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

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Background: We conducted a systematic review of epidemiological evidence to evaluate the association between alcohol drinking and total cancer risk among the Japanese population.
Methods: Original data were obtained from MEDLINE searches using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility as previously evaluated by the International Agency of Research on Cancer.
Results: Of eight cohort studies identified, six studies, three of which included women, were subjected to evaluation. In men, all six studies showed a weak to moderate positive association between alcohol drinking and total cancer risk. While light drinking had little effect on total cancer risk, heavy drinking of more than 46–69 g of alcohol per day contributed to total cancer risk for most of these Japanese populations. However, no association was reported in women in any of the three studies.
Conclusion: We conclude that there is convincing evidence that alcohol drinking increases the risk of total cancer in the Japanese population, specifically among heavy drinking men.

Key words: Epidemiol-Prevention – total cancer – alcohol drinking – Japanese – systematic review

INTRODUCTION

Alcohol consumption and the proportion of heavy drinkers have been increasing for decades in Japan (1), and alcohol drinking is now recognized as an important and preventable public health problem. The frequent identification of chronic alcohol consumption as a risk for cancer suggests that public health policies should be formulated with consideration to the qualitative and, more importantly, quantitative estimation of its effects on not only specific cancers but also total cancers.

Until recently, evidence for the association between alcohol consumption and total cancer risk has been derived

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mainly from Western populations (2). However, the distribution of cancer sites, which differs between Japanese and Western populations, may influence the total magnitude of the association. In addition, types of beverages commonly consumed and genetic polymorphisms for alcohol-related enzymes among Japanese differ from those among Western populations, and it has been speculated that the magnitude of association among Japanese differs from that among other populations. Recently, a number of major large-scale cohort studies on this association in Japanese appeared almost simultaneously, to facilitate systematic review of the association.

Here, we review epidemiological studies on alcohol drinking and total cancer risk among Japanese. This report is one of a series of articles by our research group, which is investigating the association between lifestyle and the major types of cancer in Japan (3–9).

METHODS

A MEDLINE search using PubMed was conducted to identify epidemiological studies of the association between alcohol drinking and total cancer incidence or mortality among Japanese from 1965 to 2005, using the search terms 'alcohol', 'cancer', 'cohort study', 'case–control study', 'Japan' and 'Japanese' as keywords found in the abstract. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also done to identify studies written in Japanese from 1983 to 2005. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. Results for individual papers are summarized in Table 1.

Evaluation was based on the magnitude of association and the strength of evidence. First, relative risks (RRs) in each epidemiologic study were grouped by magnitude of association, with consideration of statistical significance (SS) or no statistical significance (NS) as: strong, <0.5 or >2.0 (SS); moderate, either (1) <0.5 or >2.0 (NS), (2) >1.5–2 (SS), or (3) 0.5– <0.67 (SS); weak, either (1) >1.5–2 (NS), (2) 0.5– <0.67 (NS) or (3) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (10), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation by the International Agency for Research on Cancer (IARC) (11). In cases of multiple publication of analyses of the same or overlapping datasets, only data from the largest or most updated results were included, and incidence was given priority over mortality as an outcome measure. Notwithstanding the use of this quantitative assessment rule, arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. Final judgment was therefore made on the basis of a consensus among the research group members, and was therefore not necessarily objective. Details of evaluation methods are described elsewhere (3).

MAIN FEATURES AND COMMENTS

A total of eight cohort studies (12–19) were identified (Table 1), four in men and women (14,15,17,19) and four in men only (12,13,16,18). No case–control studies of the association between alcohol drinking and total cancer risk were identified.

After excluding two studies due to fewer subjects and fewer detail categories (13) or a shorter study analysis period (16) than another study in the same population, six results for men and three for women were available for further evaluation. A summary of the magnitude of association for these studies is shown in Table 2.

In men, all six studies consistently found a positive association between alcohol drinking and total cancer risk. The associations were moderate in two and weak in four. In all studies, only heavy or frequent drinking showed a significant positive association. Statistically significant positive dose– or frequency–response relationships were observed in all recent studies which evaluated trend (17–19). In women, in contrast, all three studies reported no association (14,17,19).

To date, quantitative assessment of the magnitude of association between alcohol drinking and the risk of overall cancers has been conducted mainly in Western populations, and most studies have targeted cancer mortality rather than incidence (20–26). These studies observed a weak or moderate increase in risk of no more than 2 among the heaviest consumption category in each study (20–25) and in a meta-analysis (26), a finding reflective of the estimations in our present review of Japanese studies.

