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

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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.

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Conflict of interest statement

None declared.

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

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Background: We reviewed epidemiological studies on alcohol drinking and breast cancer among the Japanese population. This report is one among a series of articles by our research group evaluating the existing evidence concerning the association between health-related lifestyles and cancer.
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 for Research on Cancer.
Results: Three cohort studies and eight case-control studies were identified. There were inconsistent results regarding alcohol drinking and breast cancer risk among cohort studies. A significant positive association was observed in one, but another showed nonsignificant inverse association. Out of the eight case-control studies, two studies showed a significantly increased risk among women who drink daily and who had higher intake of alcohol, respectively. Experimental studies have supported the biological plausibility of a positive association between alcohol drinking and breast cancer risk.
Conclusion: We conclude that epidemiologic evidence on the association between alcohol drinking and breast 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 – breast cancer – Japanese

INTRODUCTION

Many epidemiologic studies have identified chronic alcohol consumption as a risk factor for breast cancer. Previous meta-analyses have shown a positive association between alcohol intake and breast cancer (1–9). However, most of the component studies have been conducted among western populations. We reviewed epidemiological studies on alcohol drinking and breast cancer among the Japanese population. This report is one among a series of articles by our research group, investigating the associations between lifestyles and major types of cancer in Japan.

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METHODS

A MEDLINE search was conducted to identify epidemiological studies on the association between alcohol drinking and breast cancer incidence or mortality among Japanese from 1980 to 2006. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also done to identify the studies written in Japanese from 1983 to 2006. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included.

Individual results were summarized in the tables separately by study design as cohort or case-control studies. Relative risks (RRs) or odds ratios (ORs) in each epidemiologic 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 to <0.67 (SS); weak, either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (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 from the International Agency for Research on Cancer (IARC) (11). 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, and incidence was given priority over mortality as an outcome measure. Details on the evaluation methods are described elsewhere (12).

MAIN FEATURES AND COMMENTS

We identified three cohort studies (13–15) and eight case-control studies (16–23). Tables 1 and 2 give details of the component studies including age range, study period, numbers of women enrolled, RR or OR of breast cancer for alcohol drinking and covariates used in adjustment. Studies that presented separate estimates of RR or OR were subdivided by drinking status, frequency of alcohol drinking, alcohol consumption, type of alcohol, or/and menopausal status.

Summaries of the magnitudes of association for these studies are shown in Tables 3 and 4.

There was an inconsistency of results among the cohort studies. A significantly increased risk was observed in women with high intake of alcohol (≥15 g/day) in one study (15). Decreased risk among daily drinkers was reported in one of the remaining cohort studies, although this association was not statistically significant (13).

Among case-control studies, a significantly increased risk among daily drinkers (OR = 1.35) as compared with others was reported in the study by Kato et al. (16). A significantly increased risk (OR = 2.03) was observed among pre-menopausal women with high intake of alcohol (1 go/day) (1 go is about 23 g of alcohol) as compared with non-drinkers in the study by Hirose et al. (20). These two studies were conducted in the same institute, but the study time was not overlapped. A significantly decreased risk was reported in one study (17). The other studies found no significant associations between breast cancer risk and any of variables related to alcohol drinking.

