Table 1
Comparison of selected characteristics between cases and controls

Characteristics	Level	*n* (%)		*P*-value
		Case ($N=73$)	Control ($N=253$)	
Mean age (years)		68.9	68.3	0.384
Gender	Male	35 (47)	131 (52)	0.434
Possible cause of infection[a]	Transfusion	24 (33)	97 (38)	0.980
	Operation	22 (30)	69 (27)	
Mean duration until first identification of liver disease (years)				
From relevant infection[a]		21.8	21.6	0.926
Mean duration until beginning of the study period (years)				
From relevant infection[a]		38.2	35.5	0.136
From first identification of liver disease		19.8	16.7	0.023
From first OCUH visit		7.1	6.4	0.135
Family history of liver diseases	Present	28 (38)	69 (27)	0.069
Interferon therapy	Present	18 (25)	91 (36)	0.072
	Never	36 (49)	125 (49)	0.960
Smoking	Former	19 (26)	64 (25)	
	Current	18 (25)	64 (25)	
	Never	32 (44)	96 (38)	0.137
Alcohol drinking	Former	23 (32)	67 (27)	
	Current	18 (25)	90 (36)	
Mean volume of cumulative ethanol consumption (g/dL)		232	334	0.396
Body mass index	≥22.5	31 (42)	131 (52)	0.216
Platelet count ($\times 10^4$ μL^{-1})	<10	29 (40)	28 (11)	0.000
Aspartate aminotransferase (IU/L)	≥80	40 (55)	96 (38)	0.010
Alanine aminotransferase (IU/L)	≥80	48 (66)	143 (57)	0.159
Albumin (g/dL)	<3.5	10 (14)	9 (4)	0.001
Alphafetoprotein (ng/mL)	≥20	25 (34)	37 (15)	0.000
Fasting blood sugar (mg/dL)	≥126	13 (18)	18 (7)	0.005
US score	Severe	51 (70)	90 (36)	0.000

[a] Data from 46 cases and 166 controls because of missing information.

cance. Cumulative consumption of black tea did not indicate an association, either. Thus, these results suggest that coffee drinking (both frequency of intake and cumulative intake) is associated with a decreased risk of HCC.

Additionally, we examined the changes in frequency of consumption of coffee after first identification of liver disease. The proportion of subjects who reported a decreased frequency of coffee drinking was nearly the same in both cases and controls (27% versus 24%). After excluding these subjects from the analysis, ORs inversely associated with frequency of intake of coffee were also observed (OR at <1 cup/day, 0.99; 95% CI: 0.35–2.79; $P=0.987$ and OR at ≥1 cup/day, 0.35; 95% CI: 0.12–1.06; $P=0.063$).

4. Discussion

The present study reveals that coffee intake may decrease the risk of HCC among patients with chronic type C liver disease. There are several studies which also report similar results, but they have two major limitations. First, these studies did not adequately control for status of HCV infection although this is an overwhelming risk factor for HCC. Therefore, the association detected between any variables including coffee and HCC might have been largely affected. This problem could occur in cohort studies with no baseline data on HCV infection or in case–control studies with a substantial difference in prevalence of HCV infection between the compared groups. The present study, however, could overcome this limitation, since both cases and controls were patients with HCV infection.

Second, it has been pointed out that the decreased consumption of coffee due to already-developed liver dysfunction may bring about the apparent protective effect of coffee for HCC. However, the present study made it possible to analyze the data on coffee consumption by separating them into two periods, i.e., before and after first identification of liver disease. The decreased OR with increasing coffee intake is shown by the downward stepwise slope during both periods (Table 2). Furthermore, this inverse relationship was also observed even after excluding the subjects who reported a reduced coffee consumption after liver disease identification. Thus, it can be considered that prior coffee consumption influenced subsequent development of HCC.

However, this study may be underpowered to detect relevant association before first identification of liver disease. If there are some potential changes in coffee drinking habit due to progression of liver disease, that habit before first identification of liver disease would represent original true coffee drinking pattern. The negative association between the fre-

Table 2
Odds ratio for hepatocellular carcinoma according to frequency of consumption of the caffeine-containing beverages, calculated before and after first identification of liver disease: Japan

