on the CSQ and who were ANA positive (titer $>$1:40) were examined by a rheumatologist to confirm the diagnosis of SLE. Controls were female residents of the same study area who participated in one of the screening events but had negative results for SLE on the CSQ.

Exposure status. Data were collected using in-person interviews, similar to the interview used in the Carolina Lupus Study (9,17), which were administered by trained community outreach workers. A detailed lifetime work history was obtained, focusing on participants' primary jobs and followed by a structured checklist involving 15 specific jobs likely to involve exposure to silica dust or solvents (e.g., custodial/janitorial work, dry-cleaning, construction work, making pottery, or manufacturing china, ceramics, or computer wafers). For each job, participants were asked at what age employment started and the number of years, months per year, and hours per week worked at this job. For some jobs, additional clarifying questions about tasks and activities on the job were included. The questionnaire also asked about 8 specific occupational exposures to various compounds (i.e., stains, varnish, or other wood finishes; paints, paint products, paint thinner or paint remover; perchloroethylene or tetrachloroethylene [Solvene] cleaning solvents; trichloroethylene [Triasol, Carbona], scouring powder, or other dry abrasive cleansers; mercury; lead; and pesticides). Additional information obtained for each of these exposures included the age at which the participant first started using the material, the number of years the material was used, whether use occurred on 10 or more days during a 1-year period, and, for some materials, whether there was ever a spill or leak of the material in the participant's presence.

Other sociodemographic variables such as age, ethnicity, education level, residential history, family history of SLE, smoking history, and health care access were also ascertained. The assessment of silica and solvent exposure status was based on independent evaluation of the occupational history by 2 reviewers who were blinded to each participant's disease status, using the algorithms that had been developed for the Carolina Lupus Study (10,17–19). Exposures were initially classified as probable, possible, or unlikely. For the statistical

analysis, the "possible" and "probable" categories were combined because of the small sample size.

Statistical analysis. Patients and controls were matched for age (within 5 years) and ethnicity. Past occupational exposures were considered until the age at which SLE was diagnosed (in patients) or until the corresponding reference age in controls. Comparisons of the baseline disease characteristics were based on paired *t*-tests for normal continuous variables and the chi-square test for dichotomous variables. We then used multivariate conditional logistic regression to analyze the association between the binary outcome—SLE diagnosis—with the exposure status. These procedures produced estimates of the odds ratios (ORs) and 95% confidence intervals (95% CIs) as measures of association between exposure and disease. We tested the null hypothesis that the exposure status is not associated with SLE against the 2-sided alternative that an association does exist.

All analyses were adjusted for parity (nulliparous/parous prior to diagnosis), smoking (never smoked or ever smoked prior to diagnosis), and education level (number of years). We also investigated a possible linear trend of increasing risk of SLE with longer duration of exposure. Furthermore, we considered whether cigarette smoking modifies the effect of occupational exposure, as has been previously described for the association between silica exposure and SLE (17) and silica exposure and rheumatoid arthritis (20), using a multiplicative interaction term between occupational exposures and smoking.

RESULTS

Among the 197 controls, 6 had positive results on the CSQ and were positive for ANA and were excluded; 1 of these 6 subjects had been diagnosed with SLE by a rheumatologist and was included in the analysis as a patient. Ninety percent of all SLE cases were identified at 1 of the 6 hospitals included in this study, 1% were identified at 1 of 2 community hospitals in the greater Boston area, and 9% were identified in the community. Of the 215 eligible patients with SLE in the study region who were identified through hospital databases, 28% did not respond to up to 3 letters and phone calls, 18% chose not to participate, and 7% could not be contacted. From among 100 patients with SLE, 5 were excluded because no corresponding matched control could be located.

