Occupational Risk Factors for the Development of Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** There have been few studies of occupational exposures and systemic lupus erythematosus (SLE). We examined the association between the risk of SLE and occupational exposures (mercury, solvents, and pesticides), specific jobs (ever worked in teaching, healthcare, and cosmetology), and working night or rotating shifts.

Methods. Patients with recently diagnosed SLE (n = 265) were recruited through 4 university based and 30 community based rheumatology practices in North Carolina and South Carolina, USA. Controls (n = 355) were identified through driver's license records and were frequency matched to patients by age, sex, and state. Data collection included an in-person interview with detailed farming and work histories.

Results. Associations were seen with self-reported occupational exposure to mercury (OR 3.6, 95% CI 1.3, 10.0), mixing pesticides for agricultural work (OR 7.4, 95% CI 1.4, 40.0), and among dental workers (OR 7.1, 95% CI 2.2, 23.4). Although these associations were fairly strong and statistically significant, the prevalence of these exposures was very low and thus these estimates are based on a small number of exposed cases and controls. Weaker associations were seen between SLE and shift work (OR 1.6, 95% CI 0.99, 2.7) and among healthcare workers with patient contact (OR 1.7, 95% CI 0.99, 2.9). There was no association of SLE with use of solvents or among teachers or cosmetologists.

Conclusion. This study reveals the potential contribution of occupational exposures to the development of SLE, and highlights some exposures and experiences that should be examined in other studies using more extensive exposure assessment techniques and in experimental studies of autoimmunity. (J Rheumatol 2004;31:1928–33)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS AUTOIMMUNE DISEASE
OCCUPATION MERCURY SOLVENTS PESTICIDES

Genetic susceptibility clearly plays a role in the etiology of systemic lupus erythematosus (SLE), but the concordance among monozygous twins of 25% to 35%[1,2] suggests that other factors are also involved in the etiology of this disease. Environmental (or nongenetic) stimuli of the initiation and progression of the disease could include infectious agents as well as chemical or other compounds with immunomodulating potential. However, the role of environmental factors in SLE is poorly understood.

Few population based epidemiologic studies have examined occupational risk factors for SLE, but experimental studies provide some evidence of exposures that may affect risk, from the development of autoreactive cells to the development of clinical features of disease. For example, studies in several strains of rodents have shown that mercury can induce autoimmune related glomerulonephritis and accelerate various indicators of autoimmune disease in lupus-prone mice[3-5]. Acceleration of an autoimmune response (increased antinuclear antibodies and immunoglobulin production) has been seen in MRL +/+ mice exposed through drinking water to the solvent trichloroethylene[6]. In humans, a history of use of organochlorine pesticides was associated with low titer antinuclear antibody levels in a population based study of 322 residents in Saskatchewan, Canada[7]. However, mercury, solvents, and pesticide exposures have not been examined extensively in

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Supported by the Division of Intramural Research of the National Institute of Environmental Health Sciences and the National Center for Minority Health and Health Disparities of the National Institutes of Health.

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Submitted August 29, 2003; revision accepted April 7, 2004.

occupational or population based epidemiologic studies of SLE.

A recent study reported a higher than expected rate of autoimmune disease mortality among school teachers, including a weak association also seen with lupus related mortality[8]. Working night shifts has been associated with the risk of breast cancer, possibly through mechanisms involving the effect of melatonin suppression on estrogen production or on immune mediated mechanisms[9], but this relationship has not been previously examined with respect to SLE. Melatonin has proinflammatory effects, stimulating production of interleukin 1 and other cytokines, and so may influence the development of SLE and other autoimmune diseases[10].

We examined the association between the risk of developing SLE and specific occupational exposures (mercury, solvents, and pesticides), jobs (teaching, healthcare, and cosmetology), and shift work. We were interested in healthcare workers because they often work night or rotating shifts and they have an increased risk of exposure to infectious agents.

