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# Risk of Hepatocellular Carcinoma in Diabetic Patients and Risk Reduction Associated With Anti-Diabetic Therapy: A Population-Based Cohort Study

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OBJECTIVES: **Using population-based representative insurance claims data, the risk of developing hepatocellular carcinoma (HCC) among diabetes mellitus (DM) patients, as well as whether DM medications alter the risk of developing HCC were investigated.**

METHODS: **From the Taiwan National Health Insurance Research Database, 19,349 newly diagnosed DM patients 20 years and older and 77,396 comparison subjects without DM were identified from claims from 2000 to 2005. The incidences of HCC at the end of 2008 and the risks associated with hepatitis B and hepatitis C were determined. Whether metformin and thiazolidinediones reduce the risk of developing HCC was also measured.**

RESULTS: **The incidence of HCC was twice higher in the DM group compared with the non-DM group (21.0 vs. 10.4 per 10,000 person-years), with an adjusted hazard ratio (HR) of 1.73 (95% confidence interval (CI) = 1.47–2.03) using multivariable Cox proportional hazard regression. Male sex, cirrhosis, hepatitis B, and hepatitis C were significant independent factors that predict HCC, with HRs of 2.32, 8.65, 2.52, and 5.61, respectively. In the stratified analysis, the HR increased to 72.4 (95% CI = 42.9–122) among patients with DM, cirrhosis, and hepatitis C. HCC risk reduction was greater for diabetics taking metformin than those taking thiazolidinediones (51 vs. 44% reduction).**

CONCLUSIONS: **Comorbidity with cirrhosis and/or hepatitis appears to be associated with an extremely increased risk of developing HCC among DM patients. These high-risk patients should be closely monitored for HCC. The use of metformin or thiazolidinediones may reduce the risk of developing HCC.**

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## INTRODUCTION

Hepatitis B and hepatitis C are well-known etiological factors that lead to hepatocellular carcinoma (HCC) in Taiwan. More than 90% of patients with HCC are positive for the hepatitis B surface antigen and/or antibodies against the hepatitis C virus (1). In addition to viral infections, non-viral causes of HCC have been proposed in studies. Cirrhosis, obesity, diabetes mellitus (DM), fatty liver disease, hereditary hemochromatosis, alcohol, smoking, and other dietary and environmental exposures are also factors that contribute to the development of HCC (2,3).

To date, there is accumulating evidence that shows patients with DM are more prone to cancer (4–6). A recent American population-based case–control study that consists of 2,061 patients with HCC and 6,183 noncancer controls has shown a significant association between DM and the risk of HCC with an odds ratio of 2.87 (4). A study of site-specific cancer mortality in Asian populations has also reported that DM is associated with higher risk of mortality from liver and pancreatic cancer (1.51 and 1.78, respectively) (6).

HCC has been the most lethal cancer for decades in Taiwan, with a mortality rate of 33.6 per 100,000 persons ($n = 7759$), becoming the second leading cause of cancer deaths after lung

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**Table 1. Baseline demographic status and comorbidities in the diabetic and non-diabetic groups**

| | Diabetes | | | | |
|---|---|---|---|---|---|
| | No, *n*=77,396 | | Yes, *n*=19,349 | | |
| | *n* | % | *n* | % | *P* value[a] |
| *Sex* | | | | | 1.00 |
| Women | 34,228 | 44.2 | 8,557 | 44.2 | |
| Men | 43,168 | 55.8 | 10,792 | 55.8 | |
| *Age group (years)* | | | | | 1.00 |
| 20–39 | 8,112 | 10.5 | 2,028 | 10.5 | |
| 40–64 | 47,740 | 61.7 | 11,935 | 61.7 | |
| ≥65 | 21,544 | 27.8 | 5,386 | 27.8 | |
| Mean (SD, years) | 56.4 | 13.8 | 55.5 | 13.4 | 0.78 |
| *Comorbidities*[b] | | | | | |
| Obesity | 371 | 0.5 | 497 | 2.6 | <0.0001 |
| Cirrhosis | 1,021 | 1.3 | 583 | 3.0 | <0.0001 |
| Alcoholic liver damage | 613 | 0.8 | 413 | 2.1 | <0.0001 |
| Nonalcoholic fatty liver disease | 1,047 | 1.4 | 695 | 3.6 | <0.0001 |
| Hereditary hemochromatosis | 2 | 0.00 | 3 | 0.02 | 0.06[c] |
| Hepatitis B | 1,367 | 1.8 | 502 | 2.6 | <0.0001 |
| Hepatitis C | 758 | 1.0 | 324 | 1.7 | <0.0001 |

