Jpn J Clin Oncol 2007;37(3)168–174
doi:10.1093/jjco/hyl146

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

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Received August 23, 2006; accepted October 23, 2006; published online March 1, 2007

Background: The relationship between alcohol consumption and risk of lung cancer is controversial. Based on a systematic review of epidemiologic 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 MEDLINE searches using PubMed or from searches of the *Ichushi* database, 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 seven cohort studies and two case-control studies. One cohort study demonstrated a strong positive association between alcohol drinking and the risk of female lung cancer, but the association almost disappeared after adjustment for smoking. The other eight studies showed a weak positive or no association. Although smoking is the best-established risk factor for lung cancer, only five cohort studies presented smoking-adjusted risks out of all nine identified. Furthermore, only two studies explicitly reported the risk estimate for ex-drinkers who may have quit alcohol drinking after the development or diagnosis of the disease and have an apparently higher risk.

Conclusion: We conclude that the epidemiologic evidence on the association between alcohol drinking and lung cancer risk remains insufficient in terms of both the number and methodological quality of studies among the Japanese population.

Key words: systematic review – epidemiology – alcohol drinking – lung neoplasms – Japanese

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INTRODUCTION

Although alcohol consumption is an established risk factor for cancers of the oral cavity, pharynx, larynx, esophagus and liver (1), its relationship with lung cancer still remains controversial. The review of epidemiologic studies by the World Cancer Research Fund and the American Institute for Cancer Research concluded in 1997 that alcohol drinking

possibly increases the risk of lung cancer (1). According to the review article by Bandera et al. (2) of 2001, there was an increasing body of literature suggesting that alcoholic beverages may increase lung cancer risk after adjustment for cigarette smoking.

More recently, Korte and coworkers (3) indicated, based on their meta-analysis, that after controlling for cigarette smoking, evidence of an association between alcohol consumption and lung cancer is largely limited to groups consuming ≥2000 g of ethanol per month (≥2.9 Japanese drinks [gou] per day). Freudenheim et al. (4) found a 21 and 16% greater risk of lung cancer for the drinkers of ≥30 g alcohol per day than that for non-drinkers in men and women, respectively, in a pooled analysis of cohort studies. Most of the studies included in these analyses, however, were conducted in Western countries, where the types of alcoholic beverages consumed are quite different from those in Japan. Furthermore, Japanese may be more susceptible to alcohol in terms of carcinogenesis because the *aldehyde dehydrogenase 2* (*ALDH2*) Glu^{487}Lys polymorphism is more common in Japanese than in Western populations (5,6). The ^{487}Lys allele results in a lower *ALDH2* activity and a higher blood concentration of acetaldehyde (5), which is the initial metabolite of alcohol shown to be carcinogenic in animal experiments (7).

We therefore attempted to review epidemiologic studies on alcohol drinking and lung cancer risk in Japanese populations. This report is one among a series of articles by our research group, who are investigating the association of lifestyles with the risks of total and major specific cancers in Japan (8).

METHODS

The original data for this review were identified by searches of MEDLINE using PubMed and by those of the *Ichushi* (*Japana Centra Revuo Medicina*) database, complemented by manual searches of references from relevant articles when necessary. We identified all epidemiologic studies on the association between alcohol drinking and lung cancer incidence or mortality among Japanese published from January 1980 to June 2006, using the search words 'alcohol', 'drinking', 'lung cancer', 'case-control studies', 'cohort studies', 'Japan' and 'Japanese'. Papers written in either English or Japanese were reviewed. Only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately according to study design as cohort or case-control studies.

We evaluated the studies based on the magnitude of association and the strength of evidence. First, the hazard ratios, rate ratios, or odds ratios in each epidemiologic study were grouped by the magnitude of association, considering statistical significance (SS) or no statistical significance (NS), into: strong (symbol ↑↑↑ or ↓↓↓), <0.5 or >2.0 (SS); moderate (symbol ↑↑ or ↓↓), either (1) <0.5 or >2.0 (NS), (2) >1.5–2.0 (SS), or (3) 0.5 to <0.67 (SS); weak (symbol ↑ or ↓), either (1) >1.5–2.0 (NS), (2) 0.5 to <0.67 (NS), or (3) 0.67–1.5 (SS); or no association (symbol —), 0.67–1.5 (NS). We thus defined the magnitude of association by its strength, that is, the size of hazard ratios, rate ratios, or odds ratios for the highest intake category of the group of current or ever drinkers versus non- or never drinkers, and its statistical significance. Two-sided *P* values less than 0.05 were considered statistically significant. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included.

After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (9), 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 judgment of the most recent evaluations from the International Agency for Research on Cancer (IARC) (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 judgment was made based on a consensus of the research group members, and it was therefore not necessarily objective. To assure the validity of the systematic review, at least seven authors of the article checked the evidence tables (Tables 1 and 2 in this paper) and the summary tables (Tables 3 and 4) with other members of our research group, in order to make conclusions based on consensus.

