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Original article

Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents

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Abstract

Objectives. We examined occupational and non-occupational exposures in relation to risk of SLE in a case–control study conducted through the Canadian Network for Improved Outcomes in SLE (CaNIOS).

Methods. SLE cases ($n = 258$) were recruited from 11 rheumatology centres across Canada. Controls (without SLE, $n = 263$) were randomly selected from phone number listings and matched to cases by age, sex and area of residence. Data were collected using a structured telephone interview.

Results. An association was seen with outdoor work in the 12 months preceding diagnosis [odds ratio (OR) 2.0; 95% CI 1.1, 3.8]; effect modification by sun reaction was suggested, with the strongest effect among people who reported reacting to midday sun with a blistering sunburn or a rash (OR 7.9; 95% CI 0.97, 64.7). Relatively strong but imprecise associations were seen with work as an artist working with paints, dyes or developing film (OR 3.9; 95% CI 1.3, 12.3) and work that included applying nail polish or nail applications (OR 10.2; 95% CI 1.3, 81.5). Patients were more likely than controls to report participation in pottery or ceramics work as a leisure activity, with an increased risk among individuals with a total frequency of at least 26 days (OR 2.1; 95% CI 1.1, 3.9). Analyses of potential respirable silica exposures suggested an exposure–response gradient (OR 1.0, 1.4. and 2.1 for zero, one and two or more sources of exposure, respectively; trend test $P < 0.01$).

Conclusions. This study supports the role of specific occupational and non-occupational exposures in the development of SLE.

Key words: Systemic lupus erythematosus, Risk factors, Silica, Ultraviolet radiation, Solvents, Occupation, Environment.

CLINICAL SCIENCE

Introduction

There have been considerable advances in the past decade in understanding the role of environmental exposures in the development and progression of SLE and other systemic autoimmune diseases [1]. Recent research has focused on occupational respirable silica exposure and tobacco smoke [2, 3], and a variety of epidemiological and experimental studies have provided data pertaining to these exposures. Relatively strong and consistent findings have been seen in studies of respirable silica dust exposure and SLE and other systemic autoimmune diseases, and mechanistic studies in New Zealand mixed mice and in animal models of silicosis have provided additional insights into the adjuvant effects of silica at the molecular level. We expanded the scope of occupational

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and environmental research to include non-occupational sources of silica exposure and other potential risk factors, based on hypotheses drawn from experimental studies in animals (e.g. solvents such as trichloroethylene, phthalates), clinical observations (e.g. ultraviolet radiation) and previous studies of SLE or other systemic autoimmune diseases (e.g. mercury, pesticides). This analysis was undertaken as part of the Genes and Environment in Systemic Lupus Erythematosus (GenES) study, a case–control study conducted through the Canadian Network for Improved Outcomes in SLE (CaNIOS).

Methods

Details of the study protocol have been described previously [4]. SLE patients were recruited from 11 centres across Canada. Patients were eligible if they had four or more of the revised ACR classification criteria and had two live parents who also agreed to participate in the study (the latter criterion due to the requirement for genetic material from family members, for a companion study). Data pertaining to the ACR classification criteria for SLE were abstracted from the centre's study database or medical records. Potential control households were randomly selected from phone number listings, with selection of individuals within a household based on strata defined by the age, sex and geographical area (based on telephone area code) of the patients. Of the 7973 working phone numbers that were not a business or fax number, 2908 numbers were not screened for eligibility because of repeated no answers or refusal of the phone respondent. Of the 5065 numbers that were screened for an eligible participant, 4075 were found to be not eligible, primarily because no one in the designated age–sex strata was a member of the household ($n = 3538$), or self-report of diagnosis with lupus or other systemic autoimmune disease ($n = 43$). Of the 990 households that were screened and that had a potentially eligible control, 492 (50%) declined to participate in the study and 88 (9%) were passive refusals (e.g. repeated missed appointments), leaving 410 potential controls who agreed to receive more detailed information about the study by mail or e-mail. Of these, 268 enrolled in the study (65% of those who received the study information; 27% of the eligible persons identified through the screening interview). We excluded five controls who did not complete the study interview, leaving 258 patients and 263 controls in the analysis. The study was approved by the ethics review boards of all participating institutions (University Health Network, Research Ethics Board; Hôpital Notre-Dame, Comité d'éthique de la recherché; Montreal General Hospital, Genetics/Population Research/Gen Investigator Initiated Studies Research Ethics Committee; Université de Montréal, Comité d'éthique de la recherché; Capital Health, Research Ethics Board; University of Western Ontario, Research Ethics Board; University of Calgary, Conjoint Health Research Ethics Board; University of Manitoba, Research Ethics Board; Universitaire de Sherbrooke et de l'Université de Sherbrooke, Comité d'éthique de la recherche en santé chez l'humain du Centre Hospitalier; Mount Sinai Hospital, Research Ethics Board; Ottawa Hospital, Research Ethics Board). Participants were informed of the confidentiality procedures used to protect privacy and that answering each question was voluntary.

