Cigarette Smoking, Alcohol Consumption, and Risk of Systemic Lupus Erythematosus: A Case-control Study in a Japanese Population

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ABSTRACT. ***Objective.*** Cigarette smoking may be associated with increased risk of systemic lupus erythematosus (SLE), whereas the role of alcohol consumption is unknown. We examined the association between SLE risk and smoking or drinking.

Methods. We investigated the relationship of smoking and drinking compared to SLE risk among 171 SLE cases and 492 healthy controls in female Japanese subjects. Unconditional logistic regression was used to compute OR and 95% CI, with adjustments for several covariates.

Results. Compared with nonsmoking, current smoking was significantly associated with increased risk of SLE (OR 3.06, 95% CI 1.86–5.03). The higher the level of exposure to cigarette smoke, the higher the risk of SLE. Inhalation was also associated with increased SLE risk (OR 3.73, 95% CI 1.46–9.94 for moderate inhalation; OR 3.06, 95% CI 1.81–5.15 for deep inhalation). In contrast, light/moderate alcohol consumption had a protective effect on SLE risk (OR 0.38, 95% CI 0.19–0.76). As for beer, the risks for non-beer drinkers and beer drinkers were similar. This also applies to alcoholic beverages other than beer.

Conclusion. Our results suggest that smoking was positively associated with increased SLE risk whereas light/moderate alcohol consumption was inversely associated with SLE risk, irrespective of the type of alcoholic beverage. Additional studies are warranted to confirm these findings. (First Release May 15 2012; J Rheumatol 2012;39:1363–70; doi:10.3899/jrheum.111609)

Key Indexing Terms:
ALCOHOL CONSUMPTION EPIDEMIOLOGY JAPAN RISK FACTOR SYSTEMIC LUPUS ERYTHEMATOSUS SMOKING

Despite intensive research, the etiology of systemic lupus erythematosus (SLE) remains unclear. Many environmental exposures, including smoking, ultraviolet light, medications, infectious agents, hair dyes, and dietary factors have been hypothesized to be associated with the development of SLE[1,2,3,4,5], although the strength of the evidence implicating each of these factors varies. Studies of twin concordance are commonly used in epidemiology to estimate the role of genetics and the influence of environmental factors on disease susceptibility. Disease concordance is much higher in monozygotic twins (24%–57%) than in dizygotic twins (2%–5%), suggesting a genetic component to SLE[6,7,8]. However, identification of these genetic factors has been slow. The genetic basis of SLE is very complex, and it is difficult to predict how

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many genes contribute to SLE susceptibility; it has been estimated that over 100 genes may be involved[9].

SLE, like other common multifactorial diseases, results from a complex interplay of genetic and environmental risk factors. However, triggering events for SLE may include many environmental factors[10]. A recent metaanalysis of 9 studies revealed a significantly increased risk for the development of SLE among current smokers compared with nonsmokers (summary OR 1.50, 95% CI 1.09–2.08)[5]. In contrast, another metaanalysis suggested that moderate alcohol consumption (the reference category was nondrinkers) was significantly associated with a decreased risk of SLE (summary OR 0.66, 95% CI 0.49–0.89) based on 5 studies, excluding our preliminary study[11], where the reference category was subjects who drank less than 1 day per week[12].

In this case-control study, we further examined the association between SLE risk and either detailed smoking or drinking habits in a population of Japanese women. We also examined the interaction between smoking and alcohol consumption in relation to SLE risk since many studies examined each factor individually. An additive interaction as well as a multiplicative interaction between these 2 factors in SLE risk was investigated.

MATERIALS AND METHODS

Study subjects. The Kyushu Sapporo SLE (KYSS) study was a case-control evaluation of risk factors for SLE among women. Patients with SLE (n = 129) were recruited from outpatients of Kyushu University Hospital, Saga University Hospital, and their collaborating hospitals in Kyushu from 2002 to 2005, while 51 patients with SLE were recruited from outpatients of Sapporo Medical University Hospital and its collaborating hospital in Hokkaido from 2004 to 2005. All patients (n = 180) fulfilled the American College of Rheumatology 1982 revised criteria for SLE[13]. The mean duration of SLE was 11.9 (SD 8.55) years. Controls were not, individually or in larger groups, matched to cases. Controls (n = 268) were recruited from nursing college students and care workers in nursing homes (n = 57) in Kyushu, while in Hokkaido, controls (n = 188) were recruited from participants at a health clinic in a local town.

