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Cigarette Smoking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among Japanese

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

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

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Background: Emerging epidemiologic data suggest that cigarette smoking may increase the risk of primary liver cancer. We evaluated this association based on a systematic review of epidemiologic evidence among Japanese populations.
Methods: Original data were obtained from MEDLINE searches using PubMed, complemented with manual searches. The evaluation was performed in terms of the magnitude of association ('strong', 'moderate', 'weak' or 'no association') in each study and the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient'), together with biological plausibility as previously done by the International Agency for Research on Cancer.
Results: A total of 12 cohort studies and 11 case–control studies were identified. Nine cohort studies (two with adjustment for hepatitis B and C virus infections and seven without it) reported weak to strong positive associations between smoking and liver cancer, with dose–response relationships shown in three studies. Five case–controls studies (three with the virus adjustment and two without it) demonstrated such positive associations, with a dose–response relationship shown in only one study, while in six case–control studies, the observed associations were judged to be of the lowest magnitude or inverse due to the lack of any dose–response relationship.
Conclusion: We conclude that cigarette smoking 'probably' increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

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

INTRODUCTION

Primary liver cancer is one of the most common cancers in Japan (1). Its primary prevention remains to be a major concern for both clinicians and epidemiologists, since patients with this tumor still present poor prognosis (1,2). More than 90% of primary liver cancers in Japan are known to be hepatocellular carcinomas (2), which are mostly attributable to chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) (2,3). However, emerging evidence suggests that hepatocarcinogenesis is a multistage process, in which environmental factors other than hepatitis viruses may play additional roles (4). One of such candidates is cigarette smoking, which has not yet attracted much attention of clinicians or the public. Recently, the International Agency for Research on Cancer listed liver cancer as a tobacco-related malignancy (5). In this context, the objective of the present study was to review and summarize epidemiological findings on cigarette smoking and liver cancer among Japanese populations. This work was

*Research group members: Shoichiro Tsugane [principal investigator], Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (National Cancer Center, Tokyo); Ichiro Tsuji [since 2004], Yoshitaka Tsubono [in 2003], Taichi Shimazu (Tohoku University, Sendai); Kenji Wakai (Aichi Cancer Center, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (Kyushu University, Fukuoka); Keitaro Tanaka (Saga University, Saga).

For reprints and all correspondence: Keitaro Tanaka, MD, Department of Preventive Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan; E-mail: tanakake@post.saga-med.ac.jp

conducted as part of a project of systematic evaluation of the epidemiological evidence regarding lifestyles and cancers in Japan (6).

METHODS

The details of the evaluation method have been described elsewhere (6). In brief, original data for this review were identified by MEDLINE searches using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and liver cancer incidence or mortality among the Japanese from 1963 to 2005, including papers in press if available, were identified using the search terms 'smoking', 'liver', '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 a 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 relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) 'strong' (symbol ↓↓↓ or ↑↑↑) when RR < 0.5 (SS) or RR > 2.0 (SS); (ii) 'moderate' (symbol ↓↓ or ↑↑) when RR < 0.5 (NS), 0.5 ⩽ RR < 0.67 (SS), 1.5 < RR ⩽ 2.0 (SS) or RR > 2.0 (NS); (iii) 'weak' (symbol ↓ or ↑) when 0.5 ⩽ RR < 0.67 (NS), 0.67 ⩽ RR ⩽ 1.5 (SS) or 1.5 < RR ⩽ 2.0 (NS) and (iv) 'no association' (symbol −) when 0.67 ⩽ RR ⩽ 1.5 (NS). When RRs for three or more exposure levels were reported, that for the highest level was employed for this classification. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included. After this process, the strength of evidence was evaluated in a similar manner 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 corresponded to the judgment of the most recent evaluation from the International Agency for Research on Cancer (5). Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. 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.

MAIN FEATURES AND COMMENTS

We identified a total of 12 cohort studies (8–19) (Table 1) and 11 case–control studies (20–30) (Table 2). Of the cohort studies, three presented results by sex (9,14,19), four for men only (8,10,11,18) and five only for men and women combined (12,13,15–17). The respective numbers for the case–control studies are one (29), five (20,24–27) and five (21–23,28,30). One cohort study showed results separately in two different areas (11), and two case–control studies reported results separately based on hospital controls and community controls (25,29).

