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Relationship of cigarette smoking and alcohol consumption to incidence of systemic lupus erythematosus in the Black Women's Health Study

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Abstract

Objective: Systemic lupus erythematosus (SLE) affects Black women more frequently than other racial-gender groups. In past studies, largely of Whites and Asians, cigarette smoking was associated with increased SLE risk and moderate alcohol consumption with decreased SLE risk. We used data from a long-term, prospective follow-up study to assess associations of smoking and alcohol consumption with risk of incident SLE among Black women.

Methods: The Black Women's Health Study enrolled 59,000 Black women in 1995 and collected data on demographics, health status, and medical and lifestyle variables. Follow-up questionnaires every two years identified incident disease and updated risk factors. We confirmed incident SLE meeting American College of Rheumatology 1997 criteria through medical record review. We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for associations of cigarette smoking and alcohol intake with incidence of SLE.

Results: We confirmed 127 incident SLE cases during 1995–2015 (mean age 43 at diagnosis). Compared to never smokers, the risk of SLE among ever smokers was elevated but not significantly (HR = 1.45, 95% CI 0.97–2.18). Risk was similar for current and past smoking and increased non-significantly with increasing pack-years. The HR was 0.71 (95% CI 0.45–1.12), for current drinking relative to never drinking, with a HR of 0.43 (95% CI 0.19–0.96) for ≥4 drinks/week.

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Conclusion: Findings from this first large study among Black women are consistent with previous findings in other populations of increased risk of SLE associated with cigarette smoking and decreased risk with moderate alcohol consumption.

Keywords

alcohol; cigarette; smoking; systemic lupus erythematosus; SLE; prospective; risk factor; black women

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that affects Black individuals more frequently than Whites, and women more frequently than men.[1–4] The mean age of onset is also younger among Blacks. [4–6] The role of environmental factors in the pathogenesis of SLE is of great interest as genetic factors do not explain a major portion of the incidence.[3]

Cigarette smoking has been associated with SLE risk in several, but not all, past studies.[7–12] Two past meta-analyses of these studies have pointed to current smoking, more than past smoking, in increasing SLE risk.[13,14] A recent prospective study demonstrated an increased risk of anti-double stranded DNA positive (anti-dsDNA+) SLE, but not overall SLE, with current smoking.[10] Components from cigarette smoke are associated with adverse effects on immune function and damage to proteins and DNA.[15–17] Several studies have reported inverse associations of alcohol with SLE,[7,9,18] and long-term moderate alcohol consumption has been prospectively associated with reduced SLE risk among women in the Nurses' Health Studies.[19] Moderate alcohol consumption has an anti-inflammatory effect and has been associated with reduced risk of rheumatoid arthritis as well.[20] Most previous studies have investigated SLE risk among predominantly White or Asian populations.

In view of the disproportionate occurrence of SLE among Black women, studies identifying modifiable risk factors in this racial-gender group are particularly needed. We report here an updated prospective analysis of cigarette smoking and alcohol consumption in relation to incidence of SLE in the Black Women's Health Study (BWHS), a follow-up study of Black women from across the U.S. In an earlier BWHS study based on 67 self-reported SLE cases identified between 1995 and 1999,[12] current and past smoking were associated with nonsignificant increases in incidence, and there was no association with alcohol consumption. Of the 67 BWHS cases included in that analysis, 34 were confirmed by medical record review to have three or more of the American College of Rheumatology (ACR) 1997 classification criteria for SLE.[21] The present report is based on 127 cases of SLE identified during follow-up in the BWHS (1995 to 2015), all of which were confirmed through medical records as having four or more ACR criteria for the disease. We hypothesized that current cigarette smoking and increased pack-years of smoking would be associated with increased SLE risk and that moderate alcohol consumption would be associated with decreased SLE risk.

Materials and Methods

The Black Women's Health Study.