Patients and controls completed a detailed, structured 30–45 min telephone interview, including demographic factors, smoking history, use of hair dyes, sun exposure, an extensive work history section and additional sections on leisure activities and hobbies. Patients were also asked about the length of time between initial symptoms and diagnosis of SLE. Sun exposure history included questions about skin tone and skin reaction in the sun, and a set of questions about work outdoors (defined as $\geqslant 20$ h/week for $\geqslant 2$ months of the years during the ages 13–19, 20–29, 30–39 and 40–49 years). We also asked about work outdoors (using the same definition) in the 12 months preceding diagnosis (for patients) or in the last 12 months (for controls).

The work history included a set of questions about tasks with potential respirable silica exposure (six questions: plastering; drilling or cutting sheet rock or dry wall; loading, pouring or mixing concrete; drilling, cutting or chipping concrete or abrasive grinding of rocks or stone; grinding drilling, cutting or chipping concrete or abrasive grinding of rocks or stone; and sandblasting), with follow-up questions pertaining to age first employed, number of years, months per year and hours per week worked. Another set of questions asked about 27 specific jobs, with follow-up questions pertaining to age, duration and main activities. This set included 16 silica-related jobs: making pottery; manufacturing china, ceramics or computer wafers; work as a stone or brick mason; in a quarry; as a miner or in a mine; as an artist making pottery or other works with clay; commercial painting; construction of roads or tunnels; construction or demolition of buildings; railroad work involving loading cars or track maintenance; work in a dental laboratory or dental office that involved pouring moulds; manufacturing of glass; manufacturing plastics, petroleum products, rubber, chemicals or dyes; manufacturing paint; manufacturing cosmetics or drugs; and manufacturing powder soaps or abrasive cleaners. The manufacturing work questions were each followed by two probes pertaining to pouring or mixing powder fillers, and dry sweeping, vacuuming or using pressurized air to clean up dirt, dust or other material. Only positive responses to either of these two probes were considered as positive for silica exposure at these jobs. For all jobs, a positive response was defined as work for at least 8 h/week.

Other occupational exposures were assessed using a combination of responses from the job and task history. Exposure to gasoline fumes was based on questions about work as a taxi, bus or truck driver, and a task question about work involving pumping gas. Exposure to stains, varnishes or paint strippers was based on responses to a specific follow-up question about this type of work within the sections asking about jobs held in furniture repair or refinishing, commercial painting, custodial

work, landscaping or farm work. Exposure to pesticides was based on responses to questions about work as an exterminator, spraying insecticides or bug killers in custodial jobs, mixing pesticides in landscaping or mixing or applying pesticides in farm work. Exposure to metal cleaning solvents was based on a positive response to questions about cleaning metal parts within the construction and landscaping jobs sections and one question in the tasks section. Mercury exposure was based on responses to a question in the dental work section about work preparing mercury fillings and on another question about any job with mercury exposure (used or worked with mercury) at least once per week. Additional questions to respondents who worked as a hairstylist, barber or manicurist/pedicurist asked about applying permanents, relaxers or dyes and about applying nail polish or nail applications (did you apply, and if so how many times per week?).

The hobbies section included specific questions on stained or leaded glass and pottery and ceramics. To be counted as a positive response to these exposures, the total frequency (product of number of days per year and number of years before diagnosis or reference age) had to be $\geqslant 5$.

