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Public Health Reports

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

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Although alcohol drinking is considered as an important risk factor for esophageal cancer, the magnitude of the association might be varied among geographic areas. Therefore, we reviewed epidemiologic studies on the association between alcohol drinking and esophageal cancer among the Japanese population. Original data were obtained from MEDLINE, searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient') and the magnitude of association ('strong', 'moderate', 'weak' or 'no association'), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer. We identified four cohort studies and nine case–control studies. All cohort studies and case–control studies showed strong positive associations between esophageal cancer and alcohol drinking. All cohort studies and six case–control studies showed that alcohol drinking had the dose- or frequency-response relationships with esophageal cancer. In addition, four case–control studies showed that acetaldehyde dehydrogenase Glu504Lys polymorphism had strong effect modification with alcohol drinking. We conclude that there is convincing evidence that alcohol drinking increases the risk of esophageal cancer in the Japanese population.

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

INTRODUCTION

The association between alcohol drinking and the risk of esophageal cancer has been consistently reported from all over the world. In the most recent evaluation by the International Agency for Research on Cancer (IARC), ethanol in alcoholic beverages are evaluated as Group 1: carcinogenic to humans (1,2). In the second report published by the World Cancer Research Fund and the American Institute for Cancer Research, the panel judged that alcoholic drinks are convincing cause of esophageal cancer (3). Thus, alcohol drinking was a well-established risk factor for esophageal cancer. IARC referred to acetaldehyde, an oxidative

metabolite of ethanol, as a potential causative agent behind alcohol-induced carcinogenesis based on evidence about interaction between alcohol consumption and acetaldehyde dehydrogenase (ALDH2) enzyme gene polymorphisms for the risk (2,4).

On the other hand, the risk of esophageal cancer might be varied among geographic areas and clustered in specific areas such as 'Esophageal cancer belt' (5). The types of beverages commonly consumed among Japanese differ from those among other populations. Other difference is histology of esophageal cancer. Most of the esophageal cancer cases are squamous cell carcinoma among the Japanese in contrast to adenocarcinoma among Western population (6–9). In addition, ethnicity is another cause of difference. The sensitivity to alcohol might differ between each ethnicity because the distribution of genetic polymorphisms was different. For example, *ALDH2* Glu504Lys polymorphism affects the metabolism of acetaldehyde. Those with *ALDH2* Lys allele show a high concentration of blood acetaldehyde after alcohol drinking due to the low catalytic activity of ALDH2 enzyme. Therefore, the magnitude of the association between alcohol drinking and esophageal cancer among the Japanese population might differ from the other regions.

We review epidemiological studies on alcohol drinking and esophageal cancer risk among the Japanese. This report is one of a series of articles by our research group (10–23), which is investigating the association between lifestyle and the major types of cancer in Japan.

PATIENTS AND METHODS

The details of the evaluation method have been described elsewhere (10). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi* (*Japana Centra Revuo Medicina*) databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between alcohol drinking and esophageal cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichusi* database) to January 2010, including papers in press if available, were identified using the following as keywords: alcohol, esophagus, esophageal cancer, cohort, follow-up, case–control, Japan and Japanese. 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 as cohort or case–control studies. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included, and incidence was also given priority in a single publication describing both incidence and mortality.

The evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS) or no association (symbol -), 0.67–1.5 (NS). When the multiple RRs were shown in the single study, we considered the largest RR. Criteria for the magnitude of association are summarized in Table 1. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (24), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. In brief, the following criteria were used (10): convincing: evidence based on a substantial number between exposure and disease, with little or no evidence to the contrary, with a biologically plausible association. Probable: evidence based on epidemiologic studies showing fairly consistent associations, but with perceived shortcomings in the available evidence or some evidence to the contrary that precludes a more definite judgment. Possible: evidence based mainly on findings from case–control and cross-sectional studies, requiring more studies to support the tentative associations, which should also be biologically plausible. Insufficient: evidence based on findings of a few studies that are suggestive, but insufficient to establish an association, requiring more well-designed research to support the tentative associations. We assumed that biological plausibility corresponded to the judgment of the recent evaluation from the IARC (2). The final judgment is made based on the consensus of research group members.

In addition, when there was 'convincing' or 'probable' evidence of a positive or inverse association, meta-analysis was conducted to obtain summary estimates of the association. In general, studies that reported RRs and their confidence intervals (CIs) by comparing ever drinkers with never or non-drinkers were included in the

Table 1. Evaluation of the magnitude of association in the present report

Magnitude of association	Definition	Statistical significance	Symbol
Strong	RR < 0.5 or RR > 2.0	SS	↑↑↑ or ↓↓↓
Moderate	RR < 0.5 or RR>2.0	NS	↑↑ or ↓↓
	1.5 < RR ≤ 2.0	SS	
	0.5 ≤ RR < 0.67	SS	
Weak	1.5 < RR ≤ 2.0	NS	↑ or ↓
	0.5 ≤ RR < 0.67	NS	
	0.67 ≤ RR ≤ 1.5	SS	
No association	0.67 ≤ RR ≤ 1.5	NS	-

RR, relative risk; SS, statistically significant; NS, not statistically significant.

meta-analysis. In case the subject study reported RRs separately according to multiple drinking status or levels, we estimated summary RR for ever drinkers relative to never drinkers by meta-analysis within the study and the study-specific summary RR was included in the final 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 examined by testing the Q statistic (25), with the model used to determine summary RR and its 95% CI, namely a random or fixed effect model, selected according to the SS in the Q statistic. Publication bias was assessed by using funnel plot and Egger's test (26). Meta-analysis was done using the 'metan' and 'metabias' command of STATA statistical package version 10 (Stata Corp LP, College Station, TX, USA).