For analysis, 18 subjects (8 cases, 10 controls) were excluded because of male sex. Because data on smoking status and alcohol consumption were insufficient for 1 case and 11 controls, they were excluded. In total, 171 cases and 492 healthy controls remained for final analysis.

All patients with SLE and controls provided written informed consent for cooperation in the study. The study was approved by the institutional review boards of Kyushu University Graduate School of Medical Sciences, Sapporo Medical University, and the other institutions involved.

Questionnaire survey. Cases were asked to complete a self-administered questionnaire about their lifestyle before the diagnosis of SLE, while controls completed the questionnaire about current lifestyle. Subjects were considered current smokers if they smoked or had stopped smoking < 1 year before either the date of diagnosis (patients with SLE) or the date of completion of the questionnaire (controls). Nonsmokers were defined as those who had never smoked in their lifetime. Former smokers were those who had stopped smoking ≥ 1 year before either the date of diagnosis (patients with SLE) or the date of completion of the questionnaires (controls). Smokers were asked about the duration of smoking in years, number of cigarettes smoked per day on average, number of cigarettes smoked per day during peak smoking period, fraction smoked per cigarette (0, < one-half, one-half to two-thirds, and almost all), and smoke inhalation [nonsmokers, no inhalation (puff only), moderate, and deep inhalation]. Cigarette-years of smoking were calculated as the number of cigarettes smoked per day times the number of years smoked. Similarly, subjects were considered current drinkers if they consumed alcohol before either the date of diagnosis of SLE (SLE patients) or completion of the questionnaire (controls). Nondrinkers were defined as those who had never consumed alcohol in their lifetime. Since 3 controls were remote former drinkers (> 8 years since they stopped drinking), they were included in the nondrinkers category. Unlike cigarette smoking, ingested alcohol is eliminated from the body by various metabolic mechanisms, and the alcohol elimination process begins almost immediately. We assessed consumption of 5 types of alcoholic beverages: beer, sake (Japanese rice wine), whiskey, shochu (Japanese distilled spirit), and wine. Current drinkers were asked about the frequency of drinking per week (< 1 day, 1–3 days, and 4–7 days weekly). Total ethanol consumption per day for drinkers was estimated based on beverage-specific ethanol concentrations. Subjects were also asked about education background as a surrogate for socioeconomic status (junior high school, high school, junior college/vocational college, and university/postgraduate school). Details of the health examination and the self-administered questionnaire have been published[11].

Statistical analysis. Unconditional logistic regression was used to compute OR (95% CI) with adjustments for several covariates (age, region of residence, smoking status, alcohol intake, and education background). Age was treated as a continuous variable. The remaining covariates were treated as categorical variables. Number of cigarettes smoked per day on average was classified into 3 categories (0, 1–19, ≥ 20 cigarettes/day); number of cigarettes smoked per day during peak smoking period into 3 (0, 1–19, ≥ 20 cigarettes/day); cigarette-years of smoking into 3 (0, 1–59, ≥ 60 cigarette-years); ethanol consumption per week on average was classified into 4 categories [nondrinker (0 ml), light (1–70 ml), moderate (71–210 ml), and heavy drinker (> 210 ml)]; and region of residence into 2 (Kyushu and Hokkaido).

To test for biological interactions between smoking status and drinking habits, we entered interaction terms (statistical interaction) reflecting the product of smoking status and drinking habits into the logistic models. In a logistic regression model, interaction refers to a departure from multiplicativity. Statistical interaction refers to departure from the underlying form of a statistical model (additive or multiplicative). Rothman has argued that interaction estimated as departure from additivity better reflects biologic interaction on the basis of the sufficient component cause model[14,15,16], because information concerning an additive interaction between 2 factors is more relevant to disease prevention and intervention. Three measures for biologic interaction as departure from additivity, namely the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI), were calculated by the method described by Andersson, *et al*[17]. The RERI is the excess risk due to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease that is due to interaction among individuals with both exposures. SI is the excess risk from exposure (to both factors) when there is interaction relative to the risk from exposure (to both factors) without interaction. Biological interaction was absent if RERI and AP are equal to 0, and SI and the multiplicative interaction term are equal to 1.

