

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

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Background: It remains unclear whether alcohol drinking is causally associated with colorectal cancer. On the basis of a systematic review of epidemiological evidence, we evaluated this association among the Japanese population, who may be more susceptible to alcohol-related diseases than Western populations.

Methods: Original data were obtained from searches of MEDLINE using PubMed, complemented with manual searches. The evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility as previously evaluated by the International Agency for Research on Cancer.

Results: We identified 5 cohort studies and 13 case–control studies. A moderate or strong positive association was observed between alcohol drinking and colon cancer risk in all large-scale cohort studies, with some showing a dose–response relation, and among several case–control studies. The risk of colon or colorectal cancer was increased even among moderate drinkers consuming <46 g of alcohol per day, levels at which no material increase in the risk was observed in a pooled analysis of Western studies. A positive association with rectal cancer was also reported, but it was less consistent, and the magnitude of the association was generally weaker compared with colon cancer.

Conclusion: We conclude that alcohol drinking probably increases the risk of colorectal cancer among the Japanese population. More specifically, the association for the colon is probable, whereas that for the rectum is possible.

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

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INTRODUCTION

In Japan, colorectal cancer has markedly increased over the last several decades (1) and its incidence is now among the highest levels in the world (2). Such chronological trend in colorectal cancer may be attributable to collective changes in various aspects of lifestyles including diet and physical activity. However, the increasing male-to-female gap in colorectal cancer mortality since 1970 in Japan (1) is of note and the contribution of tobacco smoking or alcohol drinking, both of which are much more prevalent in men than in women (3), is suspected. In our previous work (4), however, we did not find consistent

data suggesting a close link of colorectal cancer to smoking among the Japanese.

Although numerous studies reported a positive association between alcohol drinking and colorectal cancer risk, it remains unclear whether alcohol drinking is causally related to carcinogenesis of the colorectum. A report from the World Cancer Research Fund and American Institute for Cancer Research concluded that alcohol drinking 'probably' increases colorectal cancer risk (5), whereas a recent report of a Joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Consultation did not include colorectal cancer in the list of alcohol-related malignancies (6). However, the influence of alcohol drinking is of particular concern for the Japanese because of their relatively high prevalence of the slow-metabolizing ALDH variant (7), associated with higher levels of acetaldehyde in alcohol drinkers.

The objective of the present study was thus to review epidemiological findings regarding the association between alcohol drinking and colorectal cancer among the Japanese population. This work is conducted as a systematic review of epidemiological evidence regarding lifestyles and major forms of cancer in Japan (4,8).

METHODS

The original data for this review were identified by searches of MEDLINE using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiological studies on the association between alcohol drinking and colorectal cancer incidence or mortality among Japanese published from 1965 to 2005 were identified using the search terms 'alcohol', 'colorectal cancer', 'colon cancer', 'rectal cancer', 'cohort studies', 'case-control studies', 'Japan', and 'Japanese' as keywords found in the abstract. Papers written in either 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 a study design as cohort or case-control studies and, if available, by cancer site as colon, rectum or colorectum.

An evaluation was made on the basis of the magnitude of association and the strength of evidence. First, the relative risks in each epidemiological study were grouped by the magnitude of association, while considering statistical significance (SS) or no statistical significance (NS), as strong, <0.5 or >2.0 (SS); moderate, either (i) <0.5 or >2.0 (NS), (ii) >1.5 to 2.0 (SS), or (iii) 0.5 to <0.67 (SS); weak, either (i) >1.5 to 2.0 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67 – 1.5 (SS); or no association, 0.67 – 1.5 (NS). In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or most updated results were included, and the incidence was given priority over mortality as an outcome measure. The incidence was also given priority in a single publication describing both incidence and mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (6), in

which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility, based on evidence in experimental animals and mechanistic and other relevant data, corresponded to the judgement of the most recent evaluations from the International Agency for Research on Cancer [IARC (9,10)]. Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgement was therefore made on the basis of a consensus of the research group members, and it was therefore not necessarily objective.

MAIN FEATURES AND COMMENTS

A total of 5 cohort studies (11–16) and 13 case-control studies (17–29) were identified (Tables 1 and 2, respectively). As regards Hirayama's study, we referred to two sources; one contained results for the colon and rectum with some additional data for sigmoid colon (13), whereas the other included results of detailed analysis for the sigmoid colon (12). Among the cohort studies, four (12–16) presented results by gender, one (10) for men only. The respective numbers for the case-control studies are two (17,25) and four (19,20,26,29), and the remaining seven studies (18,21–24,27,28) presented results for men and women combined. A summary of the magnitude of association for these studies is shown in Tables 3 and 4 for the cohort studies and case-control studies, respectively.

