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Meta-Analysis

Alcohol Drinking and Colorectal Cancer in Japanese: A Pooled Analysis of Results from Five Cohort Studies

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Colorectal cancer is an alcohol-related malignancy; however, the association appears to be stronger among Asian populations with a relatively high prevalence of the slow-metabolizing aldehyde dehydrogenase variant. To examine the association between alcohol consumption and colorectal cancer in Japanese, the authors analyzed original data from five cohort studies that measured alcohol intake using validated questionnaires at baseline. Hazard ratios were calculated in the individual studies, with adjustment for a common set of variables, and then combined using a random-effects model. During 2,231,010 person-years of follow-up (ranging variously from 1988 to 2004), 2,802 colorectal cancer cases were identified. In men, multivariate-adjusted pooled hazard ratios for alcohol intakes of 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and $\geq$92 g/day, compared with nondrinking, were 1.42 (95% confidence interval (CI): 1.21, 1.66), 1.95 (95% CI: 1.53, 2.49), 2.15 (95% CI: 1.74, 2.64), and 2.96 (95% CI: 2.27, 3.86), respectively (p for trend < 0.001). The association was evident for both the colon and the rectum. A significant positive association was also observed in women. One fourth of colorectal cancer cases in men were attributable to an alcohol intake of $\geq$23 g/day. An alcohol-colorectal cancer association seems to be more apparent in Japanese than in Western populations. Whether this difference can be ascribed to genetic or environmental factors needs to be clarified.

alcohol drinking; colonic neoplasms; colorectal neoplasms; rectal neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study.

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Colorectal cancer is a common malignancy in developed countries (1). In Japan, after a marked increase over the last several decades (2), the incidence of colorectal cancer is currently among the highest in the world (1). Epidemiologic data generally support the hypothesis that alcohol drinking increases colorectal cancer risk (3–5), and in the latest evaluation by the International Agency for Research on Cancer, colorectal cancer was added to the list of alcohol-related malignancies (6, 7). However, the influence of alcohol drinking could be greater among Asian populations because of their relatively high prevalence of the slow-metabolizing aldehyde dehydrogenase variant (8), which is associated with increased blood levels of acetaldehyde, a potential carcinogen (9), after alcohol ingestion (10). In line with this concern, in a meta-analysis of cohort studies, Moskal et al. (5) reported a stronger association with alcohol drinking for colon cancer (but not rectal cancer) in Asian studies as compared with Western studies.

In our 2006 review of epidemiologic studies carried out among Japanese (11), we identified a fairly consistent association between heavy alcohol intake and increased risk of colorectal cancer, and in all recent cohort studies (12–15), men in the highest category of alcohol intake have had nearly twice the risk of colon cancer as men in the lowest category. However, several issues remain unresolved. First, because cutpoints for alcohol intake varied by study, we were unable to obtain summary estimates according to amount of alcohol consumed. Second, the association for colon cancer appears to be more consistent than that for rectal cancer, but random variation may account for the difference. Third, the association was unclear among women, who consumed much lower amounts of alcohol than men, on average. From an international perspective, a seemingly stronger association with alcohol drinking in Japanese may simply reflect greater alcohol intake among Japanese drinkers than among their Western counterparts. A comparison of risks incurred at identical levels of exposure is required for confirmation. To address these issues, we conducted a pooled analysis of data from five large-scale cohort studies carried out in Japan.

MATERIALS AND METHODS

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer in Japanese, in parallel with systematic reviews of the relevant literature. Topics for the pooled analysis were determined on the basis of discussion among all authors from the viewpoints of scientific and public health importance. To maintain high quality and comparability of data, we set inclusion criteria for the present purpose a priori: population-based cohort studies that were conducted in Japan, started between the mid-1980s and the mid-1990s, included more than 30,000 participants, obtained information on diet, including alcohol intake, using a validated questionnaire or a similar one at baseline, and collected incidence data for colorectal cancer during the follow-up period. We identified four ongoing studies that met these criteria: 1) the Japan Public Health Center-based Prospective Study (JPHC) (16), 2) the Japan Collaborative Cohort Study (JACC) (17), 3) the Miyagi Cohort Study (18), and 4) the Takayama Study (19). The JPHC was treated as two independent studies (JPHC I and JPHC II) because of a difference in the dietary questionnaires used; thus, data from a total of five studies were analyzed. We excluded data for subjects with extreme energy intakes (>3 standard deviations from the mean log-transformed energy intake in each study), missing information on alcohol consumption, or a history of cancer at baseline. Selected characteristics of these studies are presented in table 1. Each study was approved by the relevant institutional ethical review board. Results on the association between alcohol intake and colorectal cancer risk in each cohort have been reported (12–15). For the present analysis, we used updated data sets with an extended follow-up period for JPHC I, JPHC II, and JACC.

