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Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study

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Abstract Many risk factors have been proposed for systemic lupus erythematosus (SLE). However, there is little information about the relationship between lifestyles and SLE in Japan. Two case control studies were conducted in Kyushu, southern Japan, and in Hokkaido, northern Japan, to examine the relationship between lifestyles and development of SLE in females. The participants were 78 patients and 329 controls in Kyushu and 35 patients and 188 controls in Hokkaido. Smoking was associated with an increased risk of SLE after adjusting for age in both regions. However, in Hokkaido, this association between smoking and SLE did not reach statistical significance after adjusting for alcohol drinking. The present study suggests that smoking may increase the risk of SLE among Japanese females.

Key words Epidemiology · KYSS study · Risk factors · Systemic lupus erythematosus (SLE)

Introduction

The Japanese Ministry of Health and Welfare designated systemic lupus erythematosus (SLE) as an intractable disease because there is no established way to cure or prevent it.[1] It is a serious, chronic inflammatory autoimmune disease that affects many tissues and organs.[2–4] The frequency is 8–10 per 100000 in the general Japanese population,[4] and females are 9–10 times more likely to suffer from SLE than males.[4] Serdula and Rhoads[5] reported that the age-adjusted prevalence of SLE was greater in Japanese (18.2 per 100000) than Caucasians (5.8 per 100000) in Hawaii, but

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they could find no reason for the high prevalence of SLE in Japanese ancestry.

The etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development.[2,4] Several studies have demonstrated that smoking is a risk factor for SLE,[6–10] while it has been suggested that drinking alcohol decreases the risk.[6,7,10] Several investigators reported the following as risk factors for SLE among the Japanese population: smoking,[6] family histories of asthma[6] and collagen disease,[6] medical histories of operation[11] and blood transfusions,[11] working in a cold environment,[11] skin sensitivity to sunlight,[11] first menstrual period occurred at age 15 or later,[6] menstrual irregularity,[12] the frequent intake of meat;[12] while drinking alcohol[6] and milk[6] reduced the risk of SLE. However, there is little information about the relationship between lifestyles and SLE among the Japanese population.[6,11] In addition, these studies[6,11] showed only age- and sex-adjusted risk of SLE. Thus, the present study was conducted to investigate the influence of smoking, drinking, sleeping habits, and other lifestyle factors on the development of SLE in Japanese women.

Methods

Profile of Kyushu Sapporo SLE (KYSS) study

The Kyushu Sapporo SLE (KYSS) study was a case control study to evaluate risk factors for SLE. From 2002 to 2005, cases were recruited from outpatients of Kyushu University Hospital and Saga University Hospital and their collaborating hospitals in Kyushu while eligible cases were outpatients of Sapporo Medical University Hospital and its collaborating hospital in Hokkaido during the period from 2004 to 2005.

All patients fulfilled the American College of Rheumatology 1982 revised criteria for SLE.[13] Controls were recruited from nursing college students and care workers in nursing homes in Kyushu while in Hokkaido controls were recruited from participants of a health checkup in a local town.

Kyushu is located in the extreme southwestern edge of Japan and has a temperate climate (the world swimming championship series were held in Fukuoka). On the other hand, Hokkaido is the northernmost island of Japan and has a subarctic climate (the Winter Olympics were held in Sapporo).

A self-administered questionnaire was obtained from SLE patients and controls, along with written informed consent for cooperation in the study. A section of the participants also agreed to donate blood samples, which were stored until use for DNA extraction and genotyping of the candidate genes of SLE.

The present study was approved by the institutional review boards of Kyushu University Graduate School of Medical Sciences, Sapporo Medical University, and each of the other institutions involved.

