Influence of Coffee Drinking on Subsequent Risk of Hepatocellular Carcinoma: A Prospective Study in Japan

Manami Inoue, Itsuro Yoshimi, Tomotaka Sobue, Shoichiro Tsugane

For the JPHC Study Group

Background: **An association between coffee drinking and reduced risk of liver cancer has been suggested by animal studies, but epidemiologic evidence of such an association in a high-risk population is lacking. We conducted a large-scale population-based cohort study of the association between coffee drinking and hepatocellular carcinoma (HCC) in a Japanese population.** ***Methods:*** **Newly diagnosed case patients (250 men and 84 women) with HCC were identified from a 10-year follow-up of the Japan Public Health Center-based Prospective Study, which consists of 90 452 middle-aged and elderly Japanese subjects (43 109 men and 47 343 women). Case patients were grouped according to coffee intake and were stratified by hepatitis virus infection, sex, age, diet, lifestyle factors, and previous history of liver disease. Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for HCC were calculated with Cox proportional-hazards modeling. All statistical tests were two-sided.** ***Results:*** **Subjects (men and women combined) who consumed coffee on a daily or almost daily basis had a lower HCC risk than those who almost never drank coffee (HR = 0.49 [95% CI = 0.36 to 0.66]); risk decreased with the amount of coffee consumed (compared with nondrinkers, the HR for 1–2 cups per day = 0.52 [95% CI = 0.38 to 0.73]; for 3–4 cups per day = 0.48 [95% CI = 0.28 to 0.83]; for ≥5 cups per day = 0.24 [95% CI = 0.08 to 0.77],** $P_{trend} < .001$**). The risk of liver cancer in almost never drinkers in this population was 547.2 cases per 100 000 people over 10 years, but it was 214.6 cases per 100 000 people with drinking coffee on a daily basis. The inverse association persisted when the participants were stratified by lifestyle factors. Similar associations were observed when the analysis was restricted to hepatitis C virus-positive patients (all daily drinkers compared with nondrinkers: HR = 0.57 [95% CI = 0.37 to 0.86]), to hepatitis B virus-positive patients (HR = 0.60 [95% CI = 0.31 to 1.18]) and to subjects with no past history of chronic liver disease (HR = 0.45 [95% CI = 0.30 to 0.67]).** ***Conclusions:*** **In the Japanese population, habitual coffee drinking may be associated with reduced risk of HCC. [J Natl Cancer Inst 2005;97:293–300]**

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and is characterized by international variation in its distribution *(1)*; these variations are related to the distribution of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. Chronic infection with HCV or HBV has been established as a major risk factor for HCC *(2)*. Other possible risk factors for HCC have been identified, but only a few factors, such as excess alcohol consumption, which leads to liver cirrhosis, and food contamination with aflatoxin, have been recognized as important; other modifiable factors have yet to be established *(3)*.

Coffee is consumed in many parts of the world, and a wide variety of drinking habits has been documented *(4)*. Coffee drinking was introduced to Japan 200 years ago, and coffee has since become a popular beverage. Japanese individuals reportedly drink an average 10 cups of coffee per week, 63% of which is consumed at home. Instant coffee and regular roasted coffee are the major types of coffee consumed in Japan *(5)*. The potential beneficial health effects of coffee consumption have been recognized for years; coffee is known to contain a high level of anticancer compounds, such as chlorogenic acids, and animal experiments have demonstrated an inhibitory effect of coffee on liver carcinogenesis *(6)*. Epidemiologic investigation of the association between coffee drinking and HCC, however, has been limited to several case–control studies targeting high-risk populations in Southern Europe *(7–9)*, in which an inverse association between coffee drinking and HCC was observed. However, prospective analyses and reports on other high-risk populations, such as Asian populations, are lacking.

Liver cancer is one of the major forms of cancer in Japan. HCC accounts for 90% of all cases of liver cancer diagnosed in Japan, and persistent HCV or HBV infections have been identified as causative factors in 80 and 10% of all Japanese liver cancer patients, respectively *(10)*. HCV infection in Japan is thought to have originated at the end of the 19th century, and it became widely disseminated in the 1930s and 1940s *(11)*. HCC prevention among HCV carriers has recently been improved to some degree as a result of interferon therapy *(12)*. However, from a public health point of view, environmental risk modifiers for the development of HCC that are effective in all patients, even those with hepatitis virus, must be explored.

Epidemiologic studies on Japanese immigrants in Brazil have shown a drastic decrease in the rates of mortality from liver cancer *(13)* and chronic liver disease *(14)*, without apparent change in the prevalence of HBV infection *(13)*. These reports suggest that changes in the environmental factors of the host country may act to prevent chronic liver disease and liver cancer; the introduction of coffee-drinking habits after immigration is one conceivable candidate. In the present study, we attempted to determine whether an association between coffee drinking and HCC exists in the Japanese population by carrying out a prospective analysis of data from a large-scale population-based cohort study in Japan.

Affiliation of authors: Epidemiology and Prevention Division (MI, ST) and Statistics and Cancer Control Division (IY, TS), Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan.

