

# The Impact of Type 2 Diabetes on the Development of Hepatocellular Carcinoma in Different Viral Hepatitis Statuses

Chong-Shan Wang,<sup>1,2</sup> Wei-Jen Yao,<sup>3</sup> Ting-Tsung Chang,<sup>4</sup> Shan-Tair Wang,<sup>5</sup> and Pesus Chou<sup>1</sup>

<sup>1</sup>Community Medicine Research Center and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan; <sup>2</sup>A-Lein Community Health Center, Kaohsiung County, Taiwan; <sup>3</sup>Department of Radiology, Division of Gastroenterology, <sup>4</sup>Department of Internal Medicine and Institute of Clinical Medicine, and <sup>5</sup>Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

## Abstract

**Background:** The risk of type 2 diabetes on the development of hepatocellular carcinoma remains inconclusive in different hepatitis statuses.

**Methods:** We prospectively followed a community-based cohort with 5,929 persons in southern Taiwan from January 1997 through December 2004, made up of 4,117 seronegative, 982 anti-hepatitis C virus-positive [HCV(+)], 696 hepatitis B surface antigen-positive [HBsAg(+)], and 134 coinfecting persons. Before the study, 546 participants had developed diabetes. Hepatocellular carcinoma diagnoses were from the National Cancer Registry.

**Results:** After 50,899 person-years of follow-up, 111 individuals had developed hepatocellular carcinoma. The highest risk of hepatocellular carcinoma, compared with seronegative individuals without diabetes, was in anti-HCV(+) individuals with diabetes [incidence rate ratio (IRR), 76.0], then coinfecting (IRR, 46.0), anti-HCV(+) without diabetes (IRR, 26.1), HBsAg(+) with diabetes (IRR, 21.4), and seronegative with diabetes (IRR, 7.2;  $P < 0.001$ ).

Anti-HCV(+) ( $n = 132$ ) and seronegative individuals ( $n = 352$ ) with diabetes had a higher cumulative incidence rate of hepatocellular carcinoma than those without diabetes (log-rank test,  $P < 0.001$ ). Multivariate Cox proportional hazards analysis showed that gender, age, body mass index  $\geq 30$ , HBsAg(+) [hazards ratio (HR), 12.6], anti-HCV(+) (HR, 18.8), coinfection (HR, 25.9), and diabetes [HR, 2.7; 95% confidence interval (95% CI), 1.7-4.3] were independent predictors of hepatocellular carcinoma ( $P < 0.05$ ). After stratifying hepatitis status in multivariate Cox analysis, diabetes was significant for seronegative (HR, 5.4; 95% CI, 1.7-17.1) and anti-HCV(+) individuals (HR, 3.1; 95% CI, 1.7-5.4). Body mass index  $\geq 30$  was significant for HBsAg(+) individuals (HR, 3.3; 95% CI, 1.3-8.1).

**Conclusion:** Type 2 diabetes is a strong independent predictor of hepatocellular carcinoma in anti-HCV(+) and seronegative individuals but not in HBsAg(+) individuals. (Cancer Epidemiol Biomarkers Prev 2009;18(7):2054-60)

## Introduction

Hepatocellular carcinoma is the fifth most common cancer in the world and the third most common cause of cancer mortality (1). The burden of hepatocellular carcinoma is not distributed evenly in the world; it is highly related to the regional prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, HBV/HCV coinfection, and alcohol consumption. Otherwise, male gender, smoking, obesity, and environmental aflatoxin are also associated with the development of hepatocellular carcinoma (1-4). Although HBV vaccination has been implemented in many countries in recent decades, the incidence of hepatocellular carcinoma has still increased in low-rate areas such as North America, Europe, and Australia (1, 2), and even in

high-rate regions such as Japan and Taiwan (5). In the United States, the fastest growing cancer-related death rate is from hepatocellular carcinoma (1). Most of the secular trend of increasing hepatocellular carcinoma incidence is reflected in the increase in HCV-related hepatocellular carcinoma (1, 2, 5). However, the causes of this increasing incidence are not well understood.

