Association of Silica Exposure with Anti–Neutrophil Cytoplasmic Autoantibody Small-Vessel Vasculitis: A Population-Based, Case-Control Study

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Anti–neutrophil cytoplasmic autoantibodies (ANCA) are associated with a category of small-vessel vasculitis (SVV) with frequent glomerulonephritis. The goal of this study was to evaluate the association of lifetime silica exposure with development of ANCA-SVV, with particular attention to exposure dosage, intensity, and time since last exposure. A southeastern United States, population-based, case-control study was conducted. Case patients had ANCA-SVV with pauci-immune crescentic glomerulonephritis. Population-based control subjects were frequency-matched to case patients by age, gender, and state. Jobs were assessed in a telephone interview. Silica exposure scores incorporated exposure duration, intensity, and probability for each job and then were categorized as none, low/medium, or high lifetime exposure. Logistic regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). Silica exposure was found in 78 (60%) of 129 case patients and in 49 (45%) of 109 control subjects. There was no increased risk for disease from low/medium exposure relative to no exposure (OR 1.0; 95% CI 0.4 to 2.2) but increased risk with high exposure (OR 1.9; 95% CI 1.0 to 3.5; $P = 0.05$). Crop harvesting was associated with elevated risk (OR 2.5; 95% CI 1.1 to 5.4; $P = 0.03$). However, both agricultural and traditional occupational sources contributed to the cumulative silica exposure scores; therefore, the overall effect could not be attributed to agricultural exposures alone. There was no evidence of decreasing by duration of time since last exposure. High lifetime silica exposure was associated with ANCA-SVV. Exposure to silica from specific farming tasks related to harvesting may be of particular importance in the southeastern United States. Interval of time since last exposure did not influence development of ANCA-SVV.

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Occupational silica exposure has been associated with an increased risk for several autoimmune diseases (1) as well as with nephritis and end-stage renal disease (ESRD) (2–4). Studies of silica exposure in the development of small-vessel vasculitis (SVV) have consistently supported an association (4–10). However, previous studies suffered from considerable limitations, including small sample sizes, use of various case definitions, and limited information on exposure. Only one previous study incorporated information on intensity of silica exposure (11). This is particularly important because studies of associations of silica exposure in other autoimmune diseases (12,13) and general renal dysfunction (14,15) suggested that intensity of exposure may be more important than duration of exposure in terms of its influence on disease risk (8). In addition, individuals with other renal diseases were used as control subjects in two studies (5,6). Because SVV involves the kidney in 75 to 90% of patients (16), this could lead to an underestimation of the association because silica exposure is also associated with increased susceptibility to other renal diseases (2,3,17).

The purpose of this study was to assess the association between silica exposure and onset of biopsy-proven glomerulonephritis that resulted from anti–neutrophil cytoplasmic autoantibody (ANCA)-associated SVV (ANCA-SVV), a category of

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SVV that frequently involves the kidney. A population-based, case-control study in the southeastern United States was conducted to study the association.

Differential associations by gender and education were of interest because male individuals and those with lower education may have a greater opportunity for exposure given that occupations that are associated with silica exposure are generally male-dominated, working-class jobs. Associations by race were also of interest because although white individuals account for 80 to 90% of cases in United States cohorts (18,19), nonwhite individuals with ANCA-SVV, especially black Americans, are more likely to progress to kidney failure (18).

Materials and Methods

This was a population-based, case-control study, inclusive of North Carolina, South Carolina, Georgia, and southern Virginia. A structured telephone interview, modified from one that was used in a study of silica exposure and lupus (20), was used to assess lifetime silica exposure. Neither case patients nor control subjects were aware that the study was designed to assess silica exposure. Battelle Centers for Public Health Research and Evaluation managed the selection of control subjects and completed all telephone interviews using computer-assisted data entry.

Study Participants

Participants had to be aged 18 to 84 at the time of interview. Case patients had to have resided in the study area for at least 6 months during the year before their renal biopsy diagnosis; control subjects have resided in the study area at least 6 months before a uniform reference date of January 1, 2001. This date was the approximate median biopsy date among case patients. Participants had to speak and understand English.