MAIN FEATURES AND COMMENTS

After excluding one cohort study (27) and one case–control study (28) due to the analysis of the overlapping data sets, we identified four cohort studies (29–32) (Table 2) and nine case–control studies (4,33–40) (Table 3). Of those cohort studies, one (29) presented the results by sex and three (30–32) presented the results for men only. Among case–control studies, one (33) presented the results by sex, three (4,38,40) for men and women combined, three (34–36) for men only and two (37,39) for women only.

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 4 and 5, respectively. All studies showed a strong association between alcohol drinking and esophageal cancer. Moreover, the dose- or frequency-response relationships between alcohol drinking and esophageal cancer risk were shown in all cohort studies (29–32) and six case–control studies (4,34–37,40).

Additionally, two cohort studies (29,30) and one case–control study (34) investigated the type of alcoholic beverages and calculated the odds ratio (OR) for esophageal cancer by each beverage. However, the differences between the types of alcoholic beverages were not obvious. Four case–control studies (4,36,37,40) evaluated the OR for esophageal cancer by *ALDH2* Glu504Lys genotype. Subjects with *ALDH2* Glu/Lys genotype showed significantly higher ORs than those with *ALDH2* Glu/Glu genotype in these case–control studies. Facial flushing after alcohol consumption has been hypothesized for potential risk factor for esophageal cancer, because facial flushing has been considered as surrogate for *ALDH2* Glu504Lys polymorphisms (37,41–43). However, recent prospective study and large scale case–control study showed its limitation for the purpose (32,40).

Lastly, we conducted a meta-analysis to clarify the magnitude of alcohol drinking among Japanese (Fig. 1). One study was excluded because of the different reference category (4). Random effect model was selected for the meta-analysis because heterogeneity tested for Q statistics was significant ($Q = 53.90$, $P < 0.001$). Egger's test to evaluate publication bias was not significant ($P = 0.713$). Ever drinkers had significantly higher summary RR than never drinkers (RR 3.30, 95% CI 2.30–4.74). Although smoking often confounds with alcohol drinking, smoking was not adjusted in several studies. We conducted the meta-analysis only among the studies adjusted for smoking by using random effect model (32,33,39,40). After excluding eight studies without adjustment for smoking, summary RR was 3.36 (95% CI, 1.66–6.78) and heterogeneity was significant ($Q = 17.36$, $P = 0.001$).

There were several potential limitations in the Japanese studies reviewed here. One methodological issue was assessment of drinking status. Information on alcohol consumption was investigated by questionnaire in all cohort and case–control studies. However, the definition and categorization of drinking dose and frequency were different between studies. In addition, it is necessary to consider the misclassification. These might attenuate the association between alcohol drinking and esophageal cancer risk. In contrast, recall bias might intensify the association. In spite of the methodological issues, we observed strong association and clear dose- or frequency-response relationship between alcohol drinking and esophageal cancer risk.

Another methodological issue was *ALDH2* Glu504Lys polymorphism. *ALDH2* Lys allele is prevalent in Japanese, while the frequency is very rare in Caucasians. This polymorphism would cause large individual difference for esophageal cancer risk by modification of acetaldehyde metabolism as well as drinking behavior (44,45). Although *ALDH2* Glu504Lys polymorphism was investigated in some case–control studies, no cohort study has examined the polymorphism. Therefore, *ALDH2* Glu504Lys polymorphism should be considered on the esophageal cancer studies hereafter.

Lastly, the meta-analysis showed that ever drinkers had a significantly higher risk for esophageal cancer than never drinkers. Because of the different alcohol consumption categories, we could not see the dose- or frequency-response relationships. The heterogeneity across studies is likely to be due to the different alcohol exposure levels by characteristics of subjects in each study, such as birth cohort, age, sex and base-population. Therefore, a pooled analysis using common alcohol consumption categories is warranted.

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

From these results, and on the bases of assumed biological plausibility, we conclude that there is convincing evidence that alcohol drinking increases the risk of esophageal cancer in Japanese population.

