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Original Research

Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus

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Abstract ***Background:*** Whether metformin therapy affects incident prostate cancer risk in Asian patients with type 2 diabetes mellitus (T2DM) has not been investigated.
Methods: The National Health Insurance reimbursement database of Taiwanese male patients with new-onset T2DM between 1998 and 2002 and aged ⩾40 years ($n = 395{,}481$) were retrieved to follow up prostate cancer incidence until the end of 2009. Metformin was treated as a time-dependent variable. Of the patients studied, 209,269 were never-users and 186,212 were ever-users. A time-dependent approach was used to calculate prostate cancer incidence and estimate hazard ratios using Cox regression for ever-users, never-users and subgroups of metformin exposure (tertiles of cumulative duration and cumulative dose). Sensitivity analyses were conducted in various subgroups, using time-dependent and non-time-dependent approaches.
Results: During the follow-up, 2776 metformin ever-users and 9642 never-users developed prostate cancer, representing an incidence of 239.42 and 737.10 per 100,000 person-years, respectively. The hazard ratio (95% confidence intervals) after adjustment for propensity score (PS) for ever- versus never-users was 0.467 (0.446–0.488). The PS-adjusted hazard ratios for the first, second and third tertiles of cumulative duration of metformin therapy were 0.741 (0.698–0.786), 0.474 (0.441–0.508) and 0.231 (0.212–0.253), respectively (P-trend < 0.001); and were 0.742 (0.700–0.786), 0.436 (0.406–0.468) and 0.228 (0.208–0.251) for the respective cumulative dose (P-trend < 0.001). Sensitivity analyses consistently supported a protective effect of metformin on incident prostate cancer.
Conclusions: Metformin use is associated with a decreased risk of incident prostate cancer in Taiwanese male patients with T2DM.

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1. Introduction

The incidence of prostate cancer varies by 25-fold among different countries [1]. In general, developed countries in Europe and North America have a higher incidence than less developed countries in Asia and Africa [1]. In contrast to the decreasing incidence in well-developed countries, the incidence in Asian populations is increasing [1]. In Taiwan, the age-standardised incidence of [2] and mortality from [3] prostate cancer are both increasing in the general population.

Metformin is a commonly used oral antidiabetic drug in patients with type 2 diabetes mellitus (T2DM), and may exert anticancer effects [4]. However, whether metformin can affect the risk of incident prostate cancer is still a matter of debate. While some studies suggested a null association [5–9], a potential beneficial effect was observed in others [10,11]. One study even suggested a significantly higher risk for patients having >36 metformin prescriptions [12]. A recent meta-analysis including four studies [2,6,12,13] showed a null association with a pooled hazard ratio of 0.92 (95% confidence interval: 0.73–1.17) [14].

Because the association between metformin and incident prostate cancer is controversial and studies conducted in Asian populations are still sparse, the present study aimed to evaluate whether metformin use could be associated with the risk of incident prostate cancer in Taiwanese male patients with T2DM using the National Health Insurance (NHI) database. A new-user design and a time-dependent approach for metformin use in data analyses were applied in order to minimise the potential confounding factors and biases commonly seen in studies using an administrative database.

2. Materials and methods

This population-based retrospective cohort study was approved by the ethics review board of the National Health Research Institutes (approval number 99274). The study used the NHI database and included all patients with a diagnosis of diabetes mellitus during the period from 1996 (the earliest database available) to 2009. A detailed description of the NHI database can be seen elsewhere [2,15]. Diabetes mellitus was coded 250.1–250.9 and prostate cancer, 185, based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

To create a cohort of male patients with new-onset T2DM and aged ⩾40 years at diabetes diagnosis during 1998–2002, female patients, patients with diabetes onset at the age of <40 years and patients with a diabetes diagnosis at outpatient clinics during 1996–1997 (to exclude prevalent cases of diabetes) were excluded. After further excluding patients with type 1 diabetes, those with a diagnosis of prostate cancer before diabetes diagnosis, and those with a duplicated identification number, unclear information on date of birth or sex and a follow-up duration of <180 days, male patients with a diagnosis of new-onset T2DM during 1998–2002 were identified for the study.

