HMW adiponectin (p for trend=0.06) when further variables (alcohol and coffee consumption, ALT levels) were added to the model. However, this association was attenuated after we excluded 17 cases diagnosed in the first 3 years (multivariate p for trend=0.10 for total and 0.16 for HMW adiponectin). When we restricted analysis to the 71 cases of liver cancer death, the positive association remained (multivariate p for trend=0.01 for both total and HMW adiponectin). Adiponectin levels were also associated with an increased risk of liver cancer development in the first 7 years after blood collection (multivariate p for trend=0.01 for both total and HMW adiponectin), but not liver cancer development after the first 7 years.

For stratified analyses, plasma levels of adiponectin were dichotomized at the median values for 2 groups, high and low (Table 3). The multivariable ORs for the high versus low group were 3.08 (95% CI=1.62-5.86) for total adiponectin and 2.03 (1.09-3.78) for HMW adiponectin. The magnitudes of association between plasma adiponectin levels and primary liver cancer risk tended to be greater in women than in men. The p value for interaction between HMW adiponectin and sex was borderline significant (p=0.05). Analyses stratified according to hepatitis virus infection status, BMI, and diabetes showed no remarkable differences between the 2 strata for either total or HMW adiponectin.

Discussion

One strength of the present study of the association between plasma adiponectin levels

and the risk of primary liver cancer development is that blood samples were collected from a nested case-control cohort of approximately 1,500 adults with hepatitis virus infection, a subset derived from a large-scale population-based prospective cohort. Because the measurements preceded the onset of outcomes, we were able to clarify the temporal association between the putative exposure and the hypothesized outcome. In addition, the cases and controls were selected from the same cohort, minimizing the possibility of the selection bias inherent to case-control studies. This study is thus an important contribution to the research into the role of adiponectin in liver carcinogenesis.

We did not find an inverse association between plasma levels of adiponectin and primary liver cancer development risk, in spite of ccumulating evidence that adiponectin plays a protective role in carcinogenesis. However, we do not believe the results of our study contradict earlier findings. No epidemiological studies have actually shown an inverse association between circulating levels of adiponectin and the occurrence of liver cancer: earlier studies have shown either a positive association or no association. One cohort study in Japan indicated that patients with chronic hepatitis C and high serum adiponectin levels had a higher risk of developing HCC; our results support this finding (14). In another cohort study in France, serum levels of adiponectin measured in 248 patients with compensated HCV cirrhosis were found to be unassociated with HCC occurrence (15). This study differed from ours, however, in that the subjects were Caucasian, and all of them had been clinically diagnosed with cirrhosis. A nested-case control study in Japan of 59 patients with liver cancer and 334 controls showed no statistically significant association between serum levels

of total, HMW, middle-molecular weight and low-molecular weight adiponectin and the incidence of or mortality from liver cancer (16). However, this study did not include hepatitis virus infection status as a matching variable and treated anti-HCV as a confounding factor. Although *in vitro* and *in vivo* studies have indicated that adiponectin exerts antitumor effects against HCC by inducing apoptosis or suppressing tumor angiogenesis (12, 13), it is not unusual for the results of epidemiological studies to contradict those of experimental studies. In addition, the insulin-sensitizing properties of adiponectin do not explain the connection with liver cancer. After adjustment and stratification for BMI and diabetes (determinants of insulin resistance), we observed an association between adiponectin and primary liver cancer. Thus, the association appears to be independent of BMI and diabetes, even though adiponectin has been seen as a mediator of obesity in cancer development (7, 8). It does not seem likely, therefore, that the link between adiponectin and liver cancer can be explained by the potential mechanisms underlying the protective role of adponectin in carcinogenesis.

The observed positive association between adiponectin and primary liver cancer risk may lead to adiponectin being regarded as a risk marker for primary liver cancer. Some studies have shown that circulating adiponectin levels are higher in subjects with liver cirrhosis (29-32), and that they increase in line with fibrosis stage (33, 34). Tietge et al reported that adiponectin levels in cirrhosis correlated negatively with the parameters of hepatic protein synthesis capacity (including serum albumin levels and blood-coagulating factors), and positively with the parameters of hepatic hemodynamics (including portal

pressure, hepatic vascular resistance, and decreased hepatic blood flow) (31), thus demonstrating that liver function determined circulating adiponectin levels. In one animal study, common bile duct ligation was performed in mice, which led rapidly to an accumulation of serum adiponectin (32), demonstrating that biliary excretion is involved in the clearance of adiponectin. To summarize, impaired liver function or biliary secretion due to liver disease (including cirrhosis) appears to lead to hyperadiponectinemia. In our study, therefore, the adiponectin levels observed in participants with hepatitis virus infection might have been a reflection of the progression of virus-related liver disease. This hypothesis is supported by the positive association between adiponectin and liver cancer observed in our subgroup analysis restricted to cases of liver cancer death and liver cancer cases diagnosed in the first 7 years after blood collection, and by the null association between adiponectin and liver cancer revealed when we excluded 17 cases diagnosed in the first 3 years after blood collection. We believed, therefore, that circulating adiponectin is probably just a risk marker of primary liver cancer caused by hepatitis virus infection and not a causal factor. If this is the case, future studies are needed to investigate whether adiponectin measurement in patients with hepatitis virus infection is a valid marker in predicting the risk of primary liver cancer development.

