Cigarette Smoking and Disease Activity in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective***. To investigate the effect of cigarette smoking on disease activity and cumulative organ damage in systemic lupus erythematosus (SLE).

Methods. Extensive clinical and demographic variables, including current and previous cigarette smoking, were collected from 111 SLE patients using a detailed interview-administered questionnaire. Disease activity was estimated with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Cumulative organ damage was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR). Smoking status was correlated with disease activity and cumulative organ damage, while statistically adjusting for the individual effects of potentially confounding demographic and clinical variables using analysis of variance followed by Fisher's least significant difference method.

Results. Current smokers demonstrated significantly higher ($p < 0.001$) SLEDAI scores (15.6 ± 7.8) than ex-smokers (9.63 ± 6.00), and never smokers (9.03 ± 5.75). This association remained significant ($p = 0.001$) after adjusting for all covariates, including ethnicity, education level, income level, alcohol use, age of onset of SLE, current age, mean duration of SLE, marital status, and hydroxychloroquine therapy. Current smokers also demonstrated significantly ($p = 0.003$) higher scores for both the neurological and non-neurological components of SLEDAI. There was no significant difference in the SLICC/ACR scores across the various smoking groups, although there was a trend for more severe disease in current smokers.

Conclusion. Cigarette smoking is associated with increased disease activity in SLE. These data further establish the association of SLE with cigarette smoking, and suggest that individuals with SLE should avoid all exposure to tobacco products. (J Rheumatol 2003;30:1215–21)

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

The temporal variation in disease activity of systemic lupus erythematosus (SLE) may be in part related to endogenous factors, including genetic susceptibility, but clearly environmental and exogenous factors may also play important roles in disease exacerbations[1-6]. Factors that have been associated with increased SLE disease activity include exposure to ultraviolet light, hormonal manipulations, and infections[1-9]. Recently, we and others have demonstrated a significant association between cigarette smoking and the prevalence of SLE[9-16]. If this association were fundamental, one might expect that cigarette smoking would also be associated with increased SLE disease activity.

In this line, various aspects of the relationship between cigarette smoking and SLE activity and outcome have been investigated[3-18]. Ward and Studenski found that smoking was significantly associated with a more rapid development of end-stage renal disease among SLE patients[3]. McAlindon, *et al*, however, demonstrated that smoking did not have a significant effect in predicting glomerulonephritis in SLE[4]. In the Hopkins Lupus Cohort, Petri found that smokers were more likely to develop avascular necrosis, fracture, pulmonary fibrosis, and myocardial infarction[5]. Petri and colleagues also found that smoking was associated with the presence of discoid lupus[11]. Rahman, *et al* found that smoking was associated with a decreased efficacy of antimalarial therapy in cutaneous lupus[12]. Few studies to date, however, have determined the association between cigarette smoking and formal measures of SLE disease activity and cumulative damage[19,20].

Based on our prior study linking cigarette smoking with an increased prevalence of SLE, we hypothesized that if the association between cigarette smoking and SLE were fundamental, that cigarette smoking would be associated not only

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with an increased prevalence of SLE, but also with increased SLE disease activity and injury among active smokers[10]. To address this hypothesis, we determined the relationship of current and past cigarette smoking with SLE disease activity and injury as measured by widely used and extensively validated SLE activity and injury scales[19,20].

MATERIALS AND METHODS

Study population and research design. The study cohort was 125 well-characterized SLE outpatients randomly selected from the University of New Mexico Systemic Lupus Data Base. Exclusion criteria included individuals less than 18 years old, SLE overlap disease, individuals greater than 65 years old, and SLE of less than one year duration. Of the 125 subjects considered for the study, 111 qualified and agreed to participate. The diagnosis of SLE was confirmed in each subject using the American Rheumatism Association's 1982 and American College of Rheumatology 1997 revised criteria[21,22]. A rheumatologist confirmed the diagnosis of SLE after an in-depth face-to-face interview, medical history, physical examination, chart-review, and appropriate laboratory testing. The study design was a cross-sectional investigation of the SLE cohort of 111 subjects using prospective interview to determine exposure status of cigarette smoking. A single interviewer collected all epidemiologic data using an individual interview and a standardized questionnaire form designed to record the following demographic details: cigarette smoking, alcohol consumption, education, income, and potential confounding variables.

