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Original Article

The role of thiazolidinediones in hepatocellular carcinoma risk reduction: a population-based cohort study in Taiwan

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Abstract: Objectives: The aim of this study was to investigate the effect of thiazolidinediones (TZDs) on the risk of hepatocellular carcinoma (HCC) development among diabetes mellitus (DM) patients. Methods: We conducted a population-based case-control study in Taiwan based on data from the Taiwan National Health Insurance Research Database. A total of 76,349 newly diagnosed DM patients were identified from claims between 2000 and 2010. Among diabetics, 3,026 and 12,104 patients respectively, received or did not receive TZDs. Comparison frequency was matched with age, sex, and index date, excluding those with cancer at baseline. The incidence of HCC at the end of 2010 and the risks associated with the presence of hepatitis B and C infections were analyzed. The effect of TZDs use on the reduction of HCC risk was also assessed. Results: The incidence of HCC was lower in the TZD cohort compared with the non-TZD cohort (418.3 vs. 484.6 per 100,000 person-years), with an adjusted hazard ratio (HR) of 0.53 (95% confidence interval = 0.38-0.77) using multivariable Cox proportional hazard regression. In the stratified analysis, HCC risk reduction was greater for diabetics without the comorbidities of cirrhosis, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, end-stage renal disease, and hyperlipidemia, in the TZD cohort than in the non-TZD cohort. Male sex, cirrhosis, hepatitis B, and hepatitis C were significant independent factors predicting HCC (HRs of 1.43, 13.96, 2.31, and 2.15, respectively). Conclusions: This study suggests that the use of TZDs may reduce the risk of developing HCC among DM patients. Comorbidity with cirrhosis and/or hepatitis B/C infection appears to be associated with an extremely increased risk of developing HCC in this patient subset. These high-risk patients should be closely monitored.

Keywords: Thiazolidinediones (TZDs), peroxisome proliferator activated receptor gamma (PPARγ), hepatocellular carcinoma (HCC), diabetes mellitus (DM), cohort study

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide, particularly in Asia and Africa [1-3]. Despite remarkable advances in early detection and therapy, the incidence and mortality rate of HCC has significantly increased in recent decades. HCC development is a multistep and long-term process, and is primarily associated with hepatitis B or hepatitis C viral infection [2]. Other predisposing factors include alcoholic liver cirrhosis, nonalcoholic steatohepatitis, intake of aflatoxin B1-contaminated food, and metabolic disorder [4, 5]. Diabetes mellitus (DM), with insulin resistance, is an established independent risk factor for HCC, as reported in multiple observational studies and subsequent meta-analysis [6, 7]. As part of the metabolic syndrome, DM is believed to share many risk factors with a variety of cancers. This effect is related to insulin and hyperglycemia-induced oncogenic effects,

as well as the obesity-associated chronic inflammatory state. The underlying mechanisms responsible for the increased risk of HCC development in patients with DM are complex and remain controversial. Current evidence suggests that there may be interplay between obesity, DM, and tumorigenesis, with insulin resistance and hyperinsulinemia playing critical roles [8].

Given the significant link of DM with the risk of HCC, the use of antidiabetic medications may modify DM and reduce the risk of cancer as shown in recent research [9, 10]. Metformin and thiazolidinediones (TZDs) are widely used antidiabetic drugs. Epidemiological studies have shown that the use of metformin and probably TZDs, among diabetic patients, may be associated with a lower risk of overall cancer incidence and mortality [11, 12].

TZDs such as troglitazone, rosiglitazone, and pioglitazone are a class of oral antidiabetic drugs that improve metabolic control in patients with type 2 diabetes by increasing their insulin sensitivity. The increase in insulin sensitivity is achieved by acting on adipose, muscle, and the liver to increase glucose utilization and to decrease glucose production. TZDs exert their antidiabetic effects through a mechanism involving activation of the nuclear receptor known as peroxisome proliferator-activated receptor gamma (PPARγ). They bind to and activate one or more PPARs, which regulate gene expression in response to ligand binding [13]. The nuclear transcription factor PPARγ is a member of the nuclear hormone receptor superfamily, activated by the binding of its ligand and subsequently heterodimerizing with the retinoid X receptor. Numerous studies have demonstrated that PPARγ is involved in many important biological processes, including insulin sensitivity, glucose metabolism, and inflammation in the liver tissue, adipose tissue, and skeletal muscle tissue. Thereby, it plays an essential role in regulating adipogenesis, inflammation, tumorigenesis, and metastasis [14, 15]. PPARγ, combined with its ligands, has been shown to exert inhibitory effects on HCC cell growth, migration, and metastasis in mice and in *in vitro* models [16, 17]. TZDs have been postulated to induce cell growth arrest and apoptosis, and to prevent cancer cell invasion. Activation of PPARγ by agonists such as TZDs has been shown to exert anticancer effects *in vitro* and *in vivo* in many cancer types.

