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

References			Study period	Study population					Magnitude of association
Author	Year	(Ref. no.)		Sex	Number of subjects	Age	Event	Number of incident cases or deaths	
Hirayama T	1990	(5)	1966–1982	Women	142 857	40 years or over	Mortality	241	—
Goodman MT	1997	(6)	1979–1987	Women	22 200	NA	Incidence	161	—
Hanaoka T	2005	(7)	1990–1999	Women	21 805	40–59	Incidence	180	↑↑

NA, not available.
*↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate; ↑or↓, weak; —, no association (see text for more detailed definition).

Table 4. Summary of the association between tobacco smoking and breast cancer risk, case-control study

References			Study period	Study subjects				Magnitude of association*
Author	Year	(Ref. no.)		Sex	Age	Number of cases	Number of controls	
Hirohata T	1985	(8)	Not specified	Women	NA	212	424	—
Kato I	1989	(9)	1980–1986	Women	20 year or over	1740	8920	—
Kato I	1992	(10)	1990–1991	Women	20 year or over	908	908	—
Wakai K	1994	(11)	1990–1991	Women	20 year or over	300	900	↑↑
						168 premenopausal	472 premenopausal	—
						127 postmenopausal	390 postmenopausal	↑↑↑
Hirose K	1995	(12)	1988–1992	Women	18 year or over	607 premenopausal	15 084 premenopausal	↑
						445 postmenopausal	6215 postmenopausal	—
Hu YH	1997	(13)	1989–1993	Women	25 year or over	157	369	↑↑↑
Uegi M	1998	(14)	1990–1997	Women	26–69 year or over	145	240	↑↑↑
						65 premenopausal	96 premenopausal	↑↑
						54 postmenopausal	89 postmenopausal	↑↑↑
Tung HT	1999	(15)	1990–1995	Women	Cases (mean = 51.6)	376	430	—
					Controls (mean = 54.5)	190 premenopausal	119 premenopausal	—
						186 postmenopausal	282 postmenopausal	—

NA, not available.
*↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate; ↑or↓, weak; —, no association (see text for more detailed definition).

among women who smoke. Concerning these genotypes, Japanese appear to have higher frequency for GSTT1-null and CYP1A1*2A but not for the others compared with Caucasians (36–38). Confounding by other unmeasured factors, such as diet including phytoestrogen intake, cannot be excluded.

Integration of evidence based on case-control studies is compromised because of limitations in participants' memory of past exposure history and selection biases introduced in the recruitment of cases and controls. There was a tendency that positive association was reported in the case-control studies with small sample size. In addition, we cannot exclude the effect of publication bias. The number of cohort studies is insufficient to draw a definite conclusion.

EVALUATION OF THE EVIDENCE ON TOBACCO SMOKING AND BREAST CANCER RISK IN JAPANESE

From these results and assumed biological plausibility, we conclude that tobacco smoking possibly increases the risk of breast cancer in the Japanese population.

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

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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

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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					HBsAg and anti-HCV were not tested
						Non-smoker	2	1.0	>0.1	Age	
						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	All subjects were anti-HCV-positive and HBsAg-negative
						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	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
						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	Anti-HCV and HBsAg status was available, but not adjusted for
						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	HBsAg and anti-HCV were not tested
						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	HBsAg and anti-HCV were not tested
						Never smoker		1.00			
						Ex-smoker		2.37 (0.83–6.78)			

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	0.41	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				
						0–10.9	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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Original Article

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

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Background: It remains unclear whether alcohol drinking is causally associated with colorectal cancer. On the basis of a systematic review of epidemiological evidence, we evaluated this association among the Japanese population, who may be more susceptible to alcohol-related diseases than Western populations.

Methods: Original data were obtained from searches of MEDLINE using PubMed, complemented with manual searches. The evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility as previously evaluated by the International Agency for Research on Cancer.