Table 2. Alcohol drinking and esophageal cancer risk, cohort studies among Japanese population

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
Hirayama (29)	1965–1981 (17 years)	122 261 men, 142 857 women ≥40 years old	Population-based Kagoshima Okayama Hyogo Osaka Aichi Miyagi	Death	438 men	Alcohol drinking[a]			Not described	Age	Follow-up by death certificates and residential registry CIs were 90%
						Non-drinker	NA	1.0			
						Rare	NA	0.85 (0.61–1.19)			
						Occasional	NA	1.12 (0.87–1.46)			
						Daily	NA	2.30 (1.84–2.87)			
						Type of alcoholic beverage					
						Non-drinker	NA	1.0			
						Sake	NA	2.32 (1.81–2.97)			
						Shochu	NA	3.11 (2.38–4.08)			
						Beer	NA	2.31 (1.53–3.48)			
						Whisky	NA	4.10 (2.28–7.37)			
						Other	NA	2.00 (0.54–7.37)			
					147 women	Alcohol drinking[a]			Not described		
						Non-drinker	NA	1.0			
						Rare	NA	0.82 (0.50–1.35)			
						Occasional	NA	1.04 (0.58–1.89)			
						Daily	NA	2.41 (1.04–5.57)			
						Type of alcoholic beverage					
						Non-drinker	NA	1.0			
						Sake	NA	2.84 (0.98–8.23)			
						Shochu	NA	4.23 (1.13–15.8)			
						Beer	NA	9.29 (3.14–27.45)			
						Whisky	NA	NA			

						Other	NA	NA			
Sakata et al. (30)	1988–1999 (12 years)	46 465 men 40–79 years	Population-based 45 areas in Japan JACC study	Death	100 men	Alcohol intake status			Not described	Age and centers	One unit contains about 22 g of alcohol
						Non-drinker	9	1.0			
						Ex-drinker	8	2.43 (0.91–6.47)			
						Drinker	83	2.40 (1.20–4.80)			
						Alcohol units consumed per day[a]			$P = 0.028$		
						Non-drinker	9	1.0			
						<1.0 units/day	2	1.47 (0.28–7.68)			
						1.0–1.9	16	1.58 (0.65–3.86)			
						2.0–2.9	31	3.74 (1.62–8.66)			
						≥3.0	18	6.39 (2.54–16.12)			
						Years of alcohol drinking			$P = 0.100$		
						Non-drinker	9	1.0			
						≤25.0 years	14	1.71 (0.64–4.60)			
						25.1–35.0 years	19	3.23 (1.32–7.92)			
						35.1–45.0 years	18	3.23 (1.33–7.81)			
						≥45.1	7	2.77 (0.85–9.03)			
						Cumulative amount of alcohol intake			$P = 0.089$		
						Non-drinker	9	1.0			
						1–29.9 unit-year	4	0.68 (0.19–2.42)			
						30–39.9 unit-year	6	2.31 (0.75–7.06)			
						≥40.0 unit-year	46	3.80 (1.70–8.46)			
						Type of alcohol			Not described		
						Non-drinker	9	1.0			
						Sake	48	2.72 (1.22–6.08)			
						Shochu	15	3.40 (1.33–8.68)			
						Beer	17	1.42 (0.58–3.52)			
						Whisky	9	2.60 (0.91–7.41)			
						Wine	6	6.24 (1.53–25.37)			
Ishikawa et al. (31)	Cohort 1 1984–1992	Cohort 1: 9008 men 40 years or older	Population-based Miyagi Pref.	Incidence	Cohort 1: 38 cases	Cohort 1					

Continued

Table 2. *Continued*

References	Study period	Study population				Category	Number among cases	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis, sex, age	Source of subjects	Event followed	Number of incident cases or deaths						
						Never	2	1.0	$P = 0.017$	Adjusted for age, alcohol drinking, green tea, coffee and black tea	
						Former	6	2.31 (0.68–7.83)			
	Cohort 2 1990–1997	Cohort 2: 17 715 men 40–64 years				Daily	11	2.70 (1.20–6.06)			
					Cohort 2	Cohort 2					
					40 cases	Never	2	1.0	$P = 0.007$		
						Former	6	0.54 (0.06–4.04)			
						Daily	11	2.77 (1.26–6.09)			
						Pooled 1 and 2[a]					
						Never	2	1.0	$P = 0.0002$		
						Former	6	1.55 (0.58–4.14)			
						Daily	11	2.73 (1.55–4.81)			
Ishiguro et al. (32)	Cohort 1 1990–2004	Cohort 1 + 2, 60 876 men	Population-based JPHC study	Incidence	Cohort 1 + 2 215 cases	Alcohol consumption[a]					
						Non-drinker	24	1.0	$P = 0.001$ among drinkers	Adjusted for age at baseline, area, BMI, hot foods/ drink preference, smoking status and flushing	
	Cohort 2	40 years or older				Occasional	5	0.60 (0.21–1.75)			
	1993–2004					<149 g ethanol/w	41	1.64 (0.96–2.78)			
						150–299	55	2.59 (1.57–4.29)			
						300+	90	4.64 (2.88–7.48)			

NA, not available, CI, confidence interval; BMI, body mass index.
[a]Categories from which the magnitude of association was judged.