Correspondence to: Manami Inoue, MD, PhD, SM, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045 Japan (e-mail: mnminoue@gan2.res.ncc.go.jp).

See "Notes" following "References."

DOI: 10.1093/jnci/dji040

Subjects and Methods

Study Population

The Japan Public Health Center-based Prospective Study (JPHC Study) was launched in 1990 when Cohort I was established. Cohort II was added in 1993. Cohort I included five prefectural public health center areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo), and cohort II included six prefectural public health center areas: Mito (Ibaraki Prefecture), Kashiwazaki (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture), and Suita (Osaka Prefecture). The details of the study design have been described elsewhere *(15)*. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. The Katsushika and Suita public health center areas were excluded from the analysis because different definitions of the study population were used in these areas. Only people 40 and 50 years of age at baseline were invited to participate in these two areas, which may have limited the generalizability.

The study population was defined as all registered Japanese inhabitants in the nine public health center areas, who were between the ages of 40 and 59 years (Cohort I) and between the ages of 40 and 69 years (Cohort II) at the beginning of each baseline survey. The Japanese inhabitants were identified using population registries maintained by local municipalities. A total of 116 896 subjects were initially identified. During the follow-up period, 210 subjects were found to be ineligible for the study and were excluded because of non-Japanese nationality (n = 51), late reports of emigration occurring before the start of the follow-up period (n = 156), and ineligibility because of an incorrect birth date (n = 3). As a result, a population-based cohort of 116 686 subjects (57 583 men and 59 103 women) was established.

A baseline self-administered questionnaire on various lifestyle factors was given to participants in 1990 (Cohort I) and in 1993 and 1994 (Cohort II). A total of 95 376 subjects responded to the questionnaire, for a response rate of 82%. The questionnaire contained items on demographic characteristics; medical history (including a specific question on cirrhosis and hepatitis); family history; smoking and alcohol-, tea-, and coffee-drinking habits; dietary habits; other lifestyle factors, such as physical activity, bathing, and sleeping habits; bowel habits; and personality. Information on coffee drinking was obtained in terms of frequency and amount of coffee intake and divided into the following categories: almost never, 1–2 days per week, 3–4 days per week, and almost daily (further divided into 1–2 cups/day, 3–4 cups per day, or ≥5 cups per day). The type of coffee consumed (decaffeinated or caffeinated) was not included in the questionnaire. However, decaffeinated coffee is rarely consumed in Japan.

Subjects were followed from the date of the baseline survey through December 31, 2001. Residence status and survival were confirmed annually using the residential registers kept by each municipality in each of the study areas or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Inspection of the resident register is open to the general public under the resident registration law. In Japan, residency and death registration is required by law, and the registries are believed to be complete. Information on the cause of death was obtained by examining the death certificate provided by the Ministry of Health, Labor, and Welfare after the Ministry of Internal Affairs and Communications granted permission. Among the study subjects, 4890 died, 5211 moved out of the study area, and 47 were lost to follow-up during the follow-up period.

The occurrence of cancer was identified by active patient notification by the local major hospitals in the study area and data linkage with the population-based cancer registries with permission from each of the local governments responsible for the cancer registries. Death certificate information was used as a supplementary information source. The site and histology of each cancer were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) *(16)*. In the cancer registry system used in this study, the proportion of patients with incident cancers who first came to the attention of the cancer registry via a death certificate (death certificate notifications, or DCNs) was 8.5%, and the proportion of case patients for which information regarding cancer diagnosis was available only from death certificates (death certificate only, DCO) was 2.3% during the study period. These results were considered to be of adequate quality and completeness for the present study. Among the 361 incident liver cancers identified (ICD-O-3: C22), a total of 334 cases of newly diagnosed HCC (ICD-O-3: C22.0, 817) were identified as of December 31, 2001, after excluding 27 cases (7.5%) of liver cholangiocarcinoma (ICD-O-3: C22.1, 816). Information on hepatitis virus infection status of the case patients was obtained from the medical institutions where the case patients had been diagnosed if infection markers, such as antibodies to HCV (anti-HCV) or hepatitis B surface antigen (HbsAg), had been detected. In the present study, case patients who had been identified with anti-HCV antibodies were considered to be HCV positive, and those identified with HbsAg were considered to be HBV positive. Subjects with a present or past history of self-reported serious illness at baseline (cancer, cardiovascular disease, or myocardial infarction) were excluded from the analysis (n = 3799). After exclusion of 1125 subjects for whom the information on coffee intake was incomplete, 90 452 subjects, including 334 incident HCC case patients, were used in the analysis.

The person-years of follow-up were counted from the baseline survey until the date of HCC diagnosis, migration out of the study area, death, or the end of the study period (December 31, 2001), whichever came first. Persons lost to follow-up were censored on the last confirmed date of their presence in the study area.

