Effect of Coffee and Green Tea Consumption on the Risk of Liver Cancer: Cohort Analysis by Hepatitis Virus Infection Status

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Abstract

In spite of their anticarcinogenic potential, the effect of coffee and green tea consumption on the risk of liver cancer has not been clarified prospectively in consideration of hepatitis C (HCV) and B virus (HBV) infection. We examined whether coffee and green tea consumption was associated with a reduced risk of liver cancer by hepatitis virus infection status in the Japan Public Health Center-Based Prospective Study Cohort II. A total of 18,815 subjects ages 40 to 69 years participating in a questionnaire and health checkup survey in 1993 to 1994 were followed for the incidence of liver cancer through 2006. A total of 110 cases of liver cancer were newly documented. Hazard ratios for coffee and green tea consumption categories were calculated with a Cox proportional hazards model. Compared with almost never drinkers, increased coffee consumption was associated with a reduced risk of liver cancer in all subjects (hazard ratio for <1, 1-2, and ≥3 cups/d; P_{trend} = 0.67, 0.49, 0.54, and 0.025). A similar risk tendency was observed in those with either or both HCV and HBV infection. In contrast, no association was observed between green tea consumption and the risk of liver cancer in all subjects. Our results suggest that coffee consumption may reduce the risk of liver cancer regardless of HCV and HBV infection status, whereas green tea may not reduce this risk. (Cancer Epidemiol Biomarkers Prev 2009;18(6):1746–53)

Introduction

Coffee and green tea, the most popular beverages in the world, contain polyphenolic antioxidants, which are thought to contribute to cancer prevention (1). Although an association between these beverages and liver cancer has been speculated (2, 3), epidemiologic evidence is insufficient (4) and varies by beverage. Several cohort and case-control studies (5-15) and meta-analyses (16, 17) have reported a significant inverse association between coffee consumption and liver cancer, but none of these considered hepatitis virus infection status. Meanwhile, epidemiologic evidence for the association between green tea consumption and liver cancer is sparse (10, 14, 18), and little is known about its effects on liver cancer.

For both beverages, few studies have taken account of hepatitis virus infection status in evaluating risk (8, 10, 11, 13-15), although hepatitis B (HBV) and C (HCV) virus infections are the most important risk factors of liver cancer (19). This problem is particularly prominent in cohort studies having no baseline data on hepatitis virus infection. Indeed, because we had insufficient data, our previous analysis of coffee consumption and liver cancer (5) also failed to take account of hepatitis virus infection status at baseline.

To investigate the association between these putatively anticarcinogenic beverages and liver cancer in consideration of HCV and HBV infection status, we conducted a cohort analysis of the association between the consumption of coffee and green tea and the risk of liver cancer using a large-scale population-based study in Japan, which has a relatively high incidence of liver cancer (20). Our main purpose was to clarify whether coffee and green tea consumption reduce the risk of liver cancer in those with HCV or HBV infection (or both), who are at high risk of liver cancer, using a prospective study design. Infection status was determined at baseline using stored blood samples.

Materials and Methods

The Japan Public Health Center-Based Prospective Study Cohort II was initiated in 1993 to 1994. Subjects were drawn from six public health center areas across Japan. The study design has been described in detail previously (21). The study population was defined as all residents ages 40 to 69 years at the start of the baseline survey. A part of one public health center area was excluded because its study population was defined differently to

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Note: Study group members are listed in the Appendix.

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the others. Initially, we defined a population-based cohort of 68,975 subjects after exclusion of ineligible subjects (n = 103). The study was approved by the Institutional Ethical Review Board of the National Cancer Center.

Baseline Survey. A self-administered questionnaire survey on various lifestyle factors was conducted at baseline (response rate, 82%). Among respondents, 39% voluntarily provided 10 mL blood during health checkups provided by their local government. The plasma and buffy layer were divided into four tubes holding 1.0 mL each (three tubes for plasma and one for the buffy layer) and stored at −80°C until analysis.

For the present analysis, we restricted subjects to those who responded to the questionnaire and for whom blood samples were available. We further excluded those with a history of liver cancer and those with missing data on variables included in the statistical model, including coffee and green tea consumption, smoking status, weekly ethanol intake, body mass index, history of diabetes mellitus, serum alanine aminotransferase (ALT) level, and HCV and HBV infection status. Finally, a total of 18,815 individuals were included in the present analysis.