MATERIALS AND METHODS

The Carolina Lupus Study was based in 60 contiguous counties in eastern and central North Carolina and South Carolina. Patients with recently diagnosed SLE were identified through community based rheumatologists and university based rheumatology practices in the study area. All patients fulfilled the American College of Rheumatology classification criteria for SLE[11]. Of the 285 referrals, 265 (93%) enrolled in the study. Population based controls were identified through driver's license records and were frequency matched to the cases by age (5-year age groups), sex, and state. The 355 controls who enrolled in the study represent 75% of the screened and eligible controls who were invited to participate. The study protocol was approved by the review boards of all participating institutions. Details of the subject recruitment procedures and demographic characteristics of participants have been described[12].

Ninety percent of the 265 SLE cases in the Carolina Lupus Study were female, 60% were African American, and the mean age at diagnosis was 39 years. The median time from diagnosis to enrollment in the study was 13 months, and 75% were interviewed within 1.7 years of diagnosis. The frequency of clinical immunologic and clinical features[13] is similar to other lupus cohorts.

Data collection included a structured 60-minute in-person interview. Occupational exposure to silica dust in relation to risk of SLE was assessed in this study, as reported[12]. In the work history section, we asked about each job held for ≥ 12 months. Specific questions included job title, description of main tasks or activities, type of company, and duration of employment (years, months per year, and hours per week). The job titles and descriptions of jobs held for ≥ 12 months were used to categorize specific types of jobs for analysis (teachers and childcare workers, beautician/barber/cosmetologists, healthcare workers with patient contact, and dental workers). The healthcare group did not include administrative or other jobs that were not likely to have patient contact, and dental workers were also included in the healthcare workers group. The other large categories of jobs held by participants in this study were clerical and support services, administrative (supervisory) work, and sales. We did not have an *a priori* basis for examining these job categories, and so did not include them in the analysis.

The questionnaire also asked, for each job, whether the participant worked mostly days, evenings, nights, or rotating shifts. For the analysis of shift work, work in either night shifts or rotating shifts that included nights was considered "positive".

The job history also included specific questions about jobs or tasks with the potential exposure to solvents (e.g., cleaning metal parts; paint manufacturing or commercial painting; furniture manufacturing, repair, or refinishing; artist or sculptor; arts and crafts using glues, paints, or solvents; beautician, barber, or cosmetologist; dry cleaning; medical diagnostic laboratory; pathology laboratory; and research laboratory). A positive response to these questions was based on employment for any length of time (i.e., even less than 12 months) in these jobs. Age first employed, years worked, and months per year worked in each of these job was ascertained. We also asked about use of specific materials at least once a week on a job [e.g., stains, varnish, or other wood finishes; paints, paint products, or paint thinner or remover, perchlorethylene (PERC) or tetrachlorethylene (Solvene); trichloroethylene (Triasol, Carbona); benzene, xylene, or toluene]. This materials checklist also collected information on age when use of the material started, years worked with the material, and days per year used.

Work in a dental laboratory or office and use of mercury were also included in the job and materials checklists, respectively. Other potential occupational sources of mercury exposure, such as in certain mining operations and in battery manufacturing, were also evaluated based on the job history data. Exposure to pesticides was ascertained within the context of the farming history section, and was based on questions about mixing insecticides (ever mixed, how often mixed, and use of rubber gloves or a respirator) and applying insecticides (ever applied, how often applied) during 4 age groups (ages 10–15, 26–29, 20s and 30s, and after age 40).

Three reviewers (one industrial hygienist and 2 epidemiologists trained in the assessment of occupational exposures) reviewed the job and task descriptions of each job in conjunction with the checklist data and rated the potential exposure to mercury and solvents. A dichotomous rating scheme (i.e., yes, no) was used for mercury. For solvents, 5 rating categories were used: likely–high, possible–high, possible–moderate, indirect (e.g., bookkeeper in an automobile repair shop), and none. The farming pesticide data was used to create pesticide exposure categories of none, applied but did not mix, and mixed pesticides.

