						Male, 60–79 years	($n = 11628$)				
						Never drinker		1.00			
						Ex-drinker		3.48 (1.86–6.54)			
						Current drinker		0.75 (0.43–1.31)			
						Female, 40–59 years	($n = 22528$)				
						Never drinker		1.00			
						Ex-drinker		3.85 (0.48–30.93)			
						Current drinker		0.23 (0.03–1.80)			
						Female, 60–79 years	($n = 16103$)				
						Never drinker		1.00			
						Ex-drinker		4.18 (1.47–11.88)			
						Current drinker		0.59 (0.25–1.43)			
Nakaya et al. (32)	1990–97	21201 men	Residents in 14 municipalities of Miyagi prefecture	Incidence	48 men	Never drinker	3	1.0	0.21	Age, smoking, education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato	HBsAg and anti-HCV were not tested.
						Ex-drinker	10	6.6 (1.8–24.2)			
						Current drinker	35	2.7 (0.8–8.9)			
						<22.8 g alcohol/day	11	2.8 (0.8–10.1)			
						≥22.8 g alcohol/day	24	2.7 (0.8–8.9)			
Ikeda et al. (33)	1995–2005	846 (473 men and 373 women)	Patients with HCV-associated chronic hepatitis or cirrhosis at Kyoto University Hospital and 14 affiliated core hospitals	Incidence	237 (151 men and 86 women)	Patients with chronic hepatitis	($n = 576$)			Sex, age, smoking, alcohol consumption, response to interferon therapy, anti-HBc	All subjects were anti-HCV-positive and HBsAg-negative.
						None	57	1.00 (reference)			
						<30 g/day	14	0.75 (0.39–1.44)			
						≥30 g/day	23	0.65 (0.37–1.12)			
						Patients with cirrhosis	($n = 270$)				
						None	99				

Continued

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						
								1.00 (reference)			
						<30 g/day	11	0.42 (0.22–0.83)			
						≥30 g/day	33	1.03 (0.65–0.83)			
Ohki et al. (34)	1994–2006	1431 (727 men and 704 women)	Patients with positive HCV-RNA at Tokyo University Hospital	Incidence	340	Alcohol consumption				Age, sex, diabetes, body mass index, serum albumin, bilirubin, ALT, prothrombin time, platelets, alpha-fetoprotein	All subjects were anti-HCV-positive and HBsAg-negative.
						≤80 g/day		1.00			
						>80 g/day		1.41 (1.07–1.86)			

CI, confidence interval; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; HCV, hepatitis C virus; anti-HBs, antibody to hepatitis B surface antige; LC, liver cirrhosis; AST, aspartate aminotransferase; ALT, alanine aminotransferse; O/E ratio, ratio of observed to expected number; HCV-RNA, hepatitis C virus RNA.

similar classification was possible based on the type of controls: hospital or community controls (35,37,40–46,48,49,51–56,58) ($n = 18$) vs. patients with CLD (39,47,50,56,57) or HBV carriers (36) ($n = 6$; one study (56) included hospital controls as well) (Table 2). In six case–control studies, both HCV and HBV infections were taken into account or were controlled for (46,47,50,56–58).

A summary of the magnitude of association for the cohort and case–control studies is shown in Tables 3 and 4, respectively. Among all 22 cohort studies identified, nine (13,16,21,23,24,27–30) reported strong positive associations between alcohol drinking and liver cancer, three (14,19,32) reported moderate positive associations and two reported weak positive associations (26,34) (Tables 1 and 3). Of the remaining eight studies, three (18,20,25) observed no association and five (15,17,22,31,33) demonstrated weak to moderate inverse associations; such inverse associations were detected mostly in follow-up studies of patients with CLD (particularly, cirrhotic patients) (15,17,22,33). In some cohort studies targeting mostly healthy subjects, the observed risk was higher in former than current drinkers (19,31,32). Among the seven cohort studies in which mostly healthy subjects were followed, five (13,14,16,19,32) revealed at least weak positive associations, whereas eight (21,23,24,27–30,34) out of the 14 follow-up studies of patients with CLD showed such positive associations.

Among all 24 case–control studies identified, strong positive associations were found in 14 (35,36,40,42–44,47,49–51,54–56,58), moderate positive associations in four (38,41,45,53) and a weak positive association in one (37) (Tables 2 and 4). For the remainder, no association was reported in four (39,46,48,52) and a moderate inverse association was reported in one (57). In the 18 case–control studies employing hospital or community controls, 15 (35,37,40–45,49,51,53–56,58) demonstrated at least weak positive associations, whereas four (36,47,50,56) out of six case–control studies using controls of CLD patients or HBV carriers afforded such positive associations.

Overall, about 60% of the cohort studies identified reported weak to strong positive associations between alcohol drinking and liver cancer risk, although all such studies are done on mostly healthy subjects lacking information on hepatitis virus infection. Since there is no reason to consider that individuals with chronic HCV or HBV infection tend to consume more alcohol than those without, potential confounding by such viral infection is unlikely to explain the positive associations found. Cohort studies of mostly healthy subjects demonstrated fairly consistent positive associations, yet several follow-up studies on CLD patients (particularly, cirrhotic patients) reported no association (18,20) or even inverse associations (15,17,22,33), which may be due to the following reasons.

First, among CLD patients, the severity of liver disease may confound the association with alcohol consumption. If patients with more severe liver disease tend to drink less alcohol at baseline for any reason (e.g. impaired liver

Table 2. Case–control studies on alcohol drinking 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					
Inaba et al. (35)	1977–79	Hospital-based (7 hospitals in Yamanashi)	Cases: 58% were histologically confirmed; Controls: patients without hepatic disease	62 (49 men and 13 women)	62 (49 men and 13 women)	Not daily	1.0		Matched (1:1) for sex, age, and hospital Adjusted for matching factors	HBsAg was tested but not adjusted for. Anti-HCV was not tested.
						Daily	3.2 ($P < 0.05$)			
Oshima et al. (36)	1972–80	Nested case–control (HBsAg-positive blood donors at Osaka Red Cross Blood Center)	Cases: confirmed by record linkage with the Osaka Cancer Registry; Controls: healthy HBV carriers	20 men	40 men	None or <1 go/day	1.0	<0.05	Matched (1:2) for birth year Adjusted for smoking	All subjects were HBsAg-positive. Anti-HCV was not tested.
						1–<3 go/day	5.4			
						≥3 go/day	8.0			
Hiraga et al. (37)	1981–85	Hospital-based (one university hospital)	Cases: 50% were histologically confirmed as HCC; Controls: inpatients or outpatients with various diseases	78 men	78 men	Not daily	1.0		Matched (1:1) for age and residential area Adjusted for matching factors	HBsAg was tested but not adjusted for. Anti-HCV was not tested.
						Daily	1.7 (0.8–4.0)			
Kiyosawa et al. (38)	1980–87	Nested case–control (military men who had undergone angiography with thorotrast between 1943 and 1946)	Cases: confirmed by autopsy and/or serological and imaging examinations; Controls: no liver tumor by biochemical and serological tests and imaging examinations	36 men	67 men	For primary liver cancer			No matching	HBsAg was tested but not adjusted for.
						≥80 g/day	1.0		No adjustment	Anti-HCV was not tested.
						<80 g/day	1.21 (0.54–2.74)			The relative risk was not described in the original paper, and was estimated by one of the authors (KT).
						For HCC				
						≥80 g/day	1.0			
						<80 g/day	2.91 (0.95–8.92)			
Kobayashi et al. (39)	1975–88	Hospital-based (Kanazawa University Hospital)	Cases: cirrhotic patients with HCC at autopsy; Controls: cirrhotic patients without HCC at autopsy	48 (40 men and 8 women)	40 (27 men and 13 women)	Alcohol intake (≥75 g/day, ≥10 years)			No matching	HBsAg was tested but not adjusted for.
						No	1.0		No adjustment	Anti-HCV was not tested.
						Yes	1.4 (0.6–3.4)			The relative risk was not described in the original paper, and was estimated by one of the authors (KT).
Tsukuma et al. (40)	1983–87	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	229 (192 men and 37 women)	266 (192 men and 74 women)	Not heavy	1.0		Frequency-matched for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, smoking, and family history of liver cancer	Anti-HCV was not tested. Heavy drinking was defined as drinking 3 'go's of sake per day for >10 years.
						Heavy	3.2 (2.0–5.1)			
						0–9999 'go's	1.0	0.03		
						10 000–39 999 'go's	1.0 (0.6–1.6)			

