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Alcohol, Smoking, and Dietary Status and Susceptibility to Malignant Lymphoma in Japan: Results of a Hospital-based Case-control Study at Aichi Cancer Center

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Recent increase in the incidence of malignant lymphoma (ML) suggests possible involvement of lifestyle or environmental factors in its genesis. However, evidence for an effect of lifestyle factors, especially diet, on ML risk among Japanese is lacking. To explore the possibility that lifestyle factors exert an influence, we have conducted a hospital-based case-control study with 333 histologically confirmed ML cases and 55 904 non-cancer controls who first visited Aichi Cancer Center Hospital between 1988 and 1997. Multiple logistic regression analysis showed regular alcohol consumption to be associated with reduced risk of ML, whereas no risk change was observed for smoking. Some other factors including intake of vegetables (carrots and pumpkin), pork and fish showed partial associations, but their significance needs further clarification. From the previous study on genetic background for ML [Matsuo *et al., Blood,* 97, 3205–3209 (2001)], genetic variation combined with limited environmental factors should be targeted in future studies.

Key words: Malignant lymphoma — Lifestyle — Alcohol — Case-control study

Malignant lymphoma (ML) is a rapidly increasing malignancy in developed countries,[1–3] including Japan, where the age-standardized incidence rates were 8.2 for males and 5.0 for females in 1993, as opposed to 5.7 and 3.0, respectively in 1975.[4] The increasing trend suggests possible involvement of environmental factors in lymphomagenesis, in line with descriptive epidemiological observations that mortality from non-Hodgkin's lymphomas among persons who migrate and in subsequent generations more closely resembles that in the host country than that in the country of origin.[5]

Many epidemiological studies have been conducted mainly in Western countries to assess the relationship between ML susceptibility and various environmental influences, including pesticides,[6] occupations,[7–9] viruses (human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV-1),[10] and others), *Helicobacter pylori* infection,[11] blood transfusion,[12] primary[13] or secondary[14] immunodeficiency, radiation,[15] smoking,[16,17] diet (animal protein,[18–21] milk,[22] fruits and vegetables,[23,24] and fat[20]) and other miscellaneous factors. In Japanese, epidemiological studies concerning ML have been mainly concentrated on HTLV-I related factors because of the extremely high incidence of HTLV-I infection and adult T-cell leukemia/lymphoma in some areas.[10] Concerning dietary factors, only eleven epidemiological studies[18–28] have been conducted previously across the world, and no information has been published for Japanese to our knowledge. Similarly, evidence is lacking for the influence, if any, of alcohol and smoking status.

To evaluate possible associations between these lifestyle factors and ML susceptibility, we therefore conducted a hospital-based case-control study using data from the Hospital Epidemiological Research Program at Aichi Cancer Center (HERPACC).

MATERIALS AND METHODS

Study subjects General characteristics of the study population and the data collection procedures were as described elsewhere.[29–31] Briefly, a self-administered questionnaire about lifestyle factors has been given routinely to first-visit outpatient adults at the Aichi Cancer Center Hospital, Nagoya since 1988. An expert interviewer checks all written responses at the time of collection within the first-visit day after medical examinations. The questionnaire includes questions on demographics, past medical history, family history, smoking and drinking habits, general health condition, reproduction, and beverage and food intake. The present study is based on data for individuals

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Abbreviations: ML, malignant lymphoma; OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; HTLV-I, human T-cell leukemia virus; HERPACC, Hospital Epidemiologic Research Program at Aichi Cancer Center; US, the United States.

who completed questionnaires between January 1988 and December 1997.

During the study, questionnaires were handed out to 67 854 (91.3%) first-visit outpatients (n=74 280). Of this total, the number of respondents was 66 885 (98.6%). Among these, 10 981 were diagnosed as having cancer and registered with the hospital cancer-registry system of Aichi Cancer Center Hospital. The number of non-cancer patients was 55 904. From all cancer patients, 333 cases diagnosed histologically as having primary malignant lymphomas at Aichi Cancer Center were selected as cases by identification via the hospital cancer registry system using the ICD-10 code (C81–85). Cancer cases with multiple organ involvement were excluded. The non-cancer outpatients were all employed as controls. Matching was not conducted to avoid reduction of statistical power.[32] Age and sex distribution for the two groups are shown in Table I.

