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研究成果の刊行に関する一覧表

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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

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Public Health Report

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. $\geq$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)			