Research Article

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Association of Alcohol Intake with the Risk of Malignant Lymphoma and Plasma Cell Myeloma in Japanese: A Population-Based Cohort Study (Japan Public Health Center–based Prospective Study)

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Abstract

Few studies have evaluated the association between alcohol intake and the risk of the lymphoid neoplasms malignant lymphoma (ML) and plasma cell myeloma (PCM) among Asian populations. We conducted a large-scale population-based cohort study of 95,520 Japanese subjects (45,453 men and 50,067 women; age 40-69 years at baseline) with an average 13 years of follow-up, during which a total of 257 cases of ML and 89 of PCM were identified. Hazard ratios and 95% confidence intervals were estimated using a Cox regression model adjusted for potential confounders. Alcohol intake of ≥300 g/week was associated with a significantly lower risk of lymphoid neoplasms (hazard ratio, 0.60; 95% confidence interval, 0.37-0.98) than occasional drinking at a frequency of <1 day/month, and the trend for alcohol consumption was significant (P = 0.028). A similar trend was observed for the subcategories of ML, PCM, and non–Hodgkin lymphoma (NHL), albeit that the results were significant only for alcohol consumption at ≥300 g/week in NHL patients, probably due to the small number of subjects in each category. In conclusion, we found that alcohol had an inverse association with the risk of lymphoid neoplasms, particularly the risk of NHL, among a Japanese population. *Cancer Epidemiol Biomarkers Prev; 19(2); 429–34.* ©*2010 AACR.*

Introduction

The association between alcohol consumption and the risk of lymphoid neoplasms, including malignant lymphoma (ML) and plasma cell myeloma (PCM), has been investigated in several case-control and cohort studies in Western populations. Most studies reported an inverse association between alcohol consumption and the risk of ML (1-6), but reported inconsistent results with regard to that of PCM (6-9). In contrast to the number of studies in Western populations, however, little research has been conducted in Asian populations. Although we previously reported an inverse association between alcohol consumption and the risk of ML in a hospital-based case-control study in a Japanese population (10), no large cohort study in an Asian population has been done. Furthermore, no large case-control and cohort study specific to the association between alcohol and risk of PCM has been conducted. For several reasons, however, epidemiologic research into ML and PCM in large Asian cohorts is important: the incidence of ML and PCM in Asian countries is substantially lower than that in Western countries (11); in Japan, for example, the respective age-adjusted incidence rates of ML and PCM in 2002 were 7.7 and 1.6 for men and 4.9 and 1.1 for women (12), or almost half those in Western countries (11, 13); and the distribution of ML differs in Asian and Western countries, with marginal zone B-cell lymphoma being frequent in Asia, for example, whereas Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma are rare (11, 14, 15).

Here, we investigated the effect of alcohol intake on the risk of ML and PCM in a large-scale population-based cohort study in a Japanese population.

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Table 1. Baseline characteristics of study subjects according to alcohol drinking category

	Nondrinkers	Occasional drinkers	Weekly ethanol intake (g/wk)		
			1-149	150-299	≥300
Men (n = 45,453)					
No. of subjects	10,519	4,171	10,344	9,091	11,328
Proportion (%)	23.1	9.2	22.8	20.0	24.9
Age (y) ± SD	54.0 ± 8.4	50.3 ± 7.4	51.5 ± 8.1	51.8 ± 7.9	50.9 ± 7.3
Smoking status (%)					
Never	28.0	32.7	28.8	20.0	16.1
Former	24.8	20.5	25.4	24.5	22.2
Current	47.2	46.9	45.8	55.5	61.7
BMI (kg/m^2) ± SD	22.9 ± 3.0	23.5 ± 3.0	23.0 ± 2.8	23.0 ± 2.7	23.1 ± 2.9
Women (n = 50,067)					
No. of subjects	39,473	4,832	4,577	720	465
Proportion (%)	78.8	9.7	9.1	1.4	0.9
Age (y) ± SD	53.1 ± 8.1	48.9 ± 6.9	50.1 ± 7.5	49.3 ± 7.3	48.3 ± 6.6
Smoking status (%)					
Never	94.7	89.9	85.1	61.0	50.3
Former	1.1	2.3	2.9	6.3	5.8
Current	4.2	7.8	12.0	32.8	43.9
BMI (kg/m^2) ± SD	23.1 ± 3.2	23.0 ± 3.0	22.6 ± 2.9	22.6 ± 3.2	23.0 ± 3.3

