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Original Research

Use of metformin and risk of kidney cancer in patients with type 2 diabetes

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Abstract ***Background:*** The anticancer effect of metformin has been reported in the literature but requires additional confirmation in epidemiologic studies. With respect to kidney cancer scarce data are available. This study investigates whether metformin use in patients with type 2 diabetes mellitus (T2DM) might affect kidney cancer risk.
Methods: The reimbursement database of the National Health Insurance in Taiwan was used. T2DM patients aged ≥40 years and newly treated with either metformin (n = 171,753, "ever users of metformin") or other antidiabetic drugs (n = 75,499, "never users of metformin") within 1998–2002 were followed for at least 6 months for kidney cancer until 31 December 2009. The treatment effect was estimated by Cox regression using propensity score weighting by inverse probability of treatment weighting approach. Hazard ratios were estimated for ever versus never users, and for tertiles of cumulative duration of metformin therapy.
Results: During follow-up, 917 ever users and 824 never users developed kidney cancer, with respective incidence of 80.09 and 190.30 per 100,000 person-years. The hazard ratio (95% confidence intervals) for ever versus never users is 0.279 (0.254–0.307); and is 0.598 (0.535–0.668), 0.279 (0.243–0.321) and 0.104 (0.088–0.124), respectively, for the first, second, and third tertile of cumulative duration of <14.5, 14.5–45.8 and >45.8 months. In subgroup analyses, the lower risk of kidney cancer associated with metformin use is consistently

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observed in both sexes, and in patients with or without concomitant use of other antidiabetic drugs.
Conclusion: Metformin use is associated with a decreased risk of kidney cancer in patients with T2DM.

1. Introduction

Renal cell carcinoma is the most common type of kidney cancer, representing approximately 85% of all kidney cancers [1,2]. It has a poor prognosis and nearly half of the patients die within 5 years after diagnosis [3]. The incidence of kidney cancer is increasing steadily throughout the world, but is generally higher in European and North American countries than in Asian and South American countries [1].

In Taiwan, renal cell carcinoma represented 92.4% and 90.4% of all kidney cancers in men and in women, respectively [4,5]. In a 10-year population-based follow-up from 1998 to 2007, the standardized incidence ratio for kidney cancer comparing patients with diabetes to the general population in Taiwan was 1.32 (95% confidence interval: 1.25–1.40), suggesting an excess risk of kidney cancer in patients with diabetes [6]. The most important risk factors for kidney cancer identified in Taiwan were age [7], male sex [7], chronic kidney disease [4,8] and urinary tract disease [4,9,10].

Studies suggest that the use of antidiabetic drugs might affect the risk of various cancers in patients with type 2 diabetes mellitus (T2DM). For example, pioglitazone has been associated with a higher risk of bladder cancer [11,12] and incretin-based therapies may increase the risk of pancreatic cancer and thyroid cancer [13]; but metformin has been associated with a lower risk of colon cancer [14], bladder cancer [15] and other malignancies involving the liver, pancreas, stomach and esophagus [16,17]. Whether metformin use can affect the risk of kidney cancer remains to be confirmed. While an observational study showed a non-significantly higher risk of kidney/pelvis cancer associated with metformin use [18], another study including two clinical trials showed a non-significantly lower risk of kidney cancer associated with metformin use [17,19].

Renal cell carcinoma is characterized by an overactivation of the mammalian target of rapamycin (mTOR), and activation of serine–threonine kinase AMP-activated kinase (AMPK) might inhibit the proliferation and growth of renal cell carcinoma [20]. Therefore, metformin is potentially protective against kidney cancer through its well-recognized effects on the activation of AMPK and inhibition of the mTOR pathway [21].

The purpose of the present study is to evaluate the association between metformin use and the risk of kidney cancer in Taiwanese patients with T2DM using the National Health Insurance (NHI) reimbursement database.

2. Materials and methods

The study was approved by the ethics review board of the National Health Research Institutes (registered approval number: 99274).