[a]$\chi^2$-Tests comparing subjects with and without diabetes.
[b]Comorbidities before index date.
[c]Fisher's exact test.

cancer in 2009 (7). In Taiwan, epidemiologic studies have found that the prevalence of DM increased from 11.3% in 1987 to 24.9% in 2005 (8–10); as a result, DM became the fifth leading cause of death in 2009 (7).

Cross-sectional and case–control studies conducted in a southern Taiwanese community with endemic dual hepatitis B and hepatitis C infections have shown that DM is not a risk factor for HCC (11). On the other hand, another community-based follow-up study in southern Taiwan found that type 2 diabetes is a strong independent predictor of HCC, with a hazard ratio (HR) of 2.7 (95% confidence interval (CI) = 1.7–4.3), compared with non-diabetic patients (12).

Given the significant link of DM with the risk of cancer, lifestyle changes or anti-diabetic drugs that prevent and reverse DM may reduce the risk of cancer. Metformin, a widely used anti-diabetic drug, has recently attracted great attention for lowering cancer risk (13–15). It has been found to inhibit cancer cell growth *in vitro* and *in vivo* (16,17). Epidemiological studies have also shown that metformin therapy is associated with reduced risks of cancer, including breast cancer and HCC (18–20). Donadon *et al.* (19) found that the odds ratio for HCC in diabetic patients treated with metformin dropped to 0.3 compared with those without this therapy. Another case–control study conducted in the United States also showed that treatment with metformin or thiazolidinediones is associated with a 70% reduction in HCC risk among diabetic patients (20). Both the case–control studies are limited, with small clinical samples of HCC. To the best of our knowledge, only one cohort study, also from Taiwan, has observed the effect of DM medication in reducing the risk of HCC among Asian populations, but only metformin was studied (21).

To clarify the role of diabetes in the risk of developing HCC, a population-based cohort study, taking advantage of a large-size data set available from the National Health Insurance program in Taiwan, was conducted. The present study investigates further whether the risk of HCC increases with the presence of hepatitis B and/or hepatitis C. Furthermore, it examines whether the HCC risk is reduced with DM therapies, including metformin and thiazolidinediones.

## METHODS

### Data sources

The National Health Insurance program in Taiwan is a universal health insurance system covering more than 99% of the country's population of 23 million (22). Computerized claims data have become available since 1996. Data used in this analysis came from the Longitudinal Health Insurance Database, which contains the claims' history of 1 million subjects randomly selected from the entire population enrolled in the insurance system in 1996–2000. This database contains registration of insurance, inpatient and

**Table 2. Incidence density of hepatocellular carcinoma estimated by sex, age, and follow-up year between the diabetic group and the non-diabetic group**

