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The Relationship of Diabetes and Smoking Status to Hepatocellular Carcinoma Mortality

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Abstract: The relationship of diabetes and smoking status to hepatocellular carcinoma (HCC) mortality is not clear. We aimed to investigate the association of smoking cessation relative to diabetes status with subsequent deaths from HCC.

We followed up 51,164 participants (aged 44–94 years) without chronic hepatitis B or C from 1 January 1998 to 31 December 2008 enrolled from nationwide health screening units in a prospective cohort study. The primary outcomes were deaths from HCC.

During the study period, there were 253 deaths from HCC. History of diabetes was associated with deaths from HCC for both total participants (adjusted hazard ratio [HR], 2.97; 95% confidence interval [CI], 2.08–4.23) and ever smokers with current or past smoking habits (HR, 1.92; 95% CI, 1.10–3.34). Both never smokers (HR, 0.46; 95% CI, 0.32–0.65) and quitters (HR, 0.62; 95% CI, 0.39–0.97) had a lower adjusted risk of HCC deaths compared with current smokers. Among all ever smokers with current or past smoking habits, as compared with diabetic smokers, only quitters without diabetes had a lower adjusted risk of HCC deaths (HR, 0.37; 95% CI, 0.18–0.78). However, quitters with diabetes were observed to have a similar risk of deaths from HCC when compared with smokers with diabetes. Regarding the interaction between diabetes and smoking status on adjusted HCC-related deaths, with the exception of quitters without history of diabetes, all groups had significantly higher HRs than nondiabetic never smokers. There was also a significant multiplicative interaction between diabetes and smoking status on risk of dying from HCC ($P = 0.033$). We suggest clinicians should promote diabetes prevention and never smoking to associate with reduced subsequent HCC mortality even in adults without chronic viral hepatitis.

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Abbreviations: ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio.

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as a leading cause of cancer death, especially in Asia-Pacific regions. Risk factors for HCC include not only chronic viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease,[1–3] but probably also metabolic risk factors such as diabetes mellitus (DM) with increasing concern.[4–13] Smoking has been established to be related to higher hepatitis B viral load, HCC risks, and HCC mortality.[14–17] However, much less research has investigated the relationship between smoking cessation and death from HCC,[18] except for some hospital-based studies.[19–21] There is also limited evidence studying the association between tobacco cessation and HCC-related death in individuals without chronic viral hepatitis.

Moreover, it usually takes much time of follow-up to study the effectiveness of smoking cessation. According to data from the Framingham Offspring Study collected from 1984 through 2011, the long-term benefit of smoking cessation for the significant reduction of cardiovascular diseases has only been shown in individuals not yet developing diabetes, rather than people with diabetes.[22] The timing of smoking cessation seemed to impact a lot for the prevention of cardiovascular diseases. But there is still no evidence regarding whether quitters not yet having diabetes are at lower risk of dying of HCC. Therefore in this prospective community-based cohort without chronic hepatitis B or C, we aimed primarily to investigate the association between smoking cessation, diabetes and subsequent HCC-related death. Second, we explored whether smoking cessation when having no DM would associate with a reduced risk of dying from HCC in adults with smoking experience.

METHODS

Participants

All participants were recruited from several nationwide health screening units in Taiwan from 1 January 1998 to 31 December 2008. The detailed information of methods including sample size estimation and laboratory measurements has been described previously.[11] We excluded participants with physician-diagnosed cancer of any types at study entry. We used a

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self-reported questionnaire to collect data including medical history, current medications, physical activity, cigarette smoking, and alcohol consumption. Participants with ''history of diabetes'' were those who took antidiabetic medications or had been diagnosed as diabetes. Ever smokers comprised both current smokers and quitters. Quitters who had no history of diabetes were classified as ''nondiabetic quitters.'' On the other hand, quitters who had history of diabetes were classified as ''diabetic quitters.'' The ''adequate physical activity'' was defined as doing at least 150 minutes of moderate exercise or 60 minutes of vigorous exercise per week. Deaths with the International Classification of Disease, 9th Revision, Clinical Modification codes 155.0 were deaths due to HCC.[11] Deaths were ascertained by computer linkage to the national death registry using ID numbers. The system of death certificates in Taiwan is supervised by Ministry of Health and Welfare and has been validated with good overall agreement rates for malignant neoplasms.[23] This study was approved by the institute Research Ethics Committee with informed consent provided.