Determination of SLE activity and injury. The SLE Disease Activity Index (SLEDAI) was used to estimate SLE disease activity and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR) to estimate SLE-associated injury[19,20]. All SLEDAI and SLICC/ACR scores were obtained by one rheumatologist blinded to the cigarette smoking status of the individual. However, smoking and nicotine have been associated with both an increased prevalence of certain neurologic syndromes, such as headache, stroke, depression, and schizophrenia, any of which might be confused with neuropsychiatric SLE (NPSLE)[22-30]. To minimize the potentially confounding effects of these factors in the analysis, (1) the individual, (2) the strictly neurologic, and (3) the strictly non-neurologic components of each index were separately compiled and analyzed. In this scheme, the individual components of SLEDAI were recorded and analyzed separately. Neuro-SLEDAI was defined as the sum of the neurologic components of the SLEDAI (seizure, psychosis, organic brain syndrome, visual disturbance, cranial neuropathy, lupus headache, stroke syndrome)[19], and Neuro-SLICC was defined by the neurologic components of SLICC/ACRDI (retinal or optic atrophy, cognitive disorder or psychosis, seizures, stroke syndrome, neuropathy, transverse myelitis)[20]. To measure non-neurologic NPSLE activity and non-neurologic NPSLE injury, the non-neurologic components of SLEDAI and SLICC/ACRDI (non-Neuro-SLEDAI and non-Neuro-SLICC, respectively) were employed[19,20]. Since this study was concerned with longterm rather than point-in-time effects on disease activity and injury, 3 scores from each index for each subject were obtained over a period of 6 months (at 0, 3, and 6 months) and averaged to obtain a mean SLEDAI score and mean SLICC score, as well as the corresponding derivative neurologic and non-neurologic scales for each individual. These mean activity and injury scores were then used for subsequent analyses.

Characterization of cigarette smoking and alcohol use. The study population was classified into 3 smoking status groups: (1) never smoker, (2) ex-smoker (defined by no smoking for one year prior to the interview date), (3) current smoker (as defined as in prior studies by smoking at least one cigarette a month for at least 3 consecutive months prior to the interview date). 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, packs per day over the last year, and age of quitting or stopping/restarting where applicable. Alcohol consumption (average drinks per week defined as a 12 ounce beer, a glass of wine, or 4 ounces of liquor) over the past year was also recorded. 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. Data were entered into Excel (Version 5, Microsoft, Seattle, WA, USA), and analyzed in SAS (SAS/STAT Software, Release 6.11, Cary, NC, USA)[31]. Analysis of variance followed by Fisher least significant method was used to compare the mean SLEDAI and the SLICC/ACR Damage Index scores among the 3 smoking groups. The same methods were used to compare the mean Non-Neuro-SLEDAI and Neuro-SLEDAI scores among the 3 smoking groups. Associations between smoking and SLE were adjusted for the following covariates: ethnicity, education, income level, alcohol use, age of onset of SLE, mean duration of SLE, and current marital status.

RESULTS

Characteristics of the patients are shown in Table 1. The mean age ± standard deviation of the 3 groups was 41 ± 13 (current smokers), 50 ± 15 (ex-smokers), and 40 ± 13 (never smokers). The mean duration ± standard deviation of SLE was 7.49 ± 6.21 (current smokers), 8.94 ± 8.40 (ex-smokers), and 8.50 ± 9.38 (never smokers). Ninety-five (95%) were female. A Hispanic population made up 69% of the current smokers, 64% of the ex-smokers, and 58% of the never smokers. All current smokers smoked at least 0.25 packs per day for at least one year. The mean SLEDAI scores among the 3 different smoking groups are seen in Table 2. The mean SLEDAI ± standard deviation for current smokers (15.63 ± 7.78) was significantly higher ($p < 0.001$) than the ex-smokers (9.64 ± 5.99) and non-smokers (9.03 ±