Table 3. Alcohol drinking and esophageal cancer risk, case–control studies among Japanese population

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Sasaki et al. (33)	1974–1979	Hospital-based (three major hospitals in Nagoya and two in Wakayama)	Case: those admitted in subject hospitals	201 (Nagoya: male 91, female 28, Wakayama: male 54, female 28) (age not described)	403 (Nagoya: male 170, female 57, Wakayama: male 115, female 61) (age not described)	Sake drinking in evenings[a]		Not described	Matched for age, sex, hospital and time of admission. Adjusted for smoking	
			Controls: non-digestive tract cancer patients in the same hospitals			Nagoya (male)				
						No	1.0			
						Yes	2.1 (1.2–3.6)			
						Nagoya (female)				
						No	1.0			
						Yes	NA			
						Wakayama (male)				
						No	1.0			
						Yes	3.1 (1.4–6.6)			
						Wakayama (female)				
						No	1.0			
						Yes	NA			
Hanaoka et al. (34)	1989–1991	Hospital-based (seven hospitals Keio Univ., Iwate Medical College, Chiba Univ., Natl Shikoku Cancer Ctr, Aichi Cancer Ctr, Tokyo Women's Medical College)	Cases: males admitted to hospitals as histologically confirmed primary esophageal cancer age under 85	141 (age not described) (hospital not described) (male only)	141 (age not described) (hospital not described) (90 with malignant neoplasms, 51 with benign diseases) (male only)	Freq. of alcohol drinking[a]		$P = 0.0001$	Matched for age, sex and prefecture of residence	

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
			Controls: males admitted to same hospitals with diseases other than lung cancer, laryngeal cancer, hepatocellular carcinoma, pulmonary emphysema, chronic pancreatitis			Non-drinker	1.0			
						≤2 g/week	1.15 (0.34–3.83)		Conditional logistic model was used	
						3–4 g/week	3.10 (1.02–9.43)			
						Everyday	6.59 (2.51–17.35)			
						Alcohol consumption		$P = 0.0001$		
						≤53 g/week	1.0		Conditional logistic model was used	
						>53 g/week	2.19 (0.92–5.18)			
						>242 g/week	5.17 (2.13–12.55)			
						> 414 g/week	5.86 (2.42–14.17)			
						Type of alcoholic beverage (drinker only)				
						Beer	1.0	Not described		

						Whiskey	1.08 (0.38–3.12)		Adjusted for
						Sake	1.17 (0.46–2.96)		freq. of drinking
						Shochu	3.02 (0.99–9.19)		
Takezaki et al. (35)	1988–1997	Hospital-based (Aichi Cancer Center Hospital)	Cases: males visited to the hospital as having esophageal cancer	346 (age 40–79) (male only)	11 936 (age 40–79) (male only)	Drinking status		Not described	Not matched	
			Controls: visited to the hospital but not having any cancer			Almost never	1.0		Adjusted for age, season of visit, drinking and raw vegetable consumption
						Former	4.4 (2.5–7.9)		
						Current	4.4 (2.9–6.7)		One drink equates to 180 ml Japanese sake equivalent
						Dose of alcohol consumption[a] (current drinkers) almost never	1.0		
						<1.5 drinks/day	1.8 (1.1–2.9)		
						≥1.5 drinks/day	8.5 (5.6–13.1)		
						(former drinkers)			
						almost never	1.0		
						<1.5 drinks/day	3.0 (1.3–7.0)		
						≥1.5 drinks/day	6.9 (3.4–14.0)		
						Years after quitting			
						almost never	1.0		
						1–9 years	5.1 (2.6–10.0)		
						≥10 years	3.5 (1.4–9.1)		
Matsuo et al. (44)	1999–2000	Hospital-based (Aichi Cancer Center Hospital)	Cases: mixture of prevalent cases and incident cases of histologically confirmed esophageal cancer	102 (age 40–76) (male 86, female 16)	241 (age 39–69) (male 118, female 123)	Drinking status[a]			Not matched	Heavy drinking: more than two drinks + ≥5 times/group/week

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
			Controls: non-cancer subjects who visited gastroenterology clinics for gastroscopy			Non-heavy	1.0	Not described	Adjusted for age, sex and smoking	
						Heavy	13.5 (6.94–26.5)			
Yokoyama et al. (36)	2000–2001	Hospital-based (National Cancer Ctr, National Cancer Ctr East, Kawasaki Municipal hospital, National Osaka Hospital	Cases: hisotologically confirmed esophageal cancer cases within 3 years from registration (male)	234 (age 40–79) (all male)	634 (age 40–79) (all male)	Alcohol drinking[a]		Not described	Not matched	ORs for drinking not described
			Controls: cancer free males visited two Tokyo clinics for annual health check-up			Never/rare	1.0		Not adjusted	ORs were calculated from table in the original article
						Light	3.90 (1.41–13.3)			
						Moderate	17.1 (6.76–55.1)			Never/rare: <1 unit/week, light:1–8.9 units/week, moderate:9–17.9 units/week, heavy: ≥18 units/week, 1 unit: 22 g ethanol
						Heavy	39.0 (15.2–126.0)			
						Ex-drinker	10.2 (3.64–28.2)			