Lifestyle factors Lifestyle factors examined included smoking, alcohol drinking, habitual physical exercise, and specific dietary items. Smoking status was categorized into three (current smoker, former smoker, and never smoker). Ever-smoker included current and former smokers. Former smokers were defined as persons who had quit smoking at least 1 year previously. Drinking status was also categorized into three (current, former, and never drinker). Former drinkers were defined as persons who had quit drinking at least 1 year previously. Consumption of each type of alcoholic beverage (Japanese sake, beer, shochu and whiskey) was determined as the average number of drinks per day, converted into Japanese sake (rice wine) equivalents. One drink equates to one "gou" (180 ml) of sake, one regular bottle (633 ml) of beer or two shots (57 ml) of whisky. One drink of "shochu" (distilled spirit) containing 25% ethanol was rated as 108 ml. Wine was not included in the present questionnaire because of its relatively limited consumption by Japanese. Total amount of alcohol consumed (ml/day) was estimated as the summarized amounts of Japanese sake, beer, shochu, and whiskey among current and former drinkers.

Dietary factors were analyzed in terms of 11 dietary habits and consumption frequency of three beverages and 23 food items. Dietary items were divided into four or five groups according to the frequency of consumption before the onset of current symptoms or the interview in the questionnaire and these were further divided into two subgroups for analyses. Details of preferences for salty and greasy food were included in general dietary habits.

Statistical analyses The effect of each lifestyle factor was assessed in terms of the odds ratio (OR). All ORs and 95% confidence intervals (CIs) were adjusted for sex and age as a continuous variable, instead of age-sex matching, using an unconditional logistic regression model. The ORs concerning each lifestyle factor were estimated for all subjects except those for whom that information was lacking, and for the subjects divided by sex. All statistical analyses were performed using STATA version 7 software (STATA Corporation, Inc., College Station, TX).

RESULTS

As shown in Table I, cases were slightly older than controls. Males were dominant in cases and females in controls.

Significantly increased ORs were observed for former smokers, but not for current smokers (Table II). The relatively small number of cases in this group (22 out of 333 cases) might have given an unstable risk estimation. The OR for ever-smokers relative to never smokers pointed to a slightly increased risk, but without statistical significance. Number of cigarettes per day in current smokers was without obvious influence.

Current drinking was associated with decreased risk of malignant lymphoma for all subjects (Table II), the age-sex-adjusted OR relative to never drinkers being 0.67

Table I. Age[a] and Sex Distribution of the Subjects in Aichi Cancer Center Hospital, 1988–1997

	References			Cases		
	All	Male	Female	All	Male	Female
Total number of subjects	55904	15811	40093	333	202	131
Age number (%)						
<30	5650 (10.1)	1351 (8.5)	4299 (10.7)	19 (5.7)	14 (6.9)	5 (3.8)
30–39	9308 (16.7)	1893 (12.0)	7415 (18.5)	28 (8.4)	22 (10.9)	6 (4.6)
40–49	17387 (31.1)	3832 (24.2)	13555 (33.8)	67 (20.1)	40 (19.8)	27 (20.6)
50–59	12789 (22.9)	4122 (26.1)	8667 (21.6)	100 (30.0)	58 (28.7)	42 (32.1)
60–69	7957 (14.23)	3323 (21.0)	4634 (11.6)	73 (21.9)	40 (19.8)	33 (25.2)
70–	2813 (5.0)	1290 (8.2)	1523 (3.8)	46 (13.8)	28 (13.9)	18 (13.8)

a) Age at diagnosis or interview.

