Ohki et al. (11)	1994–2006	1431 (727 men and 704 women)	Patients with positive HCV-RNA at Tokyo University Hospital	Incidence	340	Body mass index (kg/m^2)				Age, sex, diabetes, alcohol, serum albumin, bilirubin, ALT, prothrombin time, platelets, alpha-fetoprotein	All subjects were anti-HCV-positive and HBsAg-negative
						≤18.5		1.00			
						>18.5 to ≤25		1.52 (0.93–2.47)			
						>25 to ≤30		1.86 (1.09–3.16)			
						>30		3.10 (1.41–6.81)			
Inoue et al. (27)	1993–2006	17 590 (6092 men and 11 498 women)	Residents in six public health center areas across Japan	Incidence	102 (67 men and 35 women)	For total subjects				Age, area, smoking, alcohol, coffee, serum total cholesterol, anti-HCV, HBsAg	Anti-HCV and HBsAg status was adjusted for
						Body mass index (kg/m^2)					
						<25	64	1.00	0.019		
						25 to <27	21	2.07 (1.22–3.52)			
						≥27	17	2.72 (1.51–4.89)			
						For anti-HCV(+) subjects					
						Body mass index (kg/m^2)					
						<25	44	1.00	0.017		
						25 to <27	16	2.55 (1.34–4.85)			
						≥27	13	3.08 (1.51–6.30)			
						For anti-HCV(−) HBsAg(−) subjects					
						Body mass index (kg/m^2)					
						<25	11	1.00	0.414		
						25 to <27	4	1.91 (0.59–6.14)			
						≥27	3	1.84 (0.48–7.04)			
Kurosaki et al. (28)	1994–?	1279 (643 men and 636 women)	Patients with chronic hepatitis C who received interferon therapy at Musashino Red Cross Hospital	Incidence	68	Body mass index (kg/m^2)				Age, sex, stage of fibrosis, grade of steatosis, response to interferon, diabetes, ethanol consumption	All subjects were anti-HCV-positive and HBsAg-negative
						<23		1.00			
						≥23		1.69 (1.02–2.86)			
Bekku et al. (29)	1985–?	244 (141 men and 103 women)	Patients with hepatitis B e antigen-negative hepatitis B at Chiba University Hospital	Incidence	10	Body mass index (kg/m^2)				No adjustment	All subjects were HBsAg-positive and anti-HCV-negative
						One unit increase		0.99 (0.91–1.08)	0.855		

CI, confidence interval; HCV, hepatitis C virus; ALT, alanine aminotransferase; anti-HCV, antibody to HCV; HBsAg, hepatitis B surface antigen; BCAA, branched-chain amino acids.

variance-based method (i.e. fixed-effect model) or the method of DerSimonian and Laird (i.e. random-effects model) depending on the statistical significance of heterogeneity for RRs across studies (20,21). Such heterogeneity was tested using the Q-statistic. All statistical analyses were performed with the STATA statistical package (Stata Corp., College Station, TX, USA). Two-sided P values of <0.05 were considered statistically significant.

MAIN FEATURES

We identified nine cohort studies (11,22–29) (Table 1) and three case–control studies (30–32) (Table 2). Of those cohort studies, two presented results by sex (23,26) and seven showed results only for men and women combined (11,22,24,25,27–29). The respective numbers for the case–control studies are one (32) and two (30,31).

Study populations in the cohort studies were classified into two categories: apparently healthy subjects (local residents) (23,24,26,27) ($n = 4$) and patients with chronic liver disease (CLD) (11,22,25,28,29) ($n = 5$) (Table 1). Chronic infection with both HCV and HBV was considered in five cohort studies (11,22,27–29). In the case–control studies, a similar classification was possible based on the type of controls: apparently healthy subjects (atomic bomb survivors) (31) ($n = 1$) and patients with CLD (30,32) ($n = 2$) (Table 2). All case–control studies took into account of both HCV and HBV infections.

A summary of the magnitude of association for the cohort studies and the case–control studies is shown in Tables 3 and 4, respectively. Of all nine cohort studies identified, three (11,22,25,27) reported a strong positive association between increasing BMI and liver cancer, one (28) reported a moderate positive association and one (22) reported a weak positive association, whereas four [three on local residents with unknown hepatitis status (23,24,26) and one on HBV carriers (29)] observed no association. All three case–control studies (30–32) demonstrated a strong positive association.

Figure 1 illustrates a forest plot of the RRs for one unit increase in BMI in individual studies and the corresponding summary RR. In this figure, sex-specific estimates are separately plotted, and one cohort study (24) is excluded due to the unavailability of cut-off points for BMI categories. For the cohort studies, the RRs were not significantly heterogeneous [$Q = 11.0$ on 9 degrees of freedom (DF), $P = 0.275$], and the summary RR was estimated to be 1.07 (95% CI 1.03–1.10) based on a fixed-effect model. The RRs in the case–control studies turned out to be significantly heterogeneous ($Q = 18.7$ on 3 DF, $P < 0.001$), and an analysis with a random-effects model showed that the summary RR was 1.31 (95% CI 1.12–1.53). For the cohort and case–control studies combined ($Q = 43.6$ on 13 DF, $P < 0.001$), the summary RR was 1.13 (95% CI 1.07–1.20) with a random-effects model.