Subjects and methods in this study

In Kyushu, 180 out of 332 SLE patients (54.2%) agreed to participate in this study while 71 out of 145 SLE patients (49.0%) agreed in Hokkaido. On the other hand, 340 volunteers (262 nursing college students and 78 care workers in nursing homes) agreed to participate in this study as controls in Kyushu while 188 female participants of a health checkup in a local town agreed to take part in this study as controls in Hokkaido. Thus, a self-administered questionnaire was obtained from 180 SLE patients and 340 controls and 71 SLE patients and 188 controls in Kyushu and Hokkaido, respectively. Cases were asked to complete the self-administered questionnaire about lifestyles before the diagnosis of SLE. From among the Kyushu subjects, 11 patients and 11 controls were excluded because they were males, and 91 patients treated for SLE for more than 10 years were excluded because we were afraid that they might have been confused about when various lifestyle habits were followed, i.e., before or after the diagnosis of SLE. Thus, in the Kyushu study cases were 78 female patients and controls were 329 female volunteers (251 nursing college students and 78 care workers in nursing homes). From among the Hokkaido subjects, 7 patients were excluded because they did not fit the criteria for the ages of participants of a health checkup (i.e., between 20 and 69 years), and 29 others, who had been treated for SLE for more than 10 years, were excluded in order not to include inaccurate information about lifestyles before the diagnosis of SLE. Thus, in Hokkaido cases were 35 female patients and controls were 188 female volunteers (participants of a health checkup in a local town).

Since the number of cases was small in the present study, we could not exclude the patients treated for SLE for 5–9 years in the first analysis. To obtain accurate information before the diagnosis of SLE, however, we conducted a case control study with the patients treated for SLE for less than 5 years as well. Thus, we used two types of case: (1) patients treated for SLE for less than 10 years and (2) patients treated for SLE for less than 5 years.

Tables 1 and 2 display the age distributions of the two patient groups (age at the diagnosis of SLE) and the control group (age at the time of the survey), respectively.

Statistical analysis

A conditional logistic model was applied to evaluate the odds ratios (ORs) and their 95% confidence intervals (CIs) for SLE. Because smoking is suggested as a risk factor for SLE[6–10] and drinking is suggested as a factor that decreases the risk of SLE,[6,7,10] we used age, smoking, and drinking as other risk factors for SLE to estimate adjusted ORs in relation to lifestyle factors. Age was treated as a continuous variable, and indicator variables were used for smoking and alcohol drinking. We treated current and former smokers as smoking positive while those who drank 1 day/week or more were defined as having a drinking habit. Ages at the time of the survey were used for controls whereas the ages

Table 1. Number of patients and controls in Kyushu, southern Japan, stratified by age

Age (years)	Case A (n = 78)	Case B (n = 38)	Control K (n = 329)
10–19	15 (19.2)	8 (21.1)	73 (22.2)
20–29	33 (42.3)	12 (31.6)	188 (57.1)
30–39	15 (19.2)	10 (26.3)	17 (5.2)
40–49	9 (11.5)	4 (10.5)	27 (8.2)
50–59	3 (3.9)	3 (7.9)	20 (6.1)
60–69	3 (3.9)	1 (2.6)	4 (1.2)
Mean (SD)	30 (12)	31 (13)	26 (11)

Values are expressed as number (%) or mean (SD)
Case A: patients treated for SLE for less than 10 years; Case B: patients treated for SLE for less than 5 years; Control K: nursing college students and care workers in nursing homes

Table 2. Number of patients and controls in Hokkaido, northern Japan, stratified by age

Age (years)	Case C (n = 35)	Case D (n = 24)	Control H (n = 188)
20–29	16 (45.7)	10 (41.7)	1 (0.5)
30–39	9 (25.7)	6 (25.0)	42 (22.3)
40–49	6 (17.1)	5 (20.8)	51 (27.1)
50–59	2 (5.7)	1 (4.2)	93 (49.5)
60–69	2 (5.7)	2 (8.3)	1 (0.5)
Mean (SD)	34 (12)	35 (13)	47 (8)

Values are expressed as number (%) or mean (SD)
Case C: patients treated for SLE for less than 10 years; Case D: patients treated for SLE for less than 5 years; Control H: participants of a health checkup in a local town

at diagnosis were used for the SLE patients. All statistical analyses were conducted by use of a statistical analysis system package (SAS Institute, Cary, NC, USA). In this paper, we present the results for Kyushu and Hokkaido separately because the characteristics of controls were different between the two regions. In addition to age-adjusted ORs, we also report ORs adjusted for age, smoking, and drinking.

