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Decreased risk of renal cell carcinoma in patients with type 2 diabetes treated with sodium glucose cotransporter-2 inhibitors

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Abstract

Patients with type 2 diabetes (T2D) are at a higher risk of developing renal cell carcinoma (RCC) than the general population. In vitro and in vivo investigations of the effects of sodium glucose cotransporter-2 inhibitors (SGLT2I) have shown a significantly reduced risk of RCC. However, the impact of these drugs on the incidence of RCC in the human population is unclear. This study aimed to examine the association between SGLT2I use and RCC risk in patients with T2D. We undertook a nationwide retrospective cohort study using the Health and Welfare Data Science Center database (2016–2020). The primary outcome was the risk of incident RCC by estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Multiple Cox regression modeling was applied to analyze the association between SGLT2I use and RCC risk in patients with T2D. In a cohort of 241,772 patients with T2D who were using SGLT2Is and 483,544 participants who were not, 220 and 609 RCC cases, respectively, were recorded. The mean follow-up period of the study subjects was 2 years. There was a decreased risk of RCC for SGLT2I users after adjusting for the index year, sex, age, comorbidities, and concurrent medication (adjusted HR 0.68; 95% CI, 0.58–0.81). The sensitivity test for the propensity score 1:1-matched analyses showed similar results (adjusted HR 0.67; 95% CI, 0.55–0.81). The subgroup analysis revealed consistent results for sex, age (<70 years), and comorbidity with chronic kidney disease. The present study indicates that SGLT2I therapy significantly decreases RCC risk in patients with T2D. This finding was also consistent among the sensitivity test and subgroup analysis for those with or without chronic kidney disease/hypertension.

KEYWORDS
chronic kidney disease, comorbidity, renal cell carcinoma, SGLT2 inhibitor, type 2 DM

Gwo-Ping Jong and Tsung-Yuan Yang contributed equally to this work.

1 | INTRODUCTION

The incidence of renal cell carcinoma (RCC) has been on the rise globally over the past decade, resulting in a significant health burden.[1,2] Studies have shown that type 2 diabetes (T2D) is associated with an increased risk of RCC.[3,4] Renal cell carcinoma has a high morbidity and mortality, due to late diagnosis and limited treatment options[5–7] and poses a major management challenge for health services. Therefore, methods for decreasing the incidence of RCC are urgently needed.

Sodium glucose cotransporter-2 inhibitors (SGLT2Is) are glucose-lowering therapies that target the SGLT2 protein and are used in patients with T2D.[8,9] Several in vitro and in vivo studies have found that SGLT2Is could reduce the risk of RCC. Kuang et al. have shown intriguing RCC benefits with dapagliflozin, which could play an important role in regulating the cell cycle and apoptosis. It also reduces glucose uptake and inhibits tumor growth.[10] Similarly, Phillips et al.[11] showed in CD-1 mouse models and xenografts that empagliflozin reduced the growth of renal tumors in female mice. These findings highlight the need to investigate associations between SGLT2Is and RCC in populations with T2D. However, no epidemiological studies have investigated this exciting possibility. Therefore, we undertook a population-based study aiming to evaluate the risk of RCC associated with the use of SGLT2Is in patients with T2D using real-world data from the Health and Welfare Data Science Center (HWDC).

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

This was a retrospective population-based cohort study using the HWDC database from 2004 to 2020. It contains health-care information for more than 23 million people with a more than 99% coverage rate of Taiwanese residents.[12] This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13]

This study included adults (aged >20 years) with T2D International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code E11, who were treated with the maximum tolerated labeled dose of an SGLT2I on admission to hospital or as outpatients, between May 2016 and December 2019.