Like Arano et al, we found that the association between adiponectin levels and primary liver cancer risk was particularly pronounced in women (14). Circulating adiponectin levels are influenced by sex hormones such as testosterone. Testosterone lowers circulating levels of adiponectin (35), which might account for the weaker association

between adiponectin and liver cancer in men. However, the number of liver cancer cases in our study was relatively small, so the interpretability of our results might be limited. Further investigations are needed to clarify the sex-specific association between adiponectin levels and primary liver cancer occurrence.

A potential limitation of our study is that we had no information on the clinical severity and later progress of hepatitis or about the treatment the participants with HBV or HCV infection received before or during the study period. However, if plasma adiponectin levels reflect the progression of virus-related liver disease, the participants in the high adiponectin group are more likely to have received treatment than those in the low group, which might have led to underestimation of liver cancer occurrence and ORs in the high adiponectin group. Therefore, our finding of a positive association between plasma adiponectin levels and liver cancer risk should remain true. In addition, although JPHC Cohort II participants were selected from the general population, the participants in our study were limited to those who responded to the questionnaire and provided a blood sample. Our findings may, therefore, lack generalizability (36).

In conclusion, the present nested case-control study provides epidemiological evidence that higher plasma levels of total and HMW adiponectin are independently associated with an increased risk of primary liver cancer in middle-aged Japanese adults with hepatitis virus infection. Our findings also indicate that circulating adiponectin levels may be a risk marker for primary liver cancer.

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Table 1. Selected baseline characteristics of cases and controls

Variables		Cases (n = 90) Prevalence (%)	Controls (n = 177) Prevalence (%)	P value[a]
Age, years	40-49	2.2	3.4	Matching variable
	50-59	27.8	28.8	
	60-69	70.0	67.8	
Sex	men	68.9	68.9	Matching variable
	women	31.1	31.1	
Hepatitis virus infectious status[b]	HBV	12.2	11.9	Matching variable
	HCV	87.8	88.1	
Alcohol consumption	never	51.1	39.0	0.08
	past	11.1	7.3	
	< 150 g/week ethanol	17.8	30.5	

150 to < 450 g/week ethanol	14.4	19.8	
≥ 450 g/week ethanol	5.6	3.4	
Smoking status, current smoker	37.8	35.6	0.58
Body mass index, ≥ 25 kg/m^2	37.8	17.5	< 0.01
Diabetes, yes[c]	33.3	23.0	0.05
Coffee consumption, ≥ 1 cup/day	23.3	39.0	0.01
Alanine aminotransferase level, ≥ 70 IU/L	46.0	6.0	< 0.01
Vegetable intake (g/day)[d]	44 (24-69)	48 (27-75)	0.33
Fish intake (g/day)[d]	45 (28-67)	43 (27-66)	0.78
Time from blood draw to diagnosis for the cases (years)[d]	6.1 (3.6-9.5)		

NOTE: HBV=hepatitis B virus, HCV=hepatitis C virus

[a]Calculated using the χ^2 test and Mann-Whitney test.

[b]Positive for hepatitis B surface antigen was regarded as indicating HBV infection and positively for anti-hepatitis C virus antibody as

indicating HCV infection.

[c]Diabetes was defined as a self-reported history of diabetes, and/or anti-diabetic medication use, and/or blood glucose ≥ 5.55 mmol/l (100 mg/dl) fasting or ≥ 7.77 mmol/l (140 mg/dl) non-fasting.

[d]Median (interquartile range).