The BWHS is a prospective cohort study that began in 1995 when 64,500 women aged 21–69 years (median age 38) enrolled by completing a 14-page postal health questionnaire on demographics, health status, and medical and lifestyle variables.[22,23] The 59,000 women whose addresses were considered to be valid a year later comprise the cohort that has been followed. Participants, self-identified as "Black" and reside across the continental U.S., with approximately equal numbers from the Northeast, South, Midwest, and West. They have been followed from baseline using biennial health questionnaires and yearly linkage with the National Death Index. Follow-up of the original cohort has been successful for >85% of potential person-years through 2015. Participants indicated their consent by choosing to fill out the questionnaires; medical records to verify diagnoses were obtained for women who signed informed consents. The study was approved by the Institutional Review Board of Boston University Medical Center.

Data collection.

The baseline questionnaire asked about many health-related factors, including cigarette smoking, alcohol intake, dietary intake,[24] height and weight, reproductive history, oral contraceptive and menopausal female hormone use, and a list of diagnoses that included "lupus". Every biennial questionnaire since then has asked about "lupus (systemic lupus erythematosus") and the date of diagnosis.

At baseline, participants reported cigarette smoking (≥1 cigarette per day for at least a year currently or in the past), number of cigarettes smoked per day for both current and past smokers, and years of smoking. Smoking status and the number of cigarettes smoked per day by current smokers was updated on biennial follow-up questionnaires. Pack-years of smoking was calculated as the product of the years of smoking and the number of cigarette packs (number of cigarettes divided by 20) smoked per day.

At baseline, participants reported whether they drank alcoholic beverages (beer, wine, wine cooler, and liquor) currently or in the past, the number of years of drinking, and the number of drinks per week consumed in the previous year. Follow-up questionnaires updated the number of alcoholic beverages consumed per week for current drinkers.

Information at baseline was also collected on height and weight, from which body mass index (BMI) was computed (kg/m^2). Information was obtained on years of education completed, menopausal status, oral contraceptive use, and menopausal female hormone use. A food frequency questionnaire was also completed.[24] All variables except height were updated on follow-up questionnaires.

SLE cases.

Potential SLE cases were identified through self-report. The physicians of women who gave consent were asked to provide relevant medical records or to fill out a check list which asked about the presence of the 1997 updated American College of Rheumatology criteria for the

classification of SLE.[21,25] We obtained medical records or check lists for 240 women, of which 127 were confirmed as being SLE after medical record review confirmed the presence of at least 4 ACR SLE classification criteria by study rheumatologists. Brigham and Women's Hospital rheumatologists (including MB, KC, CL and ST) reviewed medical records for all ACR criteria manifestations for a random sample of 62 incident and prevalent cases and compared results with prior abstractions. For these cases we confirmed a very high Kappa agreement level between any two different reviewers (0.96, 95%CI 0.89 to 1.00). An additional 30 cases were reviewed due to noted inconsistencies within their prior abstraction, and any records with discrepancy between the result of the original and new abstractions were adjudicated by a Brigham and Women's Hospital rheumatologist (n=13). Lastly, 4 new cases were reviewed independently by 2 Brigham and Women's Hospital rheumatologists, followed by a third review to adjudicate any discrepancies. Anti-dsDNA and anti-Smith (anti-Sm) antibody status at SLE diagnosis was also determined by medical record review. In addition to SLE overall, a secondary outcome comprised of cases classified as anti-dsDNA+ and/or anti-Sm+ (anti-dsDNA+/Sm+) was also assessed in our analyses.

Analytic cohort.

From the baseline cohort of 59,000 women, we excluded 755 women who reported a diagnosis of SLE at baseline, 1331 women with missing information on smoking variables at baseline, and 362 women with missing information on alcohol intake at baseline, leaving an analytic cohort of 56,552 women.