Patients who had ever been prescribed metformin after entry were defined as ever-users; never-users were defined as those who had never been prescribed metformin. Cumulative duration (months) and cumulative dose (mg) were calculated from the reimbursement database to evaluate a dose–response relationship. Exposure to other oral antidiabetic drugs (sulphonylurea, acarbose, pioglitazone, rosiglitazone and meglitinide) and insulin was also similarly defined for ever- and never-users.

Follow-up started on the first day of diabetes diagnosis and ended on 31st December 2009, at the time of a new diagnosis of prostate cancer, or at the date of the last reimbursement record. Exposure to metformin was treated as a time-dependent variable. Therefore, the metformin ever-users contributed person-years to the non-metformin group until they started using metformin, and after starting metformin, to the metformin group. The crude incidence density was calculated for the different subgroups of metformin exposure. The numerator for the incidence was the number of patients with incident prostate cancer during follow-up, and the denominator was the person-years of follow-up.

Age and various comorbidities and covariates were determined at the time of entry. These included nephropathy, hypertension, chronic obstructive pulmonary disease, stroke, ischaemic heart disease, peripheral arterial disease, eye disease, obesity, dyslipidemia, urinary tract disease, benign prostatic hyperplasia and other cancers. The ICD-9-CM codes for these comorbidities were detailed elsewhere [2,16]. Other medications included statin, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, aspirin, ticlopidine, clopidogrel, dipyridamole and non-steroidal anti-inflammatory drugs. Since the prostate-specific antigen (PSA) test may affect the detection rate of prostate cancer, the use of PSA testing was also considered as a potential confounder. These baseline characteristics of metformin never-users and ever-users were compared using Student's t test for age and the Chi-square test for other variables. Time-dependent Cox regression was performed to estimate the hazard ratios for incident prostate cancer with regard to metformin exposure after adjustment for: (1) age; (2) all variables at baseline (fully adjusted); and (3) propensity score (PS-adjusted) derived from the baseline characteristics. Since biased estimates may result from systematic differences between treatment groups in non-randomised studies, adjustment for PS may reduce this bias [17].

The following sensitivity analyses were conducted to estimate the PS-adjusted hazard ratios for ever- versus never-users of metformin after: (1) excluding insulin users, because a study suggested there was a lower risk of prostate cancer associated with insulin use [18]); (2) excluding patients aged <65 years and <75 years, respectively, for comparison with a study that recruited patients aged ⩾66 years (median: 76 years) and showed a lack of association between metformin and prostate cancer [7]); (3) excluding patients not taking any antidiabetic medications, to reduce the potential residual confounding of less diabetes severity, because some studies suggested that while early diabetes is associated with a potentially increased risk of prostate cancer, prolonged diabetes is associated with a decreased risk [19] and (4) excluding patients with a cumulative duration of metformin use <180 days, because these patients might have used metformin briefly and came off it.

To evaluate whether the finding could be consistent using a non-time-dependent approach, an additional sensitivity analysis was conducted. Male patients aged ⩾40 years with incident diabetes during 1998–2005 were recruited. An entry date was set on 1st January 2006 and patients with a prevalent diagnosis of prostate cancer before this date were excluded. The remaining patients were then followed up for 4 years until 31st December 2009. Fully adjusted hazard ratios were estimated by Cox regression for users versus non-users of antidiabetic medications at baseline. In this model, diabetes duration at entry was also included.

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

3. Results

Fig. 1 shows the flowchart for the procedures followed in creating the cohort of male patients with new-onset T2DM and aged ⩾40 years at entry during 1998–2002. At first, 411,783 male patients were recruited. After further excluding patients with type 1 diabetes ($n = 1232$), those with a diagnosis of prostate cancer before diabetes diagnosis ($n = 2641$), those with a duplicated identification number ($n = 39$), unclear information on date of birth or sex ($n = 7404$) and a follow-up duration of <180 days ($n = 11,782$), a total of 395,481 male patients were finally identified for analyses. There were 186,212 (47.1%) ever-users and 209,269 (52.9%) never-users of metformin.