Anthropometric Indices and Laboratory Measurements

At study entry, body height and weight were measured. Obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2 recommended by the World Health Organization.[24] Central obesity was defined as a waist circumference $\geq$80 cm for women or $\geq$90 cm for men. Blood pressure was measured through a standard mercury sphygmomanometer under standardized conditions. Each participant should fast for at least 12 hours prior to blood tests. Serum hepatitis B surface antigen, serum antibody to hepatitis C virus, plasma glucose, lipid, alanine aminotransferase (ALT), aspartate aminotransferase, and creatinine levels were measured as described previously.[11] Subjects who had a fasting glucose level $\geq$100 mg/dL (5.56 mmol/L) or currently on medications for hyperglycemia were classified as having a high fasting plasma glucose. A plasma triglycerides level $\geq$150 mg/dL (1.70 mmol/L) denoted the hypertriglyceridemia, and a plasma total cholesterol level $\geq$200 mg/dL (5.18 mmol/L) denoted the hypercholesterolemia. A serum high-density lipoprotein cholesterol (HDL) level $<$40 mg/dL (1.04 mmol/L) in men and $<$50 mg/dL (1.29 mmol/L) in women defined the low HDL-C. We applied the 4-variable version of the Modification of Diet in Renal Disease Study equation for Chinese Patients to calculate estimated glomerular filtration rate (eGFR).[25]

Statistical Analysis

Values were presented as either a percent or mean (standard deviation) in descriptive analyses. In univariate analyses, we utilized the χ^2 test or Fisher exact test to compare categorical data and the 2-sample Student t test to compare continuous variables. Crude hazard ratios (HRs) and 95% confidence intervals (CIs) of selected risk factors for HCC-related deaths were estimated (PROC PHREG, SAS Institute, Cary, NC). We assumed missing values over time as missing at random and did listwise deletion. Participants lost to follow-up were assumed as mortality from competing risks. We conducted multivariate Cox regression analyses to estimate the adjusted HRs and 95% CIs of smoking habits and diabetes status for HCC-related deaths. A subgroup Cox regression analysis was performed among all ever smokers with current or past smoking habits. The interaction between diabetes history and smoking cessation was tested in this subgroup. The unadjusted Kaplan–Meier survival curves of deaths from HCC for subjects with different smoking habits were drawn. A lag time sensitivity analysis was performed by excluding the follow-up periods within the first quartile, median, and the third quartile of survival time among the subjects dying of HCC. All of the abovementioned analyses were performed with SAS 9.4. Statistical significance levels were determined by 2-tailed tests ($P < 0.05$).

RESULTS

Ever since 1 January 1998, we had invited 52,472 individuals from our health screening units. Excluded were 1308 participants who had preexisting cancer of any type (Figure 1). Finally a total of 51,164 eligible participants (aged 44–94 years) were included in the cohort, of whom 41,303 individuals without chronic hepatitis B or C completed the follow-ups. The total follow-up period lasted ten years (through 31 December 2008) with the median being 3316 days. There were 2657 deaths during follow-up with 253 deaths from HCC. At baseline, there were 22,325 female and 18,978 male participants. Individuals with diabetes tended to be older, male, had higher ALT levels, BMI, and waist circumference, but lower eGFR than those without diabetes (Table 1). Subjects with diabetes also had a higher prevalence of general and central obesity, hypertension history, hypertriglyceridemia, hypercholesterolemia, low HDL-C level, and adequate physical activity.