Table II. Adjusted[a] ORs and 95%CIs According to Smoking, Drinking, and Physical Exercise

	Number of subjects (cases/references)			ORs and 95%CIs		
	All 333/55904	Male 202/15811	Female 131/40093	All	Male	Female
Smoking status[b]						
Never	148/36844	42/3648	106/33196	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Former	22/1363	18/861	4/502	1.90 (1.16–3.07)	1.75 (1.00–3.06)	3.08 (1.12–8.42)
Current	163/17635	142/11290	21/6345	1.10 (0.83–1.46)	1.06 (0.75–1.50)	1.37 (0.85–2.19)
Unknown	0/62	0/12	0/50	—	—	—
Ever	185/18998	160/12151	25/6847	1.16 (0.88–1.53)	1.11 (0.79–1.57)	1.50 (0.97–2.33)
Numbers of cigarettes for current smokers						
Never	148/36844	42/3648	106/33196	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1–19/day	51/7228	39/2988	12/4240	1.04 (0.73–1.47)	1.08 (0.70–1.69)	1.19 (0.65–2.17)
≥20/day	112/10407	103/8302	9/2105	1.12 (0.81–1.53)	1.06 (0.74–1.52)	1.68 (0.85–3.34)
Drinking status[c]						
Never	183/32873	74/4618	109/28255	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Former	14/1011	12/609	2/402	1.01 (0.85–1.77)	1.14 (0.61–2.12)	1.18 (0.29–4.80)
Current	136/21971	116/10579	20/11392	0.67 (0.52–0.85)	0.70 (0.52–0.94)	0.62 (0.29–1.00)
Unknown	0/49	0/5	0/44	—	—	—
Never/Former				1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Current				0.67 (0.52–0.85)	0.69 (0.52–0.91)	0.62 (0.38–1.00)
Amount of drinking						
Current drinkers						
Never	183/32873	74/4618	109/28255	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<1.5 drinks/day	87/17199	69/6605	18/10594	0.63 (0.48–0.83)	0.67 (0.48–0.93)	0.60 (0.36–0.99)
≥1.5 drinks/day	49/4821	47/3979	2/842	0.74 (0.52–1.04)	0.74 (0.52–1.08)	0.85 (0.20–3.48)
Former drinkers						
Never	193/32873	74/4618	109/28255	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<1.5 drinks/day	13/695	11/344	2/351	1.57 (0.87–2.82)	1.82 (0.95–3.59)	1.33 (0.33–5.43)
≥1.5 drinks/day	1/365	1/270	0/95	0.18 (0.02–1.28)	0.21 (0.03–1.53)	NE[d]

a) Age-adjustment for the analysis according to sex, and age-sex-adjustment for the combined analysis. Subjects classified as 'Unknown' were excluded from the analyses.
b) Former smokers were defined as subjects who had quit smoking at least 1 year previously.
c) Former drinkers were defined as the subjects who had quit drinking at least 1 year previously. One drink indicates one "gou" of Japanese sake which contains 27 ml of ethanol.
d) NE indicates not estimated, because no cases are in this group.

(0.25–0.85). The same trend was observed when the analysis was conducted according to sex. Drinking amount for current drinkers compared with never drinkers did not differ with a cut-off of 1.5 drinks per day, with reduced risk above and below this level. For former drinkers, similar analyses were conducted but the small number of cases in this category made stable estimation difficult.

Table III shows the age-sex-adjusted ORs for dietary factors with the subject distribution for each. Preference for salty and greasy foods was not associated with risk. Frequent consumption of raw vegetables, green vegetables, carrot, cabbage, lettuce, potato, and fruits also did not change the risk, whereas a significant reduction of risk for all subjects was evident for pumpkin. Focusing on females, carrots also showed a risk reduction. Various types of meat except pork, and milk consumption were not linked to increased or decreased ORs. For pork consumption, statistically significantly increased ORs were observed for overall and male analyses, and the OR for females showed a similar trend. Fish demonstrated a reduced OR limited to females. The ORs for soybean product as well as Japanese tea, coffee, and black tea did not point to any change in risk.