Results

Analyses of the patients treated for SLE in Kyushu, southern Japan

Tables 3 and 4 summarize the ORs for SLE and 95% CIs in relation to lifestyle factors (i.e., sleeping habits, leisure-time physical exercise, and smoking and alcohol drinking) in Kyushu, southern Japan.

As shown in Table 3, the analyses of all the patients treated within 10 years (case A) revealed that sufficient sleep was associated with a 55% reduced risk of SLE even after adjusting for age, smoking and alcohol drinking (OR = 0.45, 95% CI = 0.22 – 0.88). In contrast, after adjusting for age, smoking and alcohol drinking, walking showed a two-fold increased risk (30 min/day or more vs less than 30 min/day: OR = 2.07, 95% CI = 1.14 – 3.76) while leisure-time physical exercise showed a 66% increased risk (OR = 1.66, 95% CI = 0.94 – 2.91), but its 95% CI was rather wide.

Smoking increased the risk of SLE (current and former smokers vs never smokers: OR = 1.94, 95% CI = 1.09 – 3.45) even after adjusting for age and alcohol drinking. Current smokers (OR = 1.97, 95% CI = 1.06 – 3.65) as well as former smokers (OR = 1.85, 95% CI = 0.62 – 5.50) showed an increased age- and drinking-adjusted OR compared with never smokers, but the 95% CI for former smokers was rather wide. High-frequency drinkers (4–5 days/week or more vs less than 1 day/week: OR = 4.49, 95% CI = 1.43 – 14.08) showed an increased risk compared with never or seldom drinkers even after adjusting for age and smoking.

In Kyushu, current and former smokers were more likely to be drinkers than never smokers in both SLE patients (48.3% vs 12.5%, $P < 0.01$) and controls (26.6% vs 9.7%, $P < 0.01$) while current and former smokers were less likely to keep regular hours than never smokers only in SLE patients (41.4% vs 68.8%, $P = 0.02$) (not shown in the table).

In a mirror image, drinkers were more likely to have smoking experience than nondrinkers in both SLE patients (40.5% vs 16.7%, $P < 0.01$) and controls (70.0% vs 26.3%, $P < 0.01$). (not shown in the table). On the other hand, compared with nondrinkers, drinkers were less likely to practice leisure-time physical exercise 3 days/week or more in SLE patients (10.0% vs 43.9%, $P < 0.01$) but more likely to do so in controls (34.9% vs 20.4%, $P = 0.03$). Drinkers were more likely to feel psychological stress than nondrinkers only in controls (88.4% vs 73.9, $P = 0.04$).

The analyses of the patients treated for SLE for less than 5 years (case B) are presented in Table 4. After adjusting for age, smoking and drinking, sufficient sleep showed a decreased OR (OR = 0.47, 95% CI = 0.18 – 1.22) while walking (OR = 1.85, 95% CI = 0.82 – 4.17) and leisure-time physical exercise (OR = 1.56, 95% CI = 0.72 – 3.36) showed