Nephropathologists throughout the region (see Acknowledgments) identified all patients who had an initial renal biopsy between October 1997 and October 2003 and a diagnosis of pauci-immune crescentic glomerulonephritis, with or without granulomatous inflammation and with or without ANCA positivity. ANCA positivity, determined by immunofluorescence microscopy and/or antigen-specific ELISA (21), was verified with the patient's clinician. Medical records were reviewed to categorize patients as having cytoplasmic and/or proteinase 3-ANCA (PR3-ANCA) or perinuclear and/or myeloperoxidase-ANCA (MPO-ANCA) as determined by antigen-specific ELISA or indirect immunofluorescence microscopy (22–24). Patients with perinuclear ANCA not confirmed by MPO-ANCA ELISA required a negative antinuclear antibody test for inclusion. Consent was sought for more thorough medical record review to confirm organ involvement and disease categorization of Wegener granulomatosis, microscopic polyangiitis (MPA), or kidney-limited disease (25,26). The Birmingham Vasculitis Activity Score was used to assess disease activity at diagnosis (27).

Control subjects were identified through list-assisted random-digit dialing and were frequency-matched to case patients by age, gender, and state. Age groups for matching were 18 to 39, 40 to 59, and 60 to 84. A list of random residential telephone numbers that were selected using an equal probability method was purchased (Marketing Systems Group, Fort Washington, PA). This study was approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill (97-MED-44 and 04-MED-663) and by the home institutions of each nephropathologist (see Acknowledgments).

Interview Participation

Overall, 214 case patients met the entry criteria according to available information. The 214 case patients were from 498 potential case patients who were identified through nephropathology laboratories. Details of eligibility criteria and nonparticipation reasons were limited because all information, including age, state of residence, and ANCA positivity, was not provided to nephropathology laboratories by clinicians who requested the renal biopsy diagnosis report. Age was <18 yr in 5% (n = 24 of 455 with known age) and >84 in 1% (n = 5 of 455). No clinic or physician could be identified for 27 (5%) patients, and 61 (12%) were outside the geographic region. Seventy-seven (15%) patients died before initiation of the interviews.

Contact was attempted for the 214 case patients to verify eligibility and recruit for the full interview. Of the 214, 129 (60%) completed and two partially completed the full interview. The two partially completed were excluded because complete assessment of silica exposure could not be conducted. Thirty-six of the 214 had died. The 47 remaining patients were living, and contact was attempted but no interview was completed; 12 were ineligible with further screening (eight lived outside the geographic requirements, three were mentally incapable, and one was non–English speaking); 15 could not be contacted (nine had disconnected numbers, three did not return call after 10 attempts, and three for unknown reasons); and 20 refused to participate in the full interview. Proxy interviews were completed in an additional 29 patients: 11 who were unable to complete the full interview and 18 who were deceased. Proxy interviews were excluded from this analysis because limited silica exposure information was obtained.

For identification of control subjects, 1825 random telephone numbers were used. Of these, 913 (50%) numbers were nonresidential, nonworking, or not answered and 912 were answered. Of the answered numbers, 109 (12%) participated (99 completed and 10 partially completed), 480 (53%) declined participation (five were determined to be eligible, and 475 did not provide eligibility information), and 323 (35%) did not have an eligible participant in the household (84% did not fit the age criteria; 10% had a language barrier; and 2% each did not meet geographic criteria, were mentally incapable, or had renal disease). Although the overall response rate for control subjects among answered telephone calls was only 12%, the response rate among control subjects who were known to be eligible was 97% (109 of 114). The high frequency of households with ineligible participants (35%) suggests that if eligibility information were known, then the response rate among eligible participants would be considerably higher than 12%, albeit lower than 97%.

Exposure Assessment

A lifetime history of jobs that were held for 12 months or longer was assessed. Participants were also asked whether they ever worked in a number of specific silica-related occupations or performed specific silica-associated tasks, irrespective of duration and even if they overlapped with the overall list of occupations. Occupations and tasks that are known to be associated with silica exposure were enumerated by an occupational hygienist (L.A.N.-F.) and an epidemiologist experienced in silica assessment (C.G.P.) (28–30). Farming tasks that are known to involve silica exposure were also assessed (28). Dates when occupations and tasks were performed were evaluated for overlapping time frames so that exposure was not duplicated. Duration of silica exposure was truncated at the first kidney biopsy diagnosis date for case patients and at the reference date for control subjects.

