ORIGINAL ARTICLE

Cancer Science WILEY

Alcohol intake and stomach cancer risk in Japan: A pooled analysis of six cohort studies

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Abstract

The association between alcohol intake and stomach cancer risk remains controversial. We undertook a pooled analysis of data from six large-scale Japanese cohort studies with 256 478 participants on this topic. Alcohol intake as ethanol was estimated using a validated questionnaire. The participants were followed for incidence of stomach cancer. We calculated study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for stomach cancer according to alcohol intake using a Cox regression model. Summary HRs were estimated by pooling the study-specific HRs using a random-effects model. During 4 265 551 person-years of follow-up, 8586

stomach cancer cases were identified. In men, the multivariate-adjusted HRs (95% CIs) of stomach cancer were 1.00 (0.87-1.15) for occasional drinkers, and 1.00 (0.91-1.11) for <23 g/d, 1.09 (1.01-1.18) for 23 to <46 g/d, 1.18 (1.09-1.29) for 46 to <69 g/d, 1.21 (1.05-1.39) for 69 to <92 g/d, and 1.29 (1.11-1.51) for ≥92 g/d ethanol in regular drinkers compared with nondrinkers. In women, the multivariate-adjusted HRs were 0.93 (0.80-1.08) for occasional drinkers, and 0.85 (0.74-0.99) for <23 g/d, and 1.22 (0.98-1.53) for ≥23 g/d in regular drinkers compared with nondrinkers. The HRs for proximal and distal cancer in drinkers vs nondrinkers were 1.69 (1.15-2.47) and 1.24 (0.99-1.55) for ≥92 g/d in men, and 1.60 (0.76-3.37) and 1.18 (0.88-1.57) for ≥23 g/d in women, respectively. Alcohol intake increased stomach cancer risk in men, and heavy drinkers showed a greater point estimate of risk for proximal cancer than for distal cancer.

KEYWORDS

alcohol intake, cohort study, Japan, pooled analysis, stomach cancer

1 | INTRODUCTION

Stomach cancer is the fourth most common cancer and the third leading cause of cancer deaths worldwide; it remains the most frequent cancer in East Asia, despite a declining trend.[1] There is a consensus that *Helicobacter pylori* infection, smoking, and high salt intake are risk factors for stomach cancer.[2-5] Higher intake of vegetables, fruit, and green tea could be protective against stomach cancer.[6-9] Animal studies indicate that alcohol is harmful to the stomach,[10] partly because alcohol metabolism produces the carcinogen acetaldehyde.[11] Acetaldehyde related to alcohol intake is now considered a group 1 carcinogen by the IARC,[12] and alcohol intake is an established risk factor for several cancers, including oral cavity, head and neck, esophagus, breast, liver, and colorectal cancer.[13] A recent large meta-analysis of mainly European and American cohort and case-control studies showed that high alcohol intake of ≥50 g/d ethanol substantially increases the risk of stomach cancer.[14] However, meta-analysis using publication data cannot fully examine dose–response relationships, and epidemiological evidence for the association between alcohol intake and stomach cancer risk remains controversial.[15] In addition, few cohort studies have examined whether alcohol consumption analyzed as ethanol intake is associated with stomach cancer risk in East Asian populations with a high incidence of stomach cancer. To date, six cohort studies in Japan have examined the association between alcohol intake and stomach cancer risk, and their findings are inconsistent.[16-21] The findings from cohort studies in Korea and China are also inconclusive.[22-24] Thus, it is necessary to clarify the effect of alcohol intake on stomach cancer risk in Japan and other East Asian countries, using large datasets from cohort studies.

To address this issue, we undertook a pooled analysis of data from six large-scale Japanese cohort studies with more than 250 000 participants on the association between ethanol intake and stomach cancer risk.

2 | MATERIALS AND METHODS

2.1 | Study cohorts

Since 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been undertaking pooled analyses using original data from major cohort studies to examine the association between lifestyle factors and major cancers in Japanese people. To maintain high quality and comparability of data, the following inclusion criteria were defined a priori for the present analysis: (a) population-based cohort studies carried out in Japan; (b) studies initiated between the mid-1980s and mid-1990s; (c) studies with more than 30 000 participants; (d) studies that obtained information on alcohol intake at baseline survey using a self-administered questionnaire; and (e) studies that collected incidence data for stomach cancer during a follow-up period. We eventually identified six studies that met these criteria: (a) JPHC-I[25]; (b) JPHC-II[25]; (c) JACC[26]; (d) MIYAGI[27]; (e) OHSAKI[28]; and (f) LSS.[29] Selected characteristics of these cohort studies are summarized in Table 1. The relevant institutional review board approved each study.

We excluded data from participants with a history of any cancer at baseline, those with missing information on alcohol intake, and those with exposure to atomic bomb radiation of 100 mGy or more for LSS. Data on 256 478 participants were finally included in the present pooled analysis. The JPHC-I, MIYAGI, and JACC studies have already published results for the association between alcohol intake and stomach cancer risk.[17,19,21] In the present study, we used

TABLE 1 Characteristics of six Japanese cohort studies: pooled analysis of the association between alcohol intake and stomach cancer risk, 1988-2014

Study	Cohort	Age range at baseline survey (y)	Year of baseline survey	Cohort size	Response rate (%) for baseline questionnaire	Present pooled analysis				Size of the cohort		Number of stomach cancer cases		Outcome
						Method of follow-up	Age range (mean ± SD, y)	Last follow-up	Mean follow-up period (y)	Men	Women	Men	Women	
JPHC Study I	Japanese residents of 5 public health center areas in Japan	40-59	1990	61 595	82.0	Cancer registry and death certificate	40-59 (49.5 ± 5.9)	2013	21.0	20 239	21 633	1121	439	Incidence
JPHC Study II	Japanese residents of 6 public health center areas in Japan	40-69	1993-1994	78 825	80.0	Cancer registry and death certificate	40-69 (53.3 ± 8.9)	2013	17.3	28 080	31 909	1294	538	Incidence
JACC Study	Residents from 45 areas throughout Japan	40-79	1988-1990	110 585	83.0	Cancer registry (selected areas: 24) and death certificate	40-79 (57.8 ± 10.2)	2009	15.7	22 388	33 239	962	585	Incidence
Miyagi Cohort Study	Residents of 14 municipalities in Miyagi Prefecture, Japan	40-64	1990	47 605	92.0	Cancer registry and death certificate	40-64 (51.6 ± 7.5)	2014	21.2	21 074	18 696	1438	453	Incidence
Ohsaki Cohort Study	Residents of 14 municipalities in Miyagi Prefecture, Japan	40-79	1994	52 029	95.0	Cancer registry and death certificate	40-79 (59.6 ± 10.4)	2008	10.7	21 370	19 618	958	309	Incidence
Life Span Study	Atomic bomb survivors in Hiroshima and Nagasaki, Japan[a]	46-104	1991	20 147	100	Cancer registry and death certificate	46-104 (62.6 ± 11.6)	2003	10.7	6800	11 432	278	211	Incidence

Abbreviations: JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study.

[a]Life Span Study originally started 1950, and subjects who responded to the 1991 survey were analyzed for the present pooled analysis.

the updated dataset for JPHC-I and MIYAGI with a longer follow-up period and reanalyzed the dataset for JACC.

2.2 | Assessment of alcohol intake

Information on alcohol intake in each study was collected using a self-administered questionnaire at baseline. Although the wording of the questions varied among studies, each study calculated total alcohol intake for regular drinkers in grams per day ethanol as a continuous variable according to the alcoholic beverage type, frequency, and amount. Alcohol intake was calculated by multiplying the frequency of consumption for each type of liquor by alcohol content of the specific portion and by the portion size for one occasion. The total alcohol intake was then estimated by summing the alcohol intake over all liquor types. Each study questionnaire contained items on the intake of alcoholic beverages popular in Japan, including beer, sake, and *shochu*, but the style of the questions differed across studies. Thus, in the present study, we used only total alcohol intake from all beverages as the exposure. In Japan, the *go* is the unit most commonly used to measure the amount of alcohol intake; 1 *go* of *sake* (rice wine) is equivalent to 180 mL and contains approximately 23 g of ethanol.

According to total alcohol intake, participants were classified as follows: for men, nondrinkers (never and former drinkers), occasional drinkers (defined as those who drink less than once/week) and regular drinkers (defined as those who drink at least once/week: <23, 23 to <46, 46 to <69, 69 to <92, and ≥92 g/d ethanol); for women, nondrinkers, occasional drinkers, and regular drinkers (<23 and ≥23 g/d ethanol). Those with extremely high alcohol intake were classified into the highest categories because we did not exclude such high alcohol intake estimated with the food frequency questionnaire in each study. Sensitivity analyses were undertaken by setting never drinkers as the reference group in JPHC-II, JACC, MIYAGI, OHSAKI, and LSS, in which former drinkers were separated from nondrinkers. We also undertook an additional sensitivity analysis in which occasional drinkers and regular drinkers were defined as those who drink less than three times/week and those who drink three times/week or more, respectively. In this analysis, LSS defined regular drinkers as those who drink at least five times/week due to the format of questionnaire.