The National Health Insurance (NHI) has created the Taiwan National Health Insurance Research Database (NHIRD) for researchers in Taiwan. This database has been widely used in epidemiologic and clinical studies [18, 19]. A population-based cohort study, utilizing a large dataset available from the NHIRD program in Taiwan, was conducted to investigate the effect of TZDs on the risk of HCC development.

The aim of this study was to further investigate the risk of HCC development in the presence of diabetes, hepatitis B, hepatitis C, and comorbidities (cirrhosis, alcoholic liver disease, nonalcoholic fatty liver disease, end-stage renal disease, hypertension, and hyperlipidemia). Furthermore, the study examines the influence of TZD treatment on the clinical outcome. We hypothesized that the long-term use of TZDs may be associated with a reduced risk of HCC. Such a finding would indicate that these therapeutic agents may be potentially useful in cancer prevention.

Methods

Data sources

The NHI program in Taiwan is a universal health insurance system covering more than 99% of the country's population (23 million). We used data from the NHIRD spanning a period from 2000 to 2010. The data were provided by the Bureau of NHI of the Department of Health in Taiwan. This study adopted the Longitudinal Health Insurance Database 2005 (LHID2005), a subset of one million insurants randomly selected from the database. The LHID2005 contains encrypted medical data including gender, date of birth, registry of medical services, diagnoses, (based on the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnostic and procedure codes) and medication prescription details. All personal identification information is encrypted and de-identified prior to data release for research purposes, to protect patient privacy. The present study was approved by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (approval number 2-105-05-082), and the study protocol was performed in accordance with the Helsinki Declaration of 1975 (1983 revision). We were granted access to the NHI research database, and our study protocol was approved by the research ethics committee of the institute.