Four large-scale cohort studies (12–16) showed relative risks separately for colon and rectum. In men, three (14–16) of these studies found a moderate to strong positive association with colon cancer and one (12) reported a strong positive association with sigmoid colon cancer. In women, a moderate association was also observed for colon (14) or sigmoid colon (12). For rectal cancer, one study (15) found a strong positive association in men only, whereas three studies found a weak positive association either in men (13) or in women (14,16). Of the two cohort studies showing relative risk for colon and rectum combined, a nation-wide study (15) reported a strong positive association in men but not in women. A significant dose- or frequency-response relation was observed for cancer of the colon (14), rectum (12,16), or both (15).

Of the 13 case-control studies evaluated, 10 studies (17–21,23–25,28) provided odds ratios for the colon and rectum separately and 1 study presented data for the colon only (22). Among these studies, two studies (17,22) found a strong inverse association between alcohol drinking and colon cancer risk, whereas other three studies (22,26,29) showed a strong positive association for colon and another study (20) found a weak positive association for distal colon. Similar results were observed for rectal cancer, but the association for rectum was less clear than that for colon. Of the four case-control studies (22,27–29) reporting odds ratio for the colon and rectum combined, three (22,27,29) found a strong positive association with alcohol drinking and the remaining study (28) exhibited a weak positive association. All studies

Table 1. Alcohol drinking and colorectal cancer risk, cohort study among Japanese populations

Reference	Study period	Study population			Category	No. among cases or deaths	Relative risk (95% confidence interval or <i>P</i>)	<i>P</i> for trend	Confounding variables considered	Comments	
		No. of subjects for analysis	Source of subjects	Event followed							
Kono et al. (11)	1965–83	5130 men	Male physicians	Death	Large bowel 39	NA	1.00	NA	Age and smoking	90% confidence intervals were shown. Data for women were not presented. *Adjusted for age, smoking and green-yellow vegetables.	
						Occasional	NA	NA			
						Daily	NA	1.21 (0.54–2.72)			
						<2 go	NA	1.09 (0.45–2.68)			
						≥2	NA	1.40 (0.54–3.61)			
Hirayama (12)	1965–82	265 118 (122 261 men, 142 857 women)	Residents in six prefectures (95% of census population)	Death	Proximal colon Men (number not described)	NA	1.00		Age		
						Occasional/daily	NA	1.07 (0.85–1.35)			
						Non-drinker	NA	1.00			
						Rare	NA	1.02			
						Occasional	NA	1.09			
						Daily	NA	0.98			>0.05
						Non-drinker/rare	NA	1.00			
						Sigmoid colon 43 men	NA	3.95 (1.98–7.86)			
						Occasional/daily	NA	1.00			
						Non-daily	NA	2.14 (1.32–3.47)*			
						Daily	NA	1.00			
						Non-drinker	NA	2.03 (0.54–7.32)			
						Rare	NA	3.83 (1.55–17.42)			
						Occasional	NA	5.42 (2.24–13.99)			<0.001
						Daily	NA	1.00			
	Non-drinker	NA	4.56 (1.63–12.19)								
	Sake-drinker	NA	1.00								
	Non-drinker	NA	5.90 (2.00–17.42)								
	Shochu-drinker	NA	1.00								
	Non-drinker	NA	12.67 (3.62–43.66)								
	Bear-drinker	NA	1.00								
	Non-drinker	NA	1.92 (1.13–3.26)								
	Drinker	NA	1.00	<0.05							
	Non-drinker	NA	1.00								
	Rectum Men (number not described)	NA	0.95								
	Women	NA	1.14								
		NA	1.39								

