Increased Prevalence of Scleroderma in Southwestern Ontario: A Cluster Analysis

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ABSTRACT. ***Objective.*** To estimate the prevalence of scleroderma (systemic sclerosis, SSc) in 3 cities, Windsor, Sarnia, and Woodstock, Ontario, within our referral area, which has a referral base population of 1 million.

Methods. To compare the addresses and exposures of referrals with SSc, we performed a case control study using our patients with scleroderma and 2 age and sex matched controls from the same rheumatologist's practice.

Results. Sixty-seven of 91 patients with SSc and 87 of 154 controls responded. The mean age of patients with SSc was 53.2 years versus 52.8 years in controls. There was no statistically significant increase in the number of SSc patients from Windsor (population 197,694): 14 patients (15.4%) with SSc versus 18 controls (11.6%) ($p < 0.41$); or Sarnia (population 72,738): 7 patients (7.7%) with SSc versus 7 controls (4.5%) ($p < 0.31$). However, there were 9 cases (9.9%) from Woodstock (population 32,086) versus one control (0.64%) ($p < 0.0004$). The point prevalence of scleroderma was at least 0.71/10,000 in Windsor, 0.96/10,000 in Sarnia, and 2.8/10,000 in Woodstock. There were no significant between-group differences in exposure to industrial toxins or chemicals including vinyl chloride, silica, and benzene, but exposure rates in both groups were low. Occupations and proportion of those who were work disabled were not different. Patients with SSc were not more likely to have smoked cigarettes ($p < 0.43$); however, they were more likely to drink at least 6 drinks of alcohol per week ($p < 0.04$) and had more dental fillings ($p < 0.05$). Patients with SSc knew on average 3.2 others with this disease, and controls knew only 0.25 others with scleroderma ($p < 0.00001$). Two patients with SSc knew someone with SSc in their workplace versus none of the controls.

Conclusion. Our a priori expected higher prevalence of scleroderma in Windsor and Sarnia did not reach significance, but the cluster in Woodstock seems statistically validated, and the exact reason for this cluster remains unclear. It is unlikely that all patients with SSc in Woodstock were seen by us, so the prevalence of scleroderma is at least 2.8/10,000, which is a medium to high prevalence compared to other studies. Associations with alcohol and dental fillings require further study. (J Rheumatol 2002;29:1867–73)

Key Indexing Terms:
PREVALENCE SCLERODERMA SYSTEMIC SCLEROSIS

Scleroderma (systemic sclerosis, SSc) is a connective tissue disease causing fibrosis of the skin and visceral organs[1]. There are 2 main systemic variants: limited and diffuse scleroderma. Limited scleroderma has been defined as skin involvement distal to the elbows or knees with or without involvement of the face. Diffuse scleroderma involves sclerodermatous skin changes that also occur proximal to the elbows or knees, or on the trunk[2].

Scleroderma is rare, with an estimated mean annual incidence of 2.7 to 12 new cases per million population[1]. Previous evidence has suggested a nonrandom distribution of scleroderma between populations. An epidemiological study of scleroderma in the West Midlands, UK, estimated a minimum overall prevalence rate of 31 per million (0.31/10,000) divided into 48 and 13 per million in women and men, respectively[3]. The etiology of scleroderma is unknown and the discovery of potential etiologic factors may lend insight into this disease. Studies have suggested clustering among some populations that may reflect exposure to specific environmental or genetic factors[4]. A formal epidemiological analysis suggested a statistically significant cluster of scleroderma in areas to the south and west of London, UK[5]. London, Ontario, Canada, is a tertiary university medical center providing care for many patients from southwestern Ontario, with a referral base of about 1 million. We noted a seemingly larger proportion of cases of scleroderma referred to our outpatient clinic, coming from the areas of Windsor, Sarnia, and Woodstock. Interest was generated by the possibility that 2 of these areas have large industrial facilities (Windsor and Sarnia) whose environ-

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Submitted September 11, 2001; revision accepted March 12, 2002.

mental effects may play a role in the pathogenesis of scleroderma. Other environmental factors that may be associated with scleroderma include dental fillings, pet ownership, alcohol intake, and smoking[6].