MAIN FEATURES AND COMMENTS

We identified seven cohort studies (Table 1) (11–17) and two case-control studies (Table 2) (18,19). One additional cohort study was found (20), but its subjects were derived from a subgroup of the other study, that is, the Japan Collaborative Cohort Study (17). We therefore did not include this additional study in our review. Among the seven cohort studies, one presented results by gender (12), five for only men (11,13,14,16,17), and one for both genders combined (15). Both of the two case-control studies reported results for men and women combined (18,19).

We found three articles that mentioned the effect modification by alcohol drinking on the risk of smoking or the interaction between smoking and drinking habits. Kono et al. (11) reported no interaction between the two habits (*P* for interaction, 0.84). Murata and colleagues (14) stated that the elevated risk in smokers was consistently seen at all levels of alcohol consumption; the odds ratios for current smokers compared with never or former smokers (calculated from the published data) were 3.9, 2.2 and 2.6 for men who consumed 0, 0.1–1.0, and 1.1+ Japanese drinks (gou) per day, respectively. Nishino and coworkers (17) reported that there was no significantly increased risk of lung cancer associated with

Table 1. Alcohol drinking and lung cancer risk in cohort studies among Japanese population

Reference	Study period	Study population				Category	Number among cases		HR, RR, or OR (95% CI or *P*)		*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths								
Kono et al. (11)	1965–1983	5130 men	Membership lists of 9 prefectural medical associations	Death	74 men	Never or past		HR	1.00			Age and smoking	
						Occasional			0.45	(0.23–0.89)			
						Daily <2 Japanese drinks/day[b]			0.89	(0.49–1.61)			
						2+			1.00	(0.54–1.87)			
Hirayama (12)	1966–1982	122 261 men	95% of census population	Death	1454 men	None		RR	1.00			Age	The association between alcohol drinking and lung cancer risk turned to be not significant after adjustment for smoking in both men and women.
						Rare			0.94	(0.81–1.10)[a]			
						Occasional			0.91	(0.80–1.03)[a]			
						Daily			1.27	(1.13–1.42)[a]	$P = 0.0006$		
		142 857 women			463 women	None		RR	1.00				
						Rare			1.03	(0.79–1.32)[a]			
						Occasional			1.29	(0.95–1.75)[a]			
						Daily			2.53	(1.59–4.03)[a]	$P = 0.011$		
Masuda and Shigematsu (13)	1968–1987	3616 men	Inhabitants in Oki Islands	Death	43 men	None	16	OR	1.00			Age and smoking	
						Occasional	15		0.70	$P > 0.05$			
						Daily	12		0.69	$P > 0.05$	$P = 0.32$		
Murata et al. (14)	1984–1993	107 male cases and 214 controls (nested case-control study)	17 200 male participants in a gastric mass screening	Incident cases	107 men	Never or past	38	OR	1.0			Matched for: birth year (± 2 years) and address	
						0.1–1.0 Japanese drinks/day[b]	28		1.0		$P = 0.043$ (adjusted for smoking)		
						1.1–2.0	31		2.4	$P < 0.01$			
						2.1+	10		1.8				
Takezaki et al. (15)	1985–1999	2798 men and 3087 women	Inhabitants in a rural area	Incident cases	38 men and women	Almost never	19	HR	1.00			Age, sex, smoking, and occupation	
						< 41 g ethanol/day	11		1.50	(0.67–3.37)			
						41+	8		0.70	(0.28–1.71)	$P = 0.49$		

Nakaya et al. (16)	1990–1997	21 201 men	Inhabitants in 14 municipalities in Miyagi Prefecture	Incident cases	119 men	Never drinkers	16	HR	1.0		Age, smoking, education, and consumption of orange, other fruits, juice, spinach, carrot or pumpkin, and tomato
						Ex-drinkers	21		2.3	(1.2–4.4)	
						Current drinkers	82		1.2	(0.7–2.1)	
						< 22.8 g ethanol/day	17		1.0	(0.5–2.0)	
						22.8 +	65		1.3	(0.8–2.3)	$P = 0.30^c$
Nishino et al. (17)	1988–1999	28 536 men	Participants in municipal health check-ups, general populations, or voluntary groups	Death	377 men	Never drinkers	91	HR	1.00		Age, smoking, family history of lung cancer, and intakes of green-leafy vegetables, oranges, and fruits other than oranges
						Ever drinkers	286		0.96	(0.73–1.26)	
						Ex-drinkers	50		1.68	(1.16–2.45)	
						Current drinkers					
						0.1–24.9 g ethanol/day	113		0.81	(0.59–1.11)	
						25.0–49.9	85		0.90	(0.64–1.26)	
						50.0 +	38		0.98	(0.64–1.50)	$P = 0.92^c$

HR, hazard ratio; RR, rate ratio; OR, odds ratio; CI, confidence interval.
[a]90% confidence interval.
[b]One Japanese drink is equivalent to 23 g ethanol.
[c]*P* for trend among never and current drinkers.

