Original Article
Metabolic syndrome and related conditions

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2023 Jan 41(1): 119-128
https://doi.org/10.5534/wjmh.210157

The World Journal of MEN's HEALTH

Pioglitazone and Prostate Cancer Risk in Taiwanese Male Patients with Type 2 Diabetes: A Retrospective Cohort Study

Chin-Hsiao Tseng[1,2,3]

[1]Department of Internal Medicine, National Taiwan University College of Medicine, [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, [3]Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan, Taiwan

Purpose: This study investigated prostate cancer risk associated with pioglitazone use.

Materials and Methods: The Taiwan's National Health Insurance database was used to create a propensity score-matched cohort of male patients with type 2 diabetes mellitus newly diagnosed in 1999-2005 and aged ≥25 years at baseline. The matched cohort included 20437 ever users and 20437 never users of pioglitazone. The patients were followed up for the incidence of prostate cancer until December 31, 2011. Hazard ratios (HRs) were created from Cox regression weighted on propensity score.

Results: Prostate cancer was diagnosed in 121 ever users of pioglitazone (incidence: 175.84 per 100,000 person-years) and 143 never users of pioglitazone (incidence: 216.66 per 100,000 person-years). When ever users were compared to never users of pioglitazone, the HR was 0.815 (95% confidence interval [CI], 0.639–1.039; p=0.0987). When ever users were categorized into tertiles of cumulative duration of pioglitazone therapy (<6.83, 6.83–20.23, and >20.23 months), the HRs were 1.044 (95% CI, 0.741–1.471), 0.975 (95% CI, 0.690–1.377) and 0.539 (95% CI, 0.374–0.778), respectively. For the tertiles of cumulative dose of <5,040, 5,040–15,330, and >15,330 mg, the HRs were 1.008 (95% CI, 0.710–1.429), 1.090 (95% CI, 0.785–1.515) and 0.484 (95% CI, 0.330–0.711), respectively. A significantly lower risk associated with pioglitazone use could only be seen in patients aged <65 years (HR, 0.578; 95% CI, 0.360–0.927) but not in patients aged ≥65 years.

Conclusions: A significantly lower risk of prostate cancer is observed after a cumulative duration of pioglitazone therapy for >20.23 months or a cumulative dose of >15,330 mg. The risk reduction is mainly observed in patients aged <65 years.

Keywords: National Health Insurance; Pioglitazone; Prostate cancer; Taiwan

INTRODUCTION

Prostate cancer is the fifth leading cause of cancer mortality and the second most common cancer in men [1]. In 2012, there were 1.1 million new cases and two-thirds occurred in developed countries [1]. Incidence rates of prostate cancer vary by 25 folds in different ethnicities and the highest rates are observed in the white people while Asian populations have the lowest rates [1]. In contrary to the declining secular trend in

Received: Aug 13, 2021 **Revised:** Oct 9, 2021 **Accepted:** Oct 30, 2021 **Published online** Mar 2, 2022
Correspondence to: Chin-Hsiao Tseng https://orcid.org/0000-0001-9545-7123
Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei 100225, Taiwan.
Tel: +886-2-2388-3578, **Fax:** +886-2-2388-3578, **E-mail:** ccktsh@ms6.hinet.net

the western world, Asian populations show an increasing trend [2]. Data from Taiwan showed that both the incidence of [3] and mortality from [4] prostate cancer are increasing steadily. The discrepancy in secular trends in different countries may partly reflect the different times of adoption of prostate-specific antigen (PSA) in clinical use or as a screening tool. However, variations in genetic susceptibility and risk factors such as obesity, physical inactivity and increased animal fat consumption are also possible explanations [1].

Pioglitazone is an oral antidiabetic drug that targets the peroxisome proliferator-activator receptor gamma (PPARγ) and improves insulin resistance. Although controversial, a concern of bladder cancer associated with pioglitazone use has been raised [5,6]. However, such an increased risk of bladder cancer was not similarly observed in patients using rosiglitazone [6,7]. On the other hand, rosiglitazone may increase the risk of macrovascular disease [8], but pioglitazone shows a beneficial effect [9]. Therefore, different PPARγ agonists have different effects on vascular disease and cancer.

Pioglitazone exerts an anti-cancer effect on prostate cancer cells in *in vitro* and *in vivo* studies [10-15]. However, such a benefit has not been extensively studied in humans and findings remain controversial. Although a meta-analysis suggested a null association [6], a cohort analysis estimated a significant hazard ratio [HR] of 1.13 (95% confidence interval [CI], 1.02–1.26) for prostate cancer associated with pioglitazone use [5]. A 10-year observational follow-up of the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial suggested that the benefits of pioglitazone on macrovascular diseases are no longer observed when the drug is discontinued [16]. Though not significant, pioglitazone discontinuation after the trial was associated with an increased risk of prostate cancer (relative risk, 1.47; 95% CI, 0.93–2.34) [16]. A recent nested case-control study using the UK primary care data showed a non-significant risk reduction of prostate cancer in patients who used pioglitazone (odds ratio [OR], 0.759; 95% CI, 0.502–1.148) [17].