Analyses were limited to experiences that occurred before age at diagnosis for cases or a corresponding reference age for controls. We used logistic regression to examine the association between work history and risk of developing SLE. The associations were estimated as the odds ratio (OR) and 95% confidence interval (CI), and were adjusted for age, state, race (2 groups: whites, African Americans plus other minorities), and education (did not complete high school, high school degree, some college or technical school, and college graduate). The additional adjustment for occupational silica exposure had little effect on estimated associations and so silica was not included in the final models. Smoking was not associated with SLE, and so was not a confounder of the occupational associations. We also conducted 2 separate analyses limited to African Americans or to whites to determine if the associations were similar in these 2 groups. The interaction between race and specific exposures with respect to SLE was assessed by comparing the –2 log-likelihood statistic of models with and without the race-interaction term, with p values less than 0.15 taken as evidence of an interaction.

RESULTS

There was no evidence of an association between occupational exposure to solvents and SLE (Table 1). Associations were seen with occupational exposure to mercury (OR 3.6, 95% CI 1.3, 10.0) and with mixing pesticides for agricultural work (OR 7.4, 95% CI 1.4, 40.0). These associations were statistically significant ($p < 0.05$) but the prevalence of these exposures was very low. No association was seen with applying pesticides, which was more common than mixing pesticides, but is likely to represent a lower exposure potential. Frequency of pesticide application was not associated

Table 1. Occupational exposures and risk of developing SLE in 265 cases and 355 controls.

	Cases, n (%)	Controls, n (%)	Total Sample, Adjusted OR (95% CI)*	African Americans, Adjusted OR (95% CI)	Whites, Adjusted OR (95% CI)
Mercury**					
No	255 (96)	348 (98)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	10 (4)	7 (2)	3.6 (1.3, 10.0)	†	†
Solvents**					
None	160 (60)	214 (60)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Indirect	13 (5)	21 (6)	1.0 (0.47, 2.3)	0.69 (0.21, 2.3)	1.3 (0.45, 3.5)
Possible–low	21 (8)	30 (8)	0.94 (0.50, 2.3)	1.0 (0.37, 2.7)	0.72 (0.25, 2.1)
Possible–moderate	28 (11)	29 (8)	1.0 (0.57, 1.9)	0.52 (0.23, 1.2)	2.2 (0.87, 5.8)
Likely–high/moderate	43 (16)	61 (17)	1.0 (0.60, 1.6)	0.97 (0.44, 2.1)	1.3 (0.64, 2.5)
Pesticides***					
Neither	97 (82)	117 (84)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Applying	13 (11)	21 (15)	0.77 (0.34, 1.8)	1.5 (0.32, 6.9)	0.68 (0.18, 2.7)
Mixing	9 (8)	2 (1)	7.4 (1.4, 40.0)	†	†
Shift work††					
No	220 (83)	320 (90)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	45 (17)	35 (10)	1.6 (0.99, 2.7)	2.3 (1.1, 4.9)	1.1 (0.46, 2.4)

* Adjusted for age (continuous), sex, state, race (whites, non-whites), and education (did not complete high school, high school degree, some college or technical school, college graduate). Race-specific analyses do not include the race variable. Total sample includes other minorities (16 cases and 26 controls) in addition to African Americans and whites. ** Review of job title, industry, and description of tasks and activities for all jobs held at least 12 months and of specific job and materials checklists. *** Limited to ever worked or lived on a farm (n = 119 cases, n = 140 controls). Applying: self-reported application of pesticides, without mixing, in farming history; mixing: self-reported mixing of pesticides in farming history. †† Questions about night and rotating shifts asked for each job held ≥ 12 months. † Race-specific analyses not reported because of the limited number of positive responses (< 10 among cases or controls).

with increased risk (data not shown). Shift work was marginally associated with SLE (Table 1). The estimated effects of shift work differed somewhat by race, with a stronger effect among African Americans. However, this race interaction was not statistically significant (p value for interaction = 0.24).

There was no association between work as a teacher or beautician and risk of SLE (Table 2). Results were similar among teachers working in daycare-primary schools and in secondary schools, and there was no evidence of an increasing effect with longer duration of work as a teacher. Being a healthcare worker with patient contact was associated with SLE, and this association was strongest among those who had worked for ≥ 5 years. The association with healthcare work appeared somewhat stronger among whites, but the race interaction was not statistically significant (p value for interaction = 0.27). An association was also seen with SLE among dental workers (OR 7.1, 95% CI 2.2, 23.4).