| | Non-diabetics | | | | Diabetics | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Case | Person-years | Incidence rate[a] | *n* | Case | Person-years | Incidence rate[a] | Crude HR | 95% CI |
| All | 77,396 | 455 | 435,732 | 10.4 | 19,349 | 224 | 106,602 | 21.0 | 2.03 | 1.73–2.38 |
| *Sex* | | | | | | | | | | |
| Women | 34,228 | 129 | 195,026 | 6.61 | 8,557 | 53 | 47,867 | 11.1 | 1.73 | 1.25–2.38 |
| Men | 43,168 | 326 | 240,706 | 13.5 | 10,792 | 171 | 58,735 | 29.1 | 2.15 | 1.79–2.59 |
| *Age (years)* | | | | | | | | | | |
| 20–39 | 8,112 | 11 | 46,548 | 2.36 | 2,028 | 4 | 11,626 | 3.44 | 1.46 | 0.47–4.59 |
| 40–64 | 47,740 | 228 | 275,737 | 8.27 | 11,935 | 138 | 67,708 | 20.4 | 2.48 | 2.00–3.06 |
| ≥65 | 21,544 | 216 | 113,447 | 19.0 | 5,386 | 82 | 27,267 | 30.1 | 1.60 | 1.24–2.07 |
| *Follow-up years* | | | | | | | | | | |
| <1 | 77,396 | 77 | 76,790 | 10.0 | 19,349 | 40 | 19,072 | 21.0 | 2.09 | 1.43–3.06 |
| 1–2 | 76,193 | 99 | 75,545 | 13.1 | 18,838 | 28 | 18,629 | 15.0 | 1.15 | 0.75–1.75 |
| 2–3 | 74,891 | 48 | 74,262 | 6.46 | 18,433 | 35 | 18,257 | 19.2 | 2.97 | 1.92–4.59 |
| 3–4 | 73,598 | 72 | 66,852 | 10.8 | 18,059 | 43 | 16,341 | 26.3 | 2.44 | 1.68–3.57 |
| 4–5 | 60,317 | 59 | 53,197 | 11.1 | 14,699 | 26 | 12,939 | 20.1 | 1.81 | 1.14–2.88 |
| ≥5 | 46,494 | 100 | 89,086 | 11.2 | 11,271 | 52 | 21,365 | 24.3 | 2.25 | 1.61–3.16 |

CI, confidence interval; HR, hazards ratio.

[a]Incidence rate: per 10,000 person-years.

outpatient claims, prescribed drugs, and basic sociodemographic information, including sex and birth date.

### Design

The retrospective cohort study was composed of two study groups: a diabetic patients group and a matched non-diabetic comparison group. The diabetic group included patients with an initial diagnosis of DM (International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 code 250.xx and A-code A-181) who had been prescribed anti-diabetic drugs (e.g., metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, D-phenylalanine derivatives, dipeptidyl peptidase 4 inhibitors, and incretin mimetic agents or insulins) in 2000–2005. All subjects younger than 20 years old on the day of diagnosis were excluded. For each diabetic patient, four subjects without medical claims for diabetes who were frequency matched with sex and age (per 5 years) in the same period were randomly selected. The A-code was used, in addition to ICD-9 codes to define diseases because it had been used before ICD-9 was adapted in Taiwan. An index date for the diabetic patients was defined as their date of diagnosis. An index date was assigned for the corresponding comparison subjects as the middle date of the same index month as their matched diabetic patients. Subjects diagnosed with cancer before the index date (ICD-9 codes 140–208 and A-code A08x-A14x) were excluded from the present study. Other comorbidities presented before the index date were defined as follows: obesity (ICD-9 codes 278.00 and 278.01, and A-code A183), cirrhosis (ICD-9 codes 571.2, 571.5, and 571.6), alcoholic liver damage (ICD-9 codes 571.0, 571.1, and 571.3), nonalcoholic fatty liver disease (ICD-9 code 571.8), hereditary hemochromatosis (ICD-9 code 275.0); hepatitis B (ICD-9 codes V02.61, 070.20, 070.22, 070.30, and 070.32), and hepatitis C (ICD-9 codes V02.62, 070.41, 070.44, 070.51, and 070.54).

Both diabetic and non-diabetic groups were followed up to determine the incidence of HCC (ICD-9 codes 155, 155.0, and 155.2, and A-code A095) until the end of 2008 or censored because of death, withdrawal from the insurance program, or loss to follow-up consultations. To reduce the likelihood of misclassification of the disease, we confirmed the occurrence of HCC by linking the Longitudinal Health Insurance Database with the Registry for Catastrophic Illness Patients. Patients who apply for a cancer catastrophic illness certificate are required to provide pathological reports or other supporting documents, such as laboratory and image studies. The Bureau of National Health Insurance approves the application after reviewing all the required medical documents.