Study populations in the cohort studies were classified as two different types: mostly healthy subjects ($n = 7$) such as local residents (9,11,17–19), physicians (8) and atomic bomb survivors (14) versus patients with chronic liver disease (10,12,13,15,16) ($n = 5$) (Table 1). Chronic infections with both HCV and HBV were taken into account in only three studies, all of which followed patients with chronic liver disease (13,15,16). In the case–control studies, a similar classification was possible based on the type of controls: hospital or community controls (21–25,27–30) ($n = 9$) versus HBV carriers (20) or patients with chronic liver disease without liver cancer (26) ($n = 2$) (Table 2). In only two case–control studies, both HCV and HBV infections were controlled for (26,28).

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 3 and 4, respectively. Among all 12 cohort studies, five (9,13–15,19) reported strong positive associations of cigarette smoking with liver cancer in either sex or for both sexes combined (Tables 1 and 3); of the five studies, three (9,13,15) demonstrated clear dose–response relationships. Moderate, but not strong, positive associations were found in three cohort studies (10,11,18), and a weak association in one cohort study (17), without any presentation of dose–response relation. In the remaining three (8,12,16), virtually no association was observed. Among the seven cohort studies in which mostly healthy subjects were followed, six (9,11,14,17–19) revealed at least weak positive associations, whereas three (10,13,15) out of the five follow-up studies of patients with chronic liver disease showed such positive associations.

Among all 11 case–control studies, five (20,26–29) reported weak to strong positive associations with cigarette smoking, with a dose–response relationship presented in only one study (20) (Tables 2 and 4). In the remaining six studies (21–25,30), the observed associations were judged to be null or inverse due to the lack of dose–response relationship, although around 2- to 4-fold risk excess in light to moderate exposure categories was observed in five of them (21–25). In the nine case–control studies employing hospital or community controls, three (27–29) demonstrated at least weak positive associations, whereas both case–control studies using controls of HBV carriers or patients with chronic liver disease (20,26) afforded such positive associations.

In the cohort studies, cigarette smoking was almost consistently associated with elevated liver cancer risk. Information and selection biases may not be serious issues in those studies. However, potential confounding by chronic HBV and HCV

Table 1. Cohort studies on cigarette smoking and liver cancer among Japanese

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Kono et al. (8)	1965–1983	5130 men	Male physicians in western Japan	Death	51 men (primary 9, unspecified 42)	Never/past		1.00		Age, drinking	HBsAg and anti-HCV were not tested
						1–19 cigarettes/day		1.14 (0.59–2.20)			
						⩾20 cigarettes/day		1.04 (0.49–2.23)			
Akiba and Hirayama(9)	1966–1981	265 118 (122 261 men and 142 857 women)	95% of the census population in 29 health-center-covered areas in 6 prefectures	Death	1050 (652 men and 398 women)	For men				Age, prefecture, occupation, observation period	HBsAg and anti-HCV were not tested. Adjustment for alcohol consumption only slightly changed the relative risks
						Never	106	1.0	0.002		
						Daily	546	1.5 (1.2–1.9)			
						1–4/day	8	1.1 (0.5–2.0)			
						5–14/day	240	1.6 (1.3–2.0)			
						15–24/day	254	1.4 (1.2–1.8)			
						25–34/day	29	1.6 (1.1–2.4)			
						⩾35/day	15	1.9 (1.1–3.2)			
						For women					
						Never	334	1.0	0.001		
						Daily	64	1.6 (1.2–2.0)			
						1–4 /day	9	1.4 (0.7–2.5)			
						5–14 /day	42	1.4 (1.0–2.0)			
						⩾15 /day	13	2.5 (1.3–4.1)			
Inaba et al. (10)	1973–1988	270 men	Patients with liver cirrhosis at the Juntendo University Hospital	Death	46 men	Never		1.00		Age, HBsAg, histories of transfusion, hepatitis and surgical operation, drinking	Anti-HCV was not tested
						Current/past		2.57 (0.46–14.24)			
Shibata et al. (11)	1958–1986	639 men in a farming area and 677 men in a fishing area	Residents in a farming or a fishing area in Kyushu	Death	11 men (farming area) and 22 men (fishing area)	Farming area					
						Non-smoker	2	1.0	>0.1	Age	HBsAg and anti-HCV were not tested
						Ex-smoker	0	–			
						Current smoker	8	1.1 (0.2–4.7)			
						1–9/day	1	0.6 (0.1–3.7)			
						10–19/day	7	1.2 (0.2–5.7)			
						20–29/day	0	–			
						⩾30/day	0	–			
						Fishing area					
						Non-smoker	1	1.0	>0.1	Age	
						Ex-smoker	2	2.9 (0.3–29.0)			