Exposure Measurements. All exposures were collected at baseline. Information on coffee and green tea consumption was obtained in terms of the frequency and amount of each beverage consumed using the pre-coded answers of almost never, 1-2 days/wk, 3-4 days/wk, and almost daily (further divided into 1-2, 3-4, ≥5 cups/d). For the present analysis, we further grouped these categories based on their distribution among the subjects (coffee consumption: almost never, <1, 1-2, ≥3 cups/d and green tea consumption: <3, 3-4, ≥5 cups/d). The validity of coffee and green tea consumption reported by the cohort was assessed using dietary records for 28 days (7-day dietary records in four seasons) or 14 days. The rank correlation coefficients for coffee consumption between the questionnaire and dietary record data were 0.59 for men and 0.51 for women, whereas that for green tea consumption was 0.37 for men and 0.43 for women.

Laboratory Assays. Plasma samples were screened for anti-HCV antibody using a third-generation immunoassay (Lumipulse II Ortho HCV; Ortho-Clinical Diagnosis; ref. 22) and for HBV antigen (HBsAg) by reversed passive hemagglutination with a commercial kit (Institute of Immunology). This HBsAg detection kit is one of the most commonly used in Japan. The sensitivity of this kit (5 IU/mL) is similar to that of the radioimmunoassay method and lower than that of the chemiluminescent immunoassay method (23) and is considered suitable for the screening of general Japanese populations, particularly given the rarity of HBsAg-positive cases with low titers. In the present study, positivity for anti-HCV was regarded as indicating HCV infection and positivity for HBsAg as indicating HBV infection.

Follow-up and Identification of Liver Cancer. Subjects were followed from the date of the baseline survey until December 31, 2006. Residence status, including survival, was confirmed through the residential registry. Inspection of the registry is available to anyone under the resident registration law. Information on the cause of death was obtained from the death certificate, provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications, in which cause of death is defined according to the *International Classification of Disease, 10th Edition* (24). Resident and death registration are required by law in Japan and the registries are believed to be complete. Among study subjects, 1,894 died, 1,088 moved out of the study area, and 49 (0.3%) were lost to follow-up during the follow-up period.

Incidence data on liver cancer were obtained by active patient notification from major hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Death certificates were used as a supplementary information source. In our cancer registry system, the proportion of cases for which information was available from death certificates only was 4.7%. The site and histology of each liver cancer case were coded using the *International Classification of Diseases for Oncology, Third Edition* (C22.0; ref. 25). For the present analysis, the earliest date of diagnosis was used in subjects with multiple primary cancers at different times. A total of 110 newly diagnosed cancer cases (73 in men and 37 in women) were identified.

Analysis. The number of person-years in the follow-up period was counted from the date of completion of the baseline questionnaire until the date of liver cancer diagnosis, date of emigration from the study area, date of death, or end of the study period, whichever came first. For subjects who withdrew from or were lost to follow-up, the date of withdrawal and the last confirmed date of presence, respectively, were used as the date of censor.

The relative risk of liver cancer associated with coffee and green tea consumption was described using hazard ratios (HR) and 95% confidence intervals (95% CI). Analyses were conducted among total subjects (n = 18,815), those who were either or both anti-HCV and HBsAg positive (n = 1,499), and those who were anti-HCV positive without regard to HBV status (n = 1,058). The Cox proportional hazards model was employed to control for potential confounding factors: sex (stratified; men and women combined only), age at baseline (stratified; 5-year age categories), area (stratified; six public health center areas), smoking status (never, past, current), weekly ethanol intake (past, less than weekly, <150 g/wk, ≥150 g/wk), body mass index (<25, 25 to <27, ≥27), history of diabetes mellitus (yes, no), serum ALT level (IU/L; continuous), and HCV (anti-HCV negative, positive; not included in analyses restricted to HCV-positive subjects) and HBV (HBsAg negative, positive) infection status in addition to coffee consumption (almost never, <1, 1-2, ≥3 cups/d) and green tea consumption (<3, 3-4, ≥5 cups/d). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for liver cancer. Trend was assessed by assigning ordinal values for original coffee and green tea consumption categories. Sex, age, and area were treated as strata to allow for a different baseline hazard for each stratum. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. All statistical analyses were done using Stata 10 (Stata; ref. 26).

Results

During 238,517 person-years of follow-up (average follow-up period, 12.7 years) for 18,815 subjects (6,414

men and 12,401 women), a total of 110 cases of newly diagnosed liver cancer (73 men and 37 women) were identified and included in the analyses.

Baseline characteristics of subjects according to coffee and green tea consumption are shown in Table 1 (coffee) and Table 2 (green tea). Among total subjects, 33% almost never drank coffee, whereas 9% consumed ≥3 cups/d. In contrast, 63% of subjects consumed at least 3 cups/d of green tea. The distribution of coffee and green tea consumption was similar between those with and without HCV and HBV infection (data not shown).