Statistical Analysis

Outcome was defined as the new development of a primary HCC during the study period. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were calculated using Cox proportional-hazards models and were used to describe the relative risks of HCC that were associated with the coffee-drinking categories at baseline. Differences in characteristics between categories of coffee intake were evaluated by analysis of variance and chi-square test for homogeneity. Models were adjusted for potential confounding factors, including age at baseline (3-year age categories), study area (nine public health center areas), and in additional analysis, smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g per week or ≥150 g per week]), green vegetable intake (<3 times per week, 3–4 times per week, everyday) and

green tea intake (none, less than daily, daily) were also included. These variables are either known or suspected risk factors for cancer or had previously been found to be associated with the risk of liver cancer. Tests for linear trend in risk of HCC were assessed by assigning ordinal exposure variables as continuous terms. The HR were estimated both for men and women combined and for men and women separately. Stratified analyses were conducted to evaluate whether the association between coffee drinking and the risk of HCC varied with age, smoking status, weekly ethanol intake, green vegetable intake, green tea drinking, and past or present history of chronic liver disease. Interaction terms were generated by multiplying ordinal exposure variables by ordinal coffee-drinking categories. Because no statistically significant effect modifications were found between sex and coffee drinking ($P_{interaction}$ = .81), men and women were combined in the stratified analyses. Stata software (version 8.0) *(17)* was used to perform the statistical analyses. All statistical tests were two-sided.

Results

During 874 551 person-years of follow-up (average follow-up period: 9.7 years) of 90 452 subjects (43 109 men and 47 343 women), a total of 334 participants were newly diagnosed with HCC (250 men and 84 women). Information on the hepatitis virus infection status of the patients was available for 259 (77.5%) of the case patients. Among these 259 case patients, 164 (63.3%) were HCV positive and 60 (23.2%) were HBV positive (Table 1).

The baseline characteristics of the study subjects according to coffee consumption are shown in Table 2. Coffee was consumed almost every day by 37.1% of the subjects in the study. No substantial difference in the distribution of coffee intake frequency was observed between men and women. The proportion of current smokers increased as coffee intake increased in both sexes. However, alcohol intake increased in women and decreased in men as coffee intake increased. Frequent green vegetable intake and daily green tea drinking decreased in both sexes with increased coffee drinking. The proportion of subjects with a self-reported present/past history of chronic hepatitis and/or cirrhosis among the study subjects overall was 0.3%–3% across the coffee intake categories.

Table 1. Status of hepatitis virus infection among incident cases of hepatocellular carcinoma (HCC)*

	Total		Men		Women	
Characteristic	N	(%)	N	(%)	N	(%)
Total	334		250		84	
Case patients with information on hepatitis virus infection	259	(77.5)†	194	(77.6)†	65	(77.4)†
HCV+	164	(63.3)‡	119	(61.3)‡	45	(69.2)‡
HBV+	60	(23.2)‡	42	(21.6)‡	18	(27.7)‡
Both HCV and HBV−	43	(16.6)‡	39	(20.1)‡	4	(6.1)‡
HCV+, HBV−	156	(60.2)‡	113	(58.2)‡	43	(66.2)‡
HBV+, HCV−	52	(20.1)‡	36	(18.6)‡	16	(24.6)‡
Both HCV and HBV+	8	(3.1)‡	6	(3.1)‡	2	(3.1)‡

*Data are based on 334 newly diagnosed case patients with HCC among 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†Percentage of total.

‡Percentage among case patients with information on hepatitis.

The minimally adjusted and multivariable HR for the subsequent occurrence of HCC according to baseline coffee-drinking categories are presented in Table 3. Coffee drinking was associated with a statistically significantly lower risk for HCC. Subjects who drank coffee almost every day had a 51% lower HCC risk than those who almost never drank (HR = 0.49, 95% CI = 0.36 to 0.66), and the risk was inversely proportional to coffee intake (for 1–2 cups per day compared with no coffee intake, HR = 0.52; for 3–4 cups per day, HR = 0.48; for ≥5 cups per day, HR = 0.24; P_{trend}<.001). The risk of liver cancer in almost never drinkers in this population over 10 years of follow-up was 547.2 cases per 100 000 people. In contrast, the risk with drinking coffee almost everyday dropped to 214.6 cases per 100 000 people over the same follow-up time, 227.3 with drinking 1–2 cups per day, 205.0 with 3–4 cups per day, and 120.7 with ≥5 cups per day, respectively. Similar results were also observed in separate analyses by sex. Furthermore, when patients were analyzed according to hepatitis virus infection status, an inverse association between coffee drinking and HCC risk was observed for those who were HCV positive; however, the trend was not statistically significant for those who were HBV positive.

The inverse association between HCC risk and coffee intake persisted when participants were stratified by age, smoking status, ethanol intake, green vegetable intake, and green tea drinking (Table 4). Thus, the inverse association between coffee drinking and HCC risk is independent of these lifestyle factors. An inverse but weaker association was also observed in analyses of participants stratified by history of chronic hepatitis or cirrhosis.

We explored other possible confounders that could explain the observed association between coffee drinking and HCC, because coffee drinking is associated with many other factors. Socioeconomic status could not be assessed because of a lack of information in the questionnaire. Among the dietary factors that were examined, bread intake was positively associated with coffee drinking. However, no association was found between bread intake and HCC, and the results remained essentially unchanged when bread intake was included in the model (data not shown).