Table 2. Alcohol drinking and lung cancer risk in case-control studies among Japanese population

Reference	Study period	Study subjects				Category	Odds ratios (95% CI or *P*)	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls			
Shimizu (18)	1975–1981	Hospital-based (Aichi Cancer Center)	Cases: microscopically confirmed; Controls: patients without lung cancer	63 cases of Kreyberg Group I[a] (53 men and 10 women)	53 men and 10 women	Never Current + past	1.0 1.6 $P > 0.05$	Matched (1:1) for: sex, age (±5 years), date of interview (nearest), and residence
				36 cases of Kreyberg Group II[b] (19 men and 17 women)	19 men and 17 women	Never Current + past	1.0 1.2 $P > 0.05$	
Huang et al. (19)	1988–1998	Hospital-based (Aichi Cancer Center)	Cases: incident cases Controls: patients without cancer	950 men and 346 women without family history of lung cancer	13 775 men and 34 668 women without family history of lung cancer	Never Current	1.00 0.90 (0.78–1.05)	Age and sex
				75 men and 27 women with family history of lung cancer	741 men and 1522 women with family history of lung cancer	Never Current	1.00 0.91 (0.53–1.57)	

CI, confidence interval.
[a]Squamous cell carcinoma, large cell carcinoma, or small cell carcinoma.
[b]Adenocarcinoma or bronchiolo-alveolar cell carcinoma.

Table 3. Summary table of the association between alcohol drinking and lung cancer risk in cohort studies among Japanese population

Reference authors	Study period	Study population					Magnitude of association[a]
		Sex	Number of subjects	Age (years)	Event	Number of incident cases or deaths	
Kono et al. (11)	1965–1983	Men	5130	27–89	Death	74	–
Hirayama (12)	1966–1982	Men	122 261	40+	Death	1454	↑
		Women	142 857	40+	Death	463	↑↑↑
Masuda and Shigematsu (13)	1968–1987	Men	3616	40+	Death	43	–
Murata et al. (14)	1984–1993	Men	17 200	NA	Incidence	107	↑
Takezaki et al. (15)	1985–1999	Men and women	5885	30+	Incidence	38	–
Nakaya et al. (16)	1990–1997	Men	21 201	40–64	Incidence	119	–
Nishino et al. (17)	1988–1999	Men	28 536	40–79	Death	377	–

NA, not available.
[a]↑↑↑ or ↓↓↓, strong: ↑↑ or ↓↓, moderate: ↑ or ↓, weak; –, no association (see text for more detailed definition).

Table 4. Summary table of the association between alcohol drinking and lung cancer risk in case-control studies among Japanese population

Reference authors	Study period	Study subjects				Magnitude of association[a]
		Sex	Age (years)	Number of cases	Number of controls	
Shimizu (18)	1975–1981	Men and women	NA	101	101	↑
Huang et al. (19)	1988–1998	Men and women	18 +	1398	50 706	–

NA, not available.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition).

current alcohol consumption, regardless of smoking status in the stratified analysis. The statistical power of this analysis, however, was limited due to the small number of lung cancer deaths in most categories.

The magnitude of association for these studies is summarized in Tables 3 and 4 for cohort and case-control studies, respectively. The cohort study by Hirayama (12) demonstrated a strong positive association (↑↑↑) between alcohol drinking and the risk of female lung cancer. The author, however, stated that the clear association in women almost disappeared after adjusting for smoking. The other eight studies showed a weak positive (↑) (14,18) or no (11,13,15–17,19) association. Even in moderate to heavy drinkers who consumed more than 40 g of alcohol per day, no study found a significantly increased risk.

Some issues should be considered when examining the association of drinking habits with lung cancer risk. One is the confounding by smoking of the best-established risk factor for cancer (21). Since alcohol drinking often coexists with smoking (16,17), confounding by smoking will seemingly elevate the risk by alcohol consumption. Of all the nine studies identified, only five cohort studies (11,13,15–17) presented smoking-adjusted risks.

Diet may also be an important confounding factor (2). Because of the caloric content of alcoholic beverages, their consumption may displace other foods and nutrients from the diet, especially in heavy drinkers (16,17). Several foods and nutrients, such as vegetables, fruits, and carotenoids, potentially decrease the risk of lung cancer (1), so that the risk might be overestimated in drinkers if dietary factors are not considered. Only two studies (16,17) out of all the articles reviewed reported risk estimates allowing for dietary intakes.

Another issue concerns former drinkers (22). Patients with lung cancer may quit alcohol drinking after the development or diagnosis of the disease, which would result in an apparently higher risk in ex-drinkers. In fact, Nakaya et al. (16) and Nishino et al. (17) found a significantly increased risk among former drinkers (Table 1). If ex-drinkers are grouped into the reference category with never drinkers as in some studies (11,14), the risk for current drinkers will be underestimated. Only the studies by Nakaya et al. (16) and by Nishino and coworkers (17) explicitly reported the risk estimate for ex-drinkers. Publication bias should also be considered, but it seems to be unlikely to exist, because only one study by Nishino et al. (17) initially aimed at examining the association of alcohol drinking with lung cancer risk.

Finally, studies evaluating the effect of alcohol on lung cancer by beverage type more frequently found a positive association with beer and liquor than with wine in countries other than Japan (2,4). Because only one study (13) in our review showed the smoking-adjusted risk by beverage type and the number of lung cancer cases of this study was too small, further investigations are required to examine the separate effects of the various alcoholic drinks in Japanese populations. The role of *sake* (Japanese rice wine) in the development of lung cancer should specifically be clarified because *sake* is one of the major alcoholic beverages in Japan and is not popular in other countries.

