Silica Exposure in Anti-Neutrophil Cytoplasmic Autoantibody-Associated Glomerulonephritis and Lupus Nephritis

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Abstract. Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated small-vessel vasculitis (SVV) and systemic lupus erythematosus (SLE) are rare diseases with unknown causes. Silica dust exposure has been suggested to be an environmental factor that may increase the risk of developing these and other autoimmune disorders. This is a report of two case-control studies to determine whether silica dust exposure is independently associated with ANCA-SVV with glomerulonephritis and SLE nephritis. Patients were screened through a collaborative network of 225 private practice and university nephrologists (the Glomerular Disease Collaborative Network). Patients with ANCA-SVV or SLE, all with biopsy-proven renal involvement, were included. Control subjects were patients without ANCA-SVV or SLE who had been referred to the same renal clinics and were matched for gender, race, and age (within 5 yr). Exposures to silica, exposures to other environmental agents, and smoking histories were evaluated using a self-administered questionnaire. Enrollment consisted of 65 patients with ANCA-SVV and 51 patients with SLE nephritis. Silica dust exposure was reported by 46% of patients with ANCA-SVV, compared with 20% of control subjects ($P = 0.001$). The odds ratio of silica dust exposure was 4.4 times greater for patients with ANCA-SVV, compared with control subjects (95% confidence interval, 1.36 to 13.4; $P = 0.013$). The odds ratios for silica dust exposure were similar for patients with ANCA-SVV with lung or sinus vasculitis (odds ratio, 4.5; 95% confidence interval, 0.99 to 20.83; $P = 0.054$) and those without lung or sinus vasculitis (odds ratio, 4.7; 95% confidence interval, 1.34 to 16.24; $P = 0.016$). Silica dust exposure was reported by 12% of patients with SLE nephritis, compared with 25% of control subjects ($P = 0.047$). The odds ratio for exposure to silica dust was not statistically different for patients with SLE nephritis, compared with control subjects (odds ratio, 0.001; 95% confidence interval, <0.01 to >100; $P = 0.993$). Activities and environments known to cause high levels of exposure to silica dust were associated with ANCA-SVV but not with SLE nephritis.

Accumulating evidence suggests that silica dust exposure is associated with increased risks for a wide variety of autoimmune diseases, including scleroderma, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus (SLE), and vasculitis (1–12). Silica exposure has also been associated with impaired renal function (13–17) and end-stage renal disease (18,19). The association of silica exposure with autoimmune diseases and renal disease has been noted in numerous case reports and small case series, as well as in several large-scale epidemiologic studies. These investigations have primarily involved mortality, cohort, and case-control studies focusing on workers in occupations commonly accepted as having high levels of exposure to silica dust (1–3,6,20–25). Although these studies demonstrated a compelling increase in the relative risks of autoimmune diseases with silica exposure, they suffered from methodologic limitations. Mortality studies often underestimate the true prevalence and incidence of disease, whereas cohorts defined by particular occupations are often not large enough for the study of rare diseases, such as autoimmune diseases. Because of these limitations and because of our interest in silica exposure in vasculitic diseases with known kidney involvement, we conducted case-control studies focusing on two patient groups, *i.e.*, patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated small-vessel vasculitis (SVV) and renal involvement and patients with SLE and nephritis.

We sought to determine whether silica exposure was associated with an increased risk of ANCA-SVV or SLE nephritis in a population in the southeastern United States. For each case-control study, our specific aims were to estimate the prevalence of exposure to silica among patients and control subjects and to identify whether there was an increased risk of developing either disease with silica exposure. In the ANCA-

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SVV study, we also sought to evaluate the risk of developing the disease (*1*) within disease categories (Wegener's granulomatosis, microscopic polyangiitis, and necrotizing and crescentic glomerulonephritis alone); (*2*) with respect to organ involvement, to determine whether certain manifestations of the disease were more likely to be associated with silica exposure (*e.g.*, pulmonary or sinus involvement); and (*3*) with respect to the perinuclear ANCA (P-ANCA) *versus* cytoplasmic ANCA (C-ANCA) pattern and myeloperoxidase (MPO) *versus* proteinase 3 (PR3) antigen specificity.

