Drug Saf (2013) 36:643–649
DOI 10.1007/s40264-013-0080-4

ORIGINAL RESEARCH ARTICLE

Risk of Bladder Cancer in Diabetic Patients Treated with Rosiglitazone or Pioglitazone: A Nested Case–Control Study

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Published online: 25 June 2013

Abstract

Background Evidence has emerged that pioglitazone may increase the risk of bladder cancer, but the association has not been confirmed. This potential risk also has not been evaluated in users of rosiglitazone.

Objective Using Taiwan's National Health Insurance Research Database (NHIRD), this large population-based nested case–control study was conducted to explore the relationship between the use of rosiglitazone or pioglitazone and risk of bladder cancer in diabetic patients.

Methods We identified 3,412 cases of newly diagnosed bladder cancer and 17,060 controls (1:5 matched by age and sex) among a diabetic patient cohort from the NHIRD. We defined an index date for each case as the date of first hospitalization for bladder cancer. Each control was assigned the index date of their corresponding case. Multivariable conditional logistic regressions were used to estimate the association between exposure (timing and duration) to rosiglitazone or pioglitazone and bladder cancer. We defined rosiglitazone or pioglitazone exposure as "current" if the prescription duration covered the index date or ended at 90 days before, as "recent" if it ended 91–180 days before the index date, or as "past" if the last prescription ended more than 180 days before. Duration of rosiglitazone or pioglitazone use was defined based on the cumulative days of exposure prior to the index date: <1, 1–2 and ≥2 years.

Results Rosiglitazone and pioglitazone use were associated with risk of bladder cancer and the associations were stronger with a longer term of exposure (pioglitazone <1 year odds ratio [OR] 1.45 [95 % CI 1.12–1.87, $p < 0.01$], 1–2 years OR 1.74 [95 % CI 1.05–2.90, $p = 0.03$] and ≥2 years OR 2.93 [95 % CI 1.59–5.38, $p < 0.01$]; rosiglitazone <1 year OR 0.98 [95 % CI 0.82–1.17, $p = 0.81$], 1–2 years OR 1.78 [95 % CI 1.31–2.39, $p < 0.01$] and ≥2 years OR 2.00 [95 % CI 1.37–2.92, $p < 0.01$]).

Conclusions Long-term exposures to pioglitazone and rosiglitazone were associated with higher odds of bladder cancer, and the highest odds were seen in users with ≥2 years of exposure.

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1 Introduction

Recent evidence has emerged that pioglitazone, an oral hypoglycaemic agent, may be associated with an increased risk of bladder cancer. This potential link was first noticed in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular) trial [1, 2], with 14 cases of bladder cancer in the pioglitazone group (0.5 %) compared with six cases in the placebo group (0.2 %). There are, however, conflicting findings reported by several observational studies [3–6]. A population-based cohort study using the

French National Health Insurance Information system found a 20 % increased hazard of bladder cancer (adjusted hazard ratio [HR] 1.22; 95 % CI 1.05–1.43) [5] associated with pioglitazone. Similar results were also reported by a study using the Kaiser Permanente Northern California (KPNC) Diabetes Registry [4] as the data source. In contrast, an analysis using data derived from an Asian population [6] did not find such an association.

Additional studies are therefore warranted as evidence surrounding the bladder cancer risk among pioglitazone users is very limited due to the relatively few bladder cancer cases in existing studies [4, 6, 7]. In addition, the correlation between length of exposure to pioglitazone and bladder cancer has not been confirmed [4, 6]. Furthermore, available information on the association between bladder cancer risk and other thiazolidinediones (e.g. rosiglitazone) is very limited [3, 8]. Together, these limitations warrant a great need for more information on the safety of pioglitazone and for a comparison of the relative bladder cancer risk posed by the two thiazolidinediones. Using Taiwan's National Health Insurance Research Database (NHIRD), the objective of this large population-based nested case–control study was to explore the relationship between the use of thiazolidinediones (i.e. rosiglitazone and pioglitazone) and the risk of bladder cancer in diabetic patients.