In Taiwan, a matched case-control study that enrolled 3,513 cases with prostate cancer and 3,513 controls without prostate cancer estimated an adjusted OR of 0.59 (95% CI, 0.43–0.80) associated with pioglitazone use [18]. Because of the inherent limitations associated with the cross-sectional and matched case-control study design, the temporal correctness for a cause to precede an effect could not be assured. Furthermore, the database was derived from a sample of one million people randomly selected from the general population composing of diabetes patients and non-diabetes people. This is not appropriate for assessing the effect of pioglitazone, a drug that can only be prescribed to patients with type 2 diabetes mellitus (T2DM). Finally, the duration of pioglitazone exposure was not assessed in this study [18].

In the present retrospective cohort study conducted in Taiwan, we used the longitudinal database of the National Health Insurance (NHI) to enroll a cohort of ever users and never users of pioglitazone matched on propensity score (PS) to investigate the risk of prostate cancer associated with pioglitazone.

MATERIALS AND METHODS

Since March 1, 1995, Taiwan started to implement a unique, compulsory and universal healthcare system, the NHI. This healthcare system covers >99.6% of the population of Taiwan. Across the nation, all in-hospitals and more than 93% of all medical settings are contracted with the NHI Administration of the Ministry of Health and Welfare to provide medical services.

For the protection of privacy, personal information had been de-identified before the data were released for analyses. The system used for disease coding in the database was the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). According to this coding system, diabetes mellitus was coded by 250.XX and prostate cancer by 185.

PS was created by logistic regression that included the date of entry and all baseline characteristics shown in Table 1 as independent variables. The procedures followed to create a PS-matched cohort of ever users and never users of pioglitazone enrolled for analyses in the study are depicted in Fig. 1. All patients were newly diagnosed of diabetes mellitus between 1999 and 2005. To reduce the probability of a misdiagnosis of diabetes mellitus, the patients should have received at least two prescriptions of antidiabetic drugs at the outpatient clinics (n=423,949). After excluding ineligible patients shown in Fig. 1, 152,806 patients were identified. In consideration that ever users and never users in this unmatched original sample would have imbalanced baseline characteristics, we used the Greedy 8→1

Table 1. Characteristics of never and ever users of pioglitazone

Variable[a]	Never users (n=20,437)	Ever users (n=20,437)	Standardized difference
Age (y)	61.10±12.03	61.12±11.55	0.41
Diabetes duration (y)	6.22±2.54	6.16±2.38	-3.79
Hypertension (401–405)	14,656 (71.71)	14,688 (71.87)	0.40
Chronic obstructive pulmonary disease (490–496)	8,250 (40.37)	8,173 (39.99)	-0.91
Stroke (430–438)	4,377 (21.42)	4,306 (21.07)	-0.84
Nephropathy (580–589)	4,103 (20.08)	4,085 (19.99)	-0.16
Ischemic heart disease (410–414)	7,462 (36.51)	7,461 (36.51)	-0.02
Peripheral arterial disease (250.7, 785.4, 443.81, 440–448)	3,661 (17.91)	3,721 (18.21)	1.02
Eye disease (250.5, 362.0, 369, 366.41, 365.44)	3,253 (15.92)	3,397 (16.62)	2.68
Obesity (278)	739 (3.62)	741 (3.63)	-0.07
Dyslipidemia (272.0–272.4)	15,014 (73.46)	15,244 (74.59)	2.72
Benign prostatic hyperplasia (600)	5,500 (26.91)	5,346 (26.16)	-1.63
Urinary tract diseases (590–599)	9,583 (46.89)	9,476 (46.37)	-1.19
Statin	10,189 (49.86)	10,401 (50.89)	2.35
Fibrate	7,871 (38.51)	8,121 (39.74)	2.69
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	12,470 (61.02)	12,614 (61.72)	1.74
Calcium channel blocker	9,993 (48.90)	10,087 (49.36)	1.01
Sulfonylurea	12,781 (62.54)	13,657 (66.82)	8.75
Metformin	13,586 (66.48)	13,834 (67.69)	0.59
Insulin	633 (3.10)	593 (2.90)	-1.62
Acarbose	1,849 (9.05)	1,811 (8.86)	-1.05
Aspirin	10,229 (50.05)	10,344 (50.61)	1.20
Ticlopidine	778 (3.81)	779 (3.81)	0.07
Clopidogrel	1,352 (6.62)	1,370 (6.70)	0.44
Dipyridamole	6,394 (31.29)	6,495 (31.78)	1.26
Prostate-specific antigen	771 (3.77)	712 (3.48)	-1.78

Values are presented as mean±standard deviation or number (%).
[a]The numbers shown in parentheses are the disease codes according to the International Classification of Diseases, 9th Revision, Clinical Modification.

digit match algorithm [19] to create a cohort of 1:1 PS-matched pairs of ever and never users. According to this algorithm, the best match was first selected based on the same highest 8 digits of the PS. If no matched pair could be selected on 8 digits, ever and never users were then matched on 7 digits. Sequential matching continued to the lowest digit until a matched pair was found. As a result, 20,437 ever users and 20,437 never users of pioglitazone were enrolled for analyses.

