mass. In the liver, FFAs produce an increased production of glucose, triglycerides, and secretion of very low density lipoproteins (VLDL), with lipid/lipoprotein abnormalities such as reductions in HDL-cholesterol and an increased density of low density lipoprotein (LDL) [8]. This VLDL secretion and fatty acid β-oxidation, may in turn, result in increased triglyceride synthesis in the liver [41, 42]. A similar mechanism may also be involved in the association between metabolic factors and HCC. In this study, however, the positive association between low HDL-cholesterol and risk of HCC was not significant.

Based on this study, we speculate that metabolic factors may affect the risk of HCC not only in those with hepatitis virus infection but also without hepatitis virus infection, via a common or different pathway. More specifically, metabolic factors may play a role in those without hepatitis virus infection through NASH/NAFLD and related conditions, and in promoting carcinogenesis after infection. Nevertheless, our analyses among both HCV- and HBV infection-negative subjects were based on a small number of cases, meaning no definite conclusions can be drawn, and any interpretation requires caution. In addition, clinical investigations have shown that most HCC in this population originates from HCV- or HBV infection [7], and that the proportion of non-B/non-C HCC in all HCC has been reported to be around 10–12% since 1999 [43]. In addition, a small proportion of NAFLD/NASH patients develop HCC [44]. Together, these findings imply that the contribution of factors other than hepatitis virus infection such as NASH/NAFLD in this population may not be large, at the present time at least. However, given the increasing trend in the incidence of HCC unrelated to hepatitis virus infection, the contribution of metabolic factors among the overall etiology, if any, will soon likely increase. The small number of cases prevented us from restricting analysis to HBV-positive subjects, and is a limitation of this study. Whether the effect of metabolic factors on HCC differs between those positive and negative for hepatitis virus infection, and between those positive for HCV and for HBV, is not conclusive for lack of consistency between studies.

The major strength of this study is its prospective design, in which information was collected before the subsequent diagnosis of HCC, thereby avoiding the exposure recall bias inherent with case–control studies. Other strengths include: study subjects were selected from the general population; the proportion of loss to follow-up (0.3%) was negligible; the quality of our cancer registry system was satisfactory over the study period; and potential confounding factors could be adjusted to minimize their influence on risk values, in spite of the possible influence of residual confounding.

Against this, several obvious limitations can be identified. First, waist circumference was not available to assess exposure. However, given previous studies that a BMI of 25.0 kg/m^2 was equal to 100 cm^2 of visceral fat area as central obesity [32], misclassification by the use of BMI instead of waist circumference, if any, might be small. Likewise, we used non-fasting data, in particular non-fasting triglycerides $\geq$1.69 mmol/l (150 mg/dl), as a component of the metabolic factors, although justification for the use of the same cut-off point as for fasting status is presently under debate. In this study, nevertheless, analyses limited to fasting subjects yielded closely similar results.

Second, evaluation by single measurement of components of metabolic factors at baseline might have produced misclassification, even though this would likely have been non-differential and might lead to an underestimation of results. Further, the subjects of this study were restricted to 26% of the total study subjects with complete questionnaire responses and health checkup data. More women than men tend to participate in health checkup surveys provided by local governments. Further, participants often differ from nonparticipants in socioeconomic status and have a more favorable lifestyle profile, such as lower smoking rates, greater participation in physical exercise, and higher intake of green vegetables and fruits, particularly women [45, 46]. Differences in these factors may have influenced the association between metabolic factors and HCC. In addition, the incidence of HCC in this study population during the follow-up period was 45.7 per 100,000 person-years versus 67.5 in the whole JPHC Study, suggesting that subjects who were already under care for hepatitis virus infection or any of the components of metabolic factors may have been less willing to attend a health checkup. Together, these considerations mandate the need for caution in interpreting or generalizing these results.

Allowing for these methodological issues, metabolic factors in the aggregate may have been associated with an increased risk of HCC in the study population. The effects of overweight and high glucose state appear to have been the main contributors to this association, even under the condition of HCV infection. Our results imply the need to include obesity and diabetes as a crucial target in preventing progression to HCC, even among those already infected with HCV.

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Appendix

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ARTICLE | Annals of Internal Medicine

Declining Incidence of Hepatocellular Carcinoma in Osaka, Japan, from 1990 to 2003

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Background: Japan has the highest incidence rate of primary liver cancer attributed to chronic hepatitis C virus (HCV) infection among developed countries. Molecular clock analysis of HCV sequences revealed that the spread of HCV took place earlier in Japan than in other countries. This might influence recent temporal trends in hepatocellular carcinoma (HCC) incidence.

Objective: To characterize the contribution of HCV-related hepatocellular carcinoma (HCC) to recent changes in HCC incidence in Osaka, Japan.

Design: Population-based survey.

Setting: Osaka Cancer Registry and 10 hospitals in Osaka.

Participants: 63 862 patients with HCC that was diagnosed between 1981 and 2003 in Osaka Prefecture, including 5253 HCV-seropositive patients with HCC that was diagnosed between 1990 and 2003 at 10 hospitals.

Measurements: Incidence of HCC and estimated incidence rate of HCV-related HCC, measured by multiplying the prevalence of anti-HCV by the corresponding HCC incidence rate.

Results: Between 1981 and 2003, peak incidence of HCC among men age 50 to 59 years, 60 to 69 years, and 70 to 79 years occurred in 1986, 1995, and 2000, respectively, with marked downward trends thereafter (average annual change, −7.9, −22.3, and −12.4 per 100 000 persons, respectively). Similar trends were observed in women. Estimated sex- and age-specific incidence of HCV-related HCC (per 100 000 persons) decreased from 255 to 92 cases at the maximum in men age 60 to 69 years and from 61 to 34 cases in women age 60 to 69 years, whereas estimated incidence of non-HCV–related HCC did not change between 1990 and 2003.

Limitation: Infection was determined only by HCV seropositivity.

Conclusion: The incidence of HCC in Osaka started to decrease by 2000, mainly because of decreased HCV-related HCC.