Metabolic Risk Factors for Hepatocellular Carcinoma-related Deaths

Using multivariate Cox regression analyses (Table 2), history of diabetes was associated with deaths from HCC for both total participants (HR, 2.97; 95% CI, 2.08–4.23) and ever smokers (n = 10,282) with current or past smoking habits (HR, 1.92; 95% CI, 1.10 to 3.34). Never smokers, quitters, and current smokers had significantly different probability of HCC mortality in the Kaplan–Meier survival curves ($P < 0.0001$) (Figure 2). Both never smokers (HR, 0.46; 95% CI, 0.32 to 0.65) and quitters (HR, 0.62; 95% CI, 0.39–0.97)

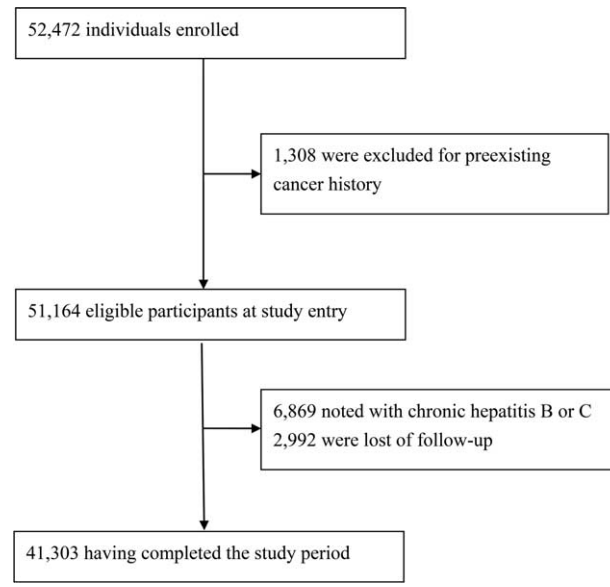

FIGURE 1. Study flowchart.

TABLE 1. Baseline Characteristics of Our Participants

Factor	Nondiabetic (n = 38,563)	Diabetic (n = 2740)	*P* Value
Age (y)	56.4 (8.8)	61.0 (8.4)	<0.001
Sex			0.006
Female	54.2	51.5	
Male	45.8	48.5	
ALT (IU/L)*	27.1 (27.9)	31.5 (27.9)	<0.001
Body mass index (kg/m^2)	24.1 (3.3)	24.9 (3.4)	<0.001
Obesity	4.4	6.6	<0.001
Waist circumference (cm)†	80.7 (9.5)	84.9 (9.1)	<0.001
Central obesity†	32.6	51.1	<0.001
Hypertension history	18.0	42.3	<0.001
High triglycerides‡	30.2	53.1	<0.001
High cholesterol‡	61.2	64.0	0004
Low HDL-C§	39.5	52.3	<0.001
eGFR (ml/min/1.73 m^2)‖	81.4 (17.5)	79.9 (20.5)	<0.001
Smoking¶			<0.001
Never	73.7	69.7	
Quitted	7.5	9.9	
Current	18.8	20.5	
Alcohol consumption**			<0.001
Never	75.9	78.0	
Past	5.0	7.2	
Habitual	19.6	14.8	
Adequate physical activity††	40.5	44.9	<0.001

Data presented as mean (standard deviation) or percent.

ALT = alanine aminotransferase, HDL-C = high-density lipoprotein cholesterol, eGFR = estimated glomerular filtration rate calculated by the 4-variable version of the Modification of Diet in Renal Disease Study equation for Chinese Patients.

* Data missing for 66 participants.
† Data missing for 30 participants.
‡ Data missing for 5 participants.
§ Data missing for 1118 participants.
‖ Data missing for 9 participants.
¶ Data missing for 2591 participants.
** Data missing for 4664 participants.
†† Data missing for 3338 participants.