The IARC evaluation (10) concluded that there was sufficient evidence for the carcinogenicity of acetaldehyde, the major metabolite of ethanol, in experimental animals. In addition, although experimental evidence is not conclusive, experimental studies indicate that alcohol itself does not initiate cancer but may potentiate the effect of carcinogens by a number of mechanisms, including facilitation of cellular entry of carcinogens and/or affecting their metabolism, inhibition of DNA repair, and tumor promotion (23). In the IARC evaluation (10), it was noted that ethanol enhanced the incidence of lung tumors induced in mice by *N*-nitrosodiethylamine or *N*-nitrosodi-*n*-propylamine.

In summary, epidemiologic evidence for the association of alcohol drinking with lung cancer risk in Japan still remains inconclusive due both to the number and methodological quality of the studies, although some experimental studies have supported the biological plausibility of the association. Further epidemiologic investigations should be conducted considering confounding by smoking and diet, excluding former drinkers from the reference group, and taking the type of alcoholic beverages into account.

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

From these results and based on assumed biological plausibility, we conclude that the epidemiologic evidence on the association between alcohol drinking and lung cancer risk remains insufficient among the Japanese population.

Acknowledgments

The authors gratefully acknowledge the assistance of Ms Chie Yoshida, Ms Izumi Suenega, and Mr Tomohiro Shintani. This work was supported by the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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Jpn J Clin Oncol 2006;36(12)800–807
doi:10.1093/jjco/hyl112

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

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Received May 28, 2006; accepted August 5, 2006

Background: We evaluated the association between tobacco smoking and gastric cancer risk among the Japanese population based on a systematic review of epidemiologic evidence.
Methods: Original data were collected by searches of MEDLINE using PubMed, 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: Ten cohort studies and 16 case-control studies were identified. In men, most studies reported moderate or strong positive associations between smoking and gastric cancer. In women, the positive association was weaker than in men. Of eight studies (three cohort studies and five case–case control studies), two cohort and three case control studies reported a weakly to strongly increased risk of gastric cancer. The summary relative risk for current smokers was estimated to be 1.56 (95% confidence intervals 1.36–1.80), 1.79 (1.51–2.12), 1.22 (1.07–1.38) for the total population, men and women, respectively.
Conclusion: We conclude that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer among the Japanese population.

Key words: systematic review – epidemiology – tobacco smoking – stomach cancer – Japanese

INTRODUCTION

Gastric cancer is still the most common cancer in Japan (1). Therefore, its prevention is one of the most important targets for cancer control.

The International Agency for Research on Cancer (IARC) concluded in 2002 that there was 'sufficient' evidence of causality between tobacco smoking and gastric cancer (2). This causality would have public health significance in Japan, where the smoking rate in men is one of the highest in the world. However, it may be premature to draw a conclusion about the association between tobacco smoking and gastric cancer in Japan, because the prevalence of risk factors such as *Helicobacter pylori* infection and salt intake in the Japanese differs from that in other countries. Also the Japanese have different genetic and environmental factors which might modify the association between smoking and the risk of gastric cancer from people of other countries. Therefore, it is necessary that the association between smoking and the risk of gastric cancer in the Japanese

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population is evaluated on the basis of previous Japanese epidemiologic studies. In addition, after the IARC conclusion, important findings about the association between smoking and gastric cancer from large-scale prospective studies in Japan were reported.

The aim of this study was to review epidemiological findings on the association between tobacco smoking and gastric cancer among the Japanese population. The findings are summarized and the magnitude of the effect is evaluated. This study was conducted as part of a systematic review of epidemiological evidence regarding lifestyle and cancer in the Japanese population (3).

METHODS

Original data for this review were collected by searches of MEDLINE using Pub Med, complemented by manual searches of references from relevant articles when necessary. All epidemiological studies on the association between tobacco smoking and gastric cancer incidence or mortality among Japanese from January 1966 to March 2005, including papers in press if available, were identified using the search terms 'tobacco smoking', 'gastric cancer', 'stomach cancer', 'cohort studies', 'case-control studies', 'Japan' and 'Japanese' as key words found in the abstract. 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 results were included, and incidence was given priority over mortality as an outcome measure. 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. First, the relative risks in each epidemiological study were grouped by magnitude of association with consideration to 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) 1.5–2 (SS) or (iii) 0.5–0.67 (SS); weak, either (i) 1.5–2 (NS), (ii) 0.5–0.67 (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 by the WHO/FAO Expert Consultation Group in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient' (4). We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the IARC (2). Notwithstanding the use of this quantitative assessment rule, arbitrary assessment cannot be avoided when considerable variation in the magnitude of association existed between the results of the study. The final judgment, therefore, was made based on the consensus of research group members and thus was not necessarily objective.