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						Current smoker	19	3.6 (0.6–22.3)			
						1–9/day	7	11.9 (1.5–96.8)			
						10–19/day	3	1.1 (0.1–10.6)			
						20–29/day	7	2.7 (0.4–19.2)			
						⩾30 /day	2	3.2 (0.4–23.7)			
						Fishing area					
						Non/ex-smoker	3	1.00		Age, drinking	
						1–19/day	10	2.10 (0.44–9.95)			
						⩾20/day	9	1.86 (0.37–9.40)			
Kato et al.(12)	1987–1990	1784	Patients with decompensated liver cirrhosis or post-transfusion hepatitis	Incidence	122	Never smoker	39	1.00		Sex, age	HBsAg and anti-HCV status was unknown
						Past smoker	10	0.94 (0.44–2.02)			
						Current smoker	23	0.96 (0.53–1.75)			
						Smoking index					
						0	39	1.00	0.82		
						1–599	11	0.83 (0.40–1.74)			
						⩾600	14	0.94 (0.47–1.89)			
Tsukuma et al. (13)	1987–1991	917 (548 men and 369 women)	Patients with chronic hepatitis or compensated cirrhosis at the Center for Adult Diseases, Osaka	Incidence	54	Among all patients				Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, drinking	HBsAg and anti-HCV status was adjusted for
						Non-smoker		1.00	0.07		
						Ex-smoker		1.68 (0.63–4.47)			
						Current smoker		2.30 (0.90–5.86)			
						Among patients with liver cirrhosis					
						Non-smoker		1.00	0.003		
						Ex-smoker		3.44			
						Current smoker		7.96			
Goodman et al. (14)	1980–1989	36 133	Atomic bomb survivors	Incidence	242 (156 men and 86 women)	For men				Sex, city, age at the time of bombing, age, radiation dose to the liver	HBsAg and anti-HCV was not tested
						Never-smoker	6	1.00			
						Ever-smoker	146	4.36 (1.93–9.86)			
						Ex-smoker	46	4.56 (1.95–10.7)			
						Quit ⩾24 years ago	14	4.04 (1.54–10.6)			
						Quit 14–23 years ago	14	4.11 (1.58–10.7)			
						Quit <14 years ago	14	5.60 (2.15–14.6)			
						Present smoker	100	4.26 (1.87–9.72)			
						1–22 pack-years	38	6.47 (2.74–15.3)			