Materials and Methods

Study Population

The Japan Public Health Center–based Prospective Study was launched in 1990 for cohort I and in 1993 for cohort II. Cohort I covered five prefectural public health center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo) and cohort II covered six (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka; Supplementary Methods). In the present analysis, we excluded all subjects in the Tokyo area because their incidence data were not available, and we also excluded some in the Osaka area because different definitions of the study population had been applied in them. A baseline self-administered questionnaire survey on various life-style factors, including alcohol intake and smoking habit, was conducted in 1990 for cohort I and in 1993 to 1994 for cohort II, with a high response rate (81%). Subjects were followed from the date of the baseline survey to December 31, 2006, and a total of 95,520 subjects (45,453 men and 50,067 women) were analyzed.

Outcome

Cancers were identified by active patient notification from major local hospitals in the study area and by data collection from population-based cancer registries with approval. Information on the cause of death was supplemented by checking death certificate files with permission. Information was available from death certificates only in 6.4% of cancer cases. ML and PCM were coded using the International Classification of Diseases for Oncology, Third Edition. The earliest date of diagnosis was used for patients who developed multiple primary cancers at different times.

Exposure Data

Weekly ethanol intake was estimated by multiplying the amount of ethanol by the score (Supplementary Methods). In the present analysis, subjects were classified by drinking habit into five categories: nondrinkers (<1 d/mo), occasional drinkers (1-3 d/mo), and three categories of regular drinkers (1-149, 150-299, and ≥300 g/wk).

Statistical Analysis

Hazard ratios (HR) and their 95% confidence intervals (95% CI) were calculated using the Cox proportional hazards model to describe the relative risk of cancer associated with the alcohol categories at baseline (nondrinkers, occasional drinkers, 1-149, 150-299, and ≥300 g/wk; Supplementary Methods). We set occasional drinkers as the reference category, and we evaluated the P value for trend for current drinkers only because former drinkers were included in the category of nondrinkers. HRs were adjusted for the following potential confounding factors: age at baseline (continuous), gender (men or women), study area (10 PHC areas), number of pack-years at study entry (0, 1-19, 20-29, 30-39, and ≥40 pack-years), and body mass index (BMI) at study entry (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m^2; Supplementary Methods). The interaction between flushing response and alcohol consumption was also assessed in current drinkers. All statistical analyses were done using the Stata version

10 software (Stata Corp.), with a P value of <0.05 considered to be statistically significant.

Results

During 1,301,317 person-years of follow-up (average, 13.6 years) for the 95,520 subjects (45,453 men and 50,067 women), a total of 257 cases of ML (152 men and 105 women) and 89 of PCM (45 men and 44 women) were newly diagnosed. Distribution of histologic subtypes of ML were diffuse large B-cell lymphoma in 80 (31.1%), follicular lymphoma in 18 (7.0%), marginal zone B-cell lymphoma in 16 (6.2%), precursor lymphoblastic leukemia/lymphoma in 11 (4.3%), Hodgkin lymphoma in 10 (3.9%), chronic lymphocytic leukemia/small lymphocytic lymphoma in 9 (3.5%), peripheral T-cell lymphoma of unspecified type in 5 (1.9%), other non–Hodgkin lymphomas (NHL) in 13 (5.1%), NHL not otherwise specified in 53 (20.6%), and ML not otherwise specified in 42 (16.3%).