Variable/level	*n* (%)		Univariate		Multivariate[a]	
	Case ($N=73$)	Control ($N=253$)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Before first identification of liver disease						
Coffee						
Non-drinker	25 (34)	63 (25)	1		1	
<1 cup/day	19 (26)	74 (29)	0.71 (0.35–1.44)	0.343	0.61 (0.18–2.03)	0.420
≥1 cup/day	29 (40)	116 (46)	0.67 (0.36–1.27)	0.219	0.38 (0.13–1.12)	0.078
			Trend: $P=0.235$		Trend: $P=0.171$	
Black tea						
Non-drinker	31 (43)	124 (49)	1		1	
<2 cup/day	22 (30)	63 (25)	1.30 (0.70–2.40))	0.405	1.26 (0.43–3.71)	0.671
≥2 cup/day	20 (27)	66 (26)	1.12 (0.57–2.19)	0.750	0.68 (0.22–2.13)	0.509
			Trend: $P=0.671$		Trend: $P=0.739$	
Green tea						
≤1 cup/day	12 (16)	67 (27)	1		1	
2 cup/day	16 (22)	56 (22)	1.67 (0.70–3.98)	0.248	5.90 (1.32–26.3)	0.020
≥3 cup/day	45 (62)	130 (51)	1.93 (0.92–4.04)	0.081	4.08 (1.20–13.9)	0.024
			Trend: $P=0.089$		Trend: $P=0.053$	
After first identification of liver disease						
Coffee						
Non-drinker	27 (37)	59 (23)	1		1	
<1 cup/day	25 (34)	83 (33)	0.66 (0.34–1.30)	0.234	0.57 (0.20–1.67)	0.307
≥1 cup/day	21 (29)	111 (44)	0.42 (0.21–0.85)	0.016	0.19 (0.05–0.71)	0.014
			Trend: $P=0.016$		Trend: $P=0.032$	
Black tea						
Non-drinker	28 (38)	111 (44)	1		1	
<2 cup/day	26 (36)	66 (26)	1.31 (0.72–2.39)	0.375	1.67 (0.59–4.69)	0.334
≥2 cup/day	19 (26)	76 (30)	0.88 (0.44–1.77)	0.728	0.64 (0.18–2.33)	0.500
			Trend: $P=0.845$		Trend: $P=0.907$	
Green tea						
≤1 cup/day	12 (16)	66 (26)	1		1	
2 cup/day	14 (19)	51 (20)	1.63 (0.68–3.93)	0.274	6.95 (1.38–35.2)	0.019
≥2 cup/day	47 (64)	136 (54)	1.98 (0.96–4.10)	0.065	4.93 (1.37–17.8)	0.015
			Trend: $P=0.067$		Trend: $P=0.029$	

[a] Model includes: duration from first identification of liver disease, body mass index at first identification of liver disease, disease severity at first OCUH visit (US score, platelet count, aspartate aminotransferase, albumin, alphafetoprotein, fasting blood sugar), family history of liver disease, interferon therapy, smoking, alcohol drinking, and other caffeine-containing beverage.

quency of this original drinking pattern and HCC persisted with a marginal significance. Thus, it seems to tell that the natural coffee drinking habit before liver disease may also affect an individual's risk for HCC.

When interpreting the present results, the following three major limitations should be discussed. The first limitation is that a selection bias might be introduced, since the source population consisted of patients who had survived to the recruitment period. The patients who developed HCC but died before the recruitment period were not included in case series, although cases were defined as those patients who had been firstly diagnosed with HCC in the recent past, i.e., within 3 years. However, there are previous studies which report significantly lower mortality rates among daily coffee drinkers than among non-drinkers [25–28]. Supposed a hypothetical situation that cases excluded because of death were included in this study, the prevalence of non-coffee-drinkers would increase in the hypothetical case series and OR would be decrease. Thus, this selection bias may operate to bias the association toward the null, but not lead to exaggerated results.

The second limitation is that the time point of relevant infection could be estimated for only 65% of subjects, although the time since HCV infection is a major risk factor for HCV-associated HCC. Therefore, we performed an analysis controlling for the duration from first identification of liver disease instead of duration since infection. This is because the mean duration from infection to first identification was similar in cases and controls, at 21.8 and 21.6 years, respectively, although there were some missing data (Table 1). Besides, the severity of liver disease at the first OCUH visit was also controlled for in the analysis, under the assumption that the longer the time that has passed since HCV infection, the more severe the liver disease becomes.

Table 3
Odds ratio for hepatocellular carcinoma according to cumulative consumption of the caffeine-containing beverages, calculated before and after first identification of liver disease: Japan