The correlation coefficients between self-reported alcohol intake and dietary records were 0.79 in men and 0.44 in women for JPHC-I,[30] 0.59 in men and 0.40 in women for JPHC-II,[31] 0.77 in men and 0.71 in women for MIYAGI,[32] and 0.70 in men for OHSAKI.[33] Although information on the validity of alcohol intake assessment was not available for JACC, the study used the same questionnaire on alcohol intake as that used in MIYAGI. The LSS also used a similar questionnaire for alcohol intake, although a validation study was not carried out.[34]

2.3 | Follow-up and case ascertainment

Participants were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993-1994; JACC, 1988-1990; MIYAGI, 1990; OHSAKI,

1994; LSS, 1991) until the last follow-up date for cancer incidence in each study (JPHC-I, 2013; JPHC-II, 2013; JACC, 2009; MIYAGI, 2014; OHSAKI, 2008; LSS, 2003), as shown in Table 1. Vital status was confirmed through the residential registry. Information on cause of death was obtained from death certificates, and the cause of death was coded according to the International Classification of Diseases, 10th Revision. Information on cancer diagnosis was collected using population-based cancer registries and active patient notifications from major local hospitals. In JACC, information on cancer diagnosis was collected in 24 of 45 study areas. Cases were coded using ICD-O-3.

The outcome in the present study was defined as stomach cancer incidence (ICD-O-3, topography code C16), which was diagnosed during the follow-up period of each study. Information on cause of death from death certificates was used to complement the registry and hospital data on cancer diagnosis. If information on the date of diagnosis was not available for stomach cancer cases confirmed by death certificate, we used the date of death from stomach cancer as the date of diagnosis. The information on stomach cancer incidence by subsite allowed us to evaluate the association between alcohol intake and the risk of stomach cancer subsite; thus, we classified stomach cancer cases as proximal (upper third) (ICD-O-3, topography code C16.0-C16.1) and distal (lower two-thirds) (C16.2-C16.6). Stomach cancer cases with no information for subsite were not included in the subsite-specific analysis.

2.4 | Statistical analyses

Person-years of follow-up were counted from the date of baseline survey in each study until the date of stomach cancer diagnosis, migration from the study area, death, or the end of follow-up, whichever came first. Each study used a Cox proportional hazard regression model to estimate sex-specific HR with 95% CI for stomach cancer incidence according to alcohol intake in the following five models. Model 1 was adjusted for age and area (JPHC-I, JPHC-II, JACC, and LSS only). Model 2 was adjusted for covariates in model 1 plus smoking status (for men, pack-years: 0, <20, 20 to <40, or ≥40; for women, pack-years: 0, <20, ≥20) and medical history of diabetes mellitus (yes, no). Model 3 was adjusted for covariates in model 2 plus total energy intake (quartiles), vegetable intake (quartiles), fruit intake (quartiles), salt intake (quartiles), and green tea consumption (cups/d: <1, 1-2, 3-4, and ≥5). In models 4 and 5, we excluded participants with stomach cancer diagnosis within 3 years from baseline in models 2 and 3, respectively. An indicator term for missing data was created for categorical covariates. Pack-years in ever smokers were calculated as (daily consumption of tobacco [number of cigarettes/d]) × (duration of smoking [y])/20. Dietary intake was adjusted for total energy intake using the residual method before categorizing subjects into quartiles.[35] Trend associations were assessed by calculating the HR for 10-g/d increase in alcohol intake and its standard error in the respective model in which nondrinkers and occasional drinkers were defined as zero for alcohol intake. In the subsite-specific analysis, those without the outcome were

TABLE 2 Results from a pooled analysis using a random effects model for stomach cancer incidence by alcohol intake in Japanese men, 1988-2014

Site of cancer	Total	Nondrinkers	Occasional drinkers (<once/wk)	Regular drinkers (≥once/wk)					P for heterogeneity for the highest category[f]	Alcohol intake as a continuous variable (per 10 g/d)		
				<23 g/d	23 to <46 g/d	46 to <69 g/d	69 to <92 g/d	≥92 g/d		HR (95% CI)	P for trend	P for heterogeneity[f]
Total												
No. of subjects	119 951	29 770	8333	22 039	24 475	20 883	9585	4866				
No. of cases	6051	1465	343	1001	1264	1206	531	241				
Person-years	1 947 366	450 844	145 094	354 254	404 442	347 640	162 231	82 861				
Incidence rate per 100 000 person-years	311	325	236	283	313	347	327	291				
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	0.99 (0.86-1.14)	0.99 (0.89-1.10)	1.10 (1.02-1.19)	1.23 (1.12-1.34)	1.27 (1.09-1.48)	1.36 (1.17-1.59)	.367	1.029 (1.015-1.043)	<.001	.001
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	1.00 (0.87-1.15)	1.00 (0.91-1.11)	1.09 (1.01-1.18)	1.18 (1.09-1.29)	1.21 (1.05-1.39)	1.29 (1.11-1.51)	.361	1.023 (1.011-1.035)	<.001	.019
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.00 (0.85-1.18)	0.98 (0.89-1.07)	1.07 (0.99-1.16)	1.15 (1.05-1.25)	1.19 (1.05-1.36)	1.23 (1.05-1.43)	.607	1.019 (1.007-1.032)	.002	.048
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.02 (0.86-1.20)	1.00 (0.91-1.10)	1.09 (1.00-1.18)	1.21 (1.10-1.33)	1.23 (1.04-1.45)	1.26 (1.08-1.48)	.652	1.019 (1.009-1.030)	<.001	.095
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	1.03 (0.86-1.23)	0.97 (0.88-1.07)	1.06 (0.97-1.16)	1.16 (1.06-1.27)	1.18 (1.04-1.33)	1.17 (1.01-1.37)	.571	1.016 (1.005-1.027)	.005	.123
Proximal (upper third)												
No. of subjects	119 951	29 770	8333	22 039	24 475	20 883	9585	4866				
No. of cases	708	171	41	113	133	144	70	36				
Person-years	1 975 692	457 143	146 827	358 886	410 636	353 535	164 704	83 961				
Incidence rate per 100 000 person-years	36	37	28	31	32	41	43	43				

(Continues)

TABLE 2 (Continued)

| Site of cancer | Total | Nondrinkers | Occasional drinkers (<once/wk) | Regular drinkers (≥once/wk) | | | | | P for heterogeneity for the highest category[f] | Alcohol intake as a continuous variable (per 10 g/d) | | |
				<23 g/d	23 to <46 g/d	46 to <69 g/d	69 to <92 g/d	≥92 g/d		HR (95% CI)	P for trend	P for heterogeneity[f]
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	1.04 (0.73-1.47)	0.93 (0.73-1.19)	1.00 (0.79-1.26)	1.21 (0.97-1.52)	1.39 (1.02-1.88)	1.77 (1.21-2.58)	.985	1.018 (1.006-1.030)	.004	.494
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	1.05 (0.74-1.49)	0.95 (0.75-1.22)	0.99 (0.79-1.25)	1.17 (0.93-1.48)	1.31 (0.97-1.77)	1.69 (1.15-2.47)	.987	1.016 (1.002-1.029)	.021	.700
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.02 (0.71-1.47)	0.96 (0.74-1.25)	1.01 (0.79-1.30)	1.22 (0.95-1.56)	1.43 (0.95-2.17)	1.95 (1.30-2.94)	.770	1.022 (1.003-1.042)	.020	.267
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.00 (0.67-1.46)	0.89 (0.68-1.16)	1.01 (0.79-1.30)	1.25 (0.99-1.59)	1.34 (0.97-1.85)	1.58 (1.04-2.40)	.830	1.016 (1.004-1.028)	.010	.624
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	0.94 (0.64-1.39)	0.90 (0.67-1.20)	1.04 (0.80-1.35)	1.30 (1.01-1.69)	1.41 (1.01-1.97)	1.79 (1.14-2.81)	.487	1.024 (1.004-1.044)	.016	.265
Distal (lower two-thirds)												
No. of subjects	119 951	29 770	8333	22 039	24 475	20 883	9585	4866				
No. of cases	3573	803	221	573	767	737	324	148				
Person-years	1 958 704	453 751	145 656	356 252	406 804	349 830	163 162	83 249				
Incidence rate per 100 000 person-years	182	177	152	161	189	211	199	178				
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	1.07 (0.87-1.33)	0.99 (0.88-1.11)	1.20 (1.05-1.36)	1.32 (1.14-1.52)	1.29 (1.08-1.54)	1.31 (1.05-1.64)	.285	1.029 (1.013-1.045)	<.001	.008
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	1.09 (0.88-1.34)	1.00 (0.89-1.11)	1.18 (1.04-1.34)	1.28 (1.11-1.47)	1.22 (1.03-1.46)	1.24 (0.99-1.55)	.284	1.023 (1.009-1.037)	.001	.034
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.12 (0.87-1.46)	0.97 (0.86-1.09)	1.13 (1.01-1.28)	1.22 (1.05-1.41)	1.17 (0.99-1.38)	1.14 (0.93-1.39)	.496	1.017 (1.004-1.030)	.013	.135