The standardized differences were calculated for all covariates as a test of balance diagnostics because standardized differences are not influenced by sample size [20]. A threshold value of >10% was considered as an indicator of potential confounding [20]. Hypothesis tests by chi-square test or Student's t-test were discouraged for assessing imbalance in covariates between two subgroups derived from PS matching because of two main reasons, as pointed out by Austin [20] and Stuart [21], respectively. First, significance levels are affected by sample size and second, "balance is a property of a particular sample" and "reference to a superpopulation is inappropriate" [20].

Kaplan–Meier curves were plotted for ever users and never users in patients aged <65 years and ≥65 years, respectively. The differences between ever users and never users were tested by logrank test.

Cumulative duration (months) and cumulative dose (mg) of pioglitazone use were calculated. A potential dose-response relationship was assessed by analyzing the HRs among the tertiles of these parameters. The incidence density of prostate cancer was calculated for different subgroups with regards to pioglitazone expo-

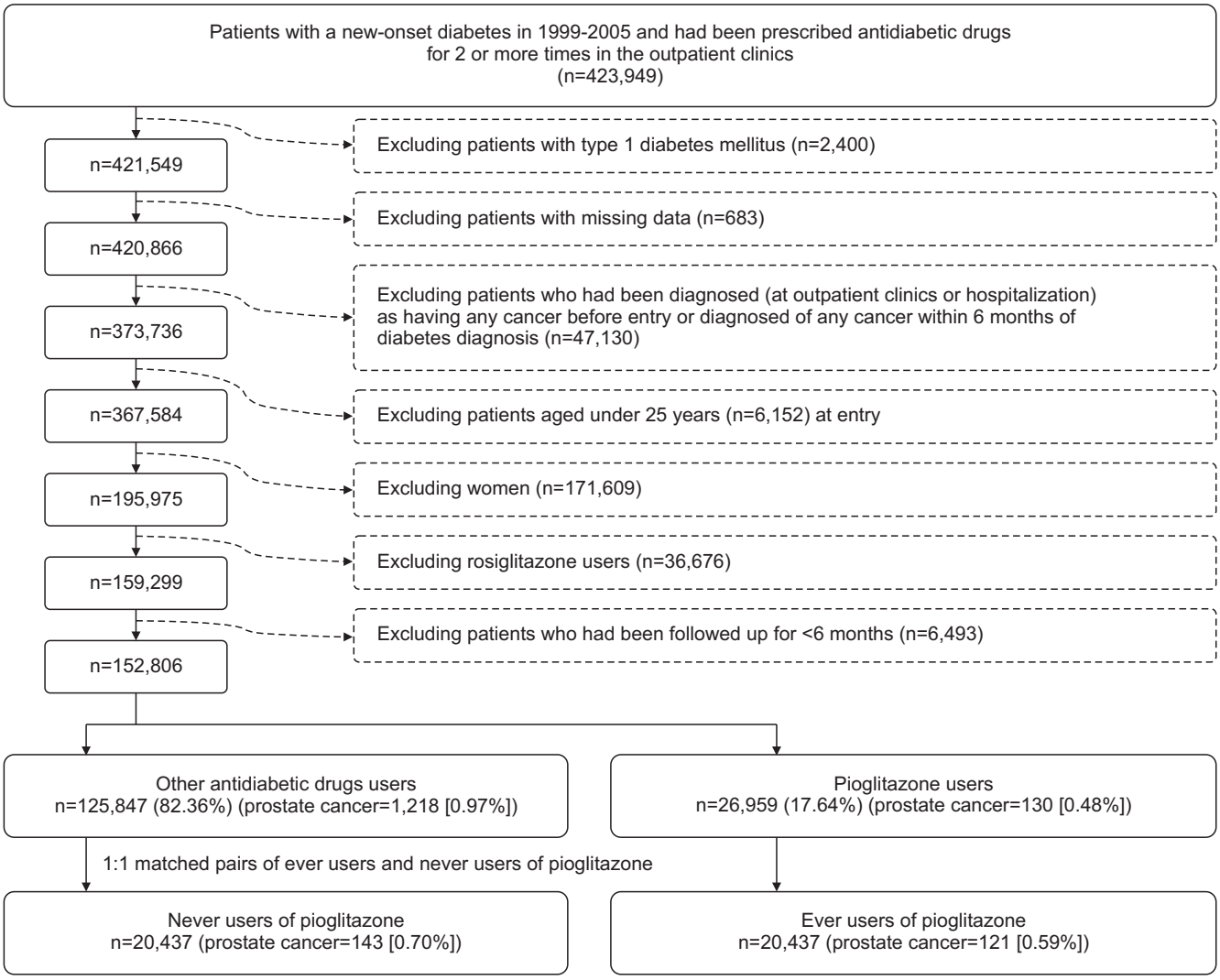

Fig. 1. The procedures followed in selecting a matched-pair sample for analyses.

sure: never users, ever users and ever users divided by the tertile cutoffs of the exposure parameters. The incident number of prostate cancer diagnosed by the end of follow-up was the numerator. The denominator was the duration of follow-up expressed as person-years. Follow-up ended when any of the following events occurred first until December 31, 2011: a patient died, a new diagnosis of prostate cancer or the last record in the database.

Cox regression was used to estimate HRs based on the incorporation of the inverse probability of treatment weighting using the PS [21]. In the main analyses, HRs for ever users *versus* never users and for each tertile of the exposure parameters *versus* never users were estimated. The dose-response relationship was also tested by p-trend for the respective parameters.