In addition, when we reached a conclusion that there was 'convincing' or 'probable' evidence of a positive or inverse association, a meta-analysis was conducted to obtain summary estimates of the association. In general, studies which reported relative risks and their confidence intervals (CIs) by comparing current smokers with never-smokers were included in the meta-analysis, but for those which categorized risk values separately according to smoking amount, such as the number of cigarettes smoked or pack-year index, meta-analysis was conducted to estimate summary risk values for current smokers, and these values were then used for further meta-analysis. Studies without information on CIs and different reference categories were excluded from meta-analysis. General variance-based methods were used to estimate summary statistics and their 95% CIs. Heterogeneity among studies was estimated by testing the Q statistic, with the model used to determine summary relative risk and its 95% CI, namely a random or fixed effect model, selected according to the statistical significance in the Q statistic. Meta-analysis was done using the meta command of STATA statistical package (5).

MAIN FEATURES AND COMMENTS

A total of 10 cohort studies and 16 case-control studies were identified (Table 1 and Table 2 respectively; these tables are available as supplementary data at http://jjco.oxfordjournals.org). Among the cohort studies, four presented results by gender (7,9,13,15) four for men only (6,11,12,14), and two for men and women combined (8,10). As for the case-control studies, the number of those that presented results by gender, for men only, for women only, and for men and women combined were seven (19–21,24,27,28,30) four (16,17,25,26), one (29) and four (18,22,23,31), respectively. After excluding one case-control study (20) owing to the unavailability of a point estimate or P value, two cohort (8,13) and two case-control studies (24,26) because of a shorter study analysis period than another study of the same population, and one cohort (11) and one case-control study (29) because subgroups of the same dataset as those used in another study were employed, we obtained a summary of the magnitude of association for the remaining studies in Table 3 and Table 4 for cohort studies and case-control studies, respectively.

All of six studies (6,7,9,12,14,15) presenting relative risks for gastric cancer in male current smokers reported a significant risk increase among the current smokers. The magnitude of increased risk was reported as strong by one study (9), moderate by three studies (6,12,14) and weak by two studies (7,15). The study of men and women combined (10) found a non-significantly increased risk of gastric cancer in subjects who smoked 20 cigarettes or over per day. The increased risk in women was weaker than in men; two

Table 3. Summary of the association between tobacco smoking and gastric cancer risk, cohort study

References			Study period	Study subjects					Magnitude of association
Author	Year	(Ref. No.)		Sex	No. of subjects	Ranged age	Event	Number of incident cases or deaths	
Kono S	1987	(6)	1965–1983	Men	5130	27–89	Death	116	↑↑
Hirayama T	1990	(7)	1966–1982	Men	122 261	≥40	Death	3,414	↑
				Women	142 857	≥40	Death	1,833	↑
Kato I	1992	(9)	1985–1991	Men	9753 (total)	≥40	Death	35	↑↑↑
				Women		≥30	Death	22	↑
Inoue M	1996	(10)	1985–1995	Men and women	5373	Not specified	Incidence	69	↑
Sasazuki S	2002	(12)	1990–1999	Men	19 657	40–59	Incidence	293	↑↑
Koizumi Y	2004	(14)	1984–1992	Men	9980	≥40	Incidence	228	↑↑*
			1990–1997	Men	19 412	40–64	Incidence	223	
Fujino Y	2005	(15)	1988–1999	Men	43 482	40–79	Death	522	↑
				Women	54 480	40–79	Death	235	–

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.
* The magnitude of association was evaluated on the results from a pooled analysis of two cohort studies.

Table 4. Summary of the association between tobacco smoking and gastric cancer risk, case-control study

References			Study period	Study subjects				Magnitude of association
Author	Year	(Ref. No.)		Sex	Ranged age	Number of cases	Number of controls	
Haenzel W	1976	(16)	1962–1964 (Hiroshima)	Men	Not specified	247 (Hiroshima)	494 (Hiroshima)	–
			1962–1965 (Miyagi)	Men	Not specified	279 (Miyagi)	558 (Miyagi)	–
Tajima K	1985	(17)	1981–1984	Men	40–70	59	111	↑↑
Hoshino H	1985	(18)	1979–1982	Men and women	Not specified	460	460	↑↑↑
Kono S	1988	(19)	1979–1982	Men	20–75	74	Hospital controls 1171	↑ (Hospital controls)
							Population controls 148	↑(Population controls)
				Women	20–75	65	Hospital controls 1403	– (Hospital controls)
							Population controls 130	– (Population controls)
Kato I	1990	(21)	1985–1989	Men	Not specified	289	1247	↑↑↑
				Women	Not specified	138	1767	↑
Tominaga K	1991	(22)	1971–1985	Men and women	Not specified	294 (188 men, 106 women)	588 (376 men, 212 women)	↑↑↑
Hoshiyama Y	1992	(23)	1984–1990	Men and women	Not specified	294 (206 men, 88 women)	Hospital controls 202	– (Hospital controls)
							Population controls 294	– (Population controls)
Murata M	1996	(25)	1984–1993	Men	Not specified	246	493	–
Inoue M	1999	(27)	1988–1995	Men	Not specified	651	12 041	↑↑↑
				Women	Not specified	344	31 805	↑↑
Kikuchi S	2002	(28)	1993–1995	Men	≤69	494	448	↑↑↑
				Women	≤69	224	435	↑↑↑
Minami Y	2003	(30)	1997–2001	Men	≥40	429	1222	↑↑
				Women	≥40	185	1222	–
Machida-Montani A	2004	(31)	1998–2002	Men and women	20–74 (cases)	122 (non-cardia cases only)	235	↑↑↑

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.

studies (7,9) reported a weakly increased risk and another reported no association (15).