Takagi et al. (39)	1990–1999	Hospital-based (Hospitalized at Osaka Med. Ctr. for Cancer and Cardiovascular Disease)	Case: hospitalized and self-administered questionnaire limited to female Control: those selected from list of hospitalized patients who did not have cancer, benign tumor, cardiovascular disease and alcoholic liver diseases	34 female (age mean: 63.4)	178 female (age mean:53.1)	Drinking status[a]		Not described	Adjusted for smoking, hot food preference and frequency of tooth brushing	
						Never	1.0			
						Ever	3.0 (1.2–7.5)			
Yokoyama et al. (37)	2000–2004	Hospital-based (National Cancer Ctr, National Cancer Ctr East, Kawasaki Municipal hospital, National Osaka Hospital	Cases: hisotologically confirmed esophageal squamous cell carcinoma within 3 years from registration (female)	52 (age 40–79) (all female)	412 (age 40–79) (all female)	Alcohol drinking[a]		Not described	Not matched	Never/rare: <1 unit/week, light 1–8.9 units/week, moderate:9–17.9 units/week, heavy: ≥18 units/week, 1 unit 22 g ethanol
			Controls: cancer free males visited two Tokyo clinics for annual health check-up			Never/rare	1.0		Adjusted for age	
						Light	1.81 (0.81–4.05)			
						Moderate	3.97 (1.40–11.26)			
						Heavy	15.35 (4.85–48.62)			
						Ex-drinker	4.58 (1.25–16.79)			
						Strong alcohol beverage		$P = 0.012$		

Continued

Table 3. *Continued*

References	Study period	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Never	1.00			
						Sometimes	2.58 (0.80–8.33)			
						Frequently	12.47 (0.97–160.1)			
Akiyama et al. (38)	1997–2008	Hospital-based (Yokohama City University Hospital)	Cases: diagnosed as having esophageal squamous cell carcinoma Controls: patients who had undergone endoscopies as part of a health checkup	253 (age 38–86) (male 225, female 28)	253 (age 38–86) (male 225, female 28)	Regular drinking habit[a]	3.228 (2.028–5.138)	$P<0.0001$	Age/sex group matched	The detail of regular drinking habit was not described
Oze et al. (40)	2001–2005	Hospital-based (Aichi Cancer Center Hospital)	Cases: histologically confirmed esophageal cancer cases	265 (age 33–79) (male 235, female 30)	530 (36–78) (male 470, female 60)	Alcohol consumption[a]		Not described	Age/sex matched Adjusted for smoking, *ALDH2* genotype fruit and vegetable intake, hot beverage intake and body mass index Adjusted for facial flushing, smoking, fruit and vegetable intake, hot beverage intake and body mass index	Moderate drinker: ≤4 days/week High-moderate drinker: <46 g ethanol and ≥5 days/week Heavy drinker: ≥46 g ethanol and ≥5 days/week

Controls: non-cancer first-visit outpatients at the same hospital	Non-drinker	1.0
	Moderate drinker	5.95 (2.56–13.80)
	High-moderate drinker	24.84 (10.29–59.95)
	Heavy drinker	95.98 (37.38–246.44)
	Alcohol consumption	
	Non-drinker	1.0
	Moderate drinker	2.34 (1.08–5.08)
	High-moderate drinker	7.75 (3.64–16.50)
	Heavy drinker	27.12 (12.38–59.43)

NA, not available; ALDH2, aldehyde dehydrogenase-2; OR, odds ratio.
[a]Categories from which the magnitude of association was judged.

Table 4. Summary of the association between alcohol drinking and esophageal cancer risk, cohort study

References	Study period	Study population						Magnitude of association
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths	Category	
Hirayama (29)	1965–1981	Men	122 261	≥40	Death	438	Daily drinking	↑↑↑
		Women	142 857	≥40	Death	147	Daily drinking	↑↑↑
Sakata et al. (30)	1988–1999	Men	46 465	40–79	Death	100	Drinking status	↑↑↑
							Units/day	↑↑↑
							Years of drinking	↑↑↑
							Cum units/year	↑↑↑
Ishikawa et al. (31)	Cohort 1							
	1984–1992	Men	9008	≥40	Incidence	38	Daily drinking	↑↑↑
	Cohort 2							
	1990–1997	Men	17 715	40–64	Incidence	40	Daily drinking	↑↑↑
Ishiguro et al. (32)	Cohort 1	Men	60 876	40–69	Incidence	215	Drinking status	↑↑↑
	1993–2004						Ethanol/week	↑↑↑
	Cohort 2							
	1995–2004							

↑↑↑, strong positive association.