The reported risk of total cancer by alcohol drinking is a 'grand sum' of the various impacts of individual sites of cancer, some of which have a causal relationship with alcohol drinking, and some of which do not. Given this variation, any discussion of the biological mechanisms behind the association may not be meaningful. However, these associations may be the result of a condition common to alcohol consumption, namely high acetaldehyde exposure, which is considered to be carcinogenic (10). We speculate from this systematic review that a certain threshold level of alcohol consumption exists, below which no increase or decrease in the risk of cancer occurs. Although the reason for this is not clear, moderate drinking may be a marker of a healthy lifestyle, as reported in one of the studies (16). The outcome of the interplay between the favorable effects of other lifestyles and the adverse effects of alcohol may vary according to the amount of alcohol involved.

In addition, a recent study identified a difference in the impact of alcohol drinking on total cancer risk between current smokers and non-smokers, in which an

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Table 1. Summary of cohort studies of alcohol drinking and total cancer risk in Japanese populations

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Kono et al. (1986) (12)	1965–83 (19 years)	5135 men	Male Japanese Physicians	Death	381 deaths	Non-drinker	78	1.00			Follow-up by permanent address (Honseki). 1 g: 180 ml, 28 ml alcohol
						Ex-drinker	35	1.1 (0.8–1.7)			
						Occasional drinker	103	1.1 (0.8–1.5)			
						<2 g/day	83	1.2 (0.9–1.6)			
						≥2 g/day	82	1.6 (1.1–2.1)			
Kono et al. (1987) (13)	1965–83 (19 years)	5130 men 27–89 years old mean 49 years old	Male Japanese Physicians	Death	380 deaths	Non-drinker		1.00		Age, smoking.	Follow-up by permanent address (Honseki). 1 g: 180 ml, 28 ml alcohol
						Occasional drinker		1.06 (0.81–1.38)			
						<2 g/day		1.16 (0.60–14.7)			
						≥2 g/day		1.54 (1.15–2.05)			
Hirayama T. (1990) (14)	1965–82 (17 years)	122,261 men 142,857 women ≥40 years old	95% census population	Death	8794 men	Non		1.00		Age	Follow-up by death certificate, residential registry; 90% confidence interval
						Rare		0.92 (0.87–0.98)			
						Occasional		0.92 (0.88–0.97)			
						Daily		1.11 (1.05–1.16)			
						Non		1.00			
						Sake		1.09 (1.04–1.15)			
						Shochu		1.12 (1.04–1.21)			
						Beer		1.10 (1.00–1.22)			
						Whisky		1.26 (1.04–1.54)			
						Other		0.75 (0.50–1.12)			
					5946 women	Never		1.00			
						Rare		0.97 (0.91–1.05)			
						Occasional		1.07 (0.97–1.17)			
						Daily		1.07 (0.87–1.31)			
						Non		1.00			
						Sake		1.15 (0.88–1.51)			
						Shochu		1.09 (0.70–1.70)			
						Beer		0.67 (0.31–1.43)			
						Whisky		—			
						Other		1.62 (0.89–2.93)			
				Death	153 men		81	0.57 (0.32–1.03)		Age	

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Takezaki et al. (1999) (15)	1988–97 (9 years)	3541 men and 4121 women (40–79 years old)	Residential register (response rate 80%)			Never/occasional (<2 g)					Follow-up by residential register and death certificate
						<2 g/day/ occasionally larger	54	0.74 (0.41–1.37)			
						≥2 g/day	13	1.00			
					87 women		Never/	occasional (<2 g)	86	—	
<2 g/day/ occasionally larger	0	—									
≥2 g/day	0	1.00									
Tsugane et al. (1999) (16)	1990–96 (6 years)	19,231 men	Residential registry (40–59 years old)	Death	214 deaths	Non-drinker	44	1.00		Age, area, education, history of hypertension, sports at leisure time, yellow vegetables, fruit, fish, miso soup, pickled vegetables, age, area, number of cigarettes smoked per day	Follow-up by residential register and death certificate
						Occasional drinker	19	0.79 (0.44–1.44)			
						1–149 g of ethanol/ week	22	0.53 (0.29–0.94)			
						150–299 g	34	0.90 (0.56–1.45)	$P = 0.002$		
						300–449 g	44	1.48 (0.94–2.35)			
						450+ g	51	1.54 (0.98–2.42)			
						Non-smokers (never, ex-)					
						Non-drinker	23	1.00			
						Occasional drinker	13	1.12 (0.57–2.22)			
						1–149 g of ethanol/ week	8	0.41 (0.18–0.91)			
						150–299 g	10	0.54 (0.26–1.14)			
						300–449 g	10	0.82 (0.39–1.74)			
						450+ g	12	1.17 (0.58–2.36)			
						Current smokers					
						Non-drinker	20	1.10 (0.59–2.04)			
						Occasional drinker	6	0.70 (0.28–1.75)			
						1–149 g of ethanol/ week	14	1.02 (0.52–2.00)			
						150–299 g	24	1.30 (0.72–2.34)			
						300–449 g	33	2.06 (1.18–3.60)			
						450+ g	37	2.18 (1.25–3.78)			
Inoue et al. (2005) (17)	1990–2001 (10 years)	73,281 (35,007 men and 38,274 women)	Residential registry (40–59 years old)	Incidence	1904 men	Non-drinker	360	1.10 (0.90–1.34)		Age, area, pack-years of smoking, green vegetables intake,	Follow-up by residential register, death certificate and cancer registry
						Occasional drinker	138	1.00			
						1–149 g of ethanol/ week	353	1.18 (0.96–1.44)			