### Statistical analysis

$\chi^2$-Tests and Student's *t*-tests were used to compare the differences between the DM group and the non-diabetic group regarding sociodemographic characteristics and comorbidities. The incidence rate was calculated as the number of HCC cases identified during the follow-up, divided by the total person-years for each group by sex, age, and follow-up years. Cox propor-

**Table 3. Adjusted hazard ratios and 95% confidence intervals of hepatocellular carcinoma associated with diabetes and covariates**

| Variable | Crude | Adjusted[a] |
|---|---|---|
| | HR (95% CI) | HR (95% CI) |
| *Sex* | | |
| Women | 1.00 (Reference) | 1.00 (Reference) |
| Men | 2.27 (1.91–2.69) | 2.32 (1.96–2.76) |
| *Age group (years)* | | |
| 20–39 | 1.00 (Reference) | 1.00 (Reference) |
| 40–64 | 4.13 (2.46–6.92) | 4.26 (2.54–7.14) |
| ≥65 | 8.14 (4.85–13.7) | 8.78 (5.22–14.8) |
| *Diabetes mellitus* | | |
| No | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 2.03 (1.73–2.38) | 1.73 (1.47–2.03) |
| *Comorbidity (yes vs. no)* | | |
| Obesity | 0.36 (0.09–1.43) | — |
| Cirrhosis | 19.2 (15.9–23.2) | 8.65 (6.93–10.8) |
| Alcoholic liver damage | 5.00 (3.47–7.21) | 1.36 (0.93–2.01) |
| Nonalcoholic fatty liver disease | 1.58 (0.98–2.57) | — |
| Hepatitis B | 6.63 (5.15–8.54) | 2.52 (1.92–3.32) |
| Hepatitis C | 16.2 (13.0–20.2) | 5.61 (4.35–7.23) |

CI, confidence interval; HR, hazards ratio.
[a]Adjusted for sex, age, and comorbidities (including cirrhosis, alcoholic liver damage, hepatitis B, and hepatitis C).

tional hazard models were used to estimate the HR with 95% CI, which determined the association between diabetes and the risk of developing HCC. The risk of developing HCC associated with comorbidities such as DM, cirrhosis, hepatitis B, and hepatitis C were also estimated. Further analysis investigated medications available for the DM treatment. The Cox proportional hazard analysis was also used to estimate whether there were reduced HCC risks associated with DM medications. All analyses were performed using the SAS software version 9.1 (SAS Institute, Cary, NC), and the statistical significance level was set at two-sided $P < 0.05$.

### Ethical considerations

All types of personal identification on files connected with the present study were scrambled using surrogate identification numbers to secure patient privacy. The present study was exempted from ethical review.

## RESULTS

### Incidence of HCC by subject characteristics

From the claims data of 2000–2005, 19,349 patients with DM met the eligibility criteria; 77,396 persons for the non-diabetic group (**Table 1**). The two groups were similar in sex and age distributions, with a mean age of 56 years. Obesity, cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, hepatitis B, and hepatitis C were more prevalent in the DM group than in the non-diabetic group at baseline ($P < 0.0001$).

By the end of follow-up, the incidence of HCC was higher in the DM group than in the non-diabetic group (21.0 vs. 10.4 per 10,000 person-years), with an HR of 2.03 (95% CI = 1.73–2.38; **Table 2**). The incidence rates of HCC, as classified by sex, age, and follow-up year, were all higher in subjects with DM. The oldest DM group had the highest incidence of HCC, but patients aged 40–64 years had the highest HR of 2.48 (95% CI = 2.00–3.06). Men had higher HCC risk than women. The stratified analysis by follow-up duration showed a higher risk of HCC within 1 year (HR = 2.09, 95% CI = 1.43–3.06), which declined and then peaked at 2–3 years to an HR of 2.97 (95% CI = 1.92–4.59), and fluctuated thereafter.

### HCC associated with comorbidities

The multivariate Cox proportional hazard regression analysis with sex, age, and comorbidities included in the model revealed an adjusted HCC HR of 1.73 (95% CI = 1.47–2.03) associated with DM (**Table 3**), with the HR increasing with age. Among the comorbidities, cirrhosis had the highest HR at 8.65 (95% CI = 6.93–10.8), followed by hepatitis C (HR = 5.61, 95% CI = 4.35–7.23) and hepatitis B (HR = 2.52, 95% CI = 1.92–3.32).