According to the baseline data of the Japan Public Health Center-based prospective study (19), the absolute difference between median values for two BMI categories of ≥ 25 and <25 kg/m^2 in both sexes combined was 4.45 kg/m^2. Applying this figure to the above summary RR resulted in an RR of 1.74 (95% CI 1.33–2.28) for overweight or obese individuals compared with those who had normal or low body weight.

COMMENTS

Overall, five out of the nine cohort studies and all three case–control studies in Japan reported a weak to strong positive association between increasing BMI and liver cancer risk, suggesting that the overall evidence in this country is also supportive of an increased risk of liver cancer among overweight or obese people, as previously reported in two systematic reviews (14,15) which included only two Japanese studies (23,31). The association was stronger in the case–control studies than in the cohort studies, as shown in the summary RR, although the number of the former was only three. It was noted that three cohort studies showing no association (23,24,26) followed local residents with unknown hepatitis status, which could possibly attenuate the strength of a true association. One cohort study with null results was exceptional, in that it targeted patients with hepatitis B e antigen-negative hepatitis B (29). Due to the limited number of relevant studies, it was difficult to examine whether the risk differed by the etiology of CLD (e.g. HCV, HBV and alcohol).

Several limitations of this systematic review should be mentioned. First, possible selection bias might have affected the results, particularly in the hospital-based case–control studies (30,32), although the rest studies were less likely to be influenced due to their prospective design. Information bias (e.g. recall bias) and measurement errors did not seem to be serious issues because BMI was likely to be calculated with actual measurements in most studies. Secondly, potential confounding factors were not always taken into account in the 12 studies evaluated. Hepatitis status, alcohol or diabetes was not considered in four (23–26), six (24–26,29,30,32) or eight studies (23–27,29,30,32), respectively, and only three studies (23,27,31) adjusted for smoking that is now regarded as a risk factor (33–35). Thirdly, studies involving cirrhotic patients (11,28–30,32) who represent a very high-risk group of liver cancer may have been affected by the presence or absence of ascites, which could have influenced BMI as an index of adiposity. Only one study took consideration of this issue (11). Fourthly, publication bias could not be ruled out, although there was no evidence of such bias using the Begg's test and the Egger's test ($P = 0.32$ and 0.16, respectively; data not shown) (20,21).

Another concern may be some assumptions in calculating the summary RR. Because the necessary information was

Table 2. Case–control studies on obesity and liver cancer among Japanese

Reference	Study period	Study subjects				Category	Relative risk (95% CI or *P* value)	*P* value for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Kabutake et al. (30)	1994–2006	Hospital-based (Tokyo Women's Medical University Hospital)	Cases: patients with alcoholic liver injury complicated with HCC Controls: patients with alcoholic cirrhosis without HCC	96 (92 men and 4 women)	65 (58 men and 7 women)	No overweight Overweight/obesity	1.00 3.40 (1.45–7.99)		No adjustment	The relative risk and 95% CI were not described in the original paper and were estimated by one of the authors (K.T.) All subjects were negative for HBsAg and anti-HCV
Ohishi et al. (31)	1970–2002	Nested case-control (atomic bomb survivors in Hiroshima and Nagasaki)	Cases: patients with incident HCC who had stored serum samples available Controls: survivors without HCC who had stored serum samples available	224 (136 men and 88 women)	644 (387 men and 257 women)	Body mass index 10 years before diagnosis ≤19.5 19.6–21.2 21.3–22.9 23.0–25.0 >25.0 One unit increase	 1.31 (0.51–3.34) 1.24 (0.43–3.54) 1.00 2.51 (0.99–6.37) 4.57 (1.85–11.3) 1.12 (1.03–1.22)	 0.01	Matched (1:3) for sex, age, city, time and method of serum storage, and radiation exposure Adjusted for matching factors, hepatitis virus infection, alcohol consumption, smoking, coffee, diabetes, radiation dose to the liver	HBsAg and anti-HCV status was adjusted for
Horie et al. (32)	2007–08	Hospital-based (72 facilities throughout Japan)	Cases: patients with alcoholic cirrhosis complicated with HCC Controls: patients with alcoholic cirrhosis without HCC	243 men and 22 women	509 men and 89 women	For men No overweight Overweight/obesity For women No overweight Overweight/obesity	 1.00 2.03 (1.48–2.78) 1.00 25.1 (7.69–82.0)		No adjustment No adjustment	The relative risks and 95% CIs were not described in the original paper and were estimated by one of the authors (K.T.). All subjects were negative for HBsAg and anti-HCV

HCC, hepatocellular carcinoma.

Table 3. Summary of cohort studies on obesity and liver cancer among Japanese

Reference	Study period	Study population					Magnitude of association
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths	
Ohata et al. (22)	1980–2000	Men and women	161 (HCV-associated chronic hepatitis or cirrhosis)	Not specified	Incidence	70	↑
Kuriyama et al. (23)	1984–92	Women	15 054	≥40 years	Incidence	31	—
		Men	12 485	≥40 years	Incidence	69	—
Khan et al. (24)	1977–2002	Men and women	1989	30–77 years	Death	8	—
Muto et al. (25)	Not described	Men and women	622 (decompensated cirrhosis)	20–75 years	Incidence	89	↑↑↑
Fujino (26)	1988–2003	Men	46 178	40–79 years	Death	463	—
		Women	12 485	40–79 years	Death	227	—
Ohki et al. (11)	1994–2006	Men and women	1431 (HCV-associated chronic liver disease)	Not specified	Incidence	340	↑↑↑
Inoue et al. (27)	1993–2006	Men and women	17 590	40–69 years	Incidence	102	↑↑↑
Kurosaki et al. (28)	1994–?	Men and women	1279 (patients with chronic hepatitis C)	Not specified	Incidence	68	↑↑
Bekku et al. (29)	1985–?	Men and women	244 (patients with hepatitis B e antigen-negative hepatitis B)	Not specified	Incidence	10	—