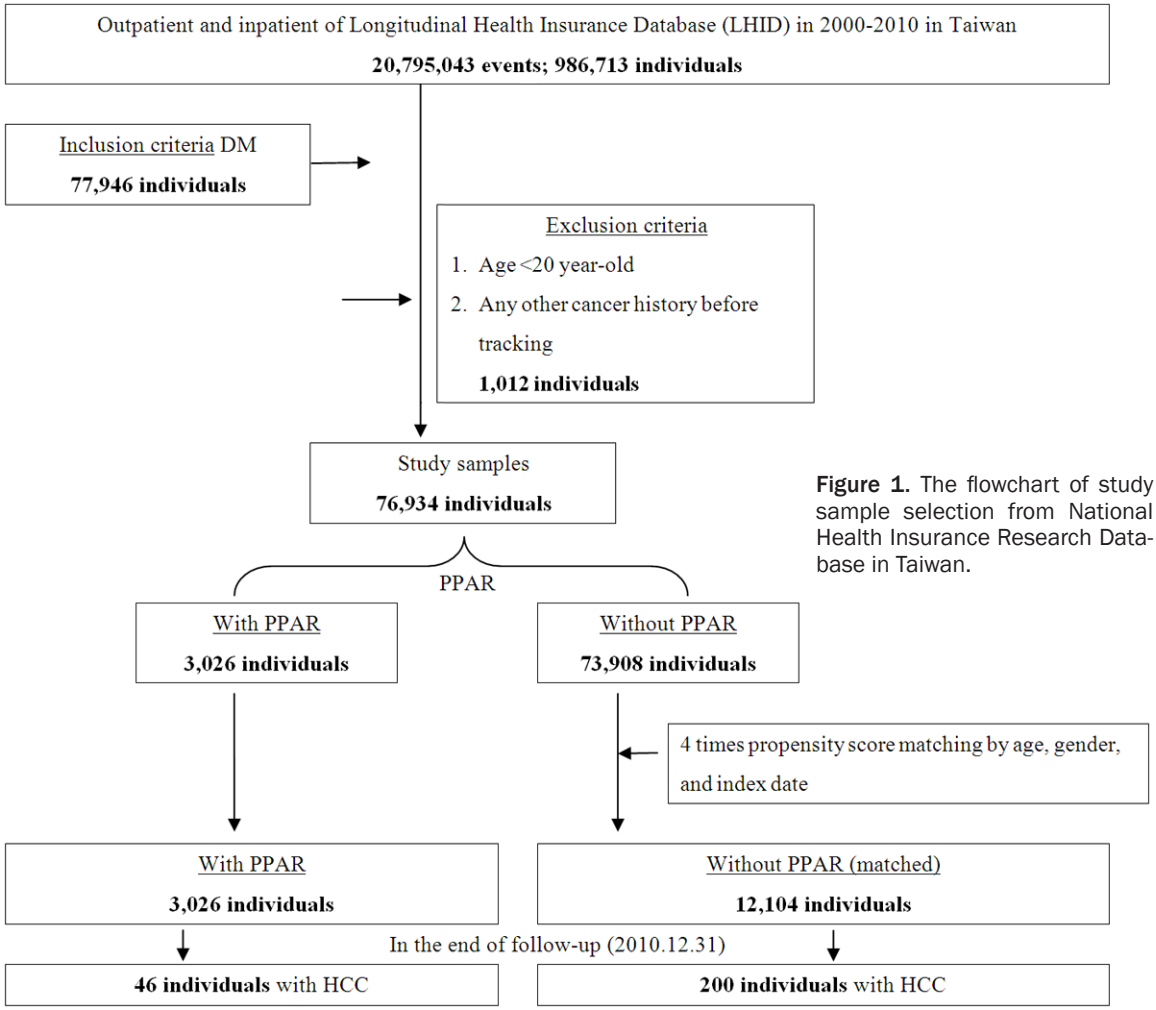

Figure 1. The flowchart of study sample selection from National Health Insurance Research Database in Taiwan.

Study population

Design: This retrospective cohort study included patients aged >20 years without a history of cancer (ICD-9-CM codes 140-208). The available data spanned between January 1, 2000 and December 31, 2010. The patients were divided into 2 cohorts: the TZD cohort included patients who had received TZD therapy, whereas the non-TZD cohort included those who had not received TZD therapy prior to and during follow-up. Among diabetic patients, those who had been prescribed rosiglitazone or pioglitazone prior to the study's end date formed the TZD cohort; all others were included in the non-TZD cohort. We conducted a population-based cohort study (**Figure 1**) to investigate the relationship between the use of TZDs in DM patients and the risk of HCC development (ICD-9-CM codes 155, 155.0 and 155.2). We included inpatients and outpatients with diagnosed DM (ICD-9-CM codes 250.xx, 160-161). The index date for these patients was defined as the date of their diagnosis.

Comorbidities in this study included hepatitis B (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, and 070.32), hepatitis C (ICD-9-CM codes V02.62, 070.41, 070.44, 070.51, and 070.54), cirrhosis (ICD-9 codes 571.2, 571.5, and 571.6), alcoholic liver disease (ICD-9 codes 571.0, 571.1, and 571.3), nonalcoholic fatty liver disease (NAFLD) (ICD-9 code 571.8), end-stage renal disease (ICD-9-CM code 585), hypertension (ICD-9-CM codes 401-405), and hyperlipidemia (ICD-9-CM code 272).

Both cohorts were followed up to determine the incidence of HCC (ICD-9 codes 155, 155.0, and 155.2) until the end of 2010 or censored due to death, withdrawal from the insurance program, or patient loss during follow-up consultations.

Table 1. Baseline demographic status and comorbidity compared between the TZDs cohorts and with comparison