Statistical analysis.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of smoking status (ever, current, past) and pack-years of smoking with SLE, relative to never smoking. Similarly we assessed the association of alcohol consumption status (ever, current, past) and current drinks per week with SLE, relative to never drinking. HRs approximate the incidence rate ratio; thus, the term "risk" will be used to imply hazard. Women contributed person time from baseline (1995) until SLE diagnosis, death, loss to follow-up, or end of follow-up (2015), whichever came first. Women who reported SLE but for whom we were unable to obtain medical records to confirm the diagnosis were censored at the date of self-report. Smoking, alcohol, and other time varying variables were updated each questionnaire cycle. For example, a current smoker in a particular questionnaire cycle contributed person-years to the current smoking category. If she reported zero (0) cigarettes smoked on the subsequent questionnaire, her person years starting with that questionnaire were contributed to the past smoking category. We also evaluated smoking and alcohol association in relation to anti-dsDNA/Smith antibody status at diagnosis. The Cox models controlled for age in 1-year intervals and questionnaire cycle. The multivariable models contained, in addition to terms for smoking and alcohol consumption, terms for BMI, ever use of oral contraceptives, menopausal status, ever use of menopausal female hormones, quintile of energy intake, years of education and quintile of neighborhood socioeconomic status score. The latter score was derived from data obtained by linking the women's addresses to U.S. Census block data on wealth, income, and education; lower scores denote lower socioeconomic status.[26] Our main analyses considered the variables of interest in relation to the occurrence of SLE two

or more years subsequently. As SLE can develop slowly over a period of years, in a sensitivity analysis, the exposure of interest was “lagged” with respect to the outcome, and thus we considered risk factors in relation to SLE with onset at least four years later.

Results

Age-adjusted baseline characteristics of study participants categorized by smoking and alcohol intake status are shown in **Table 1**. At baseline, 8,851 women (16%) were current smokers and 10,447 (18%) were past smokers. Menopausal status, oral contraceptive use, postmenopausal female hormone use and BMI did not vary substantially across smoking status categories. Past and current smokers were older than never smokers and also had higher energy intake levels. The percentage of women who completed college was highest among never smokers (50%) and lowest among current smokers (28%). Current smoking was also greater among women living in neighborhoods with the lowest socioeconomic status. At baseline, 14,001 (25%) of participants were current drinkers and 10,255 (18%) were past drinkers. Current alcohol drinking was highest among current smokers (46%). Past and current alcohol drinkers were older and had higher energy intake than never drinkers. The percentage of women who completed college was highest among never drinkers (49%) and lowest among past drinkers (36%). BMI, menopausal status, oral contraceptive use, postmenopausal hormone use, and neighborhood socioeconomic status were similar across alcohol intake categories.

The SLE case group consisted of 127 cases identified during follow-up who were judged to have at least 4 ACR criteria for SLE classification by medical record and checklist review by study rheumatologists (**Table 2**). The mean age at diagnosis was 43 years, 48% were positive for anti-dsDNA or anti-Smith, 64% had a hematologic disorder, and 31% had a renal disorder. The mean number of ACR criteria was 5.1 ± 1.3 among SLE cases.

In multivariable analyses, ever smoking compared to never smoking was associated with a non-significantly increased risk of developing SLE (HR 1.45, 95% CI 0.97–2.18) **(Table 3)**. Compared to never smoking, the point estimate of the risk of SLE associated with current smoking (MV HR 1.52, 95%CI 0.90–2.57) was somewhat higher, but not significantly so, than that for past smoking (MV HR 1.41, 95%CI 0.87–2.28). The MV HR associated with <20 pack years of smoking (1.37, 95%CI 0.89–2.11) was lower than that for ≥20 pack years (1.60, 95%CI 0.79–3.25), but this difference was also not significant. In a “lagged” analysis in which ever smoking was considered in relation to SLE occurring at least 4 years later, the risk estimate (MV HR 1.46 95%CI 0.91–2.34) was similar to that in the non-lagged analysis. Among the 61 SLE cases positive for anti-dsDNA and/or Smith antibodies, there were 18 ever smokers; there was no association of ever smoking with this category of SLE (MVHR 1.00, 95% CI 0.54–1.84) (data not shown).