						23–40 pack-years	39	4.43 (1.87–10.5)		
						⩾41 pack-years	41	3.09 (1.31–7.29)		
						For women				
						Never-smoker	61	1.00		
						Ever-smoker	20	1.60 (0.97–2.66)		
						Ex-smoker	7	1.66 (0.76–3.63)		
						Quit ⩾25 years ago	3	2.31 (0.72–7.43)		
						Quit 10–24 years ago	2	1.03 (0.25–4.24)		
						Quit <10 years ago	2	10.4 (2.51–43.5)		
						Present smoker	13	1.58 (0.86–2.88)		
						1–15 pack-years	8	1.81 (0.86–3.78)		
						⩾16 pack-years	8	1.51 (0.72–3.16)		
Chiba et al.(15)	1977–1993	412 (249 men and 163 women)	Patients with HCV-associated chronic hepatitis or compensated cirrhosis at the Tsukuba University Hospital	Incidence	63 (54 men and 9 women)	Non-smoker		1.00		Sex, age, stage of disease, serum alpha-fetoprotein, anti-HBs, anti-HBc, histories of transfusion, surgical procedure and liver cancer in family, drinking
						Smoking index <400		1.67 (0.75–3.73)		
						Smoking index ⩾400		2.46 (1.11–5.49)		
Tanaka et al. (16)	1985–1995	96 (62 men and 34 women)	Patients with liver cirrhosis at the Kyushu University Hospital	Incidence	37 (27 men and 10 women)	Never smoker	12	1.00		Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, drinking
						Past smoker	12	0.44 (0.11–1.79)		
						Current smoker				
						<20 cigarettes/day	9	1.46 (0.29–7.37)		
						⩾20 cigarettes/day	4	1.00 (0.19–5.28)		
Mori et al.(17)	1992–1997	3052 (974 men and 2078 women)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	History of cigarette smoking				Sex, age
						No	10	1.00		
						Yes	22	2.10 (0.61–7.23)		
						Never-smoker	10	1.00	0.30	
						Smoking index <200	1	3.26 (0.38–28.2)		
						Smoking index ⩾200	11	1.97 (0.57–6.87)		
Mizoue et al. (18)	1986–1996	4050 men	Residents in 4 municipalities in Fukuoka prefecture	Death	59 men	Never smoker	4	1.0		Age, study area, drinking
						Ex-smoker	22	2.9 (1.0–8.4)		
						Current smoker	33	3.3 (1.2–9.5)		
						1–24 cigarettes/day	25	3.5 (1.2–10.2)		
						⩾25 cigarettes/day	8	2.8 (0.8–9.6)		
Ogimoto et al. (19)	1988–1999	65 528 (28 287 men and 37 241 women)	Residents in 45 areas throughout Japan	Death	186 (number by sex not described)	Men (40–59 years)				Collaborating institutes
						Never smoker		1.00		
						Ex-smoker		2.37 (0.83–6.78)		

All subjects were anti-HCV-positive and HBsAg-negative
The relative risks were not described in the original paper, and were re-estimated by one of the authors (KT). HBsAg and anti-HCV status was adjusted for
Anti-HCV and HBsAg status was available, but not adjusted for
HBsAg and anti-HCV were not tested
HBsAg and anti-HCV were not tested

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						Current smoker		1.96 (0.75–5.14)			
						Men (60–79 years)					
						Never smoker		1.00			
						Ex-smoker		2.72 (1.21–6.11)			
						Current smoker		2.62 (1.18–5.84)			
						Women (40–59 years)					
						Never smoker		1.00			
						Ex-smoker		–			
						Current smoker		2.82 (0.61—13.09)			
						Women (60–79 years)					
						Never smoker		1.00			
						Ex-smoker		1.18 (0.16–8.67)			
						Current smoker		1.49 (0.46–4.87)			

CI, confidence interval; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; LC, liver cirrhosis; AST, aspartate aminotransferase.

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

Reference	Study period	Study subjects				Category	Relative risk (95%CI or P)	P for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Oshima et al. (20)	1972–1980	Nested case–control (HBsAg-positive blood donors at the Osaka Red Cross Blood Center)	Cases: confirmed by record linkage with the Osaka Cancer Registry; Controls: healthy HBV carriers	19 men	38 men	None or <10/day	1.0	>0.10	Matched (1:2) for birth year Adjusted for drinking	All subjects were HBsAg-positive. Anti-HCV was not tested
						10–29/day	1.2			
						⩾30/day	6.3			
Tsukuma et al. (21)	1983–1987	Hospital-based (Center for Adult Diseases, Osaka)	Cases: histologically confirmed as HCC; Controls: inpatients with gastrointestinal disease, or examinees for health checkups or gastroendoscopy; no liver disease, cancer, or smoking/alcohol-related disease	229 (192 men and 37 women)	266 (192 men and 74 women)	Never	1.0		Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, drinking, and family history of liver cancer	Anti-HCV was not tested
						Ex-smoker	0.7 (0.3–1.9)			
						Current smoker	2.5 (1.4–4.5)			
						1–19/day	4.2			
						20–39/day	2.2			
						⩾40/day	1.1			
						Cigarette index				
						0–399	1.0			
						400–799	1.9 (1.1–3.3)			
						800–1199	2.0 (1.1–3.6)			
						⩾1200	1.0 (0.5–1.9)			
Tanaka et al. (22)	1985–1989	Hospital-based (Kyushu University Hospital)	Cases: 40% were histologically confirmed as HCC; Controls: health examinees at a public health center	204 (168 men and 36 women)	410 (291 men and 119 women)	Non-smoker	1.0		Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of transfusion, drinking, and family history of liver disease	Anti-HCV status was available for part of the subjects, but not adjusted for
						Ex-smoker	1.5 (0.8–2.8)			
						Current smoker	1.5 (0.8–2.7)			
						Pack-years		0.41		
						0–10.9	1.0			
						11.0–26.2	1.4 (0.8–2.4)			
						26.3–35.9	1.3 (0.7–2.5)			
						⩾36.0	1.3 (0.7–2.5)			
Fukuda et al. (23)	1986–1992	Hospital-based (Kurume University Hospital)	Cases: 77% were histologically confirmed as HCC; Controls: inpatients without chronic hepatitis or cirrhosis in two general hospitals in Kurume	368 (287 men and 81 women)	485 (287 men and 198 women)	Never	1.0		Matched (1:1 for men and 1:4 for women) for sex, age (±5 years), residence, and time of hospitalization. Adjusted for sex	The odds ratios (and 95% CIs) and P value for trend were not described in the original paper, and were estimated by one of the authors (KT), based on the Mantel–Haenszel and Mantel Extension methods
						Ex-smoker	1.3 (0.8–2.2)			
						Current smoker	1.8 (1.1–3.1)			
						Cigarette index				
						Non-smoker	1.0	0.48		
						1–499	1.7 (1.0–2.8)			
						500–999	1.5 (0.9–2.5)			
						⩾1000	0.6 (0.3–1.4)			

