TABLE 2. Results from a pooled analysis (random-effects model) of colorectal cancer incidence by alcohol intake in Japanese men, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers (≥once/week)					Alcohol intake as a continuous variable (per 15 g/day)			
			0.1–22.9 g/day	23–45.9 g/day	46–68.9 g/day	69–91.9 g/day	≥92 g/day	HR†	95% CI†	*p* for trend	*p* for heterogeneity
No. of subjects	20,594	7,752	19,830	21,060	16,547	7,909	4,573				
Person-years of follow-up	218,867	81,929	207,211	220,367	175,414	83,438	45,535				
Colorectal cancer											
No. of cases	311	87	295	363	374	182	112				
Crude rate (per 100,000)	142	106	142	165	213	218	246				
Multivariate HR (95% CI)‡	1.00	1.00 (0.79, 1.28)	1.22 (0.92, 1.61)	1.42 (1.21, 1.66)*	1.95 (1.53, 2.49)*	2.15 (1.74, 2.64)*	2.96 (2.27, 3.86)*	1.11*	1.09, 1.14	<0.001	0.79
Colon cancer											
No. of cases	190	57	177	249	233	102	85				
Crude rate (per 100,000)	87	70	85	113	133	122	187				
Multivariate HR (95% CI)	1.00	1.13 (0.73, 1.75)	1.21 (0.80, 1.84)	1.60 (1.31, 1.95)*	1.97 (1.51, 2.57)*	1.90 (1.45, 2.49)*	3.44 (2.50, 4.72)*	1.12*	1.09, 1.15	<0.001	0.77
Rectal cancer											
No. of cases	119	31	118	114	139	80	28				
Crude rate (per 100,000)	54	38	57	52	79	96	61				
Multivariate HR (95% CI)	1.00	1.08 (0.71, 1.65)	1.30 (0.90, 1.89)	1.18 (0.90, 1.56)	2.01 (1.46, 2.78)*	2.75 (2.00, 3.79)*	2.10 (1.16, 3.83)*	1.11*	1.07, 1.15	<0.001	0.84

* $p < 0.05$.

† HR, hazard ratio; CI, confidence interval.

‡ Results were adjusted for the following variables: area (Japan Public Health Center-based Prospective Study (I and II) and Japan Collaborative Cohort Study), age (years; continuous), smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day), body mass index (weight (kg)/height $(m)^2$; <22, 22–24.9, 25–27.9, or ≥28), and intakes of energy (continuous), red meat (quartiles), calcium (quartiles), fiber (quartiles), and folate (quartiles).

TABLE 3. Results from a pooled analysis (random-effects model) of colorectal cancer incidence by alcohol intake in Japanese women, 1988–2004

	Nondrinkers	Occasional drinkers (<once/week)	Current drinkers (≥once/week)		Alcohol intake as a continuous variable (per 15 g/day)			
			0.1–22.9 g/day	≥23 g/day	HR†	95% CI†	*p* for trend	*p* for heterogeneity
No. of subjects	79,483	13,805	14,090	4,120				
Person-years of follow-up	884,277	137,164	138,327	38,481				
Colorectal cancer								
No. of cases	839	100	97	42				
Crude rate (per 100,000)	95	73	70	109				
Multivariate HR (95% CI)‡	1.00	0.96 (0.70, 1.32)	0.93 (0.70, 1.23)	1.57 (1.11, 2.21)*	1.13*	1.06, 1.20	<0.001	0.75
Colon cancer								
No. of cases	574	60	71	31				
Crude rate (per 100,000)	65	44	51	81				
Multivariate HR (95% CI)	1.00	0.82 (0.62, 1.09)	0.99 (0.76, 1.29)	1.66 (1.12, 2.46)*	1.14*	1.05, 1.23	0.001	0.88
Rectal cancer								
No. of cases	263	40	24	11				
Crude rate (per 100,000)	30	29	17	29				
Multivariate HR (95% CI)	1.00	1.26 (0.73, 2.19)	0.76 (0.38, 1.52)	2.39 (1.18, 4.88)*	1.14*	1.02, 1.29	0.027	0.38

* $p < 0.05$.

† HR, hazard ratio; CI, confidence interval.

‡ Results were adjusted for the following variables: area (Japan Public Health Center-based Prospective Study (I and II) and Japan Collaborative Cohort Study), age (years; continuous), smoking (never smoker, past smoker, or current smoker), body mass index (weight (kg)/height $(m)^2$; <22, 22–24.9, 25–27.9, or ≥28), and intakes of energy (continuous), red meat (quartiles), calcium (quartiles), fiber (quartiles), and folate (quartiles).

and ≥45 g/day were 1.11 (95 percent CI: 0.74, 1.67), 1.10 (95 percent CI: 0.86, 1.42), 1.35 (95 percent CI: 1.10, 1.66), 1.61 (95 percent CI: 1.32, 1.95), and 2.09 (95 percent CI: 1.65, 2.64), respectively. A significant increase in colon cancer risk was observed at an alcohol intake of ≥15 g/day, whereas increased risk of rectal cancer was confined to an intake of ≥45 g/day (data not shown).

In women, drinkers who consumed ≥23 g/day of alcohol had a significantly increased risk of colorectal cancer in comparison with nondrinkers (HR = 1.57, 95 percent CI: 1.11, 2.21; table 3). Risk for that level of alcohol intake was significantly elevated for both colon cancer (HR = 1.66, 95 percent CI: 1.12, 2.46) and rectal cancer (HR = 2.39, 95 percent CI: 1.18, 4.88). Hazard ratios per 15-g/day increase in alcohol intake among women were also statistically significant for colorectal cancer, colon cancer, and rectal cancer and were similar to those in men. When never drinkers were used as the reference group, results were not changed materially (data not shown).