Continued

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					
			disease, cancer, or smoking/alcohol-related disease			≥40 000 'go's	2.2 (1.2–4.0)			
Tanaka et al. (41)	1985–89	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-drinker	1.0		Frequency-matched for sex and age. Adjusted for sex, age, HBsAg, history of blood transfusion, smoking, and family history of liver disease	Anti-HCV status was available for part of the subjects, but not adjusted for.
						Ever-drinker	1.3 (0.9–2.0)			Heavy drinking was defined as having consumed ≥80 ml of ethanol per day for ≥10 years.
						Not heavy	1.0			The 'drink-years' was calculated by multiplying the daily alcohol use in 'drink' (23 ml of ethanol) by the number of years of consumption.
						Heavy	2.0 (1.2–3.1)			
						Non-drinker	1.0	0.02		
						0.1–33.9 drink-years	1.2 (0.7–2.1)			
						34.0–76.6 drink-years	1.0 (0.5–1.8)			
						≥76.7 drink-years	2.0 (1.2–3.5)			
						Sake				
						<10 drink-years	1.0			
						≥10 drink-years	1.6 (1.1–2.3)			
						Beer				
						<10 drink-years	1.0			
						≥10 drink-years	1.0 (0.7–1.5)			
						Shochu				
						<10 drink-years	1.0			
						≥10 drink-years	1.0 (0.6–1.6)			
						Whisky				

						<10 drink-years	1.0			
						≥10 drink-years	1.8 (1.2–2.9)			
Hamtake et al. (42)	1980–90	Hospital-based (University of Occupational and Environmental Health)	Cases: patients with surgically resected HCC; Controls: patients without liver disease	145 (120 men and 25 women)	83 (46 men and 37 women)	Alcohol index, male			Frequency-matched for age	HBsAg and anti-HCV status was available for part of the subjects, but not adjusted for.
						<60	1.0		No adjustment	The relative risk was not described in the original paper, and was estimated by one of the authors (KT).
						≥60	2.5 (1.1–5.7)			The alcohol index was calculated by multiplying the daily alcohol use in 'go' of sake (28 ml of ethanol) by the number of years of consumption.
Fukuda et al. (43)	1986–92	Hospital-based (Kurume University Hospital)	Cases: 77% were histologically confirmed as HCC; Controls: inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume	368 (287 men and 81 women)	485 (287 men and 198 women)	Non-drinker	1.00		Matched (1:1 for males and 1:4 for females) for sex, age, residence, and time of hospitalization Adjusted for matching factors, HBsAg, history of blood transfusion, and parental history of hepatic diseases	Anti-HCV status was available for part of the subjects, but not adjusted for.
						1–29 drink-years	1.75 (1.12–2.74)			The 'drink-years' represented the accumulated amount of alcohol intake by age 40, which was calculated by multiplying the daily alcohol use in 'drink' (23 ml of ethanol) by the number of years of consumption.
						30–59 drink-years	2.08 (1.14–3.79)			
						≥60 drink-years	3.23 (1.61–6.51)			
Yamaguchi (44)	1976–85	Hospital-based (Kurume University Hospital)	Cases: histologically or clinically confirmed as HCC; Controls: patients without chronic hepatic disorders	466 (385 men and 81 women)	466 (385 men and 81 women)	Male, HBsAg-negative			Matched (1:1) for the year of admission, sex, and age	Analysis was done in male HBsAg-negative subjects alone.
						None	1.0	<0.001	No adjustment	'Heavy' was defined as >540 ml of sake/day (approximately 80 ml of alcohol/day) for >10 years, and 'Moderate' as an intermediate volume.
						Moderate	1.3 (0.8–1.9)			
						Heavy	2.7 (1.8–4.0)			

Continued

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					
Une et al. (45)	1986–88	Hospital-based (hospitals or clinics located in Iizuka Health Center District)	Cases: identified by death certificates in the district; Controls: patients treated for diseases other than liver diseases in three large hospitals in the district	133 (96 men and 37 women)	132 (92 men and 40 women)	Male			Matched (1:1) for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, and smoking	Anti-HCV was not tested.
						Positive drinking	1.08 (0.57–2.05)			
						Female				
						Positive drinking	2.87 (0.57–14.40)			
						Both sexes				
						Positive drinking	1.20 (0.66–2.18)			
Tanaka et al. (46)	1992–93	Hospital-based (Center for Adult Diseases, Osaka)	Cases: patients with HCC who responded to questionnaire (no details described); Controls: patients with cancer of stomach, colon, rectum, or breast, or large intestine polyp	137 (116 men and 21 women)	334 (202 men and 132 women)	Nondrinker	1.0		No matching Adjusted for sex, age, education, smoking, HBsAg, and anti-HCV	HBsAg and anti-HCV status was adjusted for.
						Former drinker	8.7 (1.6–46.3)			
						Occasional drinker	0.7 (0.2–2.0)			
						<80 g ethanol/day	0.4 (0.1–1.4)			
						≥80 g ethanol/day	1.4 (0.4–5.5)			
Chiba et al. (47)	1991–93	Hospital-based (Tsukuba University Hospital)	Cases: HCV-associated cirrhotic patients with HCC established by histology or elevated alpha-fetoprotein together with positive imaging study; Controls: HCV-associated cirrhotic patients without HCC	76 (38 men and 38 women)	128 (63 men and 65 women)	Habitual drinking	3.27 (1.46–7.30)		No matching Adjusted for sex, age, and anti-HBV	All subjects were anti-HCV-positive and HBsAg-negative. Habitual drinking was defined as the average daily alcohol consumption of 80 g or more over a period of more than 5 years.
Murata et al. (48)	1984–93	Nested case–control (male participants in a gastric mass screening by Chiba Cancer Association)	Cases: confirmed by record linkage with Chiba Cancer Registry; Controls: participants in the screening without liver cancer	66 men	132 men	Alcohol intake (cups/day)			Matched (1:2) for sex, birth year, and the first digit of the address code No adjustment	Anti-HCV and HBsAg were not tested. One cup corresponds to 180 ml of sake containing 27 ml of ethanol.
						0	1.0	0.3		
						0.1–1.0	0.6			
						1.1–2.0	0.4			
						2.1+	1.5			