TABLE 2. Multivariate Analysis of Diabetes Status and Smoking Habits for Deaths From Hepatocellular Carcinoma in a Prospective Cohort

Model	Total (Death = 253)	Ever Smokers (Death = 113)
Diabetic versus nondiabetic	2.97 (2.08–4.23)‖	1.92 (1.10–3.34)*
Quitters versus current smokers	0.62 (0.39–0.97)*	0.69 (0.44–1.10)
Never smokers versus current smokers	0.46 (0.32–0.65)‖	–
Non-diabetic quitters versus diabetic smokers	–	0.37 (0.18–0.78)†
Non-diabetic smokers versus diabetic smokers	–	0.55 (0.28–1.07)
Diabetic quitters versus diabetic smokers	–	0.81 (0.28–2.34)
Age (y)	1.05 (1.04–1.07)‖	1.04 (1.02–1.07)§
Male versus female	1.16 (0.81–1.66)	1.63 (0.65–4.07)
Obesity (yes versus no)	1.90 (1.11–3.26)*	1.49 (0.54–4.12)
Hypertension history (yes versus no)	1.12 (0.82–1.53)	1.45 (0.92–2.27)
High triglycerides (yes versus no)	0.40 (0.28–0.58)‖	0.44 (0.27–0.72)‡
High cholesterol (yes versus no)	0.43 (0.32–0.57)‖	0.50 (0.33–0.76)‡
Serum ALT level (IU/L)	1.01 (1.01–1.01)‖	1.01 (1.01–1.01)‖
eGFR (ml/min/1.73 m^2)	0.99 (0.98 to 0.99)§	1.00 (0.99–1.01)
Past alcohol consumption versus never	1.83 (1.17–2.86)†	1.82 (1.05–3.15)*
Habitual alcohol consumption versus never	1.22 (0.86–1.74)	1.20 (0.77–1.86)
Physical activity (inadequate versus adequate)	1.23 (0.93–1.64)	1.40 (0.91–2.14)

Data presented as HR (95% CI).

ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate calculated by the 4-variable version of the Modification of Diet in Renal Disease Study equation for Chinese Patients. Ever smokers: current smokers and quitters together. Nondiabetic quitters: quitters who reported having no history of diabetes. Diabetic quitters: quitters who reported having had diagnosis of diabetes.

* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.005$.
§ $P < 0.001$.
‖ $P < 0.0001$.

had a lower adjusted risk of HCC deaths compared with current smokers (Table 2). Among all ever smokers with current or past smoking habits, as compared with diabetic smokers, only quitters without diabetes had a lower adjusted risk of HCC deaths from HCC (HR, 0.37; 95% CI, 0.18–0.78). However, quitters with diabetes were observed to have a similar risk of deaths from HCC when compared with smokers with diabetes. The lag time sensitivity analysis was performed respectively by excluding the follow-up periods within the first quartile (1233 days), median (2181 days), and the third quartile (2731 days) of survival time among our participants dying of HCC (Table 3). The reduced risk of HCC deaths in quitters without diabetes versus smokers with diabetes remained significant after leaving out all time lags of follow-up. Regarding the relationship between diabetes, smoking status, and adjusted HCC-related deaths (Table 4), with the exception of quitters without history of diabetes, all groups had significantly higher HRs than nondiabetic never smokers. There was also a significant multiplicative interaction between DM and smoking status on risk of dying from HCC ($P = 0.033$).

In subgroup analyses of quitters, neither previous smoking amount ($P = 0.569$), nor smoking-free period after quitting ($P = 0.301$) were significantly associated with risks of liver cancer-related death. A total of 17,116 participants in our cohort underwent ultrasonography and 9417 (55.0%) had hepatic steatosis. Participants with baseline hepatic steatosis had higher adjusted HCC mortality (HR, 2.73; 95% CI, 1.56–4.76). The significant association between diabetes and deaths from HCC persisted after controlling for hepatic steatosis. In the present