All statistical analyses were performed using Stata version 10.1 (Stata Corp., College Station, TX, USA). All p values were 2-sided, with values < 0.05 considered statistically significant.

RESULTS

One hundred seventy-one women with SLE and 492 healthy female controls were enrolled for study. As shown in Table 1, the age distribution was significantly different between patients with SLE and controls ($p < 0.0001$). The age of patients with SLE (mean 40.8 yrs, 95% CI 38.8–42.8) was significantly higher than that of controls (mean 33.1 yrs, 95% CI 31.8–34.3) ($p < 0.0001$). From the questionnaire, the mean age at the time of diagnosis of SLE was 28.9 years (95% CI

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Table 1. Selected characteristics of SLE cases and controls.

Characteristics	Cases, n = 171	Controls, n = 492	p
Age category, yrs, n (%)			
< 20	35 (20.5)	258 (52.4)	
20–40	89 (52.1)	130 (26.4)	
≥ 40	47 (27.5)	104 (21.1)	< 0.0001
Age, yrs, mean (95% CI)	40.8 (38.8–42.8)	33.1 (31.8–34.3)	< 0.0001
Region of residence, n (%)			
Hokkaido	51 (29.8)	186 (37.8)	
Kyushu	120 (70.2)	306 (62.2)	0.06
Smoking status, n (%)			
Nonsmoker	112 (65.5)	381 (77.4)	
Former smoker	8 (4.68)	19 (3.86)	
Current smoker	51 (29.8)	92 (18.7)	0.007
Drinking status, n (%)			
Nondrinker	77 (45.0)	142 (28.9)	
Former drinker	0 (0.0)	3 (0.61)	
Current drinker	94 (55.0)	347 (70.5)	< 0.0001
Education background, n (%)			
Junior high school	14 (9.94)	26 (5.30)	
High school	86 (50.3)	319 (65.0)	
Junior college/vocational college	49 (28.7)	137 (27.9)	
University/postgraduate school	19 (11.1)	9 (1.83)	< 0.0001

SLE: systemic lupus erythematosus.

27.1–30.6; data not shown). There was also a significant difference between the age of diagnosis (patients) and age of completion of the questionnaire (controls; p = 0.0005; data not shown). Compared with controls, cases were more likely to report a history of smoking and a higher education background. On the other hand, controls tended to have more frequent drinking than patients with SLE (p < 0.0001).

Table 2 shows the association between smoking characteristics and SLE risk among Japanese females. After adjustment for age, region, drinking status, and education background, current smoking was significantly associated with an increased risk of SLE compared with nonsmoking (OR 3.06, 95% CI 1.86–5.03). Former smokers had a marginally increased risk of SLE (OR 2.49, 95% CI 0.97–6.44). Consequently, ever-smokers were at risk of SLE (OR 2.96, 95% CI 1.85–4.76). There was a dose-dependent relationship (p for trend < 0.0001) between number of cigarettes smoked per day on average and the SLE risk (OR 3.06, 95% CI 1.84–5.09 for 1–19 cigarettes per day; OR 2.87, 95% CI 1.26–6.51 for > 20 cigarettes per day). Similarly, number of cigarettes smoked per day during the peak smoking period was dose-dependently associated (p for trend < 0.0001) with an increased risk of SLE (OR 2.77, 95% CI 1.55–4.94 for 1–19 cigarettes per day; OR 3.29, 95% CI 1.77–6.09 for > 20 cigarettes per day). The greater the cigarette-years of smoking (p for trend < 0.0001) and the longer the fraction smoked per cigarette (p for trend < 0.0001), the greater the risk of SLE. Inhalation was also associated with an increased risk of SLE (OR 3.73, 95% CI 1.46–9.94 for moderate inhalation; OR 3.06, 95% CI 1.81–5.15 for deep inhalation).