Subjects with higher coffee consumption tended to smoke more, consume less green tea, be less obese, and have less history of diabetes mellitus. These tendencies were similar between all subjects and those who were either or both HBV and HCV infection positive, except that fewer infection-positive subjects with higher coffee consumption tended to be past drinkers and more had a lower ALT level. Body mass index did not markedly differ by coffee consumption in those who were either or both HCV and HBV positive (Table 1).

Subjects with higher green tea consumption tended to consume less alcohol and less coffee, have less history of diabetes mellitus, and have a lower ALT level. These subjects had a greater tendency to be smokers, particularly those with either or both HCV and HBV infection (Table 2).

HR (95% CI) of liver cancer according to coffee consumption are shown in Table 3. Compared with those who almost never drank coffee, increased coffee consumption was associated with a lower risk of liver cancer (<1 cup/d: HR, 0.67; 95% CI, 0.42-1.07; 1-2 cups/d: HR, 0.49; 95% CI, 0.27-0.91; ≥3 cups/d: HR, 0.54; 95% CI, 0.21-1.39; P_{trend} = 0.025). A similar tendency was observed when analysis was restricted to those with either or both HCV and HBV infection (<1 cup/d: HR, 0.55; 95% CI, 0.33-0.93; 1-2 cups/d: HR, 0.47; 95% CI, 0.24-0.93; ≥3 cups/d: HR, 0.61; 95% CI, 0.23-1.62; P_{trend} = 0.036) and when further restricted to those with HCV infection (<1 cup/d: HR, 0.56; 95% CI, 0.32-0.99; 1-2 cups/d: HR, 0.40; 95% CI, 0.18-0.88; ≥3 cups/d: HR, 0.78; 95% CI, 0.28-2.15; P_{trend} = 0.065). When analyzed by sex, a more significant reduction in risk was observed in men than in women.

The association between liver cancer risk and green tea consumption differed to that with coffee (Table 4). No significant association with risk was observed for total subjects, those with either or both HCV and HBV infection, or those with HCV infection. No clear difference was seen by sex.

Among covariates in the multivariate analysis, we found significant positive associations with a history of diabetes mellitus, smoking, high body mass index, high ALT level, and positivity for HCV and HBV infection and a significant inverse association with alcohol drinking.

Discussion

In this prospective cohort study among a large Japanese population, we found that coffee and green tea consumption differed in their association with the risk of liver cancer. Specifically, coffee consumption reduced the risk of liver cancer in all subjects as well as in those who were either or both HCV and HBV infection positive. In contrast, green tea consumption showed no significant association with the risk of liver cancer overall or by HCV or HBV status.

Few studies investigating the association of coffee and green tea with liver cancer risk have taken account of hepatitis virus infection status, although HBV and HCV infection are the most important risk factors of liver cancer. Because it is difficult to obtain baseline data on virus infection status for the large populations, this problem is particularly prominent in cohort studies. A previous report from the present cohort reported an inverse association between coffee and liver cancer (5), but this finding was weakened by the lack of data on hepatitis virus infection, which could therefore not be controlled. For the present analysis, we newly analyzed the association of coffee and green tea with liver cancer by determining infection status at baseline using stored blood samples and extending the follow-up period. To our knowledge, this study is the first prospective cohort analysis of this association to consider hepatitis virus infection status.

A growing number of epidemiologic studies have observed a reduced risk of liver cancer with increased consumption of coffee (5-15), and several meta-analyses have provided confirmation (16, 17). Although several of the case-control (10, 11, 13-15) and nested case-control (8, 9) studies took HCV or HBV infection status into consideration, most adjusted for HCV or HBV infection status in the model, and only a few observed risk among those who were HCV or HBV infection positive (8, 10, 13, 14). Most observed a decreased risk trend for liver cancer with increased coffee consumption following adjustment for HCV and HBV infection status (8, 9, 11-13) or among HCV- or HBV-positive subjects (8, 10, 13, 14). Consistent with these previous reports, our present results show a clear and significant inverse association between coffee consumption and liver cancer both among total subjects after controlling for HCV and HBV infection status and among those who were either or both HCV and HBV positive, although statistical significance was observed for only one of the consumption categories. Biologically, three major components of coffee have been considered to contribute to the beneficial effects of coffee on liver carcinogenesis: chlorogenic acids, caffeine, and the coffee diterpenes cafestol and kahweol (27, 28). Because diterpene content is negligible in instant, drip-filtered, and percolated brews (29), the preparation methods most commonly used by Japanese, the main putative candidates in our population are chlorogenic acids and caffeine. Further, coffee and caffeine have been suggested to improve liver enzyme activity (30-34), and coffee has also been associated with a reduced risk of liver disease and cirrhosis (35-37), a major risk factor or pathogenic step in the process of liver carcinogenesis. Thus, coffee may act to mitigate the inflammation of liver cells, suppress the aggravation of liver disease, and ultimately prevent the development of liver cancer (10).