Because of the small number of exposed persons and the correlation between occupational mercury exposure and work in a dental office, we could not disentangle the effects of these exposures. We did examine the influence of shift work and healthcare work, adjusting for each of these exposures. These results did not differ substantially from the separate results for each exposure. Among African Americans, shift work was related to risk (OR 2.3, 95% CI 1.0, 5.2) but there was no additional association with healthcare work (OR 0.94, 95% CI 0.41, 2.2). Among whites, there was no association with shift work (OR 0.82, 95% CI 0.34, 2.0), but healthcare work was associated with risk (OR 2.5, 95% CI 1.1, 5.6).

DISCUSSION

This is the first population based epidemiologic study to evaluate the role of a variety of occupational exposures, jobs, and working conditions on the risk of developing SLE. As such, even "negative" findings of exposures that have been suggested to be related to SLE are important. We found no associations with occupational exposure to solvents or with work as a beautician. Walsh and DeChello[8] reported a higher than expected rate of autoimmune disease mortality among school teachers. In contrast, we saw no association between risk of SLE and work as a teacher or childcare worker.

We observed fairly strong associations between SLE and self-reported mercury exposure and work in a dental laboratory or office. Mercury-induced autoimmunity and glomerulonephritis has been described in animal strains that are both susceptible to and resistant to autoimmune disease[3-5], but there has been no previous human study examining the association between mercury and SLE. Only 4 of the 10 cases in our study who reported occupational mercury exposure had evidence of renal involvement (from biopsy or from at least 2 documented episodes of proteinuria), but this prevalence was roughly 2 times higher than the prevalence in nonexposed cases. In a study of scleroderma patients, Arnett, *et al* reported an increased concentration of urinary mercury in patients with antifibrillarin (U3-RNP) antibodies compared

Table 2. Job categories and risk of developing SLE in 265 cases and 355 controls.

Job Category*	Cases, n (%)	Controls, n (%)	Adjusted OR (95% CI)**	African Americans, Adjusted OR (95% CI)	Whites, Adjusted OR (95% CI)
Teaching, childcare					
Never worked this job	229 (86)	290 (82)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Ever worked	36 (14)	65 (18)	0.87 (0.53, 1.4)	0.51 (0.23, 1.1)	1.2 (0.60, 2.3)
Primary school	29 (11)	53 (15)	0.83 (0.49, 1.4)	0.59 (0.26, 1.4)	1.0 (0.48, 2.1)
Secondary school	7 (3)	12 (3)	1.2 (0.42, 3.3)	†	†
Worked < 5 years	18 (7)	29 (8)	1.0 (0.52, 1.9)	0.67 (0.23, 2.2)	1.4 (0.59, 3.3)
Worked ≥ 5 or more years	18 (7)	36 (10)	0.76 (0.39, 1.5)	0.41 (0.17, 1.3)	0.96 (0.37, 2.5)
Beauticians					
Never worked this job	248 (94)	338 (95)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Ever worked	17 (6)	17 (5)	1.6 (0.74, 3.3)	1.6 (0.36, 6.0)	2.0 (0.72, 5.4)
Healthcare					
Never worked this job	225 (85)	321 (90)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Ever worked	40 (15)	34 (10)	1.7 (0.77, 2.9)	1.2 (0.58, 2.7)	2.3 (1.1, 5.1)
Worked < 5 years	17 (6)	15 (4)	1.4 (0.64, 2.9)	1.4 (0.45, 4.2)	1.4 (0.39, 4.8)
Worked ≥ 5 years	23 (9)	19 (5)	2.0 (1.0, 4.0)	1.2 (0.44, 3.0)	3.3 (1.2, 8.7)
Dental worker					
Never worked this job**	254 (96)	351 (99)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Ever worked	11 (4)	4 (1)	7.1 (2.2, 23.4)	†	†