In Taiwan, pioglitazone 30 mg is the most commonly prescribed daily dose. However, a smaller dose may be prescribed to older patients and a higher dose may be prescribed to patients with poorer glycemic control. To examine whether the daily dose might differently affect the risk in patients aged <65 years and ≥65 years, the age-specific risk was calculated for three subgroups of daily dose of pioglitazone, *i.e.*, <30 mg/day, 30 mg/day, and >30 mg/day, at the first prescription and the last prescription, respectively. HRs were also estimated for the different subgroups of daily dose with estimation of the p-trend.

The age-specific incidence rates and the HRs for age <40 years, 40–64 years, 65–74 years and ≥75 years for the diabetes men in the present study were calculated. To compare the risk in the diabetes patients to the

non-diabetes population, the age-specific cumulative incidence rates of prostate cancer reported for the age subgroups of 40–64 years, 65–74 years and ≥75 years (data for age <40 years were not reported) in the non-diabetes general population of Taiwan during a 3-year period from 2003 to 2005 [3] were recalculated as incidence rates expressed as per 100,000 person-years as referents for comparison.

Statistical analyses were conducted by using the version 9.4 of the SAS statistical software developed by SAS Institute (Cary, NC, USA). Significant difference based on statistical hypothesis testing was defined by a p-value <0.05.

Ethics statement

The databases are handled by the National Health Research Institutes and the study was approved with number 99274 by an Ethic Review Board of the institutes. Written informed consent was not required according to local regulations because all personal data had been de-identified and the patients could not be contacted.

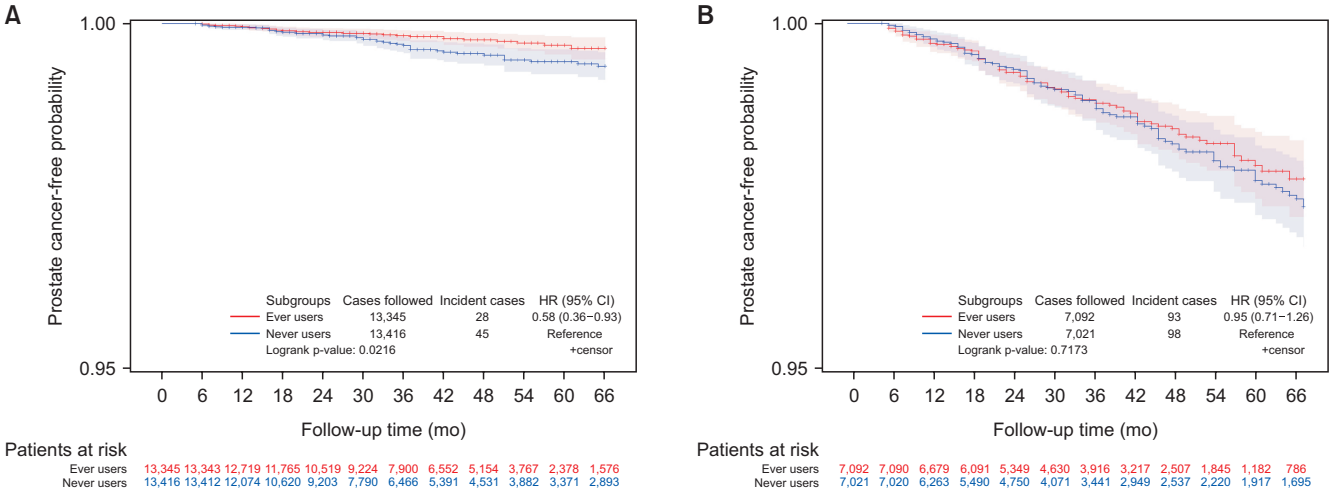

Fig. 2. Kaplan–Meier curves comparing prostate cancer-free probability between pioglitazone ever users and never users in patients aged <65 years (A) and aged ≥65 years (B), respectively. HR: hazard ratio, CI: confidence interval.