MATERIALS AND METHODS

The study was approved by our ethics committee. Ninety-one patients with diffuse or limited SSc who met the American Rheumatism Association (ARA) preliminary criteria for scleroderma[7] or CREST syndrome[8] were identified in a rheumatology outpatient practice database in Southwestern Ontario where the rheumatologist (JEP) has a research interest in scleroderma. A group of 154 controls, derived from the same practice and referred to the same rheumatologist, matched for age (within 5 years) and sex with patients, were selected in a random fashion. All patients and controls were assigned a 3 digit identification number for use throughout the study.

We thought the bias would be to refer patients with scleroderma from a larger area compared to other referral diagnoses, as scleroderma is a focus of research in this practice. This would, if anything, bias against clustering of patients with scleroderma. In addition, because there is a shortage of rheumatologists in the surrounding area, many common rheumatologic conditions are also seen in this practice. Thus, many diagnoses should come from the entire referral area.

A questionnaire was mailed to each individual in the 2 groups with a preaddressed and stamped return envelope provided. If the questionnaire was not returned after one month a reminder letter was sent. After 2 months a reminder and second questionnaire were mailed to all nonrespondents. We asked patients not willing to participate to mail back the unanswered questionnaire. The questionnaire consisted of 5 sections: (1) basic demographic information; (2) residence locations including the location of the current and all previous homes along with length of time spent at each. Information on manufacturing plants and airports near the current or any previous residences was collected; (3) alcohol intake, smoking, pets at home, dental fillings, and chemotherapeutic drug exposure; (4) employment information and chemical exposure at the workplace or at home. All questions regarding exposure were worded to account for having ever been exposed to the agent (current and past exposure); (5) the final section pertained to health, with questions about medications and family history.

For all nonrespondents a chart review was conducted. The chart review verified current residence location, disease type, smoking and alcohol habits, and chemical exposure if noted. All available data were used for the nonrespondents, but some data, such as previous residences and number of pets, were unobtainable.

Clusters were determined a priori based on the residence location. Limits of Windsor, Sarnia, and Woodstock areas were defined in advance with a map of Ontario. An estimate of the prevalence of scleroderma in the 3 regions was also sought based only on the cases in this study. To be eligible for this section the cases had to be currently living in one of the regions and had to be alive at the time of the study. The denominator population data were obtained from the 1996 census from Statistics Canada. We realized that our prevalence data would be an underestimate as, of course, not all people diagnosed with scleroderma were likely to have been seen by one physician. Using case control methodology, relative risks were determined in the scleroderma population compared to the controls using 2 tailed parametric and nonparametric statistical tests.

RESULTS

The 91 participating patients with scleroderma consisted of 77 women and 14 men with a mean age of 53.2 years (range 28–87). Forty-four women and 7 men had limited disease and 33 women and 7 men the diffuse form. A group of 154 controls (131 women, 23 men) matched for age (± 5 yrs) and sex were selected in a random fashion from the database of the same practice and mailed identical questionnaires; matching ranged from 1:1 to 2:1 (due to availability of appropriate controls). The controls did not have scleroderma or mixed connective tissue disease. They had other rheumatologic diagnoses including: fibromyalgia (23%), osteoarthritis (16%), rheumatoid arthritis (RA) (12%), arthralgia (11%), tendonitis (4%), and systemic lupus erythematosus (3%). Response rates were 74% in the scleroderma group and 56% in the control group ($p < 0.01$). Table 1 summarizes the demographic information of participants.

Prevalence. Upon testing our initial hypothesis, we discovered that 7 of 91 (7.7%) patients with scleroderma currently lived in Sarnia versus 7 of 154 (4.5%) controls ($p < 0.31$). Fourteen of 91 (15.4%) patients and 18 of 154 (11.6%) controls lived in Windsor ($p < 0.41$). However, 9 of 91 (9.9%) patients and one of 154 (0.65%) controls were living in Woodstock ($p < 0.0004$). The same trend was found in past residence. Eleven of 70 (15.7%) patients versus 9 of 97 (9.28%) controls reported ever living in Sarnia ($p < 0.21$); 16 of 73 (21.9%) patients and 24 of 104 controls (23.1%) ever lived in Windsor ($p < 0.86$); and 11 of 70 (15.7%) patients lived in Woodstock versus 2 of 94 (2.13%) controls ($p < 0.001$). In London, Ontario, the frequency of scleroderma was less than that of controls, with 24/91 (26.4%) patients versus 62/154 (40.2%) controls reporting that they lived in London. In all of the cities, the 2 groups reported no difference in the location of their residence with respect to proximity to factories or airports, as shown in Table 2.