Table 4. Summary of case–control studies on obesity and liver cancer among Japanese

Reference	Study period	Study subjects				Magnitude of association
		Sex	Age range	Number of cases	Number of controls	
Kabutake et al. (30)	1994–2006	Men and women	Not specified	96	65 (alcoholic cirrhosis)	↑↑↑
Ohishi et al. (31)	1970–2002	Men and women	Not specified	224	644	↑↑↑
Horie et al. (32)	2007–08	Men	Not specified	243	509 (alcoholic cirrhosis)	↑↑↑
		Women	Not specified	22	89 (alcoholic cirrhosis)	↑↑↑

not available from original data, external data [i.e. those from the Japan Public Health Center-based prospective study (19)] were employed to define representative values for open categories of BMI in each individual study. This assumption can be problematic particularly for studies involving cirrhotic patients. Sensitivity analyses changing those representative values in such studies (11,22,28,30,32) demonstrated that the corresponding summary RR (and 95% CI) became 1.12 (1.06–1.19) after a 0.5 kg/m^2 increase and 1.14 (1.07–1.22) after a 0.5 kg/m^2 decrease in the absolute difference between the representative values for two extreme open categories, indicating no material differences before and after these accommodations (data not shown). In addition, the assumption of a log-linear relationship between BMI and liver cancer risk may be questioned. Unfortunately, the studies included in this paper used rather different categories or a continuous variable for BMI, and so possible non-linear relationships (e.g. U-shaped or J-shaped relation) could not be evaluated based on the same categorization of BMI. This issue merits further investigation.

As for the biologic plausibility for the observed association between overweight/obesity and liver cancer, there has been sufficient evidence, as is the case with other cancers (36). Obesity frequently leads to hepatic steatosis (9), which represents a major histopathologic feature of both non-alcoholic fatty liver disease including NASH (9) and chronic hepatitis C (37) and has been shown to be a risk factor for liver cancer (22,38). Hepatic steatosis is closely associated with systemic insulin resistance (39) and hence elevated levels of insulin and insulin-like growth factor 1, which may stimulate the growth of cancer cells (36,40). Animal models of fatty livers and of insulin resistance demonstrate the development of liver tumors with an increased production of reactive oxygen species in the mitochondria of hepatocytes

Study No.	First author	Year	Reference	Sex	Design	RR (95% CI) for one unit increase in BMI
1	Ohata	2003	(22)	Men and women	Cohort	1.12 (0.95–1.32)
2	Kuriyama	2005	(23)	Women	Cohort	1.02 (0.65–1.59)
3	Kuriyama	2005	(23)	Men	Cohort	0.99 (0.65–1.52)
4	Muto	2006	(25)	Men and women	Cohort	1.42 (1.03–1.96)
5	Fujino	2007	(26)	Men	Cohort	1.00 (0.90–1.11)
6	Fujino	2007	(26)	Women	Cohort	1.04 (0.95–1.15)
7	Ohki	2008	(11)	Men and women	Cohort	1.08 (1.04–1.13)
8	Inoue	2009	(27)	Men and women	Cohort	1.18 (0.99–1.42)
9	Kurosaki	2010	(28)	Men and women	Cohort	1.15 (1.01–1.31)
10	Bekku	2011	(29)	Men and women	Cohort	0.99 (0.91–1.08)
11	Kabutake	2007	(30)	Men and women	Case–control	1.32 (1.09–1.60)
12	Ohishi	2008	(31)	Men and women	Case–control	1.12 (1.03–1.22)
13	Horie	2011	(32)	Men	Case–control	1.19 (1.10–1.28)
14	Horie	2011	(32)	Women	Case–control	1.97 (1.53–2.52)
				Summary RR	Cohort	1.07 (1.03–1.10)
					Case–control	1.31 (1.12–1.53)
					Total	1.13 (1.07–1.20)