Table 3 shows the association between drinking characteristics and SLE risk among female Japanese subjects. After adjustment for age, region, smoking status, and education background, subjects who drank < 1 day per week had a significantly decreased risk of SLE (OR 0.37, 95% CI 0.23–0.58) compared with nondrinkers. Subjects who drank 1 to 3 days per week had a marginally lower risk of SLE (OR 0.52, 95% CI 0.27–1.00), while subjects who drank 4 to 7 days per week did not have a significantly lower risk of SLE. The OR for ≤ 70 ml ethanol (light drinkers) and 70–210 ml ethanol per week (moderate drinkers) were 0.52 (95% CI 0.31–0.86) and 0.38 (95% CI 0.19–0.76), respectively. Heavy drinking was not associated with SLE risk. Compared with nondrinkers, beer drinkers had a significantly lowered risk of SLE (OR 0.44, 95% CI 0.27–0.72). Non-beer drinkers also had a significantly decreased risk of SLE (OR 0.29, 95% CI 0.17–0.50). There was a similar tendency in other types of alcoholic beverage.

Table 4 shows the interaction between smoking and drinking in SLE risk. Nondrinkers with a history of smoking (OR 6.98, 95% CI 2.87–17.0) had a higher risk of SLE than those with no history of smoking (OR 2.56, 95% CI 1.57–4.17), relative to drinkers with no history of smoking (reference). The multiplicative and additive interaction measures between smoking and drinking did not reach statistical significance.

DISCUSSION

We performed a case-control study of detailed smoking and drinking habits and SLE among 171 SLE cases and 492 controls in Japanese women. Our study provides further evidence that smoking is associated with an increased risk of SLE,

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Table 2. OR for SLE according to smoking characteristics among female Japanese subjects.

Characteristic	Cases/ Controls	OR (95% CI) Crude	Adjusted*
Smoking status, n (%)			
Nonsmoker	112/381	1.0 (reference)	1.0 (reference)
Former smoker	8/19	1.43 (0.61–3.36)	2.49 (0.97–6.44)
Current smoker	51/92	1.89 (1.26–2.81)	3.06 (1.86–5.03)
p_{trend}		0.008	< 0.0001
Ever-smoker**	59/111	1.81 (1.24–2.64)	2.96 (1.85–4.76)
Cigarettes smoked/day on average†			
0	112/381	1.0 (reference)	1.0 (reference)
1–19	43/83	1.76 (1.15–2.69)	3.06 (1.84–5.09)
20+	15/23	2.22 (1.12–4.40)	2.87 (1.26–6.51)
p_{trend}		0.001	< 0.0001
Cigarettes smoked/day during peak smoking period†			
Nonsmokers	112/381	1.0 (reference)	1.0 (reference)
1–19	27/58	1.58 (0.96–2.62)	2.77 (1.55–4.94)
20+	31/49	2.15 (1.31–3.54)	3.29 (1.77–6.09)
p_{trend}		0.001	< 0.0001
Cigarette-years of smoking†			
Nonsmokers	112/381	1.0 (reference)	1.0 (reference)
1–59	24/55	1.48 (0.88–2.51)	2.73 (1.50–4.96)
60+	33/49	2.29 (1.40–3.74)	3.63 (1.95–6.75)
p_{trend}		0.001	< 0.0001
Fraction smoked per cigarette†			
Nonsmokers	112/381	1.0 (reference)	1.0 (reference)
Less than half	14/21	2.27 (1.12–4.60)	3.63 (1.62–8.15)
Half to 2/3	28/54	1.76 (1.07–2.91)	2.62 (1.43–4.80)
Almost all	35/16	1.56 (0.83–2.91)	2.97 (1.47–6.02)
p_{trend}		0.013	< 0.0001
Smoke inhalation†			
Nonsmokers	112/381	1.0 (reference)	1.0 (reference)
No (puff only)	6/12	1.70 (0.62–4.63)	1.67 (0.56–5.00)
Moderately (in the mouth)	9/14	2.19 (0.92–5.19)	3.73 (1.46–9.94)
Deeply (into the lung)	43/85	1.72 (1.12–2.63)	3.06 (1.81–5.15)
p_{trend}		0.005	< 0.0001

* Adjusted for age, region, drinking status, and education background. ** Current and former smokers combined. † Several observations with missing values. SLE: systemic lupus erythematosus.

while light/moderate alcohol drinking is associated with a decreased risk of SLE.