Shibata et al. (49)	1992–95	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 males	115 male HCs and 115 male CCs	Based on HCs			Matched (1:1) for sex, age, 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-drinker	1.0			The 'drink-years' represented the accumulated amount of alcohol intake by age 40, which was calculated by multiplying the daily alcohol use in 'drink' (23 ml of ethanol) by the number of years of consumption.
						1–29 drink-years	0.9 (0.5–1.8)			
						30–59 drink-years	1.3 (0.6–2.6)			
						≥60 drink-years	1.9 (0.9–4.3)			
						Based on CCs				
						Non-drinker	1.0			
						1–29 drink-years	2.3 (1.1–4.6)			
						30–59 drink-years	2.0 (0.9–4.4)			
						≥60 drink-years	5.0 (2.0–12.7)			
Mukaiya et al. (50)	1991–93	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	Not daily	1.00		Matched (1:1) for age Adjusted for age	Additional adjustment for cigarette smoking, and HBV and HCV infections did not materially alter the results.
						Daily	2.31 (1.20–4.42)			
						<1/week	1.00			
						≥1/week	2.17 (1.09–4.29)			
						<20 ml ethanol/day	1.00			
						≥20 ml/day	2.36 (1.26–4.40)			
Takeshita et al. (51)	1993–96	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 smoking	All the controls were HBsAg-negative and anti-HCV-negative by definition.
						0–19 drink-years	1.0	0.007		The 'drink-years' was calculated by multiplying the daily alcohol use in

Continued

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					
										'drink' (15 ml of ethanol) by the number of years of consumption.
						20–39 drink-years	1.7 (0.8–3.5)			
						≥40 drink-years	2.7 (1.3–5.5)			
						Women				
						Not described				
Koide et al. (52)	1994	Hospital-based (Nagoya City University Hospital)	QCases: 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	1.00		Matched (1:1) for sex and age Adjusted for sex and age	Anti-HCV and HBsAg status was available, but not adjusted for.
						Current + former	1.23 (0.59–2.56)			
Iida et al. (53)	1999–2001	Hospital-based (hospitals in Yamanashi prefecture)	Cases: patients with HCC (no details described); Controls: inpatients at the hospitals same as cases (no details described)	495 (363 men and 132 women)	194 (132 men and 62 women)	Non-heavy drinker	1.00		Matched for sex, age, and time of hospitalization Adjusted for sex	Anti-HCV and HBsAg status was available, but not adjusted for.
						Heavy drinker	1.84 (1.13–2.99)			
Matsuo et al. (54)	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)	Male based on HCs			Matched for sex (1:4 for female HCs and 1:1 for other controls), age, residence (for HCs), and time of hospitalization (for HCs)	Anti-HCV and HBsAg status was available except for CCs, but not adjusted for.
						Non-drinker	1.00		Adjusted for matching factors	
						1–29 drink-years	1.31			
						30–59 drink-years	1.65			
						≥60 drink-years	1.95 ($P < 0.05$)			
						Male based on CCs				
						Non-drinker	1.00			
						1–29 drink-years	2.02 ($P < 0.05$)			
						30–59 drink-years	1.53			
						≥60 drink-years				

							3.19 ($P < 0.05$)		
						Female based on HCs			
						Non-drinker	1.00		
						1–29 drink-years	1.25		
						≥30 drink-years	1.15		
						Female based on CCs			
						Non-drinker	1.00		
						1–29 drink-years	0.50		
						≥30 drink-years	1.00		
Munaka et al. (55)	1997–98	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)	Never	1.00	Unmatched Adjusted for sex and age	Anti-HCV and HBsAg status was available, but not adjusted for.
						1 to <200 000 ml	0.31 (0.15–0.62)		
						200 000– <600 000 ml	0.79 (0.40–1.57)		
						≥600 000 ml	4.52 (2.39–8.55)		
Sakamoto et al. (56)	2001–04	Hospital-based (Saga Medical School Hospital and Saga Prefectural Hospital)	Cases: confirmed as HCC by histological, angiographical, or other radiological findings; Hospital controls (HCs): first-time visitors at the general outpatient clinic of Saga Medical School Hospital; Patients with chronic liver disease without HCC (CLDs): patients with chronic hepatitis or cirrhosis not classified as special types (e.g., biliary cirrhosis)	209 (141 men and 68 women)	275 HCs (180 men and 95 women) and 381 CLDs (205 men and 176 women)	Based on HCs		Unmatched	HBsAg and anti-HCV status was adjusted for.
						Never drinker	1.0	Adjusted for sex, age, smoking, HBsAg, and anti-HCV	One 'go' corresponds to 180 ml of sake containing 23 g of ethanol.
						Former drinker	5.3 (1.6–18.6)		
						Current drinker	2.9 (1.2–7.4)		
						Based on CLDs			
						Never drinker	1.0		
						Former drinker	1.3 (0.7–2.2)		
						Current drinker	1.8 (1.0–3.0)		
						Alcohol intake ('go's/day) during last 1–2 years, based on HCs			
						0	1.0		
						0.1–0.9	3.4 (1.1–10.1)		
						1.0–1.9			

Continued

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					
							0.8 (0.2–2.9)			
						2.0–2.9	0.6 (0.2–2.4)			
						3.0–3.9	10.2 (1.7–60.5)			
						4.0 +	18.0 (3.0–107.9)			
						Alcohol intake ('go's/day) during last 1–2 years, based on CLDs				
						0	1.0			
						0.1–0.9	1.2 (0.7–2.2)			
						1.0–1.9	1.0 (0.5–2.1)			
						2.0–2.9	1.8 (0.8–4.4)			
						3.0–3.9	5.0 (1.3–19.2)			
						4.0+	9.4 (2.5–35.4)			
Fukushima et al. (57)	2001–02	Hospital-based (Osaka City University Hospital)	Cases: HCV-RNA positive patients with HCC confirmed by either histology or radiological findings; Controls: HCV-RNA positive patients without HCC	73 (34 men and 39 women)	253 (131 men and 122 women)	Cumulative ethanol consumption (kg) during lifetime			Matched for sex, age, and the date of first visit Adjusted for matching factors, years since the first identification of liver disease, interferon treatment, ultrasonographic findings, platelet, AST, albumin, and fasting blood sugar	All patients were HCV-RNA-positive and HBsAg-negative.
						Non-drinker	1.00	0.07		
						<260	0.48 (0.18–1.31)			
						≥260	0.37 (0.13–1.07)			
						Cumulative ethanol consumption (kg) after the first identification of liver disease				
						Non-drinker	1.00	0.3		
						<200	0.48 (0.16–1.41)			
						≥200				

							0.55 (0.18–1.66)			
						Cumulative ethanol consumption (kg) after the first identification of liver disease				
						Non-drinker	1.00	0.8		
						<53	1.22 (0.48–3.10)			
						≥53	1.09 (0.35–3.36)			
Ohishi et al. (58)	1970–2002	Nested case–control (atomic bomb survivors in Hiroshima and Nagasaki)	Cases: patients with incident HCC who had stored serum samples available; Controls: survivors without HCC who had stored serum samples available	224 (136 men and 88 women)	644 (387 men and 257 women)	Alcohol consumption (g of ethanol per day)			Matched (1:3) for sex, age, city, time and method of serum storage, and radiation exposure Adjusted for matching factors, hepatitis virus infection, smoking, coffee, body mass index, diabetes, and radiation dose to the liver	HBsAg and anti-HCV status was adjusted for.
						0	1.00	0.004		
						1–19	1.27 (0.56–2.87)			
						20–39	1.02 (0.34–3.05)			
						40+	4.36 (1.48–13.0)			

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HC, hospital control; CC, community control; CLD, chronic liver disease.