Since March 1995 a compulsory and universal system of NHI was implemented in Taiwan. According to this system, all contracted medical institutes must submit computerized and standard claim documents for reimbursement. More than 99% of citizens are enrolled in the NHI, and over 98% of the hospitals nationwide are under contract with the NHI.

The National Health Research Institutes is the only organization approved, as per local regulations, for handling the NHI reimbursement database for academic research. The identification information of individuals was de-identified for the protection of privacy. Diabetes was coded as 250.XX and kidney cancer as 189, based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

A cohort of T2DM patients newly treated with antidiabetic drugs during 1998–2002 and without a history of kidney cancer was retrieved from the NHI database for analyses ($n = 525{,}821$). To assure that diabetes was first diagnosed after 1998, patients who had a diagnosis of diabetes in 1996 and/or 1997 were not included. Patients who were on diet control only and had not been using one or more antidiabetic drugs after 1 January 1998 were also not included. After excluding patients with type 1 diabetes ($n = 2397$), those with a duplicated identification number ($n = 26$), unclear information on date of birth or sex ($n = 1782$), patients aged <40 years at entry ($n = 53{,}955$, they were excluded because both diabetes mellitus [22] and kidney cancer [5,7] are rare in individuals below 40 years of age), metformin users who had been using other antidiabetic drugs before metformin was prescribed ($n = 200{,}785$), or a follow-up duration of less than 6 months ($n = 11{,}375$), a total of 247,252 patients were identified.

Patients who had received metformin as the first antidiabetic drug were enrolled as "ever users of metformin". The referent group ("never users of metformin") included patients who had received other antidiabetic drugs as the first treatment and had not received metformin throughout follow-up. As a result, there were 171,753 (69.5%) ever users and 75,499 (30.5%) never users of metformin.

Cumulative duration (months) of metformin use was calculated from the reimbursement database and tertiles of cumulative duration were used for analyses. A number of comorbidities and covariates were determined as a status/diagnosis at the end of follow-up, including nephropathy (ICD-9-CM code: 580–589), hypertension (401–405), chronic obstructive pulmonary disease (a surrogate for smoking; 490–496), stroke (430–438), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81 and 440–448), eye disease (250.5, 362.0, 369, 366.41 and 365.44), obesity (278), dyslipidemia (272.0–272.4), urinary tract disease (590–599), and other cancers (140–208; excluding 189). The accuracy of disease diagnoses in the NHI database has been studied previously. Agreements between claim data and medical records are moderate to substantial, with Kappa values range from 0.55 to 0.86 [23].

Other medications included sulfonylurea, meglitinide, acarbose, pioglitazone, rosiglitazone, insulin, statins, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, aspirin, ticlopidine, clopidogrel, dipyridamole and non-steroidal anti-inflammatory drugs.

The baseline characteristics of metformin never users and ever users were compared by Chi-square test. The crude incidence density of kidney cancer was calculated for metformin ever users and never users and for the tertiles of cumulative duration. Follow-up started on the first day of the use of antidiabetic drugs and ended on 31 December 2009, at the time of a new diagnosis of kidney cancer, or on the date of the last reimbursement record.

Logistic regression was used to create propensity score (PS) from the baseline characteristics and the treatment effect was estimated using PS-weighting with the inverse probability of treatment weighting (IPTW) approach incorporated into a Cox regression [24,25]. Hazard ratios were estimated for ever versus never users, and for each tertile of cumulative duration of metformin therapy compared to never users as referent.

The following two approaches were conducted as sensitivity analyses to confirm the findings. First, IPTW-weighted hazard ratios were estimated for ever versus never users in the following subgroups: 1) separate sexes; 2) excluding kidney cancer diagnosed within one year of follow-up to allow for biological plausibility for cancer development; and 3) patients with and without concomitant use of each of the other antidiabetic drugs.