Ninety-five patients and 191 age- and race-matched controls were included in this analysis. Baseline characteristics such as smoking, parity, education level, age, or ethnicity did not differ significantly between the 2 groups (Table 1). The overall prevalence of silica exposures longer than 1 year was 8% (14% in patients and 4% in controls), and the overall prevalence of solvent exposures longer than 1 year was 14% (16% in patients and 13% in controls). The most common occupations associated with silica exposure were making dental molds in a dental laboratory (n = 5) (21,22), working at construction or demolition sites where sandblasting occurs (n = 4), and working as a custodian using scouring powders (n = 2). The most common occupations associated with solvent exposure were working with arts and crafts involving regular use of glues, paints, or solvents for prolonged periods (n = 9), working in manufacturing jobs involving long-term use of solvents (n = 7), and working as a beautician with regular use of dyes, relaxers, or curl solutions (n = 6). In patients, the median time between the initial exposure to silica and the onset of SLE was 16 years.

Table 1. Characteristics of patients with SLE and controls*

Characteristic	Patients (n = 95)	Controls (n = 191)	*P*†
Age, mean ± SD years	44 ± 13	47 ± 15	0.51
Race/ethnicity			
African American	80 (84)	175 (92)	
Hispanic	9 (9)	8 (4)	
Caucasian	1 (1)	3 (2)	
Other	5 (5)	5 (3)	0.86
Smoking, ever‡	42 (44)	99 (52)	0.16
Parity, ever‡	72 (76)	151 (79)	0.71
Working full-time or part-time	65 (68)	135 (71)	0.95
Education level, mean ± SD years	14.4 ± 3.0	13.9 ± 2.8	0.18

* Except where indicated otherwise, values are the number (%). Characteristics are for the age at which disease onset occurred in patients with systemic lupus erythematosus (SLE) and the corresponding reference age in controls.
† By paired *t*-test for continuous variables and chi-square test for dichotomous variables.
‡ Before the age at diagnosis in patients and the corresponding reference age in controls.

Exposure to silica for more than 1 year was associated with SLE (OR 4.3, 95% CI 1.7–11.2) (Figure 1). An exposure-response effect was seen for longer duration of exposures to silica (for exposure to silica for 1–5 years, OR 4.0, 95% CI 1.2–12.9; for exposure to silica for more than 5 years, OR 4.9, 95% CI 1.1–21.9) (*P* for trend = 0.01). We found that cigarette smoking did not significantly modify the effect of silica exposure. Exposure to organic solvents for more than 1 year was not associated with SLE (OR 1.04, 95% CI 0.34–3.2), and there was no exposure-response effect with longer durations of exposure to solvents (*P* for trend = 0.17).

DISCUSSION

In this population-based case–control study, we examined the association between work history and the risk of developing SLE in an urban, predominantly female, African American population. Occupational sil-

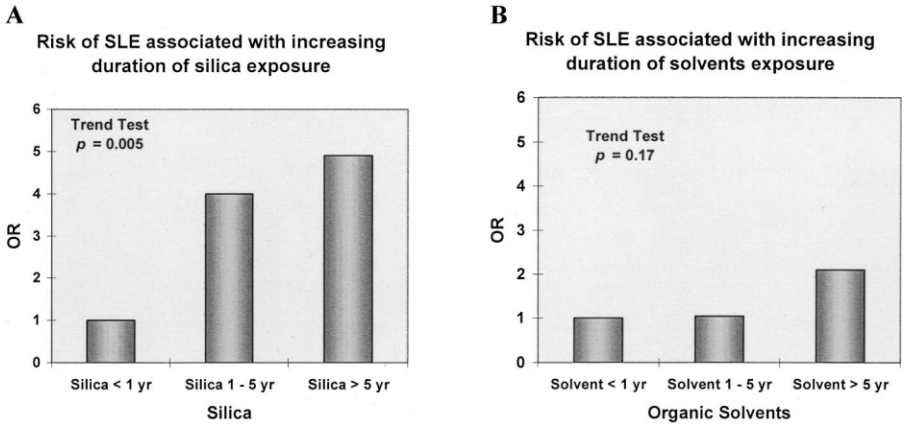

Figure 1. A, Risk of systemic lupus erythematosus (SLE) associated with silica exposure. **B,** Risk of SLE associated with solvent exposure. The risk of SLE developing, according to the different exposure categories, is represented as odds ratios (ORs), with the reference category (OR 1) being no or only brief exposures. The OR for exposure to silica for 1–5 years was 4.0 (95% confidence interval [95% CI] 1.2–12.9), and exposure to silica for >5 years had an OR of 4.9 (95% CI 1.1–21.9). Exposure to solvents for 1–5 years had an OR of 1.04 (95% CI 0.34–3.2), and exposure to solvents for >5 years had an OR of 2.1 (95% CI 0.88–5.1). A trend for an increasing risk with longer duration of exposure was tested using a trend test. All analyses were adjusted for smoking status, education level, and parity and were matched for age and ethnicity.