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

Reference	Study period	Study population					Magnitude of association
		Sex	Number of subjects	Age range (years)	Event	Number of incident cases or deaths	
Kono et al. (13)	1965–83	Men	5130	Not specified	Death	51	↑↑↑
Hirayama (14)	1966–82	Men	122261	≥40	Death	788	↑↑
Inaba et al. (15)	1973–88	Men	270 (liver cirrhosis)	Not specified	Death	46	↓↓
Shibata et al. (16)	1958–86	Men	639 (farming area)	40–69	Death	11	–
			677 (fishing area)	40–69	Death	22	↑↑↑
Kato et al. (17)	1987–90	Men and women	1784 (cirrhosis and posttransfusion hepatitis)	≥16	Incidence	122	↓↓
Tsukuma et al. (18)	1987–91	Men and women	917 (chronic liver disease)	40–69	Incidence	54	–
Goodman et al. (19)	1980–89	Men	36 133 (men and women)	Not specified	Incidence	156	–
		Women		Not specified	Incidence	86	↑↑
Chiba et al. (20)	1977–93	Men and women	412 (HCV-associated chronic liver disease)	40–72	Incidence	63	–
Ikeda et al. (21)	1980–?	Men and women	2215 (chronic hepatitis)	13–75	Incidence	89	↑↑↑
Tanaka et al. (22)	1985–95	Men and women	96 (liver cirrhosis)	40–69	Incidence	37	↓↓
Matsushita et al. (23)	1985–94	Men and women	267 (liver cirrhosis)	Not specified	Incidence	67	↑↑ (type B or C) ↑↑↑ (type C)
Aizawa et al. (24)	1981–98	Men and women	153 (HCV-associated chronic liver disease)	20–65	Incidence	Not described	↑↑↑
Mori et al. (25)	1992–97	Men and women	3052	≥30	Incidence	22	–
Noda et al. (26)	1972–92	Men	306 (alcoholics)	21–77	Death	Not described	↑
Hamada et al. (27)	1980–2000	Men and women	469 (HCV-associated chronic liver disease)	Not specified	Incidence	52	↑↑↑
Takimoto et al. (28)	1989–?	Men and women	356 (HCV-associated chronic hepatitis)	Not specified	Incidence	Not described	↑↑↑
Uetake et al. (29)	1988–2000	Men	91 (alcoholic cirrhosis)	34–72	Incidence	13	↑↑↑
Iwasaki et al. (30)	1986–2003	Men and women	792 (HCV-associated chronic liver disease with sustained response to interferon)	Not specified	Incidence	23	↑↑↑
Ogimoto et al. (31)	1988–99	Men	16 715	40–59	Death	184 (number by sex and age not described)	↓
		Men	11 628	60–79	Death		–
		Women	22 528	40–59	Death		↓↓
		Women	16 103	60–79	Death		↓
Nakaya et al. (32)	1990–97	Men	21 201	40–64	Incidence	48	↑↑
Ikeda et al. (33)	1995–2005	Men and women	576 (HCV-associated chronic hepatitis)	Not specified	Incidence	94	↓
			270 (HCV-associated cirrhosis)	Not specified	Incidence	143	–
Ohki et al. (34)	1994–2006	Men and women	1431 (HCV-associated chronic liver disease)	Not specified	Incidence	340	↑

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

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

Reference	Study period	Study subjects				Magnitude of association
		Sex	Age range (years)	Number of cases	Number of controls	
Inaba et al. (35)	1977–79	Men and women	Not specified	62	62	↑↑↑
Oshima et al. (36)	1972–80	Men	Not specified	20	40	↑↑↑
Hiraga et al. (37)	1981–85	Men	Not specified	78	78	↑
Kiyosawa et al. (38)	1980–87	Men	Not specified	36 (primary liver cancer)	67 (exposed to thorotrast)	–
				20 (hepatocellular carcinoma)	67 (exposed to thorotrast)	↑↑
Kobayashi et al. (39)	1975–88	Men and women	Not specified	48	40 (cirrhotic patients)	–
Tsukuma et al. (40)	1983–87	Men and women	≤74	229	266	↑↑↑
Tanaka et al. (41)	1985–89	Men and women	40–69	204	410	↑↑
Haratake et al. (42)	1980–90	Men	Not specified	145	83	↑↑↑
Fukuda et al. (43)	1986–92	Men and women	40–69	368	485	↑↑↑
Yamaguchi (44)	1976–85	Men	Not specified	466	466	↑↑↑ (HBsAg-negative)
Une et al. (45)	1986–88	Men	Not specified	96	92	–
		Women	Not specified	37	40	↑↑
Tanaka et al. (46)	1992–93	Men and women	40–79	137	334	–
Chiba et al. (47)	1991–93	Men and women	Not specified	76	128 (HCV-associated cirrhosis)	↑↑↑
Murata et al. (48)	1984–93	Men	Not specified	66	132	–
Shibata et al. (49)	1992–95	Men	40–69	115	115 hospital controls	↑
					115 community controls	↑↑↑
Mukaiya et al. (50)	1991–93	Men	Not specified	104	104 (chronic liver disease)	↑↑↑
Takeshita et al. (51)	1993–96	Men	Not specified	85	101	↑↑↑
Koide et al. (52)	1994	Men and women	46–79	84	84	–
Iida et al. (53)	1999–2001	Men and women	Not specified	495	194	↑↑
Matsuo et al. (54)	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. (55)	1997–98	Men and women	34–92	78	138	↑↑↑
Sakamoto et al. (56)	2001–2004	Men and women	40–79	209	275 hospital controls	↑↑↑
					381 patients with chronic liver disease	↑↑↑
Fukushima et al. (57)	2001–2002	Men and women	17–85	73	253 (HCV-RNA-positive)	↓↓
Ohishi et al. (58)	1970–2002	Men and women	Not specified	224	644	↑↑↑

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

function or physicians' advice), even in those with a similar diagnosis (e.g. chronic hepatitis or cirrhosis), alcohol drinking may seem to play no, or even protective, role. Second, among cirrhotic patients, competing risks (i.e. deaths from causes other than liver cancer) may be responsible. For example, if cirrhotic patients with alcoholism continue to drink heavily, they may die of hepatic failure or variceal bleeding before the development of liver cancer. Third, drinking habits at baseline among CLD patients may have changed substantially during follow-up, and the resultant misclassification may have distorted a true association. Fourth, alcohol consumption may actually play no important role in the development of liver cancer from cirrhosis. However, it appears difficult to differentiate these possibilities by observational studies.