Discussion

In this prospective analysis of a large-scale population-based cohort study in Japan, a statistically significant inverse association between coffee drinking and HCC was observed. The results from the present study are consistent with but more pronounced than those of previous studies *(7–9)*. The risk of liver cancer in almost never drinkers in this population was 547.2 cases per 100 000 people over 10 years, but it was 214.6 cases per 100 000 people with drinking coffee on a daily basis.

The strength of the present study is its population-based prospective design with low proportion of losses to follow-up. Nonetheless, there are some obvious limitations, such as the assessment of coffee intake solely on the basis of the self-report at a single time point and lack of determination of hepatitis virus infection status at baseline for the entire population and at follow-up for 22% of the case patients.

Information on coffee intake was collected before subsequent diagnoses of cancer, thereby avoiding the exposure recall bias that is inherent to case–control studies. Study subjects were selected from the general population, and the response rate of 82% to the baseline questionnaire is acceptable for such a study

Table 2. Baseline characteristics of the study subjects according to coffee intake*

Category		Coffee intake						
					Almost everyday			
		Almost never	1-2 days/week	3-4 days/week	1-2 cups/day	3-4 cups/day	≥5 cups/day	$P_{difference}$†
Total (n = 90 452)								
No. of subjects		29 423	17 159	10 316	23 753	7316	2485	
Proportion, %		32.5	19.0	11.4	26.3	8.1	2.7	
Age, years ± SD		54.3 ± 7.7	52.7 ± 7.7	51.2 ± 7.7	50.2 ± 7.6	47.9 ± 7.0	48.6 ± 7.3	<.001
Person-years		285 446	166 876	101 215	228 995	68 733	23 286	
Smoking status	Current smokers, %	22.7	25.2	28.6	29.1	44.4	55.4	<.001
Ethanol intake	Weekly or more, %	36.7	37.3	39.9	37.5	41.7	39.6	<.001
Green vegetable intake	≥3 times/week, %	65.1	63.3	65.4	63.4	58.0	56.4	<.001
Green tea drinking	Everyday, %	76.1	77.5	73.6	74.5	68.2	65.8	<.001
Present/past history of chronic hepatitis/cirrhosis, %		2.1	1.4	1.1	1.1	1.2	1.3	<.001
Men (n = 43 109)								
No. of subjects		13 584	8096	5162	10 718	4033	1516	
Proportion, %		31.5	18.8	12.0	24.9	9.3	3.5	
Age, y ± SD		53.5 ± 7.7	52.4 ± 7.7	51.2 ± 7.7	50.5 ± 7.5	48.4 ± 7.2	48.8 ± 7.4	<.001
Person-years		130 225	77 913	50 133	101 211	37 309	14 009	
Smoking status	Current smokers, %	44.1	49.0	52.7	56.5	69.7	76.4	<.001
Ethanol intake	Weekly or more, %	69.9	69.1	69.4	67.9	62.6	55.4	<.001
Green vegetable intake	≥ 3 times/week, %	60.6	57.8	60.8	57.6	52.7	52.3	<.001
Green tea drinking	Everyday, %	75.4	76.1	72.8	74.5	69.9	65.2	<.001
Present/past history of chronic hepatitis/cirrhosis, %		3.0	2.1	1.7	1.7	1.7	1.9	<.001
Women (n = 47 343)								
No. of subjects		15 839	9063	5154	13 035	3283	969	
Proportion, %		33.5	19.1	10.9	27.5	6.9	2.1	
Age, years ± SD		55.0 ± 7.7	52.9 ± 7.7	51.3 ± 7.7	49.9 ± 7.5	47.3 ± 6.6	48.3 ± 7.2	<.001
Person-years		155 221	88 963	51 082	127 784	31 424	9277	
Smoking status	Current smokers, %	4.3	4.0	4.4	6.5	13.2	22.6	<.001
Ethanol intake	Weekly or more, %	8.6	9.4	10.8	12.7	16.0	15.1	<.001
Green vegetable intake	≥ 3 times/week, %	68.9	68.2	70.0	68.2	64.5	62.8	<.001
Green tea drinking	Everyday, %	76.8	78.8	74.4	74.5	66.2	66.6	<.001
Present/past history of chronic hepatitis/cirrhosis, %		1.3	0.9	0.5	0.7	0.5	0.3	<.001

*Data are based on 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†$P_{difference}$ values of characteristics between categories of coffee intake (two-sided) were calculated by analysis of variance and chi-square test for homogeneity. SD = standard deviation.

setting. The proportion of losses to follow-up (0.05%) was negligible during the study period. However, because self-reported information on coffee intake was used in the present study, some misclassification may have been unavoidable. Also, changes in coffee intake that arose from symptoms related to a subsequent diagnosis of HCC after the start of the study may have resulted in some misclassification. Such misclassification, if any, is probably nondifferential and would lead to an underestimation of the results. Although the quality of the cancer registry system was satisfactory over the study period, some variations in quality between the study areas occurred. The study areas used in the analysis were adjusted to control for geographic variation. The quality of the registry system was not affected by the coffee intake status; therefore, possible misclassification of cancer occurrence by an underreporting of cancer diagnosis would be nondifferential and would also bias the results toward the null.