Table 2. *Continued*

Reference	Study period	Study subjects				Category	Relative risk (95%CI or P)	P for trend	Confounding variables considered	Comments
		Type and source	Definition	Number of cases	Number of controls					
Murata et al. (24)	1984–1993	Nested case–controls (male participants in a gastric mass screening by the Chiba Cancer Association)	Cases: confirmed by record linkage with the Chiba Cancer Registry; Controls: participants in the screening without liver cancer	66 men	132 men	Cigarettes/day			Matched (1:2) for sex, birth year (±2 years), and the first digit of the address code. No adjustment	Anti-HCV and HBsAg were not tested
						None	1.0	0.75		
						1–10	1.4			
						11–20	2.0 ($P < 0.05$)			
						⩾21	0.4			
Shibata et al. (25)	1992–1995	Hospital-based (Kurume University Hospital)	Cases: confirmed as HCC by histological, angiographical, and/or other findings; Hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume	115 men	115 male HCs and 115 male CCs	Cigarette index, based on HCs			Matched (1:1) for sex, age (±5 years for HCs and ±3 years for CCs), residence (for HCs) and time of hospitalization (for HCs). Adjusted for matching factors	Anti-HCV and HBsAg status was available, but not adjusted for
						Non-smoker	1.0			
						1-499	1.6 (0.6–4.0)			
						500-999	1.2 (0.5–2.9)			
						⩾1000	0.7 (0.2–2.0)			
						Cigarette index, based on CCs				
						Non-smoker	1.0			
						1-499	2.1 (0.9–4.7)			
						500-999	1.9 (0.8–4.6)			
						⩾1000	1.2 (0.4–3.5)			
Mukaiya et al. (26)	1991–1993	Hospital-based (Sapporo Medical University Hospital)	Cases: histologically and/or clinically confirmed as HCC; Controls: chronic liver disease (hepatitis or cirrhosis) without HCC	104 men	104 men	Non-smoker	1.00		Matched (1:1) for age (±3 years). Adjusted for age	Additional adjustment for drinking and HBV and HCV infections did not materially alter the results
						Ever-smoker	3.50 (1.41–8.70)			
						Period < 5years	1.00			
						Period ⩾ 5years	3.33 (1.34–8.30)			
						Cigarette index				
						<200	1.00			
						⩾200	3.33 (1.34–8.30)			
Takeshita et al. (27)	1993–1996	Hospital-based (20 major hospitals in the southern part of Hyogo prefecture)	Cases: 64% were histologically confirmed as HCC; Controls: outpatients or inpatients with various diseases, but without liver disease positive for HBsAg and/or anti-HCV	102 (85 men and 17 women)	125 (101 men and 24 women)	Men			Frequency matched for hospital, sex, age, and living area Adjusted for age and drinking	All the controls were HBsAg-negative and anti-HCV-negative by definition
						Non-smoker	1.0			
						Ex-smoker	0.7 (0.3–1.5)			
						Current smoker	1.6 (0.7–3.5)			
						Women				
						Not described				