Silica exposure was scored as described in a recent case-control study of silica in ANCA-positive patients (11). Each occupation that was associated with silica exposure was scored on the basis of the combination of the duration (years worked) of exposure, multiplied by

weight values for length of time worked weekly, exposure intensity, and exposure probability. The weighting for length of time worked weekly for a specific occupation/task was 0.05 for <4 hours per week, 0.30 for 4 to 20 hours per week, and 0.75 for >20 hours per week. Each job was assigned an average exposure intensity (high, moderate, low, or none) for usual tasks, which took into consideration the likely concentration and frequency of exposure during the average work week. Estimates of high and moderate intensity were based on personal exposure limits for crystalline silica in the workplace, published by the National Institute of Occupational Safety and Health (30) and by the Occupational Safety and Health Administration (31). Low exposure intensity was defined as exposure below the limit recommended by the National Institute of Occupational Safety and Health. Jobs with silica exposure at or below levels that are experienced by the general population were considered to provide no additional exposure. The industrial hygienist also assigned each intensity rating a certainty score (high, moderate, or low) on the basis of the information provided, the type of work, and the industrial hygienist's personal knowledge of the exposures in each job and task. Weighting for exposure intensity was 0 for nonexposure and 1 to 4 for increasing levels of intensity. Exposure probability was 0 for nonexposure, 0.25 for possible exposure, 0.75 for probable exposure, and 1.0 for definite exposure. The sum across scores of nonoverlapping occupations and tasks resulted in a cumulative exposure score for each participant. Overall cumulative scores were categorized as 0 for no exposure, >0 and <2 for low exposure, 2 to 4 as moderate exposure, and >4 as high exposure.

Exposure evaluation also included agricultural exposure to silica that has been documented, especially from harvesting crops, including but not limited to sweet potatoes and rice (32–34). Respirable silica exposure from agricultural tasks is known to be highly variable and can depend on many factors, including type of soil, relative humidity, soil moisture, and wind speed (32). However, observed percentages of silica levels are known to be high in North Carolina (32) and, therefore, were considered important in the southeastern US region, where farming is common, especially in North Carolina (35). Because of the high variability of silica exposure with agricultural tasks, most tasks were scored as having a low probability of exposure. The exception to this included tasks that are associated with manual harvesting of potatoes, peanuts, or tobacco, which each involve shaking clay, dirt, soil, or sand off of the product as it is pulled from the ground. These tasks were considered to have a high probability of silica exposure.

Statistical Analyses

Demographics and other measures were compared between case patients and control subjects using continuity-adjusted χ^2 and Wilcoxon rank-sum tests. Logistic regression was used to evaluate the association of silica exposure with disease, relative to control subjects. Results are expressed as odds ratios (OR) with 95 percent confidence intervals (CI) and P values. Silica exposure scores and duration of exposure were evaluated as continuous measures using quartile ranks to evaluate the trend for a dosage response. Silica exposure was then evaluated using predefined categories and modeled such that a linear association was not assumed. All reported models were adjusted for frequency-matched variables (age, gender, and state). Models that controlled for race had similar results, so reported models do not control for race.

Multiplicative interaction of silica exposure scores with gender, education, and race was explored using logistic regression models. Interaction terms with $P < 0.20$ were considered important stratification measures and were explored further using separate logistic regression models, controlling for frequency-matched variables.

Results

A total of 129 case patients and 109 control subjects participated in the interview and had data available for the assessment of silica exposure. With respect to frequency-matched variables, the state distributions were similar, but case patients were significantly older and more frequently male than control subjects (Table 1). Racial distribution was similar between case patients and control subjects. Case patients had significantly lower education (Table 1), although when age was controlled for, this difference was less pronounced ($P = 0.08$). Smoking history was similar between case patients and control subjects.

Sixty percent ($n = 78$) of case patients were ever exposed to silica, compared with 45% ($n = 49$) of control subjects (OR 1.6; 95% CI 0.9 to 2.8; $P = 0.13$; Table 2). Among those who were exposed, case patients had a median duration of 8 years longer than control subjects (13 *versus* 5 years, respectively). Compared with those who were never exposed, there was a trend for each ranked tertile of exposure duration to be associated with a 20% increased risk for the disease (OR 1.2 per tertile; 95% CI 1.0 to 1.5; $P = 0.062$). When evaluated by categories, duration of silica exposure was in the positive direction across all tertiles, with the largest effect among those in the highest tertile of exposure (>21 years; OR 2.3; 95% CI 1.0 to 5.3; $P = 0.05$; Table 2). Taking into consideration the cumulative duration in conjunction with intensity and probability of exposure, there was no evidence for increased risk for the disease from low or medium lifetime exposure (OR 1.0; 95% CI 0.4 to 2.2; $P = 0.98$), which were grouped together because of small sample sizes in these exposure categories. However, there was an increased risk for the disease with high lifetime exposure (OR 1.9; 95% CI 1.0 to 3.5; $P = 0.05$). Any history of harvesting potatoes, peanuts, and/or tobacco was associated with an increased risk for the disease (OR 2.5; 95% CI 1.1 to 5.4; $P = 0.03$), but history of work in other specific occupational exposure categories that are known to be associated with silica did not show evidence of an increased disease risk (Table 2). However, both agricultural and nonagricultural sources of silica exposure contributed to cumulative exposure scores, and the overall effect could not be attributed to agricultural exposures alone.