Although several studies have reported the beneficial effects of coffee on abnormal liver biochemistry, cirrhosis, and liver cancer (38), the mechanism of the effect of coffee on HCV and HBV is not well understood. Our present results are consistent with previous findings (13, 35), which suggest that coffee may be protective against chronic liver disease no matter whether it is caused by HCV or HBV infection. In other words, coffee may act

Table 1. Baseline characteristics of the study subjects according to coffee consumption at baseline

	Coffee consumption (cups/d)													
	Total subjects (n = 18,815)					HCV and/or HBsAg positive (n = 1,499)					HCV positive (n = 1,058)			
	Almost never	<1	1-2	≥3	P_{trend}	Almost never	<1	1-2	≥3	P_{trend}	Almost never	<1	1-2	≥3	P_{trend}
No. subjects (%)	6,324 (33.6)	5,752 (30.6)	5,093 (27.1)	1,646 (8.7)		525 (35.0)	475 (31.7)	368 (24.6)	131 (8.7)		388 (36.7)	330 (31.2)	260 (24.6)	80 (7.6)	
Men (%)	31.8	34.0	33.7	44.4	<0.001	34.5	44.4	41.6	60.3	<0.001	34.5	43.0	43.5	62.5	<0.001
Smoking status (%)															
Never	75.4	72.8	71.0	55.4	<0.001	69.5	61.0	61.4	42.7	<0.001	67.3	57.9	57.7	36.3	<0.001
Past	11.4	12.0	11.0	10.0		11.4	17.1	13.9	13.0		12.1	19.1	14.6	11.2	
Current	13.2	15.2	18.0	34.6		19.1	21.9	24.7	44.3		20.6	23.0	27.7	52.5	
Weekly ethanol intake (%)															
Past	2.4	2.0	1.4	2.2	<0.001	5.9	4.7	3.0	1.5	<0.001	6.7	6.1	4.2	2.5	<0.001
Less than weekly	66.7	63.2	58.9	52.5		62.1	56.6	55.2	48.9		61.6	55.2	53.9	48.8	
<150 g/wk	16.1	20.3	25.1	29.7		20.2	22.3	25.8	28.2		20.1	23.6	27.3	27.5	
≥150 g/wk	14.8	14.5	14.6	15.6		11.8	16.4	16.0	21.4		11.6	15.1	14.6	21.2	
Body mass index (%)															
<25	67.6	69.0	71.2	72.9	<0.001	70.9	71.2	72.8	67.9	0.985	71.7	73.6	75.8	70.0	0.621
25-<27	16.8	17.3	15.7	14.3		15.2	17.9	13.9	19.1		16.2	17.0	13.5	16.2	
≥27	15.6	13.7	13.1	12.8		13.9	10.9	13.3	13.0		12.1	9.4	10.7	13.8	
History of diabetes mellitus (%)	7.1	5.3	3.7	3.6	<0.001	7.4	4.8	4.9	3.1	<0.001	8.5	4.9	5.8	3.8	0.064
Serum ALT (mean IU/L)	20.7	20.1	19.4	19.3	<0.001	31.6	30.9	27.0	28.2	0.027	34.8	33.3	28.9	33.1	0.103
Green tea consumption (%), cups/d															
<3	32.9	32.5	45.0	47.4	<0.001	33.9	33.1	46.7	46.6	0.029	31.2	26.7	43.1	41.2	<0.001
3-4	31.6	34.0	33.1	30.2		34.3	34.3	33.2	32.8		35.6	38.5	34.2	38.8	
≥5	35.5	33.5	21.9	22.4		32.8	32.6	20.1	20.6		33.3	34.8	22.7	20.0	

Table 2. Baseline characteristics of the study subjects according to green tea consumption at baseline