In some cohort studies based on mostly healthy subjects, former drinkers experienced a higher risk of liver cancer than never drinkers (19,31,32); in all such studies,

information on hepatitis virus infection and the presence or absence of CLD was missing. In this regard, a plausible explanation is that former drinkers may have included high-risk individuals such as hepatitis virus carriers and CLD patients who had abstained from alcohol because of illness.

In the case–control studies identified, alcohol consumption was almost consistently associated with increased liver cancer risk. This was the case regardless of the type of controls (mostly healthy subjects vs. CLD patients or hepatitis virus carriers), and only one study on patients with chronic hepatitis C reported an inverse association (57), which somewhat differs from the situation in the cohort studies. A possible change in recent drinking habits among CLD patients can be taken into account in case–control studies, but not usually in cohort studies, and this matter might partly account for the above difference, although the exact reason remains unknown.

Since about 90% of patients with HCC in Japan are known to be chronically infected with HCV or HBV (6), the postulation that heavy alcohol consumption causes alcoholic cirrhosis and thereby leads to the development of HCC does not appear to play a major role. Instead, the potential modifying effect of alcohol on HCC risk among HCV- or HBV-infected individuals is likely to be more important. In this connection, most follow-up studies of patients with chronic hepatitis C over the past decade showed fairly consistent positive associations between alcohol drinking and HCC risk (21,24,27,28,30,34), with few exceptions (33). It remains unclear to what extent alcohol consumption increases the HCC risk among the Japanese general population who are not infected with HCV or HBV because no study exists on this issue.

Potential mechanisms linking the use of alcohol with the development of liver cancer are discussed elsewhere (3). As for the role of alcohol among those with HCV infection, which is the most important risk factor of HCC in Japan, several mechanisms including increased viral replication, enhanced HCV quasispecies complexity, increased liver-cell death, suppression of immune responses, iron overload and increased oxidative stress have been suggested (59,60).

The Japanese may be more susceptible than other ethnic groups, to potential carcinogenic effects of alcohol because about half of them represent heterozygous or homozygous carriers of the inactive aldehyde dehydrogenase (ALDH) 2 allele (*ALDH2*2*) (9), who have an excessive accumulation of acetaldehyde after alcohol intake; acetaldehyde has been classified as being possibly carcinogenic to humans (10). Epidemiologic data on the role of the *ALDH2* genotype in hepatocarcinogenesis has been conflicting (49,51,52,55,56,61). Overall, no material differences have been observed in the *ALDH2* genotype distribution between liver cancer patients and control subjects, although two studies of relatively small size reported a significantly increased risk among heterozygous or homozygous carriers of *ALDH2*2* (55,61). Two studies suggested a significantly elevated risk of HCC for *ALDH2*2* carriers vs. non-carriers among drinkers, but not among non-drinkers (55,56).

The IARC has concluded that there is sufficient evidence for the carcinogenicity of ethanol in experimental animals (3). Taken together, this systematic review confirms a biologically plausible positive association between alcohol drinking and liver cancer risk among the Japanese, and a meta-analysis should be conducted to obtain summary estimates for the overall magnitude of association. However, the studies included in this review employed very different categories of alcohol consumption (particularly in reference categories), which has made a meaningful meta-analysis unfeasible. A meta-analysis of several large-cohort studies using common alcohol consumption categories is now underway, and we hope it will address the above issue.

EVALUATION OF EVIDENCE ON ALCOHOL DRINKING AND LIVER CANCER RISK AMONG JAPANESE

From these results and based on assumed biological plausibility as previously evaluated by the IARC (3), we conclude that there is 'convincing' evidence that alcohol drinking increases the risk of primary liver cancer among the Japanese population. High-risk individuals such as patients with CLD and hepatitis virus carriers are strongly recommended to abstain from alcohol use.

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Conflict of interest statement

None declared.

References

1. Lieber CS. Alcohol and the liver: 1994 update. *Gastroenterology* 1994;106:1085–105.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127: S35–50.
3. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96. Consumption of Alcoholic Beverages and Ethyl Carbamate (Urethane). Lyon, France: IARC (in press).
4. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR 2007.
5. Gann Monograph on Cancer Research No. 51. Cancer Mortality and Morbidity Statistics: Japan and the World-2004. Tokyo, Japan: Scientific Societies Press 2004.
6. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. *Hepatol Res* 2007;37:676–91.