	Total		TZDs cohort		Non-TZDs cohort		P
Variables	n	%	n	%	n	%	
Total	15,130		3026	20.00	12,104	80.00	
Gender							0.999
Male	7,890	52.15	1,578	52.15	6,312	52.15	
Female	7,240	47.85	1,448	47.85	5,792	47.85	
Age (yrs) (mean ± SD)	62.13±14.31		61.57±13.94		62.27±14.40		0.124
Age groups (yrs)							0.999
20-49	3,215	21.25	643	21.25	2,572	21.25	
50-64	5,165	34.14	1,033	34.14	4,132	34.14	
≥65	6,750	44.61	1,350	44.61	5,400	44.61	
Comorbidities							
HBV							0.055
Without	14,967	98.92	3,002	99.21	11,965	98.85	
With	163	1.08	24	0.79	139	1.15	
HCV							0.126
Without	14,963	98.90	2,999	99.11	11,964	98.84	
With	167	1.10	27	0.89	140	1.16	
Liver cirrhosis							0.003
Without	14,757	97.53	2,973	98.25	11,784	97.36	
With	373	2.47	53	1.75	320	2.64	
Alcoholic liver disease							0.261
Without	15,078	99.66	3,018	99.74	12,060	99.64	
With	52	0.34	8	0.26	44	0.36	
NAFLD							0.494
Without	14,867	98.26	2,974	98.28	11,893	98.26	
With	263	1.74	52	1.72	211	1.74	
ESRD							<0.001
Without	14,691	97.10	2,974	98.28	11,717	96.80	
With	439	2.90	52	1.72	387	3.20	
Hyperlipidemia							<0.001
Without	13,848	91.53	2,823	93.29	11,025	91.09	
With	1,282	8.47	203	6.71	1,079	8.91	
Hypertension							<0.001
Without	9,114	60.24	1,966	64.97	7,148	59.05	
With	6,016	39.76	1,060	35.03	4,956	40.95	
CCI_R		0.38±0.68		0.37±0.70		0.39±0.68	0.364

P-value (category variable: Chi-square/Fisher exact test; continue variable: independent samples t-test). SD = standard deviation; CCI_R = Charlson Comorbidity Index removed. NAFLD: Nonalcoholic fatty liver disease ESRD: end-stage renal disease.

Cancer events were identified according to the Registry of Catastrophic Illness Patient Database. Cancer is categorized as a catastrophic illness in the NHI program and patients newly diagnosed with cancer may apply for a catastrophic illness certification. The certification is issued by the government following a stringent process of verification, which involves the review of medical records and images, as well as pathology reports by a panel of specialists/experts on the disease.

Statistical analysis

The distribution of age, sex, and comorbidities was expressed as a frequency of mean ± standard deviation. The categorical variables were analyzed using the chi-square test, and the continuous variables of the baseline character-

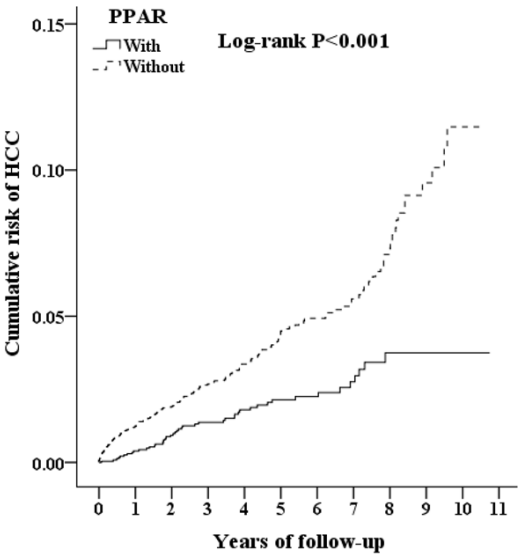

Figure 2. Kaplan-Meier for cumulative risk of HCC among DM patients over stratified by TZDs (PPAR) with log-rank test.

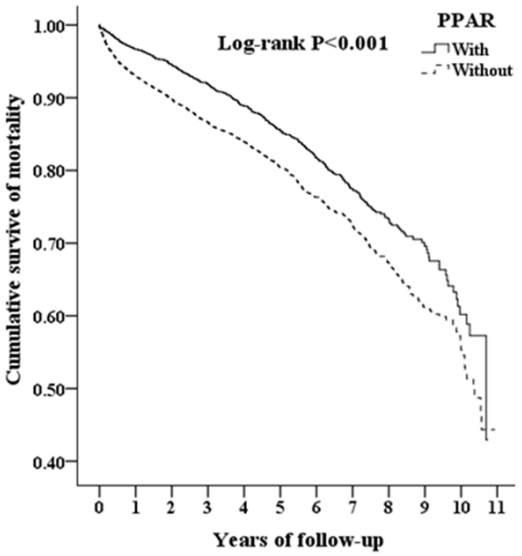

Figure 3. Kaplan-Meier for cumulative survive of mortality among DM patients over stratified by TZDs (PPAR) with log-rank test.