Second, a traditional Cox regression model was created in order to evaluate 1) whether the association between metformin use and kidney cancer risk can be consistently demonstrated; 2) whether the risk factors for kidney cancer reported in Taiwan including age, male sex, nephropathy and urinary tract disease [7–10] can be similarly observed in the present study; and 3) whether the use of other antidiabetic drugs can also be associated with kidney cancer. Patients with incident diabetes and use of antidiabetic drugs during 1998–2005 were recruited. An entry date was set on 1 January 2006 and patients with a prevalent diagnosis of kidney cancer before this date were excluded. The remaining patients were then followed up for four years until 31 December 2009. All baseline characteristics plus diabetes duration at entry were included in the Cox model to estimate the fully adjusted hazard ratios.

Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

3. Results

Table 1 summarizes the baseline characteristics of metformin ever users and never users. All baseline characteristics differ significantly.

Table 2 lists kidney cancer incidence and any cancer incidence in different subgroups of metformin use, together with the hazard ratios comparing exposed to unexposed. A smaller proportion of metformin ever users developed kidney cancer during follow-up than the never users. With longer cumulative duration, the incidence decreases. Metformin use is associated with a significantly lower risk of kidney cancer, with a hazard ratio (95% confidence interval) of 0.279 (0.254–0.307). In the tertile analysis for the cumulative duration, metformin is associated with a lower risk of kidney cancer in a dose–response pattern. The lower risk associated with metformin use can also be demonstrated in the analyses for any cancer, suggesting that the anticancer effect of metformin may not be specific to kidney cancer.

The results of the sensitivity analyses are shown in Table 3. In the subgroup analyses with IPTW using PS, all hazard ratios comparing metformin users versus never users indicate a significantly lower risk associated with metformin use in either sex, after excluding patients who developed kidney cancer within one year of follow-up, and with or without concomitant use of other antidiabetic drugs. In the traditional Cox model, the risk of kidney cancer increases with increasing diabetes duration and is significantly associated with risk factors observed in Taiwan including age, male sex, nephropathy and urinary tract disease, suggesting the validity of the study. Among the antidiabetic drugs, metformin and sulfonylurea are associated with significantly lower risk

Table 1
Baseline characteristics of metformin never users and ever users.

Variables	Metformin				*P* value
	Never users		Ever users		
	n	%	*n*	%	
n = 247,252	75,499		171,753		
Age (years)					
40–49	12,723	16.85	47,959	27.92	<0.0001
50–59	16,967	22.47	52,015	30.28	
60–69	21,210	28.09	44,619	25.98	
≥70	24,599	32.58	27,160	15.81	
Sex (men)	40,426	53.55	88,626	51.60	<0.0001
Hypertension	43,949	58.21	128,765	74.97	<0.0001
Chronic obstructive pulmonary disease	14,651	19.41	36,013	20.97	<0.0001
Stroke	15,255	20.21	37,841	22.03	<0.0001
Nephropathy	14,163	18.76	30,668	17.86	<0.0001
Ischemic heart disease	17,092	22.64	56,033	32.62	<0.0001
Peripheral arterial disease	7070	9.36	28,223	16.43	<0.0001
Eye disease	3538	4.69	22,363	13.02	<0.0001
Obesity	364	0.48	4527	2.64	<0.0001
Dyslipidemia	25,883	34.28	112,587	65.55	<0.0001
Urinary tract disease	20,383	27.00	55,953	32.58	<0.0001
Other cancers	20,296	26.88	33,191	19.32	<0.0001
Statin	14,851	19.67	80,712	46.99	<0.0001
Fibrate	8819	11.68	46,338	26.98	<0.0001
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	28,089	37.20	105,202	61.25	<0.0001
Calcium channel blocker	22,385	29.65	73,594	42.85	<0.0001
Sulfonylurea	65,865	87.24	142,349	82.88	<0.0001
Meglitinide	6223	8.24	30,817	17.94	<0.0001
Insulin	10,743	14.23	32,384	18.85	<0.0001
Acarbose	6287	8.33	41,447	24.13	<0.0001
Pioglitazone	1851	2.45	25,263	14.71	<0.0001
Rosiglitazone	2641	3.50	27,111	15.78	<0.0001
Aspirin	19,693	26.08	77,712	45.25	<0.0001
Ticlopidine	1783	2.36	5374	3.13	<0.0001
Clopidogrel	2288	3.03	9423	5.49	<0.0001
Dipyridamole	12,060	15.97	38,735	22.55	<0.0001
Non-steroidal anti-inflammatory drugs (excluding aspirin)	46,796	61.98	132,546	77.17	<0.0001

of kidney cancer, while the others are not significantly associated.