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Primary liver cancer was the fifth most common cancer worldwide by 2000, with approximately 551 000 new cases recorded (1). In most countries, hepatocellular carcinoma (HCC) comprises 85% to 90% of primary liver cancer cases. With some exceptions, developed countries, including the United States, have been experiencing an increase in the incidence of primary liver cancer, considered to be due at least in part to increased prevalence of chronic hepatitis C virus (HCV) infection (2).

Japan has had one of the highest incidence rates of primary liver cancer among developed countries (age-standardized incidence rate in 1995, 25.5 per 100 000 men and 7.7 per 100 000 women) (3). Approximately 90% of liver cancer cases are HCC, which, in Japan, is mainly caused by chronic HCV infection rather than chronic hepatitis B virus infection (4). A recent report on the age-standardized incidence of primary liver cancer among Japanese men, which was calculated from 6 population-based cancer registries, showed a sharp increase that started in the mid-1970s but leveled off in the mid-1990s (5). These distinctive trends were thought to be due to the spread of HCV infection, which began in the 1920s and increased after World War II (6–8). Thus, HCV penetrated Japan earlier than Spain, Egypt, the United States, the former Soviet Union, South Africa, and Hong Kong, as evidenced by molecular clock analysis of the sequences of HCV isolates (8). However, recent temporal trends regarding incidence rates of HCC and the contribution of HCV infection have not been clearly documented in the Japanese population.

We analyzed temporal trends for HCC incidence rates between 1981 and 2003 in Osaka Prefecture (population in 2005, 8.8 million) and interpreted these in the context of HCV infection rates.

See also:

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Conversion of graphics into slides

METHODS

Data Collection on Incident HCC Cases

We obtained data on incident HCC cases from the Osaka Cancer Registry, which was established by the Osaka Prefectural Government in 1962. The registry collects reports on patients with newly diagnosed cancer, including demographic and cancer-related information, from all medical institutions in Osaka Prefecture (9). These have been routinely supplemented by death certificates gathered

by the Osaka Prefectural Government (9). For patients with cancer who were enrolled in the registry on the basis of their death certificate, we contacted the issuing hospital to obtain information on diagnosis and treatment and to establish the date of HCC incidence, which we determined to be the time of diagnosis at that hospital. We site-coded the data according to the International Classification of Diseases for Oncology, Third Edition (10). We included patients with HCC (codes 8170 through 8180). The protocol was approved by the ethics committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

From 1981 to 2003, 48 166 men and 15 696 women with HCC were documented in the Osaka Cancer Registry. We calculated the annual age-standardized incidence rates of HCC (world population as a standard population) by sex between 1981 and 2003. To characterize temporal trends for HCC, we assessed 10-year, age-specific incidence rates of HCC between 1981 and 2003 in individuals age 50 to 79 years. We studied these particular age-specific rates because most HCV-related HCC cases in the Japanese population occur between the ages of 50 and 79 years (4). We used the annual population estimates from 1981 to 2003, which were based on the average population in each sex and age category for the Osaka Prefecture during the particular period, as denominators for calculating incidence rates. The annual population estimates were based on data from the 1980, 1985, 1990, 1995, 2000, and 2005 Japanese population censuses, with linear interpolation for the years in between.

Statistical Analysis

To identify years when a statistically significant change in the slope of the temporal trend in the incidence occurred, we applied the joinpoint regression model by using the Joinpoint Regression Program, version 3.0 (U.S. National Cancer Institute, Bethesda, Maryland). We assumed constant variance and uncorrelated errors (11) because we could not detect heteroskedasticity by the White test or autocorrelation by the Durbin-Watson test in men or women in any age group.

We computed the estimated slopes describing the average annual change of incidence rate per 100 000 persons and the corresponding 95% CIs for each trend by fitting a piecewise regression line to the rates, using calendar year as a regression variable. We used the permutation test method to identify years when a statistically significant change had occurred ($P < 0.05$) and set the number of randomly permuted data sets at 4499. We set the number of joinpoints to a minimum of 0 and a maximum of 3 in the Joinpoint Regression Program.

Data Collection on Prevalence of HCV Infection among Patients with HCC

The Osaka Cancer Registry does not collect serologic data on HCV infection in the registered patients. Therefore, we used data on HCV seropositivity from patients with HCC that was diagnosed at 10 hospitals in Osaka Prefecture (1 university hospital, 2 cancer centers, and 7 general hospitals) to estimate the prevalence of HCV infection in patients with HCC. We considered the HCC diagnosis confirmed when the patient had positive histologic or positive radiologic results by enhanced computed tomography or hepatic angiography. We collected data on the patient's sex, date of birth, date of diagnosis between 1990 and 2003, first Chinese letter of the family name, and presence of hepatitis B surface antigen and antibody to hepatitis C (anti-HCV) as assessed by any commercially available kit. We did not collect the full first and family name for reasons of confidentiality. Because anti-HCV testing first became available in Japan in 1990, we collected data on patients whose HCC diagnosis was between 1990 and 2003. One investigator checked for duplication of the data set, because some patients might have been registered multiple times among the participating hospitals as a result of referrals and recurrence of HCC. We defined HCV-related HCC as occurring in patients who were HCV-seropositive at the time of diagnosis.

We calculated the sex-specific, age-specific (50 to 59, 60 to 69, or 70 to 79 years), and period-specific (1990 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001, or 2002 to 2003) prevalences of HCV seropositivity for patients with HCC. We then multiplied prevalence rates by the corresponding strata of the HCC incidence rate obtained from the Osaka Cancer Registry data. Thus, we derived the denominators from the general population in Osaka through the denominators of the HCC incidence rate and obtained the numerators by multiplying the prevalence rates by the HCC incidence rate. We calculated the incidence rate of non–HCV-related HCC by subtracting HCV-related HCC from total HCC. Thus, we describe trends for the estimated incidence rates of HCV-related

Context

Hepatitis C virus (HCV) infection in Japan began to spread during the 1920s, increased after World War II with an explosion in parenteral amphetamine use and paid blood donation, and decreased in the 1950s to 1960s with voluntary blood donation and penalties against amphetamine use. Evidence linking the trends in HCV infection to hepatocellular carcinoma rates in Japan is limited.