Baseline characteristics of study subjects are shown in Table 1. At baseline, 68% of the men were regular drinkers, whereas most the women (79%) were nondrinkers, with only 12% being regular drinkers. In each drinking category, a smaller number of women than men were current smokers, whereas the proportion of current smokers increased in the higher ethanol intake groups in both men and women. Mean BMI was ~23 kg/m^2 in each drinking category in both men and women.

Table 2 shows the adjusted HRs by alcohol category. Alcohol intake of ≥300 g/week was significantly associated with a lower risk of lymphoid neoplasm (HR, 0.60; 95% CI, 0.37-0.98) than occasional drinking, and the trend for alcohol consumption was significant (P = 0.028). This trend was not observed among women, none of whom consumed ≥300 g of alcohol per week. Similar trends were observed for the subcategories of ML, PCM, and NHL, although the results were significant only for the category of alcohol intake of ≥300 g/wk in NHL patients, probably due to the small number of subjects analyzed in each category. We obtained almost the same

Table 2. HRs and 95% CI of lymphoid neoplasms according to alcohol-drinking status

	Nondrinkers	Occasional drinkers	Weekly ethanol intake (g/wk)			P_{trend}*
			1-149	150-299	≥300	
Lymphoid neoplasms						
Total						
Person-years	684,375	125,466	198,246	132,778	160,453	—
No. of cases	185	34	55	36	36	—
HR (95% CI)†	0.93 (0.63-1.35)	1.00 (Reference)	0.84 (0.55-1.30)	0.71 (0.44-1.15)	0.60 (0.37-0.98)	0.028
Men						
Person-years	135,724	57,245	135,702	123,094	154,340	—
No. of cases	58	24	44	35	36	—
HR (95% CI)†	0.81 (0.50-1.31)	1.00 (Reference)	0.75 (0.45-1.24)	0.67 (0.39-1.13)	0.58 (0.34-0.99)	0.049
Women						
Person-years	548,651	68,221	62,543	9,683	6,113	—
No. of cases	127	10	11	1	0	—
HR (95% CI)†	1.20 (0.62-2.31)	1.00 (Reference)	1.13 (0.48-2.67)	0.70 (0.09-5.53)	—	0.484
ML						
Person-years	684,375	125,466	198,246	132,778	160,453	—
No. of cases	134	26	39	28	30	—
HR (95% CI)†	0.90 (0.58-1.40)	1.00 (Reference)	0.78 (0.47-1.29)	0.71 (0.41-1.23)	0.64 (0.37-1.10)	0.067
PCM						
Person-years	684,375	125,466	198,246	132,778	160,453	—
No. of cases	51	8	16	8	6	—
HR (95% CI)†	1.02 (0.47-2.20)	1.00 (Reference)	1.05 (0.44-2.48)	0.73 (0.27-1.99)	0.47 (0.16-1.41)	0.233
NHL						
Person-years	684,375	125,466	198,246	132,778	160,453	—
No. of cases	96	22	30	21	19	—
HR (95% CI)†	0.80 (0.49-1.30)	1.00 (Reference)	0.73 (0.42-1.27)	0.64 (0.34-1.17)	0.47 (0.25-0.89)	0.024

*P for trend was evaluated among current drinkers.

†HRs were adjusted for age at baseline (continuous), gender (men or women), study area (10 PHC areas), number of pack-years (0, 1-19, 20-29, 30-39, and ≥40 pack-years), and BMI (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m^2).

Table 3. HRs and 95% CI of lymphoid neoplasms according to alcohol drinking status stratified by flushing response

	Nondrinkers	Occasional drinkers	Weekly ethanol intake (g/wk)			P_{trend}*
			1-149	150-299	≥300	
Lymphoid neoplasms						
Flushing (–; *n* = 51,767)						
No. of cases	103	17	26	18	22	
HR (95% CI)†	0.83 (0.48-1.41)	1.00 (Reference)	0.67 (0.36-1.24)	0.49 (0.24-0.97)	0.47 (0.24-0.91)	0.032
Flushing (+; *n* = 41,047)						
No. of cases	72	16	29	18	14	
HR (95% CI)†	1.04 (0.59-1.81)	1.00 (Reference)	1.05 (0.57-1.95)	1.02 (0.52-2.03)	0.73 (0.35-1.52)	0.395

*P for trend was evaluated among current drinkers.
†HRs were adjusted for age at baseline (continuous), gender (men or women), study area (10 PHC areas), number of pack-years (0, 1-19, 20-29, 30-39, and ≥40 pack-years), and BMI (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m^2).

results regarding the risk of lymphoid neoplasms or their subcategories by adjustment only for age at baseline, gender, and study area; it suggested that the number of pack-years or BMI had a minor effect on these risks.

