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
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. There is a consensus that *Helicobacter pylori* infection, smoking, and high salt intake are risk factors for stomach cancer. Higher intake of vegetables, fruit, and green tea could be protective against stomach cancer. Animal studies indicate that alcohol is harmful to the stomach, partly because alcohol metabolism produces the carcinogen acetaldehyde. Acetaldehyde related to alcohol intake is now considered a group 1 carcinogen by the IARC, and alcohol intake is an established risk factor for several cancers, including oral cavity, head and neck, esophagus, breast, liver, and colorectal cancer. 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. 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. 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. The findings from cohort studies in Korea and China are also inconclusive. 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; (b) JPHC-II; (c) JACC; (d) MIYAGI; (e) OHSAKI; and (f) LSS. 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. 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 | Method of follow-up | Age range (mean ± SD, y) | Last follow-up | Mean follow-up period (y) | Size of the cohort | Number of stomach cancer cases | Outcome |
|----------------|------------------------------------------------------------------------|----------------------------------|-------------------------|-------------|---------------------------------------------|----------------------|--------------------------|----------------|---------------------------|----------------|-------------------------------|----------|
| 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                | 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.

*Life Span Study originally started in 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 the style of the questions differed across studies.

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 the style of the questions differed across studies.

### 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. 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 (<once/wk) | Occasional drinkers (once/wk) | Regular drinkers (tonce/wk) | \( P \) for heterogeneity for the highest category\(^a\) | Alcohol intake as a continuous variable (per 10 g/d) |
|---------------|-------|------------------------|-----------------------------|-----------------------------|------------------------------------------------|--------------------------------------------------|
| Site          | Total | Nondrinkers (<once/wk) | Occasional drinkers (once/wk) | Regular drinkers (tonce/wk) | \( P \) for trend | \( P \) for heterogeneity\(^a\) |
| Total No. of subjects | 119 951 | 29 770 | 8333 | 22 039 | 24 475 | 20 883 | 9585 | 48 66 |
| 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 86 |
| 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) |
| 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) |
| 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) |
| 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) |
| 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) |

Proximal (upper third)

| Site of cancer | Total | Nondrinkers (<once/wk) | Occasional drinkers (once/wk) | Regular drinkers (tonce/wk) | \( P \) for heterogeneity for the highest category\(^a\) | Alcohol intake as a continuous variable (per 10 g/d) |
|---------------|-------|------------------------|-----------------------------|-----------------------------|------------------------------------------------|--------------------------------------------------|
| Site          | Total | Nondrinkers (<once/wk) | Occasional drinkers (once/wk) | Regular drinkers (tonce/wk) | \( P \) for trend | \( P \) for heterogeneity\(^a\) |
| Total No. of subjects | 119 951 | 29 770 | 8333 | 22 039 | 24 475 | 20 883 | 9585 | 48 66 |
| 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 96 |
| Incidence rate per 100 000 person-years | 36 | 37 | 28 | 31 | 32 | 41 | 43 | 43 |
| Site of cancer | Total | Nondrinkers (<once/wk) | Occasional drinkers (<once/wk) | Regular drinkers (ounce/wk) | Age- and area-adjusted HR (95% CI) as model 1<sup>a</sup> | Multivariate-adjusted HR (95% CI) in model 2<sup>b</sup> | Multivariate-adjusted HR (95% CI) in model 3<sup>c</sup> | Multivariate-adjusted HR (95% CI) in model 4<sup>d</sup> | Multivariate-adjusted HR (95% CI) in model 5<sup>e</sup> | P for heterogeneity for the highest category<sup>f</sup> | Alcohol intake as a continuous variable (per 10 g/d) | P for trend | P for heterogeneity<sup>f</sup> |
|---------------|-------|------------------------|-------------------------------|-----------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------|------------------|------------------|
| Age- and area-adjusted HR (95% CI) as model 1<sup>a</sup> | 1.00  | 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 (1.006-1.030)                                    | .004 .494                                               |
| Multivariate-adjusted HR (95% CI) in model 2<sup>b</sup> | 1.00  | 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 (1.002-1.029)                                    | .21 .700                                                |
| Multivariate-adjusted HR (95% CI) in model 3<sup>c</sup> | 1.00  | 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 (0.95-2.21)                                      | 1.76 (1.30-2.94)                                      | .770 (1.003-1.042)                                    | .20 .267                                                |
| Multivariate-adjusted HR (95% CI) in model 4<sup>d</sup> | 1.00  | 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 (1.004-1.028)                                    | .10 .624                                                |
| Multivariate-adjusted HR (95% CI) in model 5<sup>e</sup> | 1.00  | 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 (1.004-1.044)                                    | .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  | 182     | 177    | 152  | 161    | 189    | 211    | 199 | 178                       |

| Age- and area-adjusted HR (95% CI) as model 1<sup>a</sup> | 1.00  | 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 (1.013-1.045)                                    | .001 .008                                               |
| Multivariate-adjusted HR (95% CI) in model 2<sup>b</sup> | 1.00  | 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 (1.009-1.037)                                    | .01 .034                                                |
| Multivariate-adjusted HR (95% CI) in model 3<sup>c</sup> | 1.00  | 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 (1.004-1.030)                                    | .013 .135                                               |
### Table 2 (Continued)