Recently, the prevalence of type 2 diabetes has rapidly increased in most countries (6, 7) and is highly suspected to be associated with hepatocellular carcinoma (1, 3, 8-16), but some refute the association (17, 18). Most of the positive studies, except for some cohort studies (11, 13-16), were case-control (9) or cross-sectional studies or had a short-term study period (16). In addition, their study populations consisted primarily of seronegative [HBV(-) and HCV(-)] individuals. The role of type 2 diabetes on the development of hepatocellular carcinoma among different hepatitis statuses remains undetermined. A-Lein, a township in southern Taiwan, has a high prevalence of HBV infection (11.8%), HCV infection (15%), and HBV/HCV coinfection (2%) in adults >35 years old (19). Therefore,

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**Requests for reprints:** Pesus Chou, Community Medicine Research Center and Institute of Public Health, National Yang Ming University, Shih-Pai, Taipei 112, Taiwan. Phone: 886-2-2822-9695; Fax: 886-2-2820-1461. E-mail: pschou@ym.edu.tw  
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our main goal was to use the special characteristics of this community to evaluate the risks of type 2 diabetes of developing hepatocellular carcinoma in different hepatitis statuses.

## Materials and Methods

**Background Description.** A-Lein Township in southern Taiwan's Kaohsiung County has a population of about 31,000. Since January 1996, we have been conducting a population-based and community-wide screening for HBV and HCV infection for residents  $\geq 35$  y old because of the township's high hepatoma mortality rate, which is more than double that of Taiwan as a whole. Taiwan may have one of the highest hepatocellular carcinoma mortality rates in the world (19). Intensive health promotion activities for hepatitis and hepatocellular carcinoma screening were held to inform the community residents. Villagers came of their own volition, consented to the collection of blood samples, and agreed to answer questionnaires for further study. We enrolled 6,023 study participants, a response rate of 68.4% (6,023 of 8,800); all had complete datasets for viral hepatitis and diabetes statuses (19). We excluded 88 individuals who died in 1996 and 1997, and 6 who had been diagnosed with hepatocellular carcinoma before the screening. The remaining 5,929 participants were prospectively followed for 8 y, until December 31, 2004. Participants with HBV or HCV infection were called annually for liver function,  $\alpha$ -fetoprotein tests, and an abdominal ultrasonographic screening for small hepatocellular carcinoma in the A-Lein Community Health Center or in the hospitals where they were regularly followed up. Any participant found to have cirrhosis was asked to return for a recheck every 6 mo. Those without HBV or HCV infection were not called, but some might have voluntarily come back for an abdominal ultrasonographic screening. Anyone screened who had a suspected liver tumor was referred to a medical center for confirmation. Abdominal ultrasonography was done every other week in the A-Lein Community Health Center by one experienced radiologist (WJY) specially trained in ultrasonography. A real-time ultrasound scanner (Tosbee; Toshiba) equipped with a 3.5 MHz convex transducer was used. All the studied participants were assumed to be anti-HIV(-) because there were and still are no anti-HIV(+) persons reported in A-Lein. The study was approved by the Research Committee of the Kaohsiung County Bureau of Health.

Every participant's diabetes status was confirmed before the start of the study. Type 2 diabetes was defined according to the 1997 American Diabetes Association criteria as having a fasting blood sugar level  $\geq 126$  mg/dL, a nonfasting glucose level  $\geq 200$  mg/dL, or using hypoglycemic drugs prescribed by a physician before or at the time of the study.

Hepatitis B surface antigen (HBsAg) and anti-HCV were identified at the Tainan Blood Center of the Chinese Blood Service Foundation. HBsAg was determined using the Murex HBsAg (Version I) enzyme immunoassay method. Anti-HCV was tested using the third-generation Murex anti-HCV enzyme immunoassay method, which contains antigen from the HCV core, nonstructural 3

(NS3), NS4, and NS5 regions. HBsAg(+) or anti-HCV(+) cases were confirmed using a duplication test according to the standard procedures to exclude false-positive cases. In the present study, HBsAg(+) is defined as HBsAg(+)/anti-HCV(-), anti-HCV(+) is defined as HBsAg(-)/anti-HCV(+), coinfection is defined as HBsAg(+)/anti-HCV(+), and seronegative is defined as HBsAg(-)/anti-HCV(-).