The estimated prevalence of scleroderma in Woodstock was 280 per million (2.8/10,000) compared with 70.8 per million (0.7/10,000) in Windsor and 90.2 per million (0.9/10,000) in Sarnia. Table 3 summarizes these data, compared to other prevalence rates reported in the literature. All our prevalence results should be underestimates, as this was not a population study.

A subgroup analysis was performed to compare clustering in the regions of Windsor, Sarnia, and Woodstock with respect to the disease type (diffuse vs limited). There were no statistically significant differences in clustering in the 3 regions with respect to disease type, but the numbers are limited (Table 4).

A second subgroup analysis was performed to elicit possible clustering differences between men and women. Unfortunately, the absolute size of the values did not permit meaningful statistical relationships to become apparent. No large differences were evident in the number of men with scleroderma versus controls when comparing the 3 regions. There did seem to be a higher preponderance of women in the Woodstock area, which would be in keeping with the cluster found in that region (Table 5).

Exposure. There were no differences in the types of employment between the 2 groups. The nature of employment varied widely, from office work to construction. Rates of

Table 1. Demographic characteristics of scleroderma and control groups. Percentage (out of total respondents) is indicated in parentheses.

	Scleroderma	Controls	p
No. of patients	91		
Limited	51	154	
Diffuse	40		
Male:female	14:77 (15:85)	23:131 (15:85)	0.95
Mean age, yrs (range)	53.2 (28–87)	52.8 (28–86)	0.81
Respondents, n	67 (73)	87 (56)	0.01
Disease duration, yrs, mean ± SEM	6.45 ± 0.77	3.95 ± 0.15	0.0002
Disability, n	12/61 (20)	25/86 (29)	0.25
Drink alcohol, n	43/87 (49)	61/140 (44)	0.39
Drink ≥ 6 per week, n	14/74 (19)	11/124 (9)	0.04
Drinks per week, mean ± SEM	2.51 ± 0.46	1.79 ± 0.42	0.10
Current smoker	28/87 (32)	43/141 (30)	0.79
Past/present smoker	32/87 (37)	45/142 (32)	0.43
Ever owned pets	52/65 (80)	71/87 (82)	0.80
Dogs	46/65 (71)	65/87 (75)	0.59
Cats	36/65 (55)	50/87 (57)	0.79
Mean no. of dental fillings per subject ± SEM	7.56 ± 0.45	6.39 ± 0.39	0.05
Duration of time with dental fillings, yrs, ± SEM	28.8 ± 2.10	22.2 ± 1.76	0.017

Table 2. Percentage of respondents with present and past residence locations in Sarnia, Windsor, or Woodstock. N given in parentheses.

	Scleroderma	Controls	p	Relative Risk (RR)	95% CI for RR
Sarnia (%)					
Now	7.7 (91)	4.5 (154)	0.31	1.75	0.59, 5.16
Ever	15.7 (70)	9.3 (97)	0.21	1.82	0.71, 4.67
Windsor (%)					
Now	15.4 (91)	11.6 (154)	0.41	1.37	0.65, 2.91
Ever	21.9 (73)	23.4 (104)	0.86	0.93	0.46, 1.92
Woodstock (%)					
Now	9.9 (91)	0.65 (154)	0.0004	16.79	2.09, 134.87
Ever	15.7 (70)	2.13 (94)	0.001	1.54	1.83, 40.07

Table 3. Prevalence of scleroderma in Woodstock, Windsor, and Sarnia, compared to other reports.