| Site of cancer | Total | Nondrinkers (<once/wk) | Occasional drinkers (<once/wk) | Regular drinkers (once/wk) | Alcohol intake as a continuous variable (per 10 g/d) |
|----------------|-------|------------------------|-------------------------------|---------------------------|----------------------------------|
|                | HR (95% CI) in model 4 |
|                |       |                        |                               |                           | P for heterogeneity for the highest category |
|                |       |                        |                               |                           | P for trend |
|                |       |                        |                               |                           | P for heterogeneity |
| Stomach        |       |                        |                               |                           |         |
| Multivariate-adjusted HR | 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) | 0.632 |
| Nondrinkers (<once/wk) | 1.00 (ref.) | 1.20 (0.86-1.64) | 0.99 (0.88-1.21) | 1.13 (1.00-1.27) | 1.22 (1.03-1.44) | 1.17 (1.00-1.36) | 1.13 (0.91-1.40) | 0.508 |
| Occasional drinkers (<once/wk) | 1.00 (ref.) | 1.00 (0.86-1.15) | 1.00 (0.87-1.15) | 1.00 (0.91-1.10) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) |
| Regular drinkers (once/wk) | 1.00 (ref.) | 1.00 (0.86-1.15) | 1.00 (0.87-1.15) | 1.00 (0.91-1.10) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) | 1.00 (0.91-1.11) |

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

aAdjusted for age and area (Japan Public Health Center-based Study Prospective Study [JPHC-I], JPHC-II, Japan Collaborative Cohort Study, and Life Span Study only).
bAdjusted for covariates in model 2 plus total energy intake (quartiles), vegetable intake (quartiles), salt intake (quartiles), and green tea consumption (cups/d: <1, 1-2, 3-4, and ≥5).
cExcluding participants with stomach cancer diagnosis within 3 y from the baseline in model 2.
dExcluding participants with stomach cancer diagnosis within 3 y from the baseline in model 3.
eIndicating heterogeneity among the pooled cohort studies.

### Results

This study included 226,078 participants (119,911 men and 106,167 women) with 26,716 stomach cancer cases (6,871 men and 19,845 women) during 1220,571 person-years of follow-up, as shown in Table 1. Approximately half the men habitually consumed more than 20 g/d of ethanol whereas only 3% of women consumed this quantity. The median of alcohol intake in the category for ≥92 g/d alcohol was 115 g/d (range, 92-4495). The HR 95% CI for stomach cancer were 1.00 (0.87-1.15) for occasional drinkers, 1.00 (0.91-1.11) for ≥92 g/d ethanol. The HR 95% CI was 1.02 (1.01-1.03) for nondrinkers, 1.00 (0.89-1.01) for occasional drinkers, and 1.00 (0.91-1.11) for ≥92 g/d alcohol. The correlation between drinking and stomach cancer incidence was assessed using Q-statistics and I² statistics. The correlation between drinking and stomach cancer incidence was assessed using Q-statistics and I² statistics. The correlation between drinking and stomach cancer incidence was assessed using Q-statistics and I² statistics.
(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. The HR (95% CI) of stomach cancer for 10-g/d increase in ethanol (model 2) was positively but nonsignificantly associated with stomach cancer for those drinking ≥92 g/d ethanol compared with nondrinkers for 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 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 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 = .295). 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 stomach cancer for 10-g/day increase in ethanol for men 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
4 | DISCUSSION

In this pooled analysis of population-based cohort studies undertaken in Japan with more than 250,000 participants and 8,500 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 of mainly European and American cohort and case-control studies. The risk of stomach cancer was higher for alcohol intake above approximately 45 g/d ethanol (approximately 100.00 for 10-g/day increase in ethanol, HR (95% CI)

NOTE: Weights are from random effects analysis

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).