Demographic (age, gender, education level, occupation) and health behavior (cigarette smoking and alcohol consumption habits) data were obtained using a questionnaire administered to all participants by physicians or registered nurses. Anthropometric characteristics (weight and height) were checked by registered nurses before the questionnaires were filled in. Alcohol consumption was subclassified as frequent, occasional, or rare. For the present study, frequent alcohol consumption meant an average of  $>1$  drink containing the equivalent of 10 g pure alcohol per day in the 6 mo before the interview. Also, a participant without a smoking habit meant someone who had never smoked or who had quit smoking for  $>6$  mo.

**Outcome Confirmation.** Although most participants with HBV or HCV infection were called for regular abdominal ultrasonography screenings for small hepatocellular carcinoma, our final confirmation of hepatocellular carcinoma was only through matching this cohort dataset with the ICD-9-CM = 155.0 (primary liver carcinoma) dataset in the National Cancer Registry of the Department of Health, which in Taiwan collects all cancer data and requires that all hospitals report all cancer diagnoses to the National Cancer Registry. In Taiwan, about 98% of the residents have national health insurance, and any case of cancer is required to be reported to the National Cancer Registry. Therefore, any participant who relocated to another area and was diagnosed with hepatocellular carcinoma would have been picked up by this study.

**Statistical Analysis.** The person-years of follow-up for each participant were calculated from January 1, 1997, to the year in which hepatocellular carcinoma was diagnosed (from the National Cancer Registry), the year of death (from the Taiwan Department of Health), or until the end of the study (December 31, 2004). Participants free of hepatocellular carcinoma who died during the study were censored. Incidence rates of hepatocellular carcinoma were calculated by dividing the person-years of follow-up into the number of incident hepatocellular carcinoma cases. Nelson-Aalen cumulative hazard estimates and the log-rank test were used to compare the cumulative incidence of hepatocellular carcinoma between different risk factors, such as viral hepatitis status and diabetes status. A Cox proportional hazards model analysis was used to estimate the relative risk for hepatocellular carcinoma. Hazard ratios (HR) and incidence rate ratios describe the strength of the association. The data were analyzed using Stata software (20). Statistical significance was set at  $P < 0.05$ .

## Results

There were 5,929 participants in this community-based cohort: 4,117 seronegative (69.4%), 982 anti-HCV(+) (16.6%), 696 HBsAg(+) (11.7%), and 134 coinfecting individuals (2.3%). The mean prevalence of type 2 diabetes

**Table 1. Baseline data in the community cohort for the development of hepatocellular carcinoma in A-Lein, Taiwan (n = 5929)**

	Seronegative (n = 4,117)	Anti-HCV(+) (n = 982)	HBsAg(+) (n = 696)	Co-infection (n = 134)
Mean age (y)	53.9 ± 12.8	58.1 ± 11.5	49.3 ± 11.0	56.3 ± 11.3
Age onset of hepatocellular carcinoma (y)	69.0 ± 13.2	65.6 ± 7.3	55.6 ± 11.5	64.8 ± 14.3
Basic data	No. (%)	No. (%)	No. (%)	No. (%)
Gender				
Male	1,707 (41.5)	449* (45.7)	357* (51.3)	66 (49.2)
Female	2,420 (58.5)	533 (54.3)	339 (48.7)	68 (50.8)
Education level				
<9 y	3,087 (75.0)	880* (89.6)	466 (67.0)	114 (85.1)
≥9 y	1,030 (25.0)	102 (10.4)	230 (33.0)	20 (14.9)
Smoking habit				
Yes	769 (18.7)	224* (22.8)	174* (25.0)	39* (29.1)
No	3,348 (81.3)	758 (77.2)	522 (75.0)	95 (70.9)
Frequent alcohol consumption				
Yes	191 (4.6)	59 (6.0)	35 (5.0)	12* (91.0)
No	3,926 (95.4)	923 (94.0)	661 (95.0)	122 (91.0)
BMI (kg/m <sup>2</sup> )				
BMI ≥30	556 (13.5)	143 (14.6)	92 (13.2)	19 (14.2)
BMI <30	3,561 (86.5)	839 (85.4)	604 (86.8)	115 (85.8)
Type 2 diabetes before study				
Yes	352 (8.6)	132* (13.4)	47 (6.8)	15 (11.2)
No	3,765 (91.4)	850 (86.6)	649 (93.3)	119 (88.8)