We next analyzed the association between alcohol flushing and the risk of lymphoid neoplasms to evaluate whether the production of acetaldehyde modified the risk of these neoplasms (Table 3). Compared with those who do not show a flushing response to alcohol, individuals who do show such a response are considered to be slow metabolizers of acetaldehyde following alcohol intake (16). Alcohol intake of 150 to 299 g/week or ≥300 g/week was associated with a significantly reduced risk of lymphoid neoplasm among those who did not show a flushing response, but not among those who did. However, no interaction was observed between alcohol flushing and the risk of lymphoid neoplasms. To evaluate the effect of much heavier drinking for the risk of lymphoid neoplasms, the category of ≥300 g/week was further divided into 300 to 450 g/week and ≥450 g/week. The significant result was obtained only for alcohol intake of 300 to 450 g/week (HR, 0.36; 95% CI, 0.16-0.83), not for ≥450 g/week (HR, 0.59; 95% CI, 0.28-1.26) among those who do not show a flushing response.

Discussion

In this cohort study, we found that alcohol had an inverse association with the risk of lymphoid neoplasms, particularly NHL, among a Japanese population. Compared with occasional drinking, high alcohol intake of ≥300 g/week was significantly associated with a 40% decrease in lymphoid neoplasm risk, with this trend being significant. Similar trends were observed for the subcategories of ML, PCM, and NHL; in particular, there was a 53% reduced risk of NHL with alcohol intake of ≥300 g/week. To our knowledge, this is the largest cohort study conducted in an Asian population to assess the association between alcohol intake and the risk of lymphoid neoplasms.

In a large pooled analysis of nine case-control studies conducted by the International Lymphoma Epidemiology Consortium, ever drinking was associated with a 17% reduced risk of NHL than never drinking among non-Asian populations (1). Several cohort studies have supported an inverse association (4, 5). In the present study, we found a 53% reduced risk of NHL in the ≥300 g/week intake category among Japanese populations; this finding is compatible with our previous case-control study in Japan (10) and the effect of alcohol intake seems to be stronger than in Western countries. First, the consistent findings regarding the inverse association of alcohol across various ethnic backgrounds indicates a shared protective mechanism against the development of lymphoma. Several potential mechanisms for a protective effect of alcohol against lymphoma have been hypothesized. One involves the effect of alcohol on the immune system (17); namely, light to moderate drinking might improve immunologic function by increasing cellular and humoral immune responses. Moreover, light to moderate drinking is known to improve insulin sensitivity (18), which might reduce the incidence of diabetes mellitus, a risk factor for ML (19). However, we found that lymphoid neoplasm risk was strongly associated with relatively heavy alcohol consumption, ≥300 g/week, suggesting that the decreased risk may involve other mechanisms. Recently, inhibitory effect of ethanol on the mammalian target of rapamycin signaling was proposed as another possible mechanism (20). Exposure to ethanol was shown to dose-dependently inhibit the mammalian target of rapamycin pathway signaling in a lymphoid tissue–specific manner, and chronic exposure at physiologically relevant concentrations in a xenograft model resulted in the inhibition of lymphoma

growth through the disruption of mammalian target of rapamycin pathway signaling. Next, the stronger inverse association of alcohol intake with ML risk in Japanese than in Western populations can be possibly explained by their genetic difference in immune surveillance system against lymphoma cells. Generally, tumors generate by genetic damage of carcinogens and gain advantage of proliferation by escaping from host immune surveillance system. Lower incidence of lymphoma in Japan than Western countries may indicate that immune surveillance against lymphoma cells in Japanese is genetically more effective than that in Western populations. Coordinating with the immune surveillance system, alcohol may synergistically exert a stronger suppressive effect on lymphoma cells in Japanese.