Table 1. Demographics of study group (n = 111)

	Cigarette Smoking Status		
	Current	Ex-	Never
Total subjects, n	35	36	40
Women	33	35	38
Men	2	1	2
Mean current age (yrs)	41	50	40
Mean age at SLE diagnosis	33	41	31
Mean duration of SLE	7.49	8.94	8.50
Ethnic group			
White	11	13	15
Hispanic	24	23	23
Other	0	0	2
Past education			
Never completed high school	13	6	3
Completed HS	14	18	14
College or college graduate	8	12	23
Past income (US dollars)*			
< 25,000	30	19	16
25–50,000	3	10	16
> 50,000	2	6	5
Marital status			
Never married	12	3	8
Married/living with someone	14	22	22
Divorced/widowed/separated	9	11	10

* 4 patients refused to answer this question

Table 2. Distribution of mean SLEDAI values.

Smoking Status	Mean SLEDAI	SD	SE	p value
Current	15.63	7.78	1.32	< 0.001
Ex-	9.64	5.99	1.00	0
Never	9.03	5.75	0.91	0
Adjusted p values				
Ethnicity				< 0.001
Education				< 0.001
High school grades				< 0.001
Education level				= 0.001
Income level				< 0.001
Alcohol use				< 0.001
Mean duration of SLE				< 0.001
Marital status				< 0.001
Hydroxychloroquine use				< 0.001

5.75). This association remained significant (all p = 0.001) after adjusting for each of the following covariates: ethnicity, education level, high school grades, income level, alcohol use, age of onset of SLE, current age, mean duration of SLE, current marital status, and the use of hydroxychloroquine.

In response to the observed disease activity changes in the smokers versus non-smokers described above, the "dose-response" was determined using a (1) a linear regression analysis based on packs per day × years of smoking (pack-years), and (2) a linear regression analysis based on current packs per day over the last year. Both demonstrated a progressive effect of cigarette smoking intensity, that is a significant association of higher SLEDAI scores with an increasing total number of pack-years smoked (p = 0.003) and an increasing number of packs smoked over the past year (p = 0.03). When exploratory box plots and categorical analyses were used, the same essential dose response was obtained, demonstrating a progressive increase in disease activity with increasing intensity of cigarette smoking.

Individual components of SLEDAI for the respective smoking groups are shown in Table 3. As can be seen, the frequency of individual SLEDAI components are generally greater in the smoking cohort, but reach statistical significance in only 2 domains: (1) headache and (2) vasculitis. This indicated that certain manifestations, especially the neurologic components of SLEDAI, might be having a disproportionate effect on the total SLEDAI score.

To address this possibility, the SLEDAI was divided into neurologic and non-neurologic components (Neuro-SLEDAI and Non-Neuro-SLEDAI, respectively). In this analysis, current smokers had significantly (p = 0.003) higher scores of both neurological and non-neurologic SLE activity than did ex-smokers and never smokers (see Table 4). The mean Non-Neuro-SLEDAI ± standard deviation for current smokers was 9.29 ± 4.88, and 7.14 ± 3.55 and 6.08 ± 3.41 for ex-smokers and never smokers, respectively. The mean Neuro-SLEDAI ± standard deviation for current smokers was 6.40 ± 5.97, and 2.75 ± 4.55 and 2.98 ± 4.29 for ex- and current smokers, respectively. The association remained significant (p = 0.03) after adjusting for the variables above.

To address the possibility that headache in particular might be skewing the results to greater disease activity, headaches were omitted from the SLEDAI analysis. However, even with headaches omitted, the mean SLEDAI score ± standard deviation for current smokers (12.29 ± 7.31) was higher (p = 0.03) than the ex- smokers (9.02 ± 5.80) and non-smokers (8.60 ± 5.56). Thus, even when the

Table 3. Frequency of individual SLEDAI items.