DISCUSSION

The present hospital-based case-control study demonstrated a statistically significantly decreased risk of ML with habitual alcohol consumption on overall analysis, while smoking was without clear influence. Salty and

Table III. Adjusted[a] ORs and 95%CIs for Malignant Lymphoma According to Intake of Food Items

		Number of subjects (cases/controls)			Adjusted ORs and 95%CIs		
		All 333/55904	Male 202/15811	Female 131/40093	All	Male	Female
Preference for salty food	No	99/19757	50/3994	49/15763	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	234/36053	152/11793	82/24260	1.12 (0.88–1.42)	1.06 (0.77–1.46)	1.17 (0.82–1.66)
	Unknown	0/94	0/24	0/70	—	—	—
Preference for oily food	No	150/26813	72/6188	78/20325	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Yes	183/28924	130/9576	53/19348	1.02 (0.82–1.27)	1.20 (0.90–1.61)	0.82 (0.58–1.16)
	Unknown	0/167	0/47	0/120	—	—	—
Raw vegetable intake	Occasionally or less	92/13831	49/4892	43/10749	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	240/35337	152/10885	88/29238	1.08 (0.85–1.38)	1.38 (1.00–1.90)	0.84 (0.58–1.21)
	Unknown	1/146	1/30	0/106	—	—	—
Green vegetables	Occasionally or less	171/26824	111/9501	60/17323	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	162/28971	91/6277	71/22694	0.99 (0.80–1.24)	1.19 (0.90–1.57)	0.79 (0.56–1.12)
	Unknown	0/109	0/33	0/76	—	—	—
Carrot	Occasionally or less	224/31810	145/11806	79/20004	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	109/23918	57/3947	52/19971	0.86 (0.68–1.09)	1.15 (0.84–1.56)	0.63 (0.45–0.90)
	Unknown	0/176	0/58	0/118	—	—	—
Pumpkin	Occasionally or less	309/49335	190/14664	119/34671	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	24/6387	12/1078	12/5309	0.63 (0.41–0.96)	0.80 (0.44–1.44)	0.48 (0.26–0.88)
	Unknown	0/182	0/69	0/113	—	—	—
Cabbage	Occasionally or less	219/32764	134/10084	85/22680	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	112/22955	68/5669	44/17286	0.82 (0.65–1.03)	0.91 (0.68–1.22)	0.70 (0.49–1.01)
	Unknown	2/185	0/58	2/127	—	—	—
Lettuce	Occasionally or less	239/37084	146/11689	93/25395	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	93/18522	56/4037	37/14485	0.97 (0.76–1.23)	1.14 (0.84–1.56)	0.79 (0.54–1.16)
	Unknown	1/298	0/85	1/213	—	—	—
Potato	Occasionally or less	240/37968	157/12827	83/25141	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	93/17760	45/2931	48/14829	1.03 (0.81–1.32)	1.21 (0.86–1.69)	0.90 (0.63–1.28)
	Unknown	0/176	0/53	0/123	—	—	—
Fruit intake	Occasionally or less	117/17271	81/6796	36/10475	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	216/38504	121/8981	95/29523	0.90 (0.72–1.14)	1.06 (0.79–1.41)	0.73 (0.49–1.07)
	Unknown	0/129	0/34	0/95	—	—	—
Milk consumption	Occasionally or less	187/30846	124/9677	63/211969	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Everyday	145/24904	77/6081	68/18823	0.96 (0.77–1.20)	0.94 (0.70–1.25)	1.03 (0.73–1.46)
	Unknown	1/154	1/53	0/101	—	—	—
Beef	Occasionally or less	300/49869	101/14103	119/35766	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	32/5878	20/1655	12/4223	0.99 (0.69–1.43)	0.99 (0.62–1.58)	0.94 (0.52–1.70)
	Unknown	1/157	1/53	0/104	—	—	—
Pork	Occasionally or less	278/47295	169/14062	109/33233	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	55/8438	33/1693	22/6745	1.49 (1.11–2.00)	1.75 (1.20–2.56)	1.24 (0.78–1.96)
	Unknown	0/171	0/56	0/115	—	—	—
Chicken	Occasionally or less	268/44844	166/13306	102/31538	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	65/10913	36/2460	29/8453	1.09 (0.83–1.44)	1.17 (0.81–1.68)	0.99 (0.66–1.50)
	Unknown	0/147	0/45	0/102	—	—	—
Egg	Occasionally or less	117/18547	75/5985	42/12562	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	216/37261	127/9791	89/27470	1.04 (0.83–1.31)	1.04 (0.78–1.39)	1.11 (0.77–1.61)
	Unknown	0/96	0/35	0/61	—	—	—
Salty fish	Occasionally or less	302/50720	184/14236	118/36484	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	31/4978	18/1513	13/3465	0.88 (0.61–1.28)	0.87 (0.53–1.41)	0.92 (0.51–1.63)
	Unknown	0/206	0/62	0/144	—	—	—
Fish dish	Occasionally or less	226/38466	132/10819	94/27647	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	104/17287	68/4939	36/12348	0.89 (0.70–1.12)	1.07 (0.79–1.44)	0.67 (0.46–0.99)
	Unknown	3/151	2/53	1/98	—	—	—
Miso soup	Occasionally or less	103/22333	61/5620	42/16713	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	229/33504	40/10167	89/23337	1.26 (1.00–1.59)	1.22 (0.90–1.66)	1.35 (0.93–1.95)
	Unknown	1/67	1/24	0/43	—	—	—
Tofu	Occasionally or less	197/31670	128/9894	69/21776	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥3–4 times/week	136/24082	74/5859	62/18223	0.89 (0.71–1.11)	0.91 (0.68–1.22)	0.90 (0.63–1.27)
	Unknown	0/152	0/58	0/94	—	—	—
Japanese tea consumption[b]	Occasionally or less	44/8667	28/2564	16/6103	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Everyday	197/32166	121/9171	76/22995	1.04 (0.75–1.46)	1.13 (0.74–1.72)	0.95 (0.55–1.64)
	Unknown	92/15071	53/4076	39/10995	—	—	—
Coffee consumption[b]	Occasionally or less	98/16771	51/4321	47/12450	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Everyday	143/24075	98/7418	45/16657	1.07 (0.82–1.39)	1.18 (0.83–1.66)	0.97 (0.64–1.40)
	Unknown	92/15058	53/4072	39/10986	—	—	—
Black tea consumption[b]	Occasionally or less	224/37454	141/11043	83/26411	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Everyday	16/3280	8/664	8/2616	1.04 (0.62–1.73)	0.97 (0.47–1.99)	1.18 (0.57–2.45)
	Unknown	93/15170	53/4104	40/11066	—	—	—