7. Tanaka K, Ikematsu H, Hirohata T, Kashiwagi S. Hepatitis C virus infection and risk of hepatocellular carcinoma among Japanese: possible role of type 1b (II) infection. *J Natl Cancer Inst* 1996;88:742–6.
8. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907–17.
9. Goedde HW, Agarwal DP, Fritze G, Meier-Tackmann D, Singh S, Beckmann G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992;88:344–6.
10. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 71. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. Lyon, France: IARC 1999.
11. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
12. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. Geneva, WHO 2003.
13. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. *Jpn J Cancer Res* 1987;78:1323–8.
14. Hirayama T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. *Cancer Chemother Pharmacol* 1989;23(Suppl.):S114–7.
15. Inaba Y, Kikuchi S, Namihisa T, Ichikawa S. The effect of smoking and drinking habit on the process from liver cirrhosis to liver cancer. *Gan No Rinsho* 1990;36:299–304 (in Japanese).
16. Shibata A, Fukuda K, Toshima H, Tashiro H, Hirohata T. The role of cigarette smoking and drinking in the development of liver cancer: 28 years of observations on male cohort members in a farming and fishing area. *Cancer Detect Prev* 1990;14:617–23.
17. Kato I, Tominaga S, Ikari A. The risk and predictive factors for developing liver cancer among patients with decompensated liver cirrhosis. *Jpn J Clin Oncol* 1992;22:278–85.
18. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993;328:1797–801.
19. Goodman MT, Moriwaki H, Vaeth M, Akiba S, Hayabuchi H, Mabuchi K. Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan. *Epidemiology* 1995;6:36–41.
20. Chiba T, Matsuzaki Y, Abei M, Shoda J, Tanaka N, Osuga T, et al. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. *Am J Gastroenterol* 1996;91:1195–203.
21. Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998;28:930–8.
22. Tanaka K, Sakai H, Hashizume M, Hirohata T. A long-term follow-up study on risk factors for hepatocellular carcinoma among Japanese patients with liver cirrhosis. *Jpn J Cancer Res* 1998;89:1241–50.
23. Matsushita E, Kaneko S, Kobayashi K. Evaluation of background factors related to carcinogenesis in cirrhosis. *Proceedings of 20th Inuyama Symposium*. Tokyo: Chugai-igakusha 1998,159–64 (in Japanese).
24. Aizawa Y, Shibamoto Y, Takagi I, Zeniya M, Toda G. Analysis of factors affecting the appearance of hepatocellular carcinoma in patients with chronic hepatitis C. A long term follow-up study after histologic diagnosis. *Cancer* 2000;89:53–9.
25. Mori M, Hara M, Wada I, Hara T, Yamamoto K, Honda M, et al. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan. *Am J Epidemiol* 2000;151:131–9.
26. Noda T, Imamichi H, Tanaka H, Kawata A, Hirano K, Ando T, et al. Cause-specific mortality risk among male alcoholics residing in the Osaka metropolitan area. *Psychiatry Clin Neurosci* 2001;55: 465–72.
27. Hamada H, Yatsuhashi H, Yano K, Daikoku M, Arisawa K, Inoue O, et al. Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. *Cancer* 2002;95: 331–9.
28. Takimoto M, Ohkoshi S, Ichida T, Takeda Y, Nomoto M, Asakura H, et al. Interferon inhibits progression of liver fibrosis and reduces the risk of hepatocarcinogenesis in patients with chronic hepatitis C: a retrospective multicenter analysis of 652 patients. *Dig Dis Sci* 2002;47:170–6.
29. Uetake S, Yamauchi M, Itoh S, Kawashima O, Takeda K, Ohata M. Analysis of risk factors for hepatocellular carcinoma in patients with HBs antigen- and anti-HCV antibody-negative alcoholic cirrhosis: clinical significance of prior hepatitis B virus infection. *Alcohol Clin Exp Res* 2003;27:47S–51S.
30. Iwasaki Y, Takaguchi K, Ikeda H, Makino Y, Araki Y, Ando M, et al. Risk factors for hepatocellular carcinoma in hepatitis C patients with sustained virologic response to interferon therapy. *Liver Int* 2004;24:603–10.
31. Ogimoto I, Shibata A, Kurozawa Y, Nose T, Yoshimura T, Suzuki H, et al. Risk of death due to hepatocellular carcinoma among drinkers and ex-drinkers. Univariate analysis of JACC study data. *Kurume Med J* 2004;51:59–70.
32. Nakaya N, Tsubono Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev* 2005;14:169–74.
33. Ikeda K, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, et al. Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: a prospective study. *Ann Intern Med* 2007;146:649–56.
34. Ohki T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, et al. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. *Clin Gastroenterol Hepatol* 2008;6:459–64.
35. Inaba Y, Maruchi N, Matsuda M, Yoshihara N, Yamamoto S. A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. *Int J Epidemiol* 1984;13:408–12.
36. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *Int J Cancer* 1984;34:775–9.
37. Hiraga M, Araki S, Murata K, Yokoyama K, Terao H. Assessment of the interaction of hepatitis B antigen and alcohol in primary hepatocellular carcinoma: a case-control study. *Jpn J Public Health* 1986;33:636–9 (in Japanese).
38. Kiyosawa K, Imai H, Sodeyama T, Franca ST, Yousuf M, Furuta S, et al. Comparison of anamnestic history, alcohol intake and smoking, nutritional status, and liver dysfunction between thorotrast patients who developed primary liver cancer and those who did not. *Environ Res* 1989;49:166–72.
39. Kobayashi K, Unoura M, Tanaka N, Hattori N. A comparison between hepatocellular carcinoma-developing and non-carcinoma-developing patients with cirrhosis over a long follow-up period. *Hepatogastroenterology* 1990;37:445–8.
40. Tsukuma H, Hiyama T, Oshima A, Sobue T, Fujimoto I, Kasugai H, et al. A case-control study of hepatocellular carcinoma in Osaka, Japan. *Int J Cancer* 1990;45:231–6.
41. Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. *Int J Cancer* 1992;51:509–14.
42. Haratake J, Kasai T, Takeda S. An epidemiologic comparative study of hepatocellular carcinoma caused by various etiologic factors. *Gan No Rinsho* 1992;38:297–301 (in Japanese).
43. Fukuda K, Shibata A, Hirohata I, Tanikawa K, Yamaguchi G, Ishii M. A hospital-based case-control study on hepatocellular carcinoma in Fukuoka and Saga Prefectures, northern Kyushu, Japan. *Jpn J Cancer Res* 1993;84:708–14.
44. Yamaguchi G. Hepatocellular carcinoma and its risk factors–their annual changes and effects on the age at onset. *Kurume Med J* 1993;40:33–40.
45. Une H, Osajima K, Momose Y, Esaki H. A case-control study on liver cancer in the Chikuho area, Fukuoka prefecture. *Minzoku Eisei* 1993;59:241–7.
46. Tanaka H, Hiyama T, Tsukuma H, Imaoka S, Morisada K, Iwanaga T. Association of HBV, HCV, drinking and smoking with the development of hepatocellular carcinoma: a case-control study using hospitalized patients. *Shokaki Gan* 1995;5:117–22 (in Japanese).
47. Chiba T, Matsuzaki Y, Abei M, Shoda J, Aikawa T, Tanaka N, et al. Multivariate analysis of risk factors for hepatocellular carcinoma in

patients with hepatitis C virus-related liver cirrhosis. *J Gastroenterol* 1996;31:552–8.
48. Murata M, Takayama K, Choi BC, Pak AW. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev* 1996;20:557–65.
49. Shibata A, Fukuda K, Nishiyori A, Ogimoto I, Sakata R, Tanikawa K. A case-control study on male hepatocellular carcinoma based on hospital and community controls. *J Epidemiol* 1998;8:1–5.
50. Mukaiya M, Nishi M, Miyake H, Hirata K. Chronic liver diseases for the risk of hepatocellular carcinoma: a case-control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver diseases. *Hepatogastroenterology* 1998;45:2328–32.
51. Takeshita T, Yang X, Inoue Y, Sato S, Morimoto K. Relationship between alcohol drinking, ADH2 and ALDH2 genotypes, and risk for hepatocellular carcinoma in Japanese. *Cancer Lett* 2000;149: 69–76.
52. Koide T, Ohno T, Huang XE, Iijima Y, Sugihara K, Mizokami M, et al. HBV/HCV infection, alcohol, tobacco and genetic polymorphisms for hepatocellular carcinoma in Nagoya, Japan. *Asian Pac J Cancer Prev* 2000;1:237–43.
53. Iida F, Yamagata Z, Iida R, Hosoda K, Okada S, Matsuda M, et al. Hepatocellular carcinoma in Yamanashi prefecture – a trial of case-control study (third report). *Yamanashi Igaku* 2002;30:1–7 (in Japanese).
54. Matsuo M. Association between diabetes mellitus and hepatocellular carcinoma: results of a hospital- and community-based case-control study. *Kurume Med J* 2003;50:91–8.
55. Munaka M, Kohshi K, Kawamoto T, Takasawa S, Nagata N, Itoh H, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and the risk of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2003;129:355–60.
56. Sakamoto T, Hara M, Higaki Y, Ichiba M, Horita M, Mizuta T, et al. Influence of alcohol consumption and gene polymorphisms of ADH2 and ALDH2 on hepatocellular carcinoma in a Japanese population. *Int J Cancer* 2006;118:1501–7.
57. Fukushima W, Tanaka T, Ohfuji S, Habu D, Tamori A, Kawada N, et al. Does alcohol increase the risk of hepatocellular carcinoma among patients with hepatitis C virus infection? *Hepatol Res* 2006;34: 141–9.
58. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2008;17:846–54.
59. Vento S, Cainelli F. Does hepatitis C virus cause severe liver disease only in people who drink alcohol? *Lancet Infect Dis* 2002;2303–9.
60. Koike K, Tsutsumi T, Miyoshi H, Shinzawa S, Shintani Y, Fujie H, et al. Molecular basis for the synergy between alcohol and hepatitis C virus in hepatocarcinogenesis. *J Gastroenterol Hepatol* 2008;23(Suppl. 1):S87–91.
61. Kato S, Tajiri T, Matsukura N, Matsuda N, Taniai N, Mamada H, et al. Genetic polymorphisms of aldehyde dehydrogenase 2, cytochrome p450 2E1 for liver cancer risk in HCV antibody-positive japanese patients and the variations of CYP2E1 mRNA expression levels in the liver due to its polymorphism. *Scand J Gastroenterol* 2003;38: 886–93.