Contribution

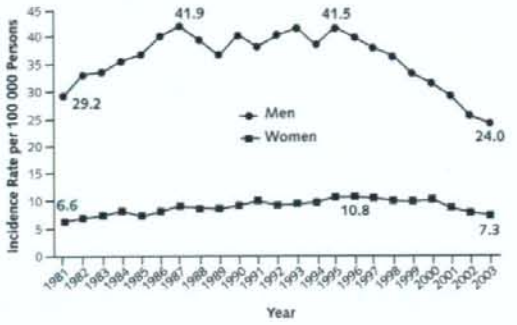
Data from the Osaka Cancer Registry and 10 Osaka hospitals suggest that hepatocellular carcinoma rates began to decrease in 2000, mainly because of a decrease in HCV-associated cancer.

Implication

Control of HCV transmission within a population seems to be followed by a decrease in hepatocellular carcinoma.

—The Editors

Figure 1. **Trends in age-standardized (world population) incidence of hepatocellular carcinoma in Osaka, Japan, 1981–2003.**



and non–HCV-related HCC between 1990 and 2003 in Osaka Prefecture. We calculated the CI of the estimated rates by multiplying the lower and upper limits of the CI of the prevalence based on SE by the corresponding HCC incidence rate.

Role of the Funding Source

This study was supported by the Osaka Prefectural Government between 1990 and 2000 and Grants-in-Aid for Hepatitis Research of the Japanese Ministry of Health, Labor, and Welfare. There is no conflict of interest in the study. The funding sources had no role in the collection, management, or analysis of data.

RESULTS

The age-standardized incidence rate of HCC in men increased between 1981 and 1987 from 29.2 to 41.9 cases per 100 000 persons, then fluctuated until 1995. After that, it steadily decreased to 24.0 cases per 100 000 persons in 2003 (**Figure 1**). Among women, the age-standardized incidence rate of HCC increased between 1981 and 1996 from 6.6 to 10.8 cases per 100 000 persons, then gradually decreased to 7.3 cases per 100 000 persons in 2003 (**Figure 1**).

Figure 2 shows the trends in the incidence of HCC among men and women age 50 to 59 years, 60 to 69 years, and 70 to 79 years in Osaka between 1981 and 2003. The HCC incidence rate increased from 1981 to 1986 among men age 50 to 59 years, from 1981 to 1995 among men age 60 to 69 years, and from 1981 to 2000 among men age 70 to 79 years (average annual change of the incidence rate [per 100 000 persons], 10.0, 10.7, and 6.2, respectively) (**Table 1**). A striking downward trend occurred after the year of peak incidence in the 3 age groups (−7.9 until 1996, −22.3 until 2003, and −12.4 until 2003, respectively). Among men age 50 to 59 years, there was a second joinpoint (a change from rapid to moderate decrease) in 1996, resulting in a slope of −3.1 until 2003. Among women age 50 to 59 years, 60 to 69 years, and 70 to 79 years, the incidence rates of HCC peaked in 1991, 1997, and 2000, respectively (**Table 1**). The rates in women seemed to increase slightly from 1981 until the year of the joinpoint, with slopes of 0.43, 2.07, and 3.10, respectively. Thereafter, HCC incidence rates in women decreased through 2003 at a statistically significant average annual rate of −0.9, −5.7, and −7.9, respectively (**Table 1**).

Figure 2. **Joinpoint analysis of the incidence rate of hepatocellular carcinoma among individuals age 50 to 79 years in Osaka, Japan, 1981–2003.**

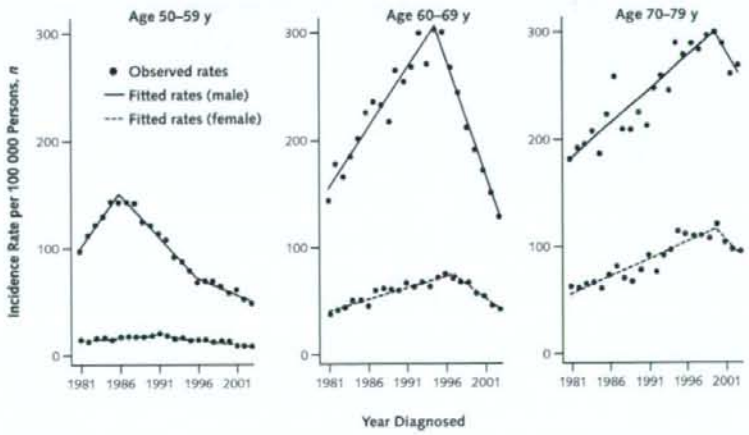


Table 1. **Joinpoint Analysis of the Hepatocellular Carcinoma Incidence Rate per 100 000 Persons in Osaka, Japan, 1981–2003**

Age Range	Peak Year	Incidence Rate per 100 000 Persons	Trend 1		Trend 2		Trend 3	
			Years	Slope (95% CI)	Years	Slope (95% CI)	Years	Slope (95% CI)
Men								
50–59 y	1986	142.0	1981–1986	10.0 (8.2 to 11.8)*	1986–1996	−7.9 (−8.6 to −7.1)*	1996–2003	−3.1 (−4.2 to −2.1)*
60–69 y	1995	299.6	1981–1995	10.7 (9.1 to 12.3)*	1995–2003	−22.3 (−26.0 to −18.6)*	–	–
70–79 y	2000	296.4	1981–2000	6.2 (4.8 to 7.5)*	2000–2003	−12.4 (−35.7 to 10.9)	–	–
Women								
50–59 y	1991	19.7	1981–1991	0.4 (0.2 to 0.7)*	1991–2003	−0.9 (−1.1 to −0.7)*	–	–
60–69 y	1997	68.5	1981–1997	2.1 (1.7 to 2.4)*	1997–2003	−5.7 (−7.3 to −4.1)*	–	–
70–79 y	2000	118.1	1981–2000	3.1 (2.5 to 3.7)*	2000–2003	−7.9 (−18.1 to 2.4)	–	–

* $P < 0.001$.