Table 2. Incidences of prostate cancer and hazard ratios by pioglitazone exposure in main analyses

Pioglitazone use	Case number	Incident cases	Person-years of follow-up	Incidence rate (per 100,000 person-years)	Hazard ratio	95% confidence interval	p-value
Total							
Never users	20,437	143	66,001.32	216.66	1.000		
Ever users	20,437	121	68,812.16	175.84	0.815	0.639–1.039	0.0987
Tertiles of cumulative duration of pioglitazone therapy (mo)							
Never users	20,437	143	66,001.32	216.66	1.000		
<6.83	6,740	43	19,592.31	219.47	1.044	0.741–1.471	0.8062
6.83–20.23	6,747	42	20,319.52	206.70	0.975	0.690–1.377	0.8840
>20.23	6,950	36	28,900.33	124.57	0.539	0.374–0.778	0.0010
p-trend							0.0259
Tertiles of cumulative dose of pioglitazone therapy (mg)							
Never users	20,437	143	66,001.32	216.66	1.000		
<5,040	6,728	41	19,370.57	211.66	1.008	0.710–1.429	0.9665
5,040–15,330	6,741	48	20,713.96	231.73	1.090	0.785–1.515	0.6066
>15,330	6,968	32	28,727.64	111.39	0.484	0.330–0.711	0.0002
p-trend							0.0227

RESULTS

The baseline characteristics of never users and ever users of pioglitazone enrolled for analyses are shown in Table 1. The two groups were well balanced in covariates because all values of standardized difference were not >10% (Table 1).

The Kaplan–Meier curves in Fig. 2 suggested a significant risk reduction in patients aged <65 years (Fig. 2A) but not in patients aged ≥65 years (Fig. 2B). The two curves for the age subgroups of <65 years did not separate until after a follow-up duration of >30 months, suggesting that the benefit of pioglitazone required a prolonged duration of its use.

The incidence of prostate cancer and the HRs in the main analyses are shown in Table 2. The number of incident cases of prostate cancer was 121 for ever users and 143 for never users. The incidence rate for ever users was 175.84 per 100,000 person-years and for never users 216.66 per 100,000 person-years. Though not statistically significant, an overall lower risk of prostate cancer was observed among ever users (HR, 0.815; 95% CI, 0.639–1.039; p=0.0987). In the tertile analyses of cumulative duration and cumulative dose, the HRs significantly indicated a lower risk in the third tertiles of >20.23 months and >15,330 mg, respectively. All values of p-trend were <0.05, suggesting a dose-response effect in terms of the two exposure parameters.

Table 3. Hazard ratios for prostate cancer according to pioglitazone daily dose

Age subgroup/prescription time/daily dose of pioglitazone	Case number	Incident case	Person-years of follow-up	Incidence rate (per 100,000 person-years)	Hazard ratio	95% confidence interval	p-value
Age <65 y							
Never users	45	13,416	43,070.11	104.48	1.000		
Ever users	28	13,345	45,526.05	61.50	0.578	0.360–0.927	0.0231
First prescription (mg/day)							
Never users	45	13,416	43,070.11	104.48	1.000		
<30	11	5,277	18,297.47	60.12	0.562	0.290–1.087	0.0868
30	17	7,901	26,680.88	63.72	0.599	0.342–1.048	0.0726
>30	0	167	547.70	0.00	-		
p-trend							0.1201
Last prescription (mg/day)							
Never users	45	13,416	43,070.11	104.48	1.000		
<30	5	3,743	12,700.55	39.37	0.367	0.146–0.925	0.0336
30	21	9,151	31,296.25	67.10	0.632	0.376–1.063	0.0840
>30	2	451	1,529.25	130.78	1.221	0.296–5.037	0.7828
p-trend							0.2495
Age ≥65 y							
Never users	98	7,021	22,931.21	427.37	1.000		
Ever users	93	7,092	23,286.10	399.38	0.951	0.715–1.265	0.7292
First prescription (mg/day)							
Never users	98	7,021	22,931.21	427.37	1.000		
<30	41	2,967	9,631.14	425.70	1.019	0.706–1.469	0.9210
30	52	4,043	13,372.10	388.87	0.915	0.653–1.284	0.6081
>30	0	82	282.87	0.00	-		
p-trend							0.3308
Last prescription (mg/day)							
Never users	98	7,021	22,931.21	427.37	1.000		
<30	31	2,362	7,612.03	407.25	0.968	0.645–1.451	0.8737
30	61	4,555	15,071.74	404.73	0.960	0.696–1.324	0.8037
>30	1	175	602.34	166.02	0.388	0.054–2.784	0.3467
p-trend							0.4699

-: not available.