Materials and Methods

Subjects and Disease Assessment

Patients with ANCA-SVV were identified through a linked database of renal biopsy diagnoses and ANCA results, through the University of North Carolina (UNC) Nephropathology Laboratory. Patients with SLE nephritis were also identified through the UNC Nephropathology Laboratory database. All patients who signed informed consent forms have been monitored from the time of diagnosis, in a patient registry maintained by the Glomerular Disease Collaborative Network. The Glomerular Disease Collaborative Network is a group of approximately 225 nephrologists from 40 private community offices and three medical schools, located primarily in North Carolina and throughout the southeastern United States. Information gathered for the registry was available for classification of organ involvement and disease categories for the patients. A cross-sectional sample of patients with ANCA-SVV and SLE nephritis from the Glomerular Disease Collaborative Network patient registries were asked to complete questionnaires at a clinic visit, regardless of the length of time since they had received diagnoses. Patients with newly diagnosed ANCA-SVV or SLE nephritis were asked to complete the questionnaires prospectively.

All renal biopsy specimens were evaluated using light, immunofluorescence, and electron microscopy, by a single nephropathologist (J.C.J.). Specimens were required to have a minimum of 10 glomeruli for classification of glomerulonephritis by light microscopy. Renal biopsy specimens for the patients with ANCA-SVV were required to exhibit pauci-immune necrotizing and crescentic glomerulonephritis, with $<2+$ Ig immune deposits (on a scale of 0 to 4+), as assessed by direct immunofluorescence microscopy. Patients with SLE nephritis fulfilled the World Health Organization recommended criteria and were observed, in renal biopsies, to have immune complex glomerulonephritis consistent with SLE nephritis (26). SLE nephritis patients were eligible for the study if they were classified as class III, IV, or V on the basis of the World Health Organization criteria (26). Medical records were retrospectively examined to establish that the patients with SLE nephritis fulfilled four or more of the 1982 American College of Rheumatology revised criteria for the classification of SLE (27).

Positive ANCA findings were defined as a C-ANCA or P-ANCA staining pattern for ethanol-fixed human neutrophils, as determined by indirect immunofluorescence microscopy (28). All P-ANCA were further characterized as MPO-specific by enzyme-linked immunosorbent assay (28). C-ANCA were determined to be specific for PR3 in 87% of test samples using an anti-PR3 enzyme-linked immunosorbent assay kit (Progen Biotechnik GmbH, Heidelberg, Germany).

All patients with ANCA-SVV exhibited biopsy-proven pauci-immune necrotizing glomerulonephritis. Pulmonary involvement in patients with ANCA-SVV was defined by the presence of hemoptysis, pulmonary hemorrhage, or respiratory failure, radiographic proof of infiltrates in the absence of evidence for an infectious cause, or biopsy proof of SVV in the lung. Upper respiratory involvement was defined by clinical or radiographic evidence of sinusitis, the presence of ulcers of the nasal passages, epistaxis, or otitis media, or biopsy proof of vasculitis in any upper respiratory tissue. Three disease categories for patients with ANCA-SVV were assigned, as follows: (*1*) necrotizing and crescentic glomerulonephritis alone; (*2*) microscopic polyangiitis, defined as biopsy-proven or clinical evidence of SVV in an organ system in addition to the kidney; and (*3*) Wegener's granulomatosis, defined by granulomatous inflammation in any organ, the presence of well defined nodular or cavitary pulmonary lesions, and/or the presence of destructive bony disease of the upper airways in addition to kidney involvement.

Control subjects for both studies were identified through the same nephrology clinics within the Glomerular Disease Collaborative Network as were the study patients. Control subjects included patients with other renal disorders who did not have a diagnosis of ANCA-SVV with or without glomerulonephritis or SLE with or without nephritis. If newly referred patients were subsequently diagnosed as having ANCA-SVV or SLE, then they were removed from the pool of control subjects. Control subjects were ANCA-negative and exhibited no evidence for SLE. They included individuals with IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulopathy, minimal-change disease, Alport's disease, amyloidosis, diabetic nephropathy, renal insufficiency attributable to hypertension, nephrolithiasis, urinary tract infection, Bartter's syndrome, tubular acidosis, acute tubulointerstitial nephritis, renal artery stenosis, gout, osteoporosis, or renal carcinoma, as well as potential kidney donors. Control subjects were matched to patients on the basis of gender, race, and age (within 5 yr). Matching was performed after the questionnaire collection period had been completed and all diagnoses had been assigned.

Assessment of Exposures

The self-administered questionnaire for the study included evaluation of numerous exposures, including smoking, pesticides, cleaning agents, and chemical vapors, as well as questions regarding demographic features, current work or disability status, and patient and family medical histories. Questionnaires were completed between March 1997 and May 1998. All patients who came to the UNC nephrology clinic were asked to complete a questionnaire as a supplement to their medical records, regardless of their diagnoses. Questionnaires were also given to patients with ANCA-SVV or SLE nephritis who received care in community-based nephrology clinics; patients either completed the questionnaire during an office visit or received the questionnaire by mail. The community-based clinics also obtained questionnaires, in the same manner, for an equivalent number of randomly selected patients (control subjects) with other renal diseases. The UNC Committee on the Protection of Human Rights approved the questionnaire. All study subjects signed consent forms for the use of their questionnaires in research. Neither study subjects nor physicians of the Glomerular Disease Collaborative Network were aware of the specific study hypothesis.