Among eight case-control studies presenting results for men, three (21,27,28) presented strongly, two (17,30) presented moderately, and one (19) presented weakly increased risks of gastric cancer in current or ever smokers compared with never smokers. In the remaining two studies (16,25), no association was observed. Of the case-control studies with men and women combined, three (18,22,31) reported a strongly increased risk of gastric cancer, and one reported no association (23). In women, two studies (27,28) showed a strongly or moderately increased risk of gastric cancer, and *P* for trend was statistically significant in both of them. One study (21) reported a non-significant weakly increased risk in subjects smoking >20 cigarettes per day and the remaining two studies (19,30) showed no association.

The summary relative risk (RR) for current smokers estimated by meta-analysis is presented in Fig. 1. In the meta-analysis, five case-control studies (16–19,25) were excluded owing to unavailability of the CIs, one cohort study (6) because of the inclusion of ex-smokers in reference category and two case control studies (22,28) because there was no report on the RR for current smokers. For men, the RR was 1.49 (95% CI 1.37–1.62) in cohort studies, 2.20 (1.84–2.62) in case-control studies, and 1.79 (1.51–2.12) in all studies. The corresponding RR for women was 1.16 (1.01–1.34), 1.16 (0.66–2.05) and 1.22 (1.07–1.38), respectively. The result of meta-analysis for men and women combined also showed a significantly elevated summary RR for cohort, case-control and all studies.

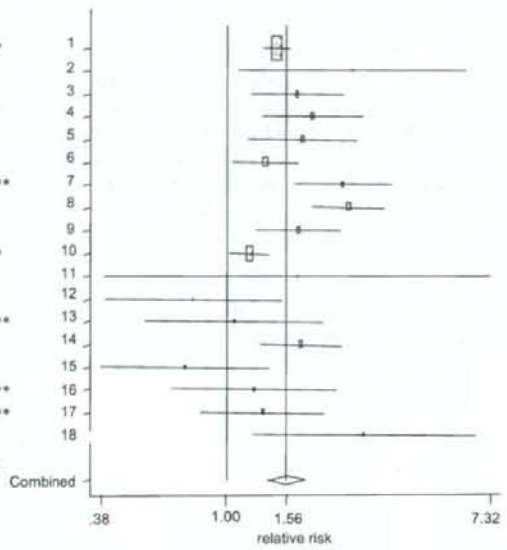
Overall, most epidemiologic studies consistently presented a statistically significant risk elevation for gastric cancer in male smokers. The results for female smokers were less consistent, five of eight epidemiologic studies showing a weakly to strongly increased risk of gastric cancer. Although the summary relative risk was elevated regardless of sex and study design, the risk was higher for case-control studies than for cohort studies and for men than for women. In case-control studies, health-conscious people might be more likely to be selected as controls especially in cases where participants in health check-ups were used as controls, and patients with gastric cancer might be more likely to report their smoking histories than controls. This selection and recall bias might lead to overestimation of the association between smoking and gastric cancer risk. One of the reasons why summary estimates of the association between tobacco smoking and gastric cancer risk for men were higher than for women was considered to be the difference in the cumulative amount of cigarettes smoked. It is not clear, however, whether there is a gender difference in susceptibility to tobacco smoking from the results of the strength of association by the stratum of amount of cigarettes smoked.

Dietary factors might be potential confounders between tobacco smoking and gastric cancer. In particular, high salt intake is an important risk factor for gastric cancer in the Japanese, who consume more salt than Westerners. Among previous studies conducted on Japanese populations, only three cohort (12,14,15) and three case-control studies (21,23,27) were adjusted for intake of salty food such as pickled vegetables or a preference for salty food. In one case-control study (23), a positive association between tobacco smoking and gastric cancer risk diminished substantially after adjustment for preference for salty foods, miso soup and pickled vegetables. However, the results of two cohort (14,15) and one case-control (21) studies were not changed substantially after multivariate-adjusted analyses. The other studies (12,27) reported only the results of multivariate-adjusted analysis, which presented a moderate to strong positive association between tobacco smoking and gastric cancer. Total consumption of salt was evaluated in only one case-control study (31). The adjusted odds ratio of gastric cancer for current smokers in this study was 2.8 (95% CI, 1.2–6.5).

In 1994, the IARC recognized *H. pylori* as a class 1 human carcinogen. *H. pylori* is an established risk factor for gastric cancer and might be one of the potential confounders between tobacco smoking and gastric cancer. No cohort study has evaluated *H. pylori* infection status and only two case-control studies (28,31) reported the odds ratio adjusted for *H. pylori* infection. A case-control study conducted in Metropolitan Tokyo (28) presented a linear association between smoking dose (cigarette–years) and the risk of stomach cancer in males and an elevated risk in 400+ cigarette–years females, even after adjustment for *H. pylori* infection. A multi-center, hospital-based case-control study in Nagano (31) reported that smoking was associated with an increased risk of non-cardia gastric cancer among both *H. pylori*-positive and -negative subjects, and that there was no statistically significant interaction between smoking and *H. pylori* infection. These studies suggested that smoking was a risk factor of gastric cancer independent of *H. pylori* infection. In addition, most studies investigating the association between *H. pylori* infection status and smoking habit in Japan presented no association (32–36) or lower prevalence of *H. pylori* infection in current smokers than in never-smokers (37,38), except for one study which reported that smoking was positively associated with *H. pylori* infection among male outpatients who underwent gastroscopy (39). Therefore, a positive association between smoking and the risk of gastric cancer is not likely to be brought about by the confounding effect of *H. pylori* infection.