ica exposure was associated with an increased risk of SLE, and longer exposure to silica dust was associated with greater risk, suggesting a dose response. In this setting, silica exposure originated from a variety of urban, industrial occupations rather than from a single occupation or workplace. We did not observe a statistically increased risk of SLE in association with occupational solvent exposures.

Silica dusts are mineral dusts such as crystalline silica or quartz that can be inhaled while working in so-called "dusty trades" and also in occupations that use quartz-containing materials, such as dental technician or chemist (10). In the US, ~1–3 million workers are exposed to silica on the job (23). There is now considerable evidence for an influence of occupational exposure to silica dust as a risk factor for SLE (8). An increased prevalence of SLE was first demonstrated in occupational cohorts of miners and workers in factories manufacturing scouring powder (24,25). A registry-linkage study also revealed an increased prevalence of SLE among patients with silicosis (26), and a population-based case–control study in North Carolina and South Carolina demonstrated a strong association between occupational silica exposures and the risk of SLE, with a 4-fold increased risk in the highest category of exposure. That study was conducted in a predominantly rural area, where silica exposure was largely from farm work and construction work (17,19). In our analysis, silica exposure was associated with very similar odds of developing SLE and a similar trend toward an increasing risk with more substantial exposures, even though the occupations were completely different. We placed the threshold for exposures at 1 year in order to exclude fleeting occupational exposures, such as those that occur during short summer jobs. We analyzed exposure duration both as a categorical variable and as a continuous variable (data not shown) and found a similar trend for a greater risk with longer exposures.

Silica exposure has been associated with other autoimmune diseases, most notably scleroderma (27,28) and rheumatoid arthritis (20). The exact mechanism by which silica promotes or accelerates the development of autoimmune diseases is unknown. In vitro studies have shown that silica can act as an adjuvant stimulating T cell responses or as an inducer of apoptosis (29,30). Silica is also known to cause a relative decrease in the number of regulatory T cells (31) and to have a cytotoxic effect on macrophages attempting to break down internalized silica particles, which causes a cascade of events, including oxidative stress, induction of the transcription of proinflammatory cytokines, chronic inflammation, and latent immune stimulation (30,31). In SLE-prone murine models, silica exposure significantly exacerbated the course of disease, with increased production of autoantibodies, rapid development of high titers of circulating immune complexes, glomerulonephritis, and proteinuria

(32). The mechanisms of silica-induced autoimmune responses seem to involve autoantibodies recognizing specific epitopes on apoptotic macrophages. It has been hypothesized that silica-induced apoptosis exacerbates autoimmune responses by exposing particular antigens to the immune system (33).

Exposure to trichloroethylene and some of its metabolites has been studied extensively in SLE-prone murine models, with effects seen on autoantibody and immunoglobulin production, activation of CD4+ T cells, and alterations in cytokine levels (34,35). In contrast, epidemiologic evidence for a role of organic solvents in the development of SLE is relatively scant and inconsistent (8). In an ecologic study in Tucson, Arizona (34), exposure to trichloroethylene and other contaminants in drinking water was associated with low titers of ANA and some (nonspecific) SLE symptoms, but there are considerable limitations to the design and interpretation of that study (11). An increased prevalence of ANA and other immunologic changes were described in residents exposed to trichloroethylene-contaminated water in Woburn, Massachusetts (36). We found no significant increased risk of SLE with occupational solvent exposure in our study in the Roxbury-Dorchester-Mattapan area of Boston. Our results are consistent with those of a population-based case–control study that also did not demonstrate an association between solvent exposure and SLE (9). Causal relationships between the development of SLE and specific chemicals might be concealed by measuring solvents as an aggregate exposure category. However, the prevalence of exposure to specific chemicals is generally too low to distinguish between types of solvents.

