Table 2. *Continued*

References	Study period	Study subjects				Category	Odds ratio (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
						Early				
						Never drinker	1.48 (0.88–2.49)	0.22		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0 + ml/day	0.88 (0.38–2.05)			
						Advanced				
						Never drinker	2.48 (1.42–4.33)	<0.01		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0 + ml/day	1.54 (0.68–3.44)			
						Proximal				
						Never drinker	1.50 (0.70–3.21)	0.21		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0 + ml/day	0.43 (0.10–2.05)			
						Middle				
						Never drinker	2.07 (1.22–3.53)	0.02		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0 + ml/day	1.34 (0.64–2.84)			
						Distal				
						Never drinker	1.69 (0.85–3.35)	0.28		
						Occasional and 0.1–134.9 ml/day	1.0			
						135.0 + ml/day	1.78 (0.67–4.71)			

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

References	Study period	Study subjects					Magnitude of association
Author		Sex	No. of subjects	Age (years)	Event	Number of incident cases or deaths	
Kono et al. (18)	1965–1983	Men	5130	27–89	Death	116	–
Ubukata et al. (19)	1961–1985	Men	14 229	NA	Incidence	225	†
Hirayama et al. (20)	1966–1982	Men	12 261	≥40	Death	3414	–
		Women	142 857	≥40	Death	1833	–
Kato et al. (21)	1985–1991	Men	9753	≥40	Death	35	†† †
		Women		≥30	Death	22	–
Masuda and Shigematsu (22)	1968–1987	Men	NA	≥40	Death	97	–
Murata et al. (23)	1984–1993	Men	17 200	NA	Incidence	246	–
Inoue et al. (24)	1985–1995	Men and women	5373	NA	Incidence	69	–
Sasazuki et al. (25)	1990–1999	Men	19 657	40–59	Incidence	293	–
Fujino et al. (26)	1988–1997	Men	18 746	≥18 in 1949	Death	261	–
		Women	26 184	≥18 in 1949	Death	118	–
Nakaya et al. (27)	1990–1997	Men	21 201	40–64	Incidence	247	–
Sauvaget et al. (28)	1980–1999	Men and women	38 576	34–98	Incidence	1270	–

–, no association; †, weak positive association; † † †, strong positive association.
Nested within the subjects.

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

References	Study period	Study subjects				Magnitude of association
Author		Sex	Age (years)	Number of cases	Number of controls	
Hoshino et al. (29)	1980–1982	Men	20–84	460	460	–
Tajima and Tominaga (30)	1981–1984	Men	40–70	59	111	–
Kono et al. (31)	1979–1982	Men and Women	20–75	139	274 (in hospital)	–
					278 (in general population)	–
Kato et al. (32)	1985–1989	Men	NA	289	1247	–
		Women	NA	138	1767	–
Tominaga et al. (33)	1971–1985	Men and women	NA	294	588	–
Kikuchi et al. (34)	1988–1990	Men and women	−40	42	42	–
Hoshiyama and Sasaba (35)	1984–1990	Men and women	NA	294	202 (in hospital)	–
					294 (in general population)	–
Iwasaki et al. (36)	1980–1986	Men	NA	83	83	–
Hirohata et al. (37)	1984–1986	Men and women	−70	150	150	–
Inoue et al. (38)	1988–1991	Men	NA	420	420	–
		Women	NA	248	248	–
Kikuchi et al. (39)	1993–1995	Men	20–69	494	448	–
		Women	20–69	224	435	–

significant. Another case–control study also presented the results by subsite, and drinking dose showed a stronger association with middle gastric cancer than with other subsites in men and women (39). Three studies reported no clear difference in risk pattern according to histologic subtype (intestinal and diffuse type) (25,32,39).