Appendix

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Meta-Analysis

Alcohol Drinking and Colorectal Cancer in Japanese: A Pooled Analysis of Results from Five Cohort Studies

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Colorectal cancer is an alcohol-related malignancy; however, the association appears to be stronger among Asian populations with a relatively high prevalence of the slow-metabolizing aldehyde dehydrogenase variant. To examine the association between alcohol consumption and colorectal cancer in Japanese, the authors analyzed original data from five cohort studies that measured alcohol intake using validated questionnaires at baseline. Hazard ratios were calculated in the individual studies, with adjustment for a common set of variables, and then combined using a random-effects model. During 2,231,010 person-years of follow-up (ranging variously from 1988 to 2004), 2,802 colorectal cancer cases were identified. In men, multivariate-adjusted pooled hazard ratios for alcohol intakes of 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and ≥92 g/day, compared with nondrinking, were 1.42 (95% confidence interval (CI): 1.21, 1.66), 1.95 (95% CI: 1.53, 2.49), 2.15 (95% CI: 1.74, 2.64), and 2.96 (95% CI: 2.27, 3.86), respectively (p for trend < 0.001). The association was evident for both the colon and the rectum. A significant positive association was also observed in women. One fourth of colorectal cancer cases in men were attributable to an alcohol intake of ≥23 g/day. An alcohol-colorectal cancer association seems to be more apparent in Japanese than in Western populations. Whether this difference can be ascribed to genetic or environmental factors needs to be clarified.

alcohol drinking; colonic neoplasms; colorectal neoplasms; rectal neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study.

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Colorectal cancer is a common malignancy in developed countries (1). In Japan, after a marked increase over the last several decades (2), the incidence of colorectal cancer is currently among the highest in the world (1). Epidemiologic data generally support the hypothesis that alcohol drinking increases colorectal cancer risk (3–5), and in the latest evaluation by the International Agency for Research on Cancer, colorectal cancer was added to the list of alcohol-related malignancies (6, 7). However, the influence of alcohol drinking could be greater among Asian populations because of their relatively high prevalence of the slow-metabolizing aldehyde dehydrogenase variant (8), which is associated with increased blood levels of acetaldehyde, a potential carcinogen (9), after alcohol ingestion (10). In line with this concern, in a meta-analysis of cohort studies, Moskal et al. (5) reported a stronger association with alcohol drinking for colon cancer (but not rectal cancer) in Asian studies as compared with Western studies.

In our 2006 review of epidemiologic studies carried out among Japanese (11), we identified a fairly consistent association between heavy alcohol intake and increased risk of colorectal cancer, and in all recent cohort studies (12–15), men in the highest category of alcohol intake have had nearly twice the risk of colon cancer as men in the lowest category. However, several issues remain unresolved. First, because cutpoints for alcohol intake varied by study, we were unable to obtain summary estimates according to amount of alcohol consumed. Second, the association for colon cancer appears to be more consistent than that for rectal cancer, but random variation may account for the difference. Third, the association was unclear among women, who consumed much lower amounts of alcohol than men, on average. From an international perspective, a seemingly stronger association with alcohol drinking in Japanese may simply reflect greater alcohol intake among Japanese drinkers than among their Western counterparts. A comparison of risks incurred at identical levels of exposure is required for confirmation. To address these issues, we conducted a pooled analysis of data from five large-scale cohort studies carried out in Japan.

MATERIALS AND METHODS

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer in Japanese, in parallel with systematic reviews of the relevant literature. Topics for the pooled analysis were determined on the basis of discussion among all authors from the viewpoints of scientific and public health importance. To maintain high quality and comparability of data, we set inclusion criteria for the present purpose a priori: population-based cohort studies that were conducted in Japan, started between the mid-1980s and the mid-1990s, included more than 30,000 participants, obtained information on diet, including alcohol intake, using a validated questionnaire or a similar one at baseline, and collected incidence data for colorectal cancer during the follow-up period. We identified four ongoing studies that met these criteria: 1) the Japan Public Health Center-based Prospective Study (JPHC) (16), 2) the Japan Collaborative Cohort Study (JACC) (17), 3) the Miyagi Cohort Study (18), and 4) the Takayama Study (19). The JPHC was treated as two independent studies (JPHC I and JPHC II) because of a difference in the dietary questionnaires used; thus, data from a total of five studies were analyzed. We excluded data for subjects with extreme energy intakes (>3 standard deviations from the mean log-transformed energy intake in each study), missing information on alcohol consumption, or a history of cancer at baseline. Selected characteristics of these studies are presented in table 1. Each study was approved by the relevant institutional ethical review board. Results on the association between alcohol intake and colorectal cancer risk in each cohort have been reported (12–15). For the present analysis, we used updated data sets with an extended follow-up period for JPHC I, JPHC II, and JACC.

Case ascertainment

Subjects were followed from the baseline survey (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, Miyagi: 1990, Takayama: 1992) to the last date of follow-up for incidence (JPHC I: 2004, JPHC II: 2004, JACC: 2001, Miyagi: 2001, Takayama: 1999) in each study. Residence status in each study, including survival, was confirmed through the residential registry. Information on cancer diagnosis was collected for the whole population in JPHC I, JPHC II, and the Miyagi Cohort Study; in these studies, cases were identified through active patient notification from major local hospitals and/or through population-based cancer registries. In the Takayama Study, active patient notification for colorectal cancer was conducted by major local hospitals. In JACC, because information on cancer diagnosis was collected in 22 out of 45 study areas, we used data from those 22 areas only. Cases were coded using the *International Classification of Diseases for Oncology*, Third Edition (20). Each study also collected information about causes of death from death certificates and coded them according to the *International Classification of Diseases*, Tenth Revision (21), which was used to complement the hospital and registry data on cancer diagnosis. The study outcome was defined as incident colorectal cancer (*International Classification of Diseases for Oncology*, Third Edition, codes C18.0–C18.9, C19.9, and C20.9; *International Classification of Diseases*, Tenth Revision, codes C18–C20) diagnosed during the follow-up period of each study.