Among case patients and control subjects who were exposed to silica, there was no difference in time from last exposure to the reference date ($P = 0.765$). Sixty percent of case patients were still being exposed to silica at their biopsy diagnosis *versus* 45% of control subjects at the reference date. Among those with exposure before the diagnosis or reference date, time since last exposure ranged from 1 to 59 years among case patients and from 1 to 56 years among control subjects. There was no indication of an association between the length of time since last exposure and disease onset (Table 2).

There was no evidence of an interaction of silica exposure with gender ($P > 0.2$, interaction). Further exploration was needed for potential multiplicative interaction between silica and race ($P = 0.189$, interaction) as well as education ($P = 0.139$, interaction). When limited to white participants, the association between high silica exposure and the disease remained statistically significant (OR 2.1; 95% CI 1.1 to 4.2; $P = 0.03$; Table 3). Evaluation of nonwhite individuals was limited because of

Table 1. Sociodemographic characteristics of ANCA-SVV case patients and population-based control subjects[a]

Characteristic	Case Patients (n = 129)	Control Subjects (n = 109)	P
Mean age (yr; mean ± SD)	62 ± 14	55 ± 17	0.001
Age groups used for matching (n [%])			
18 to 39	8 (6)	21 (19)	0.003
40 to 59	48 (37)	41 (38)	
60 to 84	73 (57)	47 (43)	
Gender			
male	77 (60)	51 (47)	0.05
female	52 (40)	58 (53)	
Race			
white	109 (85)	89 (82)	0.78
nonwhite	20 (15)	20 (18)	
State of residence (n [%])			
North Carolina	87 (67)	65 (60)	0.59
South Carolina	14 (11)	12 (11)	
Georgia	12 (9)	14 (13)	
Southern Virginia	16 (12)	18 (16)	
Education level (n [%])			
high school or less	68 (53)	42 (39)	0.04
more than high school	61 (47)	65 (61)	
Ever smoked (n [%])	80 (62)	52 (51)	0.11

[a]ANCA-SVV, anti–neutrophil cytoplasmic autoantibody-associated small-vessel vasculitis.

sample size, but no association was suggested even at the highest exposure level. An association was observed between silica exposure and the disease among those with a high school or lower education level. Although the sample size was small, there was a trend for an increased risk for the disease among those with low to medium silica exposure (OR 2.8; 95% CI 0.7 to 11.9; $P = 0.15$) and a clear increased risk with high exposure (OR 3.3; 95% CI 1.2 to 9.2; $P = 0.02$; Table 3). There was no evidence of increased risk for the disease with silica exposure among those with more than a high school education.

Among the 129 cases, the most common organs involved by patient report were the lungs (47%), upper respiratory tract (46%), and skin (24%). By definition, all case patients had kidney involvement. Among case patients, 47% had MPO-ANCA specificity, 32% had PR3-ANCA specificity, and 21% were ANCA positive with no information on specificity. No patients in this cohort were ANCA negative.

Medical chart review was available for 90 (70%) patients. Among this subset with detailed clinical information, MPO-ANCA specificity (*versus* PR3-ANCA specificity) was more common among those who were scored as having high silica exposure compared with all other case patients (67 *versus* 40%, respectively; $P = 0.02$). Documented lung involvement was similar between case patients with high and low or no silica exposure (51 and 45%, respectively; $P = 0.58$), but there was a trend for less upper respiratory disease involvement (23 and 43%, respectively; $P = 0.06$) and more frequent skin involvement (33 and 17%, respectively; $P = 0.08$). The distribution of disease categories was not statistically different between those with high exposure, with Wegener granulomatosis present among 16% of those with a high silica exposure *versus* 29% among those with lower or no exposure; MPA among 51 and 38%, respectively; and renal-limited disease among 33 and 33%, respectively, with an overall $P = 0.33$ comparing case groups with high and low or no exposure. Disease activity at the time of the renal biopsy, as measured by the Birmingham Vasculitis Activity Score, was not different between the two exposure groups (14 ± 4 for each group, $P = 0.79$).