Unlike the previous reviews of studies, the evidence for the link between alcohol drinking and breast cancer risk was weak in the present reviews of Japanese studies. However, considering the modest strength of the association between alcohol drinking and breast cancer, reports of no significant association are not surprising. The result from a recent meta-analysis including 98 studies involving 75 728 cases revealed that excess risk associated with drinking was 22% for studies judged high quality (10). Two case-control studies (19,21) in the present review reported higher risk estimates for drinkers as compared non-drinkers, although the associations were not statistically significant. The meta-analysis also showed that the risk of breast cancer increased by 10% for each additional 10 g per day intake of alcohol. Lack of information concerning alcohol consumption in most of the studies in the present review precluded us from evaluating the dose–response relationship. It also makes it difficult to estimate the average amount of alcohol. Japanese female drinkers may consume less alcohol than female drinkers in other countries previously studied, which may have lead to the lack of significant association. In fact, the percentage of heavy drinkers seems very low in Japanese women. In a cohort study reported by Lin et al., the percentage of women who had 15 g or more of alcohol per day was 2.7% (15). The percentage of women who had 1 go or more per day was 1.4% in a case-control study reported by Hirose et al. (20). However, the corresponding figures were 12.4 and 6.2%, respectively, in the previous review of 53 studies in the world (8). We also referred to general population data from other sources. According to the Japan Public Health Center-based Prospective Study in Japan, the percentage of women who had 150 g or more of alcohol per week was 2.6% (24). In the third National Health and Nutrition Examination Survey (25) in the USA, the percentages of light (0.1–6.4 g/day), moderate (6.5–25.9 g/day) and heavy (≥26 g/day) drinkers were 27.0, 12.9 and 2.8%, respectively. It is also possible that infrequent drinkers or ex-drinkers may have reported that they were non-drinkers. Such a bias may have led to underestimation of the association.

Our previous review of Japanese studies regarding smoking and breast cancer suggested that smoking possibly increases the risk of breast cancer among Japanese women (26). Therefore, there is a potential for smoking confounding the results of the association between alcohol drinking and breast cancer. Three studies (15,17,23) provided the

Table 1. Alcohol drinking and breast cancer risk, cohort study in Japanese population

References Author	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths					
Hirayama (13)	1966–1982	142 857	Census-based 6 prefectures	Death	241	None	NA	1.00		Adjusted for: age
						Rare	NA	0.97 (0.68–1.38)		
						Occasional	NA	0.87 (0.53–1.44)		
						Daily	NA	0.35 (0.06–1.84)		
						Sake	NA	0.69 (0.12–3.90)		
Goodman et al. (14)	1979–1987	22 200	Atomic bomb survivors	Incidence	161	Never drinker	106	1.00		Adjusted for: city, age, age at the time of the bomings, and radiation dose to the breast
			Tumor registry at the RERF			Drinker	40	0.91 (0.63–1.31)		
						Beer	14	0.63 (0.36–1.10)		
						Sake	9	0.81 (0.41–1.60)		
						Other	9	1.24 (0.63–2.46)		
						ml/week				
						<22	5	0.71 (0.29–1.73)		
						25–54	9	0.89 (0.45–1.76)		
						≥55	7	0.68 (0.32–1.46)	0.27	
Lin et al. (15)	1988–1997	35 844	JACC study (24 areas throughout Japan)	Incidence	151	Non drinkers	103	1.00		Adjusted for: age, BMI, study area, family history of breast cancer, walking, use of hormone, age at menarche, age at first birth, age at menopause, and number of births
						Ex-drinkers	3	0.82 (0.20–3.33)		
						Current drinkers	45	1.27 (0.87–1.84)		
						0.1–4.9(g/day)	13	1.07 (0.57–2.00)		
						5.0–14.9	5	0.83 (0.34–2.04)		
						≥15.0	11	2.93 (1.55–5.54)	0.01	
						Current drinkers				
						Age started				
						<25	3	1.02 (0.32–3.24)		
						25–35	5	0.93 (0.34–2.25)		
						>35	17	1.33 (0.78–2.28)		

BMI, body mass index; RERF, the Radiation Reseach Foundation; JACC, the the Japan Collaborative Cohort.