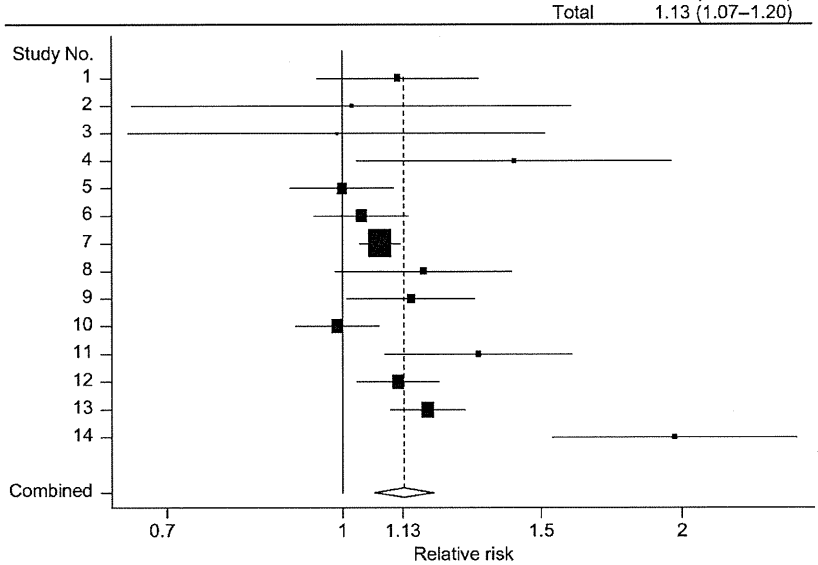

Figure 1. Forest plot of the relative risks (RRs) and their 95% confidence intervals (CIs) of liver cancer for one unit increase in body mass index (BMI) in cohort and case–control studies evaluated and the corresponding summary RR. For cohort studies, the individual RRs were not significantly heterogeneous [$Q = 11.0$ on 9 degrees of freedom (DF), $P = 0.275$], and so a fixed-effect model was used to estimate the summary RR. The individual RRs turned out to be significantly heterogeneous across case–control studies ($Q = 18.7$ on 3 DF, $P < 0.001$) and total studies combined ($Q = 43.6$ on 13 DF, $P < 0.001$), for which a random-effects model was employed.

and suggest that oxidative stress may play a pivotal role in hepatic hyperplasia (41,42). Oxidative stress has also been implicated in HCV-associated hepatocarcinogenesis in a mouse model which presents hepatic steatosis (43). Moreover, obese people have elevated levels of pro-inflammatory factors, such as tumor necrosis factor-α, interleukin-6 and C-reactive protein, and resulting chronic inflammation can promote cancer development (2,8).

EVALUATION OF EVIDENCE ON OBESITY AND LIVER CANCER RISK AMONG JAPANESE

Based on the results from the epidemiologic studies evaluated and the biologic plausibility as described above, we conclude that overweight or obesity 'probably' increases the risk of primary liver cancer, to a moderate degree, among the Japanese population. Maintaining a healthy body weight may partly prevent the development of liver cancer, particularly in high-risk individuals such as patients with CLD and hepatitis virus carriers.

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Conflict of interest statement

None declared.

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Appendix

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Breastfeeding and Breast Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Objective: We reviewed epidemiological studies on breastfeeding and breast cancer among Japanese women. This report is part of a series of articles written by our research group, whose aim was to evaluate 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 by manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility.

Results: Three cohort studies and five case–control studies were identified. Cohort studies failed to find a significant inverse association between breastfeeding and the risk of breast cancer. Most of the case–control studies observed a statistically significant or non-significant risk reduction for women who ever had breastfed or for women with a longer duration of breastfeeding. Experimental studies have supported the biological plausibility of a protective effect of breastfeeding on breast cancer risk.

Conclusions: We conclude that breastfeeding possibly decreases the risk of breast cancer among Japanese women.

Key words: systematic review – epidemiology – breastfeeding – breast cancer – Japanese

INTRODUCTION

Breastfeeding has been hypothesized to reduce the risk of breast cancer. However, early systematic reviews have not yielded consistent findings for the association between breast cancer risk and ever breastfeeding or cumulative breastfeeding duration (1–3). Recently, epidemiologic studies of breastfeeding with the risk of breast cancer have been combined in two meta-analyses (4,5). A pooled analysis from 47 epidemiologic studies, including 50 302 cases and 96 973 controls, showed a significant, 4.3% reduction in breast cancer risk for every 12 months of breastfeeding (4). A systematic review carried out

by Berrino et al. (5) for the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR) included 80 epidemiologic studies. The meta-analysis on four cohort studies as well as that on 37 case–control studies showed a 2% reduction of risk per 5 months of breastfeeding (5). The review panel concluded that evidence that breastfeeding protects against both premenopausal and postmenopausal breast cancer is convincing. Most of the component studies in the two meta-analyses have been conducted among Western populations. In addition, after these appraisals, some studies have been published in Japan. We reviewed the epidemiological studies on breastfeeding and breast cancer among Japanese women. This report is part of a series of articles by our research group, whose aim was to investigate the association between lifestyles and major types of cancer in Japan (6).

PATIENTS AND METHODS

Epidemiological studies on the association between breastfeeding and breast cancer incidence or mortality among Japanese were identified through a MEDLINE search from 1980 to 2011 using the terms 'breast cancer', 'Japan', and 'breastfeeding', 'lactation' or 'reproductive factors'. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also done to identify the studies written in Japanese from 1983 to 2011. For inclusion into the review, studies had to be of analytic epidemiological nature written in either English or Japanese and include Japanese populations living in Japan. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or most updated results had to be included. Incidence is given priority over mortality as an outcome measure. Details on the evaluation methods are described elsewhere (6).

Results from each study 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 to 2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). Some studies provided RRs or ORs according to categorized duration of breastfeeding. We mainly used the RR or OR for the longest duration category. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (7), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility is based on evidence in experimental models, human studies and other relevant data.

MAIN FEATURES AND COMMENTS

Out of 11 papers identified (8–18), 3 papers (one cohort study and two case–control studies) were based on a single project (9,10,14). We excluded the case–control studies (9,10). For another set of multiple publications (8,15), we included the one that provided information on the number of children breastfed (8). Thus, three cohort studies (14,15,18) and five case–control studies (8,11–13,17) were included in this review. 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 breastfeeding and covariates used in adjustment. These studies reported estimates of RR or OR for ever breastfeeding or duration of breastfeeding. Summaries of the magnitudes of association for these studies are shown in Tables 3 and 4.