Table 2 shows the prevalence of anti-HCV antibodies among 5253 patients age 50 to 79 years with HCC that was diagnosed at 10 hospitals in Osaka between 1990 and 2003. The prevalence was highest in men with HCC that was diagnosed in 1993 to 1995 (82.4%). The proportion of HCV-seronegative patients ranged from 18% to 29% through the observation period. The prevalence of anti-HCV was almost constant (81% to 83%) among women with HCC that was diagnosed between 1993 and 2003 (**Table 2**).

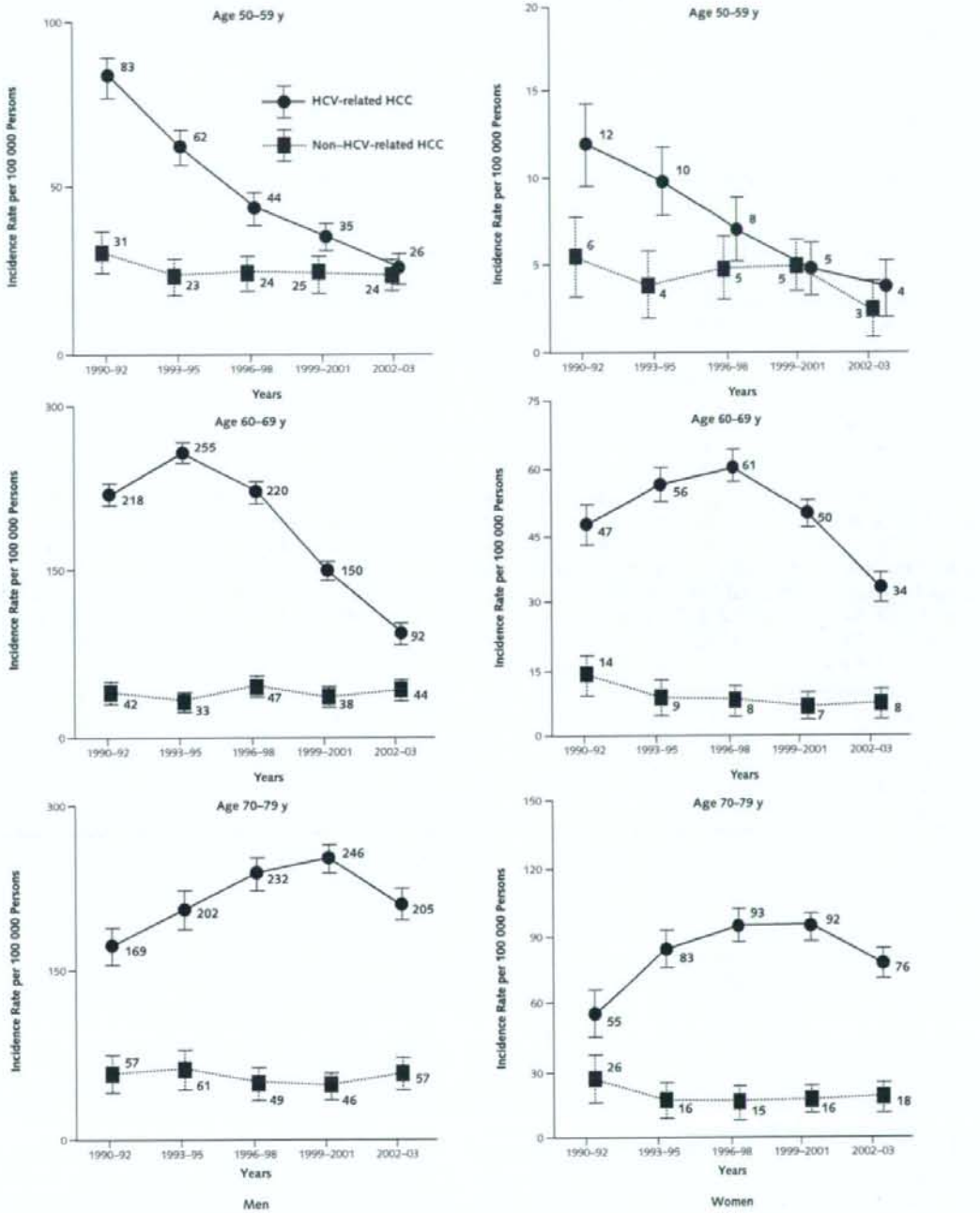
Figure 3 shows changes in the estimated incidence rate of HCV-related and non–HCV-related HCC from 1990 to 2003. Among men, the estimated incidence rate of HCV-related HCC steadily decreased among Osaka residents age 50 to 59 years from 83 (95% CI, 77 to 89) cases per 100 000 persons in 1990 to 1992 to 26 (CI, 21 to 30) cases per 100 000 persons in 2002 to 2003. Among men age 60 to 69 years, incidence seemed to peak (255 [CI, 247 to 264] cases per 100 000 persons) from 1993 to 1995. Among men age 70 to 79 years, the incidence rate increased from 1990 to 1992 (169 [CI, 153 to 186] cases per 100 000 persons) to 1999 to 2001 (246 [CI, 234 to 258] cases per 100 000 persons) and leveled off afterward. The estimated incidence rate of HCV-related HCC among women age 50 to 59 years decreased from 12.4 (CI, 10.1 to 14.7) cases per 100 000 persons during 1990 to 1992 to 4.2 (CI, 2.5 to 5.8) cases per 100 000 persons during 2002 to 2003, whereas among women age 60 to 69 years, the incidence peaked (61 [CI, 57 to 64] cases per 100 000 persons) during 1996 to 1998. The trend in women age 70 to 79 years seemed to be similar to that in men of the same age: increasing during the 1990s and leveling off in the early 2000s (**Figure 3**). The estimated incidence rate of non–HCV-related HCC was lower than that of HCV-