a) All ORs were adjusted for age. Sex is additionally adjusted in overall analyses. The subjects who were classified as ‘Unknown’ for each evaluated factor were excluded from analyses of the factor.
b) Subjects before 1990 were categorized into the ‘Unknown’ group because information on Japanese tea, coffee, and tea consumption was only collected from this time point.

greasy food preferences were also not associated with risk, while only pumpkin consumption, among vegetable and fruit, showed a significantly reduced risk. Consumption of pork, but not other animal proteins (beef, chicken, milk, and egg) was associated with elevation and fish consumption with reduction in risk, the latter only in females.

The decrease with alcohol consumption observed overall as well as for each sex is of particular interest, since the data in the literature are equivocal. The first hospital-based case-control study conducted in northern Italy evaluated alcohol consumption according to the beverage type, and found no relation.[21] Similarly, no association was seen in two studies,[25, 33] but most of the other studies did not evaluate alcohol consumption. A recent population-based case-control study conducted in the United States (US) pointed to a significant risk reduction with alcohol consumption among women and a similar but non-significant trend among men.[34] Although there is controversy about alcohol and ML risk, several cohort studies conducted in Asian countries have revealed decreased incidences of cancer in moderate alcohol consumers.[35, 36] Possible underlying mechanisms for this preventive effect remain unclear and the existence of unknown confounders could not be ruled out, but further evaluations by epidemiological or biological studies are clearly warranted.

Concerning smoking, there have been several reports of a positive association with lymphoma risk,[16, 17, 25, 27, 34, 37–40] but most population-based case-control or cohort studies have consistently shown no association except for the first report by Brown *et al.* from the US.[16] Our observations are thus in line with the literature.

Cunningham found a positive correlation between ML and protein consumption,[18] and an animal experiment yielded a high incidence of ML only among rats fed a high protein diet.[41] Several epidemiological studies have shown a high risk with high animal protein,[19–22, 25] especially of bovine origin, but conflicting results have also been reported.[23] A hypothetical mechanism for animal protein lymphomagenesis is chronic antigenic stimulation through protein absorption via the gastrointestinal epithelium that might act in concert with other factors such as viruses or genetic susceptibility.[18] A nested case-control study conducted in US showed a higher risk of lymphatic system malignancies among workers in the meat industry, and some relation to exposure to animal protein was suggested.[42] The significance of an association with pork consumption is therefore not clear.