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Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						150–299 g	359	1.17 (0.96–1.44)	$P < 0.001$	leisure-time physical activity	
						300–449 g	339	1.43 (1.17–1.75)			
						450+ g	355	1.61 (1.32–1.97)			
						Non-smokers (never, ex-)					
						Non-drinker	78	0.90 (0.62–1.31)			
						Occasional drinker	42	1.00			
						1–149 g of ethanol/ week	75	0.87 (0.60–1.28)			
						150–299 g	54	0.86 (0.57–1.29)	$P = 0.370$		
						300–449 g	37	1.03 (0.66–1.62)			
						450+ g	30	1.02 (0.64–1.64)			
						Current smokers					
						Non-drinker	196	1.39 (1.03–1.88)			
						Occasional drinker	58	1.00			
						1–149 g of ethanol/ week	202	1.69 (1.25–2.28)			
						150–299 g	226	1.64 (1.22–2.20)	$P < 0.001$		
						300–449 g	224	1.93 (1.43–2.60)			
						450+ g	257	2.32 (1.72–3.11)			
				Death	758 men	Non-drinker	161	1.10 (0.81–1.49)			
						Occasional drinker	59	1.00			
						1–149 g of ethanol/ week	138	1.06 (0.77–1.44)			
						150–299 g	119	0.92 (0.67–1.26)	$P < 0.001$		
						300–449 g	133	1.33 (0.97–1.83)			
						450+ g	148	1.58 (1.16–2.15)			
						Non-smokers (never, ex-)					
						Non-drinker	36	0.67 (0.40–1.12)	$P = 0.634$		
						Occasional drinker	25	1.00			
						1–149 g of ethanol/ week	27	0.53 (0.31–0.92)			

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						150–299 g	19	0.49 (0.27–0.91)		
						300–449 g	7	0.33 (0.14–0.78)		
						450+ g	10	0.55 (0.26–1.16)		
						Current smokers				
						Non-drinker	81	1.43 (0.89–2.31)		
						Occasional drinker	23	1.00		
						1–149 g of ethanol/week	83	1.68 (1.04–2.69)		
						150–299 g	84	1.52 (0.94–2.44)	$P < 0.001$	
						300–449 g	99	2.15 (1.35–3.44)		
						450+ g	114	2.57 (1.62–4.09)		
				Incidence	1499 women	Non-drinker	1170	0.94 (0.80–1.11)		
						Occasional drinker	178	1.00		
						1–149 g of ethanol/week	118	0.80 (0.63–1.01)		
						150–299 g	20	0.68 (0.42–1.11)	$P = 0.659$	
						300–449 g	6	0.73 (0.32–1.66)		
						450 +	7	0.68 (0.32–1.46)		
				Death	450 women	Non-drinker	368	1.08 (0.79–1.49)		
						Occasional drinker	43	1.00		
						1–149 g of ethanol/week	28	0.79 (0.49–1.27)		
						150–299 g	6	0.54 (0.19–1.52)	$P = 0.896$	
						300–449 g	3	1.27 (0.39–4.15)		
						450+ g	2	0.68 (0.16–2.86)		
Nakaya et al. (2005) (18)	1990–97 (7 years)	21,201 men	Residential registry (40–64 years old)	Incidence	882 men	Ex-drinker	92	1.3 (1.0–1.8)		Age, smoking status, education, daily consumption of orange, other fruits, fruit juice, spinach, carrot or pumpkin, and tomato
						Never-drinker	122	1.0		
						Current drinkers, all	668	1.3 (1.0–1.5)	$P = 0.001$	
						<22.8 g of alcohol/day	158	1.1 (0.8–1.3)		
						22.8–45.5 g	175	1.3 (1.0–1.7)		
						45.6+ g	335	1.3 (1.1–1.7)		
Lin et al. (2005) (19)	1988–99 (10 years)	97,432 (42,072 men and 55,360 women)	JACC study (45 areas throughout Japan, 40–79 years old)	Death	2418 men	Never-drinker	498	1.00		Age, BMI, education, smoking, exercise, history of diabetes and hypertension
						Ex-drinker	253	1.50 (1.29–1.75)		
						Current drinker				
						0.1–22.9 g	251	0.82 (0.70–0.95)		