Table 2. **Prevalence of Anti-HCV among 5253 Patients Age 50 to 79 Years with Hepatocellular Carcinoma at 10 Hospitals in Osaka, Japan, 1990–2003***

Variable	1990–1992		1993–1995		1996–1998		1999–2001		2002–2003	
	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %
Men										
Anti-HCV(+)	602	78.3 ± 1.5	677	82.4 ± 1.3	651	78.7 ± 1.4	709	76.6 ± 1.4	385	70.9 ± 1.9
Anti-HCV(+) and HBsAg(+)	18	2.3 ± 0.5	17	2.1 ± 0.5	11	1.3 ± 0.4	16	1.7 ± 0.4	8	1.5 ± 0.5
Anti-HCV(+) and HBsAg(−)	584	75.9 ± 1.5	660	80.3 ± 1.4	640	77.4 ± 1.5	693	74.8 ± 1.4	377	69.4 ± 2.0
Anti-HCV(−)	167	21.7 ± 1.5	145	17.6 ± 1.3	176	21.3 ± 1.4	217	23.4 ± 1.4	158	29.1 ± 1.9
Anti-HCV(−) and HBsAg(+)	60	7.8 ± 1.0	57	6.9 ± 0.9	71	8.6 ± 1.0	106	11.4 ± 1.0	68	12.5 ± 1.4
Anti-HCV(−) and HBsAg(−)	107	13.9 ± 1.2	88	10.7 ± 1.1	105	12.7 ± 1.2	111	12.0 ± 1.1	90	16.6 ± 1.6
Total	769	100.0	822	100.0	827	100.0	926	100.0	543	100.0
Women										
Anti-HCV(+)	165	73.0 ± 3.0	211	82.7 ± 2.4	248	82.9 ± 2.2	274	80.8 ± 2.1	200	81.0 ± 2.5
Anti-HCV(+) and HBsAg(+)	8	3.5 ± 1.2	2	0.8 ± 0.6	5	1.7 ± 0.7	2	0.6 ± 0.4	2	0.8 ± 0.6
Anti-HCV(+) and HBsAg(−)	157	69.5 ± 3.1	209	82.0 ± 2.4	243	81.3 ± 2.3	272	80.2 ± 2.2	198	80.2 ± 2.5
Anti-HCV(−)	61	27.0 ± 3.0	44	17.3 ± 2.4	51	17.1 ± 2.2	65	19.2 ± 2.1	47	19.0 ± 2.5
Anti-HCV(−) and HBsAg(+)	21	9.3 ± 1.9	17	6.7 ± 1.6	29	9.7 ± 1.7	29	8.6 ± 1.5	18	7.3 ± 1.7
Anti-HCV(−) and HBsAg(−)	40	17.7 ± 2.5	27	10.6 ± 1.9	22	7.4 ± 1.5	36	10.6 ± 1.7	29	11.7 ± 2.0
Total	226	100.0	255	100.0	299	100.0	339	100.0	247	100.0

* HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Figure 3. **Trends in estimated incidence rates of hepatitis C virus (*HCV*)–related and non–HCV-related hepatocellular carcinoma (*HCC*) in Osaka, Japan, 1990–2003.**



Information on anti-HCV status only became available after 1989. Error bars indicate 95% CIs.

related HCC in most strata. We observed no distinctive changes in the temporal trends for non–HCV-related HCC during the study period.

Discussion

Our analysis of HCC incidence in the Japanese population between 1981 and 2003 identified calendar years in which significant changes in temporal trends occurred. The HCC incidence rates in men and women age 50 to 59 years peaked during 1986 and 1991, respectively; in men and women age 60 to 69 years during 1995 and 1997, respectively; and in men and women age 70 to 79 years in 2000. We also found that temporal trends for HCC incidence between 1990 and 2003 by age group were mainly determined by trends in the incidence rates of HCV-related HCC.

The most likely explanation for these observations is the particular mode of HCV transmission in Japanese society. According to a study on molecular tracing of endemic HCV (8), the exponential spread of HCV-1b infection, a dominant genotype of HCV in Japan, started in the 1920s. This was associated with treatment of *Schistosoma japonicum* beginning in 1921 (12). Later, HCV infection coincided with an increase in parenteral amphetamine use in the devastated country during and after World War II (6, 7). Subsequently, viral spread was considered to be amplified through blood transfusions and parenteral medical procedures in the 1950s and 1960s (6, 7). Data on first-time blood donor candidates in Osaka indicate that the prevalence of anti-HCV antibodies among those born in 1925 to 1935 was much higher (7% to 10%) than that in the younger generation born in 1936 to 1955 (13). It is plausible that Japanese people born between 1925 and 1935, who were adolescents in the early 1950s, were most susceptible to HCV transmission under these circumstances. Age groups with peak incidence of HCC in men and women in the current study (1986 and 1991, respectively, for 50 to 59 years; 1995 and 1997, respectively, for 60 to 69 years; and 2000 for 70 to 79 years) included the generation for which prevalence of anti-HCV was high in Osaka (born in 1925 and 1935) (13). Stiffening of legal penalties against amphetamine use starting in 1954 and conversion from paid to voluntary blood donation in the late 1960s may have reduced HCV transmission, thereby resulting in the lower prevalence of HCV infection in generations born after 1935. Indeed, the spread of HCV in Japan essentially ended by the early 1990s at the latest, as evidenced by the current very low incidence of HCV infection among repeat blood donors (14, 15). Better detection methods introduced in the early 1980s for HCC in patients with cirrhosis through ultrasonography and measurement of α-fetoprotein may have contributed to the apparent increase in the incidence of HCC found in this study. However, the distinctive changes we observed in the age-specific incidence of HCC during the 1990s through the early 2000s cannot be explained by the increased ability to detect HCC, because the different joinpoints in age-specific incidence rates would not be derived from a single period effect of detection of HCC.