\*More prevalent than in the seronegative group ( $P < 0.05$ ).

was 9.2% (546/5,929) in the cohort: 13.4% for anti-HCV(+), 11.2% for coinfecting, 8.6% for seronegative, and 6.8% for HBsAg(+) individuals. Compared with seronegative participants, those who were anti-HCV(+) were more likely to be older and male, and to have lower educational levels (<9 years), a smoking habit, and type 2 diabetes [odds ratio, 1.7; 95% confidence interval (95% CI), 1.3-2.1;  $P < 0.001$ ], and those coinfecting were more likely to be habitual smokers and frequent consumers of alcohol (Table 1). Those who were anti-HCV(+) were more often comorbid with type 2 diabetes than those who were HBsAg(+) (odds ratio, 2.1; 95% CI, 1.5-3.1;  $P < 0.001$ ). There was no significant difference in body mass index (BMI) level or alcohol consumption between seronegative, HBsAg(+) and anti-HCV(+) participants (Table 1).

During the 8 years of follow-up, 111 participants developed hepatocellular carcinoma. Of these 111 individuals, 11.7% (13) were seronegative, 21.6% (24)

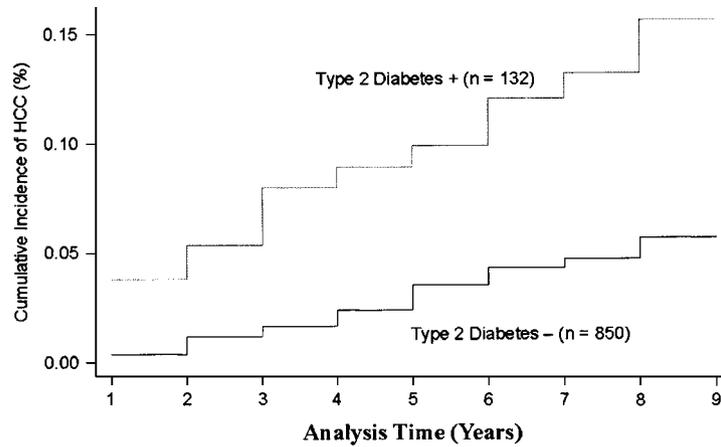
were HBsAg(+), 55.9% (62) were anti-HCV(+), and 10.8% (12) were coinfecting. In the unadjusted Cox model analysis, those who were older (≥65 years), were male, were habitual smokers, and consumed alcohol frequently were more likely to develop hepatocellular carcinoma ( $P < 0.05$ ). Those with type 2 diabetes were more likely to develop hepatocellular carcinoma than those without (HR, 3.2; 95% CI, 2.0-4.9;  $P < 0.01$ ). Those who were HBsAg(+) (HR, 2.1), anti-HCV(+) (HR, 6.7), or coinfecting (HR, 5.4) were more likely than their counterparts to develop hepatocellular carcinoma (Table 2). A BMI ≥30 was not a significant risk factor for hepatocellular carcinoma. A multivariate Cox proportional hazards model analysis, after adjusting for demographic factors, health behaviors, BMI, hepatitis status, and diabetes status before the study, showed that male gender, older age, HBsAg(+) (HR, 12.6; 95% CI, 6.4-25.0), anti-HCV(+) (HR, 18.8; 95% CI, 10.3-34.2), coinfection (HR, 25.9; 95% CI, 11.8-57.0), type 2 diabetes (HR, 2.7; 95% CI,

**Table 2. Unadjusted and multivariate Cox hazards model for hepatocellular carcinoma in a community cohort for 8 y in A-Lein, Taiwan, 1997-2004**

