Cigarette Smoking, Alcohol Consumption, and the Risk of Systemic Lupus Erythematosus: A Case-Control Study

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ABSTRACT. ***Objective.*** To investigate the effects of cigarette smoking and alcohol consumption on the development of systemic lupus erythematosus (SLE).

Methods. We interviewed 125 patients with SLE and 125 controls in a case-control study. Demographically similar controls randomly selected from outpatient clinics were matched to SLE cases for sex and age. Clinical data, including cigarette smoking, drinking habits, and other demographic variables, were collected by an interview-administered questionnaire.

Results. To minimize bias associated with reactive habits induced by disease, cigarette smoking before the diagnosis of SLE was the primary variable for subsequent analysis. Analysis of the data by multivariate conditional logistic regression revealed that both cigarette smoking before SLE diagnosis and ex-smoking before SLE diagnosis significantly increased the risk of development of SLE (OR 6.69, 95% CI 2.59, 17.28, $p < 0.001$; and OR 3.62, 95% CI 1.22, 10.70, $p = 0.02$, respectively). This association remained even when statistically controlling for the effects of family history and education, indicating an independent effect. Alcohol did not place an individual at increased risk nor did it have a protective role.

Conclusion. The results of this study provide further evidence that cigarette smoking may be an associated risk factor for the development of SLE. (J Rheumatol 2001;28:2449–53)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ALCOHOL CIGARETTE SMOKING
TOBACCO EPIDEMIOLOGY

Genetics, sex, and hormonal status are major predisposing factors associated with the development of systemic lupus erythematosus (SLE)[1-5]. However, initiation of disease and variations in temporal activity are likely influenced by the environment and other exogenous factors[6,7]. That many monozygotic twins are discordant for SLE suggests that environmental and developmental factors play important roles in disease pathogenesis[8-10]. Environmental agents that have been implicated in the initiation and exacerbation of SLE include ultraviolet (UV) light[11,12], viral infections[13], and other exogenous factors[14].

A few epidemiological studies have examined the possible association of smoking and SLE[15-19]. In 1993, Reidenberg, *et al* showed that slow acetylation phenotype and exposure to environmental amines are not principal causes of idiopathic SLE[15]. In regard to smoking, there were no differences in the smoking history between the SLE cases and the "friend" controls[15]. In 1995 Nagata, *et al* showed using self-administered questionnaires that current smoking had a significant increase in the risk of SLE[16]. In 1998 Hardy, *et al* also showed a significant increase in the risk of development of SLE in current smoking and concluded a significant positive association between SLE and smoking[17]. In the present study, the first in a predominantly Hispanic population, we further evaluate the association of cigarettes with SLE.

MATERIALS AND METHODS

Subjects and study design. A single interviewer collected epidemiological data for this study using a standard questionnaire form designed to record demographic details that included cigarette smoking, alcohol consumption, education, and income. This study was approved by the Institutional Review Board. All 137 patients with well characterized SLE from the University of New Mexico Systemic Lupus Data Base were interviewed by telephone, and the data were directly entered into the questionnaire form. The diagnosis of SLE was confirmed in each subject using the American Rheumatism Association 1982 and American College of Rheumatology 1997 revised criteria[20,21]. The diagnosis of SLE was confirmed by a rheumatologist after an in-depth face to face interview, medical history,

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physical examination, chart review, and appropriate laboratory testing. To minimize bias associated with selection of controls from populations with intrinsically lower cigarette smoking rates or lower rates of SLE, demographically similar controls matched for sex and age (within 5 years) were randomly selected from the University of New Mexico general medicine outpatient clinics, using a computer list of patients who were seen in a one month period, and interviewed in person using the same questionnaire.

