

Plasma Levels of Adiponectin and Primary Liver Cancer Risk in Middle-Aged Japanese Adults with Hepatitis Virus Infection: A Nested Case–Control Study

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Abstract

Background: Excess body weight is an independent risk factor for primary liver cancer, and the role of adiponectin in the pathogenesis of obesity-related malignancies is a focus of research interest. Few prospective studies have examined the association between circulating adiponectin and liver cancer risk, so we investigated this association in a nested case–control study of a population-based prospective cohort in Japan.

Methods: From 18,628 target participants of ages 40 to 69 years who returned the baseline questionnaire and provided blood samples, we selected those with either hepatitis B or C virus infection at baseline ($n = 1,544$). Among these, 90 were newly diagnosed with primary liver cancer from 1993 through 2006, and matched to 177 controls. The ORs of liver cancer development based on plasma levels of adiponectin were estimated with a conditional logistic regression model.

Results: Median values of total and high-molecular-weight (HMW) adiponectin tended to be higher in the patients with liver cancer, and plasma levels of adiponectin were positively associated with liver cancer risk. Body mass index– and diabetes-adjusted ORs for the highest tertile of total and HMW adiponectin levels versus the lowest were 3.30 [95% confidence interval (CI), 1.45–7.53; $P_{\text{trend}} < 0.01$] and 3.41 (95% CI, 1.50–7.73; $P_{\text{trend}} < 0.01$), respectively. There was no effect modification by body mass index and diabetes.

Conclusions: Higher plasma adiponectin levels were associated with an increased risk of primary liver cancer in middle-aged Japanese adults with hepatitis virus infection.

Impact: Circulating adiponectin levels may be a risk marker for primary liver cancer. *Cancer Epidemiol Biomarkers Prev*; 22(12); 2250–7. ©2013 AACR.

Introduction

Accumulating epidemiologic evidence suggests that excess body weight is an independent risk factor for primary liver cancer (1, 2). Even in Japan, where the prevalence of overweight and obesity is lower than that in Western countries (3) and the main cause of liver cancer is chronic hepatitis C virus (HCV) infection (4), overweight or obesity seem to increase the risk of liver cancer

(5). We have also reported that high body mass index (BMI) is associated with an increased risk of primary liver cancer, irrespective of hepatitis virus infection (6). The causal association between excess body weight and liver cancer development is probably connected with insulin resistance (7, 8). However, the underlying mechanism by which excess body weight promotes liver cancer development is still not fully understood.

The role of adiponectin in the pathogenesis of obesity-related malignancies is a focus of research interest. Adiponectin is a physiologically active polypeptide secreted by adipose tissues and its circulating levels are inversely associated with obesity (9). Earlier experimental studies suggested that adiponectin played a protective role in carcinogenesis via insulin sensitization, antiproliferation, anti-inflammation, and angiogenesis regulation (10), and data supported epidemiologic evidence that adiponectin levels were inversely associated with the risk of obesity-related malignancies, such as breast, colorectal, endometrium, and prostate cancers (10). These results also suggested that elevated levels of adiponectin would be associated with a reduced risk of primary liver cancer linked with obesity, and that hyperadiponectinemia

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might suppress liver tumorigenesis (11). Indeed, experimental studies indicated that adiponectin treatment increased apoptosis of hepatocellular carcinoma, the most common form of primary liver cancer, and inhibited its proliferation (12, 13). However, it has been pointed out that hyperadiponectinemia reflects the progression of liver disease leading to the development of liver cancer, as the liver is the main organ of adiponectin metabolism (9, 11). A recent hospital-based cohort study showed that high serum levels of adiponectin were positively associated with the development of hepatocellular carcinoma in patients with chronic hepatitis C (14). Because there have been few prospective studies (14–16), further examination of the potential association between adiponectin and liver cancer risk is warranted.

The aim of the present study was to investigate the association between plasma adiponectin levels and primary liver cancer risk in middle-aged adults with hepatitis virus infection. We used a nested case–control design based on data from a large-scale population-based prospective cohort study in Japan.

Materials and Methods

Study population

The Japan Public Health Center–based Prospective Study (JPHC Study) is an ongoing cohort study of cancer, cardiovascular disease, and other lifestyle-related diseases. The first cohort (cohort I) started in 1990 and the second cohort (cohort II) in 1993. In cohort I, the study population included all registered Japanese residents of ages 40 to 59 years of five public health center areas, and in cohort II the study population included all residents of ages 40 to 69 years of six other areas; the study design is described elsewhere (17). We investigated the hepatitis B surface antigen (HBsAg) and anti-HCV antibody (anti-HCV) measurements from the cohort II data. Our study was approved by the Institutional Review Board of the National Cancer Center (Tokyo, Japan).