Variables	All participants (N = 5929)	
	Unadjusted Cox Model	Multivariate Cox Model
	HR (95% CI)	HR (95% CI)
Gender (male vs. female)	3.3 (2.2-5.0)*	3.3 (2.0-5.0)*
Age (≥65 vs. < 65 y)	3.7 (2.6-5.4)*	3.8 (2.6-5.6)*
HBsAg(+)	2.1 (1.3-3.2)*	12.6 (6.4-25.0)*
Anti-HCV(+)	6.7 (4.6-9.8)*	18.8 (10.3-34.2)*
Coinfection	5.4 (3.0-9.9)*	25.9 (11.8-57.0)*
Type 2 diabetes before study	3.2 (2.0-4.9)*	2.7 (1.7-4.3)*
BMI (≥30 vs. <30)	1.4 (0.8-2.3)	1.7 (1.02-2.8) †
Smoking habit	2.0 (1.3-3.0)*	1.0 (0.6-1.6)
Frequent alcohol consumption	2.1 (1.1-3.9) †	1.2 (0.6-2.3)

\* $P < 0.001$ .

† $P < 0.05$ .



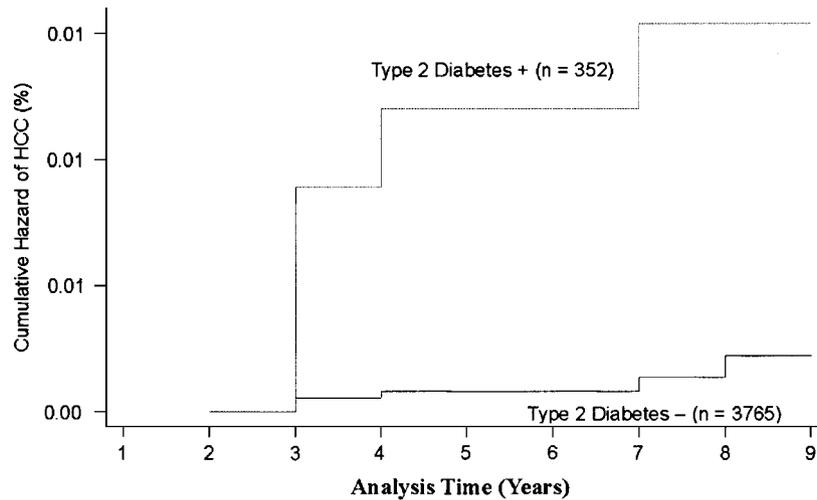
Duration(year)	1	2	3	4	5	6	7	8
Diabetes -	3/850	10/847	14/831	20/818	29/797	35/772	38/747	45/723
Diabetes +	5/132	7/127	10/115	11/106	12/100	14/93	15/88	17/83

**Figure 1.** Nelson-Aalen cumulative hazard estimates of the development of hepatocellular carcinoma (HCC) and type 2 diabetes in the anti-HCV(+) community cohort ( $n = 982$ ) from 1997 to 2004 in A-Lein, Taiwan (log-rank test,  $P = 0.0014$ ).

1.7-4.3), and BMI  $\geq 30$  (HR, 1.7; 95% CI, 1.02-2.8) were independent predictors for the development of hepatocellular carcinoma ( $P < 0.05$ ). A smoking habit and frequent alcohol consumption were not significant factors (Table 2).

The Nelson-Aalen cumulative hazard (CH) estimates for the development of hepatocellular carcinoma

showed that anti-HCV(+) individuals with diabetes ( $n = 132$ ) had a higher CH of hepatocellular carcinoma (0.1561) than those without diabetes ( $n = 850$ ; CH, 0.0567; log-rank test,  $P = 0.0014$ ; Fig. 1). Seronegative individuals with diabetes ( $n = 352$ ) also had a higher CH of hepatocellular carcinoma (0.0154) than those without



Duration(year)	1	2	3	4	5	6	7	8
Diabetes -	0/3765	0/3765	2/3735	3/3705	3/3669	3/3621	5/3541	8/3541
Diabetes +	0/352	0/352	3/336	4/323	4/310	4/305	5/298	5/287

**Figure 2.** Nelson-Aalen cumulative hazard estimates of the development of hepatocellular carcinoma (HCC) and type 2 diabetes in the seronegative community cohort ( $n = 4117$ ) from 1997 to 2004 in A-Lein, Taiwan (log-rank test,  $P < 0.001$ ).