Table 4. Incidences of prostate cancer and hazard ratios by pioglitazone exposure in different age subgroups

Age/pioglitazone use	Case number	Incident case	Person-years of follow-up	Incidence rate (per 100,000 person-years)	Hazard ratio	95% confidence interval	p-value	Incidence rate (per 100,000 person-years) in non-diabetes men[a]
Aged <40 y								
Pioglitazone (-)	695	1	1,976.72	50.59				
Pioglitazone (+)	613	0	2,049.45	0.00		-	-	-
All	1,308	1	4,026.17	24.84				
Aged 40–64 y								
Pioglitazone (-)	12,721	44	41,093.39	107.07	1.000			
Pioglitazone (+)	12,732	28	43,476.60	64.40	0.590	0.367–0.950	0.0298	
All	25,453	72	84,569.99	85.14				45.11
Aged 65–74 y								
Pioglitazone (-)	4,053	54	13,581.50	397.60	1.000			
Pioglitazone (+)	4,468	53	14,925.13	355.11	0.905	0.618–1.325	0.6069	
All	8,521	107	28,506.63	375.35				297.07
Aged ≥75 y								
Pioglitazone (-)	2,968	44	9,349.71	470.60	1.000			
Pioglitazone (+)	2,624	40	8,360.97	478.41	1.041	0.676–1.604	0.8540	
All	5,592	84	17,710.68	474.29				458.18

[a]Data adapted from Tseng CH (Diabetes Care 2011) [3] (only incidence rates for non-diabetes men aged ≥40 years are available). This column is listed for comparison.

Table 3 shows the HRs in subgroups of daily dose prescribed at the first and the last prescriptions and in patients aged <65 years and ≥65 years, respectively. A lower risk associated with pioglitazone could only be seen in patients aged <65 years; and among them, only those who used the lowest dose of <30 mg/day at the last prescription showed a significant risk reduction (HR, 0.367; 95% CI, 0.146–0.925). There was not any significant association in patients aged ≥65 years.

Table 4 shows the incidences of prostate cancer and the HRs in different age subgroups in the diabetes patients and the age-specific incidence rates in Taiwanese non-diabetes men. The benefit of pioglitazone could only be seen in patients aged <65 years. Because no case of prostate cancer was observed in pioglitazone users aged <40 years, we additionally calculated the incidence rates and HR for the age subgroup of <65 years. For age <65 years, the incidence rate was 61.50 per 100,000 person-years among ever users in comparison to 104.48 per 100,000 person-years among never users. The HR that compared ever to never users in this age subgroup was 0.578 (95% CI, 0.360–0.927; p=0.0231). Nevertheless, either the incidence rates of 64.40 per 100,000 person-years in pioglitazone users aged 40–64 years or 61.50 per 100,000 person-years in pioglitazone users aged <65 years was still higher than the incidence of 45.11 per 100,000 person-years in the non-diabetes men aged 40–64 years.

DISCUSSION

The present study suggested a reduced risk of prostate cancer among pioglitazone users in patients aged <65 years but not in those aged ≥65 years (Fig. 2). Significant benefit of pioglitazone would not be obvious until after a long follow-up of approximately 30 months (Fig. 2). In the main analyses, significantly reduced risk would be seen in the third tertile of cumulative duration of >20.23 months or in the third tertile of cumulative dose of >15,330 mg (Table 2). When analyzed by daily doses, the benefit of pioglitazone was only significant in patients aged <65 years and when the daily dose at the last prescription was <30 mg/day (Table 3). Because the incidence rate in the pioglitazone ever users was still higher than the incidence among their non-diabetes counterparts (Table 4), additional factors have to be intervened for further reduction of the risk in patients with T2DM.

Because PSA is a screening tool that may lead to detection bias, we conducted secondary analyses after excluding patients who had received such a test. The estimated HR was 0.765 (95% CI: 0.591-0.989, p=0.0409). We also calculated the p-values for the continuous variables of age and diabetes duration with Student's t test and for all other categorical variables in Table 1 with chi-square test. Six variables, *i.e.*, diabetes duration, dyslipidemia, statin, fibrate, sulfonylurea, and metformin, had p-values <0.05. A Cox model was then created by adjusting these variables and the HR was 0.799 (95% CI: 0.626–1.020; p=0.0718). These additional secondary analyses suggested that the conclusion of a potential lower risk of prostate cancer associated with pioglitazone use was rather consistent.