istics of both cohorts were analyzed using the Student's t-test. The Kaplan-Meier method was employed to plot the cumulative incidence curves of cancer for the two cohorts, and the log-rank test was performed to examine the difference between the curves. The multivariate models were simultaneously adjusted for age, sex, as well as the comorbidities of diabetes, hepatitis B and C, cirrhosis, alcoholic liver disease, NAFLD, end-stage renal disease, hypertension, and hyperlipidemia. The Cox proportional hazards regression model was adjusted for potential confounding factors to estimate hazard ratios (HRs) with a 95% confidence interval (CI). All statistical analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC, USA). *P* values <0.05 were considered statistically significant.

Results

A total of 76,934 patients with DM met the eligibility criteria. They comprised 3,026 patients in the TZD cohort and 73,908 patients in the non-TZD cohort, 4 times matched 12,104 patients on the propensity score by age, gender and index date (**Figure 1**). The baseline characteristics of patients are shown in **Table 1**. The mean age of patients in the TZD and non-TZD cohorts was 61.5±13.9 and 62.1±14.4 years, respectively. No significant differences were observed between the cohorts. The mean follow-up period was 6.63±5.97 and 4.70±5.54 years in the TZD and non-TZD cohorts, respectively.

Kaplan-Meier analysis showed that by the end of the 11-year follow-up period, the cumulative incidence of HCC was significantly lower in the TZD cohort than in the non-TZD cohort (log-rank test: P<0.001) (**Figure 2**). Moreover, the mortality rate of HCC was lower in the TZD cohort compared with that in the non-TZD cohort (**Figure 3**).

The multivariate Cox proportional hazard regression analysis of sex, age, and comorbidities is shown in **Table 2**. This analysis model revealed an adjusted HCC HR of 0.53 (95% CI = 0.38-0.77) for the TZD cohort. The HR increased with age, and the incidence was higher in male than in female patients (HR = 1.43, 95% CI = 0.32-0.61). Among the comorbidities, cirrhosis had the highest HR (HR = 13.96, 95% CI = 10.39-18.74), followed by hepatitis B (HR = 2.31, 95% CI = 1.51-3.54) and hepatitis C (HR = 2.15, 95% CI = 1.47-3.16).

Table 3 shows the comparison of incidence density of HCC between the TZD and non-TZD cohorts among comorbidity using multivariate Cox proportional hazards regression analysis. In total, 46 patients in the TZD cohort (incidence of 418.37 per 100,000 person-years)

Table 2. Adjusted hazard ratios and 95% confidence intervals of hepatocellular carcinoma associated with TZDs and covariates

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)
TZDs		
Without	1.00 Reference	1.00 Reference
With	0.44 (0.32-0.61)	0.53 (0.38-0.77)
Gender		
Male	1.75 (1.34-2.27)	1.43 (1.08-1.88)
Female	1.00 Reference	1.00 Reference
Age (years)		
20-49	1.00 Reference	1.00 Reference
50-64	1.30 (0.85-2.00)	1.43 (0.92-2.22)
65+	1.09 (0.75-1.64)	1.82 (1.82-2.78)
HBV		
Without	1.00 Reference	1.00 Reference
With	11.43 (7.70-16.97)	2.31 (1.51-3.54)
HCV		
Without	1.00 Reference	1.00 Reference
With	10.45 (7.36-14.83)	2.15 (1.47-3.16)
Liver cirrhosis		
Without	1.00 Reference	1.00 Reference
With	21.28 (16.56-27.35)	13.96 (10.39-18.74)
Alcoholic liver disease		
Without	1.00 Reference	1.00 Reference
With	0 (-)	0 (-)
NAFLD		
Without	1.00 Reference	1.00 Reference
With	1.35 (0.33-5.46)	1.33 (0.32-5.43)
ESRD		
Without	1.00 Reference	1.00 Reference
With	0.60 (0.37-0.99)	0.77 (0.47-1.27)
Hyperlipidemia		
Without	1.00 Reference	1.00 Reference
With	0.21 (0.07-0.67)	0.42 (0.13-1.33)
Hypertension		
Without	1.00 Reference	1.00 Reference
With	0.45 (0.33-0.61)	0.80 (0.58-1.11)

HR = hazard ratio, CI = confidence interval, Adjusted HR: Adjusted variables listed in the table.

and 200 patients in the non-TZD cohort (incidence of 484.64 per 100,000 person-years) (adjusted HR = 0.53, 95% CI = 0.38-0.77) were diagnosed with HCC. Patients in the TZD cohort had a 0.53-fold lower risk of cancer compared with that for patients in the non-TZD cohort.

