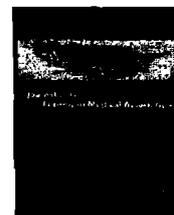




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REVIEW ARTICLE

Pioglitazone and bladder cancer in human studies: Is it diabetes itself, diabetes drugs, flawed analyses or different ethnicities?

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This article reviews human observations on pioglitazone and bladder cancer risk. The PROspective pioglitAzone Clinical Trial In macroVascular Events trial showed an imbalance in bladder cancer between users of pioglitazone and placebo (14 versus six cases, $p = 0.069$). However, after excluding bladder cancer probably ascribed to other etiology, a blind assessment concluded that the imbalance might not be related to pioglitazone. Epidemiologic studies conducted in the United States and France using insurance databases independently suggested that pioglitazone use for >2 years might confer a 20%–40% higher risk. Another study evaluating bladder cancer risk in diabetic patients using the National Health Insurance in Taiwan did not find any incident bladder cancer case among 422 pioglitazone users for a follow-up of up to 3 years. Because observational studies may suffer from selection and information bias, and inadequate adjustment for confounders may inflate the estimated risk, causal inference from these studies should be interpreted with caution. While investigating cancer risk associated with a medication, indication bias should also be attended, especially when the medication is used at a late stage of the disease. Because pioglitazone is usually a second or third line antidiabetic agent, the users are always characterized by older age, longer diabetes duration, poorer glycemic control, and higher rates of complications and comorbidities. Biased estimates will also result if these differences are not appropriately addressed in the analyses. Current evidence neither concludes nor excludes a causal role of pioglitazone on bladder cancer. Clinical trials aiming at evaluating the risk of cancer associated with a medication is not ethical and may not be expected to provide an answer on the issue of pioglitazone-related bladder cancer. However, a meta-analysis using all available clinical trials to compare the bladder cancer risk between pioglitazone and comparators will be helpful. Well-conducted epidemiologic

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observational studies are probably other options. Because bladder cancer incidence and their risk factors may differ significantly among different ethnicities, a clarification of such a link in different ethnicities is needed, better by using long-term databases with large and representative sample size and appropriate adjustment for confounders. Furthermore, the interactions with other comorbidities and concomitant medications should be addressed.

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Introduction

Peroxisome proliferator-activated receptor gamma (PPAR γ) is a nuclear hormone receptor that acts as a transcription factor. PPAR γ 1 is expressed in several tissues including the heart, skeletal muscle, kidney, pancreas, urothelium, and intestine; but, PPAR γ 2 (bearing additional 28 amino acids at the N-terminus of PPAR γ 1) is expressed exclusively in adipose tissue.¹ Activation of PPAR γ enhances insulin sensitivity and improves blood glucose metabolism. Therefore, its agonists have been developed for clinical use for the control of hyperglycemia in patients with type 2 diabetes, a disease characterized by insulin resistance. Clinically, a class of medications exerting PPAR γ agonistic effects is known as the thiazolidinedione (TZD).

The first TZD, ciglitazone, was developed in 1980s but was abandoned for marketing due to unexpected adverse events.² Three TZDs have ever been marketed and used clinically, namely troglitazone, rosiglitazone, and pioglitazone. Troglitazone was marketed in 1997 but was withdrawn from the world's market in 2000 due to its unexpected dreadful risk of liver failure.³ However, troglitazone has never been approved for clinical use in Taiwan before its worldwide withdrawal. Both rosiglitazone and pioglitazone were approved by the U.S. Food and Drug Administration (FDA) in 1999, but they were marketed in Taiwan in 2001 and 2002, respectively. Rosiglitazone was withdrawn from the market of Europe by the European Medicines Agency (EMA) in September 2010 for a possible link with myocardial infarction.⁴

Recently, the potential link between pioglitazone and bladder cancer risk has been enthusiastically discussed. The health regulatory authority of France suspended the use of pioglitazone on June 9, 2011, followed by its withdrawal on July 11, 2011. These actions have caused panic to the public, especially patients using pioglitazone and physicians who have prescribed the medication. The FDA and the EMA have requested an amendment to the package insert of pioglitazone for warning on the possible risk of bladder cancer and asked for early identification of bladder cancer cases. There are two main points as seen in the current FDA recommendations⁵: (1) "Do not use pioglitazone in patients with active bladder cancer"; and (2) "Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence."

It is deemed that a timely review of the current evidence on the possible link between pioglitazone and bladder cancer risk is urgently needed. Therefore, the present article reviews available studies conducted in humans on the related issues.