Koide et al. (28)	1994	Hospital-based (Nagoya City University Hospital)	Cases: clinically and/or histologically confirmed as HCC; community controls: selected from the same resident community as cases, with no signs of hepatic diseases or HCC	84 (64 men and 20 women)	84 (64 men and 20 women)	Never Current + former	1.00 5.41 (1.10–26.70)	Matched (1:1) for sex and age (±2 years) Adjusted for sex, age, history of blood transfusion, anti-HBc, anti-HCV, and CYP2E1	
Matsuo et al. (29)	1995–2000	Hospital-based (Kurume University Hospital)	Cases: confirmed as HCC by histological, angiographical, and/or other findings; hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume	222 (177 men and 45 women)	326 HCs (177 men and 149 women) and 222 CCs (177 men and 45 women)	Men based on HCs Non-smoker 1–24 pack-years 25-49 pack-years ⩾50 pack-years Men based on CCs Non-smoker 1–24 pack-years 25–49 pack-years ⩾50 pack-years Women based on HCs Non-smoker 1–24 pack-years ⩾25 pack-years Women based on CCs Non-smoker 1–24 pack-years ⩾25 pack-years	 1.00 2.95 ($P < 0.05$) 2.15 ($P < 0.05$) 1.13 1.00 4.39 ($P < 0.05$) 2.75 ($P < 0.05$) 2.90 ($P < 0.05$) 1.00 1.69 0.68 1.00 2.00 ∞	Matched for sex (1:4 for female HCs and 1:1 for other controls), age (±5 years for HCs and ±3 years for CCs), residence (for HCs), and time of hospitalization (for HCs) Adjusted for matching factors	Anti-HCV and HBsAg status was available except for CCs, but not adjusted for
Munaka et al. (30)	1997–1998	Hospital-based (University of Occupational and Environmental Health Hospital)	Cases: no detailed description; controls: no evidence of cancer in any organ	78 (61 men and 17 women)	139 (94 men and 44 women)	Cigarette index Never 1 ⩽ 400 400 ⩽ 800 ⩾800	 1.00 1.14 (0.58–2.25) 1.09 (0.56–2.14) 1.09 (0.56–2.15)	Unmatched. Adjusted for sex and age	Anti-HCV and HBsAg status was available, but not adjusted for

CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; anti-HCV, antibody to hepatitis C virus; HCC, hepatocellular carcinoma; HCs, hospital controls; CCs, community controls; HCV, hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; CYP2E1, cytochrome P450 2E1.

Table 3. Summary of cohort studies on cigarette smoking 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	
Kono et al. (8)	1965–1983	Men	5130	Not specified	Death	51	–
Akiba and Hirayama (9)	1966–1981	Men	122 261	⩾40	Death	652	↑↑
		Women	142 857	⩾40	Death	398	↑↑↑
Inaba et al. (10)	1973–1988	Men	270 (liver cirrhosis)	Not specified	Death	46	↑↑
Shibata et al. (11)	1958–1986	Men	639 (farming area)	40–69	Death	11	–
			677 (fishing area)	40–69	Death	22	↑↑
Kato et al. (12)	1987–1990	Men and women	1784 (cirrhosis and post-transfusion hepatitis)	⩾16	Incidence	122	–
Tsukuma et al. (13)	1987–1991	Men and women	917 (chronic liver disease)	40–69	Incidence	54	↑↑↑
Goodman et al. (14)	1980–1989	Men	36 133 (men and women)	Not specified	Incidence	156	↑↑↑
		Women		Not specified	Incidence	86	↑
Chiba et al. (15)	1977–1993	Men and women	412 (HCV-associated chronic liver disease)	40–72	Incidence	63	↑↑↑
Tanaka et al. (16)	1985–1995	Men and women	96 (liver cirrhosis)	40–69	Incidence	37	–
Mori et al. (17)	1992–1997	Men and women	3052	⩾30	Incidence	22	↑
Mizoue et al. (18)	1986–1996	Men	4050	⩾40	Death	59	↑↑
Ogimoto et al. (19)	1988–1999	Men	28 287	40–79	Death	186 (number by sex not described)	↑↑↑
		Women	37 241	40–79	Death		↑↑

HCV, hepatitis C virus; ↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.