Variable/level (cups)	*n* (%)		Univariate		Multivariate[a]	
	Case	Control	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Before first identification of liver disease[b]						
Coffee						
Non-drinker	15 (33)	49 (30)	1		1	
<5000	16 (35)	52 (31)	0.86 (0.35–2.11)	0.739	0.38 (0.05–2.69)	0.331
≥5000	15 (33)	65 (39)	1.26 (0.52–3.04)	0.612	2.95 (0.48–18.1)	0.242
			Trend: $P=0.589$		Trend: $P=0.153$	
Black tea						
Non-drinker	18 (39)	84 (51)	1		1	
<1500	16 (35)	42 (25)	2.60 (1.05–6.48)	0.040	2.31 (0.48–11.0)	0.295
≥1500	12 (26)	40 (24)	2.08 (0.71–6.16)	0.184	2.58 (0.46–14.5)	0.283
			Trend: $P=0.146$		Trend: $P=0.265$	
Green tea						
<10 000	13 (28)	68 (41)	1		1[d]	
10 000–19 999	14 (30)	34 (21)	3.42 (1.24–9.38)	0.017	60 096 (0.04–8.6×10^{10})	0.128
≥20 000	19 (41)	64 (39)	2.85 (1.12–7.22)	0.028	1 367 280 (0.10–5.9×10^{13})	0.091
			Trend: $P=0.024$		Trend: $P=0.101$	
After first identification of liver disease[c]						
Coffee						
Non-drinker	27 (37)	59 (23)	1		1	
<5000	27 (37)	117 (46)	0.51 (0.26–0.98)	0.043	0.48 (0.18–1.29)	0.144
≥5000	19 (26)	77 (30)	0.57 (0.28–1.15)	0.116	0.42 (0.15–1.22)	0.110
			Trend: $P=0.112$		Trend: $P=0.098$	
Black tea						
Non-drinker	28 (38)	111 (44)	1		1	
<5000	26 (36)	81 (32)	1.13 (0.62–2.05)	0.698	1.48 (0.60–3.68)	0.397
≥1500	19 (26)	61 (24)	1.12 (0.55–2.28)	0.763	0.81 (0.26–2.53)	0.722
			Trend: $P=0.729$		Trend: $P=0.959$	
Green tea						
<10 000	22 (30)	114 (45)	1		1	
10 000–19 999	24 (33)	82 (32)	1.54 (0.78–3.06)	0.217	1.67 (0.58–4.80)	0.338
≥20 000	27 (37)	57 (23)	2.33 (1.19–4.56)	0.014	2.69 (0.77–9.38)	0.120
			Trend: $P=0.014$		Trend: $P=0.119$	

[a] Model includes: duration from first identification of liver disease, body mass index at first identification of liver disease, disease severity at first OCUH visit (US score, platelet count, aspartate aminotransferase, albumin, alphafetoprotein, fasting blood sugar), family history of liver disease, interferon therapy, smoking, alcohol drinking, and other caffeine-containing beverage.
[b] Only subjects whose relevant infection was known (case: 46, control: 166).
[c] All subjects (case: 73, control: 253).
[d] Model did not converge because of much explanatory variables.

These adjustments for alternative variables are likely to have at least partially compensated for missing data on the time point of infection.

The third limitation is an information bias resulting from imperfect memory of distant past history of coffee consumption. However, it is hard to believe that cases and controls have a different level of recall stimulus, since the hypothesis that coffee is related to HCC or chronic liver disease is not generally recognized. Thus, this information bias, if any, can be regarded as a non-differential misclassification in which erroneous report of coffee drinking habit similarly occurs among cases and controls. Such misclassification leads to an underestimate of the association because of the diluting effect and does not materially affect to validity of the study results [29].

It is also conceivable that other life-style characteristics can account for the protective effect of coffee. In fact, there are studies which report on the correlation between coffee drinking and other life-style characteristics, such as tobacco smoking and habitual alcohol drinking [9,26]. However, the present results were obtained after adjustment for the potential confounders (e.g., alcohol drinking, smoking, BMI, and diabetes mellitus, etc.), and the results are consistent with the previous studies conducted in different populations with different culture or life style [12,13].

As to the mechanism, several previous papers suggest that coffee drinking might improve the activity of liver enzyme [30–39], decrease the risk of liver cirrhosis [40–42] and lower the mortality from liver cirrhosis [25–28]. Thus, it seems quite probable that coffee acts to mitigate the inflammation

of liver cells, suppress the aggravation of liver disease and, as a result, prevent the development of HCC. Regarding the principal ingredients, the brewing method of coffee seems to be important. Previous studies showing results similar to ours were performed in countries where most individuals drink filtered coffee [12,13]. It is therefore likely that the key substances are included in filtered coffee. However, no further discussion is meaningful, since we did not obtain any information on the type of coffee drunk. In the present study, neither green tea nor black tea showed an inverse association with HCC. It is therefore possible to infer that ingredients other than caffeine are responsible.

The positive association between green tea and HCC, although statistically insignificant when considering cumulative consumption (Table 3), was an unexpected finding in the light of previous reports. These studies have suggested no relation of green tea to liver enzyme level [31,32], HCC [9,10] and any cancers [43]. Our results can possibly be criticized because of the following two weaknesses. First, the categorization of the frequency of consumption was inappropriate for green tea, although appropriate for coffee or black tea. The highest open-ended category of $\geq$3 cup/day was too broad to separate heavy users of green tea, whereas most of previous studies draw a boundary at $\geq$5 cup/day as the highest level. Furthermore, there were too few non-drinkers to serve as the reference category for calculating OR. Second, a reverse causality or an information bias might have affected the present results, since many Japanese recognize that green tea is good for health. It is therefore quite likely that patients with severe disease drank more green tea or have greater recall about past green tea consumption than controls. Thus, it seems sensible to have reservations about this positive relationship.

In conclusion, the present study shows that coffee intake decreases the risk of HCC among patients with chronic type C liver disease. This negative relationship could not be explained by reduced consumption due to liver disease progression. This effect might be attributable to substances other than caffeine, since neither black tea nor green tea had the same effect. It is still premature to recommend drinking coffee to patients with chronic type C liver disease, since a limited number of studies of coffee and HCC risk have so far reported from few countries. Thus, further studies are needed to confirm this association.

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