Table 2. Alcohol drinking and breast cancer risk, case-control study in Japanese population

References Author	Study time	Study subjects				Category	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
Kato et al. (16)	1980–1986	Hospital-based (Achi Cancer Registry)	Cases: histologically confirmed cases;	1740	8920	Less	1.00		Adjusted for: age, smoking, marital status, residence, occupation, and family history of breast cancer
						Daily	1.35 (1.01–1.08)		
			Controls: hospital controls						
						<50 years			
						None	1.00		
						Daily	1.10 (0.76–1.60)		
						Sake: None	1.00		
						Sake: Current	0.78 (0.46–1.33)		
						Beer: None	1.00		
						Beer: Current	1.34 (1.00–1.79)		
						Whisky: None	1.00		
						Whisky: Current	0.99 (0.50–1.92)		
						≥50 years			
						None	1.00		
						Daily	1.80 (1.21–2.67)		
						Sake: None	1.00		
						Sake: Current	0.80 (0.49–1.30)		
						Beer: None	1.00		
						Beer: Current	1.56 (1.08–2.24)		
						Whisky: None	1.00		
						Whisky: Current	1.22 (0.33–4.47)		
Kikuchi et al. (17)	1988–1989	Hospital-based (2 hospitals)	Cases: histologically confirmed cases;	49	49	No	1.00		Matched (1:1) for: age (±3 years)
						Current	0.20 (0.06–0.63)		
			Controls: hospital controls and participants in breast cancer screening						
Kato et al. (18)	1990–1991	Hospital-based (10 large hospitals in 8 perfectures)	Cases: histologically confirmed cases;	908	908	None	1.00		Matched (1:1) for: age (±3 years) and hospital
						Occasional	0.99 (0.80–1.22)		
						Daily	0.97 (0.71–1.33)	0.64	
			Controls: hospital controls without hormone-related cancers						
Wakai et al. (19)	1990–1991	Hospital-based (Cancer Institute Tokyo)	Cases: histologically confirmed cases;	300	900	No	1.00		Matched (1:1) for: age
						Current	1.04 (0.77–1.39)		
			Controls: patiens without breast cancer	168 pre-menopausal	472 pre-menopausal	No	1.00		Adjusted for: menopausal status, weight, height, lactation and no.of births.
						Current	1.36 (0.92–2.00)		
				127 post-menopausal	390 post-menopausal	No	1.00		
						Current	0.71 (0.42–1.19)		

Continued

Table 2. *Continued*

References Author	Study time	Study subjects				Category	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
Hirose et al. (20)	1988–1992	Hospital-based	Cases: histologically confirmed cases;	1186	23 163				Adjusted for:age and first-visit year
				607 pre-menopausal	15 084 pre-menopausal	Non-drinker	1.00		
		Controls: First-visit outpatients without history of cancer				Drinker	1.04 (0.87–1.25)		
						Occasional	0.89 (0.72–1.10)		
						≤1 go/day*	1.18 (0.88–1.59)		
						>1 go/day	2.03 (1.36–3.03)		
				445 post-menopausal	6215 post-menopausal	Non-drinker	1.00		
						Drinker	0.88 (0.67–1.15)		
						Occasional	0.92 (0.67–1.26)		
						≤1 go/day	0.73 (0.43–1.24)		
						>1 go/day	1.26 (0.58–2.77)		
Hu et al. (21)	1989–1993	Hospital-based (Gihoku General Hospital)	Cases: histologically confirmed cases;	157	369	Never	1.00		Matched for: age and residential area
						Ex- or current	1.34 (0.80–2.24)		
			Controls: participamts in breast cancer screening						
Uegi et al. (22)	1990–1997	Tsukuba Univ. Hospital,Tsukuba Medical Center Hospital	Cases: histologically confirmed cases;	145	240	No drinking	1.00		Matched for: age and residence
						1–6 times/ month	0.70 (0.34–1.45)		
		Community controls	Controls: no history of breast cancer			7+ times/month	0.89 (0.49–1.62)	0.49	Adjusted for: family history of breast cancer, education, menopausal status, age at menarche, parity, and age at primiparity
				65 pre-menopausal	96 pre-menopausal	No drinking	1.00		
						1–6 times/month	0.94 (0.32–2.72)		
						7+ times/month	1.02 (0.42–2.48)	0.78	
				54 post-menopausal	89 post-menopausal	No drinking	1.00		
						1–6 times/month	0.48 (0.14–1.69)		
						7+ times/month	0.84 (0.30–2.36)	0.47	
Tung et al. (23)	1990–1995	Hospital-based (Osaka Medical Center for Cancer and Cardiovascular disease)	Cases: histologically confirmed cases;	376	430	Non-drinker	1.00		Adjusted for: age, age at menarche,age at first delivery, weight, height, smoking, and education
						Ex-drinker	0.42 (0.19–0.95)		
			Controls: patiens without diagnosis of cancer			Drinker	0.86 (0.61–1.22)		
				190 pre-menopausal	119 pre-menopausal	Non-drinker	1.00		
						Ex-drinker	1.09 (0.22–5.36)		
						Drinker	0.73 (0.41–1.25)		
				186 post-menopausal	282 post-menopausal	Non-drinker	1.00		
						Ex-drinker	0.43 (0.15–1.26)		
						Drinker	1.14 (0.68–1.88)		