2 Methods

2.1 Data Source

The NHIRD is a nationwide database comprising anonymous eligibility and enrollment information, as well as claims for visits, procedures and prescription medications of more than 99 % of the entire population (23 million) in Taiwan. Individual patients are recorded as entering the NHIRD when they are covered by Taiwan's mandatory National Health Insurance (NHI) programme subsequent to 1996 and leave because of death. For each visit, the NHIRD records dates of visits (outpatient visits, admissions and discharges) and up to five diagnoses coded by physicians according to the *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM codes) [9]. The completeness and accuracy of the NHIRD are ensured by the Department of Health and the Bureau of NHI of Taiwan. The longitudinal nature of NHIRD permits one to identify a cohort based upon diagnoses, health services and drug utilization, track medical history, establish a prescription drug profile and determine the endpoint of drug treatment. The database has been described in detail elsewhere and has been the source for numerous epidemiological studies published in peer-reviewed journals [10].

2.2 Study Population

Our cohort consisted of diabetic patients who had at least one record of an outpatient visit with a diagnosis of type 2 diabetes mellitus (ICD-9-CM [9] code 250.xx) between 1 January 1997 and 31 December 2008 in the NHIRD. Date of first diagnosis of diabetes was assigned as the cohort entry date for all identified patients. Patients who had any record of inpatient visit with a primary diagnosis of any cancer (ICD-9-CM codes: 140.xx–239.xx) before the entry date were excluded.

Among the diabetic cohort, we identified cases as those who were hospitalized with a primary diagnosis of bladder cancer (ICD-9-CM codes: 188.xx). Only the first hospitalization for bladder cancer was included in our study. All potential cases were validated using the Catastrophic Illness Database (including patients with cancer, chronic renal failure, cerebrovascular diseases, disorders of metabolism [including diabetes] or other immune diseases) of the NHIRD. All NHI beneficiaries diagnosed with malignant tumours are eligible to apply for a certificate of catastrophic illness to be exempted from all co-payments. Since it is a requirement to have an official certificate of cancer diagnosis from the hospital to be eligible for the certificate of catastrophic illness, we could precisely identify cancer cases and avoid potential misclassifications through the Catastrophic Illness Database. This approach has also been adopted by several published cancer studies using the NHIRD as the data source [11, 12].

We defined an index date for each case as the date of first hospitalization for bladder cancer. For each case, five matched controls were randomly selected from the same diabetic cohort using the incidence density sampling approach. Controls were matched to the cases for age (±1 year), sex and entry date (±90 days). Each control was assigned the index date of the corresponding case.

2.3 Definition of Exposure

To investigate the association between thiazolidinediones (rosiglitazone and pioglitazone) and the risk of bladder cancer, all prescriptions of thiazolidinediones before the index date were identified in the NHIRD. For each thiazolidinedione prescribed, the prescription records of the NHIRD include information on starting date (date prescription was dispensed), dosages, quantities and prescription duration. We created categories of the exposure to thiazolidinediones based on the timing and duration of use of the identified prescriptions. Study individuals were defined as "current users" if the prescription period covered 90 days on and before the index date (including index date). "Recent users" were defined as a prescription period that ended within 91 days until 180 days before index date,

and "past users" were those with a prescription period that did not overlap the last 180 days before the index date. Non-users were defined as patients without any record of use of thiazolidinediones before index date. We categorized all users of thiazolidinediones into three categories based on the cumulative days of prescription of thiazolidinediones as the duration of exposure: less than 1 year, between 1 and 2 years, and beyond 2 years. Exposure to rosiglitazone or pioglitazone was recorded separately to examine the potential different effects on risk of bladder cancer.

2.4 Statistical Analysis

Multivariable conditional logistic regressions were used to estimate the associations between the exposure to thiazolidinediones and risk of bladder cancer. We also examined the association between duration of thiazolidinedione use and risk of bladder cancer. The associations are presented as odds ratios (ORs) with 95 % confidence intervals. Two-sided *p*-values less than 0.05 were considered statistically significant.