### Interaction between diabetes and comorbidities

**Table 4** shows the stratified analyses by DM, cirrhosis, hepatitis B, and hepatitis C for the risk associated with HCC, controlling for sex, age, and alcoholic liver damage. The aforementioned factors have synergistic effects on the HCC risk. Subjects comorbid with DM, cirrhosis, and hepatitis C had the highest HR at 72.4 (95% CI = 42.9–122), greater than those having all four factors (HR = 57.0, 95% CI = 14.1–231).

### Anti-diabetic drugs and HCC risk reduction

As shown in **Table 5**, the association between anti-diabetic drugs and the risk of HCC was further analyzed. The median duration of taking metformin was 2.1 years (mean, 2.5 years), similar to that of sulfonylureas (mean, 2.4 years), but more than 1 year longer than that of other anti-diabetic drugs ($P < 0.001$). After adjusting for sex, age, and comorbidities, the patients taking metformin had the lowest HCC HR at 0.49 (95% CI = 0.37–0.66), followed by patients taking thiazolidinediones (HR = 0.56, 95% CI = 0.37–0.84). Taking insulin, sulfonylurea, and α-glucosidase inhibitors also reduced the HCC risk; however, the reductions were not statistically significant.

## DISCUSSION

HCC is usually secondary to either cirrhosis or a viral infection such as hepatitis B or hepatitis C (23). The present study demonstrates the role of DM in HCC risk. Diabetic patients have an incidence of HCC twice higher than non-diabetics, indicating that approximately 11 additional cases of HCC develop annually

**Table 4. Interaction effect on hepatocellular carcinoma between diabetes and comorbidities**

| Diabetes | Cirrhosis | Hepatitis B | Hepatitis C | Adjusted HR[a] | 95% CI |
|---|---|---|---|---|---|
| No | No | No | No | 1.00 | Reference |
| No | Yes | No | No | 10.9 | 7.65–15.4 |
| No | No | Yes | No | 5.84 | 3.71–9.20 |
| No | No | No | Yes | 15.6 | 10.7–22.6 |
| No | Yes | Yes | No | 51.9 | 33.9–79.4 |
| No | Yes | No | Yes | 60.8 | 39.4–93.9 |
| No | No | Yes | Yes | 12.1 | 5.10–28.6 |
| No | Yes | Yes | Yes | 42.4 | 15.8–113 |
| Yes | No | No | No | 2.11 | 1.74–2.56 |
| Yes | Yes | No | No | 16.5 | 11.0–24.8 |
| Yes | No | Yes | No | 4.50 | 1.86–10.9 |
| Yes | No | No | Yes | 15.2 | 8.35–27.8 |
| Yes | Yes | Yes | No | 36.0 | 16.9–76.8 |
| Yes | Yes | No | Yes | 72.4 | 42.9–122 |
| Yes | No | Yes | Yes | 6.59 | 0.92–46.9 |
| Yes | Yes | Yes | Yes | 57.0 | 14.1–231 |

CI, confidence interval; HR, hazards ratio.
[a]Adjusted for sex, age, and alcoholic liver damage.

per 10,000 diabetic patients. The incidence of HCC is higher in patients with DM regardless of sex, age, or follow-up period.

The adjusted HR for developing HCC in diabetics in the current study is 1.73, which is lower than the risk found in other studies. In the systematic review by El-Serag *et al.* (24), DM was associated with an increased risk of developing HCC (risk ratio = 2.5, 95% CI = 1.9–3.2) independent of alcohol use or viral hepatitis. Another systematic review showed that patients with DM are 3.64 times (95% CI = 2.61–5.07) more likely to develop HCC compared with non-diabetics (25). The risk of developing HCC varies with DM duration and other comorbidities (24–27).