	Population, n	Observed Cases, n	Rate per 10,000	95% CI for Prevalence per 10,000
Sarnia	72,738	7	0.96	0.25, 1.68
Windsor	197,694	14	0.71	0.34, 1.08
Woodstock	32,086	9	2.80	0.97, 4.64
London, Canada	325,646	24	0.74	0.44, 1.03
West Midlands, UK[3]	4,100,000	128	0.31	0.26, 0.37
Region in London, UK[5]	346,900	52	1.5	1.09, 1.91
South Carolina, USA[18*]	3,293,100	2	2.86	—
	(n = 6998)[†]	7*	10.0*	2.60, 17.41*
Estonia[19*]	1,400,000	2	3.5	0.40, 12.70
	(n = 5702)[†]	13*	22.8*	10.42, 35.18*
Choctaw, Oklahoma, USA[20]	21,255	14	3.1 to 46.9	—
Full-blood Choctaws	1704	8	46.9	20.3, 93.0
Non-full-blood	19,551	6	3.1	0.49, 4.98
Near Rome, Italy[22]	572	5	87.41	11.13, 163.70

* Includes non-definite scleroderma cases (scleroderma spectrum disorders). [†] n = the sample studied. The subset parameter was extrapolated to find a population estimate.

Table 4. Subgroup analysis of disease type and residence location of subjects with scleroderma. Percentage of respondents is given, N in parentheses. The relative risk (with 95% CI) for diffuse disease has been given.

	Limited	Diffuse	p	Relative Risk (RR)	95% CI for RR
Sarnia					
Now	5.5 (92)	2.2 (91)	0.38	0.48	0.09, 2.64
Ever	12.9 (70)	2.9 (70)	0.06	0.25	0.05, 1.24
Windsor					
Now	5.5 (92)	9.9 (91)	0.10	2.67	0.82, 8.73
Ever	9.6 (73)	12.3 (73)	0.26	1.90	0.62, 5.83
Woodstock					
Now	3.3 (92)	6.6 (91)	0.15	2.82	0.66, 12.08
Ever	5.7 (70)	10.0 (70)	0.13	2.74	0.71, 10.41

Table 5. Subgroup analysis by sex and residence location of scleroderma subjects and controls. Percentage of respondents is given, N in parentheses.

	Men with Scleroderma	Control Men	Women with Scleroderma	Control Women
Sarnia				
Now	7.7 (13)	8.7 (23)	7.7 (78)	3.8 (131)
Ever	14.2 (7)	15.8 (63)	21.4 (14)	7.2 (83)
Windsor				
Now	15.4 (13)	13.0 (23)	15.4 (78)	11.4 (131)
Ever	28.6 (7)	21.4 (14)	21.2 (66)	23.3 (90)
Woodstock				
Now	7.7 (13)	0 (23)	10.3 (78)	7.6 (131)
Ever	14.2 (7)	7.7 (13)	15.9 (63)	1.2 (81)

work disability were similar: 12 out of 61 (20%) in the scleroderma group were receiving disability compensation and 25 of 86 (29%) in the control group ($p < 0.25$). With regard to pet ownership, 52 out of 65 (80%) patients with scleroderma reported having a pet and 82% in the control group. Similarly, there were no differences in the types of pets — 46 (71%) patients and 65 (75%) controls owning dogs, while 36 (55%) patients and 50 (57%) controls owned cats. Sixty-one patients had on average 7.55 dental fillings, greater than the average 6.39 fillings reported in 82 controls ($p < 0.05$). Patients reported having dental fillings an average of 28.8 years compared with 22.2 years in the control group ($p < 0.02$). Many of the fillings predated the symptoms of illness in each group. We found no between-group differences with respect to smoking. Twenty-eight of 87 (32%) patients were smokers, while 43 of 141 (30%) controls smoked ($p < 0.79$). A significant difference was found between the groups for alcohol consumption: 14/74 (19%) patients with scleroderma versus 11/124 (9%) controls consumed 6 or more servings of alcohol per week ($p < 0.04$). The average number of drinks consumed per week was 1.4 times greater in the scleroderma group than in controls, with 2.5 ± 0.46 (mean ± SEM) in scleroderma patients versus 1.8 ± 0.42 in controls ($p < 0.10$). Table 1 summarizes these results.