As shown in **table 4**, the MV HRs for current and past drinking, relative to never drinking, were 0.71 (95% CI 0.45–1.12) and 0.78 (95% CI 0.50–1.25), respectively. For current drinking of ≥4 drinks per week, the MVHR was 0.43 (95% CI 0.19–0.96). In a lagged analysis, an inverse association for current drinking of ≥4 drinks per week with SLE (HR 0.33, 95% CI 0.12–0.95) was similar to that in the main analysis. In analyses based on 61

SLE cases positive for anti- dsDNA and/or anti-Sm, there were 14 current drinkers and 11 past drinkers: the MV HRs were 0.73 (95% CI 0.38–1.39) for current drinking and 0.60 (95% CI 0.30–1.23) for past drinking, compared to never drinking (data not shown).

Discussion

In the present study of women in the Black Women's Health Study, there was an estimated 45% increase in risk of SLE for ever smoking relative to never smoking, but the finding was of borderline statistical significance. Moderate current alcohol consumption, measured as ≥4 drinks per week, was associated with a 57% reduction in SLE risk. To our knowledge no previous prospective results have been presented separately for Black women except from the earlier small study from the BWHS.[12]

Our findings extend previous findings from the BWHS. The current analysis includes 127 cases, classified as definite lupus because all had 4 or more ACR criteria as determined by medical record review. A validation study that we published in 2003 indicated that 41% of women who self-reported SLE for whom we were able to obtain medical records or checklists did not have definite lupus, as defined by 4+ criteria.[27] Thus, the case group of the present study is less likely to be diluted with non-cases, a possibility in the previous BWHS study reported by Formica et al.[12] Further, the Formica study followed BWHS participants from 1995 to 1999,[12] whereas the current analysis follows them from 1995 to 2015. The additional years of follow-up, which resulted in a greater number of cases, provides greatly improved statistical power.

In the present study, SLE risk was greater among current smokers (52% elevated risk) than among past smokers (41%) smokers, and greater for ≥20 pack-years of smoking (60%) than for <20 pack-years of smoking (37%), although none of these differences was statistically significant. The estimated increases in risk among smokers are consistent with increases in risk estimated in several previous studies of Blacks, Whites and Asians. A case-control study of Black female participants found that 60% of cases (n=41) and 34.7% of controls (n=83) were past or current smokers.[28] An earlier study by the same authors reported the prevalence of smoking to be 18% among 28 cases and 15% among 73 controls.[29] Two meta-analyses demonstrated a 50–60% increase in SLE risk among current smokers,[13,14] relative to past smokers, and other case-control studies have demonstrated an increased risk among both current and past smokers.[7,30] In a recent prospective study using the Nurses' Health Study cohorts, current smoking was associated with a specific subtype of SLE characterized by anti-dsDNA antibodies (HR 1.86, 95% CI 1.14–3.04), but not with SLE overall.[10] Based on smaller numbers in the present study, there was no association of current smoking with the subtype of SLE characterized by anti-dsDNA and/or Smith antibodies.

In the current study, current and past alcohol consumption were associated with non-significant reductions in incidence of SLE, 29% and 21%, respectively. Among current drinkers who drank ≥4 drinks/week (the top category), there was a 57% risk reduction for SLE. We did not have information on the number of drinks consumed per week by past drinkers. Virtually all the drinkers in the BWHS were "moderate" drinkers, as almost none reported consuming ≥7 drinks per week. The reduced risk estimated in the present study for

current drinkers is consistent with estimates for moderate drinking from previous studies, including a meta-analysis of six case-control studies, our prior BWHS cohort study (OR 0.72, 95%CI 0.55–0.95), and a recent prospective study using the Nurses' Health Study cohorts (HR 0.57, 95% CI 0.34–0.96, p-trend <0.01).[9,19]