The inverse association between coffee drinking and HCC has been investigated from various aspects. Coffee contains large amounts of antioxidants, including chlorogenic acid, and several animal studies have shown that such coffee compounds have a direct inhibitory effect or a lack of carcinogenic potential in the liver *(6,18)*. Caffeine is another major ingredient of coffee *(5)*. In this study, the type of coffee consumed was not classified as either decaffeinated or caffeinated because this information was not included in the questionnaire. However, decaffeinated coffee is rarely consumed in Japan. Thus, based on the limited information in our population, we cannot determine whether the inverse association with coffee is mainly attributable to caffeine. Green tea is another major source of caffeine intake in the Japanese population. However, in additional analyses using the same data set, no association between green tea intake and the risk of HCC was observed (data not shown). Green tea contains large amounts of antioxidant catechins. The differences in the antioxidant components of coffee and tea may explain the different associations of these beverages with liver cancer. One study comparing the antioxidant activity of coffee and tea indicated that, on a per-cup basis, soluble coffee has higher antioxidant activity than green tea *(19)*. Other unidentified substances in coffee may also be responsible for the observed association between coffee drinking and the risk of HCC. In any case, site specificity of the effect of coffee is another important issue that must be solved.

Coffee-drinking habits were associated with habitual tobacco smoking and alcohol drinking in our study population. However, the association between coffee intake and subsequent risk of HCC persisted even after adjustment for smoking and alcohol intake. Also, separate analyses performed according to smoking and alcohol drinking status showed a similar reduced risk, without substantial effect modification by coffee drinking.

Several studies have described an inverse association between coffee drinking and liver cirrhosis *(20–22)*. Because liver cirrhosis is strongly associated with primary liver cancer *(23)*, it is possible

Table 3. Hazard ratio (HR) and 95% confidence interval (CI) for hepatocellular carcinoma (HCC) according to coffee drinking*

	Coffee intake							
				Almost everyday				
Category (n)	Almost never	1-2 days/week	3-4 days/week	Total	1-2 cups/day	3-4 cups/day	≥5 cups/day	P_{trend}
Men and women combined (334)								
Person-years	285 446	166 876	101 215	321 014	228 995	68 733	23 286	
No. of case patients	161	65	36	72	54	15	3	
HR (95% CI)†	1.00	0.75 (0.56 to 0.998)	0.75 (0.52 to 1.08)	0.53 (0.39 to 0.70)	0.56 (0.41 to 0.77)	0.51 (0.30 to 0.88)	0.27 (0.09 to 0.85)	<.001
Multivariable HR (95% CI)‡	1.00	0.75 (0.56 to 1.01)	0.79 (0.55 to 1.14)	0.49 (0.36 to 0.66)	0.52 (0.38 to 0.73)	0.48 (0.28 to 0.83)	0.24 (0.08 to 0.77)	<.001
Men (250)								
Person-years	130 225	77 913	50 133	152 528	101 211	37 309	14 009	
No. of case patients	116	43	27	59	45	11	3	
HR (95% CI)†	1.00	0.74 (0.53 to 1.03)	0.72 (0.47 to 1.10)	0.54 (0.39 to 0.75)	0.61 (0.43 to 0.86)	0.44 (0.24 to 0.83)	0.31 (0.10 to 0.98)	<.001
Multivariable HR (95% CI)‡	1.00	0.74 (0.52 to 1.05)	0.76 (0.50 to 1.16)	0.49 (0.35 to 0.69)	0.55 (0.38 to 0.80)	0.41 (0.21 to 0.77)	0.27 (0.09 to 0.87)	<.001
Women (84)								
Person-years	155 221	88 963	51 082	168 486	127 784	31 424	9277	
No. of case patients	45	17	9	13	9	4	0	
HR (95% CI)†	1.00	0.78 (0.45 to 1.38)	0.85 (0.41 to 1.75)	0.46 (0.24 to 0.88)	0.41 (0.19 to 0.86)	0.88 (0.30 to 2.56)		.029
Multivariable HR (95% CI)‡	1.00	0.77 (0.43 to 1.37)	0.89 (0.43 to 1.84)	0.48 (0.25 to 0.92)	0.43 (0.20 to 0.90)	0.89 (0.31 to 2.59)		.042
HCC with HCV+ (164) (men and women combined)								
No. of case patients	86	26	15	37	29	6	2	
HR (95% CI)†	1.00	0.57 (0.37 to 0.89)	0.64 (0.37 to 1.11)	0.60 (0.40 to 0.89)	0.66 (0.43 to 1.03)	0.45 (0.19 to 1.05)	0.37 (0.09 to 1.53)	.007
Multivariable HR (95% CI)‡	1.00	0.59 (0.38 to 0.91)	0.66 (0.38 to 1.16)	0.57 (0.37 to 0.86)	0.64 (0.41 to 0.99)	0.42 (0.18 to 0.99)	0.34 (0.08 to 1.41)	.005
HCC with HBV+ (60) (men and women combined)								
No. of case patients	24	9	9	18	12	5	1	
HR (95% CI)†	1.00	0.65 (0.30 to 1.40)	1.10 (0.51 to 2.38)	0.72 (0.38 to 1.36)	0.70 (0.34 to 1.43)	0.88 (0.33 to 2.39)	0.44 (0.06 to 3.32)	.431
Multivariable HR (95% CI)‡	1.00	0.66 (0.31 to 1.43)	1.14 (0.52 to 2.47)	0.60 (0.31 to 1.18)	0.56 (0.26 to 1.21)	0.81 (0.30 to 2.22)	0.39 (0.05 to 2.98)	.231
HCC with HCV− and HBV− (43) (men and women combined)								
No. case patients	22	10	4	7	7	0	0	
HR (95% CI)†	1.00	0.83 (0.39 to 1.75)	0.55 (0.19 to 1.61)	0.33 (0.14 to 0.80)	0.47 (0.20 to 1.11)			.006
Multivariable HR (95% CI) ‡	1.00	0.87 (0.41 to 1.87)	0.57 (0.19 to 1.70)	0.36 (0.15 to 0.87)	0.50 (0.20 to 1.20)			.010