In cohort II (1993–1994), 56,542 participants (response rate: 82%) answered a baseline questionnaire in sociodemographic characteristics, medical history, smoking and drinking habits, diet, and so on. Of the questionnaire respondents, 37% voluntarily provided 10 mL of blood in health checkups during the baseline survey (1993–1995). The blood samples were divided into plasma and buffy layers and preserved at -80°C until analysis. Study participants were informed of the objectives and methods of the study in writing, and those who responded to the questionnaire and donated blood were regarded as having given informed consent to participate. Of these, we selected only those who had no history of cancer at baseline and had provided data on basic characteristics, leaving us with a total of 18,628 participants (6,401 men and 12,227 women).

Follow-up

Participants were followed up from the date of blood collection until December 31, 2006. Residence status and

survival were confirmed annually through residential registers in the respective public health center areas. During the follow-up period, 0.3% ($n = 49$) of participants were lost to follow-up.

Incident cases of primary liver cancer were identified by active patient notification from major hospitals in the study area and data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (code: C22.0; ref. 18). In our cancer registry system, the proportion of cases for which information was available from death certificates only was 4.7%.

Selection of cases and controls

From the 18,628 participants, we selected those with either hepatitis B virus (HBV) or HCV infection at baseline ($n = 1,544$). Plasma samples were screened for HBsAg by reversed passive hemagglutination with a commercial kit (Institute of Immunology Co., Ltd.) and for anti-HCV with a third-generation immunoassay (Lumipulse II Ortho HCV; Ortho-Clinical Diagnosis K.K.; ref. 19). In this study, positivity for HBsAg was regarded as indicating HBV infection, and positivity for anti-HCV as indicating HCV infection (20). Up to the end of the study period after blood collection, we identified 91 new cases of primary liver cancer among the 1,544 participants. For each patient newly diagnosed with liver cancer, we selected two controls at random from among the participants with no history of liver cancer when the diagnosis was made. Controls were matched to each patient in terms of age (within 5 years), sex, public health center area, fasting status at blood collection, baseline menopausal status (for women), and hepatitis virus infection status (HBV/HCV). No appropriate matched controls were found for 1 patient, and only 1 matched control for each of 3 other patients, so a total of 90 patients and 177 controls were included in the present analysis.

Laboratory assay for adiponectin

Circulating adiponectin levels have been reported to be stable over time and to have high reliability (21–23), so this biologic marker is likely to be useful in epidemiologic studies. From the blood samples collected at baseline, plasma levels of total adiponectin and high-molecular-weight (HMW) adiponectin, which is considered to be the active form of the hormone (10), were analyzed with a Human Adiponectin ELISA Kit for Total and Multimers (Sekisui Medical, Co., Ltd.) by the ELISA method. Cases and matched controls were assayed in the same batch. The minimum detection level was $0.39 \mu\text{g}/\text{mL}$ for both total and HMW adiponectin. For the assays, inter-assay and intra-assay coefficients of variation from the company's quality control samples were $\leq 3.9\%$ and $\leq 5.7\%$ for total adiponectin, and $\leq 3.3\%$ and $\leq 6.2\%$ for HMW adiponectin, respectively. All samples were analyzed at a single laboratory (Mitsubishi Chemical Medience Corporation) by technicians blinded to case–control status.

Statistical analysis

All analyses were performed with STATA version 11 (STATA Corporation). All *P* values reported are two-sided, and significance level was set at $P < 0.05$.

Comparisons of the baseline characteristics between the cases and controls were made by the χ^2 or Mann–Whitney test, as appropriate. Because adiponectin levels are reportedly low in obese people and in patients with type 2 diabetes (9, 24), we confirmed whether the relation between plasma levels of total/HMW adiponectin and BMI/diabetes in the controls did not contradict existing knowledge. Spearman's rank correlation coefficients were calculated for adiponectin levels and BMI. Comparative adiponectin levels between the participants with diabetes and those without were evaluated by the Mann–Whitney test. In this study, diabetes was defined as a self-reported history of diabetes, and/or antidiabetic medication use, and/or blood glucose ≥ 5.55 mmol/L (100 mg/dL) fasting or ≥ 7.77 mmol/L (140 mg/dL) nonfasting (20).