Studies concerning vegetable consumption have mostly given inconsistent results and the magnitudes of effects were not large. For example, Zhang *et al.* reported a possible risk reduction for frequent consumers of vegetables and fruits[24] although the statistical significance was marginal (OR 0.62; 0.38–1.02). They analyzed specific nutrients (e.g., carotene, lycopene, fiber, and vitamins) but only fiber showed the risk change. The same research group analyzed vitamin supplement use in another study and found no apparent association.[28] The validity of the reduced risk observed here for pumpkin and to a certain extent carrot remains to be confirmed.

It is necessary that the background of this hospital-based case-control study program, HERPACC, be described. Because the cases and controls were selected from the same source population of first-visit outpatients, this study is internally valid and the representativeness of the subjects has already been described elsewhere.[30] Improbability of selection bias in HERPACC has been argued in detail.[31] The limitation of the present study was that the number of cases compared to controls was too small to ensure comparability. Although it is true that efficiency does not increase above a control:case ratio of 4:1 given a fixed number of cases, a higher control:case ratio certainly does not hurt efficiency, and may lead to a marginal improvement. Thus, we saw no reason not to include the entire control group in the analysis in spite of selecting a random sample. The methodological issue of using all available non-cancer individuals as a control group has already been discussed elsewhere.[32] Although this study was thus methodologically validated, careful interpretation is necessary in extrapolation of our results to the general Japanese population. ML requires specific experience for histological diagnosis and treatment because of the complex sub-classification depending on clinicopathological features, and the possibility that cases had been selected before visiting the hospital could not be completely ruled out. In addition, the fact that the influence of other factors, such as dietary fat,[43] was not examined in this study must be taken into consideration.

Considering recent developments in molecular epidemiology, future studies in this field could expand to cover genetic background and its interactions with environmental factors. Based on the results obtained in the present study, the influence of environmental factors in lymphomagenesis seems to be limited. As we previously suggested in connection with the association between ML susceptibility and folate/methionine metabolizing enzyme polymorphisms,[44] a certain genetic background could predispose to the occurrence of ML. Further epidemiological studies should cover genetic aspects as well as environmental exposures.

In conclusion, our data showed possible benefit of alcohol consumption regarding risk of malignant lymphoma among Japanese, whereas no link was evident with smoking. Some dietary factors including vegetables (carrot and pumpkin), pork and fish showed partial associations in our series but their pathogenic significance needs further clarification. While there remains controversy regarding the relevance of lifestyle factors to lymphomagenesis, our data provide a basis for further investigations.