Regular smoking was defined as smoking at least one cigarette per day for at least 3 consecutive months. Subjects who had ever smoked cigarettes on a regular basis were asked these additional questions: age of onset of smoking, number of cigarettes or packs per day, current smoking status before the diagnosis of SLE, and age of quitting or stopping/restarting before the diagnosis of SLE, where applicable. Cases and controls were classified into 3 smoking status groups: (1) never smoker, (2) ex-smoker (defined by no smoking for one year prior to the diagnosis of SLE in SLE cases or prior to the pseudodiagnosis in the case of controls), (3) current smoker (defined by smoking at least one cigarette per day for at least 3 months prior to the reference date). Alcohol consumption (average drinks per week) over the past year was also recorded for both the SLE and control groups. The number of years of school completed (not completing high school/completion of high school/college or college graduate) and approximate household income over the past year were also collected.

Statistical analysis. Controls were assigned a "pseudodiagnosis" or "dummy" age, taken as the diagnosis age of the SLE case to which that control was matched since the smoking history referred to information preceding the diagnosis of SLE. Thus, for all cases and their matched controls, analysis of all data was restricted to the exposures noted before the diagnosis of SLE for cases and "pseudodiagnosis" for controls. Data were entered into a computerized spreadsheet (Excel, Version 5, Microsoft, Seattle, WA), and analyzed in SAS (SAS/STAT Software, Release 6.11, Cary, NC)[22]. Fisher's exact test was used to compare demographic and risk factor data between the SLE and control groups. The statistical significance of smoking and alcohol consumption as risk factors in the development of SLE, after adjusting for age, sex, ethnicity, family history of SLE, education level, and past income, was analyzed using multivariate conditional logistic regression. Stepwise regression was used for predictor variable selection, to obtain a "best" model, which was verified by "all subsets" regression.

RESULTS

Characteristics of the cases and controls are shown in Table 1. Subject recruitment rates were similar, 91% for cases and 95% for controls. There was no overall difference between the SLE and control groups in regard to ethnicity, education, or income (all p values > 0.22). However, SLE patients revealed a markedly increased family history of SLE relative to the control group ($p < 0.001$).

The number of current smokers was 52 (41.6%) for the cases and 24 (19.2%) for the controls, a marked increase in cigarette smoking of all kinds in the SLE group ($p < 0.001$). All current smokers among the cases smoked at least one year prior to the diagnosis of SLE, and they smoked an average of 18 years prior to the diagnosis of SLE. The cigarette smoking and alcohol consumption distribution between the cases and controls are shown in Table 2.

Multivariate analysis of the data, using conditional logistic regression and adjusting for variables including age, ethnicity, alcohol consumption, family history, education, and income level led to a significant odds ratio (OR) for both current smokers and ex-smokers compared to never smokers. Using stepwise regression, the best model used family history, past education, and smoking as variables. The adjusted OR for current and ex-smokers are shown in Table 3. As can be seen, cigarette smoking at the time of SLE diagnosis and ex-smoking significantly increased the risk of development of SLE [OR 6.69, 95% confidence intervals (CI) 2.59, 17.28, $p < 0.001$; and OR 3.62, 95% CI 1.22, 10.70, $p = 0.02$, respectively]). Family history does not

Table 1. Demographic data of cases and controls.

	Cases	Controls	p
Total number of subjects	125	125	
Women	121	121	1.0
Men	4	4	
Mean age (yrs) at SLE diagnosis	36	36	1.0
IQR of age at diagnosis	25,46	25,47	
Mean current age, yrs	44	44	0.9
IQR of mean current age	34,55	34,55	
Mean duration of SLE	8.69		
Ethnic group			0.42
White	42	41	
Spanish American	80	74	
Black	1	5	
Asian	1	3	
Other	1	2	
Family history of SLE			< 0.001
Positive	33	2	
Negative	92	123	
Education			0.22
Never completed high school	27	39	
Completed high school	51	46	
College or college graduate	47	40	
Income (US dollars)*			0.42
< 25,000	77	79	
25–50,000	31	25	
50–100,000	8	15	
> 100,000	5	4	

* 4 cases and 2 controls refused to answer this question. IQR: interquartile range.

Table 2. Distribution of cigarette smoking and alcohol consumption of SLE cases and controls.