Cohort studies failed to observe a significant inverse association between breastfeeding and the risk of breast cancer. One study showed a non-significant increased risk (14). However, in this study, the number of breast cancer was very small and there was a non-significant decreasing trend in risk with increasing duration of breastfeeding among women who have ever breastfed (14).

Two out of the five case–control studies reported a significantly decreased risk of breast cancer for ever having breastfed when compared with never (13,17). However, history of breastfeeding was limited to that for the last child in one (13) and parity or number of births was not considered as a confounding factor in the other (17). Remaining three studies assessed the association of ever breastfeeding or duration of breastfeeding with the risk of breast cancer after considering number of births (8,11,12). Yoo et al. (8) observed a non-significant, 38% reduction of risk for ever having breastfed and the trend for decreasing risk with increasing duration of breastfeeding was statistically significant. About 40% reduction of risk was observed among women who had breastfed for more than 25 months in a study reported by Yao-Hua et al. (12), but this risk reduction was not significant.

Overall, a protective effect of breastfeeding on breast cancer risk was suggested in some, but not all studies. History of breastfeeding is closely related to other aspects of births, including number of births and age at first birth. Although most of the studies in this review considered such potential confounding effects, any single study is not large enough to discriminate the effect of breastfeeding. Considering that the risk reduction rates estimated from the earlier-mentioned international reviews were $<5\%$ per 12 months of breastfeeding (4,5), it is unlikely that individual studies could consistently present an inverse association between breastfeeding and breast cancer risk. In addition, the risk reduction should be great for extended breastfeeding but small for ever having breastfed when compared with never. In this review, studies, especially cohort studies, on the duration of breastfeeding and the risk of breast cancer were few.

On the other hand, some studies rather suggested a risk reduction greater than those estimated by the international reviews. The percentage of women choosing 'breastfeeding only' has been declining in Japan (19) but is still higher than those in other developed countries (4). Thus, women who

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

References		Study period	Study population		Event followed	Number of incident cases or deaths	Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered
Author	Year		Number of subjects for analysis	Source of subjects							
Goodman et al. (14)	1997	1979–87	22 200	Atomic bomb survivors	Incidence	161	Never	3	1.00		Adjusted for city, age, age at the time of the bomings, and radiation dose to the breast, parous women only
				Tumor registry at the RERF			Ever	56	1.31 (0.41–4.20)		
							Missing	75	1.20 (0.38–3.81)		
							Duration of breastfeeding				
							<12	18	1.00		Additional adjustment for number of full-term pregnancy
							12–23	22	0.80 (0.43–1.49)		
							24+	16	0.83 (0.42–1.64)	0.74	
Iwasaki et al. (16)	2007	1990–2002	55 537	General population			Never	61	1.00		Adjusted for age, area, history of mastopathy, BMI, height, miso soup consumption, menopausal status at baseline, age at menarche, number of births and age at first birth
				(JPHC Study)			Ever	312	0.86 (0.65–1.15)		
											Parous women only
Kawai et al. (18)	2010	1990–2003	24 064	General population			Never	49	1.00		Adjusted for age, smoking, alcohol drinking, walking, educational level, BMI, age at menarche, and family history of breast cancer, parous women only
				(Miyagi Cohort Study)			Ever	186	1.00 (0.72–1.39)		

CI, confidence interval; RERF, the Radiation Effects Research Foundation; JPHC, the Japan Public Health Center-based prospective study; BMI, body mass index.

Table 2. Breastfeeding and breast cancer risk, case–control study in Japanese population

References author	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
Yoo et al. (8)	1988–89	Hospital-based (Aichi Cancer Registry)	Cases: histologically confirmed cases;	521	521	Never	1.00		Matched (1:1) for age (±5 years) and month of visit Adjusted for age, family history among first-degree relatives, age at menarche, menstrual regularity, menopausal status, age at menopause, number of full-term pregnancies and age at first full-term pregnancy
			Controls: hospital control			Ever	0.62 (0.37–1.04)		
						No. of breastfed children			
						0	1.00		
						1	0.55 (0.30–1.00)		
						2	0.66 (0.38–1.16)		
						3	0.71 (0.34–1.51)		
						≥4	0.93 (0.12–6.96)		
						Average months of breastfeeding			
						0	1.00		
						1–3	0.71 (0.40–1.26)		
						4–6	0.75 (0.41–1.38)		
						7–9	0.47 (0.24–0.92)		
						10–12	0.59 (0.34–1.02)		
						≥13	0.53 (0.26–1.05)	<0.05	
Wakai et al. (11)	1990–91	Hospital-based (Cancer Institute Tokyo)	Cases: histologically confirmed cases;	300	900	Never	1.00		Matched (1:1) for age, adjusted for menopausal status, weight, height, lactation and no. of births
						Ever	1.08 (0.65–1.80)		
			Controls: patients without breast cancer						

