表 B.　日本人のためのがん予防法

日本人のためのがん予防法
（http://epi.ncc.go.jp/can_prev/preventive_measures.html) 2012年3月現在

喫煙　：　たばこは吸わない。他人のたばこの煙をできるだけ避ける。

ーたばこを吸っている人は禁煙しましょう。吸わない人でも他人のたばこの煙をできるだけ避けましょう。

飲酒　：　飲むなら、節度のある飲酒をする。

ーお酒を飲む場合はアルコール換算で1日あたり約23g程度まで。日本酒なら1合、ビールなら大瓶1本、焼酎や泡盛なら1合の2/3、ウィスキーやブランデーならダブル1杯、ワインならボトル1/3程度です。飲まない人、飲めない人は無理に飲まない。

食事　：　偏らずにバランスよく。

＊　塩蔵食品、食塩の摂取は最小限に。

ー食塩は1日あたり男性9g、女性7.5g未満、特に、高塩分食品（たとえば塩辛、練りうになど）は週に1回未満に控えましょう。

＊　野菜や果物不足にならない。

＊　飲食物を熱い状態でとらない。

身体活動　：　日常生活を活動的に。

ーたとえば、ほとんど座って仕事をしている人なら、ほぼ毎日合計60分程度の歩行などの適度な身体活動に加えて、週に1回程度は活発な運動（60分　程度の早歩きや30分程度のランニングなど）を加えましょう。

体形　：　適正な範囲内に。

ー中高年期男性の適正なBMI値（Body Mass Index 肥満度）は21～27、中高年期女性では19～25です。この範囲内になるように体重を管理しましょう。

BMIの求め方　BMI 値 = 体重kg / (身長m)^2

感染　：　肝炎ウイルス感染検査と適切な措置を。

ー地域の保健所や医療機関で、一度は肝炎ウイルスの検査を受けましょう。感染している場合は専門医に相談しましょう。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Obesity and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Objective: With increased interest in non-alcoholic steatohepatitis, its common co-morbid condition, obesity, has recently attracted much attention as a risk factor for liver cancer. Recent studies also suggest that obesity may play a role in the development of liver cancer in alcoholic cirrhosis or viral hepatitis and in the general population.
Methods: We systematically reviewed epidemiologic studies on overweight/obesity and liver cancer among Japanese populations. Original data were obtained by searching the MEDLINE (PubMed) and *Ichushi* databases, complemented by manual searches. The evaluation was performed in terms of the magnitude of association in each study and the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient'), together with biologic plausibility.
Results: Among nine cohort studies identified, five (four on patients with chronic liver disease and one on local residents) reported a weak to strong positive association, while four (one on patients with hepatitis B and three on local residents) found no association [summary relative risk for one unit increase in body mass index (kg/m^2) 1.07, 95% confidence interval 1.03–1.10]. All three case–control studies identified (two on cirrhotic patients and one on atomic bomb survivors) reported a strong positive association (summary relative risk 1.31, 95% confidence interval 1.12–1.53). Overall, the summary relative risk was estimated at 1.13 (95% confidence interval 1.07–1.20), and overweight/obese individuals had a relative risk of 1.74 (95% confidence interval 1.33–2.28) compared with those who had normal/low weight.
Conclusions: We conclude that overweight or obesity 'probably' increases the risk of primary liver cancer, to a moderate degree, among the Japanese population.

Key words: systematic review – epidemiology – obesity – liver cancer – Japanese

INTRODUCTION

Although chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) (1) and alcohol consumption (2–4) represent dominant risk factors for hepatocellular carcinoma, the most prevalent type (>90%) of primary liver cancer in Japan (5), recent studies have highlighted non-alcoholic steatohepatitis (NASH) as an additional risk factor that occasionally leads to this malignancy via the development of idiopathic or cryptogenic cirrhosis (6–8). NASH is the severe inflammatory form of non-alcoholic fatty liver disease characterized by hepatic steatosis in the absence of excessive alcohol consumption, and its common co-morbid conditions include obesity and type 2 diabetes mellitus like other lifestyle-related diseases (8,9). In this context, overweight and obesity have been examined in causation of liver cancer, and accumulating evidence suggests that overweight or obese people with not only NASH (8) but also alcoholic cirrhosis (10) or viral hepatitis (particularly, hepatitis C) (11) as well as those in the general population (12,13) may have an increased risk of liver cancer.