With the exception of rates of hypertension, use of calcium channel blocker and use of clopidogrel, all baseline characteristics differed significantly between the two groups. Metformin ever-users were characterised by a younger age, lower frequency of most comorbidities (except eye disease and obesity), lower frequency of other cancers and higher rates of using other medications (except ticlopidine and non-steroidal anti-inflammatory drugs) and PSA testing (Table 1).

The incidences of prostate cancer among never-users and ever-users were 737.10 and 239.42 per 100,000

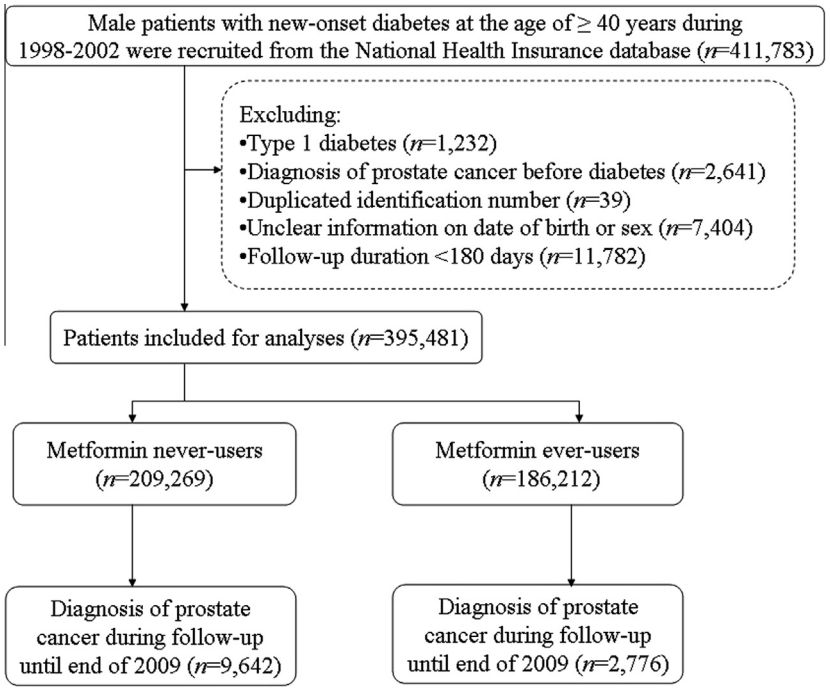

Fig. 1. Flowchart showing the procedures followed in creating a cohort of male patients with new-onset type 2 diabetes and aged ⩾40 years at entry during 1998–2002.

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

Variables	Metformin				*P*
	Never-users		Ever-users		
	n	%	*n*	%	
n = 395,481	209,269		186,212		
Age (years)*	62.6	12.4	57.1	10.6	<0.001
Hypertension	33,679	16.1	30,337	16.3	0.092
Chronic obstructive pulmonary disease	11,770	5.6	5018	2.7	<0.001
Stroke	9855	4.7	5445	2.9	<0.001
Nephropathy	10,177	4.9	3416	1.8	<0.001
Ischaemic heart disease	9423	4.5	6972	3.7	<0.001
Peripheral arterial disease	3292	1.6	2,342	1.3	<0.001
Eye disease	730	0.4	812	0.4	<0.001
Obesity	203	0.1	540	0.3	<0.001
Dyslipidemia	27,835	13.3	22,297	12.0	<0.001
Urinary tract disease	9218	4.4	6335	3.4	<0.001
Benign prostatic hyperplasia	5671	2.7	3711	2.0	<0.001
Other cancers	16,812	8.0	5954	3.2	<0.001
Statin	2038	1.0	3110	1.7	<0.001
Fibrate	2761	1.3	6421	3.5	<0.001
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	11,468	5.5	13,830	7.4	<0.001
Calcium channel blocker	11,520	5.5	10,304	5.5	0.694
Sulphonylurea	35,382	16.9	171,440	92.1	<0.001
Meglitinide	3256	1.56	37785	20.29	<0.001
Insulin	5986	2.9	43,627	23.4	<0.001
Acarbose	3128	1.5	51,279	27.5	<0.001
Pioglitazone	940	0.5	30,658	16.5	<0.001
Rosiglitazone	1355	0.7	34,939	18.8	<0.001
Aspirin	8056	3.9	7552	4.1	<0.001
Ticlopidine	569	0.3	304	0.2	<0.001
Clopidogrel	44	0.02	39	0.02	0.986
Dipyridamole	6279	3.0	5030	2.7	<0.001
Non-steroidal anti-inflammatory drug (excluding aspirin)	36,376	17.4	24,093	12.9	<0.001
Prostate-specific antigen	1781	0.85	4564	2.45	<0.001