Silica dust was presumed to be the predominant exposure for activities previously reported to be associated with this exposure (Table 1, modified from references 10 and 12). The two primary questionnaire categories included exposure to dusty conditions, such as farming, mill or textile work, sandblasting, drilling, or lumber work, and exposure to stone, clay, or glass work, including pottery, ceramics, or china manufacturing, cement, stone, or brick masonry work, and quarry or mining jobs. If subjects reported being exposed, they were asked to classify whether the exposure had been encoun-

Table 1. Industrial activities associated with silica dust exposure[a]

Mining and quarrying (metallic and nonmetallic minerals)
Stonecutting
Construction activities (tunnels, highways, and buildings)
Sandblasting
Production of
abrasives
cements and concrete
ceramics
cosmetics, soaps, and detergents
dental supplies
electrical and electronic machinery
glass
insulation products
jewels
rubber
textiles (cotton and wool)
Work involving grain dust
Work involving wool dust

[a] Modified from references (10) and (12).

tered rarely (a total of 5 to 20 times), regularly for 1 to 2 yr, or regularly for >2 yr. Only subjects who reported regular exposure for 1 to 2 yr or more were considered to have been exposed to silica.

Other exposures evaluated with the questionnaire included smoking; gasoline or other fuels, including kerosene; dry-cleaning chemicals; paint or paint products, including varnish, strippers, thinners, stains, wood finishes, and preservatives; cleaning agents, solvents, or degreasers; glues or adhesives; and pesticides, herbicides, or extermination chemicals. For all categories, only subjects who reported regular exposure for ≥1 yr were considered to have been exposed to that item.

Statistical Analyses

Comparisons of baseline information and exposure rates between patients and control subjects were performed using continuity-adjusted χ^2 tests. Means and SD are presented for continuous values that were normally distributed. Medians and interquartile ranges (the numbers between which 50% of the data lie) are presented for values that were skewed. Odds ratios and 95% confidence intervals were calculated for the matched pairs using McNemar's method and test for significance (29,30). Conditional logistic regression was used for multivariable analysis and was performed using the SAS system (31). Exposures recorded for <5% of the case or control samples were not evaluated in the multivariable analysis, because the matched case-control study with the sample size available was not robust enough for those calculations.

Results

Study Populations

A total of 292 questionnaires were collected during the study period. The subjects included 65 patients with ANCA-SVV, 51 patients with SLE nephritis, and 176 patients with other renal diseases, who represented the pool of control subjects available for matching. The questionnaires were obtained from patients from 26 different nephrology clinics. Fifty-seven percent of the questionnaires were from the UNC nephrology clinic, and the remaining 43% were from 25 community-based nephrology clinics.

Response rates were difficult to calculate, because the questionnaires were handed out as a tool to provide information on a wide variety of exposures, medical history, family history, and socioeconomic issues for clinic visits at UNC. In the private practices of the Glomerular Disease Collaborative Network, the questionnaires were either given to patients during clinic visits or mailed to the patients, whichever was more convenient for the office. Therefore, the total number of patients and control subjects who were actually given the opportunity to complete the questionnaire is unknown. The 65 completed questionnaires for the patients with ANCA-SVV represent approximately 24% of the 270 ANCA-SVV registry patients, and the 51 completed questionnaires for the patients with SLE nephritis represent approximately 32% of the 152 SLE nephritis registry patients.

The median time between renal biopsy diagnosis and completion of the questionnaire was 24 mo (interquartile range, 6 to 53 mo) for patients with ANCA-SVV and 21 mo (interquartile range, 5 to 44 mo) for patients with SLE nephritis. Because renal biopsy diagnosis was not required for control subjects, there was no index date for calculation of the time between diagnosis and questionnaire completion. Control subjects included both new and established patients visiting the same clinics in which the patients with ANCA-SVV and those with SLE nephritis were treated.