Hirayama (13)	1965-82	265 118 (122 261 men, 142 857 women)	Residents in six prefectures (95% of census population)	Death	Colon	None	NA	1.00	Age	90% confidence intervals were shown. *The significant trend association remained after adjustment for age and smoking.
					Men	Rare	NA	1.06 (0.73-1.54)		
						Occasional	NA	1.35 (1.01-1.82)		
						Daily	NA	1.24 (0.92-1.67)		NS
					Women	None	NA	1.00		
						Rare	NA	1.18 (0.88-1.57)		
						Occasional	NA	1.10 (0.74-1.63)		NS
						Daily	NA	NA		
					Sigmoid colon					
					Men	Non-drinker	NA	1.00		
						Drinker	NA	4.38 (1.75-10.97)		
					Women	Non-drinker	NA	1.00		
						Drinker	NA	1.92 (1.13-3.26)		
					Rectum					
					Men	None	NA	1.00		
						Rare	NA	0.96 (0.68-1.35)		
						Occasional	NA	1.15 (0.87-1.51)		
						Daily	NA	1.39 (1.07-1.80)		<0.05*
					Women	None	NA	1.00		
						Rare	NA	1.23 (0.89-1.70)		
						Occasional	NA	1.27 (0.84-1.94)		
						Daily	NA	0.73 (0.22-2.45)		NS
					Colon					
					108 men	Non-drinker	5	1.00		
						Current	NA	NA		
						≤36.7 g/day	45	1.79 (0.71-4.55)		
						>36.7	58	2.67 (1.06-6.76)		0.01
						Non-drinker	5	1.00		
						Sake-drinker (highest)	NA	1.91 (1.10-3.32)		
					94 women	Non-drinker	34	1.00		
						Current	NA	NA		
						≤3.75 g/day	28	1.07 (0.58-1.96)		
						>3.75	32	1.78 (1.00-3.18)		0.03
					Rectum					
					59 men	Non-drinker	8	1.00		
						Current	NA	NA		
						≤36.7 g/day	20	0.59 (0.25-1.42)		
						>36.7	31	1.17 (0.50-2.73)		0.06
					Incidence					
					Residents in Takayama					
					29 051 (13 392 men, 15 659 women)					
					1993-2000					
Shimizu et al. (14)	1993-2000				Colon					
					108 men	Non-drinker	5	1.00		
						Current	NA	NA		
						≤36.7 g/day	45	1.79 (0.71-4.55)		
						>36.7	58	2.67 (1.06-6.76)		0.01
						Non-drinker	5	1.00		
						Sake-drinker (highest)	NA	1.91 (1.10-3.32)		
					94 women	Non-drinker	34	1.00		
						Current	NA	NA		
						≤3.75 g/day	28	1.07 (0.58-1.96)		
						>3.75	32	1.78 (1.00-3.18)		0.03
					Rectum					
					59 men	Non-drinker	8	1.00		
						Current	NA	NA		
						≤36.7 g/day	20	0.59 (0.25-1.42)		
						>36.7	31	1.17 (0.50-2.73)		0.06

Table 1. Continued

Reference	Study period	Study population			Category	No. among cases or deaths	Relative risk (95% confidence interval or P)	P for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed						
Orani et al. (15)	1990–99	90 004 (42 540 men, 47 464 women)	JPHC study (cohort 8544:: 5 prefectures, cohort 8545:: 6 prefectures), residential registry	Incidence	41 women	Non-drinker	7	1.00		*Among drinkers Age, family history of colorectal cancer, body mass index, smoking, physical exercise and area
						Current	NA	NA		
						≤3.75 g/day	15	1.20 (0.44–3.26)		
						>3.75	19	1.80 (0.70–4.62)	0.17	
					Colorectum 457 men	Non-drinker	87	1.0		
						Occasional drinker	24	0.8 (0.5–1.3)		
						Regular drinker	NA	NA		
						1–149 g/week	83	1.1 (0.8–1.5)		
						150–299	107	1.4 (1.1–1.9)		
						≥300	146	2.1 (1.6–2.7)	<0.001	
					259 women	Non-drinker	230	1.0		
						Occasional drinker	12	0.5 (0.3–0.9)		
						Regular drinker	17	0.7 (0.4–1.1)	NA	
					Colon 299 men	Non-drinker	62	1.0		
						Occasional drinker	16	0.8 (0.4–1.3)		
						Regular drinker	NA	NA		
						1–149 g/week	51	1.0 (0.7–1.4)		
						150–299	71	1.3 (0.9–1.8)		
						≥300	99	1.9 (1.4–2.7)	<0.001	
	Occasional drinker	8	1.0 (0.5–2.3)							
	Regular drinker	NA	NA							
	1–149 g/week	32	1.6 (0.9–2.6)							
	150–299	36	1.7 (1.01–2.8)							
	≥300	47	2.4 (1.5–4.0)	<0.015						
Colon 220 men	Non-drinker	24	1.00 (reference)							
	Ex-drinker	19	2.01 (1.09–3.68)							
	Current drinker	177	1.97 (1.28–3.03)							
Wakai et al. (16)	1988–97	57 736 (23 708 men, 34 028 women)	JACC study (24 areas throughout Japan)	Incidence						
						1.0–1.9	63	2.22 (1.38–3.56)		
						2.0–2.9	36	1.75 (1.04–2.96)		
						≥3.0	20	2.40 (1.31–4.40)	0.85*	