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for Less than10 years in Kyushu (case A)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	53	242	Reference	Reference
7 h/day or more	25	87	1.01 (0.58–1.79)	1.01 (0.56–1.81)
Kept regular hours				
No	32	170	Reference	Reference
Yes	46	159	1.40 (0.84–2.34)	1.61 (0.94–2.75)
Had sufficient sleep				
No	16	37	Reference	Reference
Yes	62	292	0.45 (0.23–0.87)	0.45 (0.22–0.88)
Felt psychological stress				
No	13	79	Reference	Reference
Yes	65	250	1.74 (0.88–3.41)	1.54 (0.78–3.04)
Walked				
Less than 30 min/day	20	155	Reference	Reference
30 min/day or more	58	174	2.00 (1.13–3.56)	2.07 (1.14–3.76)
Leisure-time physical exercise				
Less than 3 days/week	51	256	Reference	Reference
3 days/week or more	27	73	1.64 (0.94–2.84)	1.66 (0.94–2.91)
Smoking habit				
Never smokers	48	261	Reference	Reference
Current and former smokers	29	64	2.24 (1.29–3.88)	1.94 (1.09–3.45)
Never smokers	48	261	Reference	Reference
Current smokers	24	49	2.27 (1.25–4.13)	1.97 (1.06–3.65)
Former smokers	5	15	2.11 (0.72–6.16)	1.85 (0.62–5.50)
Drinking habit				
Less than 1 day/week	57	284	Reference	Reference
1 day/week or more	20	43	2.18 (1.17–4.04)	1.80 (0.94–3.44)
Less than 1 day/week	57	284	Reference	Reference
1–3 days/week	11	37	1.43 (0.67–3.03)	1.29 (0.60–2.77)
4–5 days/week or more	9	6	6.22 (2.10–18.44)	4.49 (1.43–14.08)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

increased ORs, but none of these three factors reach the point of significance. In contrast, even after adjusting for age and alcohol drinking, current and former smokers (OR = 2.24, 95% CI = 1.04 – 4.81) and current smokers (OR = 2.45, 95% CI = 1.10 – 5.49) showed an increased OR compared with never smokers. On the other hand, those with a drinking habit (drinking 1 day/week or more) showed an increased age and smoking adjusted OR (OR = 3.20, 95% CI = 1.45 – 7.07). High-frequency of drinking was a strong risk factor for SLE (4–5 days/week or more vs less than 1 day/week: OR = 8.22, 95% CI = 2.21 – 30.50) even after controlling for age and smoking.

Analyses of the patients treated for SLE in Hokkaido, northern Japan

Tables 5 and 6 illustrate the ORs for SLE and 95% CIs in relation to lifestyles (i.e., sleeping habits, leisure-time physical exercise, and smoking and alcohol drinking) in the patients treated for SLE in Hokkaido.

Table 5 shows the result of analyses of all the patients treated for SLE for less than 10 years (case C). Smoking (current and former smokers) showed a significantly increased age-adjusted OR (vs never smokers: OR = 2.41, 95% CI = 1.01 – 5.74) but the 95% CI for smoking became rather wide after adjusting for alcohol drinking (OR = 2.44, 95% CI = 0.98 – 6.03). On the other hand, after adjusting for age and alcohol drinking, former smokers (OR = 9.07, 95% CI = 1.11 – 74.74) showed a significantly increased risk of SLE compared with never smokers while current smokers (vs never smokers: OR = 2.19, 95% CI = 0.87 – 5.76) showed a marginally increased risk. In contrast, after adjusting for age and smoking, both low frequency of drinking (1–3 days/week) and high frequency of drinking (4–5 days/week or more) failed to show any meaningful association with the development of SLE.

Among Hokkaido controls, current and former smokers were more likely to be drinkers than never smokers (43.4% vs 14.6%, $P < 0.01$) (not shown in the table). Current and former smokers were less likely to keep regular hours (45.3% vs 75.0%, $P < 0.01$), and to have sufficient sleep than never-smokers (32.1% vs 51.2%). Drinkers were more likely to have smoking experience than nondrinkers in controls (54.8% vs 21.3%, $P < 0.01$) while they were less likely to keep regular hours than their counterparts (40.5% vs