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

Reference	Study period	Study subjects				Magnitude of association
		Sex	Age range	Number of cases	Number of controls	
Oshima et al. (20)	1972–1980	Men	Not specified	19	38	↑↑
Tsukuma et al. (21)	1983–1987	Men and women	⩽74	229	266	–
Tanaka et al. (22)	1985–1989	Men and women	40–69	204	410	–
Fukuda et al. (23)	1986–1992	Men and women	40–69	368	485	↓
Murata et al. (24)	1984–1993	Men	Not specified	66	132	↓↓
Shibata et al. (25)	1992–1995	Men	40–69	115	115 hospital controls	–
					115 community controls	–
Mukaiya et al. (26)	1991–1993	Men	Not specified	104	104 (chronic liver disease)	↑↑↑
Takeshita et al. (27)	1993–1996	Men	Not specified	85	101	↑
Koide et al. (28)	1994	Men and women	46–79	84	84	↑↑↑
Matsuo et al. (29)	1995–2000	Men	40–75	177	177 hospital controls	–
					177 community controls	↑↑↑
		Women	40–75	45	149 hospital controls	–
					149 community controls	↑↑
Munaka et al. (30)	1997–1998	Men and women	34–92	78	138	–

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association; ↓, weakly inverse; ↓↓, moderately inverse.

infections was not addressed in most studies. Since, in Japan, individuals with either or both infections may have more than 100 times higher risk than those without either (3,31), only a slight change in smoking habit among such infected individuals could result in a substantial distortion of associated RRs. Alcohol consumption, another potential confounder, was not adequately controlled in some studies. In addition, the lack of dose–response relationship in three-quarters of the cohort studies has made our conclusion more conservative.

As for the case–control studies, the data have been controversial. In some studies, the recruitment of hospital controls, which possibly included those with smoking-related diseases, may have biased the RRs towards unity. Confounding issues by hepatitis virus infection and alcohol drinking were the same as those in the cohort studies. The absence of dose–response relation in majority of the case–control studies appears very perplexing. Among cases, symptoms resulting from pre-existing liver disease or physicians' advice on their health can lead to lifestyle changes including a reduction in number of cigarettes smoked per day. This might be responsible for elevated risks among light to moderate smokers observed in most case–control studies. However, the situation was similar in the cohort studies where smoking habit many years before the development of liver cancer was evaluated. Some unknown biological implications might exist in these non-linear relations.

An interaction issue between hepatitis viruses and cigarette smoking (i.e. possible difference in risk increase due to smoking according to hepatitis virus infection) should also be considered. Since the great majority of patients with hepatocellular carcinoma in Japan is known to be chronically infected with HBV or HCV (2,3), the following question naturally arises: 'Does smoking increase the risk of hepatocellular carcinoma among people without either HBV or HCV infection?' This question has not fully been addressed, probably due to the difficulty in conducting epidemiologic studies on this subject and its low practical implication in the prevention of liver cancer. It seems biologically implausible that cigarette smoking, without any hepatitis virus infection or heavy alcohol consumption, causes chronic liver disease, thereby playing a major role in hepatocarcinogenesis. On the other hand, the evaluation of the risk for smoking among people infected with HBV or HCV will be easier to be performed and will provide more practical information. It is noteworthy that, based on such evaluations, a limited number of cohort or case–control studies demonstrated clear dose–response relationships between smoking and liver cancer risk (13,15,20).

Finally, the authors consider that it will be problematic to perform a meta-analysis to obtain a summary estimate for the overall magnitude of association, since such an estimate may not be applicable to general populations of the Japanese due to the above interaction issue. Therefore, the planned meta-analysis was not conducted in this particular evaluation. In addition, the authors cannot exclude the possibility of publication bias and missing relevant epidemiologic studies, although they have long been knowledgeable about the situation of such studies in Japan.

EVALUATION OF THE EVIDENCE ON CIGARETTE SMOKING AND LIVER CANCER RISK AMONG JAPANESE

From these results and based on assumed biological plausibility as previously done by the International Agency for Research on Cancer (5), we conclude that cigarette smoking 'probably' increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

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