In the stratified analysis, patients without the comorbidities of hepatitis B (adjusted HR = 0.49, 95% CI = 0.34-0.69), hepatitis C (adjusted HR = 0.61, 95% CI = 0.43-0.86), cirrhosis (adjusted HR = 0.47, 95% CI = 0.30-0.73), NAFLD (adjusted HR = 0.52, 95% CI = 0.39-0.49), end-stage renal disease (adjusted HR = 0.56, 95% CI = 0.40-0.78), and hyperlipidemia (adjusted HR = 0.51, 95% CI = 0.37-0.72) showed a lower risk of developing HCC in the TZD cohort versus the non-TZD cohort.

Sensitivity analysis

Lastly, we also performed sensitivity analyses to assess the associations between TZDs and the risk of developing HCC according to different follow-up durations (**Table 4**). These findings suggested that, compared with the non-TZD cohort, the TZD cohort was associated with a significantly lower risk of developing HCC as the follow-up duration was increased. In particular, patients treated with TZDs and followed up for a period longer than 3 years had a significantly lower incidence of HCC (adjusted HR = 0.52, 95% CI = 0.31-0.88).

Discussion

The NHIRD used in the present investigation is an effective resource providing age- and sex-matched patient data for population-based studies. Participation in the NHI program is mandatory and all Taiwanese residents have access to medical care with low copayments. Therefore, patient loss during follow-up is low. The cancer burden in Taiwan has been a concern for the government, which in response has inspirited several prevention programs for certain cancers with high incidence. Such programs include education of the general population to avoid high-risk factors of cancer and to receive periodical cancer screening, aimed at decreasing cancer incidence and mortality rates [20]. Consequently, population-based research in the field of cancer preven-

Table 3. Incidence of subsequent hepatocellular carcinoma and multivariate Cox proportional hazards regression analysis measured hazard ratio for the study cohorts

Variable	TZDs cohort			Non-TZDs cohort			Adjust HR	95% CI	95% CI	P
	Patient	PYs	Rate (/10^5 PYs)	Patient	PYs	Rate (/10^5 PYs)				
Total	46	10,994.97	418.37	200	41,267.88	484.64	0.538	0.389	0.774	<0.001
Gender										
Male	30	5,709.74	525.42	131	21,409.48	611.88	0.520	0.349	0.776	0.001
Female	16	5,285.23	302.73	69	19,858.40	347.46	0.565	0.324	0.986	0.044
Age (yrs)										
20-49	4	1,392.03	287.35	24	5,332.98	450.03	0.300	0.099	0.911	0.034
50-64	18	3,374.00	533.49	65	11,834.98	549.22	0.647	0.379	1.103	0.110
≥65	24	6,228.94	385.30	111	24,099.92	460.58	0.497	0.318	0.777	0.002
Comorbidity										
HBV										
Without	40	10,907.71	366.71	178	41,041.80	433.70	0.494	0.349	0.698	<0.001
With	6	87.26	6,876.00	22	226.08	9,731.07	0.785	0.290	2.128	0.635
HCV										
Without	44	10,844.41	405.74	165	40,512.12	407.29	0.615	0.439	0.861	0.005
With	2	150.56	1,328.37	35	755.76	4,631.10	0.081	0.016	0.409	0.002
Liver cirrhosis										
Without	24	10,619.97	225.99	103	39,858.66	258.41	0.470	0.300	0.734	0.001
With	22	375.00	5,866.67	97	1,409.22	6,883.24	0.673	0.419	1.083	0.103
Alcoholic liver disease										
Without	46	10,966.41	419.46	200	41,708.82	479.51	0.538	0.389	0.774	<0.001
With	0	28.56	0.00	0	99.06	0.00	-	-	-	-
NAFLD										
Without	46	10,935.61	420.64	198	41,026.16	482.62	0.542	0.392	0.749	<0.001
With	0	59.36	0.00	2	241.72	827.40	0.000	-	-	0.985
ESRD										
Without	43	9,583.41	448.69	186	37,121.22	501.06	0.563	0.403	0.788	0.001
With	3	1,411.56	212.53	14	4,146.64	337.62	0.333	0.094	1.183	0.089
Hyperlipidemia										
Without	44	10,463.34	420.52	199	38,969.16	510.66	0.518	0.372	0.720	0.005
With	2	531.63	376.20	1	2,298.72	43.50	7.015	0.500	98.430	0.148
Hypertension										
Without	41	6,963.41	588.79	152	25,484.00	596.45	0.670	0.472	0.951	0.025
With	5	4,031.56	124.02	48	15,783.88	304.11	0.194	0.076	0.493	0.001