Table 5. Summary of the association between alcohol drinking and esophageal cancer risk, case–control study

References	Study period	Study subjects					Magnitude of association
		Sex	Age range (years)	Number of cases	Number of controls	Category	
Sasaki et al. (33)	1974–1979	Men	Not specified	145	285	Sake drink in	↑↑↑
		Women	Not specified	56	118	evenings	NA
Hanaoka et al. (34)	1989–1991	Men	Not specified	141	141	Freq. of alcohol drinking	↑↑↑
Takezaki et al. (35)	1988–1997	Men	40–79	346	11 936	Drinking status	↑↑↑
						Dose of alcohol consumption	
Matsuo et al. (44)	1999–2000	Men and women	40–76	102	241	Drinking status	↑↑↑
				(M: 86, F: 16)	(M: 118, F: 123)		
Yokoyama et al. (41)	2000–2001	Men	40–79	234	634	Drinking status	↑↑↑
Takagi et al. (39)	1990–1999	Women	17–87	34	178	Drinking status	↑↑↑
Yokoyama et al. (42)	2000–2004	Women	40–79	52	412	Drinking status	↑↑↑
Akiyama et al. (38)	1997–2008	Men and women	38–86	253	253	Drinking status	↑↑↑
				(M: 225, F: 28)	(M: 225, F: 28)		
Oze et al. (40)	2001–2005	Men and women	33–79	265	530	Dose of alcohol consumption	↑↑↑

↑↑↑, strong positive association; NA, not available.

ID	Author	Reference	Year	Design	Sex	Ever drinkers RR	95% CI
1	Hirayama T	29	1990	Cohort	M	1.23	0.76 – 1.99
2	Sakata K et al.	30	2005	Cohort	M	3.00	1.51 – 0.59
3	Ishikawa A et al.	31	2006	Cohort	M	2.37	1.45 – 3.87
4	Ishiguro S et al.	32	2009	Cohort	M	2.06	1.05 – 4.07
5	Sasaki R et al.	33	1990	Case-control	M	2.39	1.51 – 3.78
6	Hanaoka T et al.	34	1994	Case-control	M	3.03	1.13 – 8.10
7	Takezaki T et al.	35	2000	Case-control	M	4.40	3.15 – 6.15
8	Yokoyama A et al.	36	2002	Case-control	M	12.96	5.05 – 33.25
9	Takagi A et al.	39	2003	Case-control	F	3.00	1.20 – 7.50
10	Yokoyama A et al.	37	2006	Case-control	F	4.48	1.80 – 11.18
11	Akiyama T et al.	38	2009	Case-control	M F	3.23	2.03 – 5.14
12	Oze I et al.	40	2010	Case-control	M F	7.80	5.00 – 12.17
	Summary estimates (random effect model)				total	3.30	2.30 – 4.74
	(test for heterogeneity: Q=53.90 with df=11, p<0.001)						

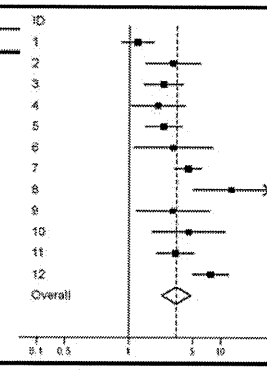

Figure 1. Summary estimates of the association between alcohol drinking and esophageal cancer risk. RR, relative risk; M, male; F, female. The boxed area represents the contribution of each study (weight) to the meta-analysis.

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Conflict of interest statement

None declared.

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Appendix

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Original Article

Body Mass Index and Mortality From All Causes and Major Causes in Japanese: Results of a Pooled Analysis of 7 Large-Scale Cohort Studies

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ABSTRACT

Background: We pooled data from 7 ongoing cohorts in Japan involving 353 422 adults (162 092 men and 191 330 women) to quantify the effect of body mass index (BMI) on total and cause-specific (cancer, heart disease, and cerebrovascular disease) mortality and identify optimal BMI ranges for middle-aged and elderly Japanese.

Methods: During a mean follow-up of 12.5 years, 41 260 deaths occurred. The Cox proportional hazards model was used to estimate hazard ratios (HRs) for each BMI category, after controlling for age, area of residence, smoking, drinking, history of hypertension, diabetes, and physical activity in each study. A random-effects model was used to obtain summary measures.

Results: A reverse-J pattern was seen for all-cause and cancer mortality (elevated risk only for high BMI in women) and a U- or J-shaped association was seen for heart disease and cerebrovascular disease mortality. For total mortality, as compared with a BMI of 23 to 25, the HR was 1.78 for 14 to 19, 1.27 for 19 to 21, 1.11 for 21 to 23, and 1.36 for 30 to 40 in men, and 1.61 for 14 to 19, 1.17 for 19 to 21, 1.08 for 27 to 30, and 1.37 for 30 to 40 in women. High BMI (≥27) accounted for 0.9% and 1.5% of total mortality in men and women, respectively.

Conclusions: The lowest risk of total mortality and mortality from major causes of disease was observed for a BMI of 21 to 27 kg/m^2 in middle-aged and elderly Japanese.

Key words: body mass index; mortality; cancer; heart disease; cerebrovascular disease

INTRODUCTION

Obesity is responsible for a serious health burden because of its association with type 2 diabetes mellitus, cardiovascular diseases, and some types of cancer.[1] As a measure of relative body weight, body mass index (BMI) is an easy-to-obtain, acceptable proxy for thinness and fatness, and has been found to be directly related to health risks and death rates in many populations. According to the World Health Organization (WHO), the currently recommended BMI cut-off points for overweight and obesity are 25 kg/m^2 or greater and 30 kg/m^2 or greater, respectively.