The study group (SGLT2I users) consisted of patients who received at least one SGLT2I prescription for 180 days during the study period. The control group (non-SGLT2I users) consisted of randomly selected T2D patients who did not receive any SGLT2I prescriptions throughout the study period. The inclusion criteria were: (1) had two or more outpatient visits within 6 months, (2) continuously received antidiabetic medication for more than 6 months during the study period, or (3) had one or more admissions with a diagnosis of T2D. Comorbidities related to RCC were recorded according to the ICD-10-CM code and included coronary heart disease (ICD-10-CM codes I20–I25), hypertension (ICD-10-CM code I10), hyperlipidemia (ICD-9-CM codes E78.1–E78.5), chronic liver disease (ICD-10-CM codes K71, K75, K76), stroke (ICD-10-CM codes I60, I61, I62, I63, I65, I66, I67.84, G45, G46), chronic obstructive pulmonary disease (ICD-10-CM code J44), atrial fibrillation and flutter (ICD-10-CM code I48), and rheumatoid arthritis (ICD-9-CM code M05). Exclusion criteria between study group and control group included: (1) a history of RCC or other cancers before the index date, (2) follow-up of less than 6 months, and (3) aged less than 20 years. To account for the differences in baseline characteristics and RCC risk between the SGLT2I users and the control group, the groups were matched for age, sex, and index date at a ratio of 1:2. The index date was defined as the first SGLT2I prescription between May 2016 and December 2019.

2.2 | Variables and study outcomes

All baseline characteristics were assessed on the index date. The baseline variables included: gender, age, diabetes duration, comorbidities, and concurrent medication. Comorbidities and medication use were restricted to prescriptions made within 6 months before the index date. The study end-point was the development of RCC, defined as the first occurrence of an RCC code (ICD-10-CM code C64) in inpatient or outpatient claim records during follow-up or follow-up to December 2020.

2.3 | Statistical analysis

The number, percentage, and SD of patients meeting each baseline characteristic were reported. Differences in baseline patient characteristics were examined using the absolute standardized differences (ASD) between SGLT2I users and nonusers. ASD mean difference ≤0.10 indicates a negligible difference in potential confounders between the two groups. In both cohorts, the incidence rates of RCC were calculated as per 10,000 person-months. A time-dependent Cox proportional hazard regression model was used to compare the risk of developing RCC between the groups. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, adjusting for important risk factors for developing events, including age, sex, index date, concurrent medication, and comorbidities. The cumulative risk of study outcomes over time for the SGLT2I group compared with controls was calculated using the Kaplan–Meier method.

A sensitivity analysis was also carried out to test the robustness of our primary findings. We performed propensity score 1:1 matching to balance baseline covariates between groups. Then the ASD was calculated to estimate the difference between the two groups. An ASD <0.10 implies a negligible difference in the potential confounders between the two groups.

Additionally, we undertook subgroup analyses stratified by sex, age, and comorbidity with or without chronic kidney disease/hypertension at baseline for the primary outcomes of RCC. The results are presented as HRs with 95% CIs. Statistical significance was considered at $p < 0.05$. All statistical calculations were carried out using SAS version 9.3 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

From May 2016 through December 2019, we identified 282,211 T2D patients who received their first SGLT2I prescriptions. After exclusions we had 241,772 individuals in the study group and 483,544 control patients matched for sex, age, and index date at a 1:2 ratio (Figure 1). The mean follow-up period of the study subjects were 2.0 years. Patients in the SGLT2I group had more comorbidities at baseline (except for rheumatoid arthritis) and used more concurrent medication (except for H2 receptor antagonists) than the control group patients (Table 1).

3.2 | Relative risk of RCC in patients matched for sex, age, and index date at a 1:2 ratio

The crude incidence rate of RCC was 0.37 per 10,000 person-months (95% CI, 0.33–0.43) for SGLT2I users compared with 0.52 (95% CI, 0.48–0.57) for non-SGLT2I users. There was a significantly lower incidence of RCC in the SGLT2I group than in the control group (crude HR 0.72; 95% CI, 0.62–0.84) (Table 2). The results did not substantially change after adjustments for the index date, sex, age, comorbidities, and concurrent medication at baseline (adjusted HR [aHR] 0.68; 95% CI, 0.58–0.81). The effects of SGLT2 inhibitor treatment on RCC incidence were illustrated in a Kaplan–Meier plot (Figure 2A). Moreover, the cumulative incidence of RCC ($p < 0.0001$) was lower in the SGLT2I group than in the non-SGLT2I group.