4. Discussion

This study demonstrated an inverse association between metformin use and kidney cancer risk. The protective effect of metformin is further supported by the tertile analyses of the cumulative duration of therapy (Table 2) and by the various sensitivity analyses (Table 3).

This study also disclosed that the reduced cancer risk associated with metformin use might not be confined to kidney cancer, but could also be extended to other cancers (Table 2). The confirmation of a protective effect of metformin on cancer risk can encourage future research in the field of therapeutic applications of this drug on kidney cancer or even other cancers. Such a simultaneous risk reduction of kidney cancer and other cancers associated with metformin use also disfavored the possibility of a spurious risk reduction of kidney cancer among metformin users resulting from the presence of competitive risk events of other cancers. Theoretically, if the development of kidney cancer and the development of other cancers are mutually exclusive events among metformin users, then a reduced risk of kidney cancer associated with metformin use might be spurious when metformin might have increased the risk of other cancers and thus prevented the development of kidney cancer.

Though not significant, the pooled odds ratio (0.38, 95% confidence interval: 0.10–1.46) derived from two randomized control trials did suggest a lower risk of kidney/pelvis cancer associated with metformin use [17]. The estimated hazard ratio of 0.279 (95% confidence interval: 0.254–0.307, Table 2) in the present study is very close to this pooled odds ratio. The small case numbers of kidney cancer in the trials might explain the lack of statistical significance in the pooled analysis [17].

It has also been pointed out that pharmacovigilance studies enrolling prevalent users of a drug can result in misleading findings, leading to the so-called "prevalent user bias". Such a bias may be introduced because of the following two possibilities [26]. First, drug users who developed the outcome of interest before the study was initiated would not have been enrolled into the study and prevalent users might have represented those with additional survival benefits. Second, influential risk factors may be changed by the studied drug before or at the start of study entry. To avoid such a "prevalent user bias", the present study recruited new users of metformin in study design.

Activation of the signaling pathway of phosphatidylinositol 3-kinase/Akt/mTOR is a characteristic of some types of cancer including kidney cancer and mTOR inhibitors have been used for the treatment of these cancers [27]. Metformin is well known for its inhibitory effect on mTOR, either through AMPK-dependent or AMPK–independent pathways [28,29]. Additionally, some tumors are characterized by a high expression of fatty acid synthase and a high rate of lipid metabolism [29]. A recent *in vitro* study suggested that free fatty acids could promote proliferation of kidney cancer cells [30]. Metformin can inhibit lipogenesis and cholesterol synthesis through AMPK activation [29]. Therefore, the preventive effect of metformin on kidney cancer or any cancer as shown in Table 2 can be ascribed partially to its inhibitory effects on mTOR or lipogenesis. However, other mechanisms involving its effects on the improvement in insulin resistance, blockade of the production of reactive oxygen species, reduction of chronic inflammatory response, inhibition of angiogenesis, stimulation of cell cycle arrest through p53/p21 axis, inhibition of

Table 2
Metformin and incidence of kidney cancer and any cancer and hazard ratios comparing exposed to unexposed.