*Data are based on 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†HR adjusted for sex (men and women combined analysis only), age (3-year age categories) and study area (nine public health centers).

‡Multivariable HR adjusted for sex (men and women combined analysis only), age (3-year age categories), study area (nine public health centers), tobacco-smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g/week, ≥150 g/week]), green vegetable intake (<3 times/week, 3–4 times/week, everyday), and green tea drinking (none, less than everyday, everyday).

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma (HCC) stratified according to selected lifestyle factors*

	Multivariable HR (95% CI) by coffee intake								
				Almost everyday					
Characteristic	Almost never	1-2 days/week	3-4 days/week	Total	1-2 cups/day	3-4 cups/day	≥5 cups/day	P_{trend}	$P_{interaction}$
Age, years									.85
<55	1.00	1.05 (0.61 to 1.78)	0.82 (0.42 to 1.59)	0.58 (0.35 to 0.97)	0.60 (0.34 to 1.06)	0.59 (0.26 to 1.31)	0.39 (0.09 to 1.64)	.021	
≥55	1.00	0.65 (0.45 to 0.93)	0.82 (0.52 to 1.27)	0.47 (0.32 to 0.69)	0.51 (0.34 to 0.78)	0.45 (0.21 to 0.98)	0.16 (0.02 to 1.12)	<.001	
Smoking									.10
Never/former	1.00	0.80 (0.54 to 1.18)	1.07 (0.68 to 1.69)	0.62 (0.41 to 0.93)	0.58 (0.37 to 0.91)	0.88 (0.44 to 1.78)	0.34 (0.05 to 2.43)	.050	
Current	1.00	0.68 (0.43 to 1.07)	0.50 (0.27 to 0.93)	0.4 (0.25 to 0.62)	0.47 (0.29 to 0.76)	0.29 (0.12 to 0.67)	0.22 (0.05 to 0.91)	<.001	
Ethanol intake									.54
Non- or ex-drinker/less than weekly	1.00	0.80 (0.54 to 1.18)	0.78 (0.47 to 1.29)	0.45 (0.30 to 0.68)	0.41 (0.25 to 0.67)	0.66 (0.34 to 1.27)	0.29 (0.07 to 1.20)	<.001	
Weekly or more	1.00	0.67 (0.42 to 1.06)	0.77 (0.45 to 1.32)	0.53 (0.34 to 0.82)	0.64 (0.41 to 1.01)	0.28 (0.10 to 0.77)	0.19 (0.03 to 1.41)	.002	
Green vegetable intake, per week									.66
<3	1.00	0.75 (0.48 to 1.19)	0.71 (0.39 to 1.27)	0.55 (0.36 to 0.86)	0.59 (0.36 to 0.95)	0.54 (0.26 to 1.13)	0.31 (0.07 to 1.28)	.006	
≥3	1.00	0.75 (0.51 to 1.11)	0.85 (0.53 to 1.36)	0.43 (0.28 to 0.67)	0.47 (0.30 to 0.75)	0.41 (0.17 to 0.94)	0.17 (0.02 to 1.24)	<.001	
Green tea intake									.40
Less than everyday	1.00	0.57 (0.34 to 0.96)	0.74 (0.42 to 1.30)	0.52 (0.34 to 0.80)	0.58 (0.36 to 0.92)	0.41 (0.19 to 0.93)	0.32 (0.08 to 1.32)	.003	
Everyday	1.00	0.83 (0.58 to 1.20)	0.78 (0.49 to 1.26)	0.45 (0.29 to 0.68)	0.46 (0.29 to 0.74)	0.52 (0.25 to 1.09)	0.16 (0.02 to 1.14)	<.001	
Past history of chronic hepatitis/cirrhosis									.17
Absent	1.00	0.85 (0.59 to 1.24)	1.15 (0.76 to 1.74)	0.45 (0.30 to 0.67)	0.46 (0.29 to 0.72)	0.52 (0.26 to 1.05)	0.15 (0.02 to 1.05)	<0.001	
Present	1.00	0.79 (0.48 to 1.30)	0.44 (0.18 to 1.11)	0.91 (0.58 to 1.41)	0.99 (0.61 to 1.61)	0.71 (0.31 to 1.67)	0.76 (0.18 to 3.16)	0.432	