TABLE 2 (Continued)

Site of cancer	Total	Nondrinkers	Occasional drinkers (<once/wk)	Regular drinkers (≥once/wk)					P for heterogeneity for the highest category[f]	Alcohol intake as a continuous variable (per 10 g/d)		
				<23 g/d	23 to <46 g/d	46 to <69 g/d	69 to <92 g/d	≥92 g/d		HR (95% CI)	P for trend	P for heterogeneity[f]
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.14 (0.89-1.47)	1.04 (0.91-1.18)	1.20 (1.05-1.37)	1.31 (1.09-1.57)	1.24 (1.05-1.48)	1.22 (0.99-1.49)	.632	1.017 (1.005-1.030)	.006	.148
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	1.20 (0.86-1.64)	0.99 (0.88-1.12)	1.13 (1.00-1.27)	1.22 (1.03-1.44)	1.17 (1.00-1.36)	1.13 (0.91-1.40)	.508	1.011 (1.004-1.018)	.002	.452

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., reference.

[a]Adjusted for age and area (Japan Public Health Center-based Study Prospective Study I [JPHC-I], JPHC-II, Japan Collaborative Cohort Study, and Life Span Study only).

[b]Adjusted for covariates in model 1 plus smoking status (pack-years: 0, <20, 20 to <40, and ≥40) and medical history of diabetes mellitus (yes, no).

[c]Adjusted for covariates in model 2 plus total energy intake (quartiles), vegetable intake (quartiles), fruit intake (quartiles), salt intake (quartiles), and green tea consumption (cups/d: <1, 1-2, 3-4, and ≥5).

[d]Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 2.

[e]Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 3.

[f]Indicating heterogeneity among the pooled cohort studies.

considered at risk. Each study also undertook a subgroup analysis of the association between drinking and stomach cancer incidence by smoking status (nonsmokers or ever smokers); we controlled for pack-years in the respective model for ever smokers. Interaction between drinking and smoking status for risk was also assessed with a model including a cross-product term (ethanol intake [continuous variable] × smoking status [ever vs never]) indicating interaction.

To obtain a single pooled estimate of the HR for stomach cancer from individual studies according to alcohol intake category, we used a random-effects model, which considers both within-study and between-study variation.[36] One study that had no cases for one alcohol intake category was not included in the pooled estimate for the category. The LSS was not included in models 3 or 5 because of no available data for dietary intake. Heterogeneity among studies was assessed using Q-statistics and I^2 statistics. The correlation between drinking and smoking status was tested by a Cochran–Mantel–Haenszel test based on the pooled distribution of individual studies. To assess a single pooled interaction between drinking and smoking status for risk, we used a random-effects model in the same manner as that used to obtain a single pooled estimate of the HR for stomach cancer from all the cohort studies. Statistical analyses were carried out using Stata statistical software version 13.1 (StataCorp). A two-tailed P value < .05 was considered statistically significant.

3 | RESULTS

This study included 256 478 participants (119 951 men and 136 527 women) and 8586 stomach cancer cases (6051 men and 2535 women) during 4 265 551 person-years of follow-up, as shown in Table 1. Approximately half the men habitually consumed more than 23.0 g/d of ethanol, whereas only 3% of women consumed this quantity.

Table 2 shows the association between alcohol intake and stomach cancer risk in men. Men with higher alcohol intake were at a significantly greater risk of stomach cancer. Compared with nondrinkers, the multivariate-adjusted HRs (95% CIs) for stomach cancer were 1.00 (0.87-1.15) for occasional drinkers, and 1.00 (0.91-1.11) for <23 g/d ethanol, 1.09 (1.01-1.18) for 23 to <46 g/d, 1.18 (1.09-1.29) for 46 to <69 g/d, 1.21 (1.05-1.39) for 69 to <92 g/d, and 1.29 (1.11-1.51) for ≥92 g/d in regular drinkers in model 2 with adjustment for age, study area, smoking status, and medical history of diabetes mellitus. The median of alcohol intake in the category for ≥92 g/d was 115 g/d (range, 92-4495). The HR (95% CI) for 10-g/d increase in ethanol was 1.023 (1.011-1.035), although the test for cross-study heterogeneity was statistically significant (P = .019). In model 3, further adjustment for intake of total energy, vegetables, fruit, salt, and green tea did not substantially change the results. The findings did not alter after excluding participants with stomach cancer diagnosis within 3 years from baseline in both models 4 and 5. The analysis by stomach cancer subsite indicated that the point estimate of risk for heavy drinkers was greater for proximal cancer than for distal cancer. Compared with nondrinkers, the multivariate-adjusted HRs
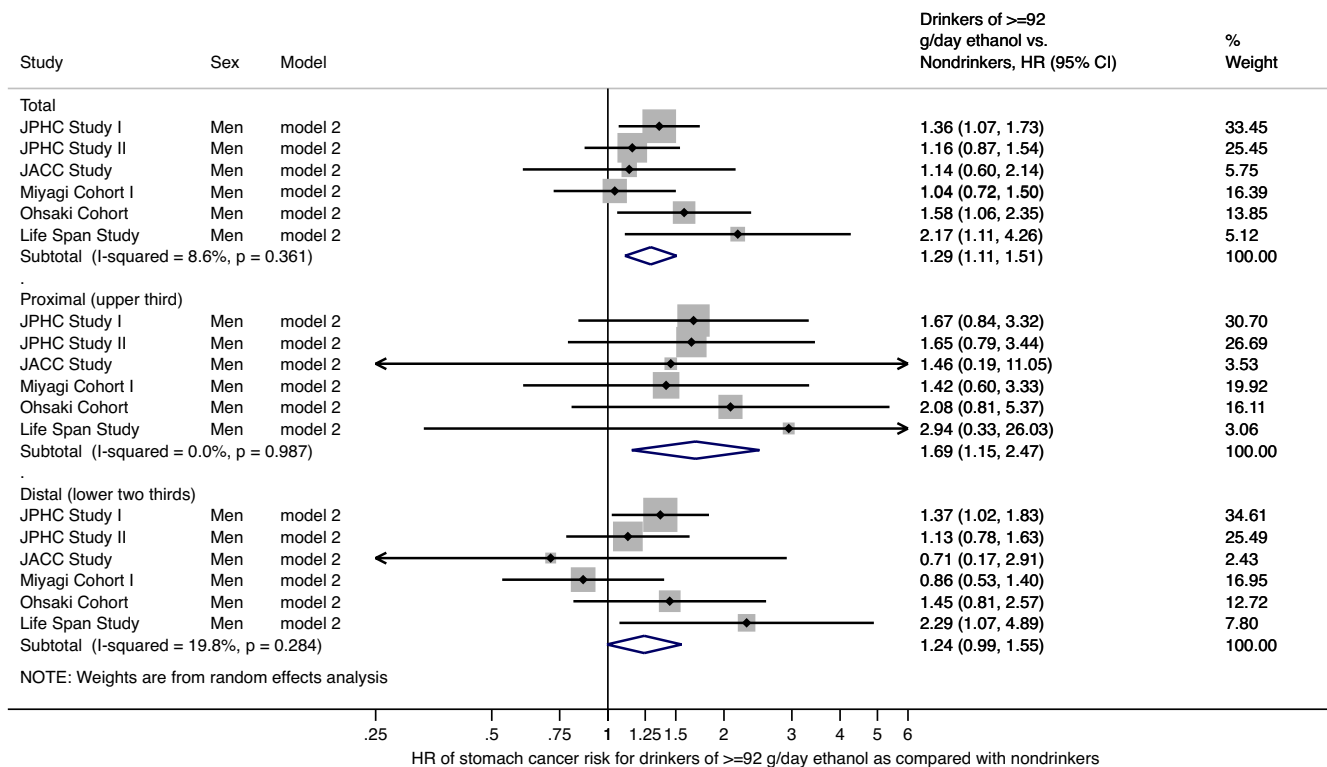
Study	Sex	Model	Drinkers of >=92 g/day ethanol vs. Nondrinkers, HR (95% CI)	% Weight
Total				
JPHC Study I	Men	model 2	1.36 (1.07, 1.73)	33.45
JPHC Study II	Men	model 2	1.16 (0.87, 1.54)	25.45
JACC Study	Men	model 2	1.14 (0.60, 2.14)	5.75
Miyagi Cohort I	Men	model 2	1.04 (0.72, 1.50)	16.39
Ohsaki Cohort	Men	model 2	1.58 (1.06, 2.35)	13.85
Life Span Study	Men	model 2	2.17 (1.11, 4.26)	5.12
Subtotal (I-squared = 8.6%, p = 0.361)			1.29 (1.11, 1.51)	100.00
Proximal (upper third)				
JPHC Study I	Men	model 2	1.67 (0.84, 3.32)	30.70
JPHC Study II	Men	model 2	1.65 (0.79, 3.44)	26.69
JACC Study	Men	model 2	1.46 (0.19, 11.05)	3.53
Miyagi Cohort I	Men	model 2	1.42 (0.60, 3.33)	19.92
Ohsaki Cohort	Men	model 2	2.08 (0.81, 5.37)	16.11
Life Span Study	Men	model 2	2.94 (0.33, 26.03)	3.06
Subtotal (I-squared = 0.0%, p = 0.987)			1.69 (1.15, 2.47)	100.00
Distal (lower two thirds)				
JPHC Study I	Men	model 2	1.37 (1.02, 1.83)	34.61
JPHC Study II	Men	model 2	1.13 (0.78, 1.63)	25.49
JACC Study	Men	model 2	0.71 (0.17, 2.91)	2.43
Miyagi Cohort I	Men	model 2	0.86 (0.53, 1.40)	16.95
Ohsaki Cohort	Men	model 2	1.45 (0.81, 2.57)	12.72
Life Span Study	Men	model 2	2.29 (1.07, 4.89)	7.80
Subtotal (I-squared = 19.8%, p = 0.284)			1.24 (0.99, 1.55)	100.00