The associations demonstrated of both cigarette smoking and alcohol intake with SLE risk are biologically plausible and may lead to insights into SLE pathogenesis. Exposure to toxic components from cigarette smoke (e.g. tars, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons and free radicals) is associated with increased oxidative stress, stimulation of autoantibody production, and can directly damage endogenous proteins and DNA.[31–33] Alcohol suppresses synthesis of pro-inflammatory cytokines (tumor necrosis factor, interleukin-6, interleukin-8).[34] Additionally, antioxidants in alcohol such as resveratrol or humulones influence cytokines and may inhibit DNA synthesis.[35,36] Furthermore, both cigarette smoking and alcohol intake may induce epigenetic changes in genes involved in inflammation and autoimmunity.[37–39]

The present study is the largest analysis yet of SLE risk among Black women, whose prevalence of SLE is the highest compared to other race/ethnic groups.[1–4] Other strengths include the confirmation of the SLE diagnoses through medical records and control for potential confounders. The time-varying analyses took into account changes in the variables of interest and of potential confounders over time. Prospective data collection reduced the possibility that the reporting of the exposures of interest was influenced by SLE disease status. We also conducted sensitivity analyses in which we 'lagged' exposure time relative to the outcome, accounting for the possibility of reverse causation. The use of incident cases reduced the possibility of bias resulting from behavior modification subsequent to disease onset. Estimates from the lagged analyses demonstrated that the observed effects of smoking or alcohol on SLE were not altered by behavioral changes in the period immediately preceding SLE diagnosis. Cigarette smoking has been associated with asthma[40] and lung cancer[41] in the BWHS, as expected, and alcohol consumption with incidence of type 2 diabetes,[42] as expected. In addition, each is associated with correlates in the directions expected—e.g., smoking with lower educational level and alcohol consumption with cigarette smoking. All these associations provide support for the validity of reporting of these habits in the BWHS.

Limitations of the current study included the relatively small number of confirmed cases in the cohort, which limited statistical power. Prevalent SLE reported at baseline or within the first questionnaire cycle of the cohort had to be excluded from these analyses as we were unable to collect exposure information prior to the diagnoses. Smoking and alcohol use were relatively uncommon among women in the BWHS cohort which also limited statistical power to detect associations or investigate interactions. Although we had extensive data on alcohol exposures, we were unable to assess type of alcohol consumed (such as beer, wine, or liquor).

The current findings among Black women, who are the demographic group at the highest risk of SLE in the U.S. population, are consistent with the previously-reported positive association of cigarette smoking with risk of SLE and inverse association of alcohol

consumption with SLE. Future studies are needed to confirm these findings and establish the biologic mechanisms by which cigarette smoking and alcohol consumption influence the risk of SLE in this population and others.

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Significance and Innovations

- Cigarette smoking has been associated with increased SLE risk and alcohol consumption has been associated with decreased SLE risk in some but not all epidemiologic studies.
- Previous epidemiologic studies evaluating smoking and alcohol consumption as risk factors for SLE have been based almost entirely on White or Asian populations.
- The present prospective cohort study is the largest investigation yet of the association of these risk factors with risk of SLE in Black women.
- In this study, cigarette smoking was associated with a nonsignificant increase in SLE risk and current alcohol consumption of 4 or more drinks per week was associated with a significant decrease in risk.
- The present results are consistent with an increase in risk associated with cigarette smoking and a decrease in risk associated with alcohol consumption. The identification of risk factors for SLE in especially important for Black women, a population at high risk of SLE.

Table 1.