Results for ANCA-SVV

Sixty-five patients with ANCA-SVV were compared with 65 matched control subjects. Matching produced equivalent gender, race, and age distributions for patients and control subjects, with 51% male subjects, 97% white subjects, and mean ages of 54 yr for the patients and 55 yr for the control subjects (Table 2). The demographic distribution of the patients with ANCA-SVV in this study was similar to the demographic distribution previously described for the Glomerular Disease Collaborative Network referral region (32). Eight (12%) of the patients with ANCA-SVV had necrotizing and crescentic glomerulonephritis alone, 36 (56%) had microscopic polyangiitis, and 21 (32%) had Wegener's granulomatosis. Thirty-four (52%) were C-ANCA-positive, and the remaining 31 (48%) were P-ANCA-positive. Of the 46 patients who were tested for PR3 and MPO specificity, 25 (54%) were anti-PR3-positive and 21 (46%) were anti-MPO positive. Thirty-nine patients (60%) had disease involving the lungs or upper airways. The matched control subjects had the following diagnoses: glomerular disease (48%), renal insufficiency caused by hypertension (32%), tubular disorders (5%), urologic disorders (1%), and other (14%) (which included kidney donors and patients with renal artery stenosis, transitional cell carcinoma, osteoporosis, or gout).

Patients with ANCA-SVV and control subjects were similar in terms of work and disability status at the time of the questionnaire. Patients with ANCA-SVV *versus* control subjects were classified as follows: currently working outside the

home, 34% *versus* 42%; retired, 23% *versus* 22%; receiving disability payments, 18% *versus* 20%; homemakers, 12% *versus* 6%; students, 2% *versus* 2%; unemployed, 0% *versus* 0%; unknown because the question was not answered, 11% *versus* 9%.

Forty-six percent ($n = 30$) of patients with ANCA-SVV, compared with 20% ($n = 13$) of control subjects, reported silica-related exposure ($P = 0.001$). Among both patients with ANCA-SVV and control subjects who reported silica exposure, approximately 84% reported regular exposure for >2 yr, with the remaining 16% reporting regular exposure for 1 to 2 yr. Current and previous smoking exposures were similar for patients and control subjects, as were the frequencies of other exposures, including exposures to pesticides, gasoline or other fuels, cleaning agents, glues or adhesives, and paint products (Table 2).

The matched-pair odds ratio comparing silica exposure between patients with ANCA-SVV and control subjects was calculated to be 4.6 (95% confidence interval, 1.8 to 12.1; $P = 0.002$). With control for other exposures, including smoking, pesticides, gasoline or other fuels, cleaning agents, glues, and paint products, the odds ratio of silica exposure was 4.4 and remained statistically significant ($P = 0.013$) (Table 3). No other exposures reached statistical significance univariately or with control for other exposures (Table 3). The frequency of exposure to dry-cleaning chemicals was too low to yield reliable estimates, so this exposure was not included in the multivariate model.

We explored the possibility that silica dust exposure was more likely to be associated with a specific ANCA pattern or disease category. The results demonstrated odds ratios of 4.0 for patients with C-ANCA ($P = 0.013$) and 7.0 for patients with P-ANCA ($P = 0.069$), compared with matched control subjects (Table 4). The results were similar when the anti-PR3-positive and anti-MPO-positive subgroups were evaluated, although the sample sizes were small (data not shown). Similarly, we explored the relationship between silica dust exposure and disease category subgroups. The results demonstrated odds ratios of 3.5 for patients with Wegener's granulomatosis ($P = 0.118$) and 5.0 for those with microscopic polyangiitis ($P = 0.011$) (Table 4). Because they comprised such a small group ($n = 8$), patients with ANCA and necrotizing and crescentic glomerulonephritis alone were included with the patients with microscopic polyangiitis for this analysis. It is important to note that the number of matched pairs available for each subgroup limits the statistical power to detect differences. Therefore, it is not surprising that the *P* values do not all reach statistical significance. However, the matched-pair odds ratios were all positive and within the same range of values.

Because the pathway of entry for silica is through the airways, we proposed that patients with lung or sinus manifestations of SVV would exhibit higher rates of exposure. In fact, we observed similar matched-pair odds ratios for patients with lung and/or sinus involvement (odds ratio, 4.5; $P = 0.054$) and those with no lung or sinus involvement (odds ratio, 4.7; $P = 0.016$) (Table 4).

Results for SLE Nephritis

Fifty-one patients with SLE nephritis were compared with 51 matched control subjects. Matching produced equivalent gender, race, and age distributions for patients with SLE and control subjects, with 25% male subjects, 60% white subjects, and a mean age of 34 to 35 yr (Table 2). The demographic age and gender distributions of the SLE nephritis patients in this

Table 2. Description of patients and matched control subjects[a]

	ANCA-SVV Patients ($n = 65$)	ANCA-SVV Control Subjects ($n = 65$)	SLE Nephritis Patients ($n = 51$)	SLE Nephritis Control Subjects ($n = 51$)
Demographic features				
age (yr) (mean ± SD)	54 ± 16	55 ± 16	34 ± 14	35 ± 13
white race (%)	97	97	60	60
male gender (%)	51	51	25	25
Percent exposed to				
silica[b]	46	20	12	25
smoking (previous or current)	48	52	23	37
gasoline or other fuels[c]	16	16	19	2
pesticides or extermination chemicals	17	10	8	5
cleaning agents, solvents, or degreasers	16	13	14	18
glues or adhesives	6	5	2	6
paint or paint products	16	13	6	11
dry-cleaning chemicals	5	2	4	2

[a] ANCA, anti-neutrophil cytoplasmic autoantibody; SVV, small-vessel vasculitis; SLE, systemic lupus erythematosus.

