Smoking, Alcohol Consumption, and Risk of Systemic Lupus Erythematosus in the Black Women's Health Study

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ABSTRACT. ***Objective.*** Several case-control studies, mostly of prevalent disease, have suggested that systemic lupus erythematosus (SLE) is positively associated with cigarette smoking and inversely associated with alcohol consumption. We prospectively investigated the associations of smoking and alcohol consumption with incident SLE in the Black Women's Health Study (BWHS).

Methods. In 1995, 64,500 African-American women provided information on demographic characteristics, reproductive and medical histories, smoking, and alcohol consumption. Followup questionnaires in 1997 and 1999 ascertained incident cases of SLE. Cox proportional hazards regression was used to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results. Sixty-seven women reported a new diagnosis of SLE and use of appropriate medication for that illness. In multivariate analyses, the IRR for current and past smoking were 1.6 (both 95% CI 0.8–3.3). The risk was greater for women who began smoking before age 19 years (IRR 1.9, 95% CI 1.0–3.6). Neither current alcohol consumption (IRR 1.0, 95% CI 0.4–2.4) nor past alcohol consumption (IRR 0.9, 95% CI 0.3–2.7) was associated with SLE.

Conclusion. Our results suggest an increased risk of SLE among smokers, but no effect of alcohol consumption on risk. The inverse association of alcohol consumption with SLE found in studies of prevalent disease may have resulted from women with SLE giving up drinking. (J Rheumatol 2003;30:1222–6)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS SMOKING ALCOHOL EPIDEMIOLOGY LUPUS

Systemic lupus erythematosus (SLE) is a serious, chronic autoimmune disease that can affect multiple organ systems, resulting in considerable disability, and even death. SLE occurs more commonly among Black women than other demographic groups and may also be more severe. Black women with SLE are more likely to have central nervous system involvement and are 3 times more likely to die than affected White women[1].

Given the high prevalence and severe consequences of SLE in Black women, it is important to identify risk factors for SLE in this group, particularly modifiable risk factors. Several case-control studies, mostly of prevalent disease, have suggested that SLE is associated positively with cigarette smoking[2-6] and inversely with alcohol consumption[2,3,6]. These associations have yet to be studied prospectively, or among Black women.

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We prospectively investigated the associations of smoking and alcohol consumption with incident SLE in the Black Women's Health Study (BWHS), a followup study of African-American women.

MATERIALS AND METHODS

Study population and data collection. The BWHS is a followup study of 64,500 African-American women throughout the United States which began in 1995. Most women were recruited through mailings to subscribers to Essence magazine, a general readership magazine targeted to African-American women. Small numbers were recruited through mailings to members of professional organizations of African-Americans and friends and relatives of early participants[7]. The 1995 baseline questionnaire elicited information on demographic characteristics, reproductive and medical histories (including SLE), and lifestyle characteristics such as cigarette smoking and alcohol consumption. Followup questionnaires were mailed biennially to obtain information on disease occurrence and on selected exposures. The 1997 and 1999 followup questionnaires were completed by 53,322 (83%) and 51,279 (80%) participants, respectively. Our study is based on those women who responded to either the 1997 or 1999 followup questionnaire (n = 57,613).

Information on age, marital status, years of education, history of oral contraceptive use, height, and weight was obtained with the 1995 baseline questionnaire. We calculated body mass index (BMI) by dividing weight in kilograms by height in meters squared. We also obtained information on history of cigarette smoking and alcohol consumption with the 1995 baseline questionnaire. Participants were asked if they had ever smoked one cigarette or more every day for at least one year, with response categories of current smoker, past smoker, and never smoker. Smokers were asked the age they started smoking regularly, the amount they smoked in the past few years, and their duration of smoking, with categorical responses. We calcu-

lated pack-years of smoking by multiplying the midpoint of the amount-smoked category by the midpoint of the duration of smoking category and dividing by 20. For example, a participant who reported smoking 25–34 (midpoint = 29.5) cigarettes per day for 15–19 (midpoint = 17) years would generate 25.1 pack-years of smoking. Participants were asked if they ever drank alcoholic beverages at least once per week for at least one year, with response categories of current drinker, past drinker, and never drinker. Information on age started drinking, duration of drinking, and number of drinks per week of beer, wine, and liquor in the past year was collected, with categorical responses. We calculated total number of drinks per week in the past year by using the midpoint of each category (< 1, 1–3, 4–6, 7–13, 14–20, ≥ 21 drinks/week) and summing over the 3 beverages, beer, wine, and liquor. For example, a participant who reported drinking no beer, 1–3 glasses of wine (midpoint = 2), and 4–6 shots of liquor (midpoint = 5) would generate 7 drinks per week.