All models were adjusted for duration of diabetes, co-morbid conditions and concomitant medications. Co-morbid conditions included chronic renal failure, bladder conditions (calculus of kidney, ureter, lower urinary tract, cystitis and urinary tract infection) and chronic obstructive pulmonary disease (COPD). Concomitant medications were mainly other hypoglycaemic agents, including sulfonylureas, biguanides, α-glucosidase inhibitors and insulin. Data on co-morbid conditions and concomitant medications were obtained from diagnoses and prescriptions within 1 year before the index date. Analyses were performed with SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

3 Results

We identified 3,412 cases of newly diagnosed bladder cancer and 17,060 controls among the diabetic patients. The age and sex distributions in cases and controls were well-matched. More case patients than controls used pioglitazone (case 4.48 % vs. control 3.07 %) or rosiglitazone (case 10.14 % vs. control 9.29 %) in the year prior to index date. Case patients were also more likely than controls to use other oral hypoglycaemic agents (sulfonylureas, biguanides and α-glucosidase inhibitors), but less likely to use insulin. As expected, case patients were more likely to have bladder conditions than controls 1 year prior to their index dates. However, they were less likely to have chronic renal failure and COPD (Table 1).

"Current users" of pioglitazone were associated with an increased risk of bladder cancer (adjusted OR 2.39, 95 % CI 1.75–3.25, $p < 0.01$) after adjustment for co-morbidities and co-medications. No such association was found among "recent" (adjusted OR 1.62, 95 % CI 0.79–3.33, $p = 0.19$) or "past users" of pioglitazone (adjusted OR 1.10, 95 % CI 0.79–1.52, $p = 0.59$). A similar association was found among rosiglitazone users, with adjusted ORs significantly evident in "current users" (adjusted OR 1.89, 95 % CI 1.51–2.38, $p < 0.01$) but not in "recent" (adjusted OR 0.78, 95 % CI 0.46–1.35, $p = 0.38$) or "past users" (adjusted OR 0.95, 95 % CI 0.78–1.14, $p = 0.56$) [Table 2].

Significantly, the association between exposure to thiazolidinediones and risk of bladder cancer was stronger with a longer term of exposure. The adjusted ORs of exposure to pioglitazone <1, 1–2 and ≥2 years were 1.45 (95 % CI 1.12–1.87, $p < 0.01$), 1.74 (95 % CI 1.05–2.90, $p = 0.03$) and 2.93 (95 % CI 1.59–5.38, $p < 0.01$), respectively.

Table 1 Basic characteristics of bladder cancer cases and their matched controls

Characteristics	Cases (n = 3,412)	Controls (n = 17,060)	p-value
Age [year; mean ± SD]	66.29 ± 10.28	66.28 ± 10.28	0.96
Male [n (%)]	2,337 (68.49)	11,685 (68.49)	1.00
Follow-up duration [days; mean ± SD]	1,322.0 ± 893.7	1,324.3 ± 894.1	0.98
Thiazolidinediones			
Pioglitazone [n (%)]	153 (4.48)	523 (3.07)	<0.01*
Rosiglitazone [n (%)]	346 (10.14)	1,585 (9.29)	0.12
Co-medication			
Sulfonylurea [n (%)]	1,576 (46.19)	6,185 (36.25)	<0.01*
Biguanides [n (%)]	1,333 (39.07)	4,823 (28.27)	<0.01*
α-Glucosidase inhibitors [n (%)]	241 (7.06)	928 (5.44)	<0.01*
Insulin	458 (13.42)	3,834 (22.47)	<0.01*
Co-morbidities			
Chronic renal failure [n (%)]	403 (11.81)	2,750 (16.12)	<0.01*
Bladder condition[a] [n (%)]	2,181 (63.92)	3,164 (18.55)	<0.01*
COPD [n (%)]	201 (5.89)	1,597 (9.36)	<0.01*

* $p < 0.05$

COPD chronic obstructive pulmonary disease, *SD* standard deviation

[a] Bladder conditions included calculus of the kidney, ureter, lower urinary tract, cystitis and urinary tract infection

Table 2 Relationship between use of pioglitazone/rosiglitazone and risk of bladder cancer

