Original Article

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 life-styles 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.

Keywords: systematic review − epidemiology − alcohol drinking − breast cancer − Japanese

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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.

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.

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)		

Hirose et al. (20)	1988–1992	Hospital-based	Cases: histologically confirmed cases;	1186 607 pre-menopausal	23 163 15 084 pre-menopausal	Non-drinker	1.00		Adjusted for:age and first-visit year
			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 Ex- or current	1.00 1.34 (0.80–2.24)		Matched for: age and residential area
			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 1–6 times/ month	1.00 0.70 (0.34–1.45)		Matched for: age and residence
		Community controls	Controls: no history of breast cancer	65 pre-menopausal	96 pre-menopausal	7+ times/month No drinking	0.89 (0.49–1.62) 1.00	0.49	Adjusted for: family history of breast cancer, education, menopausal status, age at menarche, parity, and age at primiparity
						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).

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 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.

Acknowledgments

Appendix

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Conflict of interest statement
None declared.

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