To evaluate the representativeness of case patients who participated in the complete interview, we compared demographics of case patients who had more severe symptoms and completed a brief interview through a proxy interviewer ($n = 29$) with case patients who were identified during the study period and did not participate in the study ($n = 340$). Case patients who were interviewed by proxy were similar to those who completed the full interview with respect to gender (men 60 *versus* 55%, respectively), and although there were no statistical differences, there was a trend for patients who were interviewed by proxy to be older (66 ± 13 yr) and less frequently white (69%) than those who completed the full interview (62 ± 14 yr and 85%, respectively). Case patients who were interviewed by proxy were more likely to have a high school or lower education (82%) than those who completed the full interview (53%; $P = 0.0032$). Only limited demographic information was available for case patients who did not participate in the full or proxy interviews, but male gender (55%), age (62 ± 15 yr), and white race (83%) were similar to those who completed the full interview.

Table 2. Association of silica exposure measures with ANCA-SVV with glomerulonephritis

Parameter	Case Patients (n = 129)	Control Subjects (n = 109)	OR (95% CI)[a,b]	P
Silica exposure (n [%])				
ever (yes/no)	78 (60)	49 (45)	1.6 (0.9 to 2.8)	0.13
Median duration in years among exposed (interquartile range)[c]	13 (2 to 28)	5 (2 to 22)	1.2 (1.0 to 1.5)	0.06
Duration of exposure (years; tertiles; n [%])[c]				
never (0)	51 (40)	60 (55)	Referent	
short duration (>0 to 3)	27 (21)	19 (12)	1.5 (0.7 to 2.2)	0.26
medium duration (>3 to 21)	20 (15)	17 (16)	1.2 (0.5 to 2.6)	0.69
long duration (>21 to 74)	31 (24)	13 (12)	2.3 (1.0 to 5.3)	0.05
Duration, intensity, and probability score (n [%])				
none (score = 0)	51 (40)	60 (55)	Referent	
low to medium (score >0 to 4)	17 (13)	17 (16)	1.0 (0.4 to 2.2)	0.98
high (score >4)	61 (47)	32 (29)	1.9 (1.0 to 3.5)	0.05
History of work in specific silica-associated occupation categories (n [%])				
ever lived/worked on a farm	63 (49)	41 (40)	1.1 (0.6 to 1.9)	0.82
ever harvested crops[d]	28 (22)	10 (9)	2.5 (1.1 to 5.4)	0.03
industrial trades[e]	25 (19)	18 (17)	1.2 (0.6 to 2.4)	0.64
painting/furniture work	20 (16)	23 (21)	0.6 (0.3 to 1.3)	0.21
construction/railroad jobs	23 (18)	20 (18)	0.7 (0.3 to 1.5)	0.33
janitorial work	6 (5)	9 (8)	0.6 (0.2 to 1.7)	0.33
other occupations[f]	5 (4)	4 (4)	1.2 (0.3 to 4.9)	0.75
Time since last exposure to silica (n [%])				
not exposed	51 (40)	60 (55)	Referent	
longest time (>25 yr)	16 (12)	9 (8)	1.3 (0.4 to 4.3)	0.69
medium time (>0 to 25 yr)	9 (7)	5 (5)	1.8 (0.7 to 4.9)	0.20
exposed at diagnosis/reference date	53 (41)	35 (32)	1.5 (0.8 to 2.9)	0.18

[a]OR, odds ratio; CI, confidence interval.
[b]Adjusted for frequency-matched variables (age, gender, and North Carolina *versus* other states).
[c]Duration of exposure was truncated at the date of renal biopsy for case patients and at the reference date (January 1, 2001) for control subjects.
[d]Includes harvesting potatoes, peanuts, and/or tobacco, which involves shaking clay, dirt, soil, or sand off of the product as it is pulled from the ground.
[e]Industrial trades include but are not limited to mining, sandblasting, quarrying, construction, and railroad work.
[f]Other occupations include dental, pottery making, and dry-cleaning jobs.

Discussion

The present study suggests that high levels of lifetime silica exposure are associated with the onset of ANCA-SVV, using an exposure rating that incorporated the intensity, duration, and probability of exposure. The association was most notable from agricultural silica exposure through harvesting of crops. The observed association in the current study is in agreement with previous case-control studies (4–8,10,11) (Table 4). This study expands on known information with respect to the impact of duration of exposure, time since last exposure to silica, and the important contribution of silica exposure from agricultural sources in the southeastern United States that may contribute to the development of this disease.

In this study, patients with ANCA-SVV were almost two times more likely to be exposed to the highest score category for silica exposure compared with control subjects. Other studies have reported higher OR estimates ranging from 3.0 to 14.0 for associations with various case definitions of SVV (4–9,11). All of the previous studies were smaller, and, indeed the CI across studies overlap and incorporate the estimates and CI that were observed in this study (Table 4).