198 women	Non-drinker	149	1.00 (reference)	
	Ex-drinker	6	1.56 (0.68–3.60)	
	Current drinker	43	1.03 (0.72–1.45)	
	0.0–0.9 (go/day)	22	1.06 (0.67–1.68)	
	≥ 1.0	5	1.22 (0.49–3.03)	0.96*
Rectum				
150 men	Non-drinker	30	1.00 (reference)	
	Ex-drinker	14	1.25 (0.66–2.38)	
	Current drinker	106	1.01 (0.67–1.52)	
	0.0–0.9 (go/day)	16	0.61 (0.33–1.13)	
	1.0–1.9	35	1.01 (0.62–1.65)	
61 women	2.0–2.9	29	1.21 (0.72–2.04)	
	≥ 3.0	12	1.32 (0.67–2.63)	0.027*
	Non-drinker	50	1.00 (reference)	
	Ex-drinker	1	0.78 (0.11–5.78)	
	Current drinker	10	0.71 (0.35–1.42)	
	0.0–0.9 (go/day)	5	0.69 (0.27–1.74)	
	≥ 1.0	2	1.53 (0.36–6.47)	0.36*

NA, not available; NS, not significant.

Table 2. Alcohol drinking and colorectal cancer risk, case-control study among Japanese populations

Reference	Study period	Study subjects		Category	Odds ratio (95% confidence interval or P)	P for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls			
Kondo (17)	1967-73	Hospital-based (Three hospitals in Nagoya)	Cases: 91% were histologically confirmed; Controls: inpatients without history of cancer of the digestive organs, oral cavity, pharynx, lung or larynx, or other diseases of the colorectum	Colon 93 men	406 men*		Matched (1 : 2) for age (± 5 years) and sex	*Total no. of controls for colorectal cancer cases. No. for each site was not shown.
				Rectum 112 men	406 men*			
				99 women	174 women*			

Table 2. Continued

Reference	Study period	Type and source	Study subjects		Category	Odds ratio (95% confidence interval or P)	P for trend	Confounding variables considered	Comments
		Definition	No. of cases	No. of controls					
Kato et al. (21)	1986–90	Hospital -based (Aichi Cancer Center Hospital)	Distal colon 756 men	16 600 men	Non-drinker	1.00			
					Occasional	1.40 (1.12–1.74)			
					Daily	1.33 (1.11–1.58)	NA		
					Sake	1.15 (0.97–1.37)			
					Beer	1.65 (1.34–2.04)			
			Rectum 1611 men	16 600 men	Whisky	1.33 (0.85–2.08)			
					Non-drinker	1.00			
					Occasional	1.39 (1.19–1.63)			
					Daily	1.06 (0.93–1.22)	NA		
					Sake	1.10 (0.97–1.85)			
					Beer	1.88 (1.62–2.18)			
					Whisky	1.35 (0.98–1.85)			
			Colon 132 (M: 79, F: 53)	578 (M: 377, F: 201)*	Never	1.00		Matched for residence, sex and age (5-year age group)	*Common controls for cases of cancer of the colon and rectum
					Past	2.81 (1.33–5.97)			
					Daily	0.77 (0.44–1.33)			
					Non-whisky drinker	1.00			
					Whisky drinker	0.93 (0.50–1.75)			
Yoshida et al. (22)	1987–90	Hospital -based (Sapporo medical college and affiliated hospitals)	Rectum 91 (M: 60, F: 31)	578 (M: 377, F: 201)*	Never	1.00			
					Past	4.30 (1.76–10.52)			
					Daily	1.64 (0.84–3.18)			
					Non-whisky drinker	1.00			
					Whisky drinker	1.16 (0.59–2.31)			
			Colorectum 330 (M: 171, F: 159)	660 (M: 342, F: 318)	Alcohol intake (g/day)*			Matched (1 : 2) for sex and age (±3 yrs)	*Reference is of other categories of consumption. For instance, >10 is compared with ≤10. **OR is not shown.
					>10	1.46 (1.04–1.96)			
					>35	1.52 (1.10–2.11)			
					>50	1.60 (1.13–2.29)			
					>80	1.76 (1.10–2.83)			
			171 men	342 men	>100	2.05 (1.13–3.70)			
					>35	1.48 (1.03–2.13)			
					>50	1.55 (1.05–2.27)			
					>80	1.79 (1.09–2.96)			
					spoon				