3.3 | Sensitivity analysis of the relative risk of RCC in propensity score matching

A sensitivity analysis of the relative risk of RCC in a propensity score 1:1 matching analysis was carried out. Initially, the Cox regression analysis indicated that SGLT2I users had a 33% reduction compared with nonusers (crude HR 0.67; 95% CI, 0.56–0.81) (Table 2). After adjusting the index date, sex, age, comorbidities, and concurrent medication, the results were consistent with the main findings (aHR 0.67; 95% CI, 0.55–0.81; Table 2).

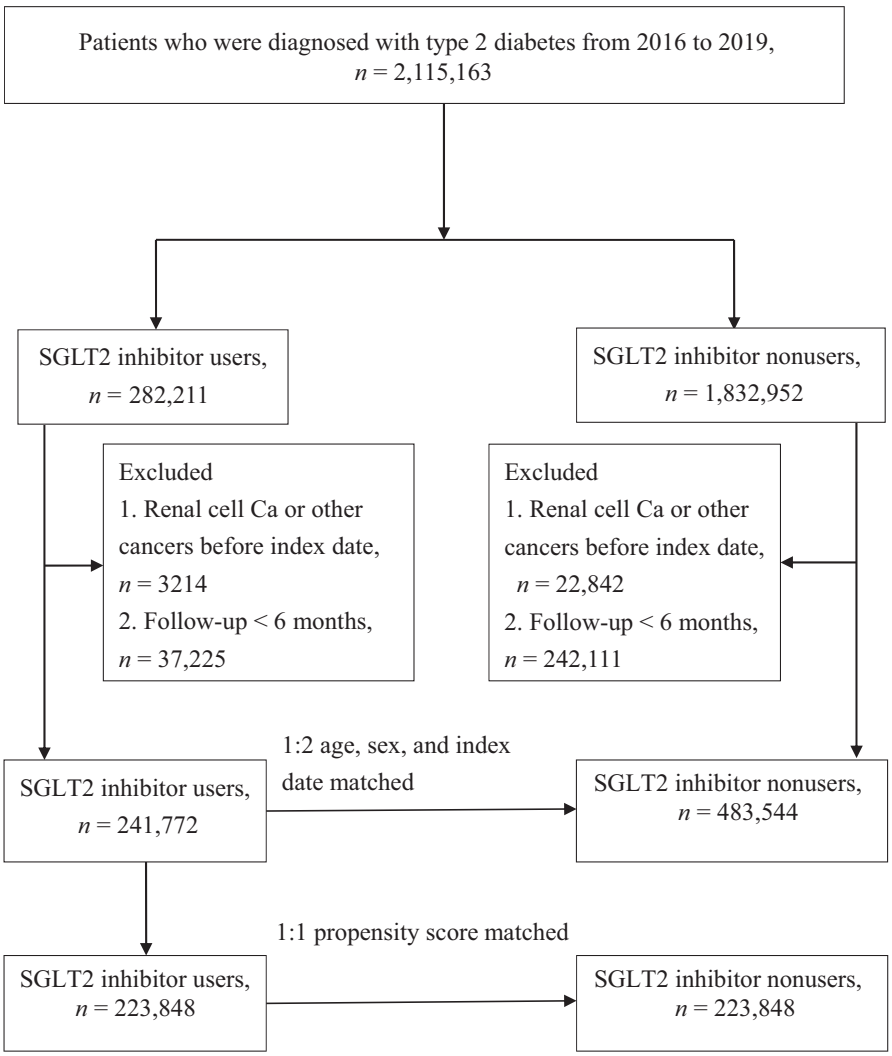

FIGURE 1 Patient flowchart. Ca, cancer; SGLT2, sodium glucose cotransporter-2.

TABLE 1 Baseline characteristics of type 2 diabetes patients treated with sodium glucose cotransporter-2 inhibitor (SGLT2I) and matched control patients.