Category of user	Total (n = 20,472) [n (%)]	Case (n = 3,412) [n (%)]	Control (n = 17,060) [n (%)]	Crude OR		Adjusted OR	
				OR (95 % CI)	p-value	OR (95 % CI)	p-value
Pioglitazone							
Non-users	19,796 (96.7)	3,259 (95.5)	16,537 (96.9)	1.00 (Reference)		1.00 (Reference)	
Current users	262 (1.3)	82 (2.4)	180 (1.1)	2.32 (1.78–3.03)	<0.01*	2.39 (1.75–3.25)	<0.01*
Recent users	50 (0.2)	13 (0.4)	37 (0.2)	1.85 (0.98–3.51)	0.06	1.62 (0.79–3.33)	0.19
Past users	364 (1.8)	58 (1.7)	306 (1.8)	0.96 (0.73–1.28)	0.80	1.10 (0.79–1.52)	0.59
Rosiglitazone							
Non-users	18,541 (90.6)	3,066 (89.9)	15,475 (90.7)	1.00 (Reference)		1.00 (Reference)	
Current users	539 (2.6)	154 (4.5)	385 (2.3)	2.02 (1.67–2.45)	<0.01*	1.89 (1.51–2.38)	<0.01*
Recent users	121 (0.6)	19 (0.6)	102 (0.6)	0.91 (0.56–1.49)	0.70	0.78 (0.46–1.35)	0.38
Past users	1,271 (6.2)	173 (5.1)	1,098 (6.4)	0.80 (0.68–0.94)	<0.01*	0.95 (0.78–1.14)	0.56

* $p < 0.01$

OR odds ratio

Table 3 Duration of exposure to pioglitazone/rosiglitazone and risk of bladder cancer

Duration of exposure	Total (n = 20,472) [n (%)]	Case (n = 3,412) [n (%)]	Control (n = 17,060) [n (%)]	Crude OR		Adjusted OR	
				OR (95 % CI)	p-value	OR (95 % CI)	p-value
Pioglitazone							
Non-users	19,796 (96.7)	3,259 (95.5)	16,537 (96.9)	1.00 (Reference)		1.00 (Reference)	
<1 year	502 (2.5)	104 (3.1)	398 (2.3)	1.34 (1.07–1.67)	0.01*	1.45 (1.12–1.87)	<0.01**
1–2 years	106 (0.5)	24 (0.7)	82 (0.5)	1.48 (0.94–2.35)	0.09	1.74 (1.05–2.90)	0.03*
≥2 years	68 (0.3)	25 (0.7)	43 (0.3)	2.99 (1.82–4.92)	<0.01**	2.93 (1.59–5.38)	<0.01**
P_{trend}[a]					<0.01**		0.03*
Rosiglitazone							
Non-users	18,541 (90.6)	3,066 (89.9)	15,475 (90.7)	1.00 (Reference)		1.00 (Reference)	
<1 year	1,435 (7.0)	215 (6.3)	1220 (7.2)	0.89 (0.77–1.04)	0.14	0.98 (0.82–1.17)	0.81
1–2 years	309 (1.5)	78 (2.3)	231 (1.4)	1.68 (1.30–2.19)	<0.01**	1.78 (1.31–2.39)	<0.01**
≥2 years	187 (0.9)	53 (1.6)	134 (0.8)	1.99 (1.44–2.75)	<0.01**	2.00 (1.37–2.92)	<0.01**
P_{trend}[a]					<0.01**		<0.01**

* $p < 0.05$, ** $p < 0.01$

OR odds ratio

[a] P_{trend} were calculated using a two-sided test for trend in the logistic regression models. Duration of rosiglitazone/pioglitazone was included as a categorical variable

A clear pattern of increased exposure duration and risk of bladder cancer was also observed among rosiglitazone users. The adjusted ORs of exposure to rosiglitazone <1, 1–2 and ≥2 years were 0.98 (95 % CI 0.82–1.17, $p = 0.81$), 1.78 (95 % CI 1.31–2.39, $p < 0.01$) and 2.00 (95 % CI 1.37–2.92, $p < 0.01$), respectively (Table 3).

4 Discussion

In this population-based nested case–control study, we provide further evidence of an increased association between use of pioglitazone and the risk of bladder cancer. In addition, a similar association among rosiglitazone users was found in our study. Long-term exposure to pioglitazone and rosiglitazone was associated with higher odds of bladder cancer, and the highest odds were seen in thiazolidinedione users with ≥2 years of exposure.