In stratified analyses, the association between alcohol consumption and colorectal cancer risk was pronounced in lean persons: Among men with a body mass index of <22, the hazard ratio for alcohol consumption of ≥69 g/day was 3.25 (95 percent CI: 2.12, 4.99), and the *p* value for heterogeneity across categories of body mass index was 0.04 at that level of intake (table 4). Although the association was relatively weak in nonlean persons, a statistically significant increase in risk with greater alcohol consumption (≥46 g/day) was also observed among men with body mass indices of 22–24.9 or ≥25. Hazard ratios for the greatest alcohol intake did not differ appreciably across tertiles of folate intake, although at lower levels of alcohol consumption, hazard ratios were somewhat lower in men with the highest folate intakes than in men with lower intakes.

Based on the risk estimates in the present study, the percentage of colorectal cancer cases attributable to an alcohol intake of ≥23 g/day was 27 percent for men and 1.4 percent for women.

DISCUSSION

In this pooled analysis of major population-based cohort studies carried out in Japan, we found a clear dose-response relation between alcohol consumption and colorectal cancer risk in men, with heavy drinkers who consumed ≥46 g/day of alcohol showing a risk nearly twice that of nondrinkers. The association was evident for both the colon and the rectum. A significant positive association was also observed in women.

In experimental animals, there is sufficient evidence for the carcinogenicity of acetaldehyde (9), a metabolite of alcohol. Specific mechanisms by which alcohol drinking influences colorectal carcinogenesis in humans remain elusive. However, alcohol or acetaldehyde may induce DNA hypomethylation, an early step in colonic carcinogenesis, through

TABLE 4. Pooled multivariate hazard ratios† (random-effects model) for the association between alcohol intake and colorectal cancer incidence by body mass index and folate intake in Japanese men, 1988–2004

Risk factor	Current drinkers (≥once/week)								Alcohol intake as a continuous variable (per 15 g/day)			
	0.1–22.9 g/day		23–45.9 g/day		46–68.9 g/day		≥69 g/day‡		HR	95% CI	*p* for trend	*p* for heterogeneity
	HR§	95% CI§	HR	95% CI	HR	95% CI	HR	95% CI				
Body mass index¶												
<22	1.20	0.83, 1.72	1.54*	1.16, 2.05	2.36*	1.64, 3.38	3.25*	2.12, 4.99	1.15*	1.09, 1.22	<0.001	0.15
22–24.9	1.22	0.84, 1.77	1.39	0.93, 2.08	1.77*	1.22, 2.56	2.12*	1.57, 2.87	1.09*	1.05, 1.14	<0.001	0.99
≥25	1.13	0.81, 1.56	1.13	0.82, 1.56	1.72*	1.25, 2.38	1.83*	1.26, 2.67	1.11*	1.06, 1.16	<0.001	0.98
Tertile of folate intake												
Lowest	1.27	0.93, 1.75	1.50*	1.03, 2.17	2.07*	1.54, 2.79	2.43*	1.76, 3.37	1.11*	1.07, 1.15	<0.001	0.79
Middle	1.22	0.74, 2.03	1.57*	1.11, 2.22	2.11*	1.17, 3.80	2.52*	1.73, 3.67	1.13*	1.08, 1.18	<0.001	0.96
Highest	1.19	0.93, 1.53	1.24	0.96, 1.60	1.66*	1.25, 2.20	2.30*	1.64, 3.20	1.12*	1.06, 1.19	<0.001	0.17

* $p < 0.05$.

† Reference category: nondrinkers (hazard ratio = 1). Results were adjusted for the following variables: area (Japan Public Health Center-based Prospective Study (I and II) and Japan Collaborative Cohort Study), age (years; continuous), smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day), and intakes of energy (continuous), red meat (quartiles), calcium (quartiles), and fiber (quartiles). Results were additionally adjusted for folate intake (quartiles) and body mass index (<22, 22–24.9, 25–27.9, or ≥28) in the analyses stratified by body mass index and folate intake, respectively.

‡ Across categories of body mass index, *p* for heterogeneity = 0.04; across tertiles of folate intake, *p* for heterogeneity = 0.85.

§ HR, hazard ratio; CI, confidence interval.

¶ Weight (kg)/height $(m)^2$.

its antifolate effects (27). Moreover, acetaldehyde generated by intestinal bacteria may increase the risk of colorectal cancer via folate deficiency (28) or its carcinogenic effects on the intestine. Alcohol and its metabolites may also interfere with intestinal absorption of potentially anticarcinogenic nutrients, including folate (29) and calcium (30).

In a meta-analysis of cohort studies, Moskal et al. (5) identified study region as a significant modifier of colon cancer risk and reported a higher summary relative risk of colon cancer among Asian studies than among European or US studies. However, such a finding may simply reflect a difference in alcohol intake in the highest category across studies. Thus, a comparison using the same exposure cut-points would be of interest (see figure 1). In the pooled analysis of Western studies (22), relative risks of colorectal cancer for male drinkers consuming 30–44.9 g/day and ≥45 g/day versus nondrinkers were 1.11 (95 percent CI: 0.86, 1.45) and 1.41 (95 percent CI: 1.11, 1.79), respectively. In Japanese men in the present study, hazard ratios at the corresponding levels of alcohol consumption were 1.61 (95 percent CI: 1.32, 1.95) and 2.09 (95 percent CI: 1.65, 2.64), respectively. Moreover, the pooling study among Western populations (22) did not show a measurable increase in colon cancer risk with alcohol intakes of 30–44.9 g/day (the relative risk for women and men combined was 1.08) (22), whereas in the present study we detected a significantly increased risk at these intake levels (HR = 1.91, 95 percent CI: 1.41, 2.89). Likewise, the relative risk of colon cancer associated with an alcohol intake of 15–29.9 g/day was 1.08 in the European Prospective Investigation into Cancer and Nutrition (31), while it was significantly increased in the present study (HR = 1.48, 95 percent CI: 1.11, 1.97). The association between alcohol drinking and colorectal cancer or colon cancer appears to be stronger in Japanese populations than in Western populations.