Metformin use	Cases followed	Incident cases of cancer	Person-years	Incidence rate (per 100,000 person-years)	Hazard ratio (95% confidence interval)	*P*
Kidney cancer						
Ever versus never use						
Never use	75,499	824	433,005.63	190.30	1.000	
Ever use	171,753	917	1,144,982.21	80.09	0.279 (0.254–0.307)	<0.0001
Cumulative duration (months)						
Never use	75,499	824	433,005.63	190.30	1.000	
<14.5	62,326	495	295,659.20	167.42	0.598 (0.535–0.668)	<0.0001
14.5–45.8	51,678	266	340,464.36	78.13	0.279 (0.243–0.321)	<0.0001
>45.8	57,749	156	508,858.65	30.66	0.104 (0.088–0.124)	<0.0001
Any cancer						
Ever versus never use						
Never use	69,327	14,124	409,674.40	3447.62	1.00	
Ever use	164,680	26,118	1,105,145.49	2363.31	0.386 (0.378–0.394)	<0.0001
Cumulative duration (months)						
Never use	69,327	14,124	409,674.40	3447.62	1.000	
<14.1	54,193	10,561	256,189.52	4122.34	0.801 (0.781–0.822)	<0.0001
14.1–45.4	54,468	8497	354,346.31	2397.94	0.426 (0.414–0.437)	<0.0001
>45.4	56,019	7060	494,609.66	1427.39	0.195 (0.190–0.201)	<0.0001

the expression of c-myc (an oncogene), modulating the expression of various microRNAs in cancer cells, affecting cancer stem cells, and inhibiting the formation of tumor sphere [29,31] remain to be explored.

The lower risk associated with sulfonylurea ("Traditional Cox model" in Table 3) has not been previously reported and should be viewed as preliminary. In *in vitro* studies, glibenclamide might induce apoptosis in cells expressing sulfonylurea receptor 1, including pancreatic β-cells and human embryonic kidney 293 cells [32,33]. Sulofenur (LY 186641, a diarylsulfonylurea) has demonstrated antitumor activity in cell lines derived from human colon cancer, human melanoma and monkey kidney cancer [34]. Sulofenur also showed promising antitumor activity in patients with advanced renal cell adenocarcinoma in an early phase II clinical trial [35]. Future studies evaluating individual sulfonylureas (i.e., chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride and gliquidone) and the risk of kidney cancer in a dose–response relationship among new users are required to confirm the findings.

Although insulin is not associated with kidney cancer risk in the present study (Table 3), future studies are required to evaluate the effect of insulin with regards to different types of insulin (e.g., insulin analogues versus human insulin), different durations of insulin exposure and different mean daily dose of insulin.

Obesity is a well-known risk factor for both type 2 diabetes mellitus [22] and kidney cancer [36]. In the analyses, a diagnosis of obesity was used as a surrogate and it was noted that this could much underestimate the true prevalence of obesity in either the metformin ever or never users (Table 1). In a previous epidemiologic survey, the prevalence of obesity in patients with diabetes was 33.5% and 7.1%, respectively, by using a body mass index cutoff of $\geq$25 and $\geq$30 kg/m^2 [37]. Therefore, a lack of actual measurement of anthropometric factors for adjustment in the present study might have led to a biased estimate. However, because metformin is always recommended for patients with obesity (this was also observed in the present study as shown in Table 1), the lack of actual measurement of anthropometric factors for defining obesity in the present study might only have underestimated the beneficial effect of metformin on kidney cancer risk.

There are several strengths in the present study. First, we made a special request to include all patients diagnosed as having diabetes from the NHI database covering the whole period since its availability in 1996. Such an approach avoided the possibility of selection bias and insufficient cases of kidney cancer for subgroup analyses if the data were derived from a subsample of the whole population. Second, the consistency and dose–response relationship of a lower risk of kidney cancer associated with metformin (Tables 2 and 3) strengthened the preventive role of metformin on kidney cancer. Third, the database included outpatients and inpatients, and we included diagnoses from both sources. Fourth, cancer is considered a severe morbidity by the NHI and most medical co-payments can be waived. Furthermore, there is a low drug cost-sharing required by the NHI and patients from a low-income household, veterans or patients with prescription refills for chronic diseases are exempted from the drug cost-sharing. Therefore, the detection rate of kidney cancer would tend not to differ among different social classes. The use of medical records also reduces bias related to self-reporting.