[b] Silica dust exposure was statistically more frequent among patients with ANCA-SVV ($P = 0.001$) and statistically less frequent among patients with SLE nephritis ($P = 0.047$) than among disease-matched control subjects.

[c] Exposure to gasoline or other fuels was statistically more frequent among patients with SLE nephritis than among control subjects ($P = 0.008$).

Table 3. Multivariate analysis for patients with ANCA-SVV *versus* matched control subjects ($n = 65$)[a]

Exposures[b]	Matched-Pair Odds Ratio	95% Confidence Interval	*P* Value
Silica	4.43	1.36 to 14.38	0.013
Smoking (previous or current)	0.66	0.25 to 1.78	0.412
Gasoline or other fuels	0.43	0.10 to 2.01	0.284
Pesticides or extermination chemicals	2.32	0.47 to 11.5	0.303
Cleaning agents, solvents, or degreasers	1.00	0.25 to 3.96	0.994
Glues or adhesives	0.49	0.05 to 4.65	0.536
Paint or paint products	0.80	0.25 to 6.07	0.801

[a] Each exposure was evaluated while controlling for the other exposures in the table.
[b] Dry-cleaning chemicals were not evaluated because the exposure was noted for <5% of the control subjects.

Table 4. Multivariate analysis of silica exposure for ANCA-SVV subgroups[a]

	Exposed Patients, Control Subjects (%)	Matched-Pair Odds Ratio	95% Confidence Interval	*P* Value
All ANCA ($n = 65$)	46, 20	4.43	1.36 to 14.38	0.013
ANCA pattern				
cytoplasmic ANCA ($n = 34$)	59, 23	4.0	1.34 to 11.96	0.013
perinuclear ANCA ($n = 31$)	35, 16	7.0	0.86 to 56.90	0.069
Disease category				
Wegener's granulomatosis ($n = 21$)	48, 24	3.5	0.73 to 16.80	0.118
microscopic polyangiitis ($n = 44$)	48, 18	5.0	1.45 to 17.30	0.011
Airway involvement				
lung and/or sinus ($n = 39$)	44, 24	4.5	0.99 to 20.83	0.054
no lung or sinus ($n = 26$)	50, 18	4.7	1.34 to 16.24	0.016

[a] Multivariate analysis for each subgroup was performed while controlling for smoking, pesticides, gasoline or other fuels, cleaning agents, glues, and paint products.

study were similar to the patients with SLE nephritis previously described for the Glomerular Disease Collaborative Network referral region (33). Whites represented a larger proportion of the sample in this study (60%) as compared with the referral region (43%) (33). Thirty-four (67%) of the patients with SLE nephritis were categorized as having class IV diffuse proliferative SLE glomerulonephritis, 14 (27%) as having class III focal proliferative SLE nephritis, and 3 (6%) as having class V lupus membranous glomerulonephritis. The matched control subjects had the following diagnoses: glomerular disease (50%), renal insufficiency caused by hypertension (27%), tubular disorders (10%), urologic disorders (4%), and other (10%) (which included kidney donors and patients with polycystic kidney disease).

Patients with SLE nephritis and control subjects were similar in terms of work and disability status at the time of the questionnaire. Patients with SLE nephritis *versus* control subjects were classified as follows: currently working outside the home, 31% *versus* 33%; retired, 2% *versus* 6%; receiving disability payments, 29% *versus* 24%; homemakers, 6% *versus* 10%; students, 14% *versus* 12%; unemployed, 6% *versus* 4%; unknown because the question was left unanswered, *versus* 12%.

Twelve percent ($n = 6$) of the patients with SLE nephritis, compared with 25% ($n = 13$) of the matched control subjects, reported silica exposure ($P = 0.047$). Of the six patients with SLE nephritis who reported exposure to silica, four reported exposure for >2 yr and two reported regular exposure for 1 to 2 yr. Smoking exposures were not statistically different between patients and control subjects, although 37% of control subjects reported current or previous smoking habits, compared with only 23% of the patients with SLE ($P = 0.133$). The frequencies of other exposures, including exposures to pesticides, cleaning agents, glues or adhesives, and paint products, were not different between patients and control subjects (Table 2). Exposure to gasoline or other fuels was reported by 19% of patients and only 2% of control subjects ($P = 0.008$).