If there is a difference in the magnitude of the association between alcohol drinking and risk of colorectal cancer, especially colon cancer, between Japanese and Western

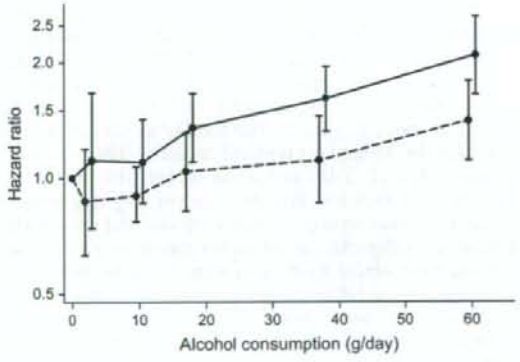

FIGURE 1. Hazard ratios for colorectal cancer by alcohol intake in Japanese (solid line) and Western (dashed line) populations. The solid line shows results for Japanese men from the present pooled analysis of five cohort studies (16–19); the dashed line shows results for Western men from a previous pooled analysis of eight cohort studies (22). The midpoint (mean) of the interval was assigned to each category of alcohol intake except the highest one (≥45 g/day), to which a value of 60 was assigned. Bars, 95% confidence interval.

populations, what are the plausible explanations? Japanese have a high prevalence of the slow-metabolizing variant of the aldehyde dehydrogenase gene (8). The variant induces increased and persisting blood levels of acetaldehyde after alcohol ingestion (10). The modifying effect of the aldehyde dehydrogenase variant on the association between alcohol drinking and colorectal cancer risk was suggested in an earlier Japanese study (32); however, it has recently been challenged by large-scale studies (33, 34). Therefore, it remains unclear whether the seemingly stronger association among Japanese is explained by a genetic difference in the efficiency of metabolizing alcohol among regular drinkers. Alternatively, the clearer contrast in risk between drinkers and nondrinkers in Japanese may be ascribed to more precise classification of the nonexposure reference group, which presumably included a higher proportion of lifetime abstainers who were genetically unable to metabolize acetaldehyde.

Nongenetic factors may contribute to the heterogeneity in risk among populations. Folate deficiency is hypothesized to enhance the adverse effect of alcohol (35), and if Japanese alcohol drinkers have a higher prevalence of folate deficiency than their Western counterparts, a stronger association may emerge. However, in the present study as well as the pooled analysis of Western studies (22), there was only limited evidence suggesting a modifying effect of dietary folate on the alcohol-colorectal cancer association. Thus, folate probably does not explain the difference in the strength of association between the Japanese and Western studies. Instead, we found a pronounced association with alcohol intake in men with the lowest body mass indices, a finding compatible with results from the pooled analysis of Western studies (22).

This differential association by body composition has been interpreted on the basis of the insulin hypothesis: Alcohol drinking improves insulin resistance (36), which is increased in obese people (37) and may be related to increased risk of colorectal cancer (38) or colon cancer (39); thus, the carcinogenic potential of alcohol could be partially cancelled through its favorable effects on insulin resistance among obese persons. However, such a favorable action of alcohol may not benefit lean persons, whose risk of developing cancer through an insulin-mediated pathway may be minimal. The apparently stronger alcohol-colorectal cancer association in Japanese is thus attributable, at least in part, to their lower body mass index relative to that of Westerners. Nevertheless, our finding for obese men, showing a significant increase in risk with alcohol intake—a finding that was not observed in the pooled analysis among Western populations (22)—suggests that other characteristics of Japanese may intensify the effects of alcohol in colorectal carcinogenesis.

We also found a significant association with an alcohol intake of $\geq$23 g/day in women. Although the data did not allow us to assess risk for specific categories of greater alcohol intake, the hazard ratio associated with a 15-g/day increase in alcohol consumption in women was comparable to that for men (HRs were 1.13 for women and 1.11 for men). As previously suggested (22, 31), the effects of alcohol drinking on colorectal cancer risk may be similar in magnitude for men and women.

There were several strengths in the present study. First, we analyzed data from cohort studies that used validated questionnaires to collect data on alcohol consumption. Second, each study controlled for a common set of variables that are known or suggested to cause or prevent colorectal cancer, and all investigators confirmed that additional adjustment for physical activity did not alter their results. Third, with a large number of habitual drinkers in men, we were able to examine the risk of moderate drinking with reasonable statistical power. This point should be important from a public-health point of view; even a small increase in risk for an exposure category with a large number of drinkers leads to a considerable increase in the total number of cases, as for the present case in men (but not in women). Lastly, we estimated hazard ratios with and without exclusion of ex-drinkers from the reference category, by which we could infer the influence of ex-drinking on the association between alcohol drinking and colorectal cancer.

Our study also had some limitations. First, we used only baseline information on alcohol drinking, and thus we could not assess the effects of lifetime alcohol consumption or changes in drinking habits during follow-up on colorectal cancer risk. Second, random variation related to exposure measurement might have attenuated the associations. Third, although investigators in each study adjusted their results extensively for factors associated with colorectal cancer risk, we cannot exclude the possibility that our estimates were distorted because of residual confounding.

In summary, this pooled analysis of data from large prospective studies carried out in Japan confirmed that alcohol drinking is associated with increased risk of colorectal cancer in a dose-response manner in men and women. Although moderate drinking is associated with decreased risk of overall mortality (40), the present finding in men, showing a statistically significant 42 percent increase in colorectal cancer risk with an alcohol intake of 23–45.9 g/day, calls for attention. If the present association is causal, one fourth of all cases of colorectal cancer among Japanese men are attributable to an alcohol intake of $\geq$23 g/day. Moderation of alcohol drinking is an important aspect of the prevention of colorectal cancer. Further research is required to elucidate the roles of genetic and environmental factors that modify the alcohol-colorectal cancer association.