Several studies (12,14,24,28,29) investigated the effect of smoking on gastric cancer according to anatomic subsites. The results of two cohort studies were not consistent. The JPHC study (12) reported an increased risk of cardia cancer and differentiated-type distal cancer for current smokers, whereas no relationship with undifferentiated-type distal cancer was found. However, a pooled analysis of two prospective studies in Miyagi (14) revealed a significantly increased risk associated with smoking only in the antrum but not in the cardia or body. A case-control study conducted

No.	Study Author	Ref.	(Year)	Sex	Design	event	Current smokers RR	(95%CI)	
1	Hirayama T	7	(1990)	M	CH	Death	1.45	(1.31- 1.60)	*
2	Kato I	9	(1992)	M	CH	Incidence	2.58	(1.09- 6.10)	
3	Sasazuki S	12	(2002)	M	CH	Incidence	1.70	(1.20- 2.40)	
4	Koizumi Y	14	(2004)	M	CH	Incidence	1.91	(1.31- 2.79)	
5	Koizumi Y	14	(2004)	M	CH	Incidence	1.76	(1.17- 2.66)	
6	Fujino Y	15	(2005)	M	CH	Death	1.33	(1.04- 1.70)	
7	Kato I	21	(1990)	M	CC		2.40	(1.67- 3.45)	**
8	Inoue M	27	(1999)	M	CC		2.50	(1.91- 3.27)	
9	Minami Y	30	(2003)	M	CC		1.71	(1.25- 2.36)	
10	Hirayama T	7	(1990)	W	CH	Death	1.18	(1.02- 1.37)	*
11	Kato I	9	(1992)	W	CH	Death	1.69	(0.39- 7.31)	
12	Fujino Y	15	(2005)	W	CH	Death	0.77	(0.39- 1.50)	
13	Kato I	21	(1990)	W	CC		1.06	(0.54- 2.08)	**
14	Inoue M	27	(1999)	W	CC		1.74	(1.28- 2.36)	
15	Minami Y	30	(2003)	W	CC		0.72	(0.38- 1.37)	
16	Inoue M	10	(1996)	MW	CH	Death	1.22	(0.65- 2.29)	**
17	Hoshiyama Y	23	(1992)	MW	CC		1.31	(0.82- 2.09)	**
18	Machida-Montani A	31	(2004)	MW	CC		2.80	(1.20- 6.50)	



Summary estimates: Men		Total	1.79 (1.51- 2.12)	(Random effect model; Test for heterogeneity: Q=23.792 with df=8, p=0.002)
		Cohort studies	1.49 (1.37- 1.62)	(Fixed effect model; Test for heterogeneity: Q=5.513 with df=5, p=0.357)
		Case-control studies	2.20 (1.84- 2.62)	(Fixed effect model; Test for heterogeneity: Q=3.501 with df=2, p=0.174)
	Women	Total	1.22 (1.07- 1.38)	(Fixed effect model; Test for heterogeneity: Q=10.126 with df=5, p=0.072)
		Cohort studies	1.16 (1.01- 1.34)	(Fixed effect model; Test for heterogeneity: Q=1.727 with df=2, p=0.422)
		Case-control studies	1.16 (0.66- 2.05)	(Random effect model; Test for heterogeneity: Q=6.738 with df=2, p=0.034)
	Total	Total	1.56 (1.36- 1.80)	(Random effect model; Test for heterogeneity: Q=50.153 with df=17, p<0.001)
		Cohort studies	1.39 (1.30- 1.50)	(Fixed effect model; Test for heterogeneity: Q=15.985 with df=9, p=0.067)
		Case-control studies	1.70 (1.31- 2.21)	(Random effect model; Test for heterogeneity: Q=21.178 with df=7, p=0.004)

RR: Relative risk, CH: cohort study, CC: case-control study, NA: not available, M: men, W: women
The boxed area represents the contribution of each study (weight) to the meta-analysis.
*95%CI of reference (7) was estimated from the RR and 90%CI given.
**RR and 95%CI of reference (10), (21), and (23) was estimated from those estimated for daily amount of smoking categories by meta-analysis.
References (16-20) and (25) were excluded from the meta-analysis since point estimate and/or confidence intervals were not available or unble to estimate from other given values.
References (8), (13), (24) and (26) was excluded from the meta-analysis due to shorter study period in the reports from the same population.
References (11) and (29) was excluded from the meta-analysis due to subgroup in the reports from the same population
Reference (6) was excluded from the meta-analysis due to the inclusion of ex-smokers in reference category.
References (22) and (28) was excluded from the meta-analysis due to no report on the RR for current smokers.