According to the second report published by the World Cancer Research Fund and the American Institute for Cancer Research (2), there is limited evidence suggesting that greater body fatness is a cause of liver cancer. However, two recent systematic reviews (14,15) conclude that overall evidence is suggestive of an increased liver cancer risk in obese and overweight individuals; the summary relative risks (RRs) were estimated to be 1.17 [95% confidence interval (CI) 1.02–1.34] for those who were overweight and 1.89 (1.51–2.36) for those who were obese, when compared with persons of normal weight (14). The objective of this systematic review was to review and summarize up-to-date epidemiologic findings on overweight, obesity and liver cancer among the Japanese who predominantly possess viral origins (i.e. HCV and HBV) of liver cancer (5,16). This work was conducted as part of a project of systematic evaluation of the epidemiologic evidence regarding lifestyles and cancers in Japan (17).

METHODS

The details of the evaluation method have been described elsewhere (17). In brief, original data for this review were identified by searching 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 overweight/obesity and liver cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to July 2011, including papers in press if available, were identified using the search terms 'obesity', 'body mass index', 'liver neoplasms', 'hepatocellular', 'cohort', 'follow-up', 'case-control', 'Japan' and 'Japanese' as keywords. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately by study design as cohort or case–control studies.

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying the RR in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) 'strong' (symbol $\downarrow\downarrow\downarrow$ or $\uparrow\uparrow\uparrow$) when RR $<$ 0.5 (SS) or RR $>$ 2.0 (SS); (ii) 'moderate' (symbol $\downarrow\downarrow$ or $\uparrow\uparrow$) when RR $<$ 0.5 (NS), 0.5 $\leq$ RR $<$ 0.67 (SS), 1.5 $<$ RR $\leq$ 2.0 (SS) or RR $>$ 2.0 (NS); (iii) 'weak' (symbol $\downarrow$ or $\uparrow$) when 0.5 $\leq$ RR $<$ 0.67 (NS), 0.67 $\leq$ RR $\leq$ 1.5 (SS) or 1.5 $<$ RR $\leq$ 2.0 (NS); and (iv) 'no association' (symbol –) when 0.67 $\leq$ RR $\leq$ 1.5 (NS); the RR used in this paper denotes ratio measures of effect, including risk ratios, rate ratios, hazard ratios and odds ratios. When RRs for three or more exposure levels were reported, the RR for the highest level was employed for this classification. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or most updated results were included. Studies that reported RRs for indefinite exposure levels or did not provide RRs or data necessary for the present authors to calculate relevant RRs were excluded.

After the above process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient' (18). Biologic plausibility was also taken into account for this evaluation. The final judgment was made based on a consensus of the research group members. When we reach a conclusion that there is 'convincing' or 'probable' evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

In meta-analyses of this paper, we estimated the summary RR for one unit increase in the body mass index (BMI; weight in kilograms divided by the square of height in meters) to fully utilize and summarize data from as many studies as possible. When a study of interest reported the RRs for three or more categories of BMI, we performed a variance-weighted log-linear regression analysis within each study to obtain the RR corresponding to the above summary measure, by assigning mid-point values to closed categories (e.g. 21–23 kg/m^2) or assumed representative values to open categories (e.g. <25 kg/m^2), for which appropriate values based on original data could not be obtained from the corresponding authors in relevant studies. These representative values were derived from sex-specific median values for the corresponding BMI categories according to the baseline data of the Japan Public Health Center-based prospective study (19). For studies reporting the RR comparing two open categories (e.g. ≥25 vs. <25 kg/m^2), the representative value was similarly assigned to each category. After calculating the corresponding RR in each study, we obtained the summary RR and its 95% CI based on either the general