	Cases	Controls	p**
Smoking status*			
Never smoker (%)	48 (38.4)	85 (68)	< 0.001
Ex-smoker (%)	25 (20)	16 (12.8)	
Current (%)	52 (41.6)	24 (19.2)	
No. of drinks/week***			
0 (%)	93 (74.4)	105 (84)	0.08
1–2 (%)	25 (20)	11 (8.8)	
3–5 (%)	5 (4)	6 (4.8)	
> 6 (%)	2 (1.6)	3 (2.4)	

* Smoking status refers to the period prior to the diagnosis of SLE. ** Analysis by Fisher's exact test. *** Based on the average number of drinks over the past year.

Table 3. Odds ratios (OR) of SLE for smoking status.

	OR**	95% CI	p
Smoking status*			
Never (%)	1.00	Not applicable	Not applicable
Ex-smoker	3.62	1.22, 10.70	0.02
Current smoker	6.69	2.59, 17.28	< 0.001

* Smoking status refers to the period prior to the diagnosis of SLE.
** Adjusted for family history and education.

alter the effect of smoking on SLE. Dichotomizing the pack-year variable according to whether a subject had smoked at least 10 pack-years or not (restricting the analysis to current and ex-smokers) showed there was no significant difference among pack-years smoked and SLE (OR 1.05, 95% CI 0.33, 3.31, p = 0.93). There were no significant associations (positive or negative) between alcohol consumption and SLE (OR 0.7, p > 0.5), and no significant interactions between alcohol consumption and smoking on SLE (p > 0.5).

DISCUSSION

The results of this study provide further evidence for smoking as an important risk factor for the development SLE, and this is the first study showing an association between SLE and smoking in a predominantly Hispanic group. The results show that both current and ex-smokers before the diagnosis of SLE are at higher risk of developing SLE compared to never smokers. Nagata, *et al*, using a different patient population, also found that current cigarette smokers had a significantly increased risk of SLE (OR 2.31, 95% CI 1.34–3.97)[16]. The same study found that current smokers who smoked more than 20 pack-years had a significantly increased risk of SLE (OR 4.17, 95% CI 1.09–16.03). Hardy, *et al* also found that current smokers had a significantly increased risk of SLE (OR 1.95, 95% CI 1.14–3.31)[17]. McAlindon, *et al* in the Black Women's Health Study showed that both current and prior smoking were associated with SLE (OR 1.5, 95% CI 1.0–2.1)[18]. Many other epidemiological studies have found a positive association between smoking and other autoimmune conditions[23-31]. For example, cigarette smoking has been associated with rheumatoid arthritis, autoantibodies, Raynaud's phenomenon, Goodpasture's syndrome, Graves' disease, and severity of autoimmune disease[32,33].

It is not surprising that cigarettes might have some effect on autoimmunity, as there are at least 55 chemical factors that affect cell growth or viability in cigarette smoke, including carbon monoxide, cyanide, hydrazine, hydroquinone, and others[34-36]. Certain of these chemicals are metabolized, which generate active species, including free radicals, which then can interact with DNA, cause mutations, activate tumor suppressor genes and oncogenes, and oxidatively damage nuclear constituents[30,35-40]. The individual response to these chemical factors may have a strong genetic association that might contribute to SLE or lupus-like diseases[41-44]. Similarly, cigarette smoke enhances T and B cell polyclonal mitogenesis, expression of monocyte tissue factor, and production of immunomodulatory factors[33,45].

It is also possible that cigarette smoking may act in concert with other environmental triggers, such as infection, to initiate the autoimmune process[13]. Since cigarette smoke has immunosuppressive qualities, cigarette induced immunosuppression might make the host more susceptible to the postulated infectious trigger of SLE[13,43]. However, the mechanisms by which cigarette smoking might enhance autoimmunity are still largely speculative, but may involve not just exposure, but the presence of an underlying predisposing genetic substrate that permits environmental induction of autoimmune processes[46].