The mechanisms of how pioglitazone may reduce the risk of prostate cancer remain to be answered. The effects of different PPARγ agonists including troglitazone, ciglitazone, rosiglitazone and pioglitazone may not be the same [22,23]. In cellular studies, pioglitazone reduced the expression of PSA *via* an inhibition of the androgen activation of PSA promoter [10], induced p21 (a cyclin-dependent kinase inhibitor) [12], up-regulated the expression of E-cadherin (a protein controlling cell migration and invasion) [14], inhibited prostate cancer cell growth in a three-dimensional multicellular tumor spheroid culture system [24] and increased reactive oxygen species [25]. An animal study suggested that pioglitazone significantly reduced prostate carcinogenesis through reducing cyclin D1 and inactivating p38 mitogen-activated protein kinase and nuclear factor κB [15].

Recent *in vitro* studies suggested that there are dual effects of PPARγ agonists on the development and progression of prostate cancer [26]. Stimulation of PPARγ may directly play a role in the carcinogenicity of prostate cancer *via* androgen receptor-dependent or -independent pathways [26]. However, PPARγ agonists may also inhibit the development or growth of prostate cancer *via* proteasomal degradation of transcription factor specificity protein 1, inhibition of the AKT signaling pathway and some other PPARγ-independent pathways [26]. A study suggested that excessive fatty acids may facilitate the PPARγ-promoted malignant progression of prostate cancer [27]. Therefore, the interaction between androgen/fatty acids and pioglitazone, which has not been previously investigated, may partly explain the inconsistent results observed in studies

conducted in different ethnicities.

Pioglitazone use is associated with an increased body weight, up to 4 kg within 16 weeks in Caucasians [28] and 1.2 kg within 12 weeks in a Taiwanese study [29]. The greater increase in body weight in Caucasians may also explain the potentially higher risk of prostate cancer associated with pioglitazone use in these people [5].

The prevalence of obesity diagnosed according to the ICD-9-CM code was only approximately 3.6% in either the ever users or never users (Table 1). This was an underestimation of the real prevalence of obesity. An epidemiological survey showed that when body mass index ≥25 kg/m^2 and ≥30 kg/m^2 was used to define obesity, the corresponding prevalence of obesity would be 33.5% and 7.1%, respectively, in the diabetes patients [30]. Therefore, a residual confounding from obesity could not be completely excluded. Future studies are required to rule out the potential risk associated with the increased body weight, body mass index or waist circumference after pioglitazone use.

The patients were enrolled from 1999 to 2005 and followed up until 2011. This database seemed to be too old. However, the study period was deliberately selected to reduce potential biases for the following reasons. First, the PROactive trial published in 2005 suggested a potentially higher risk of bladder cancer associated with pioglitazone use [16]. This might have led to behavior changes in drug prescription by the doctors and drug adherence by the patients after 2005. Second, the Bureau of the NHI started to promote the use of ICD-10-CM in Taiwan since 2012 and therefore a potential bias resulting from a mixture of two disease coding systems might have happened if the follow-up ended after 2012.

The present study has several strengths. First, the findings had a high generalizability to the general population because the database covers the whole population. Second, the identification of prostate cancer could be more complete because all sources of claims records from the outpatient visits and hospital admission were considered. Third, the detection rate of prostate cancer is less biased by different social classes because most medical co-payments in patients with cancer can be waived by the NHI. Furthermore, co-payments are actually low for patients with low incomes, for veterans and for those who receive drug refills for chronic disease. Fourth, by using medical records, bias resulting from self-reporting could be reduced.

There are several limitations. First, we did not have actual measurement data for confounders such as family history, dietary factors, anthropometric factors, physical activity, lifestyle, smoking, alcohol drinking, hormonal profiles, and genetic parameters. Second, the impact of biochemical data could not be evaluated. Third, we were not able to do more detailed analyses based on the pathology, grading and staging of prostate cancer because of lack of information.

CONCLUSIONS

In summary, this study suggests a lower risk of prostate cancer associated with pioglitazone use when it has been used for >20.23 months or when the cumulative dose reaches 15,330 mg. This benefit is especially significant in patients younger than 65 years old and in those who use a daily dose of <30 mg/day by the end of follow-up. The potential usefulness of pioglitazone in patients with prostate cancer, in either the diabetes or non-diabetes patients, is worthy of future research.

Conflict of Interest

The author has nothing to disclose.