Previous literature has consistently reported the association of HCC with other comorbidities, particularly for DM patients with cirrhosis, hepatitis B, and/or hepatitis C (1–3,26,27) In line with these findings, the present study observed a synergistic effect between DM and liver comorbidities regarding the development of HCC. Furthermore, the prevalence rates of cirrhosis, hepatitis B, and hepatitis C were higher in the DM group than in the non-DM group. The HCC risk was strongly associated with these three comorbidities, particularly cirrhosis (HR = 8.65). Patients with hepatitis C are at twice higher HCC risk than those with hepatitis B (HR = 5.61 vs. HR = 2.52). A new and significant finding is that HCC increased markedly to an HR of 72.4 for diabetics with cirrhosis and hepatitis C compared with patients without those disorders. A Netherlands study found that, in patients with chronic hepatitis C and advanced cirrhosis, DM is also independently associated with HCC development, with an HR of 3.28 (95% CI = 1.35–7.97) (27). Beasley *et al.* (28) found that in Taiwan, the incidence of primary HCC among carriers of the hepatitis B surface antigen is 223 times higher than that among non-carriers. However, hepatitis C is more important than hepatitis B in the present study.

Several studies have assessed the association between anti-diabetic drugs and the risk of developing HCC; all found reduced risk associated with metformin treatment (19–21). The results of the present study confirm the effect of metformin. Furthermore, we found that thiazolidinedione treatment is also significantly associated with a reduced incidence of HCC. To our knowledge, only one hospital-based case–control study in the United States (20) has shown that thiazolidinediones may reduce the risk of HCC, which is consistent with our observation. Evidence from *in vivo* studies has shown that thiazolidinediones inhibited tumor formation in the liver (29), providing a plausible biological basis for our observations.

Previous case–control studies have shown that sulfonylurea users have an increased risk of developing HCC compared with non-users (19,20). In contrast, the present study shows a 25% risk reduction in patients using sulfonylureas, but the association was not statistically significant. We found that 92.5% of sulfonylurea users have switched to other anti-diabetic drugs, which might, to some extent, offset the unfavorable effect of sulfonylurea on risk of HCC. Further prospective studies may be helpful for clarifying the association of sulfonylureas with HCC.

A hospital-based case–control study in the United States found that patients that have had diabetes for >10 years have a 2.2-fold increased risk of developing HCC (95% CI = 1.2–4.8) compared

**Table 5. Cox proportional hazard ratios and 95% confidence intervals of hepatocellular carcinoma associated with anti-diabetic drugs for patients with diabetes mellitus**

| | *n* | Years use[a] | No. of patients | Incidence rate[b] | Crude HR | 95% CI | Adjusted HR[c] | 95% CI |
|---|---|---|---|---|---|---|---|---|
| *Insulins* | | | | | | | | |
| Not used | 7,713 | — | 83 | 21.14 | 1.00 | Reference | 1.00 | Reference |
| Used | 11,636 | 1.4 (0.8) | 141 | 20.94 | 0.97 | 0.74–1.27 | 0.98 | 0.74–1.28 |
| *Metformin* | | | | | | | | |
| Not used | 3,067 | — | 66 | 45.89 | 1.00 | Reference | 1.00 | Reference |
| Used | 16,282 | 2.5 (2.1) | 158 | 17.13 | 0.37 | 0.28–0.49 | 0.49 | 0.37–0.66 |
| *Sulfonylureas* | | | | | | | | |
| Not used | 3,255 | — | 46 | 30.13 | 1.00 | Reference | 1.00 | Reference |
| Used | 16,094 | 2.4 (1.9) | 178 | 19.49 | 0.63 | 0.45–0.87 | 0.75 | 0.54–1.04 |
| *Thiazolidinediones* | | | | | | | | |
| Not used | 15,514 | — | 199 | 23.99 | 1.00 | Reference | 1.00 | Reference |
| Used | 3,835 | 1.3 (0.8) | 25 | 10.56 | 0.43 | 0.28–0.65 | 0.56 | 0.37–0.84 |
| *α-Glucosidase inhibitors* | | | | | | | | |
| Not used | 14,900 | — | 184 | 23.04 | 1.00 | Reference | 1.00 | Reference |
| Used | 4,449 | 1.1 (0.6) | 40 | 14.96 | 0.64 | 0.46–0.90 | 0.72 | 0.51–1.01 |