There were several methodological concerns in the Japanese studies reviewed here. First, assessment of drinking status was not detailed. Few studies assessed drinking status with validated questionnaires (25,27,28) in cohort studies. Therefore, it is necessary to consider the possible misclassification of drinking dose or frequency that would attenuate the association between alcohol drinking and gastric cancer risk. Moreover, early studies reviewed here did not differentiate between never and past drinkers. It is important to evaluate the risk of gastric cancer in past drinkers, because past drinkers could include those who gave up drinking due to ill health. Some recent studies have investigated the association with gastric cancer by distinguishing between past and never drinkers (24,26–28,34,35,38). Compared with never drinkers, two studies reported an increased risk of gastric cancer in past drinkers (24,38). In addition, the types of alcoholic beverages consumed among Japanese differ from those consumed by other populations, but this was considered in only two studies (22,31).

Second, few studies reported an adjusted risk of gastric cancer by important possible confounding factors. Although *H. pylori* is an established risk factor for gastric cancer (40), only one case–control study reported the OR adjusted for *H. pylori* infection (39). If alcohol drinking is related to *H. pylori* infection status, it could confound the association between alcohol drinking and gastric cancer. However, a cross-sectional study among Japanese men showed that alcohol drinking was not associated with *H. pylori* IgG antibody seropositivity (41). Thus, *H. pylori* infection status may not confound the association between alcohol drinking and gastric cancer risk. In fact, one case–control study presented the association between alcohol drinking and gastric cancer after adjustment for *H. pylori* infection and smoking status (39), and the magnitude of the association was similar to that in studies without adjustment for *H. pylori* infection status. Compared with never drinkers, the OR in the highest category of drinking dose (pure alcohol intake/day multiplied by years of drinking) was 1.40 (0.85–2.31) in men and 0.75 (0.43–1.30) in women. In the evaluation from the IARC, confounding by *H. pylori* infection was not considered as a major concern, because an association was seen in areas where the majority of the population had been infected by *H. pylori* (2).

Smoking is a potential confounder. Our previous review of Japanese studies regarding smoking and gastric cancer concluded that there is convincing evidence that tobacco smoking moderately increases the risk of gastric cancer (14). Since alcohol drinking is often related to smoking, confounding by smoking could elevate the risk of alcohol drinking. Of all the 22 studies reviewed, seven cohort studies (18,19,21–23,25,27) and three case–control studies (35,36,39) reported their results after adjustment for, or stratification by, smoking status.

Dietary factors are also potential confounders to be considered. Especially, it is important to consider salt intake, and fruit and vegetable consumption, which potentially increase and decrease gastric cancer risk (3), respectively. Two cohort studies reported their results after adjustment for consumption of fruit and vegetables (25,27), and one cohort study reported its results after adjustment for consumption of salty foods (25).

Third, misclassification of cardia cancer could occur because, until recently in Japan, the upper third of the stomach was called the cardia based on the guidelines for gastric cancer classification (42). This misclassification might have attenuated any positive association between alcohol drinking and cardia cancer if there is a causal relationship between alcohol drinking and cardia cancer, as suggested by several case–control studies among Western populations (3).

In experimental animals, the IARC evaluated the carcinogenic effect of ethanol on various sites including the forestomach, and concluded that there is sufficient evidence of carcinogenicity (1,2). However, epidemiologic findings on the association between alcohol drinking and gastric cancer among the Japanese population are inconclusive due to the quality of the methodology employed. Further, well designed epidemiologic studies are needed to provide a more detailed assessment of alcohol drinking, possible important confounding factors and anatomical subsites of gastric cancer.

Evaluation of Evidence on Alcohol Drinking and Gastric Cancer Risk in Japanese

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

Funding

Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement
None declared.

APPENDIX

Research group members: Shoichiro Tsugane (principal investigator), Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (until 2006), Norie Kurahashi (since 2007), Taichi Shimazu (since 2007) (National Cancer Center, Tokyo); Ichiro Tsuji (since 2004), Yoshitaka Tsubono (in 2003) (Tohoku University, Sendai); Yoshikazu Nishino (Miyagi Cancer Research Institute, Natori, Miyagi);

Kenji Wakai (Nagoya University, Nagoya); Keitaro Matsuo (since 2006) (Aichi Cancer Center, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (International Medical Center of Japan, Tokyo); Keitaro Tanaka (Saga University, Saga).