* Based on job and industry coding for all jobs held at least 12 months. ** Adjusted for age (continuous), sex, state, race (whites, non-whites), and education (did not complete high school, high school degree, some college or technical school, and college graduate). Race-specific analyses do not include the race variable. Total sample includes other minorities (16 cases and 26 controls) in addition to African Americans and whites. † Race-specific analyses not reported because of the limited number of positive responses (less than 10 among cases or controls).

with patients without these autoantibodies and to controls[14]. Only one of the mercury-exposed cases in our study had anti-RNP antibodies, but this is somewhat noteworthy in that this patient was one of the 6 white mercury-exposed cases. Anti-RNP antibodies are uncommon among whites (5% among all white patients in our study, 3% of those who did not report occupational mercury exposure).

Although our data suggest an association of occupational mercury exposure with SLE, it is difficult to separate these effects given the small numbers of individuals in these groups, and it is difficult to examine mercury exposure apart from exposure to other exposures in the medical or dental environment. More than half the mercury-exposed individuals in this study worked in a dental environment, many during the mid to late 1980s. We conducted followup interviews to assess potential exposure to mercury and other agents in our study participants who had worked in a dental laboratory or office, specifically focusing on exposures from models and composite materials, including quartz[15] and acrylic resins (methyl methacrylate)[16]. Exposure to crystalline silica (quartz) was associated with SLE in our study population[12], and has been associated with the development of pneumoconiosis in dental laboratory workers[17]. Methacrylates, often associated with hypersensitivity responses, may also act as adjuvants[18] and in this way could contribute to the development of autoimmunity. Based on the followup interviews, we found that most workers were exposed to multiple agents and that the use of personal protection from dusts and vapors was sporadic. Thus, although we cannot rule out a primary effect of mercury exposure, other plausible risk factors may contribute to the observed association among dental workers.

A history of mixing pesticides for farm work was associated with SLE in our study. This association was based on small numbers of exposed individuals, however, and so was a fairly imprecise (although statistically significant) measure of association. Most experimental studies of specific pesticides have focused on immunosuppressive effects. Although a dual effect of immune suppression and enhancement (increased levels of immunoglobulin and autoantibody production) may be relevant for the development of autoimmune diseases, the relationship between pesticide exposure and autoimmunity has not been extensively examined in humans or in animals[19].

We saw some evidence of associations between risk of SLE and healthcare work involving patient contact and between SLE and work that involved rotating or night shifts. Adjusting for each of these factors had little effect on the estimated effects. Although cases were slightly more likely to work in nursing compared to controls (12% vs 8%), having a history of administering chemotherapeutic drugs or work with anesthetic gases were extremely rare and there was no apparent difference in the percentage of cases and controls reporting these work experiences. We did not attempt to evaluate exposures to specific infectious pathogens. We did not collect other information about type

of patient contact or potential exposure to infectious agents (e.g., through needlestick injuries), so we could not explore this issue to any greater extent. Shift work and resulting exposure to light at night can suppress the production of melatonin, which is known to play a role in the interaction between the hypothalamic-pituitary-adrenal axis and immune system[20], and may thereby affect the development of SLE. Lupus-prone mice [MRL/MS-fas (lpr)] appear to have disturbances in the circadian response to light/dark cycling, but it is not clear whether alterations in the neuroimmune interactions affect susceptibility to autoimmunity in this model[21].

This is the first large population based case-control study to examine a broad range of occupational exposures and specific jobs in relation to risk of developing SLE. The study was conducted in the southeastern United States and included adequate numbers of African Americans and whites to allow separate analyses within each of these groups. Because of restrictions on access to medical records, we did not systematically record from all study sites information on eligible patients who were not referred to the study, and so cannot provide a definitive estimate of the number of patients that were missed in this recruitment strategy. We did not match by race in the sampling design for the controls because we wanted the control sample to represent the racial distribution of the population in the study area. Matching can be a cost-effective way to improve the efficiency of a study design, but matching by race is not necessary to produce unbiased effect estimates[22].