NOTE: Weights are from random effects analysis

.25   .5   .75   1 1.25 1.5   2   3   4   5 6

HR of stomach cancer risk for drinkers of >=92 g/day ethanol as compared with nondrinkers

FIGURE 1 Forest plot of study-specific and pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of stomach cancer risk for Japanese men in model 2 with adjustment for age, study area, smoking status, and medical history of diabetes mellitus: comparison of drinkers (≥92 g/d ethanol) and nondrinkers. Bars show 95% CIs; arrows show that the CIs extend beyond the effect size range (−0.25 to 6.00). *P* values indicate heterogeneity among the pooled cohort studies. JACC, Japan Collaborative Cohort; JPHC, Japan Public Health Center-based Prospective Study

(95% CIs) for ≥92 g/d were 1.69 (1.15-2.47) for proximal cancer and 1.24 (0.99-1.55) for distal cancer in model 2. These findings were almost the same when former drinkers were separated from nondrinkers as a sensitivity analysis using data from JPHC-II, JACC, MIYAGI, OHSAKI, and LSS, as shown in Table S1. When regular drinkers were defined as those who drink at least three times/wk (at least five times/wk only for LSS), the associations were almost unchanged. Compared with nondrinkers, the multivariate-adjusted HRs (95% CIs) for ≥92 g/d in model 2 were 1.29 (1.10-1.51) for all stomach cancer, 1.69 (1.15-2.49) for proximal cancer, and 1.24 (0.98-1.55) for distal cancer. The HRs (95% CI) for 10-g/d increase in ethanol (model 2) were 1.022 (1.010-1.035) for all stomach cancer, 1.016 (1.002-1.029) for proximal cancer, and 1.022 (1.009-1.036) for distal cancer. Figure 1 shows the forest plot for HRs (95% CIs) of stomach cancer for those drinking ≥92 g/d ethanol compared with nondrinkers for men in model 2. Figure 2 shows the forest plot for HRs (95% CIs) of stomach cancer for 10-g/day increase in ethanol for men in model 2. Almost all of the cohort in the pooled analysis showed a significant or nonsignificant positive association between alcohol intake and stomach cancer risk.

Table 3 shows the association between alcohol intake and stomach cancer risk in women. Consumption of ≥23 g/d ethanol was positively but nonsignificantly associated with stomach cancer risk. Compared with nondrinkers, the multivariate-adjusted HRs (95% CIs) of stomach cancer were 0.93 (0.80-1.08) for occasional drinkers, and 0.85 (0.74-0.99) for <23 g/d and 1.22 (0.98-1.53) for ≥23 g/d ethanol in regular drinkers in model 2. The median of alcohol intake in the category for ≥23 g/d was 34 g/d (range, 23-2297). The HR (95% CI) of stomach cancer for 10-g/d increase in ethanol was 1.031 (0.984-1.079) with no significant cross-study heterogeneity (*P* = .259). Further adjustment for dietary intake in model 3 strengthened the association; compared with nondrinkers, the multivariate-adjusted HR (95% CI) of stomach cancer risk was 1.38 (1.10-1.74) for ≥23 g/d ethanol. These results were essentially unchanged after excluding participants with stomach cancer diagnosis within 3 years from baseline in both models 4 and 5. As in men, the analysis stratified by stomach cancer subsite showed that the point estimate of risk associated with alcohol intake was greater for proximal cancer than for distal cancer, although the associations were not statistically significant. Compared with nondrinkers, the multivariate-adjusted HRs (95% CIs) for ≥23 g/d ethanol were 1.60 (0.76-3.37) for proximal cancer and 1.18 (0.88-1.57) for distal cancer in model 2. The findings were again essentially unchanged when we separated former drinkers from nondrinkers as a sensitivity analysis using data from JPHC-II, JACC, MIYAGI, OHSAKI, and LSS, as shown in Table S2. When regular drinkers were defined as those who drink at least three times/wk (at least five times/wk only for LSS), the associations were almost unchanged. Compared with nondrinkers, the multivariate-adjusted HRs (95% CIs) of stomach cancer for ≥23 g/d in model 2 were 1.27 (1.01-1.60) for all stomach cancer, 1.86
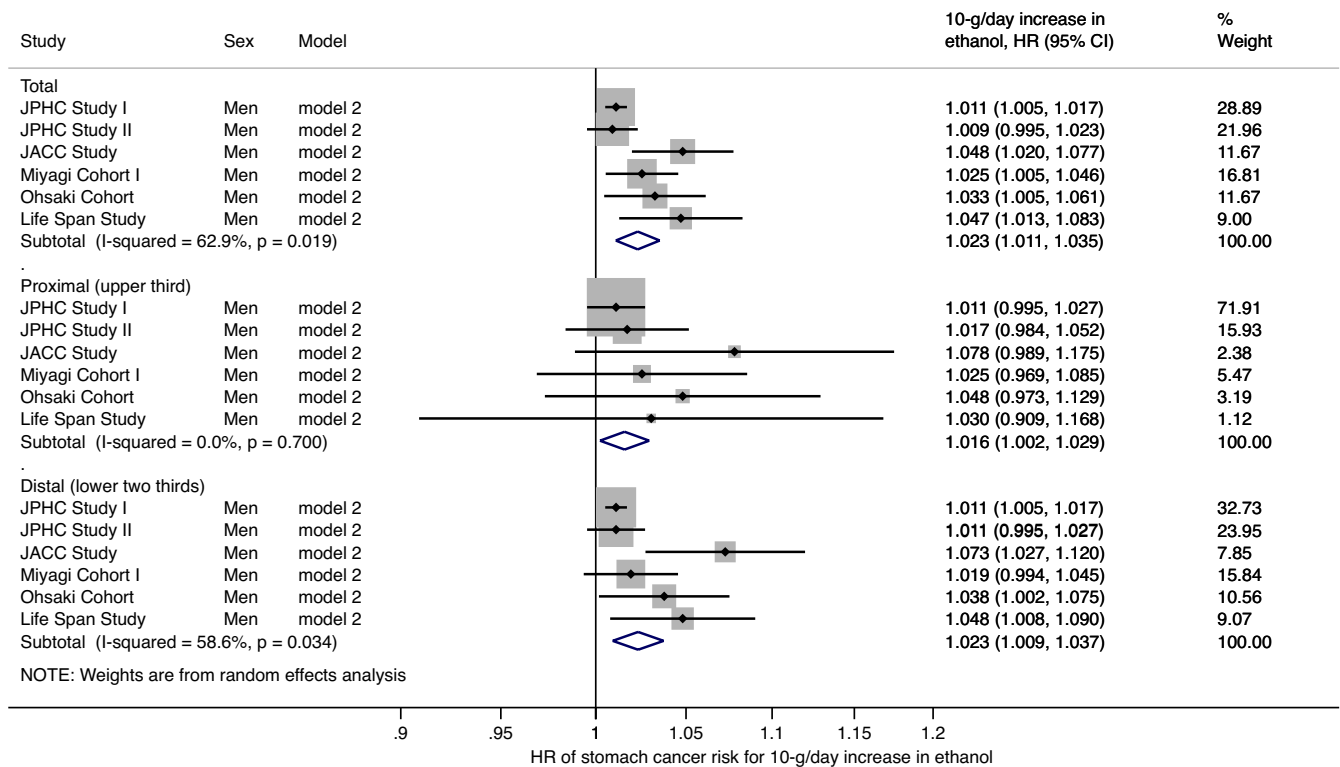
Study	Sex	Model		10-g/day increase in ethanol, HR (95% CI)	% Weight
Total					
JPHC Study I	Men	model 2		1.011 (1.005, 1.017)	28.89
JPHC Study II	Men	model 2		1.009 (0.995, 1.023)	21.96
JACC Study	Men	model 2		1.048 (1.020, 1.077)	11.67
Miyagi Cohort I	Men	model 2		1.025 (1.005, 1.046)	16.81
Ohsaki Cohort	Men	model 2		1.033 (1.005, 1.061)	11.67
Life Span Study	Men	model 2		1.047 (1.013, 1.083)	9.00
Subtotal (I-squared = 62.9%, p = 0.019)				1.023 (1.011, 1.035)	100.00
.					
Proximal (upper third)					
JPHC Study I	Men	model 2		1.011 (0.995, 1.027)	71.91
JPHC Study II	Men	model 2		1.017 (0.984, 1.052)	15.93
JACC Study	Men	model 2		1.078 (0.989, 1.175)	2.38
Miyagi Cohort I	Men	model 2		1.025 (0.969, 1.085)	5.47
Ohsaki Cohort	Men	model 2		1.048 (0.973, 1.129)	3.19
Life Span Study	Men	model 2		1.030 (0.909, 1.168)	1.12
Subtotal (I-squared = 0.0%, p = 0.700)				1.016 (1.002, 1.029)	100.00
.					
Distal (lower two thirds)					
JPHC Study I	Men	model 2		1.011 (1.005, 1.017)	32.73
JPHC Study II	Men	model 2		1.011 (0.995, 1.027)	23.95
JACC Study	Men	model 2		1.073 (1.027, 1.120)	7.85
Miyagi Cohort I	Men	model 2		1.019 (0.994, 1.045)	15.84
Ohsaki Cohort	Men	model 2		1.038 (1.002, 1.075)	10.56
Life Span Study	Men	model 2		1.048 (1.008, 1.090)	9.07
Subtotal (I-squared = 58.6%, p = 0.034)				1.023 (1.009, 1.037)	100.00