References

1. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007;8:292–3.
2. International Agency for Research on Cancer. Volume 96 Alcoholic Beverage Consumption and Ethyl Carbamate (Urethane). Meeting Summary http://monographs.iarc.fr/ENG/Meetings/index1.php (accessed 1 June 2007).
3. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Perspective. 1997 Washington: American Institute for Cancer Research.
4. Takeshita T, Morimoto K, Mao XQ, Hashimoto T, Furuyama J. Phenotypic differences in low Km aldehyde dehydrogenase in Japanese workers. *Lancet* 1993;341:837–8.
5. Agarwal DP, Goedde HW. Pharmacogenetics of alcohol metabolism and alcoholism. *Pharmacogenetics* 1992;2:48–62.
6. The EUROGAST Study Group. An international association between Helicobacter pylori infection and gastric cancer. *Lancet* 1993;341:1359–62.
7. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Volume VIII. Lyon: IARC 2002.
8. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
9. Mizoue T, Inoue M, Tanaka K, Tsuji I, Wakai K, Nagata C, et al. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:25–39.
10. Wakai K, Inoue M, Mizoue T, Tanaka K, Tsuji I, Nagata C, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:309–24.
11. Nagata C, Mizoue T, Tanaka K, Tsuji I, Wakai K, Inoue M, et al. Tobacco smoking and breast cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:387–94.
12. Tanaka K, Tsuji I, Wakai K, Nagata C, Mizoue T, Inoue M, et al. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol* 2006;36:445–56.
13. Mizoue T, Tanaka K, Tsuji I, Wakai K, Nagata C, Otani T, et al. Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:582–97.
14. Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, et al. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:800–7.
15. Wakai K, Nagata C, Mizoue T, Tanaka K, Nishino Y, Tsuji I, et al. Alcohol drinking and lung cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2007;37:168–74.
16. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition, the Prevention of Chronic Disease. Report of a Joint WHO/FAO Expert Consultation. Geneva: WHO 2003.
17. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 44. Alcohol drinking. Lyon. France: IARC 1988.
18. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. *Jpn J Cancer Res* 1987;78:1323–8.
19. Ubukata T, Nakao M, Oshima A, Sobue T, Tsukuma H, Morinaga K, et al. Drinking and smoking in the etiology of stomach cancer. *Nippon Koshu Eisei Zasshi* 1988;35:286–92 (in Japanese).
20. Hirayama T. Life-style and mortality. A large-scale census-based cohort study in Japan. Contributions to Epidemiology and Biostatistics, Volume 6. Basel, Switzerland: Karger 1990.
21. Kato I, Tominaga S, Matsumoto K. A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Jpn J Cancer Res* 1992;83:568–75.
22. Masuda N, Shigematsu T. A cohort study of adult residents in Oki Island, Shimane, Japan—effects of smoking and drinking habits on main causes of death. *Med Bull Fukuoka Univ* 1992;19:435–43 (in Japanese).
23. Murata M, Takayama K, Choi BC, Pak AW. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev* 1996;20:557–65.
24. Inoue M, Tajima K, Kobayashi S, Suzuki T, Matsuura A, Nakamura T, et al. Protective factor against progression from atrophic gastritis to gastric cancer—data from a cohort study in Japan. *Int J Cancer* 1996;66:309–14.
25. Sasazuki S, Sasaki S, Tsugane S, for the Japan Public Health Center Study Group. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer* 2002;101:560–6.
26. Fujino Y, Tamakoshi A, Ohno Y, Mizoue T, Tokui N, Yoshimura T, for the JACC Study Group. Prospective study of educational background and stomach cancer in Japan. *Prev Med* 2002;35:121–7.
27. Nakaya N, Tsubono Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev* 2005;14:169–74.
28. Sauvaget C, Lagarde F, Nagano J, Soda M, Koyama K, Kodama K. Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). *Cancer Causes Control* 2005;16:773–80.
29. Hoshino H. A study on gastric cancer risk factors—a case-control study based on medical records (1) Matched pair method. *Gan No Rinsho* 1984;30(Suppl):1457–67 (in Japanese).
30. Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985;76:705–16.
31. Kono S, Ikeda M, Tokudome S, Kuratsune M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res* 1988;79:1067–74.
32. Kato I, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, et al. A comparative case-control analysis of stomach cancer and atrophic gastritis. *Cancer Res* 1990;50:6559–64.
33. Tominaga K, Koyama Y, Sasagawa M, Hiroki M, Nagai M. A case-control study of stomach cancer and its genesis in relation to alcohol consumption, smoking, and familial cancer history. *Jpn J Cancer Res* 1991;82:974–9.
34. Kikuchi S, Inaba Y, Wada O, Miki K, Nakajima T, Nishi T, et al. Jyakunen igan no yobou ni tsuite. *Gan No Rinsho* 1991;3:235–8 (in Japanese).
35. Hoshiyama Y, Sasaba T. A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control* 1992;3:441–8.
36. Iwasaki J, Ebihira I, Uchida A, Ogura K. Case-control studies of lung cancer and stomach cancer cases in mountain villages and farming-fishing villages. *J Jpn Assoc Rural Med* 1992;41:92–102 (in Japanese).
37. Hirohata I. Gastric cancer and dietary habits—a case-control study in Japan. J Kurume Med Assoc 1993;56:23–37 (in Japanese).
38. Inoue M, Tajima K, Hirose K, Kuroishi T, Gao CM, Kitoh T. Life-style and subsite of gastric cancer—joint effect of smoking and drinking habits. *Int J Cancer* 1994;56:494–9.
39. Kikuchi S, Nakajima T, Kobayashi O, Yamazaki T, Kikuichi M, Mori K, et al. U-shaped effect of drinking and linear effect of smoking on risk for stomach cancer in Japan. *Jpn J Cancer Res* 2002;93:953–9.
40. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. Schistosomes, Liver Flukes and Helicobactor Pylori. Lyon, France: IARC 1994.
41. Tsugane S, Kabuto M, Imai H, Gey F, Tei Y, Hanaoka T, et al. Helicobacter pylori, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. *Cancer Causes Control* 1993;4:297–305.
42. Japanese Research Society for Gastric Cancer. The General Rules for the Gastric Cancer Study. 12th edn. Tokyo: Kanehara 1993.