Manifestation	Current Smoker %	Ex and Never Smokers %	p
Seizure	9	5	0.67
Psychosis	6	4	0.65
Organic brain syndrome	20	16	0.60
Visual disturbance	3	0	0.32
Cranial nerve disorder	0	0	1.00
Lupus headache	50	25	0.02
CVA	0	0	1.00
Vasculitis	17	1	0.004
Arthritis	80	62	0.08
Myositis	0	0	1.00
Urinary casts	0	4	1.00
Hematuria	0	3	0.52
Proteinuria	11	8	0.72
Pyuria	0	0	1.00
New rash	40	34	0.67
Alopecia	14	9	0.51
Muscosal ulcers	46	43	0.84
Pleurisy	49	38	0.31
Pericarditis	0	1	1.00
Low complement	31	34	0.83
Increased DNA	17	9	0.34
Thrombocytopenia	11	11	1.00
Leukopenia	20	17	0.79
Fever	3	2	1.00

CVA: cerebrovascular accident

Table 4. Distribution of mean SLEDAI values.

	Non-neurological Mean SLEDAI	SD	SE	p
Smoking status				
Current	9.29	4.88	0.82	0.003
Ex-	7.14	3.55	0.59	
Never	6.08	3.41	0.54	
	Neurological			
Smoking status				
Current	6.40	5.97	1.01	0.003
Ex-	2.75	4.55	0.76	
Never	2.98	4.29	0.68	

neurological components of SLEDAI and headache in particular were excluded from the analysis, SLEDAI was increased in smokers.

The SLICC/ACRDI did not significantly differ between the 3 smoking groups (Table 5, p = NS). However, there was a trend for more damage in smokers as follows: the mean scores ± standard deviation of the SLICC/ACR Damage Index were 4.34 ± 2.41, 3.89 ± 2.68, and 3.60 ± 2.85 for current, ex-, and never smoker, respectively.

DISCUSSION

In our study of 111 subjects followed in a university rheumatology clinic, current smoking was shown to be associated with significantly increased disease activity as measured by the SLEDAI compared to ex-smoking and never smoking. A number of studies have examined different associations between smoking and SLE activity and outcome[3,4,18]. Ward and Studenski found that smoking was significantly associated with a more rapid development of end stage renal disease (ESRD) among SLE patients[3]. In their retrospective cohort study, the median time to ESRD among smokers was 145 months and among non-smokers it was greater than 273 months. However, McAlindon, *et al* found no significant effect of smoking on predicting glomerulonephritis in their cross-sectional survey, and Petri also did not find any association of smoking with either renal insufficiency or renal failure[4,18]. In the Hopkins Lupus Cohort, smoking was a risk factor for discoid lupus, leg ulcers, and pulmonary hypertension[11]. They also found that smokers were more likely to develop avascular necrosis, fracture, pulmonary fibrosis, and myocardial infarction, all indications of greater injury[5]. A retrospective cohort study from the University of Toronto Lupus Clinic showed that smoking appears to decrease the efficacy of antimalarial therapy in cutaneous lupus[12].

Other epidemiological studies have found a positive association between smoking and other autoimmune conditions[32-40]. For example, cigarette smoking has been associated with rheumatoid arthritis, autoantibodies, Raynaud's phenomenon, Goodpasture's syndrome, Graves's disease, and severity of autoimmune disease[41,42].

It is not surprising that cigarettes might have an effect on the disease activity of SLE, as there are multiple chemical factors that affect cell growth or viability in cigarette smoke, including carbon monoxide, cyanide, hydrazine, hydroquinone, and others[43-45]. When certain of these chemicals are metabolized, they generate active species, including free radicals, which then can interact with DNA, induce mutations, activate tumor suppressor genes and oncogenes, and oxidatively damage nuclear constituents[39,44-49]. The individual response to these chemical factors may have a strong genetic association, which might contribute to SLE or lupus-like diseases[50-53]. Similarly, cigarette smoke enhances T and B cell polyclonal mitogenesis, expression of monocyte tissue factor, and production of immunomodulatory factors[42,54]. Smoking also facilitates platelet formation of thrombaxane A_2 and increases fibrinogen levels, which may enhance endothelial dysfunction[55]. Smoking is also associated with decreased nitric oxide activity, and nitric oxide is believed to play a central role in protecting against vascular disease[56].