The two-fold association in the southeastern United States may represent a smaller effect than that observed in other regions. Traditional "dusty trades," such as sandblasting, mining, quarrying, construction, and railroad work, were evident among those who were exposed to silica but were represented similarly between case patients and control subjects. However, harvesting crops accounted for the single highest occupational exposure among case patients and was significantly more common than among control subjects. Although harvesting of crops has been recognized as a source of silica exposure and can exceed industry standards (32,34,36–38), the amount of silica in soil dust can vary geographically, even within a single farm or field (28,38,39). Therefore, the variation in agricultural silica

Table 3. Association of lifetime silica exposure with ANCA-SVV with glomerulonephritis by racial group and by education

Silica Exposure Level by Parameter	Case Patients (*n* [%])	Control Subjects (*n* [%])	OR (95% CI)[a]	*P*
Racial groups				
white	*n* = 109	*n* = 89		
none	41 (38)	48 (54)	Referent	
low to medium	14 (13)	15 (17)	1.0 (0.4to2.4)	0.96
high	54 (50)	26 (29)	2.1 (1.1to4.2)	0.03
nonwhite	*n* = 20	*n* = 20		
none	10 (50)	12 (60)	—[c]	
low to medium	2 (10)	1 (5)	—[c]	
high	8 (40)	7 (35)	—[c]	
Education groups[b]				
≤12 yr education	*n* = 68	*n* = 42		
none	21 (31)	24 (57)	Referent	
low to medium	9 (13)	4 (10)	2.8 (0.7to11.9)	0.15
high	38 (56)	14 (33)	3.3 (1.2to9.2)	0.02
>12 yr education	*n* = 61	*n* = 65		
none	30 (49)	34 (52)	Referent	
low to medium	7 (11)	12 (18)	0.5 (0.2to1.5)	0.23
high	24 (39)	19 (29)	1.1 (0.5to2.6)	0.82

[a]Adjusted for frequency-matched variables: age, gender, and state.
[b]Information on education level was not reported by two control subjects, so they are excluded from this subgroup analysis.
[c]Not computed because of small sample size.

exposure over time and place makes the assessment of exposure intensity difficult to quantify (28) and may contribute to the observed lower impact of silica in this study. Agricultural sources of silica were not evaluated in most previous case-control studies of SVV. One study found a risk for SVV from working with livestock or crops within the year of diagnosis, but working with crops alone was not associated with the disease (8).

In this study, only the predefined level of highest exposure to silica was found to be associated with ANCA-SVV. Only two previous studies evaluated dose-response gradients of silica exposure and ANCA and/or SVV (8,11). In one study, the highest category of silica exposure was associated with primary vasculitis, and both intermediate and high categories of exposures were associated with the subgroup of MPA (8). Levels of exposure in our study were determined using the method defined by Beaudreuil *et al.* (11). In their study, as in ours, only the highest level of silica exposure was associated with ANCA-positive patients (OR 6.9; 95% CI 1.2 to 35.1; $P = 0.002$). Exposure scores of medium or less were not associated with the disease in either study, although our study showed a trend toward a positive association of lower exposure levels within the lowest education group.

This study also suggests that duration of exposure is the primary aspect of silica exposure that is associated with the development of ANCA-SVV. This is in contrast to data from studies of association of silica with other autoimmune diseases, including scleroderma, systemic lupus erythematosus, and rheumatoid arthritis, which suggest that exposure intensity may be of equal if not greater importance than cumulative lifetime exposure (1,8). Our finding that the time window of exposure was not of great importance is in agreement with results described in the association of silica and lupus (13). Because internalized silica can remain in tissue for many years (40), if not indefinitely, it is conceivable that reactions or adjuvant exposures could be triggered long after the silica exposure has ended (13).

We presumed that those with less education more frequently worked in jobs that are associated with silica exposure. However, high silica exposure among control subjects was similar between those with higher education (33%) and those with lower education (29%). Given that there are effects observed among the subset with lower education, the overall effect is not due to confounding by education. Well-described associations between lower socioeconomic status and environmental risks such as poor water quality, hazardous wastes, and air pollutants suggest that multiple environmental factors contribute to disease disparities (41). Although ANCA are likely pathogenic (42,43), several exogenous factors are probably necessary for disease activation (44,45). In addition to silica (5–9,11,17), other factors may include solvents (8), pesticides (9), and infectious agents (46–48), with multiple or sequential exposures needed to induce disease.