*HR adjusted for sex (men and women combined analysis only), age (3-year age categories), study area (nine public health centers), tobacco-smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g/week, ≥150 g/week]), green vegetable intake (<3 times/week, 3-4 times/week, everyday), and green tea drinking (no, less than everyday, everyday), other than the variable for stratification.

that the observed association between coffee drinking and HCC actually represents an association with liver cirrhosis. In addition, an inverse association between coffee and alcoholic but not nonalcoholic cirrhosis has been reported *(18)*, and other cross-sectional observations have suggested an inhibitory effect of coffee on the alcohol-related increase in serum liver enzymes, such as aminotransferase and gamma-glutamyltransferase *(24–26)*. However, because a previous study found that caffeine metabolism was impaired in fasting subjects with liver cirrhosis, subjects with chronic liver disease may have reduced their coffee consumption to avoid the side effects of caffeine *(27)*, and that may have led to a superficial decrease in HCC risk by coffee drinking. One limitation of the present study is that we determined whether the subjects with chronic liver disease who did not drink coffee at baseline had quit drinking coffee after their chronic liver disease emerged. However, because a recent case–control study reported a strong association between coffee drinking and HCC among patients with HCV-associated chronic liver disease *(28)*, it is still possible to speculate that coffee drinking reduces the risk of HCC even after acquisition of a chronic liver disease. In any case, potential targets of coffee, HCC, liver cirrhosis, or both conditions, and whether a restriction to alcohol-related conditions exists, remain to be determined in future studies.

In addition, the lower risk associated with coffee intake among HCC case patients with HCV infections was somewhat stronger than that for HCC case patients with HBV infections, although these observations are not sufficient to confirm viral specificity for the association with coffee on the carcinogenesis of HCC. During hepatocarcinogenesis, direct integration of the viral sequence into the host genome is thought to substantially increase genomic instability in HBV-associated HCC, whereas the reaction of the host immune system against virus-infected cells is more important to the development of HCV-associated HCC *(29)*. Furthermore, it is also possible that the difference in the association according to virus infection status is attributed to differences between HBV-induced hepatocarcinogenesis and HCV-induced hepatocarcinogenesis. In this study, the virus infection status at baseline was not determined for the entire population, thus preventing clarification of a relationship between coffee drinking and HCC risk among subjects who are positive for each virus infection. Moreover, information on the virus infection status was not available for 22% of the case patients; most of the missing information resulted from the deletion of stored medical records after expiration of their holding period. Although a previous study analyzed the effect of coffee on the risk of HCC according to the hepatitis status of the subjects and reported a lower risk in those who drank coffee frequently than in those who drank it infrequently among both hepatitis-positive and -negative subjects *(9)*, risk differences according to the type of hepatitis virus infection have not been determined.

The present cohort analysis confirmed a statistically significant inverse association between habitual coffee drinking and HCC (that was not due to any confounders we analyzed). Further studies are warranted to assess whether the present results can be generalized to or are representative of other populations.

References

(1) Ferlay J, Bray F, Pisani P, Parkin DM. Globocan2000: Cancer incidence, mortality and prevalence worldwide. Vol 1.0. IARC Cancer Base, No. 5. Lyon (France): IARC Press; 2001.

(2) Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. Cancer Epidemiol Biomarkers Prev 1997;6:387–400.

(3) World Cancer Research Fund /American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.

(4) International Agency for Research on Cancer. Coffee, tea, mate, methylxanthines, and methylgloxyal. IARC Monogr Eval Carcinog Risks Hum 1991:51:41–206.

(5) All Japan Coffee Association. Biannual report of the trend survey of coffee in Japan. Tokyo (Japan): All Japan Coffee Association, 2003.

(6) Tanaka T, Nishikawa A, Shima H, Sugie S, Shinoda T, Yoshimi N, Iwata H, Mori H. Inhibitory effects of chlorogenic acid, reserpine, polyprenoic acid (E-5166), or coffee on hepatocarcinogenesis in rats and hamsters. Basic Life Sci 1990;52:429–40.

(7) Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, Trichopoulos D, Stuver SO. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498–502.

(8) La Vecchia C, Ferraroni M, Negri E, D'Avanzo B, Decarli A, Levi F, Franceschi S. Coffee consumption and digestive tract cancers. Cancer Res 1989;49:1049–51.

(9) Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, Lagiou P, Trichopoulos D. Does coffee protect against hepatocellular carcinoma? Br J Cancer 2002;87:956–9.

(10) Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, Teratani T, Tohgo G, Toda N, Ohashi M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. Hepatology 1995;22:1027–33.