	Green tea consumption (cup/d)											
	Total subjects (n = 18,815)				HCV and/or HbsAg positive (n = 1,499)				HCV positive (n = 1,058)			
	<3	3-4	≥5	P_{trend}	<3	3-4	≥5	P_{trend}	<3	3-4	≥5	P_{trend}
No. subjects (%)	7,023 (37.7)	6,137 (32.6)	5,655 (29.7)		563 (37.6)	508 (33.9)	428 (28.5)		354 (33.5)	385 (36.4)	319 (30.1)	
Men (%)	38.0	32.1	31.5	<0.001	46.2	37.4	40.7	0.053	43.5	38.7	42.6	0.786
Smoking status (%)												
Never	69.9	73.4	71.9	0.009	61.1	66.1	60.1	0.610	59.6	62.9	55.8	0.251
Past	12.0	11.1	10.9		16.3	11.2	14.0		16.7	12.2	16.0	
Current	18.1	15.5	17.2		22.6	22.6	25.9		23.7	24.9	28.2	
Weekly ethanol intake (%)												
Past	2.0	1.5	2.5	<0.001	5.1	2.4	5.8	<0.001	6.8	2.6	7.9	0.031
Less than weekly	57.8	63.9	66.2		51.2	60.8	61.9		52.3	59.0	58.9	
<150 g/wk	23.1	21.0	18.3		24.5	23.6	20.1		23.7	25.4	21.0	
≥150 g/wk	17.1	13.6	13.0		19.2	13.2	12.2		17.2	13.0	12.2	
Body mass index (%)												
<25	67.6	71.5	69.5	0.007	70.7	73.0	69.6	0.703	73.7	74.0	71.5	0.062
25-<27	17.1	15.7	16.5		17.2	14.2	16.8		15.3	15.6	16.6	
≥27	15.3	12.8	14.0		12.1	12.8	13.6		11.0	10.4	11.9	
History of diabetes mellitus (%)	5.8	4.5	5.5	0.367	7.8	3.5	5.1	0.045	9.6	3.4	6.3	<0.001
Serum ALT (mean IU/L)	20.8	19.7	19.5	<0.001	31.4	29.8	28.3	0.328	35.8	31.7	30.6	0.337
Coffee consumption (%), cup/d												
Almost never	29.7	32.5	39.7	<0.001	30.7	35.4	40.2	<0.001	34.2	35.8	40.4	<0.001
<1	26.6	31.9	34.1		27.9	32.1	36.2		24.9	33.0	36.1	
1-2	32.6	27.5	19.7		30.6	24.0	17.3		31.6	23.1	18.5	
≥3	11.1	8.1	6.5		10.8	8.5	6.3		9.3	8.1	5.0	

on the clinical condition underlying the chronic liver disease rather than on the HCV or HBV itself (13) by the mechanisms mentioned above (10). Further basic research to clarify the mechanism of this effect is warranted.

The effect of green tea on liver cancer is not well understood. Several experimental studies have suggested a hepatoprotective effect and anticarcinogenic potential in the liver (39, 40). Only a few epidemiologic studies have

Table 3. HR (95% CI) of liver cancer according to coffee consumption

	Total	Coffee consumption				
		Almost never	<1 cup/d	1-2 cups/d	≥3 cups/d	P_{trend}
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
All subjects						
No. subjects	18,815	6,324	5,752	5,093	1,646	
Person-years	238,517	80,378	73,155	64,331	20,654	
No. cases	110	51	35	18	6	
Sex, age, and area adjusted		1.00 (Reference)	0.77 (0.50-1.18)	**0.50 (0.29-0.88)**	0.54 (0.23-1.27)	**0.019**
Multivariate adjusted*		1.00 (Reference)	0.67 (0.42-1.07)	**0.49 (0.27-0.91)**	0.54 (0.21-1.39)	**0.025**
Men		1.00 (Reference)	0.79 (0.46-1.37)	**0.37 (0.17-0.81)**	0.32 (0.10-1.10)	**0.006**
Women		1.00 (Reference)	0.39 (0.15-1.03)	0.92 (0.36-2.38)	0.69 (0.11-4.22)	0.615
HCV and/or HBsAg positive						
No. subjects	1,499	525	475	368	131	
Person-years	18,050	6,327	5,725	4,415	1,584	
No. cases	92	43	28	15	6	
Sex, age, and area adjusted		1.00 (Reference)	0.66 (0.41-1.07)	**0.51 (0.28-0.95)**	0.50 (0.21-1.22)	**0.026**
Multivariate adjusted*		1.00 (Reference)	**0.55 (0.33-0.93)**	**0.47 (0.24-0.93)**	0.61 (0.23-1.62)	**0.036**
Men		1.00 (Reference)	0.67 (0.37-1.22)	**0.36 (0.15-0.84)**	0.40 (0.12-1.38)	**0.017**
Women		1.00 (Reference)	**0.23 (0.06-0.93)**	1.43 (0.45-4.50)	0.94 (0.11-7.92)	0.833
HCV positive						
No. subjects	1,058	388	330	260	80	
Person-years	12,474	4,595	3,908	3,043	928	
No. cases	80	38	24	12	6	
Sex, age, and area adjusted		1.00 (Reference)	0.70 (0.42-1.19)	**0.40 (0.20-0.82)**	0.62 (0.25-1.53)	**0.028**
Multivariate adjusted*		1.00 (Reference)	**0.56 (0.32-0.99)**	**0.40 (0.18-0.88)**	0.78 (0.28-2.15)	0.065
Men		1.00 (Reference)	0.67 (0.34-1.31)	**0.31 (0.12-0.81)**	0.53 (0.14-1.92)	**0.032**
Women		1.00 (Reference)	0.39 (0.10-1.61)	0.72 (0.17-3.11)	2.54 (0.22-29.37)	0.964