Although these criteria were intended for international use, debate has centered on using the same cut-off points for Asian populations because of the high prevalence in those populations of type 2 diabetes mellitus and cardiovascular

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disease risk factors in individuals with a BMI less than 25 kg/m^2, as well as differences in the relationships between BMI, body fat percentage, and body fat distribution.[2] In 2002, a WHO expert consultation addressed this issue and concluded that there were no clear cut-off points for overweight and obesity in Asians. Based on international classifications, the consultation defined a BMI cut-off point of 23 kg/m^2 or greater as "increased risk" and a cut-off point of greater than 27.5 kg/m^2 as "high risk".[3] However, in a recent, large pooled analysis of more than 1.1 million Asians, different patterns of association were observed between East Asians (Chinese, Japanese, and Koreans) and other Asians (Indians and Bangladeshis).[4] Among East Asians, the lowest risk of death was seen among those with a BMI of 22.6 to 27.5, and the risk was elevated among those with a BMI higher or lower than that range. In the cohorts comprising Indians and Bangladeshis, the risk of death was increased for a BMI of 20.0 or less as compared with those with a BMI of 22.6 to 25.0, and there was no increase in risk associated with a high BMI. Considering the variation just within Asia, country-specific BMI cut-off points should be developed for public health interventions.

To date, many prospective cohort studies have evaluated the association between BMI and mortality in the Japanese population[5–10]; some showed a U-shaped[7,9] or reverse J-shaped association,[10] but others did not.[5,6,8] These studies defined BMI categories differently and controlled for different confounding variables. In the present study, we pooled 7 cohort studies in Japan to clarify the role of relative body weight on total mortality and major causes of mortality (cancer, heart disease, and cerebrovascular disease) in the Japanese population. In the present analysis of more than 350 000 subjects we also aimed to identify an optimal BMI range for middle-aged and elderly Japanese.

METHODS

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer and mortality in Japanese. Topics for the pooled analysis were determined on the basis of discussions among all authors and were evaluated with respect to their scientific and public health importance.[11,12] To maintain the quality and comparability of data, we established a priori inclusion criteria: namely, population-based cohort studies that (1) were conducted in Japan and started in the mid-1980s to mid-1990s, (2) included more than 30 000 participants, (3) obtained information on BMI calculated by height and weight reported in a validated questionnaire at baseline, and (4) collected any cause of mortality during the follow-up period. Seven ongoing studies that met these criteria were identified: the Japan Public Health Center-based Prospective Study, Cohort I (JPHC-I)[13]; the Japan Public Health Center-Based Prospective Study, Cohort II (JPHC-II)[13]; the Japan Collaborative Cohort Study (JACC)[14]; the Miyagi Cohort Study (MIYAGI)[15]; the Ohsaki National Health Insurance Cohort Study (OHSAKI)[16]; the Three-Prefecture Aichi (3-pref AICHI)[17]; and the Takayama Study (TAKAYAMA).[18] When analyzing individual results of each study, subjects with a previous history of any cancer, stroke, or myocardial infarction or with missing or implausible data (BMI <14 or ≥40) on BMI were excluded. Table 1 profiles the studies included in the analyses. Each study was approved by the appropriate institutional review board.

Follow-up and outcome ascertainment

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; JACC, 1988–1990; MIYAGI, 1990; OHSAKI, 1994; 3-pref AICHI, 1985; TAKAYAMA, 1992) to the last date of follow-up for any cause of mortality (JPHC-I, 2005; JPHC-II, 2005; JACC, 2006; MIYAGI, 2004 [2001 for cause-specific mortality]; OHSAKI, 2006; 3-pref AICHI, 2000; TAKAYAMA, 1999) in each study. Residence status, including survival, was confirmed through the residential registry.

Information on cause of death was obtained from death certificates provided by the Ministry of Health, Labour and Welfare with the permission of the Ministry of Internal Affairs and Communications. Cause of death was defined according to the International Classification of Disease, 10th version (ICD-10).[19] Resident and death registration are required by law in Japan. The outcome of the present study was defined as all-cause mortality, including the 3 major causes of death among Japanese, specifically, cancer (ICD-10: C00–C97), heart disease (ICD-10: I20–I52), and cerebrovascular disease (ICD-10: I60–I69).

BMI assessment

Body weight and height were self-reported in the baseline questionnaire conducted at each study. BMI was calculated as weight divided by the square of the height (kg/m^2). It was then divided into 7 categories using cut-off points that were identical among the studies, that is, 14 to 18.9, 19 to 20.9, 21 to 22.9, 23 to 24.9 (reference), 25 to 26.9, 27 to 29.9, and 30 to 39.9 kg/m^2. The cut-off points were derived from a US study (<21, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ≥30.0 kg/m^2) that enrolled a reasonably large number of subjects and carefully accounted for methodologic problems.[20] Due to the large number of lean people, individuals with a BMI less than 21 kg/m^2 were subdivided into 2 groups in the present analysis: 14.0 to 18.9 kg/m^2 and 19 to 20.9 kg/m^2. This decision was based on our observation in the JPHC study that both BMI extremes are important determinants of total mortality[9] and cancer occurrence and mortality.[21]