NAFLD: Nonalcoholic fatty liver disease; ESRD: end-stage renal disease.

tion epidemiology, such as the current study of HCC risk among patients with DM, is ongoing.

Previous literature has consistently reported the association of HCC with DM. In the systematic review conducted by El-Serag *et al.* [21], 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. A population-based case-control study in the United States [22], demonstrated that DM is associated with a 2- to 3-fold increase in the risk of HCC, regardless of the presence of other major HCC risk factors. An additional study showed that there is a 3.64-fold (95% CI = 2.61-5.07) increased risk for the development of HCC in patients with DM compared with non-diabetics [23]. The findings of this population-based study suggested that DM is an independent risk factor for HCC.

On this basis, several studies have assessed the association between the use of antidiabetic drugs and the risk of developing HCC. Metformin, an insulin sensitizer, reduces the levels of circulating glucose and insulin, and exerts

Table 4. Cox proportional hazards model for the risk of developing HCC inthe study cohorts by the follow-up year

Years of follow-up	TZDs cohort			Non-TZDs cohort			Adjust HR	95% CI		P
	Patient	PYs	Rate (/10^5 PYs)	Patient	PYs	Rate (/10^5 PYs)				
Total	46	10,994.97	418.37	200	41,267.88	484.64	0.538	0.389	0.774	<0.001
<1	9	160.70	5,600.50	75	2,000.68	3,748.73	0.737	0.364	1.489	0.395
≥1, <2	11	427.36	2,573.94	28	4,079.64	686.34	1.446	0.691	3.054	0.327
≥2, <3	8	764.69	1,046.18	25	5,095.14	490.66	0.925	0.409	2.093	0.852
≥3	18	9,642.22	186.68	72	30,912.42	232.92	0.524	0.310	0.886	0.016

protective effects against carcinogenesis in patients with insulin resistance and hyperinsulinemia.

Metformin has been shown to have a chemopreventive effect and to reduce the risk of HCC [24-26]. Similarly, TZDs as PPARγ agonists increase insulin sensitivity and trigger cell cycle arrest, apoptosis, as well as anti-proliferative, anti-angiogenic, and pro-differentiation pathways, thus contributing to the down-regulation of carcinogenesis [27]. Several preclinical *in vitro* and *in vivo* studies have shown that PPARγ may reduce the risk of HCC. Moreover, a hospital-based case-control study conducted by Hassan *et al.* in the United States [28] has shown that TZDs may reduce the risk of HCC. Furthermore, another cohort study [9] demonstrated a decrease in the risk of HCC development as the duration of TZD administration, a finding consistent with our observations in the present study. Furthermore, the current study suggests that HCC risk reduction was greater for diabetics without the comorbidities of cirrhosis, hepatitis B and C, NAFLD, end-stage renal disease, and hyperlipidemia in the TZD cohort compared with the non-TZD cohort.

In 2002, Galli et al. [29] demonstrated that TZDs may significantly reduce the development of liver fibrosis induced in rats. These early results showing the importance of PPARγ activation in the pathogenesis of fibrosis have since been confirmed by others [30]. Likewise, a randomized double-blind placebo-controlled study assessed the effect of pioglitazone versus a placebo in patients with nonalcoholic steatohepatitis [31]. The study assessed fibrosis on liver biopsy prior to and after 6 months of a calorie-restricted diet with or without pioglitazone. The administration of pioglitazone led to metabolic and histological improvement in patients with nonalcoholic steatohepatitis.