Hosgood et al. (8) reported a significant inverse association between alcohol intake and the risk of PCM in a population-based case-control study in the United States; one daily alcohol consumption was associated with a 70% decrease in the risk of PCM compared with less than two drinks of alcohol per month. Gorini (7) also reported a significant 53% decrease in the risk of PCM for alcohol intake of 126 to 221.9 g/week versus nondrinkers in a population case-control study in Italy. On the contrary, other studies found no significant association (6, 9). Compared with occasional drinking, alcohol intake in the present study of 150 to 299 g/day and ≥300 g/day was associated with a 27% and 53% decreased risk of PCM, albeit without statistical significance for any. The association of alcohol and PCM risk should be investigated in larger studies.

Heavy drinkers might be exposed to high amounts of acetaldehyde, which plays an important role in the pathogenesis of other cancers (21). On the basis that flushing after drinking is mainly dependent on the speed of acetaldehyde catalysis by aldehyde dehydrogenase 2 (ALDH2), we evaluated the effect of acetaldehyde on the risk of lymphoid neoplasm by assessing the association of alcohol using self-reported reactions to alcohol. A significantly reduced risk of lymphoid neoplasms was observed among those who did not show a flushing response but not among those who did. In addition, much heavier drinking (≥450 g/week) weakened the potential effect of alcohol even in those who did not show a flushing response. All these findings suggested the possibility that accumulation of acetaldehyde might offset the protective effect of alcohol. However, no interaction was observed between alcohol flushing and the risk of lymphoid neoplasms. Future studies should investigate the *ALDH2* Glu504Lys polymorphism (rs671), which modulates individual differences in alcohol-oxidizing capability (22); nearly half of Japanese have the *ALDH2* Lys allele, which exerts a dominant-negative effect on the ALDH2 protein (16).

Our study had several methodologic strengths. First, it was conducted under a prospective design with a high response rate (81%) and negligible proportion of losses to follow-up. The collection of information on alcohol intake before cancer diagnosis excluded the exposure recall bias inherent to case-control studies. In addition, the study subjects were selected from the general population from various regions in Japan, and even if geographic variation due to study area was present, this was adjusted for in the analysis.

Several limitations of the study also warrant mention. First, although we adjusted for age, sex, pack-years of smoking, and BMI, we did not consider residual confounding by other known or unknown risk factors. For example, socioeconomic status is inversely associated with the NHL risk (1) and can confound with drinking. Considering the U-shaped correlation between drinking behavior and low socioeconomic status in Japan (23), bias by lack of adjustment by socioeconomic status would be limited. For unknown factors, direction and magnitude of bias could be variable. Second, the statistical power in each stratified category may have been low as the number of cases in each was relatively small, and therefore any interpretation of the findings in each histologic subtype should be made with caution. Third, information on alcohol consumption was obtained solely on the basis of a single self-report, and no consideration was given to any subsequent change in drinking. Statistics from the National Tax Agency Japan indicated gradual decrease of alcohol consumption through 1990 to 2007 (24). Effect of this overall change on the association is less clear. Misclassification of the self-reported alcohol consumption would probably be nondifferential and may underestimate the true relative risk. Last, we set occasional drinkers as the reference category because former drinkers could not be separated from the category of nondrinkers in the cohort I data set. However, in the analysis of cohort II, exclusion of former drinkers and setting never drinkers as the reference category did not change the association between the risk of lymphoid neoplasms and alcohol intake (data not shown).

In conclusion, we found that alcohol had an inverse association with the risk of lymphoid neoplasms, particularly the risk of NHL, among a Japanese population. Further studies are required to determine the mechanisms underlying these findings in our subject population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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