Statistical analysis

Time at risk was calculated as the duration from the date of the baseline survey in each study until the date of death or end of follow-up, whichever came first. In each study, sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated for all-cause and cause-specific (cancer, heart disease, cerebrovascular disease, and other) mortality for each BMI category using the Cox proportional hazards model. Each study performed 2 types of adjustment for estimation of HRs: age (years, continuous) and area (JPHC-I, JPHC-II, and JACC only) (HR1). Further multivariate adjustments were conducted by including covariates in the model that were either known or suspected confounding factors, ie, cigarette smoking (for men: never smoker, past smoker, current smoker of 1 to 19 cigarettes/day or ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), alcohol drinking (nondrinkers [never- and ex-drinker], occasional drinkers [less than once per week], regular drinkers [almost daily for OHSAKI and 3-pref AICHI; ≥5 days/week for JPHCI, JPHCII, and JACC; ≥5 times/week for MIYAGI; and ≥4 to 6 days/week for TAKAYAMA]), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (less than almost daily, almost daily) (HR2). All included studies were population-based, and blood data were available for only a part of 1 study. We therefore used self-reported past history of diseases to control for hypertension and diabetes. We conducted an additional analysis that excluded deaths within 5 years from both the numerator and denominator (HR3).[22,23] For men, we conducted stratified analysis by smoking status, namely, of never smokers and current smokers. An indicator term for missing data was created for each covariate.[24] SAS (version 9.1; SAS Institute, Cary, NC, USA) and Stata (version 11; Stata Corporation, College Station, TX, USA) statistical software were used for these analyses.

A random-effects model was used to obtain summary measures of the HRs from the individual studies for each category. The study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. These values from the individual studies were then combined using a random-effects model. The impact of heterogeneity was measured by using the I^2 statistic, which describes the proportion of total variation in study estimates that is due to heterogeneity. Although there is no universal rule to define mild, moderate, or severe heterogeneity, it is reasonable to assume that a value less than 30% represents mild heterogeneity and that a value greater than 50% represents substantial heterogeneity.[25] Stata software was used for the meta-analysis.

In addition, to express the impact of BMI on the risk of mortality, the population-attributable fraction (PAF) was estimated and expressed as a percentage.[26] Using HR2 and prevalence in each category, we calculated the PAF attributable to high BMI (≥27 kg/m^2 for men and women), assuming subjects in these BMI categories moved to the reference category (23–25 kg/m^2). The reference category was based on the BMI range in which total mortality was lowest for men and women, respectively. We applied this reference category to all end points, and when the HR was less than 1.0, the PAF was calculated as a minus value. This occurred in only 1 category: the PAF of cancer due to a BMI of 27 to 30 kg/m^2 in men was −0.10%, and together with the PAF due to a BMI of 30 to 40 (0.29%), the PAF of cancer due to high BMI (≥27 kg/m^2) was 0.2%.

RESULTS

The present study included 353 422 adults (162 092 men and 191 330 women) from 7 ongoing large-scale, population-based, prospective studies in Japan (Table 1). During 4 399 108 person-years of follow-up (mean 12.5 years/person), 41 260 deaths were identified (25 944 men and 15 316 women), including 15 690 deaths from cancer (10 115 men and 5575 women), 5940 deaths from heart disease (3378 men and 2562 women), 5071 deaths from cerebrovascular disease (2820 men and 2251 women), and 14 451 deaths from other causes (8950 men and 5501 women). The baseline characteristics of the study subjects by BMI category have been previously published.[4,5,7,8,20,26–28]

Table 2 summarizes the results of pooled analyses of BMI and mortality in men. When the model was fully adjusted for confounding variables (HR2), a reverse J-shaped association was observed for mortality from all causes, cancer, and other causes. Regarding these outcomes, a statistically significant increased risk was observed for all 3 categories among individuals with a BMI less than 23. As compared with a BMI range of 23 to 25 kg/m^2, the HRs for BMI ranges 14 to 19, 19 to 21, and 21 to 23 kg/m^2 were 1.78, 1.27, and 1.11 for all-cause death, 1.44, 1.23, and 1.10 for cancer death, and 2.15, 1.42, and 1.17 for other-cause death, respectively. The HR continued to decrease even for a BMI greater than 25 kg/m^2, and the BMI range 25 to 27 kg/m^2 seemed to be the lowest risk group for these outcomes. Increased risk among individuals with a high BMI was limited to those with a BMI of 30 to 40 kg/m^2 (obesity); the HR was 1.36 for all-cause death (statistically significant), 1.20 for cancer death (not statistically significant), and 1.29 for other-cause death (not statistically significant).

For heart disease and cerebrovascular disease, a U-shaped or J-shaped association was observed. A statistically significant increased risk was observed for both the high and low BMI ranges. The HR was similar or slightly higher for a high BMI; the HRs for a BMI of 14 to 19, 19 to 21, and 30 to 40 kg/m^2 were 1.45, 1.11, and 1.71 for heart disease and 1.53, 1.28, and 1.64 for cerebrovascular disease, respectively.

When subjects who died in the first 5 years of follow-up were excluded, most results were attenuated, but still significant (HR3). Through this process, the I^2 for the lowest