The limitations of the study may include a lack of the histological types of kidney cancer for analysis.

Table 3
Sensitivity analyses for metformin use and risk of kidney cancer.

Model/variable	Hazard ratio (95% confidence interval)	*P*
I. Subgroup analyses with inverse probability of treatment weighting using propensity score[a]		
Men	0.281 (0.246–0.320)	<0.0001
Women	0.278 (0.242–0.319)	<0.0001
Excluding kidney cancer diagnosed within one year of follow-up	0.322 (0.291–0.356)	<0.0001
Patients using sulfonylurea	0.244 (0.219–0.271)	<0.0001
Patients not using sulfonylurea	0.420 (0.329–0.537)	<0.0001
Patients using meglitinide	0.222 (0.164–0.299)	<0.0001
Patients not using meglitinide	0.298 (0.270–0.330)	<0.0001
Patients using acarbose	0.195 (0.139–0.275)	<0.0001
Patients not using acarbose	0.328 (0.297–0.363)	<0.0001
Patients using pioglitazone	0.195 (0.102–0.373)	<0.0001
Patients not using pioglitazone	0.317 (0.288–0.349)	<0.0001
Patients using rosiglitazone	0.230 (0.144–0.367)	<0.0001
Patients not using rosiglitazone	0.308 (0.279–0.339)	<0.0001
Patients using insulin	0.198 (0.152–0.258)	<0.0001
Patients not using insulin	0.303 (0.274–0.336)	<0.0001
II. Traditional Cox model[b]		
Age, every 1-year increment	1.031 (1.029–1.033)	<0.0001
Sex, men versus women	1.077 (1.024–1.132)	0.0039
Diabetes duration		
1–2.9 years versus <1 year	1.124 (0.991–1.275)	0.0684
3–4.9 years versus <1 year	1.180 (1.042–1.336)	0.0091
≥5 years versus <1 year	1.398 (1.251–1.562)	<0.0001
Metformin, users versus non-users	0.526 (0.486–0.569)	<0.0001
Insulin, users versus non-users	0.959 (0.876–1.050)	0.3628
Sulfonylurea, users versus non-users	0.573 (0.530–0.619)	<0.0001
Meglitinide, users versus non-users	1.043 (0.948–1.148)	0.3861
Acarbose, users versus non-users	1.024 (0.935–1.122)	0.6096
Pioglitazone, users versus non-users	0.983 (0.848–1.139)	0.8209
Rosiglitazone, users versus non-users	1.051 (0.955–1.155)	0.3080
Nephropathy, yes versus no	1.644 (1.534–1.762)	<0.0001
Urinary tract disease, yes versus no	1.533 (1.441–1.631)	<0.0001

[a] Hazard ratios are estimated for ever versus never users of metformin.
[b] All variables in Table 1 are included in the model.

However, because renal cell carcinoma represents more than 90% of all kidney cancers in Taiwan [5], the findings of the present study are best applied to renal cell carcinoma. Second, although some cases of kidney cancer may have been misclassified, such an occurrence was probably low in the present study because labeled diagnoses should be printed on all prescriptions handed out to patients in Taiwan. Mislabeling of a cancer diagnosis would not be acceptable to patients when they saw the diagnosis. Third, we have not considered the potential impact of biochemical data such as levels of glucose, insulin, C-peptide and insulin-like growth factors. Fourth, some other important risk factors such as workplace exposure to certain substances (cadmium, herbicides, and organic solvents), lifestyle factors and family history of kidney cancer are not investigated in the present study because of the lack of information in the NHI database.

In summary, based on a large cohort of diabetic patients recruited from the whole nation, this study supports a protective effect of metformin on the development of kidney cancer in Taiwanese patients with T2DM.

Author contributions

C.H. researched data and wrote manuscript.

Conflict of interest

None.

Novelty & impact statements

This study evaluated whether metformin use in patients with type 2 diabetes mellitus might affect kidney cancer risk. Findings suggested a reduced risk of kidney cancer associated with metformin use in a dose–response pattern.

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