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 5 years in Kyushu (case B)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	28	242	Reference	Reference
7 h/day or more	10	87	0.75 (0.34–1.68)	0.74 (0.32–1.73)
Kept regular hours				
No	16	170	Reference	Reference
Yes	22	159	1.34 (0.68–2.69)	1.67 (0.80–3.48)
Had sufficient sleep				
No	7	37	Reference	Reference
Yes	31	292	0.51 (0.21–1.26)	0.47 (0.18–1.22)
Felt psychological stress				
No	7	79	Reference	Reference
Yes	31	250	1.56 (0.64–3.71)	1.13 (0.46–2.79)
Walked				
Less than 30 min/day	11	155	Reference	Reference
30 min/day or more	27	174	1.78 (0.83–3.82)	1.85 (0.82–4.17)
Leisure-time physical exercise				
Less than 3 days/week	25	256	Reference	Reference
3 days/week or more	13	73	1.57 (0.75–3.29)	1.56 (0.72–3.36)
Smoking habit				
Never smokers	20	261	Reference	Reference
Current and former smokers	17	64	3.17 (1.56–6.46)	2.24 (1.04–4.81)
Never smokers	20	261	Reference	Reference
Current smokers	15	49	3.51 (1.66–7.44)	2.45 (1.10–5.49)
Former smokers	2	15	1.92 (0.41–9.05)	1.42 (0.29–7.02)
Drinking habit				
Less than 1 day/week	22	284	Reference	Reference
1 day/week or more	15	43	4.17 (1.99–8.74)	3.20 (1.45–7.07)
Less than 1 day/week	22	284	Reference	Reference
1–3 days/week	8	37	2.65 (1.09–6.44)	2.33 (0.94–5.82)
4–5 days/week or more	7	6	12.75 (3.89–41.76)	8.22 (2.21–30.50)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

73.6%, $P < 0.01$). There was no meaningful association between lifestyle-related factors among the Hokkaido SLE patients.

Analyses restricted to the patients treated for SLE for less than 5 years (case D) are shown in Table 6. Leisure-time physical exercise (3 times/week or more vs less than 3 times/week: OR = 2.81, 95% CI = 0.94 – 8.37) showed a marginally increased risk of SLE after adjusting for age, smoking and alcohol drinking. Compared with never smokers, current and former smokers (OR = 2.66, 95% CI = 0.93 – 7.57), and current smokers (OR = 2.50, 95% CI = 0.86 – 7.25) showed a nonsignificantly increased OR adjusted for age and drinking while either low frequency of drinking (1–3 days/week) or high frequency of drinking (4–5 days/week or more) showed no meaningful relation to the risk of SLE.

Discussion

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease,[2–4] and subjective sleep quality is reported to influence immunity.[14] These findings suggest that good sleeping habits may reduce the risk of SLE. However, there is little information about the relationship between sleep hygiene and the risk of SLE except the study by Nagai et al.,[11] who reported that sleeping 8 h/day or more failed to reduce the risk of SLE. In the present study, neither the length of sleep nor keeping regular hours showed any meaningful relation to the development of SLE. In contrast, the case control study in Kyushu revealed that sufficient sleep decreased the risk of SLE although it failed to show any meaningful association with SLE in Hokkaido. The following possibilities may explain the different results in the two regions. Firstly, controls in Kyushu were not free from selection bias because the lifestyles of nursing college students and care workers may be different from those of the general population. Another explanation is that this result may be a chance phenomenon, because the number of SLE patients analyzed in both regions was small. An additional study is needed to clarify whether quality of sleep influences the development of SLE.

Physical activity is reported to reduce the risk of cancer[15,16] and coronary artery disease.[17] However, as with sleep hygiene, there is little information about leisure-time physical exercise and the risk of SLE. Nagai et al.[11] reported that