A very interesting and potentially important pathogenic mechanism for inducing both SLE and increased SLE disease activity in a SLE-susceptible individual is the production of chemically altered DNA by reactive elements in cigarette smoke, and subsequently the well-recognized production of autoantibodies specifically against altered DNA in cigarette smokers[57-59]. Cigarette smoke contains many organic compounds including benzopyrene and related compounds, which are then converted by the cytochrome P-450 monooxygenase systems into highly reactive metabolites that combine with exposed DNA creating the highly antigenic benzo[a]pyrene diolepoxide-DNA adduct and related compounds[57,59]. Specific circulating autoantibodies are created to this benzo[a]pyrene diolepoxide-DNA adduct, and can be measured in cigarette smokers without SLE[59]. However, females produce considerably more of these anti-benzo[a]pyrene diolepoxide-DNA adduct antibodies than do males despite the males smoking a greater number of cigarettes[58]. The effect of benzo[a]pyrene diolepoxide-DNA adduct and related DNA-cigarette smoke metabolite compounds on the immune system of an individual genetically susceptible to SLE is unknown, but highly antigenic chemically altered DNA and similar compounds consisting of other nuclear and cytoplasmic antigens could in part explain the associations between cigarette smoking and increased prevalence and activity of SLE[1-10].

In our study, current smokers, but not ex-smokers, demonstrated increased SLE disease activity (SLEDAI scores) that was not restricted to either neurologic or non-neurologic manifestations, suggesting a generalized increase in SLE activity. This is important because cigarette smoking has been associated with changes in the prevalence of neuropsychiatric disorders in non-SLE populations, and these types of changes could confound the effects of cigarettes on primary SLE activity[23-30]. The fact that non-neurologic as well as neurologic SLE disease activity was increased with cigarette smoking and that alcohol use was not different between the populations suggests that

Table 5. Distribution of SLICC-ACR Damage Index scores.

	Mean SLICC-ACR	SD	SE	p
Smoking status				
Current	4.34	2.41	0.41	NS
Ex-	3.89	2.68	0.45	
Never	3.60	2.85	0.45	

psychoreactive use of cigarettes was not a major source of bias in this study[10]. It is possible that inclusion of headache could induce a random or non-random bias, as headaches can occur spontaneously and from other causes. However, current smokers with headaches compared to those smokers with no headaches had an increased frequency of the following: (1) organic brain syndrome (29 vs 11%), (2) new rash (53% vs 28%), (3) mucosal ulcers (59% vs 33%), (4) pleurisy (59 vs 39%), and (5) increased DNA (24 vs 11%). Due to the small sample size in each, none of the values were statistically significant by Fishers exact test, however, these data do suggest headaches were accompanied by other signs of flare. In addition, the mean SLEDAI values for current smokers were higher than they were for ex- and never smokers, even after omitting headache from analysis. Thus, the inclusion of headache in the SLEDAI did not skew the present results.

Current smokers did have a higher SLICC-ACR Damage Index score (mean 4.34 ± 2.41) than ex-smokers (3.89 ± 2.68) and never smokers (3.60 ± 2.85), although these differences were not significant at the $p = 0.05$ level. One would expect greater organ damage with great disease activity, especially when viewed longterm. These results suggest that the effects of cigarette smoking on SLICC/ACR damage scores may require longer periods of observation to demonstrate statistical changes, although certainly a trend is present.

As with all cross-sectional investigations, our study has certain limitations and potentials for bias. We cannot be certain of the causal relationship between cigarette smoking and increased SLE activity because the study was a purely cross-sectional epidemiological study. Moreover, cigarette smoking was not introduced prospectively and in a randomized fashion into the SLE population, which although very interesting scientifically, would be highly unethical. However, obvious sources of bias associated with selection of subjects were minimized by (1) prospectively rather than retrospectively acquiring the data, (2) randomly selecting the subjects from a well-characterized SLE cohort, (3) not using self-reporting of the diagnosis of SLE, but rather by having the diagnosis of SLE confirmed by laboratory testing and careful examination of the subject by a rheumatologist, (4) the smoking status and SLEDAI- SLICC/ACRDI scores being determined independently by independent observers (interviewer and rheumatologist, respectively), and (5) the true cross-sectional nature of the study with very few patients in the SLE cohort refusing to participate.