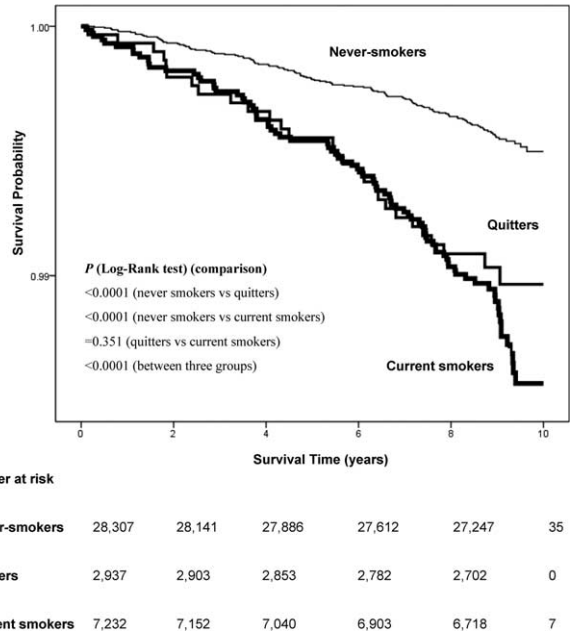

FIGURE 2. Kaplan–Meier survival curves for never smokers, quitters, and current smokers. The log-rank test is significant with $P < 0.0001$ between never smokers and quitters, between never smokers and current smokers, and between total participants with different smoking habits. The Log-Rank test is not significant between quitters and current smokers with $P = 0.351$.

cohort, a total of 2082 (76.0%) participants with diabetes received regular antidiabetic agents. Participants with diabetes and history of regular anti-diabetic agents had a similar risk of deaths from HCC (HR, 1.23; 95% CI, 0.56–2.70) compared with participants with diabetes but without regular antidiabetic agents, adjusted for age, sex, serum ALT level, eGFR, obesity, hypertension history, high triglycerides, high cholesterol level, smoking, alcohol consumption, and adequate physical activity.

TABLE 4. Relationship Between Diabetes and Smoking Status on Deaths From Hepatocellular Carcinoma in a Prospective Cohort

Diabetes	Smoking Status	n (Death)	HR (95% CI)
No	Never smoker	26,582 (98)	1.00 (Referent)
No	Quitters	2703 (23)	1.53 (0.91–2.59)
No	Current smokers	6774 (74)	2.49 (1.71–3.64)†
Yes	Never smoker	1848 (25)	4.24 (2.68–6.70)†
Yes	Quitters	262 (5)	3.28 (1.29–8.38)*
Yes	Current smokers	543 (11)	4.73 (2.44–9.17)†

Data presented as HR (95% CI). Adjusted by age, sex, obesity, serum alanine aminotransferase level, estimated glomerular filtration rate, alcohol consumption (habitual, past, never), adequate physical activity, hypertension history, high triglycerides, and high cholesterol level. Data missing about smoking status for 2591 participants (17 HCC deaths).
HR = Hazard ratio.
* $P < 0.05$.
† $P < 0.0001$.

DISCUSSION

Accumulating efforts have been made to reduce the burden of HCC, including early identification of potential risk factors other than the established ones like chronic viral hepatitis and excess alcohol consumption.[2,12] A study analyzing patients with HCC referred to a specialist multidisciplinary team in England between 2000 and 2010 reported that nonalcoholic fatty liver disease increased dramatically and became the most common risk factor for HCC (34.8%) by 2010.[26] Although chronic viral hepatitis remains a major risk factor of HCC in Taiwan,[27,28] we have observed the association between certain viral factor, such as hepatitis B viral load and selected host metabolic factors.[29–31] Furthermore, we demonstrated that diabetes was associated with increased HCC mortality even in the absence of chronic hepatitis B or C.[11] Another prospective study in Taiwan also showed a higher risk of HCC mortality in those with type 2 DM, current smoking and use of insulin for over 10 years.[17] However, that study could not adjust or exclude the major

TABLE 3. Multivariate Lag-time Analysis of Diabetes Status and Smoking Habits for Deaths From Hepatocellular Carcinoma Among Ever Smokers