Patients and controls reported no overall difference in exposure to chemicals and no difference in exposure to individual chemicals including silica, benzene, toluene, white spirit, perchlorethylene, trichlorethylene, trichlorethane, vinyl chloride, urea formaldehyde, meta-phenylenediamene, bicromade, turpentine, aromatic hydrocarbons, and aliphatic hydrocarbons. The 2 groups reported no difference in exposure to medications implicated with scleroderma in previous research, such as bleomycin, fenfluramine, diethylpropion, carbidopa, and L-5 hydroxytryptophan (Table 6). It is possible that subjects may have underreported their exposure to chemicals due to ignorance of the names used in the questionnaire and unknown exposure of specific chemicals in the workplace and elsewhere.

DISCUSSION

Scleroderma is a difficult disease to study epidemiologically because it is rare and subtle cases may go undiagnosed. It has been well documented that scleroderma has a female preponderance that ranges from 3:1 to 8:1, which is consistent in our population, with a female excess 6:1[3,9-17]. To date, there is no widely accepted biological explanation for the marked female preponderance in scleroderma.

Studies have shown an association between increased alcohol use and scleroderma[14]. This finding was consistent with our results, where scleroderma patients were more likely to drink at least 6 drinks per week compared to controls. We do not think the respondents had different alcohol consumption history than nonrespondents, as a chart

Table 6. Percentage of subjects who sustained chemical and other exposure. Total number of respondents (N) given in parentheses. All questions regarding exposure accounted for current and past exposure to the agent. Due to confusion between scientific versus generic names of chemicals, subjects may have underreported epxosure.

Exposure	Scleroderma	Controls	p	Relative Risk (RR)	95% CI for RR
Chemicals	43.8 (64)	42.5 (87)	0.88	1.03	0.55, 2.02
Family chemical exposure	44.6 (65)	47.1 (87)	0.76	0.95	0.48, 3.55
Silica	4.6 (65)	11.5 (87)	0.12	0.4	0.71, 10.18
Toluene	6.2 (65)	8.0 (87)	0.65	0.76	0.37, 4.76
Benzene	9.2 (65)	11.5 (87)	0.65	0.8	0.44, 3.71
White spirit	3.1 (65)	4.6 (87)	0.63	0.67	0.12, 3.71
Perchlorethylene	3.1 (65)	3.4 (87)	0.90	0.91	0.14, 5.48
Trichlorethylene	3.1 (65)	3.4 (87)	0.90	0.91	0.14, 5.48
Trichlorethane	1.5 (65)	2.3 (87)	0.90	0.65	0.06, 7.60
Vinyl chloride	1.5 (65)	6.9 (87)	0.09	0.22	0.02, 1.80
Urea formaldehyde	15.4 (65)	9.2 (87)	0.24	1.67	0.67, 4.84
Meta-phenylenediamene	0 (65)	1.2 (87)	0.29	0	—
Bicromade	0 (65)	1.2 (87)	0.29	0	—
Turpentine	47.7 (65)	44.8 (87)	0.72	1.06	0.59, 2.14
Aromatic hydrocarbons	6.2 (65)	4.6 (87)	0.67	1.35	0.33, 5.66
Aliphatic hydrocarbons	1.5 (65)	2.3 (87)	0.74	0.65	0.06, 7.48
Fenfluramine	1.5 (65)	0 (87)	0.19	—	—
Diethylpropion	1.5 (65)	0 (87)	0.19	—	—
L-5 hydroxytryptophan	0 (65)	1.2 (87)	0.29	0	—
Carbidopa	0 (65)	0 (87)	NA	0	—
Bleomycin	1.6 (64)	0 (87)	0.18	—	—
Vibrating machines	17.4 (63)	14.9 (87)	0.68	1.17	0.50, 2.90