Recruitment/response rates were excellent for this study, with 91% both qualifying for the study and agreeing to participate. Analysis of the demographics of those who did not participate reflected the cigarette smoking proportion reported in the study, indicating that selection bias by exclusion was not a cause for the results.

The experimental design, which employed self-reported data on smoking, could potentially be associated with recall and social expectation bias. The potential of bias was reduced, however, because previous and current smoking, stopping, and restarting were specifically asked and recorded in the interview, and the interviewer was very careful to be open, non-threatening, and non-judgmental during collection of this data. Bias induced by underreporting of cigarette smoking at the time of the interview was minimized by the study design in which subjects were not specifically aware of the immediate study purpose (as they had previously given broad informed consent for the longterm SLE outcome database including multiple interviews and broad demographic factors, including cigarette smoking). These individuals were interviewed multiple times for different reasons, but all under the broadly based informed consent, so that this arm of the study was not specifically identified as a "cigarette smoking" study, thus further reducing recall bias. Moreover, most investigators conclude that for assessment and epidemiological studies, self-reports of smoking status are sufficiently accurate to warrant their use[60-62].

The SLEDAI and the SLICC/ACR are validated tools used to assess disease activity and cumulative organ damage with smoking status and other demographic variables[19,20,62]. Bias was minimized by using a single experienced rheumatologist blinded to cigarette smoking status who prospectively calculated all SLEDAI and SLICC/ACR scores after a detailed history, physical examination, and laboratory testing, and not by retrospective review of notes or charts. The derivative measures, the Neuro-SLEDAI, Non-Neuro-SLEDAI, and the corresponding components of the SLICC/ACRDI, demonstrated that the increases in disease activity were not solely due to an increase in neurologic or psychiatric symptoms (which could be confused with the primary effects of nicotine or psychoreactive behavior), as SLE disease activity as manifested in non-brain organ systems was also similarly increased.

However, even allowing for the potential sources of bias discussed above, the data suggest strongly that current smoking is associated with a higher disease activity as measured by the SLEDAI. This study gives yet another possible reason for SLE patients to avoid all contact with tobacco and its products, that is, possibly preventing greater disease activity and poorer outcome. 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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REFERENCES.

1. Pisetsky DS. Systemic lupus erythematosus: epidemiology, pathology, and pathogenesis. In: Klippel JH, editor. Primer on the

rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997:246-50.
2. Davis P, Percy JS. Effect of ultraviolet light on disease characteristics of NZB/W mice. J Rheumatol 1978;5:125-8.
3. Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis. Arch Intern Med 1992;152:2082-8.
4. McAlindon T, Giannotta, Taub N, D'Cruz D, Hughes G. Environmental factors predicting the nephritis in SLE. Ann Rheum Dis 1993;52:720-4.
5. Petri M. Smoking is a risk factor for musculoskeletal, pulmonary, and cardiac disease in SLE [abstract]. Arthritis Rheum 1997;40 Suppl:S118.
6. Collins RL, Turner RA, Nomeir AM, et al. Cardiopulmonary manifestations of systemic lupus erythematosus. J Rheumatol 1978;5:299-306.
7. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest 1997;15;100:3019-26.
8. Tebbe B, Orfanos CE. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus 1997;6:96-104.
9. Strom BL, Reidenberg MM, West S, Snyder ES, Freundlich B, Stolley PD. Shingles, allergies, family medical history, oral contraceptives, and other potential risk factors for systemic lupus erythematosus. Am J Epidemiol 1994;140:632-42.
10. Ghaussy NO, Sibbitt WL Jr, Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: a case-control study. J Rheumatol 2001;28:2449-53.
11. Brown K, Petri M, Goldman D. Cutaneous manifestations of SLE: Associations with other manifestations of SLE and with smoking [abstract]. Arthritis Rheum 1995;38 Suppl:R27.
12. Rahman P, Gladmann DD, Urowitz MB. Smoking interferes with efficacy of antimalarial therapy in cutaneous lupus. J Rheumatol 1998;25;25:1716-9.
13. Nagata C, Fujita S, Iwata H, et al. SLE: A case controlled epidemiological study in Japan. Int J Dermatol 1995;34:333-7.
14. Hardy CJ, Palmer BP, Muir KR, Sutton AJ, Powell RJ. Smoking history, alcohol consumption, and systemic lupus erythematosus: a case controlled study. Ann Rheum Dis 1998;57:451-5.
15. Benoni A, Nilsson A, Nived O. Smoking and inflammatory bowel disease: Comparison with systemic lupus erythematosus: A case control study. Scand J Gastroenterol 1990;25:751-5.
16. McAlindon T, Felson D, Palmer J, Zheng L, Rosenberg L. Associations of cigarette smoking and alcohol with systemic lupus erythematosus among participants in the Black Women's Health Study [abstract]. Arthritis Rheum 1997;40 Suppl:S162.
17. Reidenberg MM, Drayer DE, Lorenzo B, et al. Acetylation phenotypes and environmental chemical exposure of people with idiopathic systemic lupus erythematosus. Arthritis Rheum 1993;36:971-3.
18. Petri M. Hopkins Lupus Cohort 1999 Update. Rheum Dis Clin N Am 2000;26:199-213.
19. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prongnosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
20. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. Arthritis Rheum 1996;39:363-9.
21. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
22. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725-34.
23. Sacco RL. Newer risk factors for stroke. Neurology 2001;57 Supp l2:S31-4.
24. Herbert M, Foulds J, Fife-Schaw C. No effect of cigarette smoking on attention or mood in non-deprived smokers. Addiction 2001;96:1349-56.
25. Gonzalez-Pinto A, Gutierrez M, Ezcurra J, et al. Tobacco smoking and bipolar disorder. J Clin Psychiatry 1998;59:225-8.
26. Torelli P, Manzoni GC. What predicts evolution from episodic to chronic cluster headache? Curr Pain Headache Rep 2002;6:65-70.
27. Koren G. The association between maternal cigarette smoking and psychiatric diseases or criminal outcome in the offspring: a precautionary note about the assumption of causation. Reprod Toxicol 1999;13:345-6.
28. Cirillo M, Stellato D, Lombardi C, De Santo NG, Covelli V. Headache and cardiovascular risk factors: positive association with hypertension. Headache 1999 Jun;39:409-16.
29. Patten CA, Gillin JC, Golshan S, Wolter TD, Rapaport M, Kelsoe J. Relationship of mood disturbance to cigarette smoking status among 252 patients with a current mood disorder. J Clin Psychiatry 2001;62:319-24.
30. Dalack GW, Becks L, Hill E, Pomerleau OF, Meador-Woodruff JH. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology 1999;21:195-202.
31. SAS Institute Inc. SAS/STAT Software: Changes and enhancements through Release 6.11, Cary, NC: SAS Institute Inc.; 1996.
32. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and risk of rheumatoid arthritis. J Rheumatol 1999;26:1:47-54.
33. Voight LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994;5:525-32.
34. Heliovaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. J Rheumatol 1993;20:1830-5.
35. Hazes JMW, Dijkmans BAC, Vandenbroucke JP, P de Vries RR, Cats P. Lifestyle and the risk of rheumatoid arthritis cigarette smoking and alcohol consumption. Ann Rheum Dis 1990;49:980-2.
36. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis Rheum 1999;42:910-7.
37. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56:463-9.
38. Hernandez Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology 1990;1:285-91.
39. Finette BA, O'Neill JP, Vacek PM, Albertini RJ. Gene mutations with characteristic deletions in cord blood T lymphocyte associated with passive maternal exposure to tobacco smoke. Nat Med 1998;4:1144-51.
40. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996;39:732-5.
41. Wallace DJ. Principles of therapy and local measures. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 5th ed. Baltimore: William and Wilkins; 1997:1101.
42. George J, Levy Y, Shoenfeld Y. Smoking and immunity: an additional player in the mosaic of autoimmunity. Scand J Immunol 1997;45:1-6.
43. Mongey AB, Hess EV. The role of environment in SLE and associated disorders. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 5th ed. Baltimore: Williams and Wilkins; 1997:31-2.
44. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl

Cancer Inst 1999;91:1194-210.
45. Pyatt DW, Stillman WS, Irons RD. Hydroquinone, a reactive metabolite of benzene, inhibits NF-kappa B in primary human CD4+ T lymphocytes. Toxicol Appl Pharmacol 1998;149:178-84.
46. McKinnon RA, Nebert DW. Possible role of cytochromes P450 in lupus erythematosus and related disorders. Lupus 1994;3:473-8.
47. Yang Q, Hergenhahn M, Bartsch H. Epstein-Barr virus episomes as targets for cigarette smoke- and gamma-irradiation-induced DNA damage: studies on the EBNA-1 region by a new gene-specific technique. Carcinogenesis 1997;18:1401-5.
48. Muller T. Expression of c-fos in quiescent Swiss 3T3 cells exposed to aqueous cigarette smoke fractions. Cancer Res 1995;55:1927-32.
49. Suzuki N, Wakisaka S, Takeba Y, Mihara S, Sakane T. Effects of cigarette smoking on Fas/Fas ligand expression of human lymphocytes. Cell Immunol 1999;192:48-53.
50. Hirvonen A. Genetic factors in individual responses to environmental exposures. J Occup Environ Med 1995;37:37-43.
51. Reidenberg MM, Durant PJ, Harris RA, De Boccardo G, Lahita R, Stenzel KH. Lupus erythematosus-like disease due to hydrazine. Am J Med 1983;75:365-9.
52. Spector TD, Blake DR. Effect of cigarette smoking on Langerhans' cells. Lancet 1988;2:1028-9.
53. Scofield RH, James J. Immunization as a model for systemic lupus erythematosus. Arthritis Rheum 1999;29:140-7.
54. Holschermann H, Terhalle HM, Zakel U, et al. Monocyte tissue factor expression is enhanced in women who smoke and use oral contraceptives. Thromb Haemost 1999;82:1614-20.
55. Kaufman LD, Varje J. Cigarette smoking and other acquired risk factors for rheumatoid arthritis. In: Rheumatic diseases and the environment. London: Oxford University Press; 1999:111-29.
56. Klesges RC, Debon M, Ray JW. Are self-reports of smoking rate biased? Evidence from the Second National Health and Nutrition Examination Survey. J Clin Epidemiol 1995;48:1225-33.
57. Kim SY, Chung JH, Kang KW, Joe CO, Park KH. Relationship between activities of cytochrome P-450 monooxygenases in human placental microsomes and binding of benzo(a)pyrene metabolites to calf thymus DNA. Drug Chem Toxicol 1992;15:313-27.
58. Mooney LA, Perera FP, Van Bennekum AM, et al. Gender differences in autoantibodies to oxidative DNA base damage in cigarette smokers. Cancer Epidemiol Biomarkers Prev 2001;10:641-8.
59. Pulera N, Petruzzelli S, Celi A, et al. Presence and persistence of serum anti-benzo[a]pyrene diolepoxide-DNA adduct antibodies in smokers: effects of smoking reduction and cessation. Int J Cancer 1997;70:145-9.
60. Petitti DB, Friedman GD, Kahn W. Accuracy of information on smoking habits provided on self-administered research questionnaires. Am J Public Health 1981;71:308-11.
61. Luepker RV, Pallonen UE, Murray DM, Pirie PL. Validity of telephone surveys in assessing cigarette smoking in young adults. Am J Public Health 1989;79:202-4.
62. Gladman DD, Goldsmith CH, Urowitz MB, et al. Sensitivity to change of 3 systemic lupus erythematosus disease activity indices: international validation. J Rheumatol 1994;21:8:1468-71.