Hoshiyama et al. (23)	1984–90	Hospital -based (Saitama Cancer Center Hospital)	Cases: histologically confirmed cases; Controls: population controls	159 women	318 women	>5	1.79 (1.08–2.95)	Adjusted for sex and age	*Common controls for cases of cancer of the colon and rectum; **daily drinker versus never drinker
						>10	2.13 (1.21–3.73)		
						>35	1.73 (0.83–3.64)		
				Colon					
				177 (M: 81, F: 96)	354 (M: 162, F: 192)	>10	1.75 (1.11–2.76)		
						>35	1.98 (1.25–3.13)		
						>50	1.97 (1.20–3.25)		
						>80	2.17 (1.13–4.15)		
						>100	2.46 (1.11–5.44)		
							NS**		
	Rectum	153 (M: 90, F: 63)	306 (M: 180, F: 126)	Colon	79 (M: 37, F: 42)	653 (M: 343, F: 310)*	Never	1.0	
							Past	0.4 (0.0–2.0)	
							Occasional	0.6 (0.3–1.1)	
							Daily	NA	
							<50 ml/day	0.3 (0.1–0.8)	
							≥50	0.3 (0.1–0.9)	
							Sake**	0.5 (0.1–1.4)	
							Beer**	0.5 (0.1–1.7)	
							Spirits**	0.6 (0.2–1.8)	
							Never	1.0	
	Lifetme consumption	<500 l	≥500	0.4 (0.1–1.0)	0.7 (0.2–1.8)	0.46			
	Rectum	102 (M: 61, F: 41)	653 (M: 343, F: 310)*	Never	1.0				
				Past	0.3 (0.0–1.7)				
				Occasional	0.5 (0.2–1.0)				
				Daily	NA				
				<50 ml/day	0.5 (0.2–1.1)				
				≥50	0.6 (0.3–1.3)				
				Sake**	1.4 (0.6–3.3)				
				Beer**	1.1 (0.4–2.7)				
				Spirits**	0.8 (0.3–2.4)				
				Never	1.0				
	Lifetme consumption	<500 l	≥500	0.7 (0.3–1.6)	0.9 (0.4–2.2)	0.98			

Table 2. Continued

Reference	Study period	Study subjects			Category	Odds ratio (95% confidence interval or <i>P</i>)	<i>P</i> for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls				
Kotake et al. (24)	1992–94	Hospital-based (10 hospitals in Kanto region)	Cases: histologically confirmed cases; Controls: screening controls and hospital controls, including cancer patients	Colon 187 (M: 111, F: 76)	187 (M: 111, F: 76)	Non-drinker Daily	1.0 0.8 (0.2–3.9)	Matched for sex, age (5-year age group)	
			Rectum 176 (M: 103, F: 73)		176 (M: 103, F: 73)	Non-drinker Daily	1.0 1.4 (0.4–5.9)		
Inoue et al. (25)	1988–92	Hospital-based (Aichi Cancer Center Hospital)	Cases: histologically confirmed cases; Controls: first-visit outpatients free from cancer	Colon: Proximal 51 men 43 women	8 621 men* 23 161 women*	Never Ever (habitual) Never Ever (habitual)	1.0 1.3 (0.7–2.5) 1.0 0.8 (0.3–1.8)	Adjusted for age	*Common controls for cases of cancer of the colon and rectum
			Colon: Distal 75 men 62 women		8 621 men* 23 161 women*	Never Ever (habitual) Never Ever (habitual)	1.0 1.1 (0.7–1.9) 1.0 0.8 (0.4–1.5)		
Murata et al. (26)	1984–93	Nested case-control study (participants of stomach cancer screening by the Chiba Cancer Association)	Cases: confirmed by a record linkage to cancer registry data; Controls: screeners free from any cancer during the follow-up period	Rectum 131 men 70 women	8 621 men* 23 161 women*	Never Ever (habitual) Never Ever (habitual)	1.0 1.1 (0.7–1.6) 1.0 1.3 (0.7–2.2)	Matched (1 : 2) for sex, birth, age (±2 years) and residence	*One cup of sake (180 ml) includes 27 ml of ethanol. Intake of other beverages was converted to sake-equivalents; **compared with non-drinker
			Colon 61 men		122 men	Non-drinker Drinker ≤1.0 cups/day* 1.1–2.0 ≥2.1	1.0 NA 3.5 (<0.01) 1.9 (NS) 3.2 (<0.05)		
			Colon 61 men		122 men	Non-drinker ≤1.0 cups/day* ≥1.1	1.0 3.5 (<0.01) 2.3 (NS)		NA