Our findings on long-term use of pioglitazone and bladder cancer were consistent with research done by Lewis et al. [4] and Azoulay et al. [3]. In these studies the increased risk of bladder cancer associated with >24 months of pioglitazone therapy were demonstrated with an HR of 1.4 (95 % CI 1.03–2.00) [4] and an

OR of 1.99 (95 % CI 1.14–3.45) [3]. This association was confirmed in our study, which showed that ≥2 years of pioglitazone was associated with a significantly increased odds of bladder cancer (OR 2.93, 95 % CI 1.59–5.38). However, the studies by Lewis et al. [4] (<12 months, HR 0.8, 95 % CI 0.6–1.3) and Azoulay et al. [3] (<12 months, OR 0.56, 95 % CI 0.07–4.42) did not report the association among short-term users of pioglitazone that ours did (<1 year, OR 1.45, 95 % CI 1.12–1.87). Another study performed by Tseng [6] in a random sample from the NHI database in Taiwan also did not find an association between pioglitazone use and bladder cancer risk (HR 1.305, 95 % CI 0.661–2.576). The relatively small number of bladder cancer cases in the studies by Lewis et al. ($n = 90$ among pioglitazone users and $n = 791$ among non-pioglitazone users) [4], Azoulay et al. [3] ($n = 376$) and Tseng ($n = 165$) [6] may explain such estimates.

By using Taiwanese nationwide data, the large number of bladder cancer cases ($n = 3{,}412$) among diabetic patients in our study may provide a more precise estimate with power to reveal gradients of relative odds for different durations of exposure to pioglitazone. This is supported by a duration of exposure–response relationship observed in our study (ORs of exposure to pioglitazone <1, 1–2 and ≥2 years and risk of bladder cancer were 1.45 [95 % CI 1.12–1.87, $p < 0.01$], 1.74 [95 % CI 1.05–2.90, $p = 0.03$] and 2.93 (95 % CI 1.59–5.38, $p < 0.01$]). These findings were also comparable with those of the study by Neumann et al. [5], which was based on data from the French National Health Insurance information system with 175 and 1,841 cases of bladder cancer among patients exposed and not exposed to pioglitazone, respectively (HRs of exposure to pioglitazone <1, 1–2 and ≥2 years and risk of bladder cancer were 1.05 [95 % CI 0.82–1.87, $p = 0.68$], 1.34 [95 % CI 1.02–1.75, $p = 0.03$] and 1.36 [95 % CI 1.04–1.79, $p = 0.02$]) .

Furthermore, our study provided additional information on a potential association between rosiglitazone use and risk of bladder cancer. Although the potential signal is weaker among rosiglitazone users than pioglitazone users, a clear duration of the exposure–response relationship was also found in our study with a twofold increased odds in patients who use rosiglitazone for more than 2 years (OR 2.00, 95 % CI 1.37–2.92). Our findings were consistent with study results reported by Mamtani et al. [8]. Using a cohort study design, Mamtani et al. [8] found that both pioglitazone and rosiglitazone were associated with an increased risk of bladder cancer in type 2 diabetic patients, and direct comparison of these two drugs showed no significant differences in cancer risk, indicating the possibility of a class effect. However, this potential class effect was not reported by Azoulay et al. [3]. Differences in cohort definition and reference group between the study by Azoulay et al. [3] and our study may explain such inconsistencies. On the other hand, no obvious biological mechanism links thiazolidinediones to bladder cancer yet. Thiazolidinediones are peroxisome proliferator-activated receptor gamma (PPARγ) ligands that relate to cell differentiation. Although PPARγ ligands have been shown to alter cell proliferation rates and differentiation in human cancer cell lines, including bladder cancer cells [13–15], inconsistent findings remain among studies using cell line and animals [14, 16, 17]. Future studies are therefore warranted to examine the risk of bladder cancer among rosiglitazone users. However, the class effect observed in our study is biologically plausible as both thiazolidinediones share similar mechanisms of action (PPAR agonists) and share similar adverse effects (e.g. congestive heart failure) [18].