NOTE: Weights are from random effects analysis

.9   .95   1   1.05   1.1   1.15   1.2
HR of stomach cancer risk for 10-g/day increase in ethanol

FIGURE 2 Forest plot of study-specific and pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of stomach cancer risk for 10-g/d increase in ethanol in Japanese men in model 2 with adjustment for age, study area, smoking status, and medical history of diabetes mellitus. Bars show 95% CIs. *P* values indicate heterogeneity among the pooled cohort studies. JACC, Japan Collaborative Cohort; JPHC, Japan Public Health Center-based Prospective Study

(0.88-3.92) for proximal cancer, and 1.21 (0.88-1.64) for distal cancer. The HRs (95% CI) for 10-g/d increase in ethanol (model 2) were 1.031 (0.987-1.077) for all stomach cancer, 1.031 (0.959-1.107) for proximal cancer, and 1.044 (0.991-1.101) for distal cancer. Figure 3 shows the forest plot for HRs (95% CIs) of stomach cancer for those drinking ≥23 g/d ethanol compared with nondrinkers for women in model 2. Figure 4 shows the forest plot for HRs (95% CIs) of stomach cancer for 10-g/d increase in ethanol for women in model 2.

A positive correlation between drinking and smoking status was observed in both men and women based on the pooled distribution of individual studies (*P* < .001, respectively). We therefore explored the association between alcohol intake and stomach cancer risk by smoking status (nonsmokers or ever smokers), as shown in Tables S3 and S4 for men and Tables S5 and S6 for women. The direction of the associations was essentially the same as for the overall results, although the number of stomach cancer cases was small for male nonsmokers and female ever smokers. We detected no significant interaction between drinking and smoking status for stomach cancer risk in any models in men (*P* > .10), although the interaction in women was significant in models 1-3 (*P* = .003, .001 and .001, respectively) but not in models 4-5 (*P* > .10).

4 | DISCUSSION

In this pooled analysis of population-based cohort studies undertaken in Japan with more than 250 000 participants and 8500 stomach cancer cases, we found that male regular drinkers had a greater risk of stomach cancer than nondrinkers. The positive associations did not substantially change after excluding participants with stomach cancer diagnosis within 3 years from baseline. These associations were especially marked in male heavy drinkers. Heavy drinkers had a greater point estimate of risk for proximal cancer than for distal cancer.

These findings on the association between alcohol intake and stomach cancer risk are consistent with the results from a recent large meta-analysis by Tramacere et al[14] of mainly European and American cohort and case-control studies. The risk of stomach cancer in moderate and heavy drinkers observed here was similar to the results of Tramacere et al; we found that the multivariate-adjusted HRs (95% CIs) of stomach cancer in men were 1.18 (1.09-1.29) for 46 to <69 g/d, 1.21 (1.05-1.39) for 69 to <92 g/d, and 1.29 (1.11-1.51) for ≥92 g/d, compared with nondrinkers. Tramacere et al found a relative risk of 1.20 (95% CI, 1.01-1.44) for heavy drinkers of ≥4 drinks/d (≥50 g/d ethanol) compared with nondrinkers. Although their subgroup analysis showed no association between heavy drinking and stomach cancer risk in Asia, the present study found that drinkers of ≥50 g/d ethanol had a significantly greater risk of stomach cancer using a quantitative pooled analysis of original data from each study and common alcohol intake categories across studies. Our findings are also consistent with a report from the World Cancer Research Fund/American Institute for Cancer Research, which indicated that alcohol intake above approximately 45 g/d ethanol (approximately three drinks a day) is probably associated with stomach cancer risk.[37]

TABLE 3 Results from a pooled analysis using a random effects model for stomach cancer incidence by alcohol intake in Japanese women, 1988-2014

Site of cancer	Total	Nondrinkers	Occasional drinkers (<once/wk)	Regular drinkers (≥once/wk)		P for heterogeneity for the highest category[f]	Alcohol intake as a continuous variable (per 10 g/d)		
				<23 g/d	≥23 g/d		HR (95% CI)	P for trend	P for heterogeneity[f]
Total									
No. of subjects	136 527	106 537	11 588	14 068	4334				
No. of cases	2535	2051	187	210	87				
Person-years	2 318 185	1 806 791	207 565	231 270	72 559				
Incidence rate per 100 000 person-years	109	114	90	91	120				
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	1.02 (0.87-1.19)	0.91 (0.75-1.11)	1.36 (1.10-1.69)	.987	1.027 (0.995-1.060)	.094	.484
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	0.93 (0.80-1.08)	0.85 (0.74-0.99)	1.22 (0.98-1.53)	.722	1.031 (0.984-1.079)	.202	.259
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.04 (0.88-1.22)	0.93 (0.75-1.15)	1.38 (1.10-1.74)	.892	1.031 (0.992-1.071)	.120	.364
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.03 (0.88-1.22)	0.95 (0.79-1.15)	1.30 (1.02-1.65)	.657	1.020 (0.983-1.059)	.294	.435
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	1.07 (0.91-1.26)	0.98 (0.79-1.20)	1.36 (1.05-1.77)	.374	1.023 (0.985-1.061)	.239	.503
Proximal (upper third)									
No. of subjects	136 527	106 537	11 588	14 068	4334				
No. of cases	172	139	12	13	8				
Person-years	2 331 498	1 817 505	208 598	232 381	73 014				
Incidence rate per 100 000 person-years	7	8	6	6	11				
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	1.24 (0.58-2.68)	1.27 (0.70-2.29)	1.79 (0.87-3.68)	.969	1.029 (0.966-1.097)	.371	.984
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	1.03 (0.56-1.90)	1.14 (0.63-2.06)	1.60 (0.76-3.37)	.832	1.030 (0.955-1.109)	.445	.958
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.23 (0.56-2.69)	1.29 (0.67-2.47)	1.85 (0.87-3.91)	.901	1.041 (0.967-1.120)	.286	.916
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.16 (0.59-2.31)	1.30 (0.68-2.49)	1.77 (0.80-3.92)	.932	1.033 (0.958-1.114)	.396	.967
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	1.17 (0.58-2.37)	1.28 (0.63-2.62)	1.93 (0.86-4.32)	.926	1.045 (0.972-1.123)	.237	.928

TABLE 3 (Continued)