Jpn J Clin Oncol 2007;37(9)692–700
doi:10.1093/jjco/hym085

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

Manami Inoue[1], Kenji Wakai[2], Chisato Nagata[3], Tetsuya Mizoue[4], Keitaro Tanaka[5], Ichiro Tsuji[6] and Shoichiro Tsugane[1] for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan[†]

[1]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, [2]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, [3]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [4]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo, [5]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga and [6]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Received January 15, 2007; accepted May 2, 2007; published online August 18, 2007

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

For reprints and all correspondence: Manami Inoue, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: mninoue@gan2.res.ncc.go.jp

[†]Research group members: Shoichiro Tsugane (principal investigator), Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (National Cancer Center, Tokyo); Ichiro Tsuji (since 2004), Yoshitaka Tsubono (in 2003), Taichi Shimazu (Tohoku University, Sendai); Yoshikazu Nishino (Miyagi Cancer Research Institute, Natori, Miyagi); Kenji Wakai (Nagoya University, Nagoya); Keitaro Matsuo (since 2006; Aichi Cancer Center, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (International Medical Center of Japan, Tokyo); and Keitaro Tanaka (Saga University, Saga).

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 I. 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)			

Continued

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)			

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

Age, smoking status, education, daily consumption of orange, other fruits, fruit juice, spinach, carrot or pumpkin, and tomato	Follow-up by residential register and population-based cancer registry	
Age, BMI, education, smoking, exercise, history of diabetes and hypertension	Follow-up by residential register and death certificate	

Continued

Table 1. *Continued*

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

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

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

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

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

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

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

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

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

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

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

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

Acknowledgments

The authors gratefully acknowledge the assistance of Ms Izumi Suenaga. This study was supported by the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

References

1. The Editorial Board of the Cancer Statistics in Japan. Cancer Statistics in Japan 2005. Tokyo: Foundation for Promotion of Cancer Research 2005.
2. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. Alcohol consumption and the risk of cancer: a meta-analysis. *Alcohol Res Health* 2001;25:263–70.
3. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
4. Mizoue T, Inoue M, Tanaka K, Tsuji I, Wakai K, Nagata C, Tsugane S, Research Group for the Development, Evaluation of Cancer Prevention Strategies in Japan. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:25–39.
5. Wakai K, Inoue M, Mizoue T, Tanaka K, Tsuji I, Nagata C, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:309–24.
6. Nagata C, Mizoue T, Tanaka K, Tsuji I, Wakai K, Inoue M, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Tobacco smoking and breast cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:387–94.
7. Tanaka K, Tsuji I, Wakai K, Nagata C, Mizoue T, Inoue M, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol* 2006;36:445–56.
8. Mizoue T, Tanaka K, Tsuji I, Wakai K, Nagata C, Otani T, Inoue M, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:582–97.
9. Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsugane S, Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:800–807.
10. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition, the prevention of chronic disease. Report of a joint WHO/FAO Expert Consultation. Geneva: WHO, 2003.
11. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 44. Alcohol Drinking. Lyon: IARC, 1988.
12. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Alcohol and mortality: a cohort study of male Japanese physicians. *Int J Cancer* 1986;15:527–32.

13. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and cancer mortality: A cohort study of male Japanese physicians. *Jpn J Cancer Res* 1987;78:1323–8.
14. Hirayama T. A life-style and mortality. A large-scale census-based cohort study in Japan. Contributions to Epidemiology and Biostatistics, Volume 6. Basel: Karger 1990.
15. Takezaki T, Tajima K, Yoshida M, Tominaga S. Risk of death by health habit index from a cohort study among the residents of a rural area in Aichi, Japan. *Nippon Koshu Eisei Zasshi* 1999;46:904–14 (in Japanese).
16. Tsugane S, Fahey MT, Sasaki S, Baba S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. *Am J Epidemiol* 1999;150:1201–207.
17. Inoue M, Tsugane S. Impact of alcohol drinking on total cancer risk: data from a large-scale population-based cohort study in Japan. *Br J Cancer* 2005;92:182–7.
18. Nakaya N, Tsubono Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, Fukudo S, Shibuya D, Tsuji I. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev* 2005;14:169–74.
19. Lin Y, Kikuchi S, Tamakoshi A, Wakai K, Kawamura T, Iso H, Ogimoto I, Yagyu K, Obata Y, Ishibashi T, The JACC Study Group. Alcohol consumption and mortality among middle-aged and elderly Japanese men and women. *Ann Epidemiol* 2005;15:590–97.
20. Blot WJ. Alcohol and cancer. *Cancer Res* 1992;52:2119s–2123s.
21. Fuchs CS, Stampfer MJ, Colditz GA, Giovannucci EL, Manson JE, Kawachi I, Hunter DJ, Hankinson SE, Hennekens CH, Rosner B. Alcohol consumption and mortality among women. *New Engl J Med* 1995;332:1245–50.
22. Renaud SC, Gueguen R, Schenker J, d'Houtaud A. Alcohol and mortality in middle-aged men from eastern France. *Epidemiology* 1998;9:184–8.
23. Theobald H, Johansson SE, Bygren LO, Engfeldt P. The effects of alcohol consumption on mortality and morbidity: a 26-year follow-up study. *J Stud Alcohol* 2001;62:783–9.
24. Berberian KM, van Duijn CM, Hoes AW, Valkenburg HA, Hofman A. Alcohol and mortality. Results from the EPOZ (Epidemiologic Study of Cardiovascular Risk Indicators) follow-up study. *Eur J Epidemiol* 1994;10:587–93.
25. Gaziano JM, Gaziano TA, Glynn RJ, Sesso HD, Ajani UA, Stampfer MJ, Manson JE, Hennekens CH, Buring JE. Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *J Am Coll Cardiol* 2000;35:96–105.
26. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. Alcohol consumption and the risk of cancer: a meta-analysis. *Alcohol Res Health* 2001;25:263–70.
27. Agarwal DP, Harada S, Goedde HW. Racial differences in biological sensitivity to ethanol: the role of alcohol dehydrogenase and aldehyde dehydrogenase isozymes. *Alcohol Clin Exp Res* 1981;5:12–16.
28. Matsuo K, Hamajima N, Shinoda M, Hatooka S, Inoue M, Takezaki T, Tajima K. Gene–environment interaction between an aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer. *Carcinogenesis* 2001;22:913–6.
29. Yokoyama A, Muramatsu T, Ohmori T, Higuchi S, Hayashida M, Ishii H. Esophageal cancer and aldehyde dehydrogenase-2 genotypes in Japanese males. *Cancer Epidemiol Biomarkers Prev* 1996;5:99–102.
30. Anderson LM, Koseniauskas R, Burak ES, Logsdon DL, Carter JP, Driver CL, Gombar CT, Magee PN, Harrington GW. Suppression of *in vivo* clearance of N-nitrosodimethylamine in mice by cotreatment with ethanol. *Drug Metab Dispos* 1994;22:43–49.
31. Van de Wiel JA, Fijneman PH, Teeuw KB, Van Ommen B, Noordhoek J, Bos RP. Influence of long-term ethanol treatment on rat liver biotransformation enzymes. *Alcohol* 1993;10:397–402.