Increases in the incidence of and deaths from liver cancer in the 1970s to 1990s have been reported in Japan (5, 16), Australia (2), the United Kingdom (17), France (2, 18), Italy (2, 18), and the United States (2, 19). The increases in Japan and the United States are attributable to increased seroprevalence of HCV (6, 13, 20, 21), whereas this relationship has not been clearly established in the other countries.

Certain limitations of this study should be considered. First, because cancer reporting in Osaka is not mandated by law, HCC could have been underreported. However, because it is fatal, most of the unreported cases should have been detected by examination of the death certificate. In addition, because the proportion of persons with HCC included only on the basis of their death certificate was almost constant (22% to 25%) during the observation period (22–24), such underreporting would not be expected to affect the temporal trends for HCC incidence rates shown in our study. Second, the proportion of HCV-seropositive patients among the 5253 cases diagnosed at 10 hospitals might differ somewhat from the entire cohort of patients with HCC in Osaka. However, all Japanese patients, including those with HCC, have easy access to hospitals because of the national medical insurance system, and the 10 participating hospitals did not select patients with HCC on the basis of their etiologic background. Therefore, it is realistic to suppose that selection bias on prevalence of anti-HCV among these 5253 patients would have been limited. Finally, the temporal trends seen in the present study might differ from those among the entire Japanese population. We previously reported age-specific incidence rates of liver cancer by birth year in Japanese men between 1962 and 1997 (5) by using 6 population-based cancer registries from Cancer Incidence in Five Continents (9) (registries for Miyagi, Yamagata, Osaka, Hiroshima, Saga, and Nagasaki). Our previous study found the peak incidence of HCC among those born between 1931 and 1935 (5). In addition, the age-dependent prevalence of anti-HCV among first-time blood donors in Osaka (13) was similar to those in other areas of Japan (25). These findings may indicate that the timing of the outbreak of HCV infection and its reduction were similar in the different geographic areas of the country.

In conclusion, our calculation of HCC incidence rates demonstrated that they are already decreasing in both sexes in Osaka, Japan. That the outbreak of HCV infection in Japan after World War II and its termination occurred earlier in Japan than in the rest of the world is the most likely explanation for these observations. These findings confirm that HCV-related HCC is a preventable disease that can be decreased by controlling parenteral HCV transmission. In the early 1990s, interferon therapy for patients

with chronic HCV infection was started in Japan to reduce the risk for HCC (26, 27). A nationwide, community-based anti-HCV screening system targeting individuals age 40 to 70 years was introduced by municipal governments in Japan in 2002. Further observation of the temporal trends of HCC incidence is needed to assess the efficacy of these interventions in Japan.

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

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Background: Although alcohol consumption has been recognized as a risk factor for primary liver cancer, it will be informative to summarize relevant epidemiologic data in the Japanese who have characteristic environmental determinants (e.g. hepatitis C virus infection) and genetic traits (e.g. presence of poor acetaldehyde metabolizers).
Methods: We systematically reviewed epidemiologic studies on alcohol drinking and liver cancer among Japanese populations. Original data were obtained through searches of the MEDLINE (PubMed) and *Ichushi* databases, 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 assessed by the International Agency for Research on Cancer.
Results: Among 22 cohort studies identified, 14 (64%) reported weak to strong positive associations between alcohol and liver cancer risk, 3 (14%) reported no association and five (23%) reported weak to moderate inverse associations; such inverse associations were found mostly in follow-up studies of patients with chronic liver disease (particularly, cirrhotic patients), yet recent studies on patients with chronic hepatitis C presented fairly consistent positive associations. Of 24 case–control studies identified, 19 (79%) showed weak to strong positive associations, whereas the remainder demonstrated no association ($n = 4$) or a moderate inverse association ($n = 1$).
Conclusion: We conclude that there is 'convincing' evidence that alcohol drinking increases the risk of primary liver cancer among the Japanese population.

Keywords: systematic review – epidemiology – alcohol – liver cancer – Japanese

INTRODUCTION

Alcohol has long been viewed as a hepatotoxic agent, and its heavy consumption is known to cause hepatocellular injury that can lead to enhanced fibrosis and eventually to liver cirrhosis through various mechanisms presumed (1). Alcohol drinking has also been implicated in the etiology of primary liver cancer that often develops from cirrhosis (2). In the most recent evaluation by the International Agency for Research on Cancer (IARC), the occurrence of liver cancer has been 'causally' related to the consumption

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of alcoholic beverages (3). In the second report published by the World Cancer Research Fund and the American Institute for Cancer Research, the Panel has judged that alcohol consumption is 'probably' a direct cause of liver cancer (4).

Primary liver cancer is one of the most common cancers in Japan (5). More than 90% of primary liver cancers in this country are hepatocellular carcinomas (HCCs) that are mostly attributable to chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) (6,7); HCV and HBV infections are estimated to account for 70 and 15%, respectively, of the recent occurrences of HCC in Japan (6). This tendency clearly contrasts with the situation in south-east Asia and sub-Saharan Africa where HBV represents a dominant risk factor of HCC, and with that in Western countries where HCV infection plays an increasingly important role (2,8). The role of alcohol in hepatocarcinogenesis might differ between Japan and such areas. Moreover, ~50% of the Japanese are poor metabolizers of acetaldehyde (9), the first metabolite of ethanol, which has been recognized as being possibly carcinogenic to humans (10). Such poor metabolizers have not been found in Africans or Caucasians (9), and thus the Japanese as Mongoloids might be more susceptible to alcohol than other ethnic groups.

The aim of the present study was to review and summarize epidemiologic findings on alcohol drinking and liver cancer among Japanese populations. This work was conducted as part of a project of systematic evaluation of the epidemiologic evidence regarding lifestyles and cancers in Japan (11).

PATIENTS AND METHOD

The details of the evaluation method have been described elsewhere (11). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi* (*Japana Centra Revuo Medicina*) databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between alcohol drinking and liver cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2008, including papers in press if available, were identified using the following as keywords: alcohol, liver, hepatocellular, cohort, follow-up, case–control, Japan and Japanese. 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 as cohort or case–control studies.