Site of cancer	Total	Nondrinkers	Occasional drinkers (<once/wk)	Regular drinkers (≥once/wk)		P for heterogeneity for the highest category[f]	Alcohol intake as a continuous variable (per 10 g/d)		
				<23 g/d	≥23 g/d		HR (95% CI)	P for trend	P for heterogeneity[f]
Distal (lower two-thirds)									
No. of subjects	136 527	106 537	11 588	14 068	4334				
No. of cases	1475	1176	123	125	51				
Person-years	2 323 363	1 811 056	207 860	231 718	72 729				
Incidence rate per 100 000 person-years	63	65	59	54	70				
Age- and area-adjusted HR (95% CI) as model 1[a]		1.00 (ref.)	1.07 (0.88-1.29)	0.89 (0.65-1.23)	1.29 (0.97-1.71)	.823	1.038 (0.991-1.087)	.119	.656
Multivariate-adjusted HR (95% CI) in model 2[b]		1.00 (ref.)	0.99 (0.82-1.19)	0.86 (0.65-1.13)	1.18 (0.88-1.57)	.624	1.036 (0.985-1.090)	.170	.467
Multivariate-adjusted HR (95% CI) in model 3[c]		1.00 (ref.)	1.08 (0.88-1.31)	0.94 (0.67-1.32)	1.28 (0.94-1.74)	.811	1.036 (0.980-1.095)	.212	.671
Multivariate-adjusted HR (95% CI) in model 4[d]		1.00 (ref.)	1.08 (0.89-1.32)	0.93 (0.66-1.30)	1.30 (0.96-1.76)	.783	1.046 (0.989-1.107)	.116	.597
Multivariate-adjusted HR (95% CI) in model 5[e]		1.00 (ref.)	1.10 (0.90-1.36)	0.98 (0.69-1.40)	1.32 (0.96-1.82)	.640	1.044 (0.984-1.108)	.157	.640

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., reference.

[a]Adjusted for age and area (Japan Public Health Center-based Prospective Study I [JPHC I], JPHC II, Japan Collaborative Cohort Study, and Life Span Study only).

[b]Adjusted for covariates in model 1 plus smoking status (pack-years: 0, <20, and ≥20) and medical history of diabetes mellitus (yes, no).

[c]Adjusted for covariates in model 2 plus total energy intake (quartiles), vegetable intake (quartiles), fruit intake (quartiles), salt intake (quartiles), and green tea consumption (cups/d: <1, 1-2, 3-4, and ≥5).

[d]Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 2.

[e]Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 3.

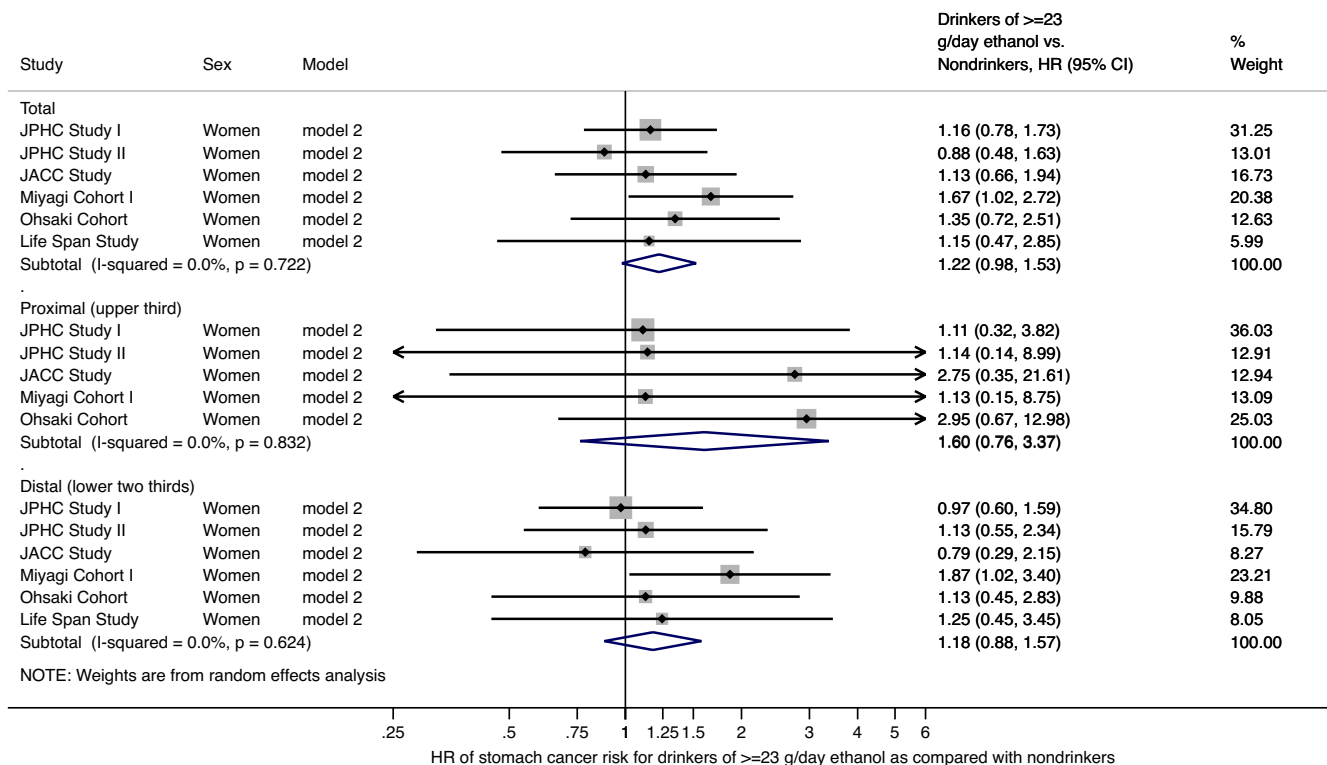[f]Indicating heterogeneity among the pooled cohort studies.

FIGURE 3 Forest plot of study-specific and pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of stomach cancer risk for Japanese women in model 2 with adjustment for age, study area, smoking status, and medical history of diabetes mellitus: comparison of drinkers (≥23 g/d ethanol) and nondrinkers. Bars show 95% CIs; arrows show that the CIs extend beyond the effect size range (−0.25 to 6.00). *P* values indicate heterogeneity among the pooled cohort studies. JACC, Japan Collaborative Cohort; JPHC Study, Japan Public Health Center-based Prospective Study

Moderate Japanese drinkers could be at an increased risk for stomach cancer. Alcohol metabolism produces the carcinogen acetaldehyde, and the ALDH2 enzyme plays an important role in oxidizing harmful alcohol-related acetaldehyde into harmless acetate. This activity depends on polymorphism in the *ALDH2* gene (rs671).[38] Individuals with inactive *ALDH2* alleles are exposed to higher concentrations of acetaldehyde after drinking; approximately 40% of the Japanese population has inactive ALDH2 enzyme,[39] whereas few European and American people have inactive ALDH2 enzyme.[40] Interestingly, two case-control studies in Japan showed a substantial association and interaction between *ALDH2* polymorphism (rs671), alcohol intake, and stomach cancer risk,[41,42] indicating that drinkers with inactive *ALDH2* alleles had a higher risk of stomach cancer compared with nondrinkers carrying homozygous active alleles. Given that inactive *ALDH2* alleles are specific to East Asian people,[40] alcohol intake might have a greater effect on stomach cancer risk in East Asian populations than in European and American populations. It is interesting that the subgroup analysis in the meta-analysis by Tramacere et al[14] showed a substantial increase in stomach cancer risk for drinkers compared with nondrinkers in non-Asian countries but not in Asia: the HRs (95% CIs) were 1.12 (1.01-1.24) and 1.02 (0.95-1.09), respectively. This association, however, could stem from differences in the amount of alcohol intake between the two regions, because drinkers without inactive *ALDH2* alleles (ie, most drinkers in European and American populations) can consume

more alcohol than drinkers with these alleles. The mediation analyses undertaken in two case-control studies also suggest that individuals with inactive *ALDH2* alleles experience two opposing effects of alcohol intake on the stomach; namely, a carcinogenic effect (ie, a direct effect mediated by increased alcohol-related acetaldehyde after drinking due to reduced activity of ALDH2 enzymes) and a protective effect (ie, an indirect effect mediated by changing drinking behavior).[42,43] Therefore, the amount of alcohol intake and the direct and indirect effects of the *ALDH2* polymorphism (rs671) might be associated with stomach cancer risk related to alcohol intake in a complex way. A nested case-control study in Japan also suggested that the genes related to alcohol metabolism, including *ALDH2* polymorphisms (rs671), interacted with the association between alcohol intake and stomach cancer risk.[44] In that study, individuals with inactive *ALDH2* alleles who drank ≥150 g/wk ethanol had a significantly greater stomach cancer risk than those individuals without the allele who drank 0 to <150 g/wk; the multivariate-adjusted odds ratio was 2.08 (95% CI, 1.05-4.12) (*P* for interaction = .08).