Information on passive smoking in childhood was obtained with the 1997 followup questionnaire. Participants were asked if they were ever in the same room with a smoker for at least 1 hour a day for at least 12 consecutive months at different age ranges, including 0–10 years and 11–20 years.

Case definition. We identified women who developed incident SLE subsequent to the baseline questionnaire based on self-reported information, followed where possible by review of medical records. Women were asked in both the 1997 and 1999 followup questionnaires whether they had been diagnosed with SLE by a physician within the previous 2 years. The women were also asked to list any medications they were currently taking at least 3 times per week. Appropriate medication for SLE was considered to be use of steroids, corticosteroids, cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, hydroxychloroquine, chloroquine, mepacrine, azathioprine, cyclophosphamide, or methotrexate *and* no reported use of gold, sulfasalazine, or penicillamine.

We requested consent to obtain medical records and/or a physician criteria-checklist from the women who reported a diagnosis of SLE subsequent to baseline and reported appropriate medication use. The physician criteria-checklist consisted of a table of the updated American College of Rheumatology (ACR) criteria for SLE[8,9] with columns in which to indicate which of these criteria had been observed, and the years in which they first occurred. Participants who did not respond to the request to release medical records after 2 reminder letters were sent a third reminder letter requesting consent for only the physician criteria-checklist. Identifying information was removed from the medical records prior to chart review. Two rheumatologists independently reviewed the medical records and checklists for ACR criteria for SLE[8,9] and for year of diagnosis. Reviews discordant on number of ACR criteria were evaluated by consensus for a final decision. The case group for analyses comprised all women who reported a new diagnosis of SLE and appropriate medication use in the 1997 or 1999 followup questionnaire. We also assessed a subgroup, "confirmed" cases. Studies excluding SLE cases with < 4 criteria may bias against patients early in disease progression and certain subsets of SLE patients[10]. Therefore, confirmed SLE cases were the subset for whom medical record review or physician criteria-checklists documented at least 3 ACR criteria for SLE.

Statistical analyses. Because of the rarity of SLE at older ages, we excluded women aged 60 or older at baseline (n = 3030). We also excluded women who reported a diagnosis of SLE at baseline (n = 659). The remaining 53,924 subjects contributed 204,197 years of followup. Cox proportional hazards regression models stratified by 5-year age group were used to estimate the hazard rate ratio (i.e., the incidence rate ratio, IRR) and 95% confidence interval (CI). The followup was from age at enrollment in the BWHS to age at last followup or age at SLE diagnosis. All analyses were adjusted for age (5-year age categories), years of education (≥ 16, 13–15, ≤ 12), oral contraceptive use in years (< 1, 1–4, 5–9, ≥ 10), and BMI (≤ 19, 20–24, 25–29, ≥ 30). All smoking analyses were adjusted for alcohol use, and all alcohol analyses were adjusted for smoking.

RESULTS

Sixty-seven women reported a new diagnosis of SLE and use of appropriate medication. Forty-seven of the cases provided consent to release medical records; records and/or physician criteria-checklists were obtained for 38. There were 34 women (89%) whose records documented at least 3 ACR criteria for SLE and these made up the confirmed case group. The remaining 4 women all had a diagnosis of SLE and appropriate SLE medication use documented in their medical records or physician criteria-checklists, and their documented ACR criteria for SLE ranged from 0 to 2; they were included in the total case group, but not the confirmed group. Characteristics of the total SLE case group, the subset of confirmed SLE cases, and the total cohort are given in Table 1. At baseline, the total case group and the confirmed cases were similar in age, education, oral contraceptive use, BMI, smoking habits, passive smoking in childhood, and alcohol consumption. Women who went on to develop SLE were slightly younger than the total cohort, had slightly lower BMI, and were more likely to have smoked.

Table 1. Baseline (1995) characteristics of SLE cases in the Black Women's Health Study*.

	Confirmed SLE, n = 34, %	Total SLE Case Group, n = 67, %	Total Cohort, n = 53,924, %
Age, yrs			
< 30	24	25	22.9
30–39	38	39	34.9
40–49	32	31	29.3
50–59	6	4	12.9
Education, yrs			
≥ 16	50	43	45.9
13–15	35	37	36.6
≤ 12	12	18	16.2
Smoking			
Current smoker	18	21	15.9
Past smoker	24	21	18.1
Never smoker	59	58	65.6
Passive smoking in childhood			
Ever	59	58	55.0
Never	32	34	29.5
Alcohol use			
Current drinker	29	31	28.2
Past drinker	12	13	14.1
Never drinker	56	54	56.7
Oral contraceptive use, yrs			
< 1	41	39	41.1
1–4	32	27	27.1
5–9	18	21	19.3
≥ 10	9	13	12.6
Body mass index, kg/m^2			
< 20	15	10	5.7
20–24	35	28	32.7
25–29	29	34	30.6
≥ 30	21	27	29.5

* Percentages may not total 100% because of missing values.