The median difference between diagnosis age and current age among patients was 9 years; the reference age for controls was determined by subtracting this value from their current age. We used this reference age in conjunction with the data on age at which a job or activity began and duration of the experience to exclude jobs, tasks and hobbies that occurred after diagnosis (patients) or reference age (controls). Because controls were matched to cases using a frequency matching, rather than individual matching procedure, this average value was used for all controls. An exception to this procedure was the variable pertaining to outdoor work in the 12 months preceding diagnosis. Because of the way this question was framed in the questionnaire, the time period for this exposure for controls was the 12 months preceding the study interview.

We compared the distribution of demographics and specific exposure variables between patients and controls using frequency tables and plots of continuous variables. Logistic regression was used to evaluate the association of specific exposures with SLE. Results are expressed as odds ratios (ORs) with 95% CIs. Models were adjusted for age (continuous variable), sex and area (using dummy variables for Ontario, Quebec and other provinces, with Ontario being the referent group). Because of sparse data, we dropped sex and the area variables from some models (as indicated in the tables) to obtain a better model fit. To explore potential effect modification, we examined the interaction between sex and the occupational variables for the occupations with at least five men and five women who had a history of the job or exposure. We also examined the interaction between sun exposure and the skin tone and sun reaction variables. For these analyses, $P < 0.15$ was used as an indicator of interaction. We used SAS, version 9.1 (SAS Institute, Cary, NC, USA) for all analyses.

Results

Patients and controls were similar in terms of demographic background. Ninety per cent of the SLE patients are female, and 82% are white (Table 1). The largest share of participants came from Ontario and Quebec, but relatively fewer controls compared with patients lived in other provinces. Similar proportions of each group were born outside Canada (Table 1). More than 40 countries were represented in the list of countries of origin, but only one of these (UK) was the source of more than five study participants. When grouped by region (Africa, eastern Asia, southwestern Asia, eastern Europe, northern Europe, southern Europe, Middle East, Pacific, Caribbean, South America), the numbers within most of these groups were still very sparse. Only northern Europe, southern Europe and eastern Asia produced more than five emigrants, and there was no discernable difference in the country or region of origin when comparing patients and controls

Table 1 Demographic characteristics of GenES study SLE patients and controls

	Patients ($n = 258$) n (%)	Controls ($n = 263$) n (%)	P-value
Sex			
Female	231 (90)	245 (93)	0.14
Male	27 (10)	18 (7)	
Current age, years, mean (S.D.)	34.0 (9.4)	35.6 (9.7)	
18–29	92 (36)	87 (33)	0.82
30–39	85 (33)	88 (33)	
40–49	67 (26)	69 (26)	
50–60	14 (5)	19 (7)	
Ethnicity[a]			
Asian	40 (16)	14 (5)	
Other ethnicity	21 (8)	27 (10)	
White	210 (82)	224 (86)	0.28
Education			
Less than high school	11 (5)	26 (10)	0.22
Completed high school	29 (13)	35 (13)	
Some college	97 (44)	116 (44)	
Completed college	82 (37)	86 (33)	
Province			
Ontario	139 (54)	119 (45)	0.03
Quebec	53 (21)	50 (19)	
Other	66 (26)	94 (36)	
Country of birth			
Canada	212 (82)	213 (81)	0.73
Other country	46 (18)	50 (19)	
Age immigrated—years, mean (S.D.)[b]	7.5 (6.7)	14.0 (7.6)	<0.001
Age $\leqslant$10 years	32 (74)	15 (47)	
Age >10 years	11 (25)	17 (53)	

Missing data: ethnicity—2 patients, 1 control; education—39 patients. [a]Could choose more than one category. P-value compares whites and all other groups. [b]Excluding three patients and 18 controls who immigrated after diagnosis age and reference age, respectively.

(data not shown). However, the SLE patients born outside Canada had immigrated at an earlier age compared with controls (mean age 7.5 and 14.3 years, respectively, for patients and controls). An association was seen between young age at immigration and risk of SLE (OR 2.0, 95% (CI 1.0, 3.9) for immigration age $\leqslant$10 years compared with individuals born in Canada), but no association was seen with older age at immigration (OR 0.69; 95% CI 0.31, 1.5 for immigration age $>$10 years compared with individuals born in Canada).