(11) Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci U S A 2002;99:15584–9.

(12) Omata M, Yoshida H. Prevention and treatment of hepatocellular carcinoma. Liver Transpl 2004;10(Suppl):S111–4.

(13) Tsugane S, Gotlieb SL, Laurenti R, de Souza JM, Watanabe S. Cancer mortality among Japanese residents of the city of Sao Paulo, Brazil. Int J Cancer 1990;45:436–9.

(14) Tsugane S, Gotlieb SL, Laurenti R, Souza JM, Watanabe S. Mortality and cause of death among first-generation Japanese in Sao Paulo, Brazil. Int J Epidemiol 1989;18:647–51.

(15) Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. J Epidemiol 2001;11(6 Suppl):S24–9.

(16) World Health Organization. International classification of diseases for oncology. 3rd ed. Geneva (Switzerland): WHO; 2000.

(17) Stata Corporation. Stata statistical software, version 8.0. College Station (TX): Stata Corporation; 2003.

(18) Hasegawa R, Ogiso T, Imaida K, Shirai T, Ito N. Analysis of the potential carcinogenicity of coffee and its related compounds in a medium-term liver bioassay of rats. Food Chem Toxic 1995;33:15–20.

(19) Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. J Agric Food Chem 2001;49:3438–42.

(20) Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol 2002;12:202–5.

(21) Klatsky AL, Armstrong MA. Alcohol, smoking, coffee and cirrhosis. Am J Epidemiol 1992;136:1248–57.

(22) Tverdal A, Skurtveit D. Coffee intake and mortality from liver cirrhosis. Ann Epidemiol 2003;13:419–23.

(23) La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998;7:315–20.

(24) Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, Zakouji H. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol 1998;27:438–43.

(25) Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, Umeda T, Wakabayashi K, Imanishi K, Nishikawa H, Ogawa S, Katsurada M, Nakagawa K, Yoshizawa N. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol 2001;54:823–9.

(26) Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997;146:1019–24.
(27) Wahllander A, Renner E, Preisig R. Fasting plasma caffeine concentration. A guide to the severity of chronic liver disease. Scand J Gastroenterol 1985;20:1133–41.
(28) Fukushima W, Tanaka T, Ofuji S, Hirota Y. Dietary habits and the risk of hepatocellular carcinoma among subjects with hepatitis C virus associated liver diseases. J Epidemiol 2004;14(1 Suppl):S47.
(29) Szabo E, Paska C, Kaposi Novak P, Schaff Z, Kiss A. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis. Pathol Oncol Res 2004;10:5–11.

NOTES

The authors thank all staff members in each study area for their unfailing efforts to conduct the baseline and follow-up surveys. Gratitude is hereby expressed to the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing the incidence data. The authors also thank Dr. Shunji Mishiro for his helpful comments. This work was supported by a Grant-in-Aid for Cancer Research and by the Second- and Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan.

Members of the JPHC Study Group include the following: S. Tsugane, T. Sobue, T. Hanaoka, M. Inoue, National Cancer Center; J. Ogata, S. Baba, T. Mannami, A. Okayama, National Cardiovascular Center; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, Iwate Prefectural Ninohe Public Health Center; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, Akita Prefectural Yokote Public Health Center; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Nagano Prefectural Saku Public Health Center; Y. Kishimoto, E. Tanaka, M. Kinjo, T. Fukuyama, M. Irei, Okinawa Prefectural Chubu Public Health Center; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, Katsushika Public Health Center; A. Murata, K. Minato, K. Motegi, T. Fujieda, Ibaraki Prefectural Mito Public Health Center; K. Matsui, T. Abe, M. Katagiri, Niigata Prefectural Kashiwazaki Public Health Center; M. Doi, Y. Ishikawa, A. Terao, Kochi Prefectural Chuo-higashi Public Health Center; H. Sueta, H. Doi, M. Urata, F. Ide, Nagasaki Prefectural Kamigoto Public Health Center; H. Sakiyama, N. Onga, H. Takaesu, Okinawa Prefectural Miyako Public Health Center; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, Osaka Prefectural Suita Public Health Center; S. Matsushima, S. Natsukawa, Saku General Hospital; S. Watanabe, M. Akabane, Tokyo University of Agriculture; M. Konishi, K. Okada, Ehime University; H. Iso, Y. Honda, Tsukuba University; H. Sugimura, Hamamatsu University School of Medicine; Y. Tsubono, Tohoku University; N. Kabuto, National Institute for Environmental Studies; S. Tominaga, Aichi Cancer Center; M. Iida, W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease; S. Sato, Osaka Medical Center for Health Science and Promotion; N. Yasuda, Kochi Medical School; S. Kono, Kyushu University; K. Suzuki, Research Institute for Brain and Blood Vessels Akita; Y. Takashima, Kyorin University; E. Maruyama, Kobe University; M. Yamaguchi, Y. Matsumura, S. Sasaki, National Institute of Health and Nutrition.

Manuscript received June 25, 2004; revised December 13, 2004; accepted December 15, 2004.