	2:1 sex, age, and index date matching			After PSM		
	Non-SGLT2I $n=483,544$	SGLT2I $n=241,772$	ASD	Non-SGLT2I $n=223,848$	SGLT2I $n=223,848$	ASD
Sex						
Female	211,986 (43.84)	105,993 (43.84)	0.0000	97,578 (43.59)	98,220 (43.88)	0.0058
Male	271,558 (56.16)	135,779 (56.16)		126,270 (56.41)	125,628 (56.12)	
Age (years)						
<50	105,778 (21.88)	53,406 (22.09)	0.0000	49,404 (22.07)	49,338 (22.04)	0.0000
50–59	137,296 (28.39)	68,495 (28.33)		63,537 (28.38)	63,454 (28.35)	
60–69	155,756 (32.21)	77,635 (32.11)		71,869 (32.11)	71,964 (32.15)	
≥70	84,714 (17.52)	42,236 (17.47)		39,038 (17.44)	39,092 (17.46)	
Comorbidity						
CAD	58,378 (12.07)	42,839 (17.72)	0.1591	36,801 (16.44)	37,304 (16.66)	0.0060
Hypertension	270,162 (55.87)	146,939 (60.78)	0.0996	136,777 (61.10)	134,837 (60.24)	0.0177
Hyperlipidemia	281,900 (58.30)	163,149 (67.48)	0.1909	151,766 (67.80)	149,284 (66.69)	0.0236
Chronic kidney disease	116,031 (24.00)	65,447 (27.07)	0.0705	62,368 (27.86)	60,166 (26.88)	0.0221
Chronic liver disease	63,966 (13.23)	32,309 (13.36)	0.0040	29,940 (13.38)	29,942 (13.38)	0.0000
Stroke	27,170 (5.62)	12,463 (5.15)	0.0206	11,760 (5.25)	11,719 (5.24)	0.0008
COPD	24,327 (5.03)	12,318 (5.09)	0.0029	11,153 (4.98)	11,358 (5.07)	0.0042
Atrial fibrillation and flutter	5496 (1.14)	3728 (1.54)	0.0353	3237 (1.45)	3271 (1.46)	0.0013
Rheumatoid arthritis	4168 (0.86)	1781 (0.74)	0.0141	1645 (0.73)	1675 (0.75)	0.0016
Medication						
NSAIDs	331,680 (68.59)	168,918 (69.87)	0.0276	155,455 (69.45)	156,006 (69.69)	0.0053
Corticosteroids	121,243 (25.07)	62,024 (25.65)	0.0133	56,542 (25.26)	57,184 (25.55)	0.0066
PPI	41,778 (8.64)	21,436 (8.87)	0.0080	19,465 (8.70)	19,714 (8.81)	0.0039
H2 blocker	161,872 (33.48)	80,348 (33.23)	0.0052	73,906 (33.02)	74,379 (33.23)	0.0045
Aspirin	108,928 (22.53)	70,943 (29.34)	0.1560	63,562 (28.40)	63,328 (28.29)	0.0023
Statin	263,670 (54.53)	170,447 (70.50)	0.3345	156,551 (69.94)	154,353 (68.95)	0.0213
Biguanides	265,293 (54.86)	158,915 (65.73)	0.2234	144,271 (64.45)	144,161 (64.40)	0.0010
Sulfonylureas	172,372 (35.65)	112,233 (46.42)	0.2203	101,364 (45.28)	100,139 (44.74)	0.0110
Alpha glucosidase inhibitors	52,869 (10.93)	49,134 (20.32)	0.2607	39,383 (17.59)	40,782 (18.22)	0.0163
Thiazolidinediones	49,594 (10.26)	47,906 (19.81)	0.2698	38,770 (17.32)	39,690 (17.73)	0.0108
DPP4	109,914 (22.73)	103,178 (42.68)	0.4351	88,313 (39.45)	87,975 (39.30)	0.0031
Insulin	65,668 (13.58)	52,420 (21.68)	0.2138	44,323 (19.80)	45,047 (20.12)	0.0081
GLP-1	5495 (1.14)	5135 (2.12)	0.0780	4266 (1.91)	4311 (1.93)	0.0053

Note: Data are shown as *n* (%).

Abbreviations: ASD, absolute standardized difference; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PSM, propensity score matching.

3.4 | Subgroup analysis

Subgroup analyses were undertaken to compare the HRs of study outcomes between the SGLT2I group and the non-SGLT2I group. Similar results were also seen for gender (male and female), age <70 years, and comorbidity with or without chronic kidney disease/hypertension. However, an overall null effect of SGLT2I use on RCC risk was seen for patients older than 70 years (aHR 0.78; 95% CI, 0.55–1.10; Table 3).

TABLE 2 Incidence rate of renal cell carcinoma in type 2 diabetes patients treated with sodium glucose cotransporter-2 inhibitor (SGLT2I) and matched control patients.