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of primary liver cancer based on plasma adiponectin levels

	Tertile			
Plasma level	Low	Middle	High	P value[a]
Total adiponectin				
Range (μg/mL)	≤ 3.40 for men and ≤ 5.32 for women	3.41-5.68 for men and 5.33-8.50 for women	> 5.68 for men and > 8.50 for women	
No. cases/controls	17/60	36/56	37/61	
OR (95% CI)	1.00 (reference)	2.23 (1.14-4.38)	2.25 (1.11-4.55)	0.03
Multivariable OR (95% CI)[b]	1.00 (reference)	2.59 (1.22-5.50)	3.30 (1.45-7.53)	< 0.01
Multivariable OR (95% CI)[c] + alcohol and coffee consumption, ALT level	1.00 (reference)	2.44 (0.60-9.95)	3.76 (1.06-13.42)	0.04
HMW adiponectin				
Range (μg/mL)	≤ 1.05 for men and	1.06-2.56 for men and	> 2.56 for men and	

	≤ 2.37 for women	2.38-4.30 for women	> 4.30 for women	
No. cases/controls	17/60	37/58	36/59	
OR (95% CI)	1.00 (reference)	2.39 (1.18-4.86)	2.38 (1.15-4.93)	0.03
Multivariable OR (95% CI)[b]	1.00 (reference)	2.77 (1.26-6.06)	3.41 (1.50-7.73)	< 0.01
Multivariable OR (95% CI)[c] + alcohol and coffee consumption, ALT level	1.00 (reference)	2.89 (0.76-11.07)	3.85 (0.99-15.05)	0.06

NOTE: HMW=high-molecular-weight, ALT=alanine aminotransferase

[a]Linear trends were tested using the exposure categories as ordinal variables.

[b]Adjusted for body mass index (<18.5, 18.5-21.9, 22.0-24.9, ≥25.0 kg/m^2) and diabetes (yes or no).

[c]Further adjusted for alcohol consumption (never, past, <150, 150 to <450, ≥450 g/week ethanol), coffee consumption (almost never, 1 time/week to <1 cup/day, ≥1 cup/day), and ALT level (<30, 30-69, ≥70 IU/L).

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of primary liver cancer associated with plasma adiponectin levels by subgroups

		Total adiponectin		HMW adiponectin	
		Low	High	Low	High
	Range (μg/mL)	≤ 4.33 for men and ≤ 6.12 for women	> 4.33 for men and > 6.12 for women	≤ 1.59 for men and ≤ 2.74 for women	> 1.59 for men and > 2.74 for women
All participants					
	No. cases/controls	30/89	60/88	36/89	54/88
	Mutivariable OR (95% CI)[a]	1.00 (reference)	3.08 (1.62-5.86)	1.00 (reference)	2.03 (1.09-3.78)
Sex					
Men	No. cases/controls	24/61	38/61	30/61	32/61
	Mutivariable OR (95% CI)[a]	1.00 (reference)	2.43 (1.11-5.34)	1.00 (reference)	1.27 (0.60-2.65)
Women	No. cases/controls	6/28	22/27	6/28	22/27

	Mutivariable OR (95% CI)[a]	1.00 (reference)	9.90 (1.96-50.14)	1.00 (reference)	9.93 (1.97-50.18)
	P value[b]	0.27		0.05	
Hepatitis virus infectious status					
HBV	No. cases/controls	5/11	6/10	6/11	5/10
	Mutivariable OR (95% CI)[a]	1.00 (reference)	1.46 (0.18-11.48)	1.00 (reference)	1.15 (0.12-10.70)
HCV	No. cases/controls	25/78	54/78	30/78	49/78
	Mutivariable OR (95% CI)[a]	1.00 (reference)	3.18 (1.58-6.39)	1.00 (reference)	2.13 (1.08-4.18)
	P value[b]	0.87		0.97	
Body mass index					
< 25.0 kg/m^2	No. cases/controls	15/66	41/80	20/68	36/78
	Mutivariable OR (95% CI)[c]	1.00 (reference)	3.01 (1.42-6.38)	1.00 (reference)	1.95 (0.97-3.89)
≥ 25.0 kg/m^2	No. cases/controls	15/23	19/8	16/21	18/10
	Mutivariable OR (95% CI)[c]	1.00 (reference)	3.88 (1.10-13.70)	1.00 (reference)	2.60 (0.72-9.44)

	P value[b]	0.41		0.47	
Diabetes					
No	No. cases/controls	17/63	43/75	21/64	39/74
	Mutivariable OR (95% CI)[c]	1.00 (reference)	3.14 (1.45-6.80)	1.00 (reference)	1.98 (0.96-4.06)
Yes	No. cases/controls	13/26	17/13	15/25	15/14
	Mutivariable OR (95% CI)[c]	1.00 (reference)	3.28 (0.89-12.08)	1.00 (reference)	1.90 (0.52-6.96)
	P value[b]	0.73		0.84	

NOTE: HBV=hepatitis B virus, HCV=hepatitis C virus, HMW=high-molecular-weight

[a]Adjusted for body mass index and diabetes using a conditional logistic model.

[b]Statistical interaction between adiponectin levels and stratified variables was tested with a likelihood ratio test.

[c]We used an unconditional logistic model adjusted for age, sex, public health center area, fasting status at blood collection, hepatitis virus infectious status, baseline menopausal status, body mass index, and diabetes except for stratified variable.