All smoking characteristics we examined affected SLE risk. The greater the exposure to cigarette smoke, the higher the SLE risk. No studies examining the associations between fraction smoked per cigarette or smoke inhalation and SLE have been published to date. Although we did not measure the validity of self-reported inhalation, previous studies suggested that self-reported inhalation correlated well with carboxyhemoglobin saturation levels (a biomarker of exposure to cigarette smoke)[18]. It has been observed that the self-reported length of cigarette smoked was similar to the actual average[19]. As with the number of cigarettes smoked per day (index of smoking intensity), fraction smoked per cigarette was dose-dependently associated with an increased risk of lung cancer[20]. Several studies investigated the association between smoking and SLE[3,11,21,22,23,24,25,26,27,28] but produced conflicting results. A recent metaanalysis based on 9 studies showed that current smokers were at risk for the development of SLE (summary OR 1.50, 95% CI 1.09–2.08)[5]. In that study, current smoking was significantly associated with an increased risk of SLE (OR 3.06, 95% CI 1.86–5.03). Because cigarette smoking has been proposed as a trigger for the development of SLE, it is plausible that cigarette smoking is associated with SLE risk. Although the biologic pathway through which cigarette smoking acts to increase the instantaneous risk of SLE is not known, several potential mechanisms exist. Cigarette smoke contains several thousand chemicals, of which about 50 compounds are known carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines, and N-nitroso compounds. Because hydrazine, a drug containing aromatic amines, is a known inducer of SLE[29], aromatic amines in cigarette smoke may explain the association between smoking and SLE. Cigarette smoke affects a wide range of immunological functions in humans[30,31]. Because reactive oxygen species (ROS) promote the autoimmune response[32], exposure to ROS through cigarette smoking may be associated with increased risk of SLE. Like SLE, rheuma-

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Table 3. OR for SLE according to drinking characteristics among female Japanese subjects.

Characteristic	Cases/ Controls	OR (95% CI) Crude	Adjusted*
Frequency of drinking, n (%)			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Less than 1 day/week	56/261	0.40 (0.27–0.60)	0.37 (0.23–0.58)
1–3 days/week	22/61	0.68 (0.39–1.19)	0.52 (0.27–1.00)††
4–7 days/week	16/25	1.20 (0.60–2.39)	0.63 (0.28–1.44)
p_{trend}		0.379	0.040
Drinkers	94/347	0.51 (0.36–0.73)	0.41 (0.27–0.63)
Alcohol consumed (ml)/wk on average†			
0	77/145	1.0 (reference)	1.0 (reference)
1–70 (light)	46/136	0.64 (0.41–0.98)	0.52 (0.31–0.86)
71–210 (moderate)	18/69	0.49 (0.27–0.88)	0.38 (0.19–0.76)
211+ (heavy)	18/32	1.06 (0.56–2.01)	0.67 (0.31–1.46)
p_{trend}		0.216	0.037
Type of alcohol			
Beer			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Non-beer drinkers	35/187	0.35 (0.22–0.56)	0.29 (0.17–0.50)
Drinkers	59/160	0.69 (0.46–1.04)	0.44 (0.27–0.72)
Sake (rice wine)			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Non-sake drinkers	76/308	0.46 (0.32–0.67)	0.38 (0.24–0.59)
Drinkers	18/39	0.87 (0.47–1.62)	0.61 (0.29–1.26)
Whisky			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Non-whisky drinkers	84/315	0.50 (0.35–0.72)	0.41 (0.27–0.64)
Drinkers	10/32	0.59 (0.27–126)	0.36 (0.15–0.87)
Shochu (distilled spirit)			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Non-shochu drinkers	74/261	0.53 (0.37–0.78)	0.41 (0.26–0.64)
Drinkers	20/86	0.44 (0.25–0.77)	0.38 (0.20–0.73)
Wine			
Nondrinkers	77/145	1.0 (reference)	1.0 (reference)
Non-wine drinkers	79/300	0.50 (0.34–0.72)	0.39 (0.25–0.61)
Drinkers	15/47	0.60 (0.32–1.14)	0.48 (0.23–0.99)

* Adjusted for age, region, smoking status, and education background. † Several observations with missing values. †† p = 0.05. SLE: systemic lupus erythematosus.

Table 4. Interaction between drinking and smoking with regard to SLE risk in female Japanese subjects.