review obtained alcohol histories on most cases and controls. The controls were not drinking less alcohol due to use of certain medications (such as methotrexate), as the majority of controls did not have RA; and only a small number of patients with RA were taking methotrexate. One would assume that alcohol consumption would be lower in patients with scleroderma since it can worsen gastroesophageal reflux disease, which occurs in most patients with scleroderma. Others have found an association between pet ownership and scleroderma. Silman, *et al* discovered an association with an increased rate of pet exposure (dogs or cats) and female patients who later developed scleroderma compared to a friend control group[6]. Interestingly, this association was "dose dependent," with the greatest risk being observed in those with more than one pet. Our results showed no significant difference in pet ownership (dogs or cats) between the scleroderma group and the controls. The association between dental fillings and scleroderma is of interest, as there has been speculation about the role of heavy metals, specifically mercury, in the pathogenesis of scleroderma. We found a difference between the scleroderma patients and controls in both the number of dental fillings and the duration of time the dental fillings were in place. This association may be explained by a difference in the environment of the oral cavities between the 2 groups. Patients with scleroderma often complain of decreased salivation and it is estimated that 25% can have associated sicca symptoms. This difference in the oral cavity may predispose patients with scleroderma to more tooth decay and cavities and, as a result, more dental fillings. However, many of the dental fillings predated symptoms of scleroderma. The disease duration was longer in patients with scleroderma than in the controls, but dental fillings had been placed on average 29 years previously in scleroderma patients versus 22 years in the controls.

In 1989, a study of scleroderma in the general population of South Carolina, USA, exposed a prevalence of 286 per million (2.86/10,000)[18], considerably higher than found in the West Midlands, UK[3]. In Estonia an overall prevalence of 350 per million (95% CI 40-1270) was found[19]. There is wide variation in the observed prevalence of scleroderma. Unfortunately, any support for clustering based on prevalence is subject to criticism because in practice underlying prevalence can only be estimated, and it will always be an underestimate. In addition, because some prevalence studies also describe scleroderma spectrum disorders, these may tend to overestimate the possible cases of scleroderma. We found the prevalence of scleroderma in our area to range from 70.8 to 280 per million, with the highest prevalence in Woodstock, which is more supportive of the prevalence data from South Carolina and much higher than the prevalence found in the West Midlands, UK.

Our case control study found a statistically significant geographic cluster of scleroderma in Woodstock, which supports the higher prevalence found in that city. The data from the Windsor and Sarnia areas did not reach statistical significance. However, in both areas there was a tendency for higher numbers of patients with scleroderma compared

with controls. It may be that our study lacked sufficient power to detect geographic clusters in these 2 areas.

Cluster analyses are of interest in scleroderma to identify populations with higher prevalences of scleroderma. What remains unknown is whether these clusters are based on intrinsic (genetic) factors or exposure to an extrinsic variable (environmental toxin) or the interaction of both. A cluster of scleroderma was identified in Choctaw Native Americans in southeastern Oklahoma, USA[20]. The prevalence of scleroderma in this population was 4690 per million for full-blooded Choctaws (46.9/10,000) and 310 per million for non-full-blood Choctaws (3.1/10,000). This was 4 year period prevalence data, which could certainly be higher than point prevalence data. The case control study of the Choctaw failed to identify any environmental exposures associated with scleroderma and the southeastern Oklahoma community. The population was closely related, but relatives who moved did not have as high a prevalence of scleroderma.

Family studies in scleroderma have found no common genetic markers. Family studies have shown a higher incidence of asymptomatic relatives with antinuclear antibodies than controls[21]. Several population studies have shown an increase in the prevalence of certain HLA types (DR1, DR3, and DR5) in patients with SSc, but not consistently.

Studies have shown an association between low socioeconomic status and scleroderma[14]. However, there was no difference between the percentage of low income households, families, or individuals in the 3 communities we studied based on 1996 census data. There was a difference according to university education, with 5.4% of the population in Woodstock holding university degrees versus 10.0% in Windsor and 8.7% in Sarnia. This difference could be explained by the size and nature of employment in each of the 3 cities.

Clustering around major airports has no obvious plausible biologic explanation[5]. A geographic cluster of scleroderma was observed in a small rural area in the province of Rome, Italy[22]. That study found 5 out of 572 people in the village with scleroderma, a prevalence of 8741 per million, 282 times higher than expected from the UK data. Again, no known environmental factor was identified.