Yamada et al. (27)	1991–93	Health check-up- based (PL Tokyo Health Care Center, multiphasic health check-up)	Cases: histologically confirmed cases; Controls: examinees without history of colorectal cancer and inflammatory bowel disease	Colorectum 66 (M: 55, F: 11)	132 (M: 110, F: 22)	Non-drinker	1.0	Matched (1 : 2) for sex, age and history of prior health check-up at the centre; adjusted for body mass index and smoking	Results for carcinoma <i>in situ</i> (<i>n</i> = 129) were also presented.
						Current	NA		
						1–2 times/month	0.4 (0.1–2.1)		
						1–3 times/week	1.1 (0.4–3.1)		
						Almost daily	1.2 (0.5–3.1)		
						Non-drinker	1.0		
						1–20 g/day	1.1 (0.4–3.1)		
						21–40	0.7 (0.3–1.9)		
						≥41	2.0 (0.7–5.4)		
						Non-drinker	1.0		
					Index of cumulative consumption	1–1000 g/year	0.7 (0.3–1.8)	0.4	
						1001–2000	1.3 (0.5–3.7)		
						≥2001	3.2 (1.0–10.1)		
						Type of beverage	Sake**	3.0 (<0.01)	
							Others**	2.8 (<0.05)	
							Non-drinker	1.0	
							≤1.0 cups/day*	30.7 (<0.01)	
							≥1.1	12.4 (<0.05)	
							Sake**	20.6 (<0.01)	
							Others**	23.0 (<0.01)	
							Non-drinker	1.0	
							≤1.0 cups/day*	1.4 (NS)	
							≥1.1	1.0 (NS)	
						Type of beverage	Sake**	1.3 (NS)	NA
							Others**	1.1 (NS)	
							Non-drinker	1.0	
							≤1.0 cups/day*	1.4 (NS)	
							≥1.1	1.0 (NS)	
							Sake**	1.3 (NS)	
							Others**	1.1 (NS)	
							Non-drinker	1.0	
							Drinker	NA	
							≤1.0 cups/day*	0.8 (NS)	
						Type of beverage	1.1–2.0	1.9 (NS)	NS
							≥2.1	1.4 (NS)	
							Non-drinker	1.0	
							Drinker	NA	
							≤1.0 cups/day*	0.8 (NS)	
							1.1–2.0	1.9 (NS)	
							≥2.1	1.4 (NS)	
							Non-drinker	1.0	
							Drinker	NA	
							≤1.0 cups/day*	0.8 (NS)	

Table 2. Continued

Reference	Study period	Study subjects		Category	Odds ratio (95% confidence interval or P)	P for trend	Confounding variables considered	Comments
		Type and source	Definition	No. of cases	No. of controls			
Ping et al. (28)	1986–94	Health check-up-based (Tokyo University Hospital: health check-up examinees)	Cases: histologically confirmed cancer-free examinees	Colorectum 100 (M: 77, F: 23)	265 (NA)	NA	Matched (1 : 3) for sex, age (± 2 years), data of health checking (± 3 months) and residence; 35 controls were excluded owing to a lack of lifestyle data	*Large consumption of alcohol; definition of 'large consumption' is not described; reference comprises non-drinkers and other drinkers
Murata et al. (29)	1989–97	Hospital-based case-control study (Chiba Cancer Center Hospital)	Cases: those who underwent surgery Controls: outpatients free from cancer	Colorectum 267 men	395 men	1.00	Adjusted for age (10-year age group)	Women were also included in the study, but the association with alcohol.
						NA		
						0.51 (0.30–0.87)		
						0.85 (0.54–1.3)		
						1.81 (1.03–3.2)		
						2.19 (1.2–4.2)		
				Colon 157 men	395 men	1.00		
						NA		
						0.53 (0.29–0.99)		
						0.81 (0.48–1.4)		
						1.66 (0.88–3.1)		
						2.19 (1.1–4.5)		
				Rectum 110 men	395 men	1.00		
						NA		
						0.48 (0.22–1.02)		
						0.84 (0.45–1.6)		
						2.04 (0.97–4.3)		
						2.10 (0.61–4.9)		

NA, not available; NS, not significant; M, men; F, women.