Drinking Status + Smoking Status	Cases/ Controls	OR (95% CI) Crude	p	Adjusted*	p
Drinking + nonsmoking	49/249	1.0 (reference)		1.0 (reference)	
Drinking + ever-smoking	45/98	2.33 (1.46–3.72)	< 0.0001	3.44 (2.03–5.82)	< 0.0001
Nondrinking + nonsmoking	63/132	2.43 (1.58–3.72)	< 0.0001	2.56 (1.57–4.17)	< 0.0001
Nondrinking + ever-smoking	14/13	5.47 (2.42–12.4)	< 0.0001	6.98 (2.87–17.0)	< 0.0001
Multiplicative interaction measure		0.97 (0.38–2.47)	0.944	0.79 (0.29–2.18)	0.653
Additive interaction measure					
Relative excess due to interaction		1.71 (–2.57–5.99)	0.433	1.98 (–3.90–7.86)	0.509
Attributable proportion due to interaction		0.31 (–0.25–0.87)	0.272	0.28 (–0.40–0.91)	0.796
Synergy index		1.62 (0.59–4.49)	0.352	1.50 (0.53–4.19)	0.444

* Adjusted for age, region, and education background. SLE: systemic lupus erythematosus.

toid arthritis (RA) is an autoimmune disease characterized by altered inflammatory and impaired immune responses causing immune-mediated destruction of tissues and organs. Although the etiology of these autoimmune diseases is not completely known, some of their environmental determinants may be considered similar. In a recent metaanalysis based on 16 stud-

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ies[35], smoking constituted a significant risk factor for the development of RA. The result of the metaanalysis supports our finding that smoking contributes to an increased risk of SLE.

To date, 6 studies in 7 populations, including our preliminary study, have examined the association between alcohol consumption and SLE risk. Three studies reported that drinking was significantly[24,27] or nonsignificantly[23] associated with a decreased risk of SLE. Four studies, including our preliminary study, showed no association between alcohol drinking and SLE risk[11,25,28,36]. A recent metaanalysis reported that no association was found between moderate alcohol consumption and SLE (summary OR 0.78, 95% CI 0.49–1.24) when limited to patients with SLE treated for < 5 years, while moderate alcohol consumption had a significant protective effect on SLE risk (summary OR 0.72, 95% CI 0.55–0.95) when limited to patients treated for < 10 years[12]. The OR of moderate alcohol consumption in the former analysis were heterogeneous, while those in the latter were homogeneous[12]. When our preliminary study[11] was excluded from the metaanalysis of the former analysis, the summary OR changed to 0.66 (95% CI 0.49–0.89)[12]. As the reference category in our preliminary study (drank < 1 day per week) was different from that in other studies (nondrinkers), we reanalyzed the association between alcohol use before diagnosis (patients with SLE may be more likely to stop drinking after diagnosis) using the same reference category as in other studies. As in those studies[23,24,27], light/moderate alcohol consumption had a protective effect on the development of SLE (Table 3). There is a U-shaped relationship between alcohol consumption and mortality from all causes[37]. Moderate drinkers may have lower SLE risk than nondrinkers and heavy drinkers. The biological mechanisms whereby alcohol may affect SLE remain speculative. First, alcoholic beverages potentially attenuate the risk of inflammatory disease such as SLE[38]. It has been suggested that the overproduction of interleukin 6 (IL-6) in patients with SLE may lead to pathogenesis of the disease[39]. Moderate alcohol consumption inhibits production of proinflammatory cytokine IL-6[40]. Antioxidants such as resveratrol or humulones contained in wine or beer have also been shown to influence cytokine cascades *in vitro*[41]. Beer is a rich source of niacin (vitamin B3), with a 350-ml serving of regular beer providing about 2.8 mg according to the food composition table[42]. As niacin possesses strong antioxidant and antiinflammatory properties[43], it may be preventive for development of SLE. In addition, beer (significantly), wine (nonsignificantly), and other types of alcoholic beverages have varying tendencies to decrease the risk of SLE. However, in comparison with nondrinkers, OR for non-beer drinkers and beer drinkers were comparable. Ethanol or its metabolites, rather than specific substances in alcoholic beverages, may modulate cytokine release, which in turn will decrease risk for SLE. Therefore, it is biologically plausible that appropriate drinking is associated with a deceased risk of SLE.