Assessment of alcohol intake

Alcohol drinking status was assessed by means of self-administered questionnaires at baseline. Although the style of the questions differed by study, investigators in each study were able to calculate average daily alcohol consumption in grams of ethanol for regular drinkers on the basis of beverage type, frequency, and amount. The questionnaire in each study contained queries on the intake of alcoholic beverages popular in Japan, including beer, sake, and shochu,

TABLE 1. Characteristics of five Japanese cohort studies included in a pooled analysis of alcohol consumption and colorectal cancer risk, 1988–2004

Study (ref. no.)	Population	Age (years) at baseline	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow-up	Current pooled analysis						
							Age (years)	Last follow-up time	Mean duration of follow-up (years)	Cohort size (no.)		No. of cancer cases	
										Men	Women	Men	Women
JPHC* I (16)	Japanese residents of five public health center areas in Japan	40–59	1990	61,595	82	Cancer registry and death certificates	40–59	2004	13.5	19,767	21,392	434	260
JPHC II (16)	Japanese residents of six public health center areas in Japan	40–69	1993–1994	78,825	80	Cancer registry and death certificates	40–69	2004	10.5	27,458	31,609	473	308
Japan Collaborative Cohort Study (17)	Residents from 45 areas throughout Japan	40–79	1988–1990	110,792	83	Cancer registry (22 selected areas) and death certificates	40–79	2001 (1994–2000 in some areas)	10.4	16,276	23,723	339	223
Miyagi Cohort Study (18)	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92	Cancer registry and death certificates	40–64	2001	11.0	20,551	18,232	318	164
Takayama Study (19)	Japanese residents of Takayama, Gifu, Japan	≥35	1992	31,552	92	Hospital records (selected sites) and death certificates	≥35	1999	6.9	14,213	16,542	160	123
Total										98,265	111,498	1,724	1,078

* JPHC, Japan Public Health Center-based Prospective Study.

but the style of the questions differed across studies. Therefore, in the present study we used only total alcohol intake from all beverages as the exposure. In Japan, the *go* is the most commonly used unit of alcohol consumption; 1 go of sake (Japanese wine), equivalent to 180 ml, contains approximately 23 g of ethanol. Consumption was divided into categories using identical cutpoints across the studies (nondrinkers (never and ex-drinkers), occasional drinkers (<once/week), and regular drinkers (≥once/week: for men, 0.1–22.9 g/day, 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, or ≥92 g/day; for women, 0.1–22.9 g/day or ≥23 g/day)). Analysis using the same exposure categories as those used in a pooled analysis among Western populations (22) was also conducted for comparison. Correlation coefficients for the correlation between alcohol consumption estimated from the questionnaire and that from the dietary record were: JPHC—0.77 in men and 0.55 in women (23); Miyagi—0.77 in men and 0.71 in women (24); and Takayama—0.72 in men and 0.64 in women (19). The JACC, for which information on the validation of alcohol consumption was not available, utilized the same questions on alcohol consumption as the Miyagi Cohort Study. The analysis was repeated by using never drinkers as the reference group in the JACC, the Miyagi Cohort Study, and JPHC II, in which ex-drinkers were distinguishable from never drinkers.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of colorectal cancer, migration from the study area, death, or the end of follow-up, whichever came first. Age was used as the primary time variable. In each individual study, sex-specific hazard ratios and 95 percent confidence intervals for colorectal cancer, colon cancer, and rectal cancer were estimated for each alcohol intake category using a Cox proportional hazards model. In all analyses, adjustments were made for age (continuous), area within each study (for JPHC I, JPHC II, and JACC), smoking (for men: never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), body mass index (weight (kg)/height $(m)^2$; <22, 22–24.9, 25–27.9, or ≥28), energy intake (continuous), and energy-adjusted dietary intakes of red meat (quartiles), calcium (quartiles), fiber (quartiles), and folate (quartiles) in each study. An indicator term for missing data was created for each covariate. Physical activity was not included in the common set of covariates because of large variation in the assessment of physical activity among the studies, but investigators from each study confirmed that additional adjustment for physical activity did not alter the results. SAS (version 9.1; SAS Institute, Inc., Cary, North Carolina) or Stata (version 9.2; Stata Corporation, College Station, Texas) statistical software was used for these estimations.

A random-effects model (25) was used to obtain a single pooled estimate of the hazard ratios from the individual studies for each category. The study-specific hazard ratios were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: Investigators from each study calculated the regression coefficient per 15-g increase in alcohol intake and its standard error, and then these values from the individual studies were combined using a random-effects model. We tested for heterogeneity among studies by means of the Q statistic (25). Meta-regression was used to assess interactions with other risk factors. To estimate the impact of alcohol drinking on the risk of colorectal cancer, we calculated the population attributable fraction percentage according to the formula $pd \times (HR - 1)/HR$, where pd is the proportion of cases exposed to the risk factor(s) (26) and HR is the hazard ratio. Stata was used for meta-analysis.

RESULTS

The present study included 209,763 subjects (98,265 men and 111,498 women) and 2,802 colorectal cancer cases (1,724 men and 1,078 women) accumulated during 2,231,010 person-years of follow-up (table 1). The proportions of colon cancer cases were 63 percent for men and 68 percent for women. Half of the men consumed ≥23 g of alcohol per day. In contrast, 71 percent of women were nondrinkers, and the majority of female drinkers consumed alcohol occasionally (<once/week) or at a level of 0.1–22.9 g/day; only 4 percent consumed ≥23 g/day.

As table 2 shows, alcohol intake was associated with increased risk of colorectal cancer in a dose-response manner in men (p for trend < 0.001). A statistically significant increase in risk was observed among drinkers who consumed ≥23 g/day of alcohol; hazard ratios for 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and ≥92 g/day (compared with nondrinking) were 1.42 (95 percent confidence interval (CI): 1.21, 1.66), 1.95 (95 percent CI: 1.53, 2.49), 2.15 (95 percent CI: 1.74, 2.64), and 2.96 (95 percent CI: 2.27, 3.86), respectively. The test for heterogeneity across studies was not statistically significant for the hazard ratio summarizing risk per 15-g/day increase in alcohol intake ($p > 0.2$). When ex-drinkers were defined separately from never drinkers, similar results were obtained: Hazard ratios for drinkers of 23–45.9 g/day, 46–68.9 g/day, 69–91.9 g/day, and ≥92 g/day versus nondrinkers were 1.57 (95 percent CI: 1.27, 1.94), 2.00 (95 percent CI: 1.30, 3.08), 2.19 (95 percent CI: 1.65, 2.90), and 2.98 (95 percent CI: 1.83, 4.85), respectively. A dose-response relation with alcohol consumption was evident for both the colon and the rectum (p for trend < 0.001), and the hazard ratios associated with alcohol intake of ≥46 g/day were similar. However, an alcohol intake of 23–45.9 g/day was significantly associated with the risk of colon cancer (hazard ratio (HR) = 1.60, 95 percent CI: 1.31, 1.95) but not the risk of rectal cancer (HR = 1.18, 95 percent CI: 0.90, 1.56). When never drinkers were used as the reference group, the risk of colon cancer with these intake levels was increased (HR = 1.93).

In analysis for men using the same exposure categories as those used in the pooled analysis of Western studies (22), hazard ratios for colorectal cancer associated with alcohol intakes of 0.1–4.9 g/day, 5–14.9 g/day, 15–29.9 g/day, 30–44.9 g/day,