Table 3. Summary of the association between alcohol drinking and colorectal cancer risk, cohort study

Reference	Study period	Study population					Magnitude of association*		
		Sex	No. of subjects	Age range (years)	Event	No. of incident cases or deaths	Colon	Rectum	Colorectum
Kono et al. (11)	1965–83	Men	5130	27–89	Death	39	NA	NA	—
Hirayama (12,13)	1965–82	Men	122 261	≥40	Death	256**	—***	↑	NA
		Women	142 857	≥40	Death	318**	—***	—	NA
Shimizu et al. (14)	1993–2000	Men	13 392	≥35	Incidence	161	↑↑↑	—	NA
		Women	15 659	≥35	Incidence	134	↑↑	↑	NA
Otani et al. (15)	1990–99	Men	42 540	40–69	Incidence	457	↑↑	↑↑↑	↑↑↑
		Women	47 464	40–69	Incidence	259	NA	NA	—
Wakai et al. (16)	1988–97	Men	23 708	40–79	Incidence	370	↑↑↑	—	NA
		Women	34 028	40–79	Incidence	259	—	↑	NA

NA, not available.

*↑↑↑or ↓↓↓ strong; ↑↑or ↓↓, moderate; ↑or ↓, weak; —, no association (see text for more detailed definition).

**Colon only.

***Positive association was observed for sigmoid colon in men (↑↑↑) and in women (↑↑).

Table 4. Summary of the association between alcohol drinking and colorectal cancer risk, case–control study

Reference	Study period	Study subjects				Magnitude of association*		
		Sex	Age range	No. of cases	No. of controls	Colon	Rectum	Colorectum
Kondo (17)	1967–73	Men	Not specified	205	408	↓↓↓	↓↓↓	NA
		Women	Not specified	188	174	—	—	NA
Watanabe et al. (18)	1977–83	Men and women	Not specified	203 (M: 110, F: 93)	203 (M: 110, F: 93)	—	—	NA
Tajima and Tominaga (19)	1981–83	Men	40–79 years	52	111	—	—	NA
Kato et al. (20)	1979–87	Men	≥20 years	3327	16 600	—**	—	NA
Kato et al. (21)	1986–90	Men and women	Not specified	223	578	—	↑	NA
Yoshida et al. (22)	1987–90	Men and women	25–79 years	330 (M: 171, F: 159)	660 (M: 342, F: 318)	↑↑↑	—	↑↑↑
Hoshiyama et al. (23)	1984–90	Men and women	40–69 years	181 (M: 98, F: 83)	653 (M: 343, F: 310)	↓↓↓	↓	NA
Kotake et al. (24)	1992–94	Men and women	Not specified	363 (M: 214, F: 149)	363 (M: 214, F: 149)	—	—	NA
Inoue et al. (25)	1988–92	Men	24–86 years	257	8621	—	—	NA
		Women	24–88 years	175	23 161	—	—	NA
Murata et al. (26)	1984–93	Men	Not specified	104	208	↑↑↑	—	NA
Yamada et al. (27)	1991–93	Men and women	34–80 years	66 (M: 55, F: 11)	132 (M: 110, F: 22)	NA	NA	↑↑↑
Ping et al. 1998 (28)	1986–94	Men and women	40–84 years	100 (M: 77, F: 23)	265 (NA)	NA	NA	↑
Murata et al. (29)	1989–97	Men	Not specified	267	395	↑↑↑	↑↑	↑↑↑

NA, not available; M, men; F, women.

*↑↑↑or ↓↓↓, strong; ↑↑or ↓↓, moderate; ↑or ↓, weak; —, no association (see text for more detailed definition).

**Weak positive association (↑) was observed for distal colon.

(22,26,27,29) showing a strong positive association also reported a significant dose–response relation.

We should mention methodological issues in general and specific to the Japanese studies reviewed here. Attention should be paid when interpreting the results of case–control studies. First, patient recall of lifestyles in the remote past may be influenced by recent lifestyles. Secondly, many diseases are potentially alcohol-related, and this may be a source of bias in case–control studies using patient group as the reference.