Smoking history was similar in patients and controls (Table 2). Patients were slightly more likely to be former smokers and less likely to be current smokers at the time of diagnosis. The data pertaining to symptoms did not suggest that initiation of symptoms led to a decision to quit smoking, or that the symptoms occurred as a consequence of smoking cessation (data not shown).

SLE patients were somewhat less likely to characterize their skin tone as fair or very fair compared with controls, and were more likely to characterize their reaction to 2 h of midday sun as producing sunburn with blistering or with a rash (Table 3). When limited to white participants, there was little change in the skin tone association, but the association with skin reaction was somewhat stronger (OR 2.6; 95% CI 1.4, 4.9 for sunburn with blistering or with rash).

An association was seen with outdoor work in the 12 months preceding diagnosis (OR 1.9; 95% CI 1.0, 3.7), but there was no association with total number of years of outdoor work (Table 3). The association with outdoor work in the 12 months before diagnosis did not vary substantially by skin tone (interaction $P = 0.67$; OR 2.3 and 1.5 for fair/very fair and olive/dark/

Table 2 Smoking characteristics of GenES study SLE patients and controls

	Patients ($n = 258$) n (%)	Controls ($n = 263$) n (%)	OR (95% CI)[a]
Smoking Status			
Never smoked	169 (66)	164 (62)	1.0 (referent)
Ever smoked	89 (35)	99 (38)	0.92 (0.64, 1.3)
Former smoker	26 (10)	23 (9)	1.2 (0.67, 2.3)
Current smoker	63 (24)	76 (29)	0.83 (0.55, 1.2)
Age began smoking, mean (s.d.), years	15.6 (3.2)	16.1 (3.3)	(0.30)
<16	50 (56)	44 (44)	1.2 (0.74, 1.9)
$\geqslant 16$	39 (44)	55 (56)	0.71 (0.44, 1.2)
Cigarettes per day, mean (s.d.)	12.4 (9.7)	13.0 (7.9)	(0.62)
1–9	38 (43)	27 (27)	1.4 (0.81, 2.4)
10–19	28 (33)	44 (44)	0.66 (0.39, 1.1)
$\geqslant 20$	22 (25)	28 (28)	0.85 (0.46, 1.6)

[a]Adjusted for current age (continuous), sex and area (Ontario, Quebec, other provinces); the never smoked category is the referent group for analysis of age smoking began and amount smoked.

Table 3 Comparison of sun-related exposure in GenES study SLE patients and controls

	Patients ($n = 258$) n (%)	Controls ($n = 263$) n (%)	OR (95% CI)[a]
Skin characteristics			
Skin tone			
Fair or very fair	187 (72)	209 (79)	0.72 (0.48, 1.1)
Olive, dark or very dark	71 (28)	54 (21)	1.0 (referent)
Reaction to sun—2 h, midday			
Tan or darken without burning	50 (20)	56 (22)	1.0 (referent)
Sunburn	101 (39)	140 (54)	0.88 (0.55, 1.4)
Sunburn with blistering or rash	88 (34)	55 (21)	2.1 (1.3, 3.6)
Other	17 (7)	9 (3)	2.4 (0.96, 6.0)
Outdoor work ($\geqslant$20 h/week, $\geqslant$2 months/year)			
In 12 months before diagnosis (patients) or past 12 months (controls)	32 (12)	16 (6)	1.9 (1.0, 3.7)
Total years, mean (s.d.)	1.2 (3.5)	1.6 (3.6)	($P = 0.29$)
0	185 (72)	181 (69)	1.0 (referent)
1–4	54 (21)	50 (19)	1.0 (0.67, 1.6)
$\geqslant$5 or more	18 (7)	32 (12)	0.62 (0.32, 1.2)
Outdoor work in the 12 months before diagnosis, among people whose reaction to the midday sun is to:[b]			
Tan or darken without burning	4 (8)	5 (9)	0.75 (0.18, 3.2)
Sunburn	14 (14)	8 (6)	2.7 (1.0, 6.9)
Sunburn with blistering or rash	13 (15)	1 (2)	7.9 (0.97, 64.7)