Baseline characteristics of 56,552 Black Women's Health Study participants by smoking and alcohol status at baseline[1]

	Smoking status			Alcohol consumption status		
	Never	**Past**	**Current**	**Never**	**Past**	**Current**
Participants at baseline, number	37,254	10,447	8,851	32,296	10,255	14,001
Mean age, years	36.8	44.4	40.8	37.6	41.5	39.7
Mean BMI, kg/m^2	27.9	28.8	27.8	27.9	28.9	27.6
Energy intake, kcal\day	1489	1587	1669	1473	1652	1583
Education ≥16 years, %	50	40	28	49	36	42
Quintiles of neighborhood SES, %				Quintiles of neighborhood SES, %		
1, low	17	18	26	17	22	19
2	18	18	21	18	20	18
3	18	18	18	19	18	18
4	19	19	15	19	17	18
5, high	20	19	13	19	15	20
Alcohol intake status %				Smoking status, %		
Never	69	30	32	79	49	45
Past	13	32	22	11	32	27
Current	17	38	46	10	19	28
Premenopausal, %	77	76	75	77	75	76
Ever oral contraceptive use, %	83	87	85	82	85	87
Ever female hormone use, %	14	16	17	14	16	16

[1] Percentages standardized to the age distribution of the cohort at baseline

Table 2.

Characteristics of participants at SLE diagnosis in the Black Women's Health Study (n=127)

Age at diagnosis (mean, SD)	43 ± 8.2
ANA positive, n (%)	123 (97%)
Anti-dsDNA or Smith positive, n (%)	61 (48%)
Anti-dsDNA only	37 (29%)
Anti-Smith only	10 (8%)
Anti-dsDNA and Anti-Smith	14 (11%)
Arthritis, n (%)	101(80%)
Hematologic disorder (leukopenia, lymphopenia, thrombocytopenia, hemolytic anemia), n (%)	82 (64%)
Renal disorder, n (%)	39 (31%)
Mean number of ACR criteria (of 11 total), ± SD	5.1 ± 1.3

Table 3.

Cigarette smoking in relation to risk of incident SLE among women in the Black Women's Health Study

Smoking	# Cases	Person years	Age- adjusted HR[1]	MV-adjusted HR[2]	95% CI
Never smoked	81	610,444	1.00(ref)	1.00(ref)	---------
Ever smoked	46	317,638	1.23	1.45	(0.97–2.18)
Current	20	116,338	1.25	1.52	(0.90–2.57)
Past	26	201,250	1.22	1.41	(0.87–2.28)
< 20 pack-years	36	248,725	1.19	1.37	(0.89–2.11)
≥ 20 pack-years	10	68,913	1.43	1.60	(0.79–3.25)

MV=multivariable, HR=hazard ratio; CI= confidence interval, pack-years=pack-years of smoking

[1]Age-adjusted HR was also adjusted for questionnaire cycle.

[2]MV adjusted in addition for alcohol consumption, BMI, ever use of oral contraceptives, menopausal status, ever use of menopausal female hormones, quintile of energy intake, years of education and quintile of neighborhood socioeconomic status score.

Table 4.

Alcohol drinking in relation to incidence of SLE among women in the in the Black Women's Health Study

Drinking	# Cases	Person-years	Age-adjusted HR[1]	MV HR[2]	95% CI
Never drank	67	394,902	1.00 (ref)	1.00 (ref)	
Past drinker	29	251,324	0.86	0.78	(0.50–1.25)
Current drinker	31	281,855	0.78	0.71	(0.45–1.12)
1–3 drinks/week	24	186,826	0.94	0.87	(0.53–1.41)
≥ 4 drinks/week	7	95,029	0.49	0.43	(0.19–0.96)

MV=multivariable, HR=hazard ratio; CI= confidence interval

[1]Age-adjusted HR was also adjusted for questionnaire cycle.

[2]MV adjusted in addition for cigarette smoking, BMI, ever use of oral contraceptives, menopausal status, ever use of menopausal female hormones, quintile of energy intake, years of education and quintile of neighborhood socioeconomic status score.