**Table 3. Cox proportional hazards model for the hepatocellular carcinoma in a community cohort, stratified by viral hepatitis status, in A-Lein, Taiwan, from 1997-2004**

	Seronegative (n = 4,117)	Anti-HCV(+) (n = 982)	HBsAg(+) (n = 696)	Coinfection (n = 134)
Number of participants (N = 5,929)				
Risk factors	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Gender (male vs. female)	22.9 (2.8-183.8)*	2.3 (1.3-4.1)*	3.8 (1.1-12.8)*	3.1 (0.8-13.0)
Age (≥65 vs. <65 y)	10.4 (2.8-38.9)*	3.0 (1.8-5.0)*	3.8 (1.5-9.1)*	5.3 (1.6-17.0)*
Smoking habit	0.3 (0.1-1.4)	1.1 (0.6-2.0)	1.9 (0.8-4.8)	1.1 (0.3-4.4)
Alcohol consumption	3.9 (1.01-14.8) <sup>†</sup>	1.1 (0.4-2.7)	1.1 (0.3-3.9)	-
BMI (≥30 vs. <30)	2.1 (0.4-9.5)	1.0 (0.5-2.2)	3.3 (1.3-8.1) <sup>†</sup>	1.2 (0.3-6.2)
Diabetes before study	5.4 (1.7-17.1)*	3.1 (1.7-5.4)*	1.3 (0.3-5.6)	0.6 (0.1-4.9)

NOTE: After adjusting for gender (male vs. female), age (≥65 vs. <65 y), smoking habit (yes vs. never or quit in the 6 mo), alcohol consumption (frequent vs. occasional or rare), BMI (≥30 vs. <30), and diabetes status before the study (yes vs. no).

\* $P < 0.01$ .

<sup>†</sup> $P < 0.05$ .

diabetes ( $n = 3765$ ; CH, 0.0022; log-rank test,  $P < 0.001$ ; Fig 2).

A multivariate Cox proportional hazards model, after adjusting for the same variables listed in Table 2 in different viral hepatitis statuses, showed that type 2 diabetes (HR, 5.4; 95% CI, 1.7-17.1) and frequent alcohol consumption (HR, 3.9; 95% CI, 1.01-14.8) were independent predictors in seronegative participants ( $n = 4,117$ ). Type 2 diabetes (HR, 3.1; 95% CI, 1.7-5.4) was a significant predictor in anti-HCV(+) participants ( $n = 982$ ; Table 3). Otherwise, older age was significant in all hepatitis statuses, and male gender was significant in those who were seronegative and those with HCV and HBV infection. BMI ≥30 was significant for HBsAg(+) participants (HR, 3.3; 95% CI, 1.3-8.1) but was not significant for seronegative, anti-HCV(+), and coinfecting participants. Habitual smoking was not significant for all hepatitis statuses.

## Discussion

We made several important findings in this 8-year community-based cohort study with a high prevalence of HCV, HBV, and coinfection. First, type 2 diabetes was an independent predictor for the development of hepatocellular carcinoma (Table 2), even after adjusting for other major risk factors of hepatocellular carcinoma, such as age, gender, HBV, HCV, coinfection, obesity (BMI ≥30), and frequent alcohol consumption (1-4). Second, the effect of diabetes on the increasing risk of hepatocellular carcinoma was mainly in seronegative (HR, 5.4) and anti-HCV(+) participants (HR, 3.1) but not in HBsAg(+) participants, based on a multivariate Cox hazards model analysis for different viral hepatitis statuses. Third, HCV infection (HR, 18.8) had much higher risk for developing hepatocellular carcinoma than HBV infection (HR, 12.6), even after adjusting for related risk factors (Table 2). In addition, anti-HCV(+) individuals with diabetes had a 3 to 4 times higher risk than those with HBV infection or those who were anti-HCV(+) without diabetes.

Although hepatocellular carcinoma is associated with diabetes (1), our previous study (21) showed that anti-HCV(+) individuals with a fatty liver, identified using ultrasonography, have a higher prevalence of type 2 diabetes than those with chronic hepatitis, cirrhosis, and hepatoma. Moreover, those with HCV have a 70% higher incidence risk than seronegative individuals of develop-

ing type 2 diabetes (22), which implies that most anti-HCV(+) individuals had type 2 diabetes before the cirrhotic stage and might have had a long-term diabetes status before the diagnosis of hepatocellular carcinoma. Therefore, this indicates a temporal relationship between type 2 diabetes and hepatocellular carcinoma and further implies that type 2 diabetes may promote hepatocarcinogenesis.