	2:1 sex, age, and index date matching			After PSM		
	Non-SGLT2I $n=483,544$	SGLT2I $n=241,772$	*p* value	Non-SGLT2I $n=223,848$	SGLT2I $n=223,848$	*p* value
Follow-up, person-months	11,618,652	5,906,610		5,384,030	5,448,354	–
New case	609	220		296	198	–
Incidence rate (95% CI)[a]	0.52 (0.48–0.57)	0.37 (0.33–0.43)		0.55 (0.49–0.62)	0.36 (0.32–0.42)	–
Crude relative risk (95% CI)	Reference	0.72 (0.62–0.84)	<0.0001	Reference	0.67 (0.56–0.81)	<0.0001
Adjusted HR (95% CI)[b]	Reference	0.68 (0.58–0.81)	<0.0001	Reference	0.67 (0.55–0.81)	<0.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; PSM, propensity score matching.

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

[b]Adjusted hazard ratio, the covariates including index date, sex, age, comorbidities, and concurrent medication at baseline.

4 | DISCUSSION

The study showed that the use of SGLT2Is in patients with T2D decreased the RCC risk. The protective effect of SGLT2I therapy persisted, even after 1:1 propensity score matching, and in the subgroup analysis in both sexes, patients aged <70 years, and comorbidity with or without chronic kidney disease/hypertension.

The protective effect of SGLT2I in reducing RCC risk is plausible. In vivo and in vitro studies have suggested that the potential antitumor effects of SGLT2I are achieved through the induction of apoptosis, inhibition of angiogenesis, and reduction of inflammation. They also reverse proinflammatory phenotypes and glucotoxicity.[10,11,14] In addition to the antineoplastic effects of SGLT2I, empagliflozin inhibits oxidative DNA damage, mutagenesis, and tumor growth in CD-1 female mouse models and xenografts.[11] Our results are consistent with these findings, indicating that SGLT2I therapy is associated with a reduced risk of incident RCC.

Previous epidemiologic studies have revealed a clear age-by-sex interaction in RCC incidence.[15–17] This study also indicated that the use of SGLT2Is was associated with a significantly reduced RCC risk in sex and young age (<70 years). However, the differences in association by age are not fully understood. They may suggest different etiological pathways for the effects of SGLT2Is on RCC risk. High blood sugar is a risk factor for RCC.[18–20] It may be caused by the decreased blood sugar effect of SGLT2Is. In addition, SGLT2I use is associated with the protection of renal function[21,22] and reduced risk of chronic renal disease,[23,24] which could subsequently contribute to the decreased RCC risk. Furthermore, older patients have more comorbidities. Another possible explanation was that "the lower dose intensity of drugs were prescribed in the older population" or "older people are more likely to develop RCC." Because our results were obtained from secondary data analyses, not primary data, we cannot rule out the possibility of selection bias. Further clinical studies to specifically test the potential effect modification by age are necessary to validate our results.

Patients with T2D with or without chronic kidney disease are at a higher risk of developing RCC because of oxidative stress from a uremic milieu or underlying cystic disease.[25–27] This study indicated a lower RCC risk in SGLT2I users with T2D with or without chronic kidney disease than in nonusers. This effect was associated with the inhibition of oxidative DNA damage, mutagenesis, and tumor growth, suggesting an antioxidant-driven mechanism.[11,28] To date, this is the first study to investigate the effect of SGLT2I use in patients with T2D with or without chronic kidney disease. Further comprehensive clinical randomized studies are necessary to confirm our findings.

Hypertension is an important risk factor for RCC.[29–31] Studies have reported that hypertension and RCC may share several common risk factors, such as obesity, low physical activity, unhealthy diet, alcoholism, and smoking.[30,31] In this study, a subgroup analysis revealed that SGLT2I therapy decreased the RCC risk in patients with hypertension. The underlying mechanisms may include decreased chronic inflammation, oxidative stress (such as lipid peroxidation, interleukin-6, insulin, and insulin-like growth factor 1), and vascular endothelial growth factor pathways in SGLT2I users.[10,11] These mechanisms should be further investigated to confirm their roles.