Continued

Table 2. *Continued*

References author	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls				
Hu et al. (12)	1989–93	Hospital-based (Gihoku General Hospital)	Cases: histologically confirmed	157	369	Duration of breastfeeding (months)			Matched for age and residential area
						0	1.00		
			Controls: participants in breast cancer screening			1–12	1.20 (0.69–2.09)		Adjusted for BMI, age at menarche, age at first birth and no. of births
						13–24	0.92 (0.49–1.74)		
						25+	0.59 (0.32–1.10)		
Minami et al. (13)	1987–91	Breast cancer screening	Cases: histologically confirmed	204	810	Breastfeeding for the last child			Matched for age and screening area and year, parous women only
						Never	1		
			Cases: participants without breast cancer			Ever	0.61 (0.39–0.94)		Adjusted for age at menarche, age at first birth, no. of parity, history of benign breast disease and family history of breast cancer
		Breast cancer screening				Duration of breastfeeding for the last child (months)			
						0	1.00		
						≤6	0.51 (0.30–0.85)		
						7–12	0.67 (0.39–1.16)		
						≥13	0.71 (0.42–1.19)	0.54	
Sacki et al. (17)	2005	Hospital-based	Cases: histologically confirmed	3434	2427	Never	1.00		Matched for age
			Controls: participants in screening for lung, gastrointestinal and gynecologic cancer			Ever	0.79 (0.65–0.96)		

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

References		Study period	Study population					Strength of association[a]
Author	Year		Sex	Number of subjects	Ranged age	Event	Number of incident cases or deaths	
Goodman et al. (14)	1997	1979–87	Women	22 200	Not specified	Incidence	161	—
Iwasaki et al. (16)	2007	1990–2002	Women	55 537	40–69	Incidence	441	—
Kawai et al. (18)	2010	1990–2003	Women	24 064	40–64	Incidence	285	—

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓ weak; -, no association (see text for more detailed definition).

Table 4. Summary of the association between breastfeeding and breast cancer risk, case–control study

References		Study period	Study subjects				Strength of association[a]
Author	Year		Sex	Age range	Number of cases	Number of controls	
Yoo et al. (8)	1992	1988–89	Women	Not specified	521	521	↓↓
Wakai et al. (11)	1994	1990–91	Women	20 year or over	300	900	–
Hu et al. (12)	1997	1989–93	Women	25 year or over	157	369	↓
Minami et al. (13)	1997	1987–91	Women	30 year or over	204	810	↓↓
Saeki et al. (17)	2008	2005	Women	45–69 years	3434	2427	↓

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see text for more detailed definition).

have never breastfed may be more likely to be those who attempted to breastfeed but were unsuccessful. Ability to successfully breastfeed may have contributed to the potential protective effects of breastfeeding. However, there is no consistent evidence for the association between experience of insufficient milk supply and the risk of breast cancer (20). Possible confounders other than the number of births and age at first birth should also be considered. Minami et al. (19) reported that Japanese women with a high educational level or with a history of breast cancer in mother were less likely to choose breastfeeding only. Inadequate control for confounding may have resulted in an overestimation of the true effect of breastfeeding. The observed risk reduction appeared to be somewhat stronger in case–control studies than that in cohort studies. This trend would be due to publication bias in case–control studies, in that more strongly 'positive' study finding may have been more likely to be accepted for publication. We cannot also deny the possibility of selection bias or recall bias in case–control studies. However, small number of studies and the lack of information on the risk associated with longer duration of breastfeeding in the cohort studies preclude us to compare the results between the cohort and the case–control studies. Besides cumulative duration of breastfeeding, characterization of breastfeeding such as initiation of breastfeeding, number of children breastfed, quantification of mixed feeding and reasons for cessation for breastfeeding would be expected for future studies.

Possible mechanisms that contributed to the protective effects of breastfeeding include reduced systemic estrogen and progesterone levels, increased prolactin, excretion of estrogens and carcinogens out of the breast ducts, terminal differentiation of breast epithelial cells brought on by breastfeeding and delay in return of ovulation (21). It is biologically plausible that breastfeeding is related to breast cancer.

EVALUATION OF EVIDENCE ON BREASTFEEDING AND BREAST CANCER RISK IN JAPANESE

From these results, we conclude that breastfeeding possibly decreases the risk of breast cancer among Japanese population. On the basis of epidemiologic studies in the world and assumed biological plausibility, some evaluations conclude that breastfeeding decreases the risk of breast cancer. This evaluation is not contradictive with their conclusions. Even in the absence of strong evidence for protection against breast cancer in this review, breastfeeding requires continued promotion and support because of its other known benefits to the mother and the child.

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Conflict of interest statement

None declared.

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Appendix

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Public Health Report

Green Tea Consumption and Gastric Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Objective: Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer. However, results from epidemiologic studies are conflicting. We evaluated the association between green tea consumption and risk for gastric cancer risk among the Japanese population based on a systematic review of epidemiologic evidence.

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 biologic plausibility.

Results: Eight cohort studies and three case–control studies were identified. Overall, we found no preventive effect on gastric cancer for green tea intake in cohort studies. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data of six cohort studies (hazard ratio = 0.79, 95% confidence interval 0.65–0.96 with $\geq$5 cups/day of green tea intake). Case–control studies consistently showed a weak inverse association between green tea intake and gastric cancer risk.

Conclusions: We conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

Key words: systematic review – epidemiology – green tea – gastric cancer – Japanese

BACKGROUND

Although the age-standardized mortality rate has been continuously declining, gastric cancer is still the second leading cause of cancer deaths among men and women in Japan (1). In addition to *Helicobacter pylori* infection or cigarette smoking, dietary factors are suggested to be associated with gastric carcinogenesis (2).

Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer (3). These experimental studies have suggested that green tea polyphenols might have a protective effect against gastric cancer through its apoptosis-inducing, antimutagenic and antioxidant activities. In 1997, a review of the World Cancer Research Fund, based on the results of case–control studies and several animal models that showed a protective effect of green tea, stated that 'green tea possibly reduce the risk of stomach cancer' (4). Since then, results from cohort studies generally have not supported the findings from case–control studies, and the more recent 2007 report concluded that 'the evidence was so limited that no firm conclusion can be made' (5).

In Japan, green tea is one of the most commonly consumed beverages, and therefore, the effect of green tea on the risk for gastric cancer may be of particular concern. We reviewed epidemiologic studies of green tea consumption and gastric cancer risk among Japanese. This work was conducted as a systematic review of epidemiologic studies on lifestyle factors and cancer based on previous publications targeting Japanese (6).

METHODS

Research Review

Details of the evaluation method have been described previously (6). Briefly, 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 green tea intake and gastric cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011 were identified using the search terms 'green tea', 'tea', 'gastric cancer', 'stomach cancer', 'cancer', 'cohort study', 'case-control study', 'Japan' and 'Japanese' as key words. In addition, we manually searched through references from relevant articles where necessary. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. 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. The individual results were summarized in the tables separately as cohort or case–control studies. Pooled data of Japanese cohort studies, including some of the individual studies already listed, were also available through the review process. To better understand the results from individual studies and finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese, findings from recent pooled analyses were also listed and considered in this report.

Evaluation of Strength of Association Between Green Tea Intake and Gastric Cancer Risk

The evaluation was made based on the magnitude 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). In cases where the frequency or amount of green tea intake had been separated into levels in a study, we used the RR derived from comparing the highest intake with the lowest. To consider the intermediate categories of intake, however, the *P* value for the trend was also considered when judging the statistical significance. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, where evidence was classified as convincing, probable, possible and insufficient (7). We assumed that biologic plausibility was based on evidence in experimental models, human studies and other relevant data.

MAIN FEATURES AND COMMENTS

Through the review process, we identified eight cohort studies (8–15), one pooled analysis of six cohort studies (16) (Table 1) and three case–control studies (17–19) (Table 2). Among cohort studies, the events followed were death in five studies (8,10,12,14,15) and incidence in the other three studies (9,11,13). Five studies showed the results for men and women separately (9,10–14), whereas three studies showed combined results only (8,13,15). The pooled analysis included four cohorts (9,10 and two cohorts in 11) listed in Table 1 and two other cohorts (20,21). For all case–control studies, the results were shown for men and women combined.

The summary of the magnitudes of association for the cohort study and the case–control study is presented in Tables 3 and 4, respectively. As shown in Table 3, among eight cohort studies, one study showed a weak positive association between green tea intake and gastric cancer risk in men (9). Women in the study and all other studies showed no association at all. When the anatomic subsite was considered, one study observed a moderate inverse association for distal cancer in women (11). On the other hand, case–

Table 1. Gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Nakachi et al. (8)	1986–99	8552	Population-based Saitama Prefecture	Death	140	Green tea, cups/day				Sex and lifestyle factors	
						≤3		1.0			
						≥10		0.69 (0.23–1.88)			
Tsubono et al. (9)	1984–92	26 311	Population-based Miyagi Prefecture	Incidence	419	Green tea, cups/day				Age, sex, types of health insurance, history of peptic ulcer, smoking status, alcohol consumption, daily consumption of rice, black tea, coffee, meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits and bean-paste soup	
		11 902 men			296 men	Total					
		14 409 women			123 women	<1	66	1.0			
						1–2	68	1.1 (0.8–1.6)			
						3–4	79	1.0 (0.7–1.4)			
						≥5	206	1.2 (0.9–1.6)	0.13		
						Men					
						<1	41	1.0			
						1–2	49	1.3 (0.8–1.9)			
						3–4	55	1.2 (0.8–1.8)			
						≥5	151	1.5 (1.0–2.1)	0.03		
						Women					
						<1	25	1.0			
						1–2	19	0.8 (0.5–1.5)			
						3–4	24	0.7 (0.4–1.3)			
						≥5	55	0.8 (0.5–1.3)	0.46		
Hoshiyama et al. (10)	Mean 8 years	72 851	Population-based 45 areas of Japan	Death	359	Green tea, cups/day				Age, smoking status, history of peptic ulcer, family history of stomach cancer, consumption of rice, miso soup, green– yellow vegetables, white vegetables, fruits and preference for salty foods	
		30 370 men			240 men	Men					
		42 481 women			119 women	<1	24	1.0			
						1–2	51	1.6 (0.9–2.9)			
						3–4	51	1.1 (0.6–1.9)			
						5–9	76	1.1 (0.6–1.9)			
						≥10	38	1.0 (0.5–2.0)	0.634		
						Women					
						<1	20	1.0			
						1–2	18	1.1 (0.5–2.5)			
						3–4	40	1.0 (0.5–2.1)			
						5–9	32	0.8 (0.4–1.6)			
						≥10	9	0.7 (0.3–2.0)	0.476		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Sasazuki et al. (11)	1990–2001	72,943	Population-based	Incidence	892	Green tea, cups/day				Age, area, cigarette smoking, consumption of fruits, green or yellow vegetables, fishgut, miso soup, black tea and coffee	
		34,832 men			665 men	Men					
		38,111 women			227 women	All sites					
						<1		1.0			
						1–2		0.95 (0.72–1.22)			
						3–4		0.84 (0.65–1.08)			
						≥5		0.98 (0.77–1.25)	0.65		
						Upper-third including cardia					
						<1		1.0			
						1–2		1.06 (0.51–2.18)			
						3–4		0.73 (0.34–1.57)			
						≥5		1.17 (0.60–2.30)	0.75		
						Distal					
						<1		1.0			
						1–2		0.88 (0.64–1.20)			
						3–4		0.79 (0.59–1.07)			
						≥5		0.92 (0.69–1.22)	0.37		
						Women					
						All sites					
						<1		1.0			
						1–2		0.85 (0.53–1.38)			
						3–4		1.04 (0.68–1.58)			
						≥5		0.67 (0.43–1.04)	0.08		
						Upper-third including cardia					
						<1		1.0			
						1–2					
						3–4		0.89 (0.34–2.33)			
						≥5			0.81		
						Distal					
						<1		1.0			
						1–2		0.88 (0.52–1.49)			
						3–4		1.00 (0.63–1.59)			
						≥5		0.51 (0.30–0.86)	0.01		