Risk Factor	Survival ≥ 1233 days n = 10,033 HCC Death = 85	Survival ≥ 2181 days n = 9748 HCC Death = 57	Survival ≥ 2731 days n = 9518 HCC Death = 29
Diabetic smokers	Reference	Reference	Reference
Nondiabetic quitters	0.33 (0.13–0.81)*	0.28 (0.09–0.82)*	0.15 (0.03–0.69)*
Nondiabetic smokers	0.57 (0.26–1.25)	0.50 (0.20–1.24)	0.37 (0.12–1.18)
Diabetic quitters	0.96 (0.28–3.22)	1.03 (0.25–4.19)	0.52 (0.06–4.82)

Data presented as HR (95% CI). The first quartile (1233 days), median (2181 days), and the third quartile (2731 days) of survival time among our ever smokers dying of HCC were chosen as the cut-off time lag. Adjusted by age, sex, serum alanine aminotransferase level, estimated glomerular filtration rate, alcohol consumption (habitual, past, never), adequate physical activity, obesity, hypertension history, high triglycerides, and high cholesterol level. Ever smokers: current smokers and quitters together. Nondiabetic quitters: quitters who reported having no history of diabetes. Diabetic quitters: quitters who reported having had diagnosis of diabetes.
HCC = hepatocellular carcinoma
* $P < 0.05$.

confounder like chronic viral hepatitis B. Neither did it directly evaluate the effect of smoking cessation. We moved on to study lifestyle factors, including the long-term benefit of smoking cessation without history of diabetes. Our results reveal that both never smokers and quitters had a lower risk of HCC deaths compared to current smokers. In addition, there was a significant multiplicative interaction between diabetes and smoking status. Only nondiabetic quitters had fewer deaths from HCC compared with diabetic smokers. Our findings are consistent with previous research regarding the positive association between DM and deaths from HCC.[11,32] However, acknowledging diabetes as a risk factor contributes little to the reduction of HCC mortality in the real world. The worldwide surveillance for HCC is performed mainly for patients with chronic hepatitis or advanced hepatic fibrosis.[1,33] Prescribing only antidiabetic agents with low risks of liver carcinogenesis is impractical and does not definitely lead to best outcomes for patients with diabetes.[10,34] Therefore, preventing DM and declining smoking are more important, as we emphasize in the present report.

Smoking is one of major modifiable risk factor for incident DM.[35,36] Smoking cessation improved insulin resistance, microalbuminuria, and the subsequent cardiometabolic complications.[37–39] Smoking cessation also alleviated the hypoxia and oxidative stress-causing pancreatic beta-cell glucotoxicity.[40] However, the benefit of smoking cessation in epidemiological studies is not so easily observed as that of never smoking. Although a 25-year prospective study reveals that early smoking cessation when having no diabetes was associated with significant reduction of cardiovascular diseases,[22] the relatively short-term studies of smoking cessation yield some conflicting results. For example, a 9.2-year cohort of 2070 Japanese men without preexisting DM showed that risk for new-onset DM peaked within 3 years and persisted at 5 years after quitting smoking among overweight individuals.[41] It was probably because investigators could not manipulate body weight after smoking cessation in this Japanese observational study. Although our 10-year cohort showed general protective effects of smoking cessation for fewer deaths from HCC (Table 2), only quitters without history of diabetes was associated with reduced HCC mortality. Once having diabetes, quitters did not independently have a lower risk of dying of HCC. The exact mechanism is unknown. A probable explanation is that diabetes was more crucial than smoking for an increased risk of dying from HCC (Table 4). Another reason is the time of smoking cessation of each quitter was not long enough to gain protection against HCC mortality.[20] Besides, quitters having relapsed during study period would weaken the protection with bias toward the null.