The biologic mechanism of silica exposure in the development of SVV with or without glomerulonephritis is not well understood. Crushing silica yields radicals that react with wa-

Table 4. Summary of case-control studies of silica exposure and SVV and/or ANCA-associated diseases

First Author, Location, Year	Case Patients (Number Studied, Disease Description[a])	Control Subjects (Selection Criteria, Number Studied)	Exposure Assessment	OR (95% CI)
Gregorini, Italy, 1993 (5)	ANCA glomerulonephritis (biopsy-proven), $n = 16$ (all male), mean age 54 yr	Male renal patients, age matched, $n = 32$	Interview by industrial hygienist, jobs lasting 6 mo or more	14.0 (1.7 to 114)
Nuyts, Belgium, 1995 (4)	Wegener granulomatosis (biopsy-proven, most ANCA positive), $n = 16$ (3 female, 13 male), mean age 57 yr	General population, age and gender matched, $n = 32$	Interview, industrial hygienist reviewed and rated exposure degree and frequency	5.0 (1.4 to 11.6)
Duna, Ohio, 1998 (9)	Wegener granulomatosis (defined by American College of Rheumatology criteria), $n = 101$ (51 female, 50 male), mean age 37 yr	"Healthy" patients from medical clinics, gender matched, $n = 54$	Interviewer-administered questionnaire, exposure assessed during the year before disease onset; exposure assessment method not described	OR not reported. Construction: 31% cases *versus* 19% controls Farm exposure: 36% cases *versus* 22% controls
Hogan, southeast US, 2001 (6)	ANCA-SVV with glomerulonephritis, $n = 65$ (32 female, 33 male), mean age 54 yr, 97% white	Other renal patients, age, gender, race matched, $n = 65$	Self-reported questionnaire, 1 yr or more of work in specified categories[b]	4.4 (1.4 to 14.4)
Flores-Suarez Mexico, 2003 (7)	ANCA positive Primary systemic vasculitis, $n = 76$	Healthy, age matched, $n = 159$	Self-reported questionnaire for several specific exposure categories	Dusty areas: 3.1 (1.5 to 6.8) Silica: 3.2 (1.1 to 9.2)
Lane, United Kingdom, 2003 (8)	Primary systemic vasculitis, $n = 75$	Hospital patients, age matched, $n = 220$	Interview, job exposure matrix to define exposure	High silica: 3.0 (1.0 to 8.4) Agricultural silica: 4.4 (1.1 to 18.1) High silica among p-ANCA+: 4.9 (1.3 to 18.6)
Beaudreuil France, 2005 (11)	ANCA-positive patients, $n = 60$	Hospital patients, age and gender matched, $n = 120$	Interview, evaluated by three occupational physicians, one epidemiologist, and one industrial hygienist	High silica: 6.9 (1.3 to 35.1) Medium silica: 2.3 (0.6 to 8.2) Low 0.8 (0.1 to 3.9)
Rihova, Czech Republic, 2005 (10)	ANCA-positive vasculitis with renal and lung involvement, $n = 31$	Office workers; age, gender, residence matched, $n = 30$	Questionnaire assessed by occupational health physicians	22% (13% silica and 9% asbestos) *versus* 0% in controls, $P < 0.05$
Hogan, Southeast US, 2006 (this study)	ANCA-SVV with renal biopsy proof of glomerular involvement, $n = 129$	Healthy, age, gender, and state matched community based	Interview, evaluated by one epidemiologist and one industrial hygienist	High: 1.9 (1.0 to 3.5) Crop Harvesting: 2.5 (1.1 to 5.4)

[a]Disease description as written in the text of each manuscript; all included in this review are encompassed within the diagnosis of ANCA-SVV.

[b]Questionnaire asked about exposure to dusty conditions such as farming, mill or textile work, sandblasting, drilling, and lumber work. Also asked about exposure to stone, clay, or glass work, including pottery, ceramics, or china manufacturing; cement, stone, or brick masonry work; and quarry or mining jobs.

ter to produce a damaging hydroxyl radical (49,50). Once absorbed into tissue, silica is not metabolized or destroyed by macrophages, which leads to the production of chemokines, inflammatory cytokines, and growth factors (51–54), and these ongoing effects likely contribute to an immune-modulating defect (13).

A noted limitation to the study is that there were differences in case patients and control subjects with respect to age and gender. However, standard statistical techniques to control for these differences likely minimize any effect on the results. Another concern is residual confounding from unknown exposures that may contribute to the development of ANCA-SVV. Traditional dusty trades and farming have a variety of hazardous exposures, although silica is common between these two occupational categories. Potential farming exposures that need further study include pesticides and fertilizers.