Khan et al. (12)	1984–2002	3158	Population-based Hokkaido	Death	51	Men				Age, smoking, health status, health education, health screening
		1524 men			36 men	Green tea ≤ several times/month		1.0		
		1634 women			15 women	Green tea ≥ several times/week		1.1 (0.4–2.5)		
						Women				
						Green tea ≤ several times/month		1.0		
						Green tea ≥ several times/week		0.7 (0.2–2.9)		
Sauvaget et al. (13)	1980–99	38 576	Atomic-bomb survivors: Hiroshima, Nagasaki	Incidence	1270	Green tea, cups/day				Sex, sex-specific age, city, radiation dose, sex-specific smoking habits and education level
		14 885 men				<2	242	1.0		
		23 691 women				2–4	680	1.03 (0.89–1.19)		
		34–98 years old				≥5	348	1.06 (0.89–1.25)	>0.50	
Kuriyama et al. (14)	All-cause	40 530	Population-based	Death	193	Green tea, cups/day				Age, sex, job status, years of education, BMI, sports or exercise, walking duration, history of HT, DM, GU, smoking, alcohol, total energy, rice, miso soup, soy bean product, total meat, total fish, dairy products, total fruits, total vegetables, oolong tea, black tea, and coffee
	1995–2005 (11 years)	19 060 men				<1	44	1.0		
		21 470 women				1–2	44	1.33 (0.86–2.04)		
	Cause-specific					3–4	38	1.00 (0.64–1.58)		
	1995–2001 (7 years)					5≤	67	1.17 (0.78–1.76)	0.72	
					138 men	<1	32	1.0		
						1–2	30	1.29 (0.78–2.16)		
						3–4	30	1.19 (0.71–2.00)		
						≥5	46	1.20 (0.74–1.95)	0.55	
					55 women	<1	12	1.0		
						1–2	14	1.32 (0.59–2.94)		
						3–4	8	0.64 (0.26–1.63)		
						≥5	21	1.08 (0.50–2.33)	0.84	
Suzuki et al. (15)	1999–2006	12 251	Population randomly chosen from all 74 municipalities in Shizuoka Prefecture	Death	68	Green tea, cups/day				Age, sex, smoking, alcohol, BMI, and physical activity
		6231 men				<1	2	1.0	Test for trend: HR = 1.04 (0.95–1.13)	
		6020 women				1–3	14	0.49 (0.11–2.28)		
		65–84y old				4–6	32	0.78 (0.19–3.30)		
						≥7	20	0.81 (0.18–3.54)		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)											
Inoue et al. (16)	1985–2004	219 080	Population-based	Incidence	3577	Green tea, cups/day					
		100 479 men			2495 men	Men				Age, area (for three cohorts only), smoking, alcohol drinking, rice, soy bean paste soup, coffee, pickled vegetables, and green-yellow vegetables intake	
		118 601 women			1082 women	All sites					
						<1	420	1.0			
						1–2	452	0.97 (0.83–1.12)			
						3–4	610	0.93 (0.81–1.08)			
						≥5	1013	1.06 (0.86–1.30)	0.74		
						Proximal (upper third)					
						<1	38	1.0			
						1–2	41	1.10 (0.70–1.73)			
						3–4	42	0.79 (0.46–1.35)			
						≥5	96	1.43 (0.96–2.14)	0.08		
						Distal (lower two-thirds)					
						<1	185	1.0			
						1–2	185	0.91 (0.73–1.12)			
						3–4	249	0.95 (0.77–1.16)			
						≥5	328	0.96 (0.79–1.17)	0.86		
						Women					
						All sites					
						<1	215	1.0			
						1–2	174	0.90 (0.73–1.10)			
						3–4	303	0.92 (0.76–1.11)			
						≥5	390	0.79 (0.65–0.96)	0.04		
						Proximal (upper third)					
						<1	8	1.0			
						≥1	45	1.17 (0.52–2.60)	0.87		
						Distal (lower two thirds)					
						<1	83	1.0			
						1–2	64	0.80 (0.57–1.13)			
						3–4	117	0.96 (0.71–1.30)			
						≥5	106	0.70 (0.50–0.96)	0.04		

NS, not significant; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; GU, gastric ulcer.