Funding

The Ministry of Science and Technology of Taiwan (MOST 107-2221-E-002-129-MY3) and the Yee Fong Charity Foundation provided financial support for the study. The funders did not have any role in study design, data collection, statistical analysis, manuscript writing, and decision for publication.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time due to legal and ethical reasons.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
3. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. Diabetes Care 2011;34:616-21.
4. Tseng CH. Prostate cancer mortality in Taiwanese men: in-

creasing age-standardized trend in general population and increased risk in diabetic men. Ann Med 2011;43:142-50.
5. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015;314:265-77.
6. Bosetti C, Rosato V, Buniato D, Zambon A, La Vecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. Oncologist 2013;18:148-56.
7. Tseng CH. Rosiglitazone is not associated with an increased risk of bladder cancer. Cancer Epidemiol 2013;37:385-9.
8. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
9. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321-31.
10. Hisatake JI, Ikezoe T, Carey M, Holden S, Tomoyasu S, Koeffler HP. Down-regulation of prostate-specific antigen expression by ligands for peroxisome proliferator-activated receptor gamma in human prostate cancer. Cancer Res 2000;60:5494-8.
11. Yang CC, Ku CY, Wei S, Shiau CW, Chen CS, Pinzone JJ, et al. Peroxisome proliferator-activated receptor gamma-independent repression of prostate-specific antigen expression by thiazolidinediones in prostate cancer cells. Mol Pharmacol 2006;69:1564-70.
12. Radhakrishnan SK, Gartel AL. The PPAR-gamma agonist pioglitazone post-transcriptionally induces p21 in PC3 prostate cancer but not in other cell lines. Cell Cycle 2005;4:582-4.
13. Chaffer CL, Thomas DM, Thompson EW, Williams ED. PPARgamma-independent induction of growth arrest and apoptosis in prostate and bladder carcinoma. BMC Cancer 2006;6:53.
14. Annicotte JS, Iankova I, Miard S, Fritz V, Sarruf D, Abella A, et al. Peroxisome proliferator-activated receptor gamma regulates E-cadherin expression and inhibits growth and invasion of prostate cancer. Mol Cell Biol 2006;26:7561-74.
15. Suzuki S, Mori Y, Nagano A, Naiki-Ito A, Kato H, Nagayasu Y, et al. Pioglitazone, a peroxisome proliferator-activated receptor γ agonist, suppresses rat prostate carcinogenesis. Int J Mol Sci 2016;17:2071.
16. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. Diabetes Obes Metab 2016;18:266-73.
17. Boxall N, Bennett D, Hunger M, Dolin P, Thompson PL. Evaluation of exposure to pioglitazone and risk of prostate cancer: a nested case-control study. BMJ Open Diabetes Res Care 2016;4:e000303.
18. Kao LT, Xirasagar S, Lin HC, Huang CY. Association between pioglitazone use and prostate cancer: a population-based case-control study in the Han population. J Clin Pharmacol 2019;59:344-9.
19. Parsons LS. Performing a 1:N case-control match on propensity score. Paper presented at: SAS Users Group International 29; 2004 May 9-12; Montreal, Canada. Paper 165-29.
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
21. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010;25:1-21.
22. Akinyeke TO, Stewart LV. Troglitazone suppresses c-Myc levels in human prostate cancer cells via a PPARγ-independent mechanism. Cancer Biol Ther 2011;11:1046-58.
23. Shiau CW, Yang CC, Kulp SK, Chen KF, Chen CS, Huang JW, et al. Thiazolidenediones mediate apoptosis in prostate cancer cells in part through inhibition of Bcl-xL/Bcl-2 functions independently of PPARgamma. Cancer Res 2005;65:1561-9.
24. Gottfried E, Rogenhofer S, Waibel H, Kunz-Schughart LA, Reichle A, Wehrstein M, et al. Pioglitazone modulates tumor cell metabolism and proliferation in multicellular tumor spheroids. Cancer Chemother Pharmacol 2011;67:117-26.
25. Srivastava N, Kollipara RK, Singh DK, Sudderth J, Hu Z, Nguyen H, et al. Inhibition of cancer cell proliferation by PPARγ is mediated by a metabolic switch that increases reactive oxygen species levels. Cell Metab 2014;20:650-61.
26. Elix C, Pal SK, Jones JO. The role of peroxisome proliferator-activated receptor gamma in prostate cancer. Asian J Androl 2018;20:238-43.
27. Forootan FS, Forootan SS, Gou X, Yang J, Liu B, Chen D, et al. Fatty acid activated PPARγ promotes tumorigenicity of prostate cancer cells by up regulating VEGF via PPAR responsive elements of the promoter. Oncotarget 2016;7:9322-39.
28. Chilcott J, Tappenden P, Jones ML, Wight JP. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. Clin Ther 2001;23:1792-823; discussion 1791.
29. Tseng CH, Huang TS. Pioglitazone with sulfonylurea: glycemic and lipid effects in Taiwanese type 2 diabetic patients. Diabetes Res Clin Pract 2005;70:193-4.
30. Tseng CH. Body mass index and blood pressure in adult type 2 diabetic patients in Taiwan. Circ J 2007;71:1749-54.