Our assessment of solvent exposure was based on expert review of job history data. This assessment strategy should reduce the likelihood of exposure misclassification and maximize the chance of seeing an effect if one were truly present. Biomarkers (in urine, blood, or hair) of mercury exposure provide a good measure of recent exposure[23,24], but this time-window may not be appropriate if exposures more distant to the clinical expression of disease are relevant to the pathogenesis of the disease. For past or cumulative exposures, work history, either by self-report or by some other form of documentation, may provide less misclassification than a biomarker.

There are important limitations to this study, however. Non-occupational sources of exposure, for example from mercury-containing hair treatments and contaminated water supplies, were not included in this assessment. The observed associations with mercury and pesticide exposure and work in a dental laboratory or office are based on very small number of exposed individuals, and so the estimated associations were fairly imprecise. Thus, although the estimated associations are statistically significant, they could ultimately be found to be spurious if not confirmed by other studies.

The level of detail collected for exposures other than silica[12] did not allow an extensive analysis of the role of specific types of solvents or pesticides. Many experimental studies of solvents in lupus-prone mice have examined trichloroethylene or its metabolites[6,25-28], but there have not been enough studies of other solvents or classes of solvents to know whether trichloroethylene is unique in its effects. Epidemiologic studies of systemic sclerosis (scleroderma) and undifferentiated connective tissue disease have generally shown associations with solvents as a broad category of exposure, with some studies also showing associations with specific solvents[29-32]. We did not observe an association between SLE and solvents in this study. Only 2 patients reported exposure to trichloroethylene, and we did not attempt additional analyses of specific compounds. Although some occupational exposures, such as silica, are associated with a spectrum of autoimmune diseases, other exposures (such as solvents) may be more specific to specific conditions. This difference in specificity of effect may be related to the mechanisms involved, and emphasize the complexity of the etiology of these diseases.

The association we observed between occupational mercury exposure and SLE adds to the considerable experimental data on mercury-induced autoimmunity. This study also provides evidence of other specific exposures and experiences that should be examined in other epidemiologic studies of SLE. The number of cases with some of the specific self-reported exposures (e.g., mercury) is very small, and so these exposures are not likely to represent major contribution to disease. Other exposures are more common (e.g., shift work), but the results should be viewed as hypothesis-generating since little previous work has focused on them. The results pertaining to work in a dental laboratory or office, other healthcare work, shift work, and pesticide exposure require replication. Future research should elicit greater detail concerning specific tasks and activities within the context of specific hypotheses (e.g., potential contact with blood-borne pathogens) or specific types of pesticides or other chemical exposures that may influence risk of developing SLE. Additional experimental studies regarding potential mechanisms that may be relevant with respect to night shifts or shift work would also be useful.

ACKNOWLEDGMENT

We thank our study manager, Lyle Lansdell, the interviewers, Alesia Sanyika, Gwen McCoy and Sara Graham, and programmers Carol Lynn and Marsha Shepherd, whose efforts made this study possible. Special thanks and appreciation are also due to the physicians who participated in the Carolina Lupus Study Group in North Carolina and South Carolina: H. Vann Austin, Faye Banks, Franc Barada, George Brothers, Walter Chmelewski, Duncan Fagundus, David Fraser, Stephen G. Gelfand, Helen Harmon, Robert A. Harrell III, John Harshbarger, G. Wallace Kernodle Jr, Elliot Kopp, Kara Martin, John L. McCain, Cathleen Melton, Gwenesta Melton, G. Radford Moeller, William Olds, David Puett, C. Michael Ramsdell, Byron Randolph, A. Silvia Ross, Gregory Schimizzi, Evelyn Schmidt, T. Smith, Claudia Svara, Anne Toohey, Randal White, and Suzanne Zorn; and Carlysle Barfield, John Brittis, Walter Bonner, William

Edwards, Gary Fink, Mitchell Feinman, Frank Harper, Peter Hyman Jr, Wendy Lee, Holly Mitchell, Alan Nussbaum, Georgia Roane, William Sheldon, and Robert Turner.

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