Results: We identified 5 cohort studies and 13 case–control studies. A moderate or strong positive association was observed between alcohol drinking and colon cancer risk in all large-scale cohort studies, with some showing a dose–response relation, and among several case–control studies. The risk of colon or colorectal cancer was increased even among moderate drinkers consuming <46 g of alcohol per day, levels at which no material increase in the risk was observed in a pooled analysis of Western studies. A positive association with rectal cancer was also reported, but it was less consistent, and the magnitude of the association was generally weaker compared with colon cancer.

Conclusion: We conclude that alcohol drinking probably increases the risk of colorectal cancer among the Japanese population. More specifically, the association for the colon is probable, whereas that for the rectum is possible.

Key words: systematic review – epidemiology – alcohol drinking – colorectal cancer – Japanese

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INTRODUCTION

In Japan, colorectal cancer has markedly increased over the last several decades (1) and its incidence is now among the highest levels in the world (2). Such chronological trend in colorectal cancer may be attributable to collective changes in various aspects of lifestyles including diet and physical activity. However, the increasing male-to-female gap in colorectal cancer mortality since 1970 in Japan (1) is of note and the contribution

of tobacco smoking or alcohol drinking, both of which are much more prevalent in men than in women (3), is suspected. In our previous work (4), however, we did not find consistent data suggesting a close link of colorectal cancer to smoking among the Japanese.

Although numerous studies reported a positive association between alcohol drinking and colorectal cancer risk, it remains unclear whether alcohol drinking is causally related to carcinogenesis of the colorectum. A report from the World Cancer Research Fund and American Institute for Cancer Research concluded that alcohol drinking 'probably' increases colorectal cancer risk (5), whereas a recent report of a Joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Consultation did not include colorectal cancer in the list of alcohol-related malignancies (6). However, the influence of alcohol drinking is of particular concern for the Japanese because of their relatively high prevalence of the slow-metabolizing ALDH variant (7), associated with higher levels of acetaldehyde in alcohol drinkers.

The objective of the present study was thus to review epidemiological findings regarding the association between alcohol drinking and colorectal cancer among the Japanese population. This work is conducted as a systematic review of epidemiological evidence regarding lifestyles and major forms of cancer in Japan (4,8).

METHODS

The original data for this review were identified by searches of MEDLINE using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiological studies on the association between alcohol drinking and colorectal cancer incidence or mortality among Japanese published from 1965 to 2005 were identified using the search terms 'alcohol', 'colorectal cancer', 'colon cancer', 'rectal cancer', 'cohort studies', 'case–control studies', 'Japan', and 'Japanese' as keywords found in the abstract. 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 and, if available, by cancer site as colon, rectum or colorectum.

An evaluation was made on the basis of the magnitude of association and the strength of evidence. First, the relative risks in each epidemiological study were grouped by the magnitude of association, while considering 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 to 2.0 (SS), or (iii) 0.5 to <0.67 (SS); weak, either (i) >1.5 to 2.0 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association, 0.67–1.5 (NS). 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, and the incidence was given priority over mortality as an outcome measure. The incidence was also given priority in a single publication describing both incidence and mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (6), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility, based on evidence in experimental animals and mechanistic and other relevant data, corresponded to the judgement of the most recent evaluations from the International Agency for Research on Cancer [IARC (9,10)]. 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 judgement was therefore made on the basis of a consensus of the research group members, and it was therefore not necessarily objective.

MAIN FEATURES AND COMMENTS

A total of 5 cohort studies (11–16) and 13 case–controls studies (17–29) were identified (Tables 1 and 2, respectively). As regards Hirayama's study, we referred to two sources; one contained results for the colon and rectum with some additional data for sigmoid colon (13), whereas the other included results of detailed analysis for the sigmoid colon (12). Among the cohort studies, four (12–16) presented results by gender, one (10) for men only. The respective numbers for the case–control studies are two (17,25) and four (19,20,26,29), and the remaining seven studies (18,21–24,27,28) presented results for men and women combined. A summary of the magnitude of association for these studies is shown in Tables 3 and 4 for the cohort studies and case–control studies, respectively.