* Age is expressed as mean and standard deviation. The median age for never-users, ever-users and all patients was 63.4, 55.8 and 59.4 years, respectively.

Table 2
Incidence of prostate cancer by metformin exposure.

Metformin use	Case number observed	Incident cases of prostate cancer	Person-years	Incidence rate (per 100,000 person-years)
Never-users	359,603	9642	1,308,099	737
Ever-users	186,212	2776	1,159,493	239
Cumulative duration (months)				
Never-users	359,603	9642	1,308,099	737
<13.7	61,507	1324	266,264	497
13.7–44.0	61,328	904	365,857	247
>44.0	63,377	548	527,371	104
Cumulative dose (mg)				
Never-users	359,603	9642	1,308,099	737
<397,900	61,449	1386	266,171	521
397,900–1,503,000	61,440	895	370,261	242
>1,503,000	63,323	495	523,061	95

person-years, respectively. With longer cumulative duration of therapy and higher cumulative dose, the incidence decreased correspondingly (Table 2).

All analyses showed a significantly lower risk of incident prostate cancer among metformin users, with significant *P*-trends for the dose–response parameters. The hazard ratios derived from the fully adjusted models and the PS-adjusted models were almost the same (Table 3).

In the time-dependent models for sensitivity analyses, the PS-adjusted hazard ratios for ever- versus never-users of metformin consistently showed a significantly lower risk of incident prostate cancer associated with metformin use. In the non-time-dependent model, metformin use at baseline was also significantly protective against prostate cancer. In addition, the use of insulin, sulphonylurea and meglitinide at baseline was also associated with a lower risk (Table 4).

4. Discussion

The findings suggested that metformin use in male patients with T2DM was significantly associated with a lower risk of incident prostate cancer, which was dose–responsive, independent of potential confounders and consistent in various sensitivity analyses (Tables 2–4).

Table 3
Metformin exposure and hazard ratios for incident prostate cancer.

Metformin use	Age-adjusted			Fully adjusted*			Adjusted for propensity score		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Ever-users	0.362	(0.345–0.380)	<0.001	0.476	(0.454–0.499)	<0.001	0.467	(0.446–0.488)	<0.001
Cumulative duration (months)									
<13.7	0.710	(0.663–0.760)	<0.001	0.748	(0.705–0.793)	<0.001	0.741	(0.698–0.786)	<0.001
13.7–44.0	0.428	(0.396–0.462)	<0.001	0.488	(0.454–0.524)	<0.001	0.474	(0.441–0.508)	<0.001
>44.0	0.173	(0158–0.189)	<0.001	0.230	(0.210–0.251)	<0.001	0.231	(0.212–0.253)	<0.001
P-trend			<0.001			<0.001			<0.001
Cumulative dose (mg)									
<397,900	0.723	(0.677–0.773)	<0.001	0.742	(0.701–0.787)	<0.001	0.742	(0.700–0.786)	<0.001
397,900–1,503,000	0.413	(0.383–0.446)	<0.001	0.445	(0.414–0.477)	<0.001	0.436	(0.406–0.468)	<0.001
>1,503,000	0.162	(0.148–0.178)	<0.001	0.228	(0.207–0.251)	<0.001	0.228	(0.208–0.251)	<0.001
P-trend			<0.001			<0.001			<0.001

Referent group, never-users of metformin; HR, hazard ratio; CI, confidence intervals.
* Adjusted for all variables in Table 1.