*1 go of sake contains about 23 g of ethanol.

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

References			Study period	Study population					Strength of association*
Author	Year	(Ref. No.)		Sex	Number of subjects	Ranged age	Event	Number of incident cases or deaths	
Hirayama	1990	(13)	1966–1982	Women	142 857	≥40 years	Death	241	↓↓
Goodman et al.	1997	(14)	1979–1987	Women	22 200	Not specified	Incidence	161	—
Lin et al.	2005	(15)	1988–1997	Women	35 844	40–79 years	Incidence	151	↑↑↑

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

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

References			Study period	Study subjects				Strength of association*
Author	Year	(Ref. No.)		Sex	Ranged age	Number of cases	Number of controls	
Kato	1989	(16)	1980–1986	Women	Not specified	1740	8920	↑
Kikuchi	1990	(17)	1988–1989	Women	30 years or over	49	49	↓↓↓
Kato	1992	(18)	1990–1991	Women	20 years or over	908	908	—
Wakai	1994	(19)	1990–1991	Women	20 years or over	300	900	—
						168 pre-menopausal	472 pre-menopausal	—
						127 post-menopausal	390 post-menopausal	—
Hirose	1995	(20)	1988–1992	Women	18 years or over	607 pre-menopausal	15 084 pre-menopausal	↑↑↑
						445 post-menopausal	6215 post-menopausal	—
Hu	1997	(21)	1989–1993	Women	25 years or over	157	369	—
Uegi	1998	(22)	1990–1997	Women	26–69 years	145	240	—
						65 pre-menopausal	96 pre-menopausal	—
						54 post-menopausal	89 post-menopausal	—
Tung	1999	(23)	1990–1995	Women	Cases (mean = 51.6)	376	430	—
					Controls (mean = 54.5)	190 pre-menopausal	119 pre-menopausal	—
						186 post-menopausal	282 post-menopausal	—

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

risk estimates after adjusting for smoking. The authors did not observe a confounding effect of smoking. Most of the other studies stated that information on smoking was obtained. It is unlikely that the observed lack of association in these studies is due to the confounding effects of smoking.

Results from experimental studies in animals have shown that ethanol intake can cause mammary tumor genesis (11). Several potential mechanisms have been also provided for potential indirect effects of alcohol, such as perturbation of estrogen metabolism and response, as well as by an effect on one carbon metabolism pathway, through reduced folic acid intake and use (27). Thus, it is biologically plausible that alcohol drinking is related to breast cancer.

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

From these results, we conclude that epidemiologic evidence on the association between alcohol drinking and breast cancer risk remains insufficient in terms of both the number and methodological quality of studies among the Japanese population. Based on epidemiologic studies in the world and assumed biological plausibility, some evaluations conclude that alcohol drinking increases the risk of breast cancer. Therefore, more epidemiologic studies with large samples, including sufficient number of drinkers and with more accurate methods for estimating alcohol intake, are needed in

Japan to clarify the risk associated with alcohol drinking and to identify the high risk group.

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Appendix

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Conflict of interest statement

None declared.

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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

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	

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)			