Thirdly, colorectal cancer risk associated with ex-drinking may be overestimated because quitting drinking might be a result of cancer manifestation. Fourthly, since few case–control studies controlled for physical activity and obesity, identified factors predictive of colorectal cancer risk (6), confounding by these factors may account for the observed association between alcohol drinking and colorectal cancer. However, recent large-scale cohort studies (14–16) that controlled for known or suspected aetiologic factors of colorectal

cancer demonstrated a moderate or strong association, a finding arguing against confounding as an explanation for the association. Cohort studies have also their inherent limitations. Since only baseline information on lifestyles was used in analysis of the relation to colorectal cancer risk, the effect of bias related to changes in alcohol drinking habit during the time course cannot be ruled out. Moreover, we identified methodological differences among cohort studies reviewed; alcohol drinking habit was determined using simple, not-validated questionnaire, and death was the study outcome in earlier cohort studies, whereas in recent ones alcohol consumption was quantitatively estimated on the basis of a detailed, validated questionnaire and incidence was the study outcome. In this regard, more emphasis should be placed on the results of recent studies.

In experimental animals, there is sufficient evidence for the carcinogenicity of acetaldehyde (10), a metabolite of alcohol, whereas there is inadequate evidence for the carcinogenicity of ethanol and of alcoholic beverages (9). Although specific mechanisms whereby alcohol drinking influences colorectal carcinogenesis remains unclear, alcohol or acetaldehyde may induce DNA hypomethylation, an early step in colonic carcinogenesis, through its anti-folate effects (30). Moreover, acetaldehyde generated by intestinal bacteria may also increase the risk of colorectal cancer via folate deficiency (31).

The magnitude of association between alcohol drinking and colorectal cancer among Japanese studies appears to differ from that among Western populations. In a pooled analysis of Western cohort studies (32), relative risk of colon cancer for heavy alcohol drinkers consuming 45 g of alcohol or over per day versus non-drinkers was 1.2. In recent cohort studies in Japan, however, relative risks for colon cancer versus non-drinker category were 2.7 (14), 2.1 (15) and 2.4 (16) for the highest category of alcohol consumption, whose cut-off values were 37, 43 and 69 g of alcohol per day, respectively. Moreover, moderate drinking (<45 g/day) was materially unrelated to colon cancer risk in Western populations (32), whereas corresponding levels of alcohol consumption were associated with 1.4- to 1.8-fold increased risk of colon cancer among Japanese populations (14–16). These findings suggest that Japanese drinkers are more likely to develop colon cancer than Western counterparts. This may be explained in part by the relatively high prevalence of the slow-metabolizing ALDH variant among Japanese (7,29). Non-genetic factors may also contribute to the heterogeneity of risk among populations. For instance, a dietary pattern typical of Japanese drinkers—low consumption of fruits and vegetables and dairy foods (33)—may enhance the carcinogenic effects of alcohol or acetaldehyde. Furthermore, lean alcohol drinkers may be more likely to develop colorectal cancer than non-lean counterparts (32), presumably because of a differential effect of alcohol on insulin metabolism according to body composition. This may also account for the stronger alcohol–colon cancer association among the Japanese, who are on average leaner than Western people.

We found a consistent, moderate to strong positive association between alcohol drinking and colon cancer among major cohort studies, with some showing a dose–response relation, and among several case–control studies. For rectal cancer, most cohort studies showed a positive association with alcohol drinking, but the association was generally weaker than that for colon cancer. However, a pooled analysis of Western studies (32) did not exhibit significant variation in the magnitude of association according to site within the large bowel, and a Japanese study of alcohol and colorectal adenoma, a precursor of cancer, found a stronger association in the rectum compared with other sites of the colorectum (34). Thus, random variation may be a reason for the apparent inconsistent association for rectal cancer among Japanese studies. Moreover, the stronger and more consistent association in men than in women among Japanese studies may be attributable to a greater proportion of heavy drinkers in men, and not to a sex difference in disease susceptibility. Unfortunately, published data to date do not allow us to conduct a meta-analysis to confirm these, because results were presented according to alcohol consumption (in grams, millilitres or go) in most cohort studies but in less than half of the case–control studies among Japanese populations, whereas only drinking frequency was asked in other Japanese studies. A meta-analysis using original data set of recent cohort studies in Japan is now under way to clarify whether the magnitude of association differs according to site of the large bowel or sex and to quantify the impact of alcohol drinking on colorectal cancer risk among the Japanese population.

EVALUATION OF EVIDENCE ON ALCOHOL DRINKING AND COLORECTAL CANCER RISK IN JAPANESE

From these results and on the basis of assumed biological plausibility, we conclude that alcohol drinking probably increases the risk of colorectal cancer among the Japanese population. More specifically, the association for colon is probable, whereas that for rectum is possible.

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