We showed that heavy drinkers had a greater point estimate of risk for proximal cancer than for distal cancer, whereas Tramacere et al[14] reported that alcohol intake was (nonsignificantly) associated with noncardia stomach cancer rather than with cardia stomach cancer. In that study, drinkers of ≥50 g/d ethanol had a summary relative risk of 1.17 (95% CI, 0.78-1.75) for gastric noncardia cancer and 0.99 (0.67-1.47) for gastric cardia cancer, compared with nondrinkers.
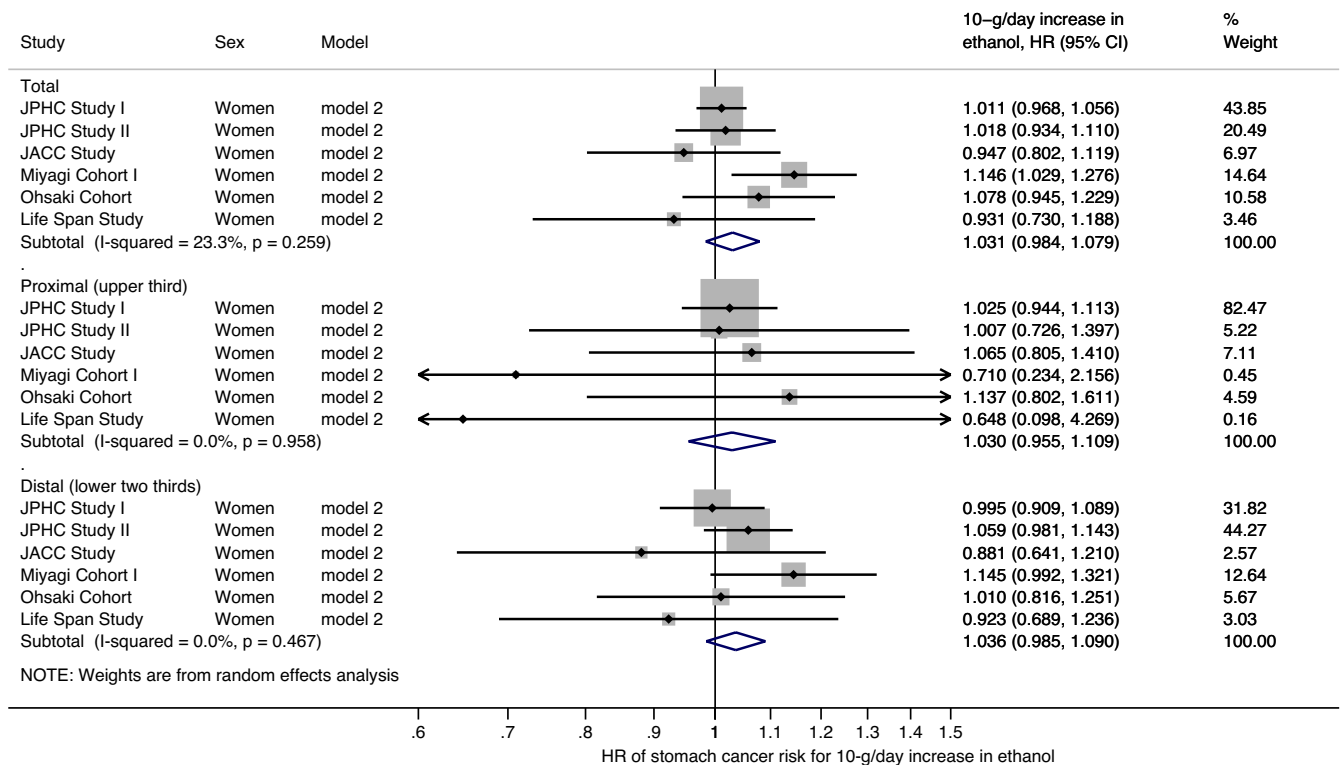
Study	Sex	Model		10–g/day increase in ethanol, HR (95% CI)	% Weight
Total					
JPHC Study I	Women	model 2		1.011 (0.968, 1.056)	43.85
JPHC Study II	Women	model 2		1.018 (0.934, 1.110)	20.49
JACC Study	Women	model 2		0.947 (0.802, 1.119)	6.97
Miyagi Cohort I	Women	model 2		1.146 (1.029, 1.276)	14.64
Ohsaki Cohort	Women	model 2		1.078 (0.945, 1.229)	10.58
Life Span Study	Women	model 2		0.931 (0.730, 1.188)	3.46
Subtotal (I-squared = 23.3%, p = 0.259)				1.031 (0.984, 1.079)	100.00
.					
Proximal (upper third)					
JPHC Study I	Women	model 2		1.025 (0.944, 1.113)	82.47
JPHC Study II	Women	model 2		1.007 (0.726, 1.397)	5.22
JACC Study	Women	model 2		1.065 (0.805, 1.410)	7.11
Miyagi Cohort I	Women	model 2		0.710 (0.234, 2.156)	0.45
Ohsaki Cohort	Women	model 2		1.137 (0.802, 1.611)	4.59
Life Span Study	Women	model 2		0.648 (0.098, 4.269)	0.16
Subtotal (I-squared = 0.0%, p = 0.958)				1.030 (0.955, 1.109)	100.00
.					
Distal (lower two thirds)					
JPHC Study I	Women	model 2		0.995 (0.909, 1.089)	31.82
JPHC Study II	Women	model 2		1.059 (0.981, 1.143)	44.27
JACC Study	Women	model 2		0.881 (0.641, 1.210)	2.57
Miyagi Cohort I	Women	model 2		1.145 (0.992, 1.321)	12.64
Ohsaki Cohort	Women	model 2		1.010 (0.816, 1.251)	5.67
Life Span Study	Women	model 2		0.923 (0.689, 1.236)	3.03
Subtotal (I-squared = 0.0%, p = 0.467)				1.036 (0.985, 1.090)	100.00

NOTE: Weights are from random effects analysis

.6　.7　.8　.9　1　1.1　1.2　1.3　1.4　1.5

HR of stomach cancer risk for 10-g/day increase in ethanol

FIGURE 4 Forest plot of study-specific and pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of stomach cancer risk for 10-g/d increase in ethanol in Japanese women in model 2 with adjustment for age, study area, smoking status, and medical history of diabetes mellitus. Bars show 95% CIs; arrows show that the CIs extend beyond the effect size range (−0.60 to 1.50). *P* values indicate heterogeneity among the pooled cohort studies. JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study

Although it is unclear why these findings differed from our own, a partial explanation might be the difference in study regions. For example, noncardia stomach cancer cases caused by *H. pylori* infection and individuals with inactive ALDH2 enzymes are much more common in East Asian populations, including the Japanese population, than in European and American populations.[40,45] As the meta-analysis by Tramacere et al[14] mainly featured Western populations, their findings may reflect a Western-specific association of alcohol intake with stomach cancer risk by subsite; however, a recent large cohort study with more than 490 000 participants in the United States found no association between higher alcohol intake and gastric noncardia cancer.[15] The observed difference in the association of alcohol intake with stomach cancer risk between subsites could be mediated by different risk factors. Additional studies are needed to elucidate the relevant factors and mechanisms.

We provided evidence for a positive association between alcohol intake and stomach cancer risk among Japanese people using a pooled analysis of data from six large-scale cohort studies. A strength of this study was that all the studies analyzed had a prospective design, a large population with a large number of stomach cancer cases, a long follow-up period, used a validated questionnaire to assess alcohol intake, and adjusted for multiple confounders. Our pooled analysis using common alcohol intake categories between studies enabled us to properly examine the dose-response relationship between alcohol intake and stomach cancer. Pooled analysis using datasets from individual studies yields more precise estimates of the association between exposure and outcome than meta-analysis using data from publications.[46] Our findings could apply not only to the Japanese population but also to other East Asian populations because they share many factors, such as a high incidence of stomach cancer, high prevalence of *H. pylori* infection, and genetic background.[1,40,45] However, the following limitations should be considered. First, we did not consider the effects of the prevalence of *H. pylori* infection on the association between alcohol intake and stomach cancer, although this is a known strong risk factor for stomach cancer.[2] Several cross-sectional studies showed that alcohol intake was not associated with *H. pylori* infection.[47,48] In addition, the IARC also states that confounding by *H. pylori* infection is not a major concern.[49] If alcohol intake is related to *H. pylori* infection, however, it could confound the association between alcohol intake and stomach cancer. Interestingly, a large-scale pooled analysis of case-control studies showed the significant interaction between alcohol intake and *H. pylori* infection for stomach cancer risk (ie, the synergistic positive effect of alcohol intake and *H. pylori* infection on stomach cancer risk).[50] Therefore, further studies that take into account *H. pylori* infection are needed. Second, we did not consider the effects of the relationship between participants' genetic background (eg, *ALDH2* polymorphisms) and alcohol metabolism on the association between alcohol intake and stomach cancer. As previous case-control and nested case-control studies

suggest an important role of *ALDH2* polymorphisms for the association between alcohol intake and stomach cancer risk,[41-44] cohort studies that examine this role could further elucidate the effect of alcohol intake on stomach cancer risk. Third, we did not examine the association between heavy drinking and stomach cancer risk in women because of the small number of female heavy drinkers. Fourth, although we controlled for the confounding effect of smoking through statistical adjustment or subgroup analysis by smoking status, it is difficult to completely rule out a possible residual confounding effect of smoking. We detected a significant interaction between drinking and smoking status for stomach cancer risk in women; however, the number of stomach cancer cases was limited in female ever smokers. In addition, as the number of heavy drinkers was limited in male nonsmokers, further examinations are required to confirm the association. Fifth, our evaluation of alcohol intake using a self-administered questionnaire at baseline could have led to misclassification in each study. If present, however, this would have been nondifferential and resulted in underestimation of the associations. Differences in information bias for drinking would not occur between participants with stomach cancer and those without, because this information was recorded before the stomach cancer diagnosis. Finally, we were unable to consider changes in drinking habits and potential confounders (eg, smoking) during the follow-up period because the information was obtained only at baseline. As people tend to reduce alcohol intake with age due to various reasons, we might overestimate their alcohol intake during the follow-up; the overestimated exposure could lead to underestimation of the associations.