In the current study, type 2 diabetes was an independent predictor of hepatocellular carcinoma in anti-HCV(+) and seronegative individuals but not in HBV(+) individuals. This result not only confirms past findings that type 2 diabetes is associated with hepatocellular carcinoma (3, 8-16), but also provides new evidence that type 2 diabetes produces different relative risks for the development of hepatocellular carcinoma in various viral hepatitis statuses: the highest in seronegative (HR, 5.4), lower in anti-HCV(+) alone (HR, 3.1), and not significant in HBV or coinfection. This finding may explain the conflicting findings about the association between type 2 diabetes and hepatocellular carcinoma in other studies: a negative or mild association in regions with a high prevalence of HBV infection but an increasing risk in regions with a low prevalence of HBV infection. There is, for example, a negative association reported in a study with a high prevalence of HBV infection in Taiwan (17), a mild association (HR, 1.86) reported in studies with moderate HBV infection (5-6%; refs. 1, 10), and a moderate to strong association (2-3 times higher) reported in studies with more seronegative subjects and HCV-related infection (1, 11, 15). Among seronegative subjects, the relative risk of type 2 diabetes (HR, 5.4) for hepatocellular carcinoma is even higher than the well-known risk factor of frequent alcohol consumption (HR, 3.9) for hepatocellular carcinoma (1, 2). Because the prevalence of type 2 diabetes has greatly increased in recent decades in most countries (6, 7), this finding explains, in part, the increasing incidence of hepatocellular carcinoma in the world, especially in the developed countries, in which hepatocellular carcinoma is found primarily in HCV-infected and seronegative individuals (1, 2).

Why type 2 diabetes is not a risk factor for HBV-related hepatocellular carcinoma is not very clear, but it

may be related to different mechanisms of hepatocarcinogenesis between HCV and HBV. Hepatocellular carcinoma in seronegative individuals or HCV-related hepatocellular carcinoma may progress from hepatic fibrosis, steatohepatitis, and cirrhosis, all three of which may be enhanced by long-term insulin resistance or diabetes status (1, 11, 23, 24). HBV-related hepatocellular carcinoma, however, except when caused by HBV-induced cirrhosis, may occur in a noncirrhotic liver and result from a combination of different interacting effects, such as the integration of HBV DNA and the *trans*-acting activity of viral proteins with the host cell genome (25). Second, in another study (5), HBV-related hepatocellular carcinoma had at least a 10-year earlier onset than hepatocellular carcinoma in seronegative individuals and HCV-related hepatocellular carcinoma because most of them were infected with HBV earlier than with HCV (5). However, in the present study, the ages of onset were 55 years old in HBV-related hepatocellular carcinoma, 65 years old in HCV-related hepatocellular carcinoma, and 69 years old in seronegative individuals (Table 1). Earlier onset in HBV-related hepatocellular carcinoma, which implies earlier mortality, may preclude the possibility of developing type 2 diabetes because the mean age of type 2 diabetes onset was 56.8 years in Taiwan (7, 22). Obesity is a predictor for HBV-related hepatocellular carcinoma (Table 3) and a well-documented risk factor for type 2 diabetes. Therefore, whether the negative association between type 2 diabetes and HBV-related hepatocellular carcinoma might be changed if the prevalence of obesity and type 2 diabetes were increased and the age of diabetes onset were younger requires further study.