Our study is limited by the use of historic exposure information rather than true biologic measures of exposure and by the use of self-reported occupational history data, which could be prone to misclassification and recall bias. Recall bias could occur because patients with a chronic disease might be more likely than controls to recall exposures. There are several reasons why we do not think our results are attributable to recall bias. First, most participants were not aware of any potential risk of developing SLE associated with silica exposure (Brome D, et al: unpublished focus group observations). In contrast, the lupus activists in the communities we studied were concerned about the potential risk of lupus posed by neighborhood hazardous waste sites. We found no association between residential proximity to hazardous waste sites and the risk of SLE (13).

Compared with controls, patients did not report more work experiences with solvent-related jobs, which suggests that the observed association with silica is not explained by differential recall. Furthermore, using previous jobs as markers of exposure may reduce this risk, because previous jobs are usually fairly easy to recall, to a similar degree among patients and controls (18). We initially classified the exposures into the categories of probable, possible, and unlikely but combined the "possible" and "probable" groups because of the small sample size. Misclassification of exposure status is possible but is unlikely to have been differential (i.e., more likely in patients than in controls); therefore, this source of inaccuracy would most likely attenuate the observed results.

An additional limitation of our study is the lack of patients and controls from other racial and ethnic groups in the communities we studied, which limits our ability to analyze the effect of race or to generalize our findings to other racial and ethnic groups. However, because the vast majority of participants were of African American descent, the risk of confounding from factors associated with African American ethnicity was reduced.

Another concern with case–control studies is the potential for selection bias resulting from the gathering of patients and controls from slightly different settings. If the likelihood of being a control was inversely associated with the probability of having worked with silica, an artificially low prevalence of silica exposure in the controls would have resulted in an artificially increased association. However, this seems unlikely, because control subjects were chosen from exactly the same neighborhoods, had similar ethnic composition, and had comparable educational levels and employment status. Furthermore, smoking status, parity, and age were similar between patients and controls, but we cannot exclude the possibility of residual confounding or confounding by unmeasured factors. In particular, most SLE patients with zip codes from the study area were admitted to one of the 6 study hospitals, while healthy control individuals were enrolled through community outreach programs. However, we do not believe that this is a very likely explanation for the associations seen in this study. All but 1 of the 18 cases of SLE identified through community outreach and in community health centers were also detected through the hospital databases. This probably reflects that there are few rheumatologists in private practice or at any of the community health centers in the study region, and that most community health centers in the study region are affiliated with one of the hospitals. Therefore, it seems that patients with possible SLE are referred to specialists at

the medical centers, and most patients with SLE living in the Boston area have good access to medical centers.

Another potential source of selection bias relates to the proportion of eligible patients with SLE who were effectively enrolled. Despite our efforts, 53% of all eligible patients with SLE did not respond or chose not to participate in this study. This recruitment rate among an African American population is similar to that for other studies in this population (37). Because individuals who participate in studies tend to be well educated and involved in their health, it is possible that women who did not participate in our study had lower levels of literacy and higher levels of exposure to toxins, such as solvents and silica dust, compared with women who did participate in our study. If this were the case, the study results would underestimate (bias toward the null) the true effect of such exposures.

The strengths of this study include careful verification of the SLE diagnosis by chart review, the detailed assessment of important confounders, the complete assessment of lifetime residential and occupational history, and a large population-based control group representative of a high-risk population.

It is essential to recognize environmental risk factors for SLE, because unlike genetic factors, they are modifiable. Groups who are at high risk of SLE, such as African American women, may derive the most benefit from the prevention of exposure to occupational risk factors for SLE. This study adds to a growing body of literature pertaining to the association between exposure to silica dust and an increased risk of SLE and other connective tissue diseases. In this study, silica exposure was attributable to a variety of urban, industrial occupations rather than a single occupational setting. A longer duration of exposure to silica dust was associated with greater risk. Further understanding of the association between silica exposure and the etiology of SLE may help shed light on the pathogenesis of the disease and the role of silica as an adjuvant stimulating T cell responses or as an inducer of apoptosis.

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