Missing data: reaction to sun, two patients, three controls; outdoor work before, during/past 12 months, one control; total years outdoor work, one patient. [a]Adjusted for current age (continuous), sex, area (Ontario, Quebec, other province); interaction models did not include sex or area because of lack of convergence. [b]The 'other' category of skin reaction is not included in this analysis because of the sparse numbers in both groups. Interaction $P = 0.07$.

very dark skin tone groups, respectively), or by the presence of photosensitivity (based on ACR SLE classification criteria) among the SLE patients (OR 2.4 and 1.7 for photosensitivity positive and negative, respectively). A larger variation in the association with outdoor work was seen when examined within categories of sun reaction (interaction $P = 0.07$), with the strongest effect (OR 7.9; 95% CI 0.97, 64.7) seen among people who reported a typical reaction to midday sun of getting sunburn with blisters or a rash (Table 3).

Personal use of permanent hair dyes was less common among patients compared with controls (OR 0.77; 95% CI 0.53, 1.1). There was little difference in the frequency of occupational exposure to hair dyes, permanents and relaxers, with 7 (3%) patients and 6 (2%) controls reporting this job history.

Occupational exposure to silica dust was somewhat more common among SLE patients, with an OR of 1.6 (95% CI 0.90, 2.7) (Table 4). A smoking status–silica exposure interaction was seen ($P = 0.07$), such that the silica association was seen among never smokers (silica OR 2.6; 95% CI 1.2, 5.7) compared with never-smokers with no silica exposure) but not among ever-smokers [(silica OR 0.99; 95% CI 0.46, 2.1)].

Other types of job or exposure that were associated with SLE include artist working with paints, dyes or developing film (OR 3.9; 95% CI 1.3, 12.3), work involving sterilizing dental equipment (OR 3.9; 95% CI 0.76, 20.0) and mercury (OR 3.1; 95% CI 0.77, 12.7); these are relatively imprecise estimates since they are based on small numbers of exposed individuals (Table 4). Although no association was seen with work as a hair stylist or applying hair dyes or permanents, SLE patients were more likely to have worked in a job applying nail polish or nail applications (OR 10.2, 95% CI 1.3, 81.5). The frequency of nail application/nail polish work was also higher among SLE patients, with five patients compared with zero controls reporting an average of $\geqslant 5$ per week (range 5–36).

Table 4 Comparison of occupational and other exposures to dusts and chemicals in GenES study SLE patients and controls

Exposures and activities[a]	Patients ($n = 258$) n (%)	Controls ($n = 263$) n (%)	OR (95% CI)[b]
Occupational			
Silica dust[c]	40 (16)	27 (10)	1.6 (0.90, 2.7)
Artist, working with paints, dyes or developing film	14 (5)	4 (2)	3.9 (1.3, 12.3)
Repairing or cleaning machinery or metal	15 (6)	8 (3)	1.9 (0.76, 4.7)
Stains, varnishes or paint strippers[d]	12 (5)	10 (4)	1.4 (0.54, 3.6)
Sterilizing dental equipment	6 (2)	2 (1)	3.9 (0.76, 20.0)
Mercury ($\geqslant$once per week)	7 (3)	3 (1)	3.1 (0.77, 12.7)
Nail polish or applications	9 (3)	1 (0)	10.2 (1.3, 81.5)
Gasoline—taxi, bus or truck driver or job pumping gas	10 (4)	15 (6)	0.76 (0.32, 1.8)
Pesticides[e]	9 (3)	9 (3)	1.1 (0.43, 3.0)
Drawing blood, giving injections	14 (5)	18 (7)	0.97 (0.45, 2.1)
Dry cleaning	5 (2)	4 (2)	1.5 (0.38, 5.6)
Non-occupational			
Pottery or ceramic work—ever[f]	59 (23)	42 (16)	1.7 (1.1, 2.7)
Total days—never	199 (77)	221 (84)	1.0 (referent)
5–25	19 (7)	19 (7)	1.2 (0.62, 2.4)
$\geqslant$26	39 (15)	22 (8)	2.2 (1.2, 3.9)
Home renovation with drywall—ever[g]	49 (19)	40 (15)	1.3 (0.83, 2.1)
Stained or leaded glass—ever[f]	8 (3)	3 (1)	3.0 (0.76, 11.6)
Combined silica exposure[h]			
Any	111 (43)	88 (33)	1.6 (1.1, 2.3)
Number of exposure scenarios—0	147 (57)	175 (67)	1.0 (referent)
1	79 (31)	69 (26)	1.4 (0.97, 2.1)
2	27 (10)	17 (6)	1.9 (0.97, 3.7)
3	5 (2)	2 (1)	3.7 (0.67, 20.1)