Four large-scale cohort studies (12–16) showed relative risks separately for colon and rectum. In men, three (14–16) of these studies found a moderate to strong positive association with colon cancer and one (12) reported a strong positive association with sigmoid colon cancer. In women, a moderate association was also observed for colon (14) or sigmoid colon (12). For rectal cancer, one study (15) found a strong positive association in men only, whereas three studies found a weak positive association either in men (13) or in women (14,16). Of the two cohort studies showing relative risk for colon and rectum combined, a nation-wide study (15) reported a strong positive association in men but not in women. A significant dose– or frequency–response relation was observed for cancer of the colon (14), rectum (12,16), or both (15).

Of the 13 case–control studies evaluated, 10 studies (17–21,23–25,28) provided odds ratios for the colon and rectum separately and 1 study presented data for the colon only (22). Among these studies, two studies (17,22) found a strong inverse association between alcohol drinking and colon cancer risk, whereas other three studies (22,26,29) showed a strong positive association for colon and another study (20) found a weak positive association for distal colon. Similar results were observed for rectal cancer, but the association for rectum was less clear than that for colon. Of the four case–control studies (22,27–29) reporting odds ratio for the colon and

Table 1. Alcohol drinking and colorectal cancer risk, cohort study among Japanese populations

Reference	Study period	Study population				Category	No. among cases or deaths	Relative risk (95% confidence interval or *P*)	*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Kono et al. (11)	1965–83	5130 men	Male physicians	Death	Large bowel 39	Never/past	NA	1.00	NA	Age and smoking	
						Occasional	NA	NA			
						Daily	NA	1.21 (0.54–2.72)			
						<2 go	NA	1.09 (0.45–2.68)			
						⩾2	NA	1.40 (0.54–3.61)			
Hirayama (12)	1965–82	265 118 (122 261 men, 142 857 women)	Residents in six prefectures (95% of census population)	Death	Proximal colon Men (number not described)	Non-drinker/rare	NA	1.00		Age	90% confidence intervals were shown. Data for women were not presented. *Adjusted for age, smoking and green-yellow vegetables.
						Occasional/daily	NA	1.07 (0.85–1.35)			
						Non-drinker	NA	1.00			
						Rare	NA	1.02			
						Occasional	NA	1.09			
						Daily	NA	0.98	>0.05		
					Sigmoid colon 43 men	Non-drinker/rare	NA	1.00			
						Occasional/daily	NA	3.95 (1.98–7.86)			
						Non-daily	NA	1.00			
						Daily	NA	2.14 (1.32–3.47)*			
						Non-drinker	NA	1.00			
						Rare	NA	2.03 (0.54–7.32)			
						Occasional	NA	3.83 (1.55–17.42)			
						Daily	NA	5.42 (2.24–13.99)	<0.001		
					Type of beverage	Non-drinker	NA	1.00			
						Sake-drinker	NA	4.56 (1.63–12.19)			
						Non-drinker	NA	1.00			
						Shochu-drinker	NA	5.90 (2.00–17.42)			
						Non-drinker	NA	1.00			
						Bear-drinker	NA	12.67 (3.62–43.66)			
					Women	Non-drinker	NA	1.00			
						Drinker	NA	1.92 (1.13–3.26)			
					Rectum Men (number not described)	Non-drinker	NA	1.00	<0.05		
						Rare	NA	0.95			
						Occasional	NA	1.14			
						Daily	NA	1.39			