The mechanism of type 2 diabetes related to the development of hepatocellular carcinoma is not clear, but the following pathways may be possible. First, high levels of insulin or blood sugar in type 2 diabetes are associated with nonalcoholic fatty liver disease. Long-term nonalcoholic fatty liver disease increases the progression of chronic liver injury to severe hepatic fibrosis and nonalcoholic steatohepatitis by increasing cell turnover, thereby greatly increasing the risk of cryptogenic cirrhosis and hepatocellular carcinoma (1, 11, 23). Moreover, type 2 diabetes produces a synergistic effect on liver fibrosis progression in patients with HCV infection (24) and, therefore, increases the risk of hepatocellular carcinoma. Second, liver damage may be exacerbated by oxidative stress and telomere shortening caused by long-term diabetes (26). Telomere shortening limits the proliferative capacity and induces DNA damage, replicative senescence, apoptosis, and chromosomal instability in hepatocytes (1, 26). Third, increased insulin levels also stimulate cell growth and DNA synthesis, both of which are involved in carcinogenesis and neoplastic differentiation, by decreasing apoptosis and increasing mitogenesis (27, 28). Otherwise, increased levels of insulin-like growth factors or other inflammatory cytokines in diabetic patients might be tumorigenic (27-29). Whether the duration of type 2 diabetes and the quality of diabetes control can influence the development of hepatocellular carcinoma requires further study.

HBV and HCV infection are two well-documented etiologies for hepatocellular carcinoma, but which one has the higher risk is controversial. In some countries, HBV rather than HCV infection created a higher risk of hepatocellular carcinoma (4). On the other hand, HCV rather than HBV infection created a higher risk of hepatocellular carcinoma in other countries (30, 31). The present community-based cohort with simultaneously hyperendemic HBV and HCV infection provided a good opportunity to compare the risks of these two major etiologies for hepatocellular carcinoma; it showed that HCV infection had the higher hazards ratio for developing hepatocellular carcinoma. In the present study, anti-HCV(+) individuals without diabetes did not have a significantly higher risk than HBsAg(+) individuals, but the risk significantly increased if anti-HCV(+) individuals had diabetes. This implies that HCV rather than HBV infection creates a higher risk of hepatocellular carcinoma because an HCV-infected individual has a higher risk of developing type 2 diabetes, and that the comorbidity of HCV infection and diabetes greatly increases the risk of hepatocellular carcinoma. The present study provides important implications for public health and clinical practice: that, globally, type 2 diabetes will be an important risk factor for hepatocellular carcinoma, and that the trend of increasing hepatocellular carcinoma will continue as long as type 2 diabetes is epidemic, especially in low-risk countries and in those with a high prevalence of HCV infection. Unfortunately, those infected with HCV are more likely than those not infected to develop type 2 diabetes (26). Therefore, to prevent hepatocellular carcinoma in anti-HCV(+) individuals, it is important to emphasize not only therapeutic intervention for HCV infection (32), but also a change of lifestyle to reduce the development of type 2 diabetes and then reduce its progression into hepatocellular carcinoma (6, 21, 22).

**Limitations.** Our study had some limitations. First, abdominal ultrasonography screening for small hepatocellular carcinoma was regularly arranged for HBsAg(+) and anti-HCV(+) individuals but not for seronegative participants, because such a screening for each seronegative participant was impractical. Therefore, although we might have overestimated the risk of developing hepatocellular carcinoma in viral hepatitis-positive participants compared with seronegative participants, the overestimate might have been negligible because the incidence of hepatocellular carcinoma in seronegative individuals was very low. However, the risk of type 2 diabetes on the development of hepatocellular carcinoma in each stratified hepatitis status was not affected. Second, treatments against chronic HBV and HCV infections with INF or other antiviral therapies may reduce the development of hepatocellular carcinoma (32, 33), but we did not investigate them. However, because of cost and side effects, there were very few participants with therapeutic interventions. Third, because the number of incident hepatocellular carcinoma cases was small and because the results stratified by virus infection status in the multivariate analysis may have been chance findings, further studies with larger samples are needed. Interpretation of the results of the present study should be cautious and conservative.

In conclusion, this study showed that type 2 diabetes is an independent risk factor for the development of

hepatocellular carcinoma in seronegative and anti-HCV(+) individuals. The risk of hepatocellular carcinoma greatly increases if anti-HCV(+) individuals have type 2 diabetes: their risk is 2 to 4 times higher than that for anti-HCV(+) individuals without diabetes and for HBsAg(+) individuals. To lessen the risk of hepatocellular carcinoma, in addition to therapeutic intervention, it is imperative to suggest lifestyle changes that reduce the risk of developing diabetes.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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