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REFERENCES

1) Devesea, S. and Fears, T. Non Hodgkin's lymphoma time trends—United States and international data. *Cancer Res.*, **52**, 5432–5440 (1992).
2) Weisenburger, D. D. Epidemiology of non-Hodgkin's lymphoma: recent findings regarding an emerging epidemic. *Ann. Oncol.*, **5**, S19–S24 (1994).
3) Garber, K. Lymphoma rate rise continues to baffle researchers. *J. Natl. Cancer Inst.*, **93**, 494–496 (2001).
4) Tominaga, S. and Oshima, A. (ed.). Cancer mortality and morbidity statistics. *Gann Monogr. Cancer Res.*, No. 47 (1999).
5) Haenszel, W. and Kurihara, M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J. Natl. Cancer Inst.*, **40**, 43–68 (1968).
6) Persson, B., Fredriksson, M., Olsen, K., Boeryd, B. and Axelson, O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer*, **72**, 1773–1778 (1993).
7) Metayer, C., Johnson, E. S. and Rice, J. C. Nested case-control study of tumors of the hemopoietic and lymphatic systems among workers in the meat industry. *Am. J. Epidemiol.*, **147**, 727–738 (1998).
8) Tatham, L., Tolbert, P. and Kjeldsberg, C. Occupational risk factors for subgroups of non-Hodgkin's lymphoma. *Epidemiology*, **8**, 551–558 (1997).
9) Scherr, P. A., Hutchinson, G. B. and Neiman, R. S. Non-Hodgkin's lymphoma and occupational exposure. *Cancer Res.*, **52** (Suppl.), 5503s–5509s (1992).
10) Tajima, K. The 4th nation-wide study of adult T-cell leukemia lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. *Int. J. Cancer*, **45**, 237–243 (1990).
11) Wotherspoon, A. C., Oritz-Hidalgo, C., Falzon, M. R. and Isaacson, P. G. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet*, **338**, 1175–1176 (1991).
12) Cerhan, J. R., Wallace, R. B., Folsom, A. R., Potter, J. D., Sellers, T. A., Zheng, W. and Lutz, C. T. Medical history risk factors for non-Hodgkin's lymphoma in older women. *J. Natl. Cancer Inst.*, **89**, 314–318 (1997).
13) Filipovich, A. H., Mathur, A., Kamat, D. and Shapiro, R. S. Primary immunodeficiency: genetic risk factors for lymphoma. *Cancer Res.*, **52** (Suppl.), 5465s–5467s (1992).
14) Kinlen, L. Immunosuppressive therapy and acquired immunological disorders. *Cancer Res.*, **52** (Suppl.), 5474s–5476s (1992).
15) Boice, J. D., Jr. Radiation and non-Hodgkin's lymphoma. *Cancer Res.*, **52** (Suppl.), 5489s–5491s (1992).
16) Brown, L. M., Everett, G. D., Gibson, R., Burmeister, L. F., Schuman, L. M. and Blair, A. Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. *Cancer Causes Control.*, **3**, 49–55 (1991).
17) Linet, M. S., McLaughlin, J. K., Hsing, A. W., Wacholder, S., Co Chien, H. T., Schuman, L. M., Bjelke, E. and Blot, W. J. Is cigarette smoking a risk factor for non-Hodgkin's lymphoma or multiple myeloma? Results from the Lutheran brotherhood cohort study. *Leuk. Res.*, **16**, 621–624 (1992).
18) Cunningham, A. S. Lymphomas and animal-protein consumption. *Lancet*, **ii**, 1184–1186 (1976).
19) Chiu, B. C. H., Cerhan, J. R., Folsom, A. R., Sellers, T. A., Kushi, L. H., Wallace, R. B., Zheng, W. and Potter, J. D. Diet and risk of non-Hodgkin lymphoma in older women. *JAMA*, **275**, 1315–1321 (1996).
20) Zhang, S., Hunter, D. J., Rosner, B. A., Colditz, G. A., Fuchs, C. S., Speizer, F. E. and Willett, W. C. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J. Natl. Cancer Inst.*, **91**, 1751–1758 (1999).
21) Franceschi, S., Seraino, D., Carbone, A., Talamini, R. and La Vecchia, C. Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. *Nutr. Cancer*, **12**, 333–341 (1989).
22) Ursin, G., Bjelke, E., Heuch, I. and Vollset, S. E. Milk consumption and cancer incidence: a Norwegian protective study. *Br. J. Cancer*, **61**, 454–459 (1990).
23) Ward, M. H., Zahm, S. H., Weisenburger, D. D., Gridley, G., Cantor, K. P., Saal, R. C. and Blair, A. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control*, **5**, 422–432 (1994).
24) Zhang, S. M., Hunter, D. J., Rosner, B. A., Giovannucci, E. L., Colditz, G. A., Speizer, F. E. and Willet, W. C. Intakes of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma among women. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 477–485 (2000).
25) Tavani, A., Pregnolato, A., Negrl, E., Franceschi, S., Serraino, D., Carbone, A. and La Vecchia, C. Diet and risk of lymphoid neoplasms and soft tissue sarcomas. *Nutr. Cancer*, **27**, 256–260 (1997).
26) Stefani, E. D., Fierro, L., Barrios, E. and Ronco, A. Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. *Leuk. Res.*, **22**, 445–452 (1998).
27) Fabro-Peray, P., Daures, J. P. and Rossi, J. F. Environmen-

tal risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control*, **12**, 201–212 (2001).