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REFERENCES

1. Parkin DM, Whelan SL, Ferlay J, et al, eds. Cancer incidence in five continents. Vol 8. (IARC Scientific Publication no. 155). Lyon, France: International Agency for Research on Cancer, 2002.
2. Statistics and Information Department, Minister's Secretariat, Japan Ministry of Health, Labour and Welfare. Age-adjusted death rates by prefecture: special report on vital statistics 2000. (In Japanese). Tokyo, Japan: Japan Health and Welfare Statistics Association, 2002.
3. Longnecker MP, Orza MJ, Adams ME, et al. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1990;1:59–68.
4. Bagnardi V, Blangiardo M, La Vecchia C, et al. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001; 85:1700–5.
5. Moskal A, Norat T, Ferrari P, et al. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. Int J Cancer 2007;120:664–71.
6. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007;8:292–3.
7. International Agency for Research on Cancer. Consumption of alcoholic beverages and ethyl carbamate (urethane). (Meeting summary). (IARC monographs on the evaluation of carcinogenic risks to humans, vol 96). Lyon, France: International Agency for Research on Cancer, 2007. (http://monographs.iarc.fr/ENG/Meetings/vol96-summary.pdf). (Accessed May 1, 2007).
8. Takeshita T, Morimoto K, Mao X, et al. Characterization of the three genotypes of low Km aldehyde dehydrogenase in a Japanese population. Hum Genet 1994;94:217–23.
9. International Agency for Research on Cancer. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. (IARC monographs on the evaluation of carcinogenic risks to humans, vol 71). Lyon, France: International Agency for Research on Cancer, 1999.
10. Agarwal DP, Goedde HW. Pharmacogenetics of alcohol metabolism and alcoholism. Pharmacogenetics 1992;2:48–62.
11. Mizoue T, Tanaka K, Tsuji I, et al. Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2006;36:582–97.
12. Shimizu N, Nagata C, Shimizu H, et al. Height, weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. Br J Cancer 2003;88:1038–43.
13. 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;12:1492–500.
14. Wakai K, Kojima M, Tamakoshi K, et al. Alcohol consumption and colorectal cancer risk: findings from the Japan Collaborative Cohort Study. J Epidemiol 2005;15(suppl 2):173S–9S.
15. Akhter M, Kuriyama S, Nakaya N, et al. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: The Miyagi Cohort Study. Eur J Cancer 2007;43:383–90.
16. Tsugane S, Sobue T. Baseline survey of JPHC Study—design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11(suppl):24S–9S.
17. Tamakoshi A, Yoshimura T, Inaba Y, et al. Profile of the JACC Study. J Epidemiol 2005;15(suppl 1):4S–8S.
18. Tsuji I, Nishino Y, Tsubono Y, et al. Follow-up and mortality profiles in the Miyagi Cohort Study. J Epidemiol 2004;14(suppl 1): 2S–6S.
19. Department of Epidemiology and Preventive Medicine, Gifu University School of Medicine. Profile of Takayama cohort. In: Interim report of Takayama Study. Gifu, Japan: Gifu University School of Medicine, 2005:1–8.
20. World Health Organization. International classification of diseases for oncology. Third Edition. Geneva, Switzerland: World Health Organization, 2000.
21. World Health Organization. International classification of diseases and related health problems. Tenth Revision. Geneva, Switzerland: World Health Organization, 1990.
22. Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 2004;140:603–13.
23. Marugame T, Yamamoto S, Yoshimi I, et al. Patterns of alcohol drinking and all-cause mortality: results from a large-scale population-based cohort study in Japan. Am J Epidemiol 2007; 165:1039–46.
24. Ogawa K, Tsubono Y, Nishino Y, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. Public Health Nutr 2003;6:147–57.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
26. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–19.
27. Hillman RS, Steinberg SE. The effects of alcohol on folate metabolism. Ann Rev Med 1982;33:345–54.
28. Homann N, Tillonen J, Salaspuro M. Microbially produced acetaldehyde from ethanol may increase the risk of colon cancer via folate deficiency. Int J Cancer 2000;86:169–73.
29. Sanjoaquin MA, Allen N, Couto E, et al. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 2005;113:825–8.
30. Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004;96:1015–22.
31. Ferrari P, Jenab M, Norat T, et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2007;121:2065–72.
32. Murata M, Tagawa M, Watanabe S, et al. Genotype difference of aldehyde dehydrogenase 2 gene in alcohol drinkers influences the incidence of Japanese colorectal cancer patients. Jpn J Cancer Res 1999;90:711–19.
33. Matsuo K, Wakai K, Hirose K, et al. A gene-gene interaction between *ALDH2* Glu487Lys and *ADH2* His47Arg polymorphisms regarding the risk of colorectal cancer in Japan. Carcinogenesis 2006;27:1018–23.
34. Yin G, Kono S, Toyomura K, et al. Alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms and colorectal cancer: The Fukuoka Colorectal Cancer Study. Cancer Sci 2007; 98:1248–53.
35. Giovannucci E. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. J Nutr 2004;134(suppl):2475S–81S.

36. Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. Diabetes Care 1994;17:115–19.
37. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501–13.
38. La Vecchia C, Negri E, Decarli A, et al. Diabetes mellitus and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 1997;6:1007–10.
39. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;5;166: 1871–7.
40. Tsugane S, Fahey MT, Sasaki S, et al. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. Am J Epidemiol 1999;150:1201–7.