The strengths of our study include the use of a large, population-based database. Furthermore, our findings were tested using propensity score matching to control for potential confounders, which made our hypothesis feasible. Our study is the first cohort study to provide evidence for an association between the use of SGLT2Is on RCC risk in patients with T2D. Our findings support the hypothesis that SGLT2 uptake inhibition is inversely associated with the risk of RCC.

This study has several limitations. First, the National Health Insurance Research Database (NHIRD) does not contain health behavior data, such as smoking, physical activity, alcohol intake, or body mass index. Thus, we could not account for these confounders in our data analysis. The results of this study might be distorted by the inability to adjust for the effects of these factors. However, considering that we used population-based data, we assumed that no differences existed between the SGLT2I and non-SGLT2I groups. Second, the underlying diagnosis, outcomes, and comorbidities in the NHIRD, registered by each physician, may have been miscoded or misclassified. However, because the data we used were

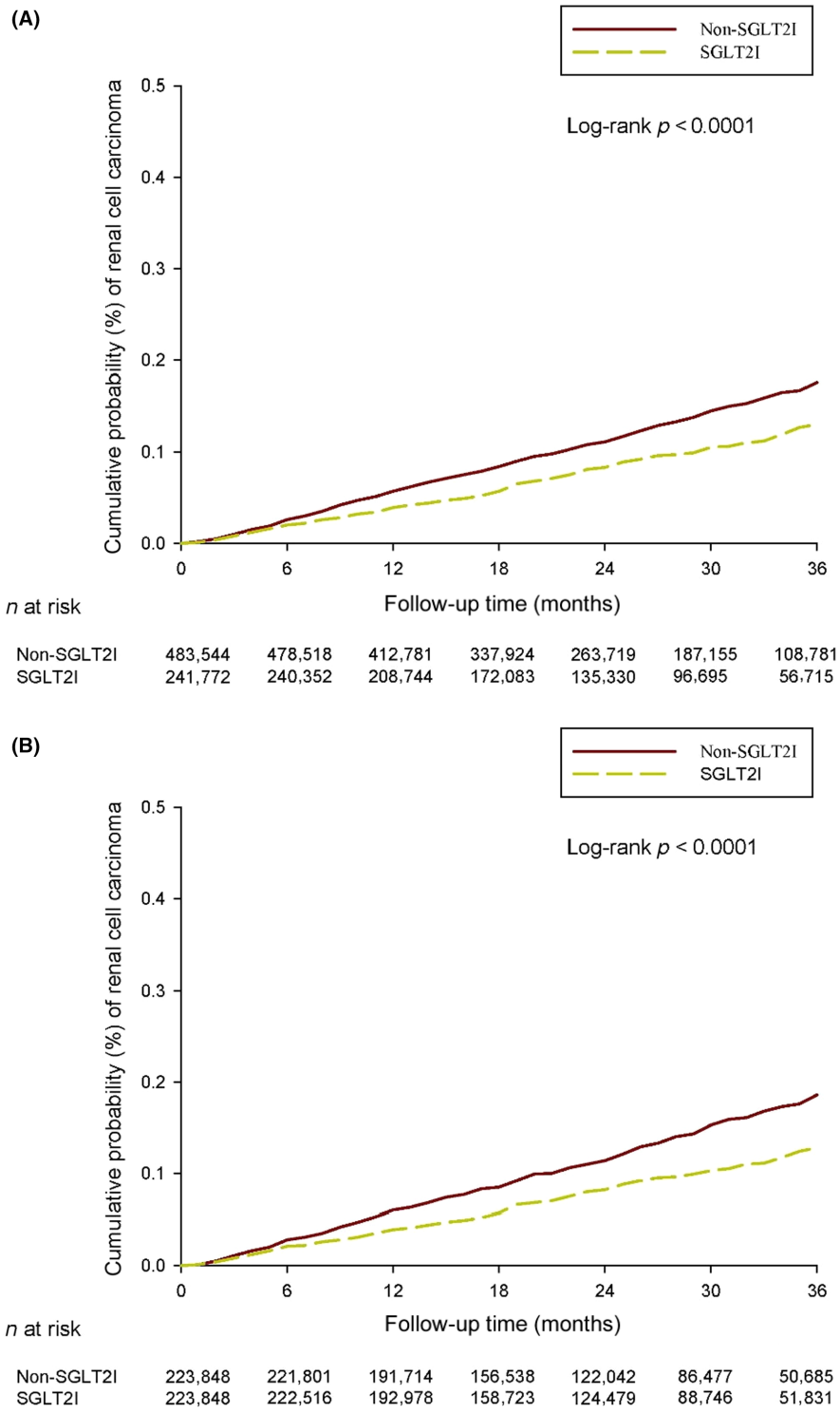

FIGURE 2 (A) Cumulative risk curve of incidental renal cell carcinoma for the study cohorts of patients with type 2 diabetes treated with sodium glucose cotransporter-2 inhibitor (SGLT2I) versus non-SGLT2I users. (B) Cumulative risk curve of incidental renal cell carcinoma for the study cohorts under propensity score matching in patients treated with SGLT2I versus non-SGLT2I users.

nation-based data, we assumed that there were no differences among the two groups. Third, laboratory data such as blood sugar levels, hemoglobin A1c levels, renal function, liver function, thyroid function, and electrocardiogram data were unavailable from the claims data. However, because the data were population-based, we assumed that there were no differences between the groups. Further prospective randomized control trials are required. Finally, the authors observed the effect of SGLT2Is with the mean follow-up period of only 2.0 years. The effect of SGLT2Is could only be to slow the growth of existing cancer. Further studies are needed with longer follow-up period.