For total and HMW adiponectin, participants were classified into sex-specific tertiles according to the frequency of distribution among the controls. Using a conditional logistic regression model, we calculated ORs and 95% confidence intervals (CI) of primary liver cancer for plasma levels of total and HMW adiponectin. Dummy variables were created for the categories of plasma adiponectin levels, and the lowest category was used as the reference category. To investigate whether adiponectin was associated with liver cancer through the pathway for insulin resistance (24), the ORs were adjusted for BMI (<18.5, 18.5–21.9, 22.0–24.9, and ≥ 25.0 kg/m²) and diabetes (yes or no). We also adjusted for the following variables previously associated with liver cancer risk (20, 25, 26): 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 serum alanine aminotransferase (ALT) levels (<30, 30–69, ≥ 70 IU/L). Because adjustment for smoking status (a suspected risk factor for liver cancer) and vegetable and fish intake [factors previously associated with liver cancer risk (27, 28)] produced ORs that were almost identical to those without adjustment, results for these variables are not presented in this article. Linear trends for ORs were tested using the exposure categories as ordinal variables. An earlier study demonstrated that high adiponectin levels might be a proxy marker increasing the likelihood of subsequent liver cancer development (14). Therefore, we performed additional analyses after excluding 17 cases of liver cancer diagnosed in the first 3 years after blood collection because of checking for temporality. In addition, subgroup analyses were performed for 71 cases of liver cancer death where cancer development was likely to have been observed in the early follow-up period, and after limiting analysis to or excluding 53 cases of liver cancer diagnosed in the first 7 years after blood collection.

In addition, we investigated whether the association between adiponectin levels and primary liver cancer risk was modified by sex, hepatitis virus infection status (HBV/HCV), BMI (<25.0, ≥ 25.0 kg/m²), and diabetes

(yes or no). For these stratified analyses, participants were divided into two groups based on median plasma levels of total and HMW adiponectin in the controls. We used unconditional logistic regression for BMI and diabetes, and included matching factors in the multivariable models. Statistical interaction between adiponectin levels and stratified variables was tested with a likelihood ratio test.

Results

Table 1 shows the baseline characteristics of the case and control groups. The prevalence of overweight, diabetes, and high ALT levels was tended to be higher and that of daily coffee consumption was lower in the case group than in the control group. Participants in the control group tended to be light (<150 g/week ethanol) to moderate (150 to <450 g/week ethanol) drinkers. The median values of total adiponectin were statistically higher among the cases than the controls (6.16 vs. 5.11 $\mu\text{g/mL}$; $P = 0.03$) and those of HMW adiponectin were marginally higher in the case group (2.66 vs. 2.06 $\mu\text{g/mL}$; $P = 0.06$; Fig. 1). In the control group, Spearman's rank correlation coefficients of BMI with total and HMW adiponectin were -0.40 ($P < 0.01$) and -0.25 ($P < 0.01$), respectively. Total and HMW adiponectin levels were lower among the participants with diabetes than those without (median: 3.45 vs. 5.34 $\mu\text{g/mL}$, $P = 0.02$ for total adiponectin; 1.26 vs. 2.25 $\mu\text{g/mL}$, $P = 0.04$ for HMW adiponectin).

Table 2 presents the conditional logistic regression results for the association between total and HMW plasma adiponectin levels and the risk of primary liver cancer. After adjustment for BMI and diabetes, we found a statistically significant positive association between plasma adiponectin and liver cancer risk ($P_{\text{trend}} < 0.01$ for both total and HMW adiponectin). The ORs for the highest tertile of total and HMW adiponectin levels versus the lowest tertile were 3.30 (95% CI, 1.45–7.53) and 3.41 (95% CI, 1.50–7.73), respectively. The positive association remained significant for total adiponectin ($P_{\text{trend}} = 0.04$) and marginal for HMW adiponectin ($P_{\text{trend}} = 0.06$) 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 $P_{\text{trend}} = 0.10$ 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 $P_{\text{trend}} = 0.01$ 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 $P_{\text{trend}} = 0.01$ 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 two 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 (95% CI, 1.09–3.78) for HMW adiponectin. The magnitudes of association between plasma

Table 1. Selected baseline characteristics of cases and controls

Variables		Cases (n = 90) Prevalence (%)	Controls (n = 177) Prevalence (%)	P ^a
Age, y	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/wk ethanol	17.8	30.5	
	150 to <450 g/wk ethanol	14.4	19.8	
	≥450 g/wk ethanol	5.6	3.4	
Smoking status, current smoker		37.8	35.6	0.58
BMI, ≥25 kg/m ²		37.8	17.5	<0.01
Diabetes, yes ^c		33.3	23.0	0.05
Coffee consumption, ≥1 cup/d		23.3	39.0	0.01
ALT level, ≥70 IU/L		46.0	6.0	<0.01
Vegetable intake, g/d ^d		44 (24–69)	48 (27–75)	0.33
Fish intake, g/d ^d		45 (28–67)	43 (27–66)	0.78
Time from blood draw to diagnosis for the cases, y ^d		6.1 (3.6–9.5)		

^aCalculated using the χ^2 and Mann–Whitney test.

^bPositive for HBsAg was regarded as indicating HBV infection and positive for anti-HCV antibody as indicating HCV infection.

^cDiabetes was defined as a self-reported history of diabetes, and/or antidiabetic medication use, and/or blood glucose ≥ 5.55 mmol/L (100 mg/dL) fasting or ≥ 7.77 mmol/L (140 mg/dL) nonfasting.