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Alcohol Drinking and Gastric Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population

Taichi Shimazu[1,2], Ichiro Tsuji[1], Manami Inoue[2], Kenji Wakai[3], Chisato Nagata[4], Tetsuya Mizoue[5], Keitaro Tanaka[6] and Shoichiro Tsugane[2] for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, [2]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, [3]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, [4]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [5]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo and [6]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga, Japan

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Background: We reviewed epidemiologic studies on the association between alcohol drinking and gastric cancer among the Japanese population. This report is one of a series of articles by our research group, which is evaluating the existing evidence concerning the association between health-related lifestyles and cancer.
Methods: Original data were collected by searches of MEDLINE using PubMed, or searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility as evaluated previously by the International Agency for Research on Cancer.
Results: Of the 11 cohort studies evaluated, nine showed no association between alcohol drinking and gastric cancer, and one study showed a strong positive association among men. All of 11 case–control studies found no association between alcohol drinking and gastric cancer. By anatomical subsites of gastric cancer, only three studies have evaluated the association between alcohol drinking and gastric cancer, and one cohort study found a positive association for cardia and upper-third gastric cancer in men. Few studies conducted among the Japanese population have made a detailed assessment of alcohol drinking, possible important confounding factors such as smoking and diet and anatomical subsites of gastric cancer.
Conclusion: We conclude that epidemiologic evidence for an association between alcohol drinking and gastric cancer risk remains insufficient due to the methodological quality of studies that have been conducted among the Japanese population.

Key words: systematic review – epidemiology – alcohol drinking – gastric cancer – Japanese

INTRODUCTION

The most recent evaluation from the International Agency for Research on Cancer (IARC) concluded in 2007 that alcoholic beverages are carcinogenic to humans (Group 1) and are causally related to cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum and female breast (1,2). However, epidemiologic studies on the association between alcoholic beverages and gastric cancer have been inconsistent and the interpretation of the findings is not clear (1–3).

For reprints and all correspondence: Taichi Shimazu, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tshimazu@gan2.res.ncc.go.jp

As the majority of these reports were based on evidence from Western populations, their applicability to the Japanese population is unknown. The Japanese commonly consume different types of beverages from Western populations and have a relatively high prevalence of the variant allele of *aldehyde dehydrogenase 2* (4), which is related to a high blood concentration of acetaldehyde (5). In addition to the factors related to alcohol, the prevalence of *Helicobacter pylori* infection (6) and the proportion of gastric cancers occurring in the distal stomach (7) are higher among the Japanese than among Western populations. Therefore, the magnitude of association among Japanese might differ from that among other populations.

The objective of the present study was to review epidemiologic studies on the association between alcohol drinking and gastric cancer among the Japanese population. The findings were summarized and the magnitude of the effect was evaluated. This report is one of a series of articles by our research group, which is investigating the associations between lifestyle factors and major types of cancer in Japan (8–15).

METHODS

Original data for this review were collected by searches of MEDLINE using PubMed complemented by manual searches of references from relevant articles when necessary. All epidemiologic studies on the association between alcohol drinking and gastric cancer incidence or mortality among Japanese from January 1966 to May 2007, including papers in press if available, were identified using the search terms 'alcohol', 'drinking', 'gastric cancer', 'stomach cancer', 'cohort studies', 'case–control studies', 'Japan' and 'Japanese' as key words found in the abstract. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also done to identify studies written in Japanese from 1983 to May 2007. Papers written in English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately by study design as cohort or case–control studies. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or the most recent studies were included, and incidence was also given priority in a single publication describing both incidence and mortality.

Evaluation was made based on the strength of evidence and the magnitude of association. Relative risks (RRs) or odds ratios (ORs) in each epidemiologic study were grouped by magnitude of association, giving consideration to statistical significance (SS) or not SS (NS), as strong, <0.5 or >2.0 (SS); moderate, either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak, either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (16), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (8): convincing: evidence based on a substantial number of epidemiologic studies showing consistent associations between exposure and disease, with little or no evidence to the contrary, with a biologically plausible association. Probable: evidence based on epidemiologic studies showing fairly consistent associations, but with perceived shortcomings in the available evidence or some evidence to the contrary that precludes a more definite judgment. Possible: evidence based mainly on findings from case–control and cross-sectional studies, requiring more studies to support the tentative associations, which should also be biologically plausible. Insufficient: evidence based on findings of a few studies that are suggestive, but insufficient to establish an association, requiring more well-designed research to support the tentative associations. We assumed that biological plausibility corresponded to the judgment of the recent evaluation from the IARC (1,2,17). The final judgment is made based on the consensus of research group members and is not necessarily objective. In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, we conducted a meta-analysis to obtain summary estimates of the association. Details of the evaluation methods are described elsewhere (8).

Main Features and Comments

We identified 11 cohort studies (18–28) and 11 case–control studies (29–39) (Tables 1 and 2, respectively). Among the cohort studies, three presented results by gender (20,21,26), six for men only (18,19,22,23,25,27) and two for men and women combined (24,28). The respective numbers for the case–control studies were three (32,38,39), three (29,30,36) and five (31,33–35,37).

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 3 and 4, respectively. Of the 11 cohort studies evaluated, most showed no association between alcohol drinking and gastric cancer. Among these studies, nine showed no association (18,20,22–28), and the other two showed a strong positive (21) and a weak positive (19) association among men, respectively. All 11 case–control studies demonstrated no association between alcohol drinking and gastric cancer (29–39).

By anatomical subsites, few studies had evaluated the association between alcohol drinking and gastric cancer, and the association was inconsistent (25,38,39), similar to studies among other populations (3). In one cohort study (25), alcohol drinking showed a moderate positive association with cardia and upper-third gastric cancer, but not with distal gastric cancer in men. One case–control study analysed the association with cardia, middle and antrum gastric cancer separately (38). The point estimate of the OR in male drinkers tended to be highest for cardia cancer and decreased towards the distal part of the stomach compared with never drinkers, although the results were not statistically

Table 1. Alcohol drinking and gastric cancer risk, cohort studies among Japanese populations