A concern regarding the competing risks in observational studies deserves evaluation.[42] Patients with diabetes and smoking habits might have earlier cardiovascular or acute lethal events, which may have impeded the occurrence of deaths from HCC. Accordingly, we performed a lag time sensitivity analysis by excluding follow-up periods within selected time lags to have fewer competing risks and less reverse causation. Nondiabetic quitters still had fewer deaths from HCC compared with diabetic smokers (Table 3). Among our participants with diabetes, there were 41 HCC-related deaths and 72 cardiovascular deaths. As for our ever smokers, there were 123 HCC-related deaths and 268 cardiovascular deaths. Even if a participant had been dead with concurrent HCC and cardiovascular disease, only 1 primary cause of death would be coded in Taiwan death certificates. Actually, the total HCC-related deaths (66.8 years, n = 253) in our cohort was younger than those with cardiovascular deaths (71.4 years, n = 535). Without autopsy, it is difficult to clarify the potential competing risks, especially if the diagnosis of HCC had never been made until death.[43]

This community-based study has to address some limitations. Our current cohort study was not fully representative of general population in Taiwan because we included only middle-aged or elderly individuals receiving health screening and excluded those infected with chronic viral hepatitis B or C. Liver fibrosis and cirrhosis is a major confounder of HCC incidence and mortality.[33] However, it could not be quantified without transient elastography, magnetic resonance imaging, or liver biopsy in these health screening units. The screening units could not access every private biopsy result for HCC incidence. We excluded HCC patients at study entry and did not get available data to adjust the staging and treatment of HCC but some studies have reported that HCC patients with diabetes had higher mortality after adjusting the staging and treatment of HCC.[13,21] In particular, Shau et al showed that the liver cancer-specific survival, liver disease-related survival, and overall survival rates were significantly worse for patients with DM than patients without DM (all $P < 0.001$). After adjusting for age, sex, tumor stage, treatment, and the presence of other comorbidities, DM remained an independent predictor of poorer liver cancer-specific survival ($P < 0.001$), liver disease-related survival ($P < 0.001$), and overall survival ($P < 0.001$).[13] Thus the associations between DM and mortality were consistent among subgroups, irrespective of tumor size, stage, treatment modality, and liver cirrhosis.

Taiwan is an endemic area of hepatitis B virus. We could not get liver tissues of all participants to eliminate the presence of occult hepatitis B virus infection, though its direct contribution to HCC-related death has not yet been established.[44] We could not access the follow-up serostatus of chronic viral hepatitis, even though the likelihood of new infection was low under national policy.[45] Several studies after 2005 reported that more cups of coffee consumption would reduce HCC incidence and mortality.[34,46–49] A large Finnish study, including over 60,000 individuals across a 19-year follow-up period, showed a dose-dependent decrease of the rate of HCC-development in the consumption of up to 6 cups of coffee per day.[48] However, we did not collect such dose-dependent information about coffee intake in our questionnaire launched from 1998.

Defining history of diabetes by patient-reported questionnaire could underestimate the prevalence of DM. The diagnostic accuracy would be improved if the fasting plasma glucose levels had been repeatedly checked based on the current diagnostic criteria.[50] Residual confounding might come from the duration or the severity of DM, class of antidiabetic agents, and statins.[34] Hepatocellular carcinoma occurrence has been reported to be positively associated with sulfonylureas and insulin,[34,51,52] but these agents still play a mainstream role in diabetes care.[50] The combination of high-risk insulin secretagogues with low-risk metformin and lipid-lowering agents is common in daily practice. In our cohort, participants with diabetes and treatment with antidiabetic agents had a similar risk of HCC mortality compared to participants with diabetes but without treatment with antidiabetic agents. Whether taking regular lipid-lowering agents or not among participants with hypertriglyceridemia had a similarly adjusted risk of deaths from HCC. In addition, we could not manipulate any change in body weight or metabolic factors after smoking cessation in this observational study. Future experimental research should investigate altogether the

effectiveness of smoking cessation and body weight control for long-term liver endpoints.

In conclusion, we prospectively demonstrated that both never smoking and smoking cessation were associated with reduced deaths from liver cancer independently of other possible confounders. Smokers should quit early when having no diabetes to associate with reduced future HCC-related deaths. Once having diabetes, quitters did not have a lower risk of dying of HCC even in adults without chronic hepatitis B or C. For daily practice especially in Asia-Pacific regions, we suggest clinicians prevent diabetes and arrange smoking cessation before patients get DM to reduce the subsequent HCC mortality.

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