The matched-pair odds ratio comparing silica exposure between patients with SLE nephritis and control subjects was estimated to be 0.11 (95% confidence interval, 0.05 to 0.88; $P = 0.037$). This means that patients with SLE nephritis were 9 times less likely to be exposed to silica than were control subjects. With control for other exposures, including exposures to smoking, pesticides, cleaning agents, and paint products, the odds ratio of silica exposure were even lower (0.001) but did not reach statistical significance ($P = 0.993$) (Table 5). The

instability of this result is attributable to the fact that the analysis is based on limited numbers of matched pairs with disparities in exposure histories, as required for matched-pair analysis. In nine pairs, the control subject reported exposure to silica, whereas the subject with SLE did not; in one pair, the control subject reported no exposure and the subject with SLE reported a positive exposure history. Although the statistical power for this sample size using matched-pair analysis was calculated to be 79%, the results are based on small numbers of pairs with exposure disagreements and thus may not be reliable for inferences for the SLE nephritis population as a whole.

No other exposures reached statistical significance by univariate analysis or with control for other exposures (Table 5). The frequencies of exposures to gasoline or other fuels, dry-cleaning chemicals, and glues were too low (<5% frequency for either patients or control subjects) to yield stable estimates; therefore, these exposures were not included in the multivariate model. Subgroup analysis of the patients with class IV SLE nephritis and the matched control subjects resulted in the same odds ratios as calculated for the group as a whole (data not shown). The other two subgroups, *i.e.*, class III SLE nephritis and class V lupus membranous glomerulonephritis, were too small to evaluate separately.

Discussion

Case reports and small case series have reported histories of silica exposure for patients with ANCA-associated diseases (34–39). Two case-control studies demonstrated an association between ANCA-associated diseases and exposure to silica dust or other silica-containing compounds (11,12). Both studies evaluated exposures for 16 patients and 32 control subjects (two control subjects were matched to each patient). Gregorini *et al.* (11) estimated that patients with ANCA-positive, rapidly progressive glomerulonephritis were 14.0 times more likely than age-matched hospital control subjects to have been exposed to silica dust (95% confidence interval, 1.7 to 113.8; $P < 0.001$). Nuyts *et al.* (12) estimated that patients with Wegener's granulomatosis were 5.0 times more likely than age-, gender-, and region-matched community control subjects to have been exposed to silica (95% confidence interval, 1.4 to 11.6).

Case reports and small case series have also indicated a possible association between silica exposure and SLE (5,8,40). In general, those studies agreed that the intensity of silica exposure and not the duration of exposure was the most influential factor. Case-control studies of patients with SLE are currently underway (41). The patients with silica-associated SLE studied by Conrad *et al.* (8) were all male patients exposed to quartz dust in uranium mines. When these patients were compared with a group of patients with SLE who were not exposed to silica, the silica-exposed patients with SLE, in addition to exhibiting a male predominance, were older and experienced a later onset of disease. Renal involvement, as defined by the American College of Rheumatology (27), was present in 36% of the uranium miners with SLE and 49% of the patients with idiopathic SLE, which was not statistically different ($P = 0.299$).

The results of this study indicate that exposures to activities and environments known to cause high levels of exposure to silica dust are associated with ANCA-SVV but not with SLE nephritis. The results for the patients with ANCA-SVV are consistent with the findings of two previously published case-control studies that included patients with ANCA-SVV (11,12). This study is considerably larger than the previous studies, allowing multivariable analysis. The statistically significant association between ANCA-SVV and silica dust exposure was not altered by adjustment for a number of other exposure variables.

In contrast, there was an inverse association between silica dust exposure and SLE nephritis, although multivariate analysis demonstrated no association. These data are also in contrast to other published findings (5,8,9,40), although this is the first published case-control study of biopsy-proven SLE nephritis and silica dust exposure. The published studies have not been limited to patients with SLE nephritis. It may be that silica dust exposure is a factor when the overall SLE population is considered but is not a factor for the subset of patients with SLE who develop severe nephritis. It is important to note that both of these diseases involve vasculitis and glomerulonephritis, with similar renal presentations, but they affect vastly different demographic populations. Furthermore, SLE nephritis is known to involve immune complexes, whereas ANCA-associated glomerulonephritis is not mediated by immune complex deposition. To further address the association between silica

Table 5. Multivariate analysis for patients with SLE nephritis *versus* matched control subjects ($n = 52$)[a]