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

After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (12), 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 IARC (3). Despite the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitudes of association among 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 22 cohort (13–34) (Table 1) and 24 case–control studies (35–58) (Table 2). Of those cohort studies, two presented the results by sex (19,31), seven for men only (13–16,26,29,32) and 13 for men and women combined (17,18,20–25,27,28,30,33,34). The respective numbers for the case–control studies are two (45,54), nine (36–38,42,44,48–51) and 13 (35,39–41,43,46,47,52,53,55–58). Several studies showed the results separately according to study areas (16), different age categories (31), the severity of chronic liver disease (CLD) (33) or different control groups (49,54,56).

Study populations in the cohort studies, except for one study based on male alcoholics (26), were classified broadly into two categories: mostly healthy subjects ($n = 7$) such as local residents (14,16,25,31,32), physicians (13) and atomic bomb survivors (19) and patients with CLD (15,17,18,20–24, 27–30,33,34) ($n = 14$) (Table 1). Chronic infections with both HCV and HBV were taken into account in 12 studies, all of which followed patients with CLD (18,20–24, 27–30,33,34). In the case–control studies, excluding one study based on military men exposed to thorotrast (38), a

Table 1. Cohort studies on alcohol drinking 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. (13)	1965–83	5130 men	Male physicians in western Japan	Death	51 men (primary 9, unspecified 42)	Never/past		1.00		Age, smoking	HBsAg and anti-HCV were not tested.
						Occasional		1.34 (0.61–2.98)			
						<2 go/day		1.80 (0.80–4.02)			
						≥2 go/day		2.36 (1.04–5.35)			
Hirayama (14)	1966–82	122261 men	95% of the census population in 29 health-center-covered areas in six prefectures	Death	788 men (liver cancer) or 123 men (primary liver cancer)	For liver cancer				Age	HBsAg and anti-HCV were not tested
						Not daily		1.00			
						Daily		1.25 ($P < 0.01$)			
						For primary liver cancer					
						Not daily		1.00			
						Daily		1.89 ($P < 0.01$)			
Inaba et al. (15)	1973–88	270 men	Patients with liver cirrhosis at Juntendo University Hospital	Death	46 men	Never		1.00		Age, HBsAg, histories of blood transfusion, hepatitis and surgical operation, smoking	Anti-HCV was not tested
						Current/past		0.41 (0.08–2.20)			
Shibata et al. (16)	1958–86	639 men in a farming area and 677 men in a fishing area	Residents in a farming area or a fishing area in Kyushu	Death	11 men (farming area) and 22 men (fishing area)	Farming area					
						Non-drinker	2	1.0	>0.1	Age	HBsAg and anti-HCV were not tested
						Sake <1 go/day	6	1.1 (0.2–5.5)			
						Sake 1–2 go/day	2	1.6 (0.2–11.6)			
						Sake ≥2 go/day	1	1.1 (0.1–13.5)			
						Fishing area					
						Non-drinker	2	1.0		Age	
						Sake <1 go/day	0	–			
						Sake 1–2 go/day	0	–			
						Sake ≥2 go/day	1	5.5 (0.6–51.1)			

						Fishing area					
						Shochu none	4	1.00	<0.01	Age, smoking	
						Shochu <2 go/day	14	5.85 (1.31–26.18)			
						Shochu ≥2 go/day	4	14.02 (2.34–83.89)			
Kato et al. (17)	1987–90	1784	Patients with decompensated liver cirrhosis or post-transfusion hepatitis	Incidence	122	Never drinker	46	1.00		Sex, age	HBsAg and anti-HCV status was unknown. The total alcohol index was obtained by multiplying the daily ethanol intake (ml) by the number of years of drinking
						Past drinker	19	0.58 (0.32–1.04)			
						Occasional drinker	4	0.43 (0.15–1.24)			
						Current drinker	5	0.41 (0.16–1.06)			
						Total alcohol index					
						0	46	1.00	0.046		
						1–1999	10	0.49 (0.23–1.02)			
						2000+	13	0.53 (0.27–1.04)			
Tsukuma et al. (18)	1987–91	917 (548 men and 369 women)	Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka	Incidence	54	Nondrinker		1.00		Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for.
						Occasional drinker		0.77 (0.20–2.99)			
						Former drinker					
						<80 g ethanol/day		1.46 (0.56–3.79)			
						≥80 g ethanol/day		1.66 (0.69–3.96)			
						Current drinker					
						<80 g ethanol/day		1.10 (0.39–3.07)			
						≥80 g ethanol/day		1.15 (0.35–3.78)			
Goodman et al. (19)	1980–89	36133	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 were not tested.
						Never-drinker	25	1.00			
						Ever-drinker	126	1.11 (0.72–1.70)			
						Ex-drinker	25	2.33 (1.34–4.07)			
						Quit ≥16 years ago	4	0.96 (0.33–2.77)			

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						
						Quit 11–15 years ago	8	2.08 (0.93–4.67)			
						Quit ≤10 years ago	12	7.87 (3.89–16.0)			
						Present drinker	100	0.98 (0.63–1.52)			
						<135 ml/week	37	1.09 (0.65–1.81)			
						135–299 ml/week	37	1.11 (0.67–1.86)			
						≥300 ml/week	37	1.12 (0.67–1.87)			
						For women					
						Never/past drinker	56	1.00			
						Present drinker	27	1.25 (0.78–1.98)			
						<27 ml/week	1	0.28 (0.04–2.02)			
						27–69 ml/week	6	1.20 (0.52–2.79)			
						≥70 ml/week	9	2.02 (0.99–4.09)			
Chiba et al. (20)	1977–93	412 (249 men and 163 women)	Patients with HCV-associated chronic hepatitis or compensated cirrhosis at Tsukuba University Hospital	Incidence	63 (54 men and 9 women)	Nondrinker		1.00		Sex, age, stage of disease, serum alpha-fetoprotein, anti-HBs, anti-HBc, histories of blood transfusion, surgical procedure and liver cancer in family, smoking	All subjects were anti-HCV-positive and HBsAg-negative.
						<150 kg ethanol		1.33 (0.60–2.93)			
						150–449 kg ethanol		1.50 (0.71–3.17)			
						≥450 kg ethanol		0.98 (0.43–2.23)			
Ikeda et al. (21)	1980–?	2215 (1544 men and 671 women)	Patients with chronic hepatitis at Toranomon Hospital	Incidence	89	All subjects	($n = 2215$)			Stage of hepatitis, gamma-glutamyl transpeptidase	HBsAg and anti-HCV status was available for all subjects.
						<500 kg ethanol		1.00			
						≥500 kg ethanol		3.04 (1.79–5.14)			
						HBsAg(+) anti-HCV(−) subjects	($n = 610$)			Indocyanine green retention rate	