Table 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 10 years in Hokkaido (case C)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	4	8	Reference	Reference
7 h/day or more	31	180	0.60 (0.14–2.69)	0.58 (0.13–2.52)
Kept regular hours				
No	19	63	Reference	Reference
Yes	16	125	1.07 (0.44–2.57)	1.34 (0.53–3.37)
Had sufficient sleep				
No	20	100	Reference	Reference
Yes	15	88	1.33 (0.57–3.12)	1.43 (0.60–3.40)
Felt psychological stress				
No	6	53	Reference	Reference
Yes	29	135	1.49 (0.51–4.33)	1.49 (0.50–4.46)
Walked				
Less than 30 min/day	13	57	Reference	Reference
30 min/day or more	22	131	1.03 (0.44–2.44)	1.13 (0.46–2.79)
Leisure-time physical exercise				
Less than 3 days/week	26	139	Reference	Reference
3 days/week or more	9	49	1.63 (0.62–4.28)	1.82 (0.67–4.95)
Smoking habit				
Never smokers	12	132	Reference	Reference
Current and former smokers	22	53	2.41 (1.01–5.74)	2.44 (0.98–6.03)
Never smokers	12	132	Reference	Reference
Current smokers	19	50	2.12 (0.86–5.18)	2.19 (0.87–5.56)
Former smokers	3	3	8.38 (1.10–63.79)	9.07 (1.11–74.41)
Drinking habit				
Less than 1 day/week	22	144	Reference	Reference
1 day/week or more	13	42	1.22 (0.51–2.94)	0.95 (0.37–2.43)
Less than 1 day/week	22	144	Reference	Reference
1–3 days/week	4	24	0.71 (0.20–2.51)	0.60 (0.16–2.22)
4–5 days/week or more	9	18	1.91 (0.65–5.65)	1.34 (0.44–4.34)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

neither outdoor sports nor physical activity had any meaningful associated with SLE. In the present study, walking showed a significantly increased risk of SLE and leisure-time physical exercise showed a marginally increased risk while sufficient sleep was associated with a significantly decreased risk of SLE in Kyushu. On the other hand, in Hokkaido, neither walking nor sufficient sleep showed any meaningful association with SLE, although leisure-time physical exercise showed a marginally increased risk. Kyushu is located in the extreme southwestern part of Japan with a temperate climate, and summer sports are popular. On the other hand, Hokkaido is the northernmost island of Japan with a subarctic climate, where winter sports are popular. Because skin sensitivity to sunlight increases the risk of SLE,[10,11] walking, which was a significant risk factor only in southern Japan, may be a surrogate of staying outdoors under the sunlight. Further studies are needed to clarify this.

Several investigators[6–10] have suggested that smoking is a risk factor for SLE. Mongey and Hess[18] stated that tobacco smoke contained chemical risk factors for SLE (i.e., hydrazine and its derivatives). Ghaussy et al.[8] reported a significantly increased risk of SLE in both current and former smokers. In contrast, the studies by Nagata et al.[6] and Hardy et al.[7] showed that the increased risk of SLE existed only in current smokers. On the other hand, Sanchez-Guerrero et al.[19] and Cooper et al.[20] reported no association with smoking history (i.e., current, former, or never-smoker) and the risk of SLE. In the present study, compared with never smokers, current and former smokers showed an increased OR. However, only a marginally increased risk of SLE was seen in Hokkaido whereas in Kyushu a significantly increased risk was seen. These findings may be explained by the fact that the number of subjects was small in the present study.

Several reports suggested that alcohol drinking may prevent the development of SLE,[6–10] whereas others disclosed no association between alcohol drinking and risk of SLE.[9,11] In the present study, there was no meaningful association between alcohol drinking and risk of SLE in Hokkaido. However, in Kyushu, high frequency drinkers showed an increased risk. It is possible to partly explain these findings in the following ways. Firstly, these results may be a chance phenomenon, because the number of subjects was small in the present study. Another explanation is that high frequency drinkers may include heavy drinkers or binge drink-

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) for SLE according to lifestyle factors among the patients treated for SLE for less than 5 years in Hokkaido (case D)