Table 1. *Continued*

Reference	Study period	Study population				Category	No. among cases or deaths	Relative risk (95% confidence interval or *P*)	*P* for trend	Confounding variables considered	Comments
		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Hirayama (13)	1965–82	265 118 (122 261 men, 142 857 women)	Residents in six prefectures (95% of census population)	Death	Colon					Age	90% confidence intervals were shown. *The significant trend association remained after adjustment for age and smoking.
					Men	None	NA	1.00			
						Rare	NA	1.06 (0.73–1.54)			
						Occasional	NA	1.35 (1.01–1.82)			
						Daily	NA	1.24 (0.92–1.67)	NS		
					Women	None	NA	1.00			
						Rare	NA	1.18 (0.88–1.57)			
						Occasional	NA	1.10 (0.74–1.63)	NS		
						Daily	NA	NA			
					Sigmoid colon						
					Men	Non-drinker	NA	1.00			
						Drinker	NA	4.38 (1.75–10.97)			
					Women	Non-drinker	NA	1.00			
						Drinker	NA	1.92 (1.13–3.26)			
					Rectum						
					Men	None	NA	1.00			
						Rare	NA	0.96 (0.68–1.35)			
						Occasional	NA	1.15 (0.87–1.51)			
						Daily	NA	1.39 (1.07–1.80)	<0.05*		
					Women	None	NA	1.00			
						Rare	NA	1.23 (0.89–1.70)			
						Occasional	NA	1.27 (0.84–1.94)			
						Daily	NA	0.73 (0.22–2.45)	NS		
Shimizu et al. (14)	1993–2000	29 051 (13 392 men, 15 659 women)	Residents in Takayama	Incidence	Colon					Age, body height, body mass index, smoking and year of education	
					108 men	Non-drinker	5	1.00			
						Current	NA	NA			
						≤36.7 g/day	45	1.79 (0.71–4.55)			
						>36.7	58	2.67 (1.06–6.76)	0.01		
						Non-drinker	5	1.00			
						Sake-drinker (highest)	NA	1.91 (1.10–3.32)			
					94 women	Non-drinker	34	1.00			
						Current	NA	NA			
						≤3.75 g/day	28	1.07 (0.58–1.96)			
						>3.75	32	1.78 (1.00–3.18)	0.03		
					Rectum						
					59 men	Non-drinker	8	1.00			

						Current	NA	NA			
						≤36.7 g/day	20	0.59 (0.25–1.42)			
						>36.7	31	1.17 (0.50–2.73)	0.06		
					41 women	Non-drinker	7	1.00			
						Current	NA	NA			
						≤3.75 g/day	15	1.20 (0.44–3.26)			
						>3.75	19	1.80 (0.70–4.62)	0.17		
Otani et al. (15)	1990–99	90 004 (42 540 men, 47 464 women)	JPHC study (cohort 8544;: 5 prefectures, cohort 8545;: 6 prefectures), residential registry	Incidence	Colorectum 457 men	Non-drinker	87	1.0		Age, family history of colorectal cancer, body mass index, smoking, physical exercise and area	*Among drinkers
						Occasional drinker	24	0.8 (0.5–1.3)			
						Regular drinker	NA	NA			
						1–149 g/week	83	1.1 (0.8–1.5)			
						150–299	107	1.4 (1.1–1.9)			
						≥300	146	2.1 (1.6–2.7)	<0.001		
					259 women	Non-drinker	230	1.0			
						Occasional drinker	12	0.5 (0.3–0.9)			
						Regular drinker	17	0.7 (0.4–1.1)	NA		
					Colon 299 men	Non-drinker	62	1.0			
						Occasional drinker	16	0.8 (0.4–1.3)			
						Regular drinker	NA	NA			
						1–149 g/week	51	1.0 (0.7–1.4)			
						150–299	71	1.3 (0.9–1.8)			
						≥300	99	1.9 (1.4–2.7)	<0.001		
					Rectum						
					148 men	Non-drinker	25	1.0			
						Occasional drinker	8	1.0 (0.5–2.3)			
						Regular drinker	NA	NA			
						1–149 g/week	32	1.6 (0.9–2.6)			
						150–299	36	1.7 (1.01–2.8)			
						≥300	47	2.4 (1.5–4.0)	<0.015		
Wakai et al. (16)	1988–97	57 736 (23 708 men, 34 028 women)	JACC study (24 areas throughout Japan)	Incidence	Colon 220 men	Non-drinker	24	1.00 (reference)		Age, area, education, family history of colorectal cancer, body mass index, smoking, walking time, sedentary work and consumptions of green leafy vegetables and beef	*Among current drinkers
						Ex-drinker	19	2.01 (1.09–3.68)			
						Current drinker	177	1.97 (1.28–3.03)			
						0.0–0.9 (go/day)	43	2.01 (1.22–3.33)			
						1.0–1.9	63	2.22 (1.38–3.56)			
						2.0–2.9	36	1.75 (1.04–2.96)			
						≥3.0	20	2.40 (1.31–4.40)	0.85*		