Missing data: number of days of pottery or ceramic work, one patient and one control. [a]Prior to diagnosis age (patients) and reference age (controls). [b]Adjusted for current age (continuous), sex and area (Ontario, Quebec, other province); referent group is those who did not do this activity. Models for sterilizing dental equipment, mercury, nail polish or applications, pesticides, dry cleaning and stain or leaded glass did not include sex or area terms because of lack of convergence. [c]Based on six silica task questions and 16 silica job questions (with follow-up probes), see 'Methods' section for details. [d]In furniture repair or refinishing, commercial painting, custodial work, landscaping or farm work. [e]In work as an exterminator, landscaping, custodial work or farm work. [f]Positive response (ever) defined as total number of days (years $\times$ average days per year) $\geqslant 5$. [g]Construction or demolition of walls or other work with drywall; positive response (ever) defined as at least one project before diagnosis age (patients) or reference age (controls). [h]Combining occupational silica dust exposure, pottery or ceramic work and home renovation with drywall.

All of the respondents who had done this work classified themselves as of white ethnicity. Weaker associations were seen with an occupational history of repairing or cleaning machinery or metal (OR 1.9; 95% CI 0.76, 4.7), or work in a dry cleaners (OR 1.5; 95% CI 0.38, 5.6), and there was little evidence of an association with occupational exposure to gasoline, pesticides or work involving drawing blood or giving injections (Table 4). In the analysis of effect modification by sex for the exposures with at least five men and five women in the exposure category (silica dust, repairing or cleaning machinery or metal, exposure to stains, varnishes or paint strippers, and exposure to gasoline), only silica exhibited any evidence of effect modification (interaction $P = 0.12$; all other interactions $P \geqslant 0.20$); as expected, exposure prevalence was higher in men (28% of male controls and 9% of female controls were classified as exposed to silica dust), and the association with SLE was also higher in men (OR 3.0 and 1.4 in men and women, respectively).

Patients were more likely than controls to report participation in non-occupational pottery or ceramics work as a leisure time activity, with an increased risk seen among individuals with a total frequency (i.e. product of number of years up to diagnosis or reference age times the average number of days per year) of at least 26 days (Table 4). Another activity with potential exposure to silica, home renovation work involving construction or demolition of walls or other work with drywall, was also somewhat more common among patients (OR 1.3; 95% CI 0.83, 2.1); a more pronounced difference was seen with activities with stained or leaded glass (OR 3.0; 95% CI 0.76, 11.6), but neither of these associations was found to be statistically significant.

Combining the occupational and non-occupational sources of silica exposure, an increasing risk was seen with increasing number of exposures (ranging from 0 to 3, trend test $P = 0.0075$) (Table 4). Combining the highest categories (and comparing with the referent of zero exposures) resulted in estimates of 1.0, 1.4 (95% CI 0.97, 2.1) and 2.1 (95% CI 1.1, 3.9) for zero, one and two or more sources, respectively. There was little evidence of confounding among the occupational and non-occupational exposures. Results from a model with multiple exposures were similar to the models that examined each exposure individually: outdoor work in the 12 months before diagnosis (OR 1.8; 95% CI 0.95, 3.6); occupational and non-occupational silica (OR 1.3; 95% CI 0.89, 2.0 for one and OR 1.8; 95% CI 0.95, 3.5 for two or more sources); artists working with paints, dyes or developing film (OR 3.6; 95% CI 1.1, 11.7); and those who work with nail polish or applications (OR 10.5; 95% CI 1.3, 86.1).