Findings from previous observational studies in humans are conflicting. The population-based case–control (1001 cases and 942 controls) study by Wright and Stanford from the United States of America (USA) showed an adjusted hazard ratio (95% confidence interval) of 0.56 (0.32–1.00) in Caucasians, but a null association in African–American men [5]. Another nested case–control (739 cases and 7359 controls) study that used the United Kingdom (UK) General Practice Research Database suggested an overall hazard ratio (95% confidence interval) of 1.23 (0.99–1.52) [12]. In the secondary analysis, a significantly higher risk could be seen among those with a higher exposure dose, with a hazard ratio (95% confidence interval) of 1.40 (1.03–1.89) for >36 metformin prescriptions [12]. Another observational population-based study using health-care administrative database in Ontario, Canada did not find an association between metformin use and incident prostate cancer, whether high-grade, low-grade or biopsy-diagnosed cancer [7]. It is not known whether ethnic differences can explain the discrepant findings between the present study conducted with a Taiwanese population and previous studies conducted mainly among white populations [5,7,12]. The Canadian study used a case–control design and included incident diabetic men aged ⩾66 years (median: 76 years) [7], but the present study used a cohort design, recruiting diabetic men aged ⩾40 years (median: 59.4 years). The discrepant findings may not be due to the differences in age distribution because the lower risk associated with

Table 4
Sensitivity analyses for antidiabetic medications and incident prostate cancer.

Model	HR (95% CI)	*P*
I. Time-dependent models*	PS-adjusted	
Excluding users of insulin	0.460 (0.438–0.482)	<0.001
Excluding age < 65 years	0.536 (0.504–0.569)	<0.001
Excluding age < 75 years	0.527 (0.467–0.595)	<0.001
Excluding patients not using antidiabetic medications	0.795 (0.748–0.845)	<0.001
Excluding cumulative duration of metformin use <180 days	0.367 (0.348–0.387)	<0.001
II. Non-time-dependent model**	Fully adjusted	
Diabetes duration		
1–2.9 years versus <1 year	1.152 (1.052–1.261)	0.0022
3–4.9 years versus <1 year	1.345 (1.231–1.470)	<0.001
⩾5 years versus <1 year	1.539 (1.421–1.667)	<0.001
Metformin, users versus non-users at baseline	0.730 (0.690–0.773)	<0.001
Insulin, users versus non-users at baseline	0.737 (0.676–0.803)	<0.001
Sulphonylurea, users versus non-users at baseline	0.392 (0.370–0.415)	<0.001
Meglitinide, users versus non-users at baseline	0.876 (0.804–0.955)	0.003
Acarbose, users versus non-users at baseline	0.987 (0.913–1.067)	0.744
Pioglitazone, users versus non-users at baseline	1.133 (0.998–1.287)	0.054
Rosiglitazone, users versus non-users at baseline	0.971 (0.892–1.057)	0.502

HR, hazard ratio, CI, confidence interval.
* Models are adjusted for propensity score (PS) and hazard ratios are estimated for ever- versus never-users of metformin.
** All variables in Table 1 are included in the model.

metformin was consistently observed in analyses after excluding patients aged <65 and <75 years, respectively (Table 4).

Although the data on metformin and prostate cancer incidence remain controversial, the effect of metformin on the progression of and mortality with diagnosed prostate cancer appears to be more unique and consistent. In a Swedish study, 44 non-diabetic men with progressive metastatic castration-resistant prostate cancer given metformin 1000 mg twice daily showed objective PSA responses and disease stabilisation. After giving metformin, a prolongation of PSA doubling time was observed in 52.3% of patients and progression-free survival at 12 weeks was seen in 36% of patients [20]. In another Canadian study, the adjusted hazard ratio for prostate cancer-specific mortality was 0.76 (95% confidence interval: 0.64–0.89) for each additional 6 months of metformin use [21]. The PS-adjusted hazard ratio of 0.231 for >44 months of metformin use for incident prostate cancer (Table 3) seemed to be comparable to what was reported in this Canadian study on prostate cancer-specific mortality [21]. A calculation from this hazard ratio of 0.76 for each 6 months of metformin use yielded a hazard ratio of 0.19 for metformin use for 36 months.