Table 1. Cohort studies on obesity and liver cancer among Japanese

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P* value)	*P* value for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Ohata et al. (22)	1980–2000	161 (106 men and 55 women)	Patients with chronic hepatitis or cirrhosis due to HCV infection	Incidence	70	Body mass index (kg/m^2)				Sex, age, diabetes, drinking, ALT, HCV serotype, HCV core titer, interferon treatment, cirrhosis, histologic grading, steatosis	All patients were anti-HCV-positive and HBsAg-negative
						<25?		1.00			
						≥25?		1.67 (0.80–3.46)			
Kuriyama et al. (23)	1984–92	27 539 (15 054 women and 12 485 men)	Residents in 3 municipalities of Miyagi Prefecture	Incidence	100 (31 women and 69 men)	For women				Age, smoking, drinking, meat, fish, fruits, green or yellow vegetables, bean-paste soup, type of health insurance, menopausal status, parity, age at menarche, age at first pregnancy	HBsAg and anti-HCV were not tested
						Body mass index (kg/m^2)					
						18.5–24.9	20	1.00	0.94		
						25.0–27.4	7	1.30 (0.54–3.16)			
						27.5–29.9	4	0.91 (0.30–2.80)			
						≥30.0	0	—			
						For men				Age, smoking, drinking, meat, fish, fruits, green or yellow vegetables, bean-paste soup, type of health insurance	
						Body mass index (kg/m^2)					
						18.5–24.9	55	1.00	0.92		
						25.0–27.4	9	0.80 (0.40–1.63)			
						27.5–29.9	5	1.14 (0.46–2.87)			
						≥30.0	0	—			
Khan et al. (24)	1977–2002	1989 (908 men and 1081 women)	Residents of Tanno and Sohbetsu towns of Hokkaido	Death	8 (6 men and 2 women)	Body mass index				Sex, age	HBsAg and anti-HCV were not tested
						Quartile 1	3	1.00			
						Quartile 2	1	0.34 (0.04–3.29)			
						Quartile 3	2	0.80 (0.13–4.82)			The cut-off points for the quartiles were not described
						Quartile 4	2	0.83 (0.14–5.09)			
Muto et al. (25)	Not described	622 (294 men and 328 women)	Patients with decompensated cirrhosis who had hypoalbuminemia	Incidence	89	Body mass index (kg/m^2)				Treatment group (BCAA supplementation and diet therapy)	Anti-HCV and, probably, HBsAg status was available but was not adjusted for
						One unit increase		1.42 (1.03–1.96)			
Fujino (26)	1988–2003	109 778 (46 178 men and 63 600 women)	Residents in 45 areas in Japan	Death	690 (463 men and 227 women)	For men				Age, study area	HBsAg and anti-HCV were not tested
						Body mass index (kg/m^2)					
						<18.5	36	1.34 (0.94–1.90)			
						18.5–24	323	1.00			
						25–29	72	1.01 (0.78–1.30)			
						≥30.0	6	1.46 (0.65–3.28)			
						For women				Age, study area	
						Body mass index (kg/m^2)					
						<18.5	8	0.56 (0.27–1.15)			
						18.5–24	134	1.00			
						25–29	53	1.31 (0.95–1.81)			
						≥30.0	5	1.09 (0.44–2.69)			

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)

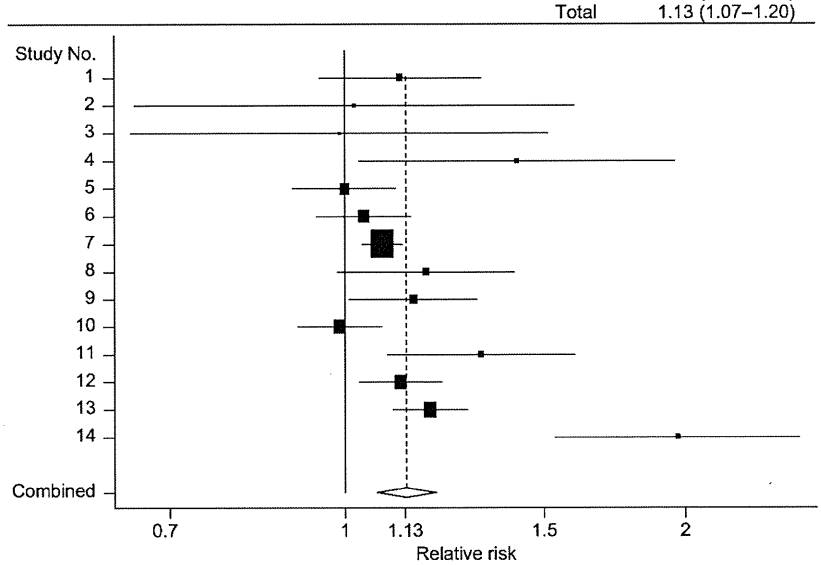

Figure 1. Forest plot of the relative risks (RRs) and their 95% confidence intervals (CIs) of liver cancer for one unit increase in body mass index (BMI) in cohort and case–control studies evaluated and the corresponding summary RR. For cohort studies, the individual RRs were not significantly heterogeneous [$Q = 11.0$ 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	
Saeki 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)		