Case ascertainment

Subjects were followed from the baseline survey (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, Miyagi: 1990, Takayama: 1992) to the last date of follow-up for incidence (JPHC I: 2004, JPHC II: 2004, JACC: 2001, Miyagi: 2001, Takayama: 1999) in each study. Residence status in each study, including survival, was confirmed through the residential registry. Information on cancer diagnosis was collected for the whole population in JPHC I, JPHC II, and the Miyagi Cohort Study; in these studies, cases were identified through active patient notification from major local hospitals and/or through population-based cancer registries. In the Takayama Study, active patient notification for colorectal cancer was conducted by major local hospitals. In JACC, because information on cancer diagnosis was collected in 22 out of 45 study areas, we used data from those 22 areas only. Cases were coded using the *International Classification of Diseases for Oncology*, Third Edition (20). Each study also collected information about causes of death from death certificates and coded them according to the *International Classification of Diseases*, Tenth Revision (21), which was used to complement the hospital and registry data on cancer diagnosis. The study outcome was defined as incident colorectal cancer (*International Classification of Diseases for Oncology*, Third Edition, codes C18.0–C18.9, C19.9, and C20.9; *International Classification of Diseases*, Tenth Revision, codes C18–C20) diagnosed during the follow-up period of each study.

Assessment of alcohol intake

Alcohol drinking status was assessed by means of self-administered questionnaires at baseline. Although the style of the questions differed by study, investigators in each study were able to calculate average daily alcohol consumption in grams of ethanol for regular drinkers on the basis of beverage type, frequency, and amount. The questionnaire in each study contained queries on the intake of alcoholic beverages popular in Japan, including beer, sake, and shochu,

TABLE 1. Characteristics of five Japanese cohort studies included in a pooled analysis of alcohol consumption and colorectal cancer risk, 1988–2004

Study (ref. no.)	Population	Age (years) at baseline	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow-up	Current pooled analysis						
							Age (years)	Last follow-up time	Mean duration of follow-up (years)	Cohort size (no.)		No. of cancer cases	
										Men	Women	Men	Women
JPHC* I (16)	Japanese residents of five public health center areas in Japan	40–59	1990	61,595	82	Cancer registry and death certificates	40–59	2004	13.5	19,767	21,392	434	260
JPHC II (16)	Japanese residents of six public health center areas in Japan	40–69	1993–1994	78,825	80	Cancer registry and death certificates	40–69	2004	10.5	27,458	31,609	473	308
Japan Collaborative Cohort Study (17)	Residents from 45 areas throughout Japan	40–79	1988–1990	110,792	83	Cancer registry (22 selected areas) and death certificates	40–79	2001 (1994–2000 in some areas)	10.4	16,276	23,723	339	223
Miyagi Cohort Study (18)	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92	Cancer registry and death certificates	40–64	2001	11.0	20,551	18,232	318	164
Takayama Study (19)	Japanese residents of Takayama, Gifu, Japan	≥35	1992	31,552	92	Hospital records (selected sites) and death certificates	≥35	1999	6.9	14,213	16,542	160	123
Total										98,265	111,498	1,724	1,078

* JPHC, Japan Public Health Center-based Prospective Study.

but the style of the questions differed across studies. Therefore, in the present study we used only total alcohol intake from all beverages as the exposure. In Japan, the *go* is the most commonly used unit of alcohol consumption; 1 go of sake (Japanese wine), equivalent to 180 ml, contains approximately 23 g of ethanol. Consumption was divided into categories using identical cutpoints across the studies (nondrinkers (never and ex-drinkers), occasional drinkers (<once/week), and regular drinkers (≥once/week: for men, 0.1–22.9 g/day, 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, or ≥92 g/day; for women, 0.1–22.9 g/day or ≥23 g/day)). Analysis using the same exposure categories as those used in a pooled analysis among Western populations (22) was also conducted for comparison. Correlation coefficients for the correlation between alcohol consumption estimated from the questionnaire and that from the dietary record were: JPHC—0.77 in men and 0.55 in women (23); Miyagi—0.77 in men and 0.71 in women (24); and Takayama—0.72 in men and 0.64 in women (19). The JACC, for which information on the validation of alcohol consumption was not available, utilized the same questions on alcohol consumption as the Miyagi Cohort Study. The analysis was repeated by using never drinkers as the reference group in the JACC, the Miyagi Cohort Study, and JPHC II, in which ex-drinkers were distinguishable from never drinkers.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of colorectal cancer, migration from the study area, death, or the end of follow-up, whichever came first. Age was used as the primary time variable. In each individual study, sex-specific hazard ratios and 95 percent confidence intervals for colorectal cancer, colon cancer, and rectal cancer were estimated for each alcohol intake category using a Cox proportional hazards model. In all analyses, adjustments were made for age (continuous), area within each study (for JPHC I, JPHC II, and JACC), smoking (for men: never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), body mass index (weight (kg)/height $(m)^2$; <22, 22–24.9, 25–27.9, or ≥28), energy intake (continuous), and energy-adjusted dietary intakes of red meat (quartiles), calcium (quartiles), fiber (quartiles), and folate (quartiles) in each study. An indicator term for missing data was created for each covariate. Physical activity was not included in the common set of covariates because of large variation in the assessment of physical activity among the studies, but investigators from each study confirmed that additional adjustment for physical activity did not alter the results. SAS (version 9.1; SAS Institute, Inc., Cary, North Carolina) or Stata (version 9.2; Stata Corporation, College Station, Texas) statistical software was used for these estimations.