28) Zhang, S. M., Giovannucci, E. L., Hunter, D. J., Rimm, E. B., Ascherio, A., Colditz, G. A., Speizer, F. E. and Willet, W. C. Vitamin supplement use and the risk of non-Hodgkin's lymphoma among women and men. *Am. J. Epidemiol.*, **153**, 1056–1063 (2001).
29) Tajima, K., Hirose, K., Inoue, M., Takezaki, T., Hamajima, N. and Kuroishi, T. A model of practical cancer prevention for out-patients visiting a hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Asian Pac. J. Cancer Prev.*, **1**, 35–47 (2000).
30) Hirose, K., Tajima, K., Hamajima, N., Inoue, M., Takezaki, T., Kuroishi, T., Yoshida, M. and Tokudome, S. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn. J. Cancer Res.*, **86**, 146–154 (1995).
31) Inoue, M., Tajima, K., Hirose, K., Hamajima, N., Takezaki, T., Kuroishi, T. and Tominaga, S. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J. Clin. Epidemiol.*, **50**, 69–77 (1997).
32) Hamajima, N., Hirose, K., Inoue, M., Takezaki, T., Kuroishi, T. and Tajima, K. Case-control studies: matched controls or all available controls? *J. Clin. Epidemiol.*, **47**, 971–975 (1994).
33) Brown, L. M., Gibson, R., Burmeister, L. F., Schumann, L. M., Everett, G. D. and Blair, A. Alcohol consumption and risk of leukemia, non-Hodgkin's lymphoma, and multiple myeloma. *Leuk. Res.*, **16**, 978–984 (1992).
34) Nelson, R. A., Levine, A. M., Marks, G. and Bernstein, L. Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. *Br. J. Cancer*, **76**, 1532–1537 (1997).
35) Tsugane, S., Fahey, M. T., Sasaki, S. and Baba, S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC study Cohort I. Japan Public Health Center. *Am. J. Epidemiol.*, **150**, 1201–1207 (1999).
36) Yuan, J. M., Ross, R. K., Gao, Y. T., Henderson, B. E. and Yu, M. C. Follow up study of moderate alcohol intake and mortality among middle aged men in Shanghai, China. *BMJ*, **314**, 18–23 (1997).
37) Siemiatycki, J., Krewski, D., Franco, E. and Kaiserman, M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int. J. Epidemiol.*, **24**, 504–514 (1995).
38) Zahm, S. H., Weisenburger, D. D., Holmes, F. F., Cantor, K. P. and Blair, A. Tobacco and non-Hodgkin's lymphoma: combined analysis of three case-control studies (United States). *Cancer Causes Control*, **8**, 159–166 (1997).
39) Freedman, D. S., Tolbert, P. E., Coates, R., Brann, E. A. and Kjeldsberg, C. R. Relation of cigarette smoking to non-Hodgkin's lymphoma among middle-aged men. *Am. J. Epidemiol.*, **148**, 833–841 (1998).
40) Herrinton, L. J. and Friedman, G. D. Cigarette smoking and risk of non-Hodgkin's lymphoma subtypes. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 25–28 (1998).
41) Ross, M. H. and Bras, G. Tumor incidence patterns and nutrition in the rat. *J. Nutr.*, **87**, 245–260 (1965).
42) Metayer, C., Johnson, E. S. and Rice, J. C. Nested case-control study of tumors of the hemopoietic and lymphatic systems among workers in the meat industry. *Am. J. Epidemiol.*, **147**, 727–738 (1998).
43) Davis, S. Nutritional factors and the development of non-Hodgkin's lymphoma: a review of the evidence. *Cancer Res.*, **52** (Suppl.), 5492s–5495s (1992).
44) Matsuo, K., Suzuki, R., Hamajima, N., Ogura, M., Kagami, Y., Taji, H., Kondoh, E., Maeda, S., Asakura, S., Kaba, S., Nakamura, S., Seto, M., Morishima, Y. and Tajima, K. Association between polymorphisms of late- and methionine-metabolizing enzymes and susceptibility to malignant lymphoma. *Blood*, **97**, 3205–3209 (2001).