No potential environmental factors could be identified for the cluster found in Woodstock. These subjects were not related. They had both limited and diffuse types of scleroderma. Most did not know each other, with the exception of meeting at scleroderma support groups. The cluster could have been spurious (due to chance). Statistics Canada 1996 data relating to the cities of Woodstock, Sarnia, Windsor, and London found no statistically significant differences in the types of industries, with the exception of agricultural industries, which were more numerous in Woodstock. That Woodstock is a more rural community than the others could be the explanation for this difference. The people of these cities are not closely related ancestrally, and the majority of our Native Peoples with scleroderma are from the Sarnia area.

Most clustering of scleroderma has been on the basis of an association with a known occupational hazard or chemical exposure (organic solvent) such as silica[23-27]. Our study showed no significant difference in silica exposure, and indeed more patients in the control group reported being exposed to silica. However, because both the subjects and the authors may be unfamiliar with the possible alternative names for substances, this may have contributed to underreporting of exposure to certain agents. In addition some exposures (e.g., solvents or certain chemicals) may have occurred too infrequently, and thus any difference between the control and patient populations would have been undetectable with our sample size.

It has been hypothesized that there are 2 risk factors for scleroderma: a female variant related to hormonal and reproductive factors and a male variant related to occupational exposure. This hypothesis has gained support from reports (described above) of male patients exposed to silica. A study of 56 male patients in the UK found most had not experienced occupational exposure to agents reported to be related to scleroderma[28]. In support of this, we found no difference in the reported exposure to chemicals between patients and controls. The cluster found in Woodstock was largely of female patients. A more suitable hypothesis may be that there are at least 2 predispositions to scleroderma: an intrinsic variant related to an inherent immune susceptibility in the patient and an extrinsic variant related to exposures.

There are a number of methodological issues to be considered when interpreting our data. In any questionnaire study the overall response rate could be considered as an inherent source of bias. Often, controls who do not have the disease in question are less likely to respond to a questionnaire, as in this study. Thus, the possibility exists that respondents within the control group may have differed from nonrespondents, resulting in a biased sample. To minimize this potential bias, we performed a chart review of all the nonrespondents to assess whether those who did respond may have had a healthier lifestyle in terms of less smoking and alcohol consumption. In addition, because some of our controls had RA, they may have been taking methotrexate, which would require that their alcohol consumption be low. However, most of our control population did not have RA. Following the detailed chart review of the nonrespondents within the control subgroup, our observations remained consistent.

Recall is also an inherent bias in questionnaire studies and it is possible our subjects had poor recall with regard to exposures. The possibility also exists that because there were more nonrespondents in the control group, recall bias may have been introduced on certain items addressed by the questionnaire. In addition, the use of both “ever exposed” and current exposure as variables may introduce another level of complexity, as subjects may not report on items accurately, leading to less clearly defined results. Some

patients could have current (new) exposures that postdated their disease, and these would not be thought to have caused the illness. In addition, disease and exposures could be associated but not pathologically related. The potential confounding factors limit the conclusions that may be drawn from a questionnaire study such as this, and it is not possible to determine cause and effect; instead we can determine factors that are correlated, and possible cause and effect relationships that require further investigation.

Southwestern Ontario is under-serviced by rheumatologists, but there are rheumatologists in London, Windsor, and Sarnia. Thus the reason for more cases being referred from Woodstock could be that there is no local rheumatologist. However, this should have increased the number of referrals from Woodstock with other diagnoses in the control group, which was not the case. Another explanation for our findings could be that scleroderma is more prevalent in many areas, including southwestern Ontario, as it may be more frequently diagnosed now than in the past. Our prevalence data could be gross underestimates, as this was not a population study.

From this study and the review of literature we conclude that it is very difficult to identify clusters of scleroderma based on prevalence data alone. Further, identifying environmental agents associated with geographical clustering of scleroderma is problematic. The prevalence of scleroderma (underestimated in this report) in southwestern Ontario is not markedly different from other reports that ranged from 70 to 240 per million. We cannot ascertain the degree of underestimation of scleroderma in these areas. The reason for increased scleroderma in Woodstock compared to other communities in southwestern Ontario remains unclear. Increased alcohol consumption may be associated with scleroderma.

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