References	Study period	Study population				Category	Number among cases	Relative risk, or odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Kono et al. (18)	1965–1983	5130 men	Male Japanese physicians	Death	116	Never or past	NA	1.00	NA	Age and smoking	Expressed as go of sake (1 go of sake; 27 ml alcohol)
						Occasional	NA	1.11 (0.69–1.79)			
						<2 go/day	NA	1.30 (0.79–2.12)			
						≥2 go/day	NA	1.17 (0.66–2.07)			
Ubukata et al. (19)	1961–1985	225 cases and 665 controls (nested case–control study)	14 229 persons who were screened for gastric cancer at the Center for Adult Diseases, Osaka	Incidence	225 men	Non or occasional	112	1.00	0.332	Matched (1:3) for sex, birth year (±5 years), occupation and year of the initial screening of the case within the cohort Adjusted for smoking, dietary habit	Expressed as go of sake (1 go of sake; 27 ml alcohol)
						<3 go/day	76	0.99 (0.70–1.39)			
						≥3 go/day	37	1.58 (0.99–2.53)			
Hirayama (20)	1966–1982	122 261 men	95% of census population	Death	3414 men	Men					
						None	NA	1.00	NS	Age	
						Rare	NA	0.90 (0.82–0.99)			
						Occasional	NA	0.85 (0.78–0.92)			
						Daily	NA	0.92 (0.85–0.99)			
		142 857 women			1833 women	Women					
						None	NA	1.00	NS	Age	
						Rare	NA	0.81 (0.70–0.93)			
						Occasional	NA	0.98 (0.82–1.16)			
						Daily	NA	0.96 (0.66–1.40)			
Kato et al. (21)	1985–1991	9753	Residental registry	Death	57	Total					Ethanol content
						None	26	1.00	NA	Age, sex, smoking cooking methods and familiy history of stomach cancer	

						Occasional	12	1.77 (0.85–3.68)			
						Daily, <50 ml	7	1.16 (0.46–2.89)			
						Daily, ≥50 ml	12	2.75 (1.20–6.29)			
					35 men	Men					
						None	8	1.00	NA	Age	
						Occasional	9	2.31 (0.88–6.07)			
						Daily, <50 ml	6	1.31 (0.45–3.81)			
						Daily, ≥50 ml	12	3.63 (1.44–9.11)			
					22 women	Women					
						None	18	1.00	NA	Age	
						Occasional	3	1.12 (0.32–3.90)			
						Daily	1	1.29 (0.17–9.69)			
Masuda and Shigematsu (22)	1968–1987	8085 adults in Oki Islands, Shimane	Residental registry	Death	97 men	None	29	1.00	NS	Age, smoking	Number of male subjects was not available
						Occasional	32	0.73 (NS)			
						Daily					
						Total	26	0.80 (NS)			
						Sake	NA	0.53 (0.26–1.06)			
						Shocyu	NA	1.32 (0.36–4.84)			
						Beer	NA	0.85 (0.10–6.92)			
						Whisky	NA	0.84 (0.30–2.34)			
Murata et al. (23)	1984–1993	246 male cases and 493 controls (nested case–control study)	17 200 male participants in a gastric mass screening by Chiba Cancer Association	Incidence	246 men	Alcohol intake (cups/day)					
						0	101	1.0	NS	Matched for sex, birth year (±2 years) and residental area (city or county)	In sake-equivalents (a cup of 180 ml of sake contains 27 ml of ethanol)
						0.1–1.0	82	1.1			
						1.1–2.0	51	1.1			
						2.1 +	12	0.5			
						Nonsmoker					
						Alcohol intake (cups/day)					
						0	62	1.0	NS		
						0.1–1.0	39	1.0			

Continued

Table 1. *Continued*

References	Study period	Study population				Category	Number among cases	Relative risk, or odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						1.1–2.0	21	1.1			
						2.1 +	4	0.4			
						Smoker					
						Alcohol intake (cups/day)					
						0	39	1.0	NS		
						0.1–1.0	43	1.2			
						1.1–2.0	30	1.1			
						2.1 +	8	0.6			
Inoue et al. (24)	1985–1995	5373	Patients who underwent gastroscopy at Aichi Cancer Center Hospital	Incidence	69	With atrophic gastritis					
						None	22	1.00		Age and sex	
						Past	8	1.88 (0.78–4.50)			
						Occasional	15	0.85 (0.42–1.71)			
						Daily	20	1.13 (0.54–2.37)			
Sasazuki et al. (25)	1990–1999	19 657 men	Residental registry	Incidence	293	Total					Alcohol consumption was divided into tertiles
			(JPHC Study)			0–3 days/month	68	1.0	0.66	Age, area, smoking, consumption of fruit, green or yellow vegetable, salted cod roe or fish gut and body mass index	
						0–161.0 g/week	54	0.8 (0.6–1.2)			
						162.0–322.0 g/week	77	1.1 (0.8–1.5)			
						322.5 + g/week	74	1.1 (0.8–1.6)			

						Cardia and upper-third gastric cancer (all histologic type)				
						0–3 days/month	3	1.0	0.66	
						0–161.0 g/week	8	2.5 (0.7–9.5)		
						162.0–322.0 g/week	13	3.3 (0.9–11.6)		
						322.5+ g/week	11	3.0 (0.8–11.1)		
						Distal gastric cancer (Differentiated type)				
						0–3 days/month	32	1.0	1.00	
						0–161.0 g/week	27	0.9 (0.5–1.5)		
						162.0–322.0 g/week	38	1.1 (0.7–1.8)		
						322.5+ g/week	27	0.9 (0.5–1.5)		
						Distal gastric cancer (Undifferentiated type)				
						0–3 days/month	17	1.0	0.07	
						0–161.0 g/week	11	0.7 (0.3–1.4)		
						162.0–322.0 g/week	15	0.9 (0.5–1.9)		
						322.5+ g/week	20	1.3 (0.7–2.6)		
Fujino et al. (26)	1988–1997	18 746 men	Participants in minicipal health checkups, general populations or voluntary groups	Death	261 men	Men				
						Never	52	1.00		Age
						Past	24	1.16 (0.71–1.87)		
						Current	146	1.16 (0.84–1.59)		
		26 184 women	(JACC Study)		118 women	Women				
						Never	82	1.00		Age
						Past	2	0.99 (0.24–4.01)		
						Current	13	1.01 (0.56–1.82)		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	Number among cases	Relative risk, or odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Nakaya et al. (27)	1990–1997	21 201 men	Residental registry	Incidence	247 men	Never-drinkers	42	1.0	0.83	Age, smoking, education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin and tomato	
			(Miyagi cohort study)			Ex-drinkers	21	0.9 (0.5–1.5)			
						Current drinkers	184	1.0 (0.7–1.4)			
						< 22.8 g/day	49	1.0 (0.6–1.5)			
						> 22.8 g/day	135	1.0 (0.7–1.5)			
Sauvaget et al. (28)	1980–1999	38 576	Atomic-bomb survivors in Hiroshima and Nagasaki	Incidence	1270	Never	475	1.00		City, sex, sex-specific age, calendar period, education and radiation dose	
						Past	690	1.09 (0.78–1.51)			
						Current	44	1.07 (0.94–1.23)			