CI, confidence interval; HR, hazards ratio.
[a]Values shown are mean (median); *P* values for differences across medication groups, $P<0.0001$.
[b]Incidence rate: per 10,000 person-years.
[c]Adjusted for sex, age, and comorbidities (including cirrhosis, alcoholic liver damage, hepatitis B, and hepatitis C).

with those that have had diabetes for 2 to 5 years (20). Thus, the risk may increase with the increasing duration of DM. In the present study, the risk of developing HCC associated with diabetes was the highest in patients 2–3 years after diagnosis of DM, without considering medications. We further assessed the risk of developing HCC in terms of the duration of taking anti-diabetic drugs. The risk of developing HCC decreased as the duration of taking the medications increased. The trend is most obvious for patients who have been taking metformin for at least 1 year. The HR was 0.49 (95% CI = 0.31–0.78) after taking metformin for 12–23 months, which decreased to 0.26 (95% CI = 0.18–0.39) after taking it for ≥24 months compared with non-users of metformin (data not shown). This trend was less pronounced among patients taking α-glucosidase inhibitors. The risk fluctuated among patients taking other medications.

The strength of the present study is its large sample size. The results are likely to illustrate the direction of HCC prevention in patients with DM. Although the concept is not novel, the population-based data set with a large sample size allows the demonstration of risk factors for HCC with a minimal tendency for selection bias in Taiwan. It likewise increased the statistical power and precision of risk estimation.

However, the present study has a number of limitations that originated from using insurance data. First, a number of suspected risk factors for HCC were not available, such as cigarette smoking, aflatoxin exposure, and body mass index. The inability to account for these factors may result in certain degrees of bias from confounding. Second, the claims' data do not contain laboratory test results. Thus, the extent of DM control among the study subjects was not accounted for because hemoglobin A1c values are not available. Third, this observational study does not explore the mechanism by which DM is related to HCC. Finally, misclassification and measurement errors in drug exposure might have occurred if the patients failed to take the prescribed drugs. Non-compliance is likely to cause underestimation of the drug effect.

## CONCLUSION

The current study suggests that patients with DM have a higher risk of developing HCC. Comorbidities such as cirrhosis, hepatitis B, and hepatitis C significantly aggravate the risk of developing HCC. The markedly elevated risk of developing HCC associated with hepatitis C and its synergism with cirrhosis provides new insights into HCC prevention. This observation may prompt the screening of high-risk patients. On the other hand, patients taking metformin or thiazolidinediones have reduced risks of developing HCC. Further investigations with larger numbers of study subjects are helpful for clarifying whether these insulin sensitizers have similar effect on HCC development among diabetic subgroups of liver comorbidities.

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## CONFLICT OF INTEREST

**Guarantor of the article:** Fung-Chang Sung, PhD, MPH.

**Specific author contributions:** Substantial contributions to the conception of this article; planned and conducted the study; initiated the draft of the article and critically revised it: Shih-Wei Lai; substantial contributions to the study concept and design; conducted data analysis and data interpretation; critically revised the article: Pei-Chun Chen; conducted data analyses; critically revised the article: Chih-Hsin Muo; participated in data interpretation; critically revised the article: Kuan-Fu Liao and Cheng-Chien Lin; substantial contributions to the concept and design, as well as data acquisition; critically revised the article: Fung-Chang Sung. All authors have approved the final revision.

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**Potential competing interest:** None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Previous studies have consistently reported a positive association between diabetes mellitus and cancer risk.
- ✓ Studies on whether diabetes is associated with increased incidence of hepatocellular carcinoma are contradictory in Taiwan.

### WHAT IS NEW HERE

- ✓ We found that patients with diabetes mellitus have an increased risk of hepatocellular carcinoma in Taiwan.
- ✓ Comorbidity of cirrhosis and/or hepatitis appears to be associated with extremely increased risk of hepatocellular carcinoma for patients with diabetes.

### HOW MIGHT IT AFFECT CLINICAL PRACTICE IN THE NEAR FUTURE?

- ✓ The high-risk patients should be closely monitored for hepatocellular carcinoma.
- ✓ Metformin and thiazolidinediones may be used to decrease the risk of developing hepatocellular carcinoma in diabetic patients.

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