*Model includes sex (stratified; men and women combined only), age (stratified; 5-year age categories), area (stratified; six public health center areas), smoking status (never, past, current), weekly ethanol intake (past, less than weekly, <150 g/wk, ≥150 g/wk), body mass index (<25, 25 to <27, ≥27), history of diabetes mellitus (yes, no), coffee consumption (never, <1, 1-2, ≥3 cups/d), green tea consumption (<3, 3-4, ≥5 cups/d), serum ALT level (IU/L; continuous), HCV infection status (anti-HCV antibody negative, positive; not included in analysis restricted to HCV-positive subjects), and HBV infection status (HbsAg negative, positive).

Table 4. HR (95% CI) of liver cancer according to green tea consumption

	Total	Green tea consumption			
		<3 cups/d	3-4 cups/d	≥5 cups/d	P_{trend}
		HR (95% CI)	HR (95% CI)	HR (95% CI)	
All subjects					
No. subjects	18,815	7,023	6,137	5,655	
Person-years	238,517	88,484	77,979	72,054	
No. cases	110	32	44	34	
Sex, age, and area adjusted		1.00 (Reference)	1.42 (0.89-2.24)	1.13 (0.69-1.85)	0.827
Multivariate adjusted*		1.00 (Reference)	1.62 (0.97-2.69)	1.44 (0.84-2.45)	0.108
Men		1.00 (Reference)	1.20 (0.64-2.23)	1.18 (0.63-2.20)	0.287
Women		1.00 (Reference)	**2.58 (1.01-6.59)**	1.48 (0.54-4.08)	0.397
HCV and/or HBsAg positive					
No. subjects	1,499	563	508	428	
Person-years	18,050	6,796	6,172	5,082	
No. cases	92	25	36	31	
Sex, age, and area adjusted		1.00 (Reference)	1.47 (0.87-2.49)	1.48 (0.86-2.56)	0.250
Multivariate adjusted*		1.00 (Reference)	1.68 (0.94-3.02)	1.64 (0.91-2.97)	0.092
Men		1.00 (Reference)	1.41 (0.69-2.88)	1.70 (0.85-3.41)	0.062
Women		1.00 (Reference)	2.41 (0.73-7.92)	0.87 (0.24-3.15)	0.951
HCV positive					
No. subjects	1,058	354	385	319	
Person-years	12,474	4,130	4,650	3,694	
No. cases	80	22	32	26	
Sex, age, and area adjusted		1.00 (Reference)	1.46 (0.83-2.57)	1.42 (0.79-2.58)	0.525
Multivariate adjusted*		1.00 (Reference)	1.79 (0.95-3.38)	1.69 (0.87-3.29)	0.154
Men		1.00 (Reference)	1.48 (0.67-3.25)	1.83 (0.84-3.99)	0.110
Women		1.00 (Reference)	3.06 (0.82-11.39)	1.07 (0.24-4.89)	0.874

*Model includes sex (stratified; men and women combined only), age (stratified; 5-year age categories), area (stratified; six public health center areas), smoking status (never, past, current), weekly ethanol intake (past, less than weekly, <150 g/wk, ≥150 g/wk), body mass index (<25, 25 to <27, ≥27), history of diabetes mellitus (yes, no), coffee consumption (never, <1, 1-2, ≥3 cups/d), green tea consumption (<3, 3-4, ≥5 cups/d), serum ALT level (IU/L; continuous), HCV infection status (anti-HCV antibody negative, positive; not included in analysis restricted to HCV-positive subjects), and HBV infection status (HbsAg negative, positive).