Figure 1. Summary estimates of the association between tobacco smoking and gastric cancer risk.

at Aichi Cancer Center showed that habitual smoking increased the risk of cardia cancer more prominently in men (24), and less prominently in postmenopausal women (29). Another case-control study in Metropolitan Tokyo (28) concluded that ever smokers had consistently elevated risks for all subsites of gastric cancer, but that the odds ratio for middle cancer was slightly lower than that for proximal and distal cancers. Therefore, it is not clear whether the effect of smoking differs among anatomical subsites. Also, it has been hypothesized that differentiated-type gastric cancer may be more affected by environmental factors than the undifferentiated type, and several studies (12,14,21,27,28,29) have investigated the effect of smoking on the risk of gastric cancer in relation to histologic type. However, there was no clear difference in risk pattern according to histologic subtype except for distal gastric cancer in the JPHC study (12).

A meta-analysis published in 1997 (40), including studies conducted in Japan and overseas, presented summary estimates weighted on both the number of cases and the inverse variance of risk. The results of the analysis weighted on the number of cases showed a higher summary relative risk in men (RR = 1.59) than in women (RR = 1.11) for ever smokers. The summary variance-weighted relative risk was calculated only for men because only one study provided confidence limits for women. The result was 1.44 and 1.47 for ever and current smokers, respectively. The results of large-scale cohort studies in the USA (41) and Europe (42), published after the meta-analysis in 1997, also showed cigarette smokers were at significantly higher risk of gastric cancer. The IARC evaluated the carcinogenic effects of tobacco smoking on various sites in a recent report and concluded that there is sufficient evidence of carcinogenicity in humans that smoking causes gastric cancer (2).

EVALUATION OF EVIDENCE ON TOBACCO SMOKING AND GASTRIC CANCER RISK IN JAPANESE

From these results and assumed biological plausibility, we conclude that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer among the Japanese population. As few previous studies have made sufficient adjustment for important potential confounding factors such as salt intake and *H. pylori* infection, the extent of any confounding effect is unclear. However, evidence currently available suggests that these factors are unlikely to exert a strong confounding effect.

Acknowledgments

This work was supported by the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan.

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Jpn J Clin Oncol 2006;36(9)582–597
doi:10.1093/jjco/hyl069

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

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Received April 4, 2006; accepted May 26, 2006; published online July 26, 2006

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

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

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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–controls 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 *P*)	*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Kono et al. (11)	1965–83	5130 men	Male physicians	Death	Large bowel 39	Never/past	NA	1.00	NA	Age and smoking	
						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)	Non-drinker/rare	NA	1.00		Age	90% confidence intervals were shown. Data for women were not presented. *Adjusted for age, smoking and green-yellow vegetables.
						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		
					Sigmoid colon 43 men	Non-drinker/rare	NA	1.00			
						Occasional/daily	NA	3.95 (1.98–7.86)			
						Non-daily	NA	1.00			
						Daily	NA	2.14 (1.32–3.47)*			
						Non-drinker	NA	1.00			
						Rare	NA	2.03 (0.54–7.32)			
						Occasional	NA	3.83 (1.55–17.42)			
						Daily	NA	5.42 (2.24–13.99)	<0.001		
					Type of beverage	Non-drinker	NA	1.00			
						Sake-drinker	NA	4.56 (1.63–12.19)			
						Non-drinker	NA	1.00			
						Shochu-drinker	NA	5.90 (2.00–17.42)			
						Non-drinker	NA	1.00			
						Beer-drinker	NA	12.67 (3.62–43.66)			
					Women	Non-drinker	NA	1.00			
						Drinker	NA	1.92 (1.13–3.26)			
					Rectum Men (number not described)	Non-drinker	NA	1.00	<0.05		
						Rare	NA	0.95			
						Occasional	NA	1.14			
						Daily	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					Age	90% confidence intervals were shown. *The significant trend association remained after adjustment for age and smoking.
					Men	None	NA	1.00			
						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		
Shimizu et al. (14)	1993–2000	29 051 (13 392 men, 15 659 women)	Residents in Takayama	Incidence	Colon					Age, body height, body mass index, smoking and year of education	
					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	No. of incident cases or deaths						
					41 women	Non-drinker	7	1.00			
						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		
Otani 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	Colorectum 457 men	Non-drinker	87	1.0		Age, family history of colorectal cancer, body mass index, smoking, physical exercise and area	*Among drinkers
						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		
					Rectum 148 men	Non-drinker	25	1.0			
						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		
Wakai et al. (16)	1988–97	57 736 (23 708 men, 34 028 women)	JACC study (24 areas throughout Japan)	Incidence	Colon 220 men	Non-drinker	24	1.00 (reference)		Age, area, education, family history of colorectal cancer, body mass index, smoking, walking time, sedentary work and consumptions of green leafy vegetables and beef	*Among current drinkers
						Ex-drinker	19	2.01 (1.09–3.68)			
						Current drinker	177	1.97 (1.28–3.03)			
						0.0–0.9 (go/day)	43	2.01 (1.22–3.33)			
						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*		