Accuracy of recall of sun exposure and other experiences may decrease with a longer time since diagnosis. To examine this issue, we repeated the analyses for skin characteristics, reaction to sun, outdoor work before diagnosis by time since diagnosis and the occupation and non-occupational silica exposure variables using the median value (9 years) to stratify the sample. There was no evidence of modification of the results by disease duration, with neither consistently stronger nor consistently weaker results seen within each stratum.

Discussion

This study examined several types of environmental and occupational exposure and risk of SLE. An increased risk of SLE has been noted in minority populations, specifically African-Americans, Hispanics, First Nations, Afro-Caribbean and Asians in the USA, Canada and the UK [5]. Although similar proportions of patients and controls in our study had immigrated to Canada, an increased risk was seen with early age at immigration (i.e. before the age of 10 years). We are not aware of other data specifically examining age at immigration in relation to SLE. The limited sample size precluded a more detailed analysis of effects of specific country or region of origin, or of interactions between environmental exposure and age at immigration. Much larger databases, such as national immigration records, would be needed to address these questions.

The data support a role of sun exposure as a trigger for SLE, or for its diagnosis, particularly among people whose reaction to midday sun is typified by sunburn with blistering or a rash. Much of the research pertaining to immune-related effects of ultraviolet radiation has focused on disease exacerbation or flares [6]. However, ultraviolet radiation may result in a redistribution of nuclear antigens to the cell surface or in the production of novel forms of autoantigens [7], effects that may be relevant given the mechanisms thought to be involved in the aetiology of SLE [1].

We also found associations with jobs or tasks that are likely to reflect exposure to solvents and other chemicals including artists, cleaning metal parts and work in a dental office or laboratory. Much of the research pertaining to solvents and autoimmune diseases has focused on scleroderma [8], with much more limited data available pertaining to SLE [9]. We observed a notable association between work involving nail polish or nail applications and SLE, with nine patients and only one control reporting this experience (OR 10.2; 95% CI 1.3, 81.5). Increased urinary dibutyl phthalate levels have been demonstrated in studies of manicurists [10, 11]; other potential occupational exposures in nail salon workers include methacrylates (e.g. ethyl methacrylate) and a variety of adhesives and solvents [12]. Respiratory symptoms and occupational-induced asthma have been reported in recent studies in this profession [13, 14]. This occupation-based research has not examined autoimmune diseases or autoimmune responses, but Lim and Ghosh [15–17] examined phthalate-induced autoreactivity in the (New Zealand black $\times$ New Zealand white) F_1 lupus-prone mouse. In addition, an association between frequent nail polish use and risk of disease was reported in a large population-based study of primary biliary cirrhosis, an autoimmune liver disease [18]. The markedly elevated risk of SLE among manicurists in our study adds further impetus for additional research on autoimmune-related effects of

specific exposures found in this setting, or possibly from the components found in cosmetics and other beauty products [19].

Immunological studies focusing on exposed-worker populations could be a useful follow-up to this study. Differences in T-cell markers and serum cytokine levels, consistent with a systemic pro-inflammatory state, were seen in 11 cement masonry workers (occupationally exposed to silica dust) compared with electrician controls [20], and increased inflammatory cytokine levels were seen in a study of 35 workers exposed to trichloroethylene [21]. Our study and other recent studies of occupational exposures and systemic autoimmune diseases [22, 23] support the need for research examining immunological effects in selected occupational settings (e.g. nail salons, dental offices, artists' studios) and their clinical consequences.

Although the estimated association we observed with a history of occupational exposure to silica dust was not statistically significant, it was similar in magnitude to associations seen in other studies of SLE [24, 25], and other systemic autoimmune diseases including scleroderma and RA [26]. A pronounced exposure–response gradient was seen when occupational and potential non-occupational sources of silica exposure were combined. Patients were more likely than controls to report participation in pottery or ceramics work as a leisure time activity, with an increased risk seen among individuals with a total frequency of at least 26 days (OR 2.2; 95% CI 1.2, 3.9). The observations pertaining to leisure-time pottery or ceramic work raises questions about exposures during these activities (e.g. silica dust, solvents); these questions could be answered by industrial hygiene assessment of a variety of workspaces used in non-occupational craftwork.