Adjusted IRR and 95% CI for the effect of smoking on SLE are shown in Table 2. The IRR for current and past smokers relative to never-smokers were 1.6 (both 95% CI 0.8–3.3). Analyses of age started smoking indicated a higher risk for those who started at a younger age. Relative to women who never smoked, the IRR was 1.4 (95% CI 0.6–3.0) for women who began smoking at age 19 or older, and 1.9 (95% CI 1.0–3.6) for women who began smoking before age 19. The risk of SLE did not increase with increasing duration of smoking or pack-years of smoking. There was no association between SLE and passive smoking in childhood in the total group (IRR 0.9, 95% CI 0.5–1.7) or among women who had never been active smokers (IRR 0.7, 95% CI 0.3–1.3). Similar associations were seen for all smoking variables in the confirmed group.

Table 3 displays the adjusted IRR and 95% CI of SLE by alcohol consumption. Relative to women who never drank, the IRR was 1.1 (95% CI 0.6–1.9) for current drinkers and 0.9 (95% CI 0.6–1.9) for past drinkers. There was also no association with amount currently consumed or age started drinking. Similar results were found among the group of confirmed SLE cases.

DISCUSSION

In our study, the incidence of SLE was greater among smokers than nonsmokers, but the finding was not statistically significant. There was no difference in risk between current and past smokers. The incidence was not increased for those with greater durations or pack-years of smoking, but risk appeared higher for those who began smoking at a younger age. The incidence of SLE was unrelated to passive smoking during childhood.

Several case-control studies investigating risk factors for SLE found smoking increased the risk of SLE, with OR ranging from 1.8 to 6.7[2-6]. Hardy, *et al* found that risk increased with increasing pack-years of smoking[2], whereas Nagata, *et al* and Bengtsson, *et al* did not find an increase[3,6]. Hardy, *et al* did not find an inverse association with age at which smoking started. However, this finding was based on a comparison of the median age at which smoking began among cases and controls[2], and a difference in the age distributions might have been missed.

The mechanism by which smoking affects the risk of SLE is unknown. Epidemiologic data indicate that the protective effect of estrogen replacement therapy on risk for hip fracture is diminished among smokers[11], suggesting an antiestrogenic effect of smoking[12]. While an antiestrogenic effect of smoking would likely reduce the risk of SLE, smoking has numerous adverse effects on the immune system[13-15], which could increase the risk of SLE.

We found no association between risk of SLE and alcohol consumption, which is consistent with the findings of Ghaussy, *et al*[5]. In contrast, several studies found an inverse association between alcohol consumption and risk of SLE, and Hardy, *et al* and Bengtsson, *et al* also found that risk decreased as amount of alcohol consumed

Table 2. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for SLE in relation to smoking status, age started smoking, duration of smoking, pack-years of smoking, and passive smoking in childhood among Black Women's Health Study participants*.

	Total SLE Case Group			Confirmed SLE		
	n	IRR†	95% CI	n	IRR†	95% CI
Smoking status						
Never smoked (reference)	39	1.0	—	20	1.0	—
Ever smoked	28	1.6	0.9–2.9	14	1.7	0.8–3.9
Past smoker	14	1.6	0.8–3.3	8	1.9	0.8-4.8
Current smoker	14	1.6	0.8–3.3	6	1.5	0.6–4.2
Age started smoking, yrs						
Never smoked (reference)	39	1.0	—	20	1.0	—
≥ 19	9	1.4	0.6–3.0	5	1.5	0.5–4.4
< 19	19	1.9	1.0–3.6	9	2.0	0.8–4.8
Duration of smoking, yrs						
Never smoked (reference)	39	1.0	—	20	1.0	—
< 10	11	2.3	1.1–4.6	5	2.1	0.7–5.6
≥ 10	17	1.5	0.8–2.9	9	1.8	0.7–4.4
Pack years of smoking						
Never smoked (reference)	39	1.0	—	20	1.0	—
< 10	17	1.9	1.0–3.6	9	2.1	0.9–5.0
≥ 10	11	1.6	0.8–3.6	5	1.7	0.6–5.0
Passive smoking in childhood						
Never (reference)	23	1.0	—	11	1.0	—
Ever	39	0.9	0.5–1.7	20	1.1	0.5–2.6
Ever (among never smokers)	18	0.7	0.3–1.3	9	0.7	0.3–1.8

* 5 cases in the total group and 3 confirmed cases are missing information on passive smoking in childhood. † Adjusted for age, education, oral contraceptive use, alcohol consumption, and body mass index.