### 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.

| Study               | Sex   | Model | 10-g/day increase in ethanol, HR (95% CI) | % Weight |
|---------------------|-------|-------|------------------------------------------|----------|
| 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    |
| Ohkasi 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     |
| Ohkasi 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    |
| Ohkasi Cohort       | Men   | model 2 | 1.038 (1.002, 1.075) | 10.56    |
| Life Span Study     | Men   | model 2 | 1.048 (1.008, 1.080) | 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.
| Site of cancer | Total | Nondrinkers (< once/wk) | Occasional drinkers (≥ once/wk) | Regular drinkers (≥ 23 g/d) | P for heterogeneity for the highest category | Alcohol intake as a continuous variable (per 10 g/d) |
|----------------|-------|-------------------------|-----------------------------|--------------------------|---------------------------------|---------------------------------|
| 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<sup>a</sup> | 1.00 | 1.02 | (0.87-1.19) | 0.91 | (0.75-1.11) | 1.36 | 0.987 | 1.027 | (0.995-1.060) | .094 | 0.484 |
| Multivariate-adjusted HR (95% CI) in model 2<sup>b</sup> | 1.00 | 0.93 | (0.80-1.08) | 0.85 | (0.74-0.99) | 1.22 | 0.722 | 1.031 | (0.984-1.079) | .202 | 0.259 |
| Multivariate-adjusted HR (95% CI) in model 3<sup>c</sup> | 1.00 | 1.04 | (0.88-1.22) | 0.93 | (0.75-1.15) | 1.38 | 0.892 | 1.031 | (0.992-1.071) | .120 | 0.364 |
| Multivariate-adjusted HR (95% CI) in model 4<sup>d</sup> | 1.00 | 1.03 | (0.88-1.22) | 0.95 | (0.79-1.15) | 1.30 | 0.657 | 1.020 | (0.983-1.059) | .294 | 0.435 |
| Multivariate-adjusted HR (95% CI) in model 5<sup>e</sup> | 1.00 | 1.07 | (0.91-1.26) | 0.98 | (0.79-1.20) | 1.36 | 0.374 | 1.023 | (0.985-1.061) | .239 | 0.503 |
| 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<sup>a</sup> | 1.00 | 1.24 | (0.58-2.68) | 1.27 | (0.70-2.29) | 1.79 | 0.969 | 1.029 | (0.966-1.097) | .371 | 0.984 |
| Multivariate-adjusted HR (95% CI) in model 2<sup>b</sup> | 1.00 | 1.03 | (0.56-1.90) | 1.14 | (0.63-2.06) | 1.60 | 0.832 | 1.030 | (0.955-1.109) | .445 | 0.958 |
| Multivariate-adjusted HR (95% CI) in model 3<sup>c</sup> | 1.00 | 1.23 | (0.56-2.69) | 1.29 | (0.67-2.47) | 1.85 | 0.901 | 1.041 | (0.967-1.120) | .286 | 0.916 |
| Multivariate-adjusted HR (95% CI) in model 4<sup>d</sup> | 1.00 | 1.16 | (0.59-2.31) | 1.30 | (0.68-2.49) | 1.77 | 0.932 | 1.033 | (0.958-1.114) | .396 | 0.967 |
| Multivariate-adjusted HR (95% CI) in model 5<sup>e</sup> | 1.00 | 1.17 | (0.58-2.37) | 1.28 | (0.63-2.62) | 1.93 | 0.926 | 1.045 | (0.972-1.123) | .237 | 0.928 |
### TABLE 3 (Continued)

| Site of cancer                  | Total   | Nondrinkers | Occasional drinkers (<once/wk) | Regular drinkers (≥once/wk) | P for heterogeneity for the highest category | Alcohol intake as a continuous variable (per 10 g/d) |
|--------------------------------|---------|-------------|--------------------------------|-----------------------------|--------------------------------------------|---------------------------------------------------|
|                                |         |             |                                |                             |                                            | HR (95% CI) | P for trend | P for heterogeneity |
| 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<sup>a</sup> | 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<sup>b</sup> | 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<sup>c</sup> | 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<sup>d</sup> | 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<sup>e</sup> | 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.

<sup>a</sup>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).

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

<sup>c</sup>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).

<sup>d</sup>Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 2.

<sup>e</sup>Excluding participants with stomach cancer diagnosis within 3 y from the baseline in model 3.

<sup>f</sup>Indicating heterogeneity among the pooled cohort studies.
Most drinkers in European and American populations) can consume two regions, because drinkers without inactive \( \text{ALDH2} \) 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 \( \text{ALDH2} \) 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 \( \text{ALDH2} \) enzymes) and a protective effect (ie, an indirect effect mediated by changing drinking behavior). Therefore, the amount of alcohol intake and the direct and indirect effects of the \( \text{ALDH2} \) polymorphism 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 \( \text{ALDH2} \) polymorphisms, interacted with the association between alcohol intake and stomach cancer risk. In that study, individuals with inactive \( \text{ALDH2} \) alleles who drank \( \geq 150 \text{g} / \text{wk} \) ethanol had a significantly greater stomach cancer risk than those individuals without the allele who drank 0 to \( < 150 \text{g} / \text{wk} \); the multivariate-adjusted odds ratio was 2.08 (95% CI, 1.05-4.12) \( P \) for interaction \( = 0.08 \).

We showed that heavy drinkers had a greater point estimate of risk for proximal cancer than for distal cancer, whereas Tramacere et al reported that alcohol intake was (nonsignificantly) associated with noncardia stomach cancer rather than with cardia stomach cancer. In that study, drinkers of \( \geq 23 \text{g} / \text{day} \) 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.

**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 (\( \geq 23 \text{g} / \text{day} \) 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.
## Forest plot of study-specific and pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of stomach cancer risk for 10-g/day 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

| 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, 1.367) | 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, 4.289) | 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 | 1.030 (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)** |         |       | 1.038 (0.985, 1.090) | 100.00   |

**NOTE:** Weights are from random effects analysis

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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. As the meta-analysis by Tramacere et al 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. 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. 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. 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. Several cross-sectional studies showed that alcohol intake was not associated with *H. pylori* infection. In addition, the IARC also states that confounding by *H. pylori* infection is not a major concern. 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). 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.\textsuperscript{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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DISCLOSURE

The authors have declared no conflicts of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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