One of the limitations of this study, as with many population-based epidemiological studies, arises from the difficulties in recruiting a comparison group that is representative of the population from which the patients were selected. The study involved a somewhat lengthy interview (30–45 min), with an optional component of a clinic visit for a blood draw. The 263 controls included in this study represent 65% of the eligible people who agreed to receive information about the study, but only 27% of those who were identified through the screening process, which involved a random selection of phone number listings. Although area was used in the frequency matching for the identification of controls, a higher proportion of controls compared with patients in the final sample came from areas other than Ontario and Quebec. However, to address the potential confounding that could occur due to the different patterns of geographical location, all of the models included variables for geographical area.

Another limitation of this study is that exposure information was based on self-reported history collected an average of 9 years after diagnosis, and so some inaccuracies can be expected. However, in the analyses stratified by duration of disease, there was little difference in the results for the sun-related and silica-related variables, suggesting that recall accuracy was not biasing the results. Interviewers were aware of the disease status (patient or control), but this awareness should have relatively little impact on the data collected given the structured nature of the questions. To minimize possible over-reporting of exposures, we based our classifications on very specific questions (i.e. use of specific products or activities) rather than on broad job titles. We also excluded what may be considered trivial exposures (i.e. a total frequency of an activity that was <5 days, or a job held <8 h/week). Thus, the classification of exposure was based on an algorithm that could not be readily influenced by knowledge of disease status. There was no difference in the frequency of several exposures (e.g. pesticides, blood drawing) that may be of high interest to the patients or to the public in general, which provides additional reassurance that the associations we observed are not likely to be due to differential reporting by patients compared with controls.

The questions pertaining to typical skin reaction to midday sun may reflect manifestations of the disease. For example, 54% of patients with photosensitivity (based on ACR criteria) reported a usual reaction of sunburn with blistering or rash, compared with 21% of patients without photosensitivity. Thus, the potential for differential misclassification of exposure (that is, relatively higher reporting on the part of SLE patients compared with controls) is a particular concern for the analyses based on reaction to the sun. However, although there was a marked increase in the association seen between outdoor work before diagnosis among people who reported a typical skin reaction of sunburn with blistering or a rash (with an OR of 7.9 for outdoor work in this group), there was much less variation in the association seen with outdoor work among patients who did and did not have photosensitivity. Thus, we do not believe that the interaction we observed between skin reaction and history of outdoor work in the 12 months preceding diagnosis is entirely due to higher reports of relevant exposures by SLE patients compared with controls. Another limitation specifically with respect to the ascertainment of outdoor work (as a proxy for sun exposure) is that the time period for this exposure differed for patients (i.e. the 12 months before diagnosis) and controls (the 12 months preceding the study interview). This could be expected to create more recall accuracy problems in the SLE cases versus the controls, which would mean that true effects are probably at least as strong as what was observed. Future research in this area would benefit from a more detailed ascertainment of ultraviolet radiation from occupational and non-occupational activities [27–29].

Another limitation arises from the case–parent triad study design of the GenES study, a design that requires participation of both parents of a patient to maximize what can be learned from the genetic analyses. Thus, GenES study patients represent a relatively young portion of the age spectrum of SLE patients. If the relative contribution of genetic factors is greater for younger patients, this

design may result in underestimating the contribution of environmental or occupational exposures to the disease experience in the broader population. It should also be noted that although this study is similar in size to other recent population-based case–control studies of SLE, the sample size precludes precise estimation of associations for relatively uncommon exposures.

This study raises several questions pertaining to potential exposures or experiences affecting the risk of developing SLE, including early age at immigration, acute immunological effects of sun exposure, immunological effects of exposures encountered by workers in nail salons and dental practices and characterization of the level and variability of respirable silica exposure in non-occupational settings. A multidisciplinary approach, built upon multisite (and potentially even international) collaborations, with detailed and valid measures of exposure, offers the most promise for advancing our understanding of the multifactorial nature of the development of SLE.

Rheumatology key messages

- Several occupations, in addition to silica-related jobs, may be associated with lupus.
- Studies of immunological effects of exposures in nail salons, dental practices and artists' studios are needed.

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