Jpn J Clin Oncol 2007;37(8)568–574
doi:10.1093/jjco/hym062

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

Chisato Nagata[1], Tetsuya Mizoue[2], Keitaro Tanaka[3], Ichiro Tsuji[4], Kenji Wakai[5], Manami Inoue[6] and Shoichiro Tsugane[6] for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, [2]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo, [3]Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga, [4]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, [5]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya and [6]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Received December 22, 2006; accepted March 10, 2007; published online August 18, 2007

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.

For reprints and all correspondence: Chisato Nagata, Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. E-mail: chisato@gifu-u.ac.jp

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 ($\geq$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 ($\geq$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 Tumor registry at the RERF	Incidence	161	Never drinker	106	1.00		Adjusted for: city, age, age at the time of the bombings, and radiation dose to the breast
						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 (Aichi 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 (Gifuoku 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: participants 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.

Acknowledgments

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

Appendix

Research group members: Shoichiro Tsugane [Principal Investigator], Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (National Cancer Center, Tokyo); Ichiro Tsuji [since 2004], Yoshitaka Tsubono [in 2003], Taichi Shimazu (Tohoku University, Sendai); Yoshikazu Nishino (Miyagi Cancer Research Institute, Natori, Miyagi); Kenji Wakai (Nagoya University, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (International Medical Center of Japan, Tokyo); Keitaro Tanaka (Saga University, Saga).

Conflict of interest statement
None declared.