Exposures[b]	Matched-Pair Odds Ratio	95% Confidence Interval	*P* Value
Silica	<0.01	<0.01 to >100	0.993
Smoking (previous or current)	0.63	0.08 to 4.95	0.524
Pesticides or extermination chemicals	2.267	0.13 to 40.65	0.578
Cleaning agents, solvents, or degreasers	1.17	0.14 to 9.98	0.889
Paint or paint products	1.01	0.04 to 26.2	0.994

[a] Each exposure was evaluated while controlling for the other exposures in the table.
[b] Gasoline or other fuels, glues or adhesives, and dry-cleaning chemicals were not evaluated because the exposure was noted for <5% of the patients or control subjects.

dust exposure and SLE, studies of subjects with SLE that are not restricted to the subpopulation of patients who develop SLE nephritis are underway (41).

This study indicated that the strength of the association between silica exposure and ANCA-SVV was no stronger when specific subgroups were considered, on the basis of the clinicopathologic phenotype, disease subgroup, or ANCA specificity. Because silica dust is primarily inhaled, we wondered whether the association with silica dust exposure for patients with ANCA-SVV with upper respiratory or lung involvement would be stronger than that for patients with no evidence of vasculitis in their airways. However, this study indicated that there was no difference in the likelihood of silica exposure between subjects with and without vasculitic disease involving the airways or lungs. Silica exposure was not greater for patients with C-ANCA-SVV, compared with P-ANCA-SVV.

The strength of the association between silica exposure and ANCA-SVV and the consistency of the results of this study with the findings of two previously published studies indicate the need for an in-depth examination of the criteria for causality. In addition to the strength and consistency of associations, findings that are important to evaluate with respect to causality include dose-response data, specificity of risks for exposure subcategories, risks for disease subgroups, temporal relationships between exposure and disease, and biologic plausibility (30). Silica exposure has often been associated with autoimmune diseases in general. In this study, the evidence for an association with ANCA-SVV, in conjunction with the lack of a relationship with SLE nephritis, demonstrates the specificity of exposure for a specific disease subgroup and is a convincing tool for assessing causality (30). The sample size did not allow evaluation of dose-response data, and the questionnaire used did not allow evaluation of specific types of silica dust exposures. These are areas in which future research could provide insights into the causal relationship between silica dust and ANCA-SVV.

It is likely that the majority of patients with ANCA-SVV in this study were exposed to silica before the onset of their disease. Eighty-three percent of the patients with ANCA-SVV reported >2 yr of exposure, and many commented that they had been exposed for multiple years. Because the median time between ANCA-SVV diagnosis and completion of the questionnaire was 24 mo, it is clear that at least one-half of the subjects experienced exposure before disease onset.

Several potential mechanisms by which silica exposure could induce ANCA-SVV with glomerulonephritis have recently been proposed (42). For instance, silica particles are potent stimulators of lymphocytes, including T cells and B cells. It is possible that silica stimulation of T cells and B cells, in certain clinical and genetic settings, causes autoimmune disease as well as the production of autoantibodies, including ANCA, antinuclear antibodies, and rheumatoid factors (42,43). A second theory suggests that silica particles activate monocytes and macrophages, resulting in the release of lysosomal enzymes such as PR3 and MPO (42). The majority of these investigations have been performed *in vitro* and, although the proposed theories regarding the mechanism of silica induction of ANCA-SVV are plausible, they have not yet been proven.

It is important to note that case-control studies are known to frequently involve biases, especially with respect to the selection of control subjects and the recall of exposure history. Because ANCA-SVV and SLE nephritis can be such progressive processes, referral to a nephrologist in the early stages is critical. By selecting control subjects with kidney disease, we were certain that all control subjects had the opportunity to be diagnosed as having either ANCA-SVV or SLE nephritis. The patients in this study originate from a restricted source, *i.e.*, the renal biopsy population. Therefore, it is appropriate to select control subjects from the same source (44). This method reduces the selection bias for control subjects, if they are selected from among persons who have the same opportunity for diagnosis as the patients (45,46). This method of selection yields control subjects who are likely to be comparable to patients in terms of medical service use and recall of their exposure experience. It may be that silica exposure is also associated with renal disease in general, in which case the association observed in this study is likely to be muted. Additionally, this study was designed to reduce biases by obtaining control subjects from the same clinics where the patients were treated and by evaluating exposure information in the same way for patients and control subjects. Furthermore, neither patients nor control subjects were aware of the study hypothesis. A limitation of this study is that the questionnaire used was not a sensitive instrument for obtaining precise information on silica dust exposure. Information on specific tasks and occupations, as well as the duration and timing of exposure, was not assessed in the questionnaire used for this study. However, because misclassification of exposure is not expected to be systematically different between patients and control subjects, the bias of risk estimates would be toward the null hypothesis, thereby diluting the true exposure-disease relationship. The consistency of the results in this study and in the previous two studies of similar patients leads us to think that there was a satisfactory estimation (although possibly an underestimation) of silica dust exposure.