Metformin is typically considered the first-line drug in the management of diabetes. Once patients have severe enough disease that diet and lifestyle changes are no longer sufficient, most patients should be started on metformin. Therefore, a comparison between ever- and never-users of metformin might essentially turn largely into a comparison of moderate-to-severe (requiring some pharmacological therapy) and mild (not requiring drugs) diabetes. However, this effect may be minimal because the findings are consistent after excluding both patients not being treated with any antidiabetic medications and those who might have used metformin briefly (i.e., cumulative duration of metformin use <180 days in Table 4).

Insulin use was associated with a lower risk of prostate cancer in one study [18], and was also demonstrated in this study, in the non-time-dependent model of Table 4. The consistent finding of a lower risk associated with metformin use after excluding patients who had been treated with insulin (under 'Time-dependent models' in Table 4) suggested that the conclusion would not be affected by the inclusion of insulin users in the primary analyses shown in Table 3. The lower risk associated with sulphonylurea and meglitinide ('Non-time-dependent model' in Table 4) has not been previously reported and should be viewed as preliminary. Future studies treating the use of various forms of insulin (i.e. human insulin and insulin analogues), sulphonylurea (i.e. chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride and gliquidone) and meglitinide (i.e. repaglinide and nateglinide) as time-dependent variables and analysing a dose–response relationship among new users are required to confirm the findings. Both sulphonylurea and meglitinide are insulin secretagogues that are always used before rosiglitazone and pioglitazone in Taiwan. The use of these insulin secretagogues might not indicate a more severe diabetes condition or a longer diabetes duration than the use of either rosiglitazone or pioglitazone. Therefore, the lower risk of incident prostate cancer associated with these insulin secretagogues could not be explained by a more severe diabetes condition or longer diabetes duration. Actually, the risk of incident prostate cancer increased in accordance to increasing diabetes duration ('Non-time-dependent model' in Table 4), suggesting a strong relationship between diabetes and prostate cancer in the Taiwanese patients. This seemed to be contradictory to what has been observed in the white populations [19], but has been consistently demonstrated in our earlier studies in terms of prostate cancer incidence [2], prevalence [22,23] and mortality [3].

Population-based screening for prostate cancer is not recommended in Taiwan because it is not cost-effective [24]. A higher proportion of metformin ever-users receiving the PSA test than never-users (Table 1) would only lead to more cases of prostate cancer detected through PSA testing among metformin users, resulting in an underestimation of the protective effect of metformin.

The lack of validation of diabetes diagnoses in the present study may be a limitation. It is not certain whether patients with a diabetes diagnosis but not taking any antidiabetic medications could be misclassified. However, since the finding after excluding patients who were not taking any antidiabetic medications was consistent (Table 4), this concern would not affect the conclusion of the study.

Another limitation of the study is the lack of grading and staging of prostate cancer. Some studies suggested that diabetes is associated with a significantly higher risk of advanced or aggressive prostate cancer [25,26]. A multivariable-adjusted hazard ratio of 1.89 (95% confidence interval: 1.02–3.50) was reported in one study on advanced prostate cancer [25]. Another study suggested that diabetes was positively associated with aggressive prostate cancer in men who were most physically active, with a relative risk of 1.63 (95% confidence interval: 1.07–2.62) [26]. Whether the protective effect of metformin on prostate cancer incidence may differ with regard to grading and staging of the cancer is an interesting issue awaiting future investigation.

In summary, the present study suggests that metformin use in male patients with T2DM is associated with a decreased risk of incident prostate cancer.

Conflict of interest statement

None declared.

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