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Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						23.0–45.9 g	422	0.96 (0.84–1.10)	$P = 0.001$		
						46.0–68.9 g	351	1.05 (0.91–1.20)			
						69.0+ g	185	1.31 (1.10–1.56)			
					1363 women	Never-drinker	1054	1.00			
						Ex-drinker	30	1.21 (0.83–1.74)			
						Current drinker					
						0.1–22.9 g	119	1.03 (0.85–1.25)	$P = 0.53$		
						23.0–45.9 g	26	1.20 (0.81–1.77)			
						46.0+ g	6	1.04 (0.46–2.33)			

increased risk associated with alcohol was seen only among current smokers (17). In that report, alcohol intake was associated with a decreased risk of both cancer incidence and mortality in male non-smokers. These findings suggest the existence of interaction of smoking and drinking in the risk of cancer. Cytochrome P450 2E1 (CYP2E1), the expression of which is induced by alcohol, metabolizes procarcinogens present in tobacco smoke and food such as *N*-nitroso compounds (27) and catalyzes the conversion of alcohol to acetaldehyde. Animal experiments suggest that carcinogens in tobacco smoke are metabolized more slowly in drinkers (27,28). While epidemiological evidence is limited, these findings from experimental studies support the biological plausibility of this interaction, which may contribute to both the incidence and mortality of overall cancer risk.

Further, approximately half of all Japanese have been found to have a phenotype deficient for aldehyde dehydrogenase-2, a key enzyme for the conversion of acetaldehyde to acetate (29), which results in higher levels of acetaldehyde exposure. To our knowledge, no studies have investigated the impact of alcohol drinking on total cancer risk among those deficient in aldehyde dehydrogenese, although some evidence has been reported for a difference in impact on alcohol-related cancers such as esophageal cancer by polymorphism of aldehyde dehydrogenese (30,31). On this basis, we speculate that the fraction of cancer risk attributable to alcohol drinking might be greater among Japanese than non-mongoloid populations. This deficiency in the key enzyme for alcohol metabolism indicates the need for caution in interpreting the results for non-drinkers. In addition, care is probably also required when non-drinker categories include ex-drinkers, since some of these subjects are unable to drink due to a diagnosis of cancer, resulting in risk inflation in this category.

The confounding factors used for adjustment differ among studies. Most early studies adjusted age only. In the recent prospective studies, however, the association of alcohol drinking and total cancer risk has been adjusted by tobacco smoking at least. These studies also included any or all of vegetable and fruit intake, body mass index, physical activity and a history of diabetes as confounders, but the results have indicated that the effect of these factors may be small compared with that of smoking.

The present study identified a difference in the magnitude of risk between men and women. Only three of eight cohort studies evaluated risk in women, and no clear association was observed. We speculate that this was because of the low number of regular/heavy women drinkers in whom risk could be assessed, rather than any sex difference in disease susceptibility.

Finally, our systematic review confirms a positive association between alcohol drinking and total cancer risk.

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Table 2. Summary of cohort studies of the association between alcohol drinking and total cancer risk

Reference	Study period	Study population					Magnitude of association*
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths	
Kono et al. (1986) (12)	1965–1983	Men	5135	27–89	Death	381	↑↑
Hirayama T. (1990) (14)	1965–1982	Men	122,261	40 +	Death	8794	↑
		Women	142,857	40 +	Death	5946	—
Takezaki et al. (1999) (15)	1988–1997	Men	7662	40–79	Death	240	↑
Inoue et al. (2005) (17)	1990–2001	Men	35,007	40–59	Incidence	1904	↑↑
		Women	38,274	40–59	Incidence	1499	—
Nakaya et al. (2005) (18)	1990–1997	Men	21,201	40–64	Incidence	882	↑
Lin et al. (2005) (19)	1988–1999	Men	42,072	40–79	Death	2418	↑
		Women	55,630	40–79	Death	1363	—

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

Because the studies included in this review used different alcohol consumption categories, however, meta-analysis for quantitative assessment could not be conducted. A meta-analysis of Japanese populations using common alcohol consumption categories, which is now on-going, will likely provide further clues to the quantitative contribution of alcohol drinking to total cancer risk.

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

From these results, and on the basis of assumed biological plausibility, we conclude that there is convincing evidence that alcohol drinking increases the risk of total cancer in the Japanese population, specifically among heavy drinking men. The clear implication of this conclusion is that the total burden of cancer in the Japanese population can be reduced by the avoidance of heavy alcohol drinking.

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Conflict of interest statement

None declared.

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