A random-effects model (25) was used to obtain a single pooled estimate of the hazard ratios from the individual studies for each category. The study-specific hazard ratios were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: Investigators from each study calculated the regression coefficient per 15-g increase in alcohol intake and its standard error, and then these values from the individual studies were combined using a random-effects model. We tested for heterogeneity among studies by means of the Q statistic (25). Meta-regression was used to assess interactions with other risk factors. To estimate the impact of alcohol drinking on the risk of colorectal cancer, we calculated the population attributable fraction percentage according to the formula $pd \times (\mathrm{HR} - 1)/\mathrm{HR}$, where pd is the proportion of cases exposed to the risk factor(s) (26) and HR is the hazard ratio. Stata was used for meta-analysis.

RESULTS

The present study included 209,763 subjects (98,265 men and 111,498 women) and 2,802 colorectal cancer cases (1,724 men and 1,078 women) accumulated during 2,231,010 person-years of follow-up (table 1). The proportions of colon cancer cases were 63 percent for men and 68 percent for women. Half of the men consumed ≥23 g of alcohol per day. In contrast, 71 percent of women were nondrinkers, and the majority of female drinkers consumed alcohol occasionally (<once/week) or at a level of 0.1–22.9 g/day; only 4 percent consumed ≥23 g/day.

As table 2 shows, alcohol intake was associated with increased risk of colorectal cancer in a dose-response manner in men (p for trend < 0.001). A statistically significant increase in risk was observed among drinkers who consumed ≥23 g/day of alcohol; hazard ratios for 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and ≥92 g/day (compared with nondrinking) were 1.42 (95 percent confidence interval (CI): 1.21, 1.66), 1.95 (95 percent CI: 1.53, 2.49), 2.15 (95 percent CI: 1.74, 2.64), and 2.96 (95 percent CI: 2.27, 3.86), respectively. The test for heterogeneity across studies was not statistically significant for the hazard ratio summarizing risk per 15-g/day increase in alcohol intake ($p > 0.2$). When ex-drinkers were defined separately from never drinkers, similar results were obtained: Hazard ratios for drinkers of 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and ≥92 g/day versus nondrinkers were 1.57 (95 percent CI: 1.27, 1.94), 2.00 (95 percent CI: 1.30, 3.08), 2.19 (95 percent CI: 1.65, 2.90), and 2.98 (95 percent CI: 1.83, 4.85), respectively. A dose-response relation with alcohol consumption was evident for both the colon and the rectum (p for trend < 0.001), and the hazard ratios associated with alcohol intake of ≥46 g/day were similar. However, an alcohol intake of 23–45.9 g/day was significantly associated with the risk of colon cancer (hazard ratio (HR) = 1.60, 95 percent CI: 1.31, 1.95) but not the risk of rectal cancer (HR = 1.18, 95 percent CI: 0.90, 1.56). When never drinkers were used as the reference group, the risk of colon cancer with these intake levels was increased (HR = 1.93).

In analysis for men using the same exposure categories as those used in the pooled analysis of Western studies (22), hazard ratios for colorectal cancer associated with alcohol intakes of 0.1–4.9 g/day, 5–14.9 g/day, 15–29.9 g/day, 30–44.9 g/day,

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

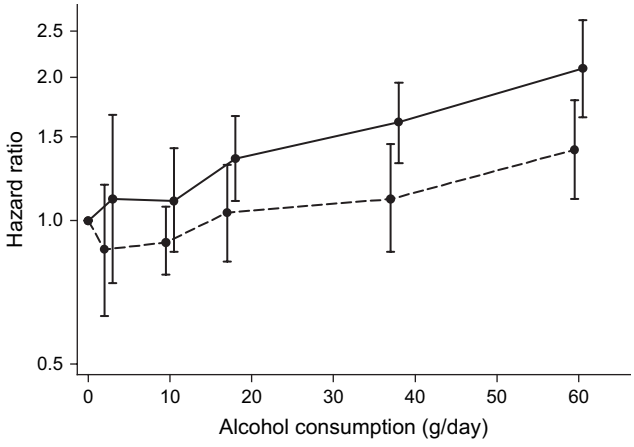

FIGURE 1. Hazard ratios for colorectal cancer by alcohol intake in Japanese (solid line) and Western (dashed line) populations. The solid line shows results for Japanese men from the present pooled analysis of five cohort studies (16–19); the dashed line shows results for Western men from a previous 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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