References

1. Longnecker M, Verlin J, Orza M, Chalmers T. A meta-analysis of alcohol consumption in relation to risk of breast cancer. *JAMA* 1988;260:652–6.
2. Howe G, Rohan T, DeCarli A, Iscovich J, Kaldor J, Katsouyanni K, et al. The association between alcohol and breast cancer risk: evidence from the combined analyses of six dietary case-control studies. *Int J Cancer* 1991;47:707–10.
3. Longnecker M. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Cause Control* 1994;5:73–82.
4. Roth HD, Levy PS, Shi L, Post E. Alcoholic beverages and breast cancer: some observations on published case-control studies. *J Clin Epidemiol* 1994;47:740–7.
5. D'Arcy C, Holman C, English D, Milne E, Winter E. Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *Med J Aust* 1996;164:141–5.
6. Corrao G, Bagnardi V, Zambon A, Arico S. Exploring the dose–response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction* 1999;94:1551–73.
7. Elison RC, Zhang Y, McLennan CE, Rothman KJ. Exploring the relation of alcohol consumption to risk of breast cancer. *Am J Epidemiol* 2001;154:740–7.
8. Collaborative group on Hormonal Factors in Breast cancer. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. *Br J Cancer* 2002;87:1234–45.
9. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. *Cancer Causes Control* 2006;17:759–70.
10. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition, the Prevention of Chronic Disease. Report of a Joint WHO/FAO Expert Consultation. Geneva: WHO 2003.
11. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 44. Alcohol Drinking. Lyon, France: IARC 1988.
12. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
13. Hirayama T. Life-style and Mortality. A Large-scale Census-based Cohort Study in Japan. *Contribution to Epidemiology and Biostatistics*, 6. Basel: Karger 1990.
14. Goodman MT, Cologne JB, Moriwaki H, Vaeth M, Mabuchi K. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. *Prev Med* 1997;26:144–53.
15. Lin Y, Kikuchi S, Tamakoshi K, Wakai K, Kondo T, Niwa Y, et al. Prospective study of alcohol consumption and breast cancer risk in Japanese women. *Int J Cancer* 2005;116:779–83.
16. Kato I, Tominaga S, Terao C. Alcohol consumption and cancers of hormone-related organs in females. *Jpn J Clin Oncol* 1989;19:202–7.
17. Kikuchi S, Okamoto N, Suzuki T, Kawahara S, Nagai H, Sakiyama S. A case control study of breast cancer, mammary cyst and dietary, drinking or smoking habit in Japan [Japanese]. *Gan No Rinsho* 1990;36; 365–9.
18. Kato I, Miura S, Kasumi F, Iwase T, Tashiro H, Fujita Y, et al. A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. *Breast Cancer Res Treat* 1992;24:51–9.
19. Wakai K, Ohno Y, Watanabe S, Sakamoto G, Kasumi F, Suzuki S, et al. Risk factors for breast cancer among Japanese women in Tokyo: a case-control study. *J Epidemiol* 1994;4:65–71.
20. Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, et al. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn J Cancer Res* 1995;86:146–54.
21. Yao-Hua H, Kuroishi T, Matsushita Y, Nagata C, Shimizu H. Birth season and breast cancer risk in Japan. *Breast Cancer Res Treat* 1996;39:315–9.
22. Ueji M, Ueno E, Osei-Hiramya D, Saito T, Takahashi H, Kano K. Risk factors for breast cancer among Japanese women: a case-control study in Ibaraki, Japan. *Breast Cancer* 1998;5:351–8.
23. Tung HT, Tsukuma H, Tanaka H, Kinoshita N, Koyama Y, Ajiki W, et al. Risk factors for breast cancer in Japan, with special attention to anthropometric measurements and reproductive history. *Jpn J Clin Oncol* 1999;29:137–46.
24. Inoue M, Tsugane S. Impact of alcohol drinking on total cancer risk: data from a large-scale population-based cohort study in Japan. *Br J Cancer* 2005;92:182–7.
25. Tseng M, Einberg CR, Umbach DM, Longnecker MP. Calculation of population attributable risk for alcohol and breast cancer. *Cancer Cause Control* 1999;10:119–23.
26. Nagata C, Mizoue T, Tanaka K, Tsuji I, Wakai K, Inoue M, et al. Tobacco smoking and breast cancer risk: an evaluation based on systematic review of epidemiological evidence among Japanese populations. *Jpn J Clin Oncol* 2006;36:387–94.
27. Singletary KW, Gapstur SM. Alcohol and breast cancer. *JAMA* 2001;286:2143–51.