We evaluated whether an interaction existed between cigarette smoking and alcohol use (Table 4). Interaction refers to the extent to which the joint effect of 2 risk factors differs from the independent effects of each of the factors. Two risk factors (smoking and nondrinking) may act independently or together, thereby increasing or decreasing the effect of one another. Nonsmoking and alcohol consumption were suggested to be protective factors for SLE in this study. An interaction was suggested, with a combination of smoking and nondrinking conferring significantly higher risk (OR 6.98, 95% CI 2.87–17.0) than a combination of nonsmoking and drinking. Smoking (OR 2.96) and nondrinking (OR 1/0.41= 2.44) acted independently ($2.96 \times 2.44 = 7.22 \approx 6.98$), however. There was no significant interaction between smoking and drinking with SLE; this could have been due to lack of an effect rather than lack of power. Although several investigations have dealt specifically with the tobacco and alcohol interaction in the etiology of SLE, studies also suggested the possibility of no interaction between smoking and drinking in development of SLE[24,25]. Although the mechanism of the biological interaction between these 2 factors has not been definitively established, either multiplicative or additive risk models appear to be plausible. Further research is needed to determine the interaction effects of tobacco and alcohol consumption.

Because low socioeconomic status (SES) is generally associated with delay in seeking medical attention (treatment), SES may have a major influence on SLE risk[45]. Education background is usually easier to determine and is often used as a substitute for SES. Unexpectedly, we found higher education background was more prevalent among cases than among controls (Table 1). It has been reported elsewhere that patients with SLE were more educated than control subjects[25,46], although the finding was nonsignificant. Adjusted OR shown in Tables 2-4 were similar between the models with and those without education (data not shown). Education may not be an independent risk factor for SLE.

Several limitations of our study warrant mention. The study may have included a bias due to self-report of smoking habits and alcohol consumption (misclassification bias). However, discrepancies between self-reported smoking habits and biochemical verification are minimal among the general population[47,48]. Similarly, the validity of self-reports on alcohol consumption is generally high[49,50]. Recall bias, which occurs when cases and controls recall exposures differently, is also a well-recognized potential problem in case-control studies. Patients with SLE may be more likely to report their prior exposures than healthy controls because they think they might be related to their disease. The purported link between smoking/drinking and SLE is not common knowledge, however. The possibility of recall bias in reporting smoking or drinking habit may be minimized, because patients with SLE are unlikely to be aware that these habits may be associated with SLE risk. Further, the 2 exposures had opposite effects on SLE risk. Inaccuracies in recall and reporting were possible

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and, because they were likely nondifferential, could cause dilution of a true association. Population-based case-control studies may have underestimated slightly the true association due to recall bias[51]. Case-control studies tend to be susceptible to selection bias, particularly in the control group. Selection bias may occur if the decision to participate is affected by exposure status. As there is a strong relationship between cigarette smoking and alcohol consumption, it is unlikely that nonsmokers with a history of drinking (or smokers with no history of drinking) would be more likely to participate in our study. In many cases, selection bias is not extreme enough to affect inference and conclusions[52]. As the possibility of recall and selection biases cannot be completely excluded in case-control studies, our findings should be interpreted with caution. A fundamental conceptual issue relating to selection of controls is whether the controls should be similar to the cases in all respects other than having the disease in question. As controls were not selected to match SLE patients on confounding factors, there were significant differences in them, such as age and education background. Although matching is one approach to control for confounding bias in study design, the confounding bias can also be controlled using a statistical modeling approach in the analysis, as in our study. Finally, we did not have data on exposure to environmental tobacco smoke (ETS). ETS may be one of the risk factors for SLE. No studies on the association between ETS and SLE have been reported, thus additional epidemiological studies on this association are needed.

Our study provides further evidence that smoking is a risk factor for SLE, but alcohol consumption is protective for SLE. All smoking variables were dose-dependently associated with an increased risk of SLE, while light/moderate alcohol consumption was associated with a decreased risk of SLE. The protective effect of alcoholic beverages on SLE risk may be exerted by ethanol or its metabolites. Testing replication in different populations is required. Additional investigations are warranted to corroborate the association among Japanese subjects suggested in this study.

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APPENDIX

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