In conclusion, we provide evidence for a positive association between alcohol intake and stomach cancer risk in men using a pooled analysis of population-based cohort studies. Better understanding of this relationship could help physicians and policymakers to develop intervention strategies to reduce stomach cancer risk caused by alcohol intake.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Montecucco C, Rappuoli R. Living dangerously: how *Helicobacter pylori* survives in the human stomach. *Nat Rev Mol Cell Biol*. 2001;2:457-466.
3. Nishino Y, Inoue M, Tsuji I, et al. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*. 2006;36:800-807.
4. Kim MK, Sasaki S, Sasazuki S, Tsugane S; Japan Public Health Center-based Prospective Study Group. Prospective study of three major dietary patterns and risk of gastric cancer in Japan. *Int J Cancer*. 2004;110:435-442.
5. Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer*. 2004;90:128-134.
6. Wang XQ, Yan H, Terry PD, et al. Interaction between dietary factors and *Helicobacter pylori* infection in noncardia gastric cancer: a population-based case-control study in China. *J Am Coll Nutr*. 2012;31:375-384.
7. Shimazu T, Wakai K, Tamakoshi A, et al. Association of vegetable and fruit intake with gastric cancer risk among Japanese: a pooled analysis of four cohort studies. *Ann Oncol*. 2014;25:1228-1233.
8. Sasazuki S, Tamakoshi A, Matsuo K, et al. Green tea consumption and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*. 2012;42:335-346.

9. Inoue M, Sasazuki S, Wakai K, et al. Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies. *Gut*. 2009;58:1323-1332.

10. Soffritti M, Belpoggi F, Cevolani D, et al. Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. *Ann NY Acad Sci*. 2002;982:46-69.

11. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol*. 2007;8:292-293.

12. IARC, Personal Habits and Indoor Combustions. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100(E). IARC, .

13. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ. Alcohol and cancer: a statement of the American Society of Clinical Oncology. *J Clin Oncol*. 2018;36:83-93.

14. Tramacere I, Negri E, Pelucchi C, et al. A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol*. 2012;23:28-36.

15. Wang S, Freedman ND, Loftfield E, Hua X, Abnet CC. Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: a 16-year prospective analysis from the NIH-AARP diet and health cohort. *Int J Cancer*. 2018;143:2749-2757.

16. Kato I, Tominaga S, Matsumoto K. A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Jpn J Cancer Res*. 1992;83:568-575.

17. Sasazuki S, Sasaki S, Tsugane S; Japan Public Health Center Study Group. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer*. 2002;101:560-566.

18. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. *Jpn J Cancer Res*. 1987;78:1323-1328.

19. Nakaya N, Tsubono Y, Kuriyama S, et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev*. 2005;14:169-174.

20. Tamura T, Wada K, Tsuji M, et al. Association of alcohol consumption with the risk of stomach cancer in a Japanese population: a prospective cohort study. *Eur J Cancer Prev*. 2018;27:27-32.

21. Li Y, Eshak ES, Shirai K, et al. Alcohol consumption and risk of gastric cancer: The Japan Collaborative Cohort study. *J Epidemiol*. 2021;31:30-36.

22. Sung NY, Choi KS, Park EC, et al. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer*. 2007;97:700-704.

23. Tran GD, Sun X-D, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*. 2005;113:456-463.

24. Moy KA, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2287-2297.

25. Tsugane S, Sawada N. The JPHC study: design and some findings on the typical Japanese diet. *Jpn J Clin Oncol*. 2014;44:777-782.

26. Tamakoshi A, Yoshimura T, Inaba Y, et al. Profile of the JACC study. *J Epidemiol*. 2005;15:S4-8.

27. Tsuji I, Nishino Y, Tsubono Y, et al. Follow-up and mortality profiles in the Miyagi Cohort Study. *J Epidemiol*. 2004;14:S2-6.

28. Tsuji I, Nishino Y, Ohkubo T, et al. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. *J Epidemiol*. 1998;8:258-263.

29. Ozasa K, Grant EJ, Kodama K. Japanese legacy cohorts: the life span study atomic bomb survivor cohort and survivors' offspring. *J Epidemiol*. 2018;28:162-169.

30. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S, JPHC. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. *J Epidemiol*. 2003;13:S125-133.

31. Otani T, Iwasaki M, Yamamoto S, et al. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center- based prospective study. *Cancer Epidemiol Biomarkers Prev*. 2003;12:1492-1500.

32. Ogawa K, Tsubono Y, Nishino Y, et al. Validation of a food- frequency questionnaire for cohort studies in rural Japan. *Public Health Nutr*. 2003;6:147-157.

33. Nakaya N, Kikuchi N, Shimazu T, et al. Alcohol consumption and suicide mortality among Japanese men: the Ohsaki Study. *Alcohol*. 2007;41:503-510.

34. Sauvaget C, Allen N, Hayashi M, Spencer E, Nagano J. Validation of a food frequency questionnaire in the Hiroshima/Nagasaki Life Span Study. *J Epidemiol*. 2002;12:394-401.

35. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997;65:1220S-1228S.

36. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

37. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and stomach cancer. dietandcancerreport.org

38. Lai C-L, Yao C-T, Chau G-Y, et al. Dominance of the inactive Asian variant over activity and protein contents of mitochondrial aldehyde dehydrogenase 2 in human liver. *Alcohol Clin Exp Res*. 2014;38:44-50.

39. Wakai K, Hamajima N, Okada R, et al. Profile of participants and genotype distributions of 108 polymorphisms in a cross-sectional study of associations of genotypes with lifestyle and clinical factors: a project in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. *J Epidemiol*. 2011;21:223-235.

40. International HapMap Consortium. The International HapMap Project. *Nature*. 2003;426:789-796.

41. Matsuo K, Oze I, Hosono S, et al. The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. *Carcinogenesis*. 2013;34:1510-1515.

42. Ishioka K, Masaoka H, Ito H, et al. Association between ALDH2 and ADH1B polymorphisms, alcohol drinking and gastric cancer: a replication and mediation analysis. *Gastric Cancer*. 2018;21:936-945.

43. Koyanagi YN, Suzuki E, Imoto I, et al. Across-site differences in the mechanism of alcohol-induced digestive tract carcinogenesis: an evaluation by mediation analysis. *Cancer Res*. 2020;80:1601-1610.

44. Hidaka A, Sasazuki S, Matsuo K, et al. Genetic polymorphisms of ADH1B, ADH1C and ALDH2, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study. *Carcinogenesis*. 2015;36:223-231.

45. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol*. 2006;12:354-362.

46. Ferro A, Morais S, Rota M, et al. Alcohol intake and gastric cancer: meta-analyses of published data versus individual participant data pooled analyses (StoP Project). *Cancer Epidemiol*. 2018;54:125-132.

47. Tsugane S, Kabuto M, Imai H, et al. *Helicobacter pylori*, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. *Cancer Causes Control*. 1993;4:297-305.

48. Tamura T, Morita E, Kawai S, et al. No association between *Helicobacter pylori* infection and diabetes mellitus among a general Japanese population: a cross-sectional study. *Springerplus*. 2015;4:602.

49. International Agency for Research on Cancer. *Personal habits and indoor combustions*. Monograph, Consumption of Alcoholic Beverages. 2012;100E:373-499.

50. Collatuzzo G, Pelucchi C, Negri E, et al. Exploring the interactions between *Helicobacter pylori* (Hp) infection and other risk factors of gastric cancer: a pooled analysis in the Stomach cancer Pooling (StoP) Project. *Int J Cancer.* 2021;149:1228-1238.

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