CI, confidence interval; NA, not available; NS, not significant.

Table 2. Alcohol drinking and gastric cancer risk, case–control studies among Japanese populations

References	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Hoshino (29)	1980–1982	Hospital-based (National Cancer Center)	Cases: gastric cancer patients operated at National Cancer Center hospital	460 men	460 men	Occasionally	NS	NA	Matched for age	
						Everyday	NS			
			Controls: patients without gastric cancer in Adult Disease Clinic							
Tajima and Tominaga (30)	1981–1984	Hospital-based (Aichi Cancer Center)	Cases: patients received surgical therapy and were newly diagnosed on the basis of both clinical and histopathological examinations	59 men	111 men	Versus non-drinkers			Matched for sex, age (± 5years) and time of interview (± 6 months) Adjusted for age and sex	
						Yes	0.68 (NS)			
						Amount (sake)				
						Less than 360 ml/day	0.66 (NS)	NA		
						360 ml or more /day	0.81 (NS)			
						Frequency				
						Sometimes	0.80 (NS)	NA		
						Every day	0.64 (NS)			
			Controls: patients without cancer							
Kono et al. (31)	1979–1982	Hospital-based (Karatsu Stomach Institute)	Cases: newly diagnosed at a single institution	139	Hospital controls	Sake	NS		Matched for sex, and year of birth	The results were described in the text
					274	Shouchu	NS			
					General population controls	Beer	NS			
					278	Whisky/brandy	NS			
			Controls: hospital control general population control							
Kato et al. (32)	1985–1989	Hospital-based (Aichi Cancer Center)	Cases: histologically confirmed cases	289 men	1247	Men			Adjusted for age and residence	
						Total				

Continued

Table 2. *Continued*

References	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Occasional	0.77 (0.53–1.11)			
						Daily	0.99 (0.71–1.37)			
						Diffuse				
						Occasional	0.70 (0.41–1.21)			
						Daily	1.06 (0.67–1.69)			
						Intestinal				
						Occasional	0.79 (0.49–1.26)			
						Daily	0.95 (0.63–1.45)			
			Controls: patients with normal gastric mucosa or mild atrophic gastritis	138 women	1767 women	Women			Adjusted for age and residence	
						Total				
						Occasional	0.64 (0.40–1.01)			
						Daily	0.73 (0.26–2.08)			
						Diffuse				
						Occasional	0.70 (0.41–1.21)			
						Daily	1.06 (0.67–1.69)			
						Intestinal				
						Occasional	0.79 (0.49–1.26)			
						Daily	0.95 (0.63–1.45)			
Tominaga et al. (33)	1971–1985	Hospital-based (Tochigi Cancer Center)	Cases: newly histologically diagnoed gastric cancer at the center	294	588	Non-drinker	1.0		Mached (1:2) for sex, age (±5 years) and area of residency	
						Sometimes	0.85 (0.57–1.27)			
						Daily	1.16 (0.78–1.72)			
			Controls: randomly selected controls, who received the same early detection program and were verified as being free of gastric cancer							
Kikuchi et al. (34)	1988–1990	Hospital-based	Cases: gastric carcinoma	42	Hospital control 42	Versus hospital control			Matched for sex and age (±3 years)	
						Current or past drinker	1.04 (NS)			
						Current drinker	0.83 (NS)			

			Controls: hospital control (inpatients with benign disease) participants in health check programs		Participants in health check programs 27	Versus participants in health check programs			
						Current or past drinker	0.95 (NS)		
						Current drinker	0.82 (NS)		
Hoshiyama and Sasaba (35)	1984–1990	Hospital-based (Saitama Cancer Center)	Cases: newly diagnosed adenocarcinoma	294	General population controls 294	Versus general population controls			Matched for sex, age and administrative division
						Alcohol drinking			Adjusted for sex, age, administrative division and smoking status
						Never	1.0	NA	
						Past	0.7 (0.3–1.8)		
						Occasional	0.8 (0.5–1.3)		
						Daily			
						<50 ml/day	0.7 (0.4–1.2)		
						≥50 ml/day	1.0 (0.5–1.7)		
						Total alcohol consumption (l/lifetime)			
						Non-drinker	1.0		$P = 0.92$
						<500	0.9 (0.5–1.6)		
						≥500	1.0 (0.5–1.9)		
			Controls: hospital control general population control		Hospitals controls 202	Versus hospital controls			
						Alcohol drinking			Adjust for sex, age (three categories), area (three categories) and smoking status
						Never	1.0	NA	
						Past	0.3 (0.1–0.8)		
						Occasional	1.1–(0.6–1.7)		
						Daily			
						<50 ml/day	1.4 (0.7–2.8)		
						≥50 ml/day	1.3 (0.6–2.4)		
						Total alcohol consumption (l/lifetime)			
						Non-drinker	1.0		$P = 0.74$