Lifestyle factors	Case no.	Control no.	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Sleeping hours				
Less than 7 h/day	3	8	Reference	Reference
7 h/day or more	21	180	0.50 (0.10–2.45)	0.52 (0.11–2.59)
Kept regular hours				
No	14	63	Reference	Reference
Yes	10	125	0.75 (0.28–2.01)	0.89 (0.32–2.45)
Had sufficient sleep				
No	15	100	Reference	Reference
Yes	9	88	0.97 (0.37–2.55)	0.98 (0.37–2.61)
Felt psychological stress				
No	4	53	Reference	Reference
Yes	20	135	1.39 (0.41–4.69)	1.46 (0.42–5.10)
Walked				
Less than 30 min/day	10	57	Reference	Reference
30 min/day or more	14	131	0.82 (0.32–2.13)	0.82 (0.30–2.20)
Leisure-time physical exercise				
Less than 3 days/week	16	139	Reference	Reference
3 days/week or more	8	49	2.38 (0.84–6.71)	2.81 (0.94–8.37)
Smoking habit				
Never smokers	8	132	Reference	Reference
Current and former smokers	16	53	2.56 (0.95–6.96)	2.66 (0.93–7.57)
Never smokers	8	132	Reference	Reference
Current smokers	14	50	2.38 (0.85–6.62)	2.50 (0.86–7.25)
Former smokers	2	3	5.31 (0.66–42.79)	5.87 (0.67–51.19)
Drinking habit				
Less than 1 day/week	15	144	Reference	Reference
1 day/week or more	9	42	1.20 (0.45–3.24)	0.88 (0.30–2.53)
Less than 1 day/week	15	144	Reference	Reference
1–3 days/week	3	24	0.73 (0.18–3.0)	0.60 (0.14–2.60)
4–5 days/week or more	6	18	1.80 (0.54–5.99)	1.20 (0.33–4.31)

Multivariate-adjusted OR: adjusted for age, smoking and drinking

ers. In the present study, drinkers were more likely to feel psychological stress than nondrinkers among controls in Kyushu, and psychological stress showed an increased OR in Kyushu although it failed to be a significant risk factor for SLE. Heavy drinkers and binge drinkers may have felt emotional stress, which is a risk factor for SLE.[21]

There are some limitations to our study. First, cases were not newly diagnosed SLE patients but patients treated for SLE for less than 10 years in both Kyushu and Hokkaido. The patients may have changed their lifestyles after the development of SLE. They may have quit smoking, drinking heavily, or participating in outdoor sports. On the other hand, their sleep quality may have become poorer because SLE female patients are more likely to suffer from poor sleep quality than healthy females.[22,23] Therefore, risk factors for SLE such as smoking, high frequency of drinking, and leisure-time physical exercise may have been underestimated, whereas preventive factors such as sleep sufficiency may have been overestimated. Second, our cases were not free from selection bias because half of eligible SLE patients did not agree to participate in this study. Some of them refused to participate in this study after we asked them to donate blood samples for DNA extraction and genotyping of the candidate genes of SLE. Third, our controls were not free from selection bias either because they were not randomly selected from the general population. In Kyushu, controls were recruited from nursing college students and care workers in nursing homes. Their lifestyles may be different from the general population. However, the risk of SLE from smoking may have been underestimated in Kyushu because the high prevalence of smoking among nursing students and nurses is a serious social problem.[24–26] On the other hand, in Hokkaido, controls were participants in a health checkup in a local town. They may well have had more healthy lifestyles than the general population. Fourth, we cannot clearly explain the reason why high frequency of alcohol consumption increased the risk of SLE in Kyushu but did not in Hokkaido. Last, although SLE is thought to be a multi-factorial disease in which complex environmental and genetic factors interact,[2,4] we did not evaluate genetic factors in this paper.

On the other hand, this study has its strengths as well. The present study showed that there was a common risk factor in the two different regions of Kyushu, southern Japan, and Hokkaido, northern Japan, even though controls were not matched. Although there are some studies on

the lifestyle related risk factors for SLE among the Japanese population,[6,11] they did not estimate the risk of SLE after controlling for other factors. As far as we know, this is the first report showing that smoking is a risk factor for SLE among Japanese females after controlling for age and other factors.

In conclusion, the present study may support the belief that smoking is a risk factor for SLE among Japanese females. In addition to smoking, walking, leisure-time physical exercise, and high frequency of drinking were proposed as the probable risk factors. On the other hand, sufficient sleep is suggested as a preventive factor. However, further studies are required to confirm the results of the present study.

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