^dMedian (interquartile range).

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 accord-

ing to hepatitis virus infection status, BMI, and diabetes showed no remarkable differences between the two 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, despite cumulating evidence that adiponectin plays a protective role in carcinogenesis. However, we do not believe that the results of our study contradict earlier findings. No epidemiologic studies

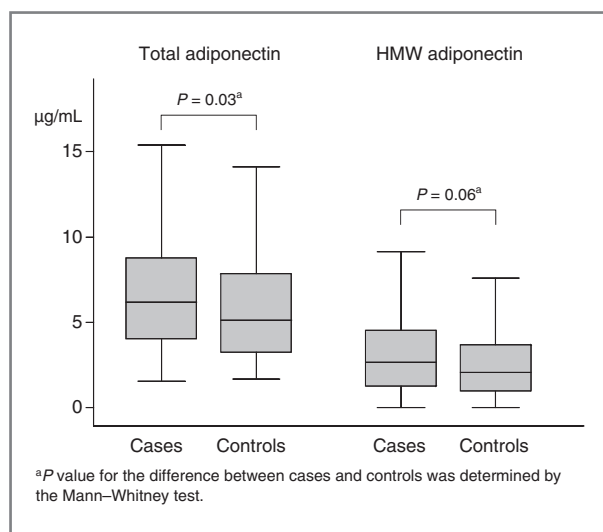


Figure 1. Box and whisker plot for plasma adiponectin levels of cases and controls.

Table 2. ORs and 95% CIs of primary liver cancer based on plasma adiponectin levels

Plasma level	Tertile			P ^a
	Low	Middle	High	
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 ≤2.37 for women	1.06–2.56 for men and 2.38–4.30 for women	>2.56 for men and >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

^aLinear trends were tested using the exposure categories as ordinal variables.
^bAdjusted for BMI (<18.5, 18.5–21.9, 22.0–24.9, ≥25.0 kg/m²) and diabetes (yes or no).
^cFurther adjusted for alcohol consumption (never, past, <150, 150 to <450, ≥450 g/wk ethanol), coffee consumption (almost never, 1 time/wk to <1 cup/d, ≥1 cup/d), and ALT level (<30, 30–69, ≥70 IU/L).

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 hepatocellular carcinoma; 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 hepatocellular carcinoma 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 anti-tumor effects against hepatocellular carcinoma by inducing apoptosis or suppressing tumor angiogenesis (12, 13), it is not unusual for the results of epidemiologic 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 seems 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 adiponectin 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 and colleagues 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; ref. 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

Table 3. ORs and 95% 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
	Multivariable 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
	Multivariable 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
	Multivariable OR (95% CI) ^a	1.00 (reference)	9.90 (1.96–50.14)	1.00 (reference)	9.93 (1.97–50.18)
	<i>P</i> ^b	0.27		0.05	
Hepatitis virus infectious status					
HBV	No. cases/controls	5/11	6/10	6/11	5/10
	Multivariable 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
	Multivariable OR (95% CI) ^a	1.00 (reference)	3.18 (1.58–6.39)	1.00 (reference)	2.13 (1.08–4.18)
	<i>P</i> ^b	0.87		0.97	
BMI					
<25.0 kg/m ²	No. cases/controls	15/66	41/80	20/68	36/78
	Multivariable 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
	Multivariable OR (95% CI) ^c	1.00 (reference)	3.88 (1.10–13.70)	1.00 (reference)	2.60 (0.72–9.44)
	<i>P</i> ^b	0.41		0.47	
Diabetes					
No	No. cases/controls	17/63	43/75	21/64	39/74
	Multivariable 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
	Multivariable OR (95% CI) ^c	1.00 (reference)	3.28 (0.89–12.08)	1.00 (reference)	1.90 (0.52–6.96)
	<i>P</i> ^b	0.73		0.84	

^aAdjusted for BMI and diabetes using a conditional logistic model.

^bStatistical interaction between adiponectin levels and stratified variables was tested with a likelihood ratio test.

^cWe 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, BMI, and diabetes except for stratified variable.

due to liver disease (including cirrhosis) seems 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 and colleagues, 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 epidemiologic 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T. Michikawa, M. Inoue, M. Iwasaki, S. Tsugane
Development of methodology: T. Michikawa, M. Inoue, M. Mizokami
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Sawada, M. Iwasaki, T. Shimazu, S. Tsugane
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Michikawa, M. Inoue, N. Sawada, M. Iwasaki, T. Yamaji, S. Tsugane
Writing, review, and/or revision of the manuscript: T. Michikawa, M. Inoue, S. Sasazuki, M. Iwasaki, T. Shimazu, T. Yamaji, S. Tsugane

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Inoue, Y. Tanaka, S. Tsugane
Study supervision: M. Inoue, S. Tsugane

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