Continued

Table 2. *Continued*

References	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						<500	1.4 (0.7–2.6)			
						≥500	1.2 (0.6–2.3)			
Iwasaki et al. (36)	1980–1986	Population-based (mountain villages in Shizuoka prefecture and farming-fishing villages in Chiba prefecture)	Cases: gastric cancer death	83 men	83 men	Everyday	0.945 (NS)		Matched for sex, age (±2 years), district and year of death (±6 years) Adjusted for smoking, dietary habit	
			Controls: general population control							
Hirohata et al (37)	1984–1986	Hospital-based (Kurume University Hospital)	Cases: histologically conformed incident cases of gastric cancer at the First Department of Surgery	150	150	Versus controls from the department of surgery			Matched for sex, age (±5 years) and residence	
						Quartiles of ethanol intake				
						Low	1.00	NS		
						Low moderate	0.63 (NS)			
						Moderate	1.30 (NS)			
						High	0.77 (NS)			
			Controls: hospital control (inpatients of the First Department of Surgery and the Department of Orthopedics)		150	Versus controls from the department of orthopedics				
						Quartiles of ethanol intake				
						Low	1.00	NS		
						Low moderate	0.52 (NS)			
						Moderate	1.44 (NS)			
						High	0.88 (NS)			
Inoue et al. (38)	1988–1991	Hospital-based (Aichi Cancer Center)	Cases: histologically confirmed incident cases	420 men	420 men	Men			Matched for age (±2 years) and time of first hospital visit (±2 months)	

			Versus non-drinker	
			Total	
			Drinker	1.23 (0.92–1.65)
			Current drinker	1.16 (0.86–1.56)
			Ex-drinker	1.87 (1.11–3.15)
			<1-year after quitting	2.60 (1.09–6.19)
			≥1-year after quitting	1.60 (0.87–2.94)
			Cardia	
			Drinkers	1.60 (0.92–2.78)
			Current drinker	1.45 (0.82–2.57)
			Ex-drinker	2.81 (1.21–6.54)
			<1-year after quitting	3.71 (1.02–13.5)
			≥1-year after quitting	2.47 (0.93–6.69)
			Middle	
			Drinkers	1.47 (0.94–2.28)
			Current drinker	1.38 (0.88–2.16)
			Ex-drinker	2.29 (1.12–4.68)
			<1-year after quitting	3.63 (1.23–1.07)
			≥1-year after quitting	1.78 (0.75–4.23)
			Antrum	
			Drinkers	1.00 (0.69–1.46)
			Current drinker	0.96 (0.65–1.41)
			Ex-drinker	1.36 (0.69–2.70)
			<1-year after quitting	2.16 (0.75–6.25)
			≥ 1-year after quitting	1.06 (0.46–2.45)
Controls: outpatients of the same hospital	248 women	248 women	Women	
			Drinker versus non-drinker	
			Total	0.89 (0.58–1.36)
			Cardia	0.86 (0.39–1.90)
			Middle	1.17 (0.66–2.07)
			Antrum	0.65 (0.65–1.24)

Continued

Table 2. *Continued*

References	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Kikuchi et al. (39)	1993–1995	Hospital-based (nine hospitals in Tokyo Metropolitan Area)	Cases: newly hospitalized with historically confirmed cases aged 40 years and under	494 men	448 men	Drinking dose (alcohol-year) Men			Adjusted for age, smoking and *Helicobacter Pylori* status	Pure alcohol intake (ml) /day multiplied by years of drinking
						Total				
						Never drinker	1.0	<0.001		
						Occasional and 0.1–134.9 ml/day	0.57 (0.33–1.00)			
						135.0–1349.0 ml/day	1.23 (0.73–2.06)			
						1350.0 + ml/day	1.40 (0.85–2.31)			
						Intestinal type				
						Never drinker	1.76 (0.94–3.32)	0.02		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0–1349.0 ml/day	2.07 (1.22–3.53)			
						1350.0 + ml/day	2.14 (1.29–3.55)			
						Diffuse type				
						Never drinker	1.74 (0.80–3.79)	<0.01		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0–1349.0 ml/day	2.20 (1.19–4.07)			
						1350.0 + ml/day	3.05 (1.68–5.56)			
						Early				
						Never drinker	1.76 (0.90–3.44)	<0.01		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0–1349.0 ml/day	2.23 (1.29–3.87)			
						1350.0 + ml/day	2.50 (1.48–4.23)			
						Advanced				
						Never drinker	1.88 (0.94–3.77)	0.02		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0–1349.0 ml/day	2.17 (1.21–3.89)			

			1350.0 + ml/day	2.38 (1.36–4.17)	
			Proximal		
			Never drinker	2.72 (1.13–6.53)	
			Occasional and 0.1–134.9 ml/day	1.0	
			135.0–1349.0 ml/day	2.24 (1.01–4.96)	
			1350.0 + ml/day	2.46 (1.17–5.17)	
			Middle		
			Never drinker	1.74 (0.84–3.57)	<0.01
			Occasional and 0.1–134.9 ml/day	1.0	
			135.0–1349.0 ml/day	2.34 (1.30–4.19)	
			1350.0 + ml/day	3.29 (1.88–5.769)	
			Distal		
			Never drinker	1.28 (0.60–2.76)	0.25
			Occasional and 0.1–134.9 ml/day	1.0	
			135.0–1349.0 ml/day	1.85 (1.00–3.41)	
			1350.0 + ml/day	1.56 (0.86–2.84)	
Controls: recruited from several health check programs in a hospital in the same area	224 women	435 women	Women		
			Total		
			Never drinker	1.0	0.016
			Occasional and 0.1–134.9 ml/day	0.54 (0.35–0.82)	
			135.0 + ml/day	0.75 (0.43–1.30)	
			Intestinal type		
			Never drinker	2.18 (1.18–4.03)	0.04
			Occasional and 0.1–134.9 ml/day	1.0	
			135.0 + ml/day	1.39 (0.55–3.53)	
			Diffuse type		
			Never drinker	1.74 (1.07–2.84)	0.06
			Occasional and 0.1–134.9 ml/day	1.0	
			135.0 + ml/day	1.02 (0.48–2.19)	

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