These studies provide insight into the prevalence of silica dust exposure in the southeastern United States. The percentages of control subjects exposed to silica were similar for the two studies, with 20% of the ANCA-SVV-matched control subjects and 25% of the SLE nephritis-matched control subjects reporting activities related to exposure. However, among those exposed, the ANCA-SVV-matched control subjects were more likely to have reported regular exposure for >2 yr (11 of 13, 85%), compared with the SLE nephritis-matched control subjects (3 of 13, 23%). This increased duration of exposure may be attributable to the differences in age, gender, and race between the two disease groups and thus their matched control subjects. The opportunity for exposure is most likely based on age, and there was a distinct age difference between the two disease groups, with mean ages of 55 yr for the ANCA-SVV-matched control subjects and 35 yr for the SLE nephritis-matched control subjects.

In summary, there is an increased risk of ANCA-SVV but not SLE nephritis among individuals exposed to silica dust. Silica dust exposure is therefore likely to be a factor that facilitates the pathogenesis of ANCA-SVV (10,43), although the proposed mechanisms of causality must be further explored.

Appendix

The Glomerular Disease Collaborative Network participating clinics are as follows: Albemarle Nephrology Associates (Elizabeth City, NC); Atlanta Nephrology Associates, P.C. (Atlanta, GA); Birmingham Nephrology Associates (Birmingham, AL); Boice-Willis Clinic (Rocky Mount, NC); Capital Nephrology Associates, P.A. (Raleigh, NC); Carolina Kidney Associates, P.A. (Greensboro, NC); Carolina Kidney Centers, P.A. (Goldsboro, NC); Central Carolina Nephrology (Concord, NC); Columbia Nephrology Associates, P.A. (Columbia, SC); Danville Urologic Clinic (Danville, VA); Durham Nephrology Associates, P.A. (Durham, NC); Eastern Nephrology Associates (Greenville, NC); Eastern Nephrology Associates (Kinston, NC); Eastern Nephrology Associates (New Bern, NC); Fayetteville Kidney Center, Inc. (Fayetteville, NC); Glen Internal Medicine Consultants (Brunswick, GA); Harrisonburg Medical Associates (Harrisonburg, VA); High Point Nephrology Associates (High Point, NC); Holt Krock Clinic (Fort Smith, AR); Kingsport Kidney Health, P.C. (Kingsport, TN); Laurinburg Internal Medicine (Laurinburg, NC); Lynchburg Nephrology, Inc. (Lynchburg, VA); Marshes Medical Diagnostic Clinic (Brunswick, GA); Marshfield Medical Clinic (Marshfield, WI); Medford Clinic (Medford, OR); Metrolina Nephrology Associates (Charlotte, NC); Mountain Kidney Associates (Asheville, NC); Nephrology and Hypertension (Dalton, GA); Nephrology and Internal Medicine (Lewiston, ME); Nephrology Associates (Chattanooga, TN); Ocala Critical Care and Kidney (Ocala, FL); Pee Dee Nephrology (Florence, SC); Piedmont Nephrology and Hypertension Associates (Hickory, NC); Pinehurst Nephrology (Pinehurst, NC); Rock Hill Nephrology Associates, P.A. (Rock Hill, SC); Southeast Renal Associates (Charlotte, NC); Southeastern Nephrology Associates, P.L.L.C. (Wilmington, NC); Spartanburg Nephrology (Spartanburg, SC); Sumpter Medical Specialists, P.A. (Sumpter, SC); SW Georgia Nephrology and Hypertension (Thomasville, GA); Thompson Medical Specialists (Lenoir, NC); Valley Hypertension and Nephrology Associates (Roanoke Rapids, NC); Valley Nephrology Associates, Ltd. (Roanoke, VA); Vancouver Clinic (Vancouver, WA); Wake Nephrology Associates, P.A. (Raleigh, NC); Winchester Medical Consultants (Winchester, VA); Nephrology Associates (Winston-Salem, NC); Charles Frazier, M.D. (Greensboro, NC); Anwar Haidary, M.D. (Wilson, NC); Jean Claude Hyppolite, M.D. (Eden, NC); Adel Korkor, M.D. (Waukesha, WI); Joseph Russell, M.D. (Wilson, NC); Saruwadee Sitti, M.D. (Florence, SC); Mohammad A. Sekkarie, M.D. (Bluefield, WV); and Hugo Tettimanti, M.D. (Winston-Salem, NC).

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