The study included only case patients with renal biopsy proof of disease involvement. Although this provided a definitive diagnosis date for use in referencing previous exposures, it is difficult to determine the time between true disease onset and the development of kidney involvement, which may be variable, and an unknown number of individuals may progress rapidly to kidney failure and not undergo a renal biopsy. Using a renal biopsy for the case definition may also lead to a selective

case sample because of access to medical care or decisions for whether to obtain a renal biopsy, especially among patients with biopsy proof of disease in another organ. However, the renal-biopsy population is likely to represent the majority of patients with ANCA-SVV because renal involvement is reported in up to 90% of patients (16) and renal biopsy results are used to guide treatment (55). Furthermore, up to 33% of patients with silicosis have kidney dysfunction (56), and silica exposure may in fact result in a higher risk for kidney impairment than silicosis or lung cancer (57). Whether silica exposure influences the development of renal disease in the setting of ANCA-SVV is not clear and cannot be determined in this study.

ANCA-SVV that is associated with high silica exposure may convey differences in disease expression, characterized by ANCA positivity that is more frequently associated with MPO than PR3 specificity, although scores for overall disease activity were similar. Considering that silica is inhaled, there is no suggestion of more frequent ANCA-SVV disease expression in the lung and upper respiratory tract, even with high levels of silica exposure. In fact, those with high silica exposure may have less frequent upper respiratory involvement. This result is consistent with our previous report, in which no difference was found in the likelihood of silica exposure between those with and without vasculitis disease involving the airways or lungs (6).

The case patients who participated in this study seem to represent the demographics of the overall population of patients who were identified during the study period and did not participate in the study. However, patients who were sicker or who had died and were interviewed by proxy were less educated than those who participated in the full interview. Attrition of case patients as a result of illness likely leads to a minimization of the association of silica exposure with ANCA-SVV from the case patients who participated in the full interview, especially given that this study suggests an increased association of silica with the disease among those with lower education. Those who are at lower socioeconomic levels may seek or obtain a diagnosis later and therefore be sicker at diagnosis, or silica exposure could contribute to more debilitating disease that is less responsive to treatment. Evaluation of the impact of silica exposure on treatment response and relapse in a future study is critical.

Conclusion

High silica exposure, characterized by many years of exposure more than high intensity, is associated with the onset of ANCA-SVV. The importance of silica exposure from agricultural sources has not always been considered and may be a particular concern in the development of this disease, especially in the southeastern United States. Risk for disease from silica exposure may still be a possibility many years after exposure has ceased, which emphasizes the need for understanding the role of multiple exposures in inducing autoimmune dysfunction in small-vessel vasculitides, including ANCA-SVV.

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Two published abstracts included preliminary results that culminated in this manuscript: (*1*) *J Am Soc Nephrol* 15: 340A, 2004; and (*2*) *Kidney Blood Press Res* 28: 169, 2005.

The following nephropathologists participated in the identification of patients with biopsy-proven ANCA-SVV with glomerulonephritis: J. Charles Jennette, MD, Harsharan Singh, MD, Department of Pathology, University of North Carolina at Chapel Hill, Chapel, Hill, NC; Samy Iskandar, MBBCh, PhD, Wake Forest University School of Medicine, Winston Salem, NC; Sally Self, MD, Medical University of South Carolina, Charleston, SC; Serena Bagnasco, MD, Emory University, Atlanta, GA; Ralph C. McCoy, New Hanover Regional Medical Center, Wilmington, NC; David N. Howell, MD, Duke University Medical Center, Durham, NC; Carol Weida, MD, Carolinas Medical Center, Charlotte, NC; William F. Glass, MD, PhD, Eastern Virginia Medical School, Norfolk, VA. Institutions listed are where the nephropathologists were located at the time of the study. Biopsies reviewed at these nephropathology laboratories are from patients who received a diagnosis within their own institution as well as from private practice nephrology practices and smaller hospitals. Renal biopsies from private practices and smaller hospitals are sent to the nephropathologist of choice. The nephropathology laboratories in the region that are not represented include East Carolina University School of Medicine and the Medical College of Georgia in Augusta. Institutional review board approval was not sought at the Medical College of Georgia because no patients were identified by renal biopsy as receiving a diagnosis of ANCA-SVV during the study period. Dr. Harsharan Singh is a nephropathologist at the University of North Carolina at Chapel Hill but was responsible for reviewing renal biopsies from Eastern Carolina University School of Medicine during identification of patients for this study. Review and recruitment of case patients who were identified by Dr. Singh were approved the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill (97-MED-44 and 04-MED-663).

Disclosures

None.

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