There are several major strengths of this study. First, the nationwide NHIRD database includes a large population of diabetic patients, which enabled us to identify a larger number of bladder cancer cases than the existing literature. There were also no significant differences in age and sex distribution between our diabetic cohort and another diabetic cohort identified from a random sample of 1,000,000 individuals in NHI databases in 2000 [6]. In addition, the cancer cases in our study were identified through linkage of the NHIRD and Catastrophic Illness Database in Taiwan. Patients with cancer are categorized as having a catastrophic disease in Taiwan's NHI system. A catastrophic illness certificate would be issued to these patients after formal reviews of their disease-related diagnoses by clinical physicians. The linkage between these two databases therefore minimizes misclassification of non-cancer cases as cases in our study [19].

Since we attempt to use observational data to answer a significant clinical question, we have cautiously adopted several methodological considerations [20] to provide unbiased estimation of treatment effects. First, we have adopted a "new cohort" design to include patients who had a first-ever diagnosis of type 2 diabetes to avoid confounding by indication (drug use indication bias and prevalent user bias). As shown in Table 1, the follow-up times (i.e. time of diagnosis of diabetes to index date or diabetes duration) were comparable between the case and control group. Second, we confirmed all of our cancer cases had a "primary" diagnosis (i.e. the main reason for hospitalization) of bladder cancer and validated them through the Catastrophic Illness Database of the NHIRD. Nevertheless, some potential limitations should be taken into account while interpreting the present study. First, although we adjusted for a wide range of potential covariates, we were unable to include variables not routinely captured in a claim database such as lifestyle factors (e.g. smoking and body mass index), laboratory data (such as glycosylated

haemoglobin) and occupational exposures. However, we used variables such as COPD to serve as a proxy for smoking and duration of follow-up for diabetes severity to reduce potential confounding effects. In addition, we ran a sensitivity analysis to include the number of hyperglycaemic agents and use of insulin 90 days prior to index date as indirect proxies for hyperglycaemia and the likelihood of use of thiazolidinediones in our models to further adjust potential effects of bias derived from the drug use indication and found similar results. However, there might have been some residual confounding from unmeasured variables such as disease severity. Second, because our data source was from a claim dataset, we could only identify whether a patient receive a prescription but could not know the adherence rates of taking those medicines.

Despite these limitations, our study of a nationwide diabetic population offers additional insight into the use of pioglitazone and the risk of bladder cancer. In addition, our findings extend the evidence from pioglitazone to rosiglitazone. The large sample size also allows us to reveal a clear dose-response relationship between pioglitazone or rosiglitazone use and the odds of bladder cancer.

5 Conclusion

Long-term exposure to thiazolidinediones (pioglitazone and rosiglitazone) were both found to be associated with higher odds of bladder cancer, and the highest odds were seen in thiazolidinedione users with $\geq$2 years of exposure.

Acknowledgments We thank the Bureau of National Health Insurance (BNHI) and National Health Research Institutes (NHRI) for making available the databases for this study. The content of this article, however, in no way represents any official position of the BNHI or NHRI. The authors bear all responsibility for the results and interpretation of the results. We thank Dr. C. Daniel Mullins of the University of Maryland and Dr. Susan Shur-Fen Gau of the National Taiwan University for providing consultation and assistance with the revised manuscript.

Author contributions Dr F.Y. Hsiao, Ms P.H. Hsieh and Dr C.S. Gau were responsible for development of the study concept and design and the preparation of the manuscript. Dr F.Y. Hsiao and Ms P.H. Hsieh contributed to data acquisition and statistical analysis. All authors participated in the analysis and interpretation of the data of the manuscript. This manuscript has been read and approved by all authors.

Financial support No sources of funding were used to conduct this study or prepare this manuscript.

Conflict of interest Pei-Hua Hsieh received a part-time research assistantship from a research project (DOH100-FDA-41100) sponsored by the Food and Drug Administration, Taiwan. Fei-Yuan Hsiao, Weng-Foung Huang, Yi-Wen Tsai and Churn-Shiouh Gau have no conflicts of interest to declare that are directly relevant to the content of this study.

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