In conclusion, SGLT2I use in patients with T2D decreased the RCC risk. Compared to nonusers, SGLT2I users showed more decreased risk of RCC not only with but also without chronic kidney disease/hypertension comorbidity. The decreased RCC risk in SGLT2I users was also greater in both sexes and aged <70 years than in nonusers. Further efforts are necessary to maximize the potential population benefit of these therapies in high-risk groups.

TABLE 3 Subgroup analysis of type 2 diabetes patients treated with sodium glucose cotransporter-2 inhibitor (SGLT2I) and matched control patients.

			Incidence rate (95% CI)[a]		
	N	New case	Non-SGLT2I	SGLT2I	aHR (95% CI)[b]
Sex					
Female	317,979	304	0.42 (0.36–0.48)	0.33 (0.27–0.41)	0.73 (0.56–0.94)
Male	407,337	525	0.61 (0.55–0.68)	0.41 (0.34–0.48)	0.67 (0.54–0.82)
Age (years)					
<50	159,184	138	0.39 (0.32–0.47)	0.28 (0.2–0.38)	0.68 (0.46–1.02)
50–59	205,791	206	0.45 (0.38–0.53)	0.31 (0.24–0.41)	0.63 (0.46–0.88)
60–69	233,391	307	0.61 (0.54–0.69)	0.42 (0.33–0.52)	0.65 (0.49–0.85)
≥70	126,950	178	0.69 (0.58–0.82)	0.53 (0.4–0.69)	0.78 (0.55–1.10)
Comorbidity					
CKD	181,478	290	0.82 (0.72–0.94)	0.44 (0.34–0.55)	0.60 (0.46–0.80)
Without CKD	543,838	539	0.44 (0.39–0.48)	0.35 (0.3–0.41)	0.75 (0.62–0.92)
Hypertension	417,101	521	0.63 (0.57–0.69)	0.43 (0.37–0.50)	0.73 (0.60–0.89)
Without hypertension	308,215	308	0.41 (0.36–0.45)	0.26 (0.21–0.32)	0.61 (0.47–0.79)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease.

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

[b]Covariates include index date, sex, age, comorbidities, and concurrent medication at baseline.

AUTHOR CONTRIBUTIONS

Chun-Huei Chiu: Conceptualization; data curation; methodology; writing – original draft. **Wei-Yao Wang:** Formal analysis; methodology. **Hung-Yi Chen:** Conceptualization; supervision. **Pei-Lun Liao:** Formal analysis. **Tsung-Yuan Yang:** Conceptualization; data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Gwo-Ping Jong:** Conceptualization; data curation; formal analysis; methodology; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: This protocol was approved by the Ethics Committee of the Chung Shan Medical University Hospital (CS2-22032).

Informed consent: Informed consent was waived because the NHIRD data are de-identified and encrypted.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

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