evaluated risk (10, 18); however, one of these observed a null association, although without considering HCV or HBV infection (18), whereas the second observed an elevated risk with increased green tea consumption among those positive for HCV (10). Our present results and a previous report in HCV-positive subjects suggest that green tea consumption does not appear to be inversely associated with liver cancer. Green tea contains vitamin C, which has antioxidant potential, but is also known to stimulate iron uptake from food (41). In the Framingham Heart Study, dietary vitamin C was positively associated with ferritin, which was used as a measure of body iron stores, whereas coffee intake was inversely associated with it (42, 43). Given the integral role of excess iron in the progression of hepatic fibrosis (44), higher consumption of green tea might harm hepatic cells by increasing iron uptake from food via dietary vitamin C. Although the contribution of green tea intake to total vitamin C intake in Japanese is ~13% (45), it is possible that the positive effect of green tea, if any, might be due to vitamin C, at least in part, and that the lack of association for green tea might result from the opposing effects of its constituents. A better understanding of this issue will require further research.

The major strength of the present study is its prospective design, in which information was collected before the subsequent diagnosis of liver cancer, thereby avoiding the exposure recall bias inherent to case-control studies. A second strength was that virus infection status was determined at baseline for the entire population, allowing us to clarify the association in a high-risk population using a prospective design. 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, the correlation coefficients were moderate for coffee and even lower for green tea. Inaccurate measurement of coffee and green tea consumption necessarily results in random misclassification, which in turn attenuates the true association. Second, misclassification might also have resulted from our evaluation of coffee and green tea consumption by a single, self-reported measurement at baseline. If present, however, this would likely have been nondifferential and led to an underestimation of results. Third, although the study was based on a cohort of ~20,000 Japanese with 13 years of follow-up, the number of cases was nevertheless relatively small, and the possibility that the results were due to chance cannot be ruled out. Fourth, we had no information on the clinical severity of hepatitis or the treatment of subjects with HCV or HBV infection before and during the study period. If infected subjects had received treatment, the occurrence of liver cancer may have been decreased. Fifth, our study subjects were restricted to those who responded to the questionnaire and provided blood samples when they participated in the baseline health checkup, suggesting that these individuals may not be representative of the entire cohort. The incidence of liver cancer in this study population during the follow-up period was 46.1 per 100,000 person-years versus 67.5 in the whole Japan Public Health Center-Based Prospective Study, suggesting that subjects who were already under care for HCV or

HBV infection may have been less willing to attend a health checkup. For these reasons, interpreting or generalizing these results should be done with care.

Allowing for these methodologic issues, we found that coffee and green tea consumption differed in their association with the risk of liver cancer. Increased coffee consumption reduced the risk of liver cancer regardless of HCV and HBV infection status, whereas green tea consumption showed no significant association with the risk of liver cancer overall or by HCV and HBV status. Although both coffee and green tea have anticarcinogenic potential, these two beverages might differ in their overall effect on the human liver. The mechanisms underlying this difference, including iron uptake, warrant further clarification.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Appendix

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References

1. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, volume 51. Coffee, tea, mate, methylxanthines, and methylgloxyal. Lyon (France): IARC; 1991.
2. Tanaka T, Nishikawa A, Shima H, et al. 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.
3. Jin X, Zheng RH, Li YM. Green tea consumption and liver disease: a systematic review. Liver Int 2008;28:990–6.
4. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: global perspective. Washington (DC): American Institute for Cancer Research; 2007.
5. Inoue M, Yoshimi I, Sobue T, Tsugane S. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. J Natl Cancer Inst 2005;97:293–300.
6. Kurozawa Y, Ogimoto I, Shibata A, et al. Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. Br J Cancer 2005;93:607–10.
7. Shimazu T, Tsubono Y, Kuriyama S, et al. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. Int J Cancer 2005;116:150–4.
8. Wakai K, Kurozawa Y, Shibata A, et al. Liver cancer risk, coffee, and hepatitis C virus infection: a nested case-control study in Japan. Br J Cancer 2007;97:426–8.
9. Ohishi W, Fujiwara S, Cologne JB, et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2008;17:846–54.
10. Ohfuji S, Fukushima W, Tanaka T, et al. Coffee consumption and reduced risk of hepatocellular carcinoma among patients with chronic type C liver disease: a case-control study. Hepatol Res 2006;36:201–8.
11. Tanaka K, Hara M, Sakamoto T, et al. Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan. Cancer Sci 2007;98:214–8.
12. Gallus S, Bertuzzi M, Tavani A, et al. Does coffee protect against hepatocellular carcinoma? Br J Cancer 2002;87:956–9.
13. Gelatti U, Covolo L, Franceschini M, et al. Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. J Hepatol 2005;42:528–34.
14. Montella M, Polesel J, La Vecchia C, et al. Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. Int J Cancer 2007;120:1555–9.
15. Kuper H, Tzonou A, Kaklamani E, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498–502.
16. Bravi F, Bosetti C, Tavani A, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. Hepatology 2007;46:430–5.
17. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. Gastroenterology 2007;132:1740–5.
18. Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control 2001;12:501–8.
19. 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.
20. The Editorial Board of the Cancer Statistics in Japan. Cancer statistics in Japan 2007. Tokyo: Foundation for Promotion of Cancer Research; 2007.