PPARγ plays an important role in carcinogenesis, and therefore TZDs are expected to inhibit the proliferation of HCC. Previous studies have suggested that overexpression of PPARγ in human HCC may be the underlying mechanism for the reduction of HCC risk [32]. The role of PPARγ in apoptosis and anoikis has been highlighted as an important pathway [33, 34]. Several *in vitro* studies have reported the induction of apoptosis in HCC cell lines. Cell adhesion and anoikis were induced independently of PPARγ expression. The effect of PPARγ agonists and antagonists on cell growth, migration, and invasion in four different HCC cell lines has also been evaluated [35]. The results indicated that treatment with a PPARγ may prevent cell growth and invasion of high-grade HCC cells.

The association of HCC with other comorbidities, particularly for DM patients with cirrhosis, hepatitis B, and/or hepatitis C has been consistently demonstrated [36-38]. Sorensen et al. [39] conducted a nationwide cohort study in Denmark to investigate the risk of HCC and other cancers in patients with cirrhosis, determining that the risk of HCC was exceptionally high (standardized incidence ratio = 36, 95% CI = 32-41). These results have been corroborated by other researchers [40-42] and are consistent with our data, indicating a markedly higher risk of HCC. Notably, liver cirrhosis has long been regarded as the most critical premalignant lesion of HCC, and research has established that liver cirrhosis is a substantial determinant for HCC development, regardless of the presence of alcoholic or nonalcoholic cirrhosis. In line with these findings, the present study observed a synergistic effect between DM and liver comorbidities with regard to the develop-

ment of HCC. The HCC risk was strongly associated with these three comorbidities, particularly cirrhosis (HR = 13.96). The risk of HCC in patients with hepatitis B is higher compared with that in those with hepatitis C (HR = 2.31 vs. HR = 2.15).

However, in the United States and several other Western countries, alcohol-related cirrhosis, hepatitis C, and NAFLD associated with obesity and metabolic syndrome, are thought to contribute to the majority of HCC cases. In contrast, chronic hepatitis B infection is the dominant predisposing factor for HCC in most areas of Asia and sub-Saharan Africa, whereas it accounts for only 23% of HCC in the developed world. This difference in the underlying etiopathogenesis of HCC may account for the differential effects observed in these diverse populations.

Our study has several limitations. Firstly, socioeconomic (e.g., educational level, occupation), environmental, and biological factors (hormone levels), well-known causes of carcinogenesis, were not included in the records of the NHIRD. In addition, we did not have access to important clinical risk factors for these patients, such as body mass index, smoking habits, lipid levels, and liver function test data. However, our results are consistent with those of previous studies.

Secondly, our estimations were based on a case-control study. Although the controls were matched by age, sex and clinic visit date to balance demographic characteristics and to conduct multivariate and stratified analyses to confirm the robustness of our observations, unmeasured confounders may exist.

Thirdly, we did not analyze the dose of TZDs administered daily. However, most patients received rosiglitazone (4-8 mg per day) once daily or split doses and pioglitazone (15-45 mg per day) once daily in the present study. The numbers of TZDs using days could be analyzed as the total dose of TZDs taken.

The large sample size is an asset of the present study. The results illustrate the direction of HCC prevention in patients with DM. Furthermore, the population-based dataset along with the large sample size allow the demonstration of risk factors for HCC with a minimal tendency for selection bias in Taiwan. This approach increased the statistical power and precision of risk estimation. Since our observations are based on a nationwide population, the results may be generalizable to other populations, at least in Asian countries.

Conclusion

This population-based retrospective cohort study suggests that the use of TZDs may be associated with a decreased risk of HCC development among DM patients.

TZDs may play a role in the chemoprevention of liver cancer. Comorbidities such as cirrhosis, hepatitis B, and hepatitis C significantly aggravate the risk of developing HCC. Further studies, particularly prospective randomized trials, are warranted to confirm our findings and the value of TZDs in HCC prevention and treatment.

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Disclosure of conflict of interest

None.

Authors' contribution

The individual authors contributions were as follows: design: Research idea and study design: Hsuan-Hwai Lin; manuscript writing: Mao-Yu Huang; data acquisition and statistical analysis Chi-Hsiang Chung, Wu-Chien Chien; results analysis/interpretation: Wei-Kuo Chang, Tsai-Yuan Hsieh, Kai-Wen Chen and Chun-Shu Lin. Each author contributed important intellectual content during the manuscript drafting or revision.

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