Table 3. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for SLE in relation to alcohol consumption, age started drinking, duration of drinking, and number of drinks per week among Black Women's Health Study participants*.

	Total SLE Case Group			Confirmed SLE		
	n	IRR†	95% CI	n	IRR†	95% CI
Alcohol consumption						
Never drank (reference)	36	1.0	—	19	1.0	—
Ever drank	30	1.0	0.6–1.8	14	1.0	0.4–2.1
Past drinker	9	0.9	0.4–2.0	4	0.9	0.3–2.7
Current drinker	21	1.1	0.6–1.9	10	1.0	0.4–2.4
Age started drinking, yrs						
Never drank (reference)	36	1.0	—	19	1.0	—
≥ 20	23	1.3	0.7–2.3	10	1.1	0.5–2.5
< 20	7	0.6	0.3–1.5	4	0.7	0.2–2.1
Duration of drinking, yrs						
Never drank (reference)	36	1.0	—	19	1.0	—
< 10	14	1.3	0.7–2.5	8	1.5	0.6–3.6
≥ 10	16	0.8	0.4–1.6	6	0.6	0.2–1.6
Number of drinks/week among current drinkers						
Never drank (reference)	36	1.0	—	19	1.0	—
< 1	2	0.5	0.1–3.6	1	0.9	0.1–6.9
1–6	16	1.3	0.7–2.4	7	1.1	0.4–2.6
≥ 7	3	0.8	0.2–2.6	2	1.0	0.2–4.6

* 1 confirmed case was missing all alcohol consumption information. † Adjusted for age, education, oral contraceptive use, smoking, and body mass index.

increased[2,3,5,6]. However, prevalent cases were used in the Hardy study, and information on current alcohol consumption was assessed[2]. It is possible that some women with SLE quit drinking alcohol upon diagnosis or symptom onset, which would have resulted in an apparent inverse association. This possibility is supported by the results of Nagata, *et al*: in their assessment of recent onset cases, they found that current drinkers had a decreased risk of SLE, but that ex-drinkers were 4.5 times more likely to develop SLE[3]. In the Bengtsson study, incident cases of SLE were used, but the median time from diagnosis to participation in the study was 9 years, which could have resulted in recall bias[6].

This is the first study to investigate risk factors for SLE prospectively, and to be based on incident cases. Prospective assessment eliminates the potential for recall bias, and the use of incident cases reduces the possibility of bias resulting from behavior modification subsequent to disease onset. Our study is also the first assessment of SLE risk factors in Black women.

Bias would be a concern if there had been selective losses during followup, e.g., if nonsmokers who developed SLE were more likely to have been lost to followup than smokers who developed SLE. However, followup rates were high, serving to minimize this type of bias.

As in most followup studies, this cohort was not a random sample of the population. In the BWHS, virtually all women have completed high school (97.5%). Among US Black women of the same ages, about 85% have completed high school[16]. Thus, the results may not be applicable to the 15% of African-American women not represented by the education levels in our study.

While we found a positive association of smoking with SLE, we could not rule out chance as an explanation. Because SLE is a rare disease, most studies rely on prevalent cases or recent onset disease to obtain adequate sample size. As noted, however, the use of prevalent cases can introduce substantial bias. We limited our study to incident cases to reduce bias, but at the expense of statistical power.

Although we found that passive smoking in childhood did not influence the risk of SLE, the information we obtained was crude. More detailed information on passive smoking in childhood, such as amount of exposure and timing of exposure, is needed to sufficiently evaluate this potential risk factor.

Our study relied on self-reported SLE. We required that cases also have reported appropriate SLE medication use, reducing the likelihood that women without SLE were included in our case group. We were only able to confirm 51% of the cases through medical record review, because many cases did not provide consent to release medical information. Among those for whom we obtained medical information, we confirmed at least 3 ACR criteria in 89% of the self-reports, which suggests a high degree of accuracy in the self-reports. We believe that the women who did not provide consent to release medical information most likely did not do so because of confidentiality concerns. Consequently, failure to provide consent would not be associated with SLE diagnosis and would not bias the results. Also, the results in

the subset of confirmed cases were similar to those of the larger total case group, suggesting minimal misclassification, although power was substantially reduced in this smaller group.

We may have missed some cases of SLE by the restriction to women who also reported appropriate medication use. Thus, our results may apply only to the most severe cases of SLE. However, most newly diagnosed cases of SLE are likely to have been taking appropriate medication, so the effect on the results of the small number of cases potentially missed would be minimal.

In summary, in the first prospective study of incident SLE, we found an increased risk of SLE among smokers, but no association with alcohol consumption. Our results confirm findings from case-control studies with respect to smoking, but refute previous results with respect to alcohol consumption, suggesting the importance of studying incident disease.

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