						<500 kg ethanol		1.00			
						≥500 kg ethanol		8.37 (2.70–25.93)			
						HBsAg(−) anti-HCV(+) subjects	(*n* = 1500)			Stage of hepatitis, γ-glutamyl transpeptidase, history of blood transfusion, albumin	
						<500 kg ethanol		1.00			
						≥500 kg ethanol		1.96 (1.06–3.62)			
Tanaka et al. (22)	1985–95	96 (62 men and 34 women)	Patients with liver cirrhosis at Kyushu University Hospital	Incidence	37 (27 men and 10 women)	Never	16	1.00		Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for. The relative risks were not described in the original paper, and were reestimated by one of the authors (KT). One 'drink' corresponds to 23 ml of ethanol.
						Past	17	0.59 (0.20–1.73)			
						Current					
						<2.4 drinks/day	1	0.06 (0.01–0.57)			
						≥2.4 drinks/day	3	0.17 (0.02–1.42)			
Matsushita et al. (23)	1985–94	267 (165 men and 102 women)	Patients with liver cirrhosis at Kanazawa University Hospital	Incidence	67	Type B or C cirrhosis	(*n* = 202)			Age, anti-HCV	All subjects analyzed were positive for anti-HCV or HBsAg.
						Positive drinking history		1.83 (1.00–3.36)			
						Type C cirrhosis	(*n* = 140)			Age	
						Positive drinking history		2.36 (1.23–4.54)			
Aizawa et al. (24)	1981–98	153 (115 men and 38 women)	Patients with chronic hepatitis or cirrhosis positive for anti-HCV at Jikei University Hospital	Incidence	Not described	Habitual heavy drinking				Sex, age, ALT, interferon therapy, histologic staging, irregular regeneration	All subjects were anti-HCV-positive and HBsAg-negative. Habitual heavy drinking was defined as an average daily consumption of 65 g of ethanol for >5 years.
						No		1.00			
						Yes		3.04 (1.31–7.09)			
Mori et al. (25)	1992–97	3052 (974 men and 2078 women)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	History of habitual alcohol consumption				Sex, age	Anti-HCV and HBsAg status was available but not adjusted for.
						No	10	1.00			
						Yes	22	1.27 (0.46–3.47)			
						Never drinker	10	1.00	0.87		One 'drink' corresponds to a glass of sake.
						1–19 drink-years	3	2.05 (0.48–8.79)			
							9				

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						
						≥20 drink-years		1.14 (0.40–3.26)			
Noda et al. (26)	1972–92	306 men	Alcoholics in Takatsuki city, Osaka, who had been diagnosed at a psychiatric institution	Death	Not described	O/E ratio for hepatocellular carinoma		1.6 (0.3–4.7)		Age, calendar year	Anti-HCV and HBsAg were not tested.
Hamada et al. (27)	1980–2000	469 (227 men and 242 women)	Patients with clinically compensated chronic hepatitis C due to blood transfusion at National Nagasaki Medical Center	Incidence	52	Alcohol consumption				Age, serum bilirubin, platelets, interferon therapy, duration from infection, fibrosis	All subjects were anti-HCV-positive and HBsAg-negative. Excessive alcohol consumption was defined as an alcohol consumption of >50 g/day for 5 years.
						Not excessive		1.00			
						Excessive		2.21 (1.00–3.58)			
Takimoto et al. (28)	1989–?	356	Patients with histologically proven chronic hepatitis C at Niigata University Hospital and one hospital in Niigata, who did not respond to interferon therapy	Incidence	Not described	Alcohol drinking				Age, sex, blood transfusion, viral load, viral subtype, stage of fibrosis, ALT, platelets, interferon dose	All subjects were anti-HCV-positive and HBsAg-negative. Alcohol drinking was defined as having consumed >80 g ethanol daily for >5 years.
						No		1.00			
						Yes		4.30 ($P = 0.048$)			
Uetake et al. (29)	1988–2000	91 men	Patients with HBsAg-negative anti-HCV-negative alcoholic cirrhosis at Jikei University Hospital	Incidence	13 men	Cumulative alcohol intake (kg)				Anti-HBc	All patients were HBsAg-negative, anti-HCV-negative, and alcoholic. The hazard ratio (and 95% confidence interval) was not described in the original paper, and was estimated by one of the authors (KT).
						1200 kg increase		7.7 (1.9–31.5)	0.0047		
Iwasaki et al. (30)	1986–2003	792 (533 men and 259 women)	Hepatitis C patients with or without Child A cirrhosis at Okayama University Hospital and participating institutions, with sustained response to interferon	Incidence	23 (20 men and 3 women)	Alcohol consumption				Fibrosis staging, age	All subjects were anti-HCV-positive and HBsAg-negative.
						<50 g/day		1.00			
						≥50 g/day		3.86 (1.58–9.44)			
Ogimoto et al. (31)	1988–99	66974 (28343 men and 38631 women)	Residents in 45 areas throughout Japan	Death	184 (number by sex and age not described)	Male, 40–59 years	($n = 16715$)			Collaborating institute	HBsAg and anti-HCV were not tested.
						Never drinker		1.00			
						Ex-drinker		8.11 (3.17–20.77)			
						Current drinker		0.65 (0.27–1.52)			

						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						
						<30 g/day	11	1.00 (reference)			
								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 aminotransferase; 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