Case-control studies, although important epidemiological tools, have the potential for the observed associations to be affected by both systematic error and unsystematic error (random error). The statistics of our study make it very unlikely that the associations reported were a chance finding related to random error. However, systematic error could be introduced by bias associated with selection of patients and controls and measurement of smoking status. Bias associated with selection of patients was minimized by having the diagnosis of SLE confirmed by laboratory confirmation, by careful examination of the patient by a rheumatologist, and by the true cross sectional nature of the study, with very few patients in the SLE cohort refusing to participate.

The SLE group had a much higher prevalence of family history of SLE, consistent with the well known genetic predisposition to this disease. Nonetheless, the association of cigarette smoking remained even when controlling for the effects of family history and education, indicating that the association of cigarette smoking with SLE was a statistically independent effect.

To minimize the potential effects of bias in the selection of controls, we randomly selected controls from the same clinic area, resulting in a cohort that was very similar to the SLE cohort in age, sex, race, education, ethnic composition, and income (Table 1). Increased smoking in the SLE group could not be attributed to differences in any of these demographic factors. The percentage of female current smokers in New Mexico in 1998 was 20.2%, according to the US Department of Health and Human Services, Centers for Disease Control and Prevention[47]. The percentage of current smokers in our control population was 19.6%, thus making it representative of the New Mexico population.

It is also possible that the increased cigarette smoking was a psychoreactive behavior induced by the presence of subclinical disease that existed before the diagnosis of SLE. However, bias induced by psychoreactive use of cigarettes was minimized by defining smoking history before SLE

onset. Psychoreactive use of substances in these populations was also less likely because alcohol use between the 2 groups was similar, and increased use of both alcohol and tobacco might be expected if the change were a psychological reaction to underlying disease. Moreover, there was no association between alcohol use and SLE, which would have been expected if psychoreactive behavior were etiologic.

The experiment design, which employed self-reported data on smoking and alcohol, could potentially be associated with recall bias. The potential of recall bias was reduced, however, because previous and current smoking, stopping, and restarting were specifically investigated and recorded in the interview, and the interviewer was careful to be open, nonthreatening, and nonjudgmental in affect during collection of these data. Since smoking at the time of the interview was not a primary outcome variable, error could only be induced by misrepresentation of previous smoking, which has less basis for secondary gain than current smoking. Moreover, most investigators conclude that for assessment and epidemiological studies, self-reports of smoking status are sufficiently accurate to warrant their use[48,49]. In addition, one study reported that telephone interviews for smoking behavior might lead to a 3–4% underreport of smoking behavior, which would only make the association between smoking and SLE stronger[50].

Recruitment/response rates also were excellent for this study, 91/100% for cases and 95/100% and for controls, indicating that differences in recruitment and response were not likely sources of bias. The issue of temporality was addressed to some extent by the design of this study and the demonstration that both current smokers and past smokers before the diagnosis of SLE were at increased risk for the development of SLE, suggesting a "triggering" phenomenon in the induction of SLE, rather than a continuous induction relationship. A dose-response relationship (intensity and duration, in this case, pack-years of smoking) could not be observed, again suggesting a triggering phenomenon. Although reversibility was not specifically addressed in this study, all patients who had stopped cigarette smoking still had a markedly increased risk of developing SLE, again suggesting a triggering phenomenon. However, since the study design focused on the presence of disease and not on disease activity, reversibility was not fully addressed, although "reversibility" in SLE might have certain limitations related to preconceived concepts of SLE as a chronic, noncurable disease, as well as the definitional criteria used for formal diagnosis of SLE[20,21].

Even allowing for the potential sources of bias discussed above, the data suggest strongly that current and ex–smokers are at a markedly increased risk for developing SLE. When the broader significance of this study is considered, the results suggest that people at increased risk for SLE (usually relatives of patients with SLE) should avoid all contact with tobacco and its products. The present data also indicate that further studies regarding the specific role of tobacco smoke and associated chemical factors in the induction and modulation of autoimmunity are required.

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