21. Tsugane S, Sobue T. Baseline survey of JPHC study-design and participation rate. Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11:S24–9.
22. Abdel-Hamid M, El-Daly M, El-Kafrawy S, Mikhail N, Strickland GT, Fix AD. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. J Clin Microbiol 2002;40:1656–9.
23. Committee for Evaluation of *In vitro* Diagnostic Devices, National Institute of Infectious Diseases. Re-evaluation of HBsAg detection kits approved for marketing in Japan. Jpn J Infect Dis 2001;54:201–7.
24. WHO. International classification of diseases and health related problem, 10th revision. Geneva (Switzerland): WHO; 1990.
25. WHO. International classification of diseases for oncology. 3rd ed. Geneva (Switzerland): WHO; 2000.
26. Stata. Stata statistical software version 10. College Station (TX): Stata.
27. La Vecchia C. Coffee, liver enzymes, cirrhosis and liver cancer. J Hepatol 2005;42:444–6.
28. Tao KS, Wang W, Wang L, et al. The multifaceted mechanisms for coffee's anti-tumorigenic effect on liver. Med Hypotheses 2008;71:730–6.
29. Urgert R, van der Weg G, Kosmeijer-Schuil TG, van de Bovenkamp P, Hovenier R, Katan MB. Levels of the cholesterol-evaluating diterpenes cafestol and kahweol in various coffee brews. J Agric Food Chem 1995;43:2167–72.
30. Tanaka K, Tokunaga S, Kono S, et al. Coffee consumption and decreased serum γ-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol 1998;27:438–43.
31. Honjo S, Kono S, Coleman MP, et al. Coffee drinking and serum γ-glutamyltransferase: an extended study of Self-Defense Officials of Japan. Ann Epidemiol 1999;9:325–31.
32. Honjo S, Kono S, Coleman MP, et al. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol 2001;54:823–9.
33. Poikolainen K, Vartiainen E. Determinants of γ-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997;146:1019–24.
34. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2005;128:24–32.
35. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A. Coffee, caffeine, and the risk of liver cirrhosis. Ann Epidemiol 2001;11:458–65.
36. Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol 2002;12:202–5.
37. Kim WR. Is coffee or tea good for your liver?. Nat Clin Pract Gastroenterol Hepatol 2006;3:482–3.
38. Cadden IS, Partovi N, Yoshida EM. Review article: possible beneficial effects of coffee on liver disease and function. Aliment Pharmacol Ther 2007;26:1–8.
39. Nishikawa T, Nakajima T, Moriguchi M, et al. A green tea polyphenol, epigalocatechin-3-gallate, induces apoptosis of human hepatocellular carcinoma, possibly through inhibition of Bcl-2 family proteins. J Hepatol 2006;44:1074–82.
40. He P, Noda Y, Sugiyama K. Green tea suppresses lipopolysaccharide-induced liver injury in D-galactosamine-sensitized rats. J Nutr 2001; 131:1560–7.
41. Lynch SR. Interaction of iron with other nutrients. Nutr Rev 1997;55: 102–10.
42. Fleming DJ, Jacques PF, Dallal GE, Tucker KL, Wilson PW, Wood RJ. Dietary determinants of iron stores in a free-living elderly population: the Framingham Heart Study. Am J Clin Nutr 1998;67:722–33.
43. Fleming DJ, Tucker KL, Jacques PF, Dallal GE, Wilson PW, Wood RJ. Dietary factors associated with the risk of high iron stores in the elderly Framingham Heart Study cohort. Am J Clin Nutr 2002;76:1375–84.
44. Philippe MA, Ruddell RG, Ramm GA. Role of iron in hepatic fibrosis: one piece in the puzzle. World J Gastroenterol 2007;13:4746–54.
45. Ministry of Health, Labour and Welfare, ed. The National Health and Nutrition Survey in Japan, 2005. Tokyo: Dai-ichi Shuppan; 2008.

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