PROactive study

In the PROspective pioglitAZone Clinical Trial In macro-Vascular Events (PROactive) study, although the use of pioglitazone in patients with type 2 diabetes can significantly reduce non-fatal myocardial infarction, stroke, and all-cause mortality,⁶⁻⁸ a concern has arisen because more bladder cancer cases developed in the pioglitazone group than in the placebo group (14 vs. 6 cases, $p = 0.069$).^{6,9} However, 11 out of these 20 cases had bladder cancer diagnosed within 1 year of randomization into the study.⁶ After excluding these 11 cases, another case found to have benign histology in the placebo group and those with other known risk factors for bladder cancer (i.e., chronic smoking, chronic bladder irritation, potential carcinogen exposure, previous vesical tumor), there were only three cases of bladder cancer left, two in the pioglitazone group, and one in the placebo group.^{6,9} Therefore, the Data and Safety Monitoring Committee⁶ concluded that "it is improbable that the imbalance is related to pioglitazone treatment."

The PROactive study is probably the first clinical trial in humans that brought into concern the possible link between pioglitazone and bladder cancer, which had been demonstrated in preclinical animal studies in male rats, but not in female rats or in mice of both sexes.¹⁰ However, the PROactive study was aimed at evaluating cardiovascular outcomes as either primary or secondary end points, and cancer risk was only monitored as one of the safety profiles. Taking into account the low incidence of bladder cancer, the PROactive study did not provide substantial statistical power for a causal inference.

U.S. pharmacy claims study

A U.S. study using the pharmacy claims database in a retrospective cohort analysis did not find any association between TZDs use and risk of cancers of the colorectum, liver, bladder, pancreas, or melanoma.¹¹ The estimated relative risk for bladder cancer was 1.05 (0.71-1.54) after adjustment for age, sex, schistosomiasis, and pelvic radiation. However, this study has limitations of being unable to discern pioglitazone from other TZDs, a small number of bladder cancer cases ($n = 178$), failure to consider important risk factors for bladder cancer such as smoking, some occupational exposure, renal function, and urolithiasis, and not considering the cumulative dose and duration of exposure. Furthermore, the ascertainment and confirmation of the bladder cancer cases and the completeness of case identification by using administrative databases are not certain.

FDA adverse event reporting system analysis

A brief report using the FDA Adverse Event Reporting System (AERS) suggested a significantly higher risk in pioglitazone users with an odds ratio of 4.30 (2.82–6.52).¹² However, the results from AERS tend to be biased, depending on the alertness and reporting willingness of the physicians. If the reporting is not enforced by the law, under-reporting can be expected. On the other hand, if the association is overemphasized by the media or the medical societies, an over-reporting of bladder cancer cases associated with pioglitazone use will prevail.

Kaiser Permanente Northern California study

Under the request of the FDA in 2003, an ongoing 10-year prospective observational study using the Kaiser Permanente Northern California (KPNC) diabetes registry has been proposed and supported by a grant from Takeda Global Research & Development Center, Inc. to evaluate whether pioglitazone use could be associated with bladder cancer. The recent interim analysis did not find an overall increase of bladder cancer risk associated with pioglitazone use, but a significantly increased risk of 40% for prolonged use of >2 years was noted.¹³ The study did not find any interaction between sexes.

Because the study recruited patients from insurance restricted to a localized region in the United States, the representativeness of this sample for the entire U.S. population is surely in doubt. Neither selection bias nor information bias could be excluded due to the inherent limitations of an observational study. Furthermore, the frequencies of missing data on potential confounders at baseline are actually very high, making biased estimates to be possible.

Although the KPNC study recruited approximately 10% of the patients of Asian ethnicities,¹³ the results may not be readily generalized to the Asian populations, who show a lower risk of bladder cancer in general and may probably have different risk factors.

French CNAMTS study

The French CNAMTS (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés) study, which covered approximately 86% of the French population, analyzed a retrospective cohort of the French health insurance databases for a 4-year period from 2006 to 2009. They concluded that a 1.22-fold higher risk of bladder cancer was noted among 155,535 pioglitazone users (of whom 175 bladder cancer cases were found) out of 1,491,060 diabetic patients when compared with nonusers.¹⁴ Like the KPNC study, the French study also suggested a possible higher risk associated with prolonged use of >2 years or a cumulative dose of >28,000 mg, with respective hazard ratios of 1.36 (1.04–1.79) and 1.75 (1.22–2.50).¹⁴ However, unlike the KPNC study, the French study showed a significant link only in men, but not in women, when the analyses were conducted in separate sexes.¹⁴

Based on the report, the French health regulatory authority (Agence française de sécurité sanitaire des

produits de santé) unilaterally suspended the use of pioglitazone on June 9, 2011,¹⁵ prior to the decision of a then ongoing review on the risk/benefit of pioglitazone by the Committee for Medicinal Products for Human Use (CHMP) of the EMEA starting in March 2011. France also withdrew the use of pioglitazone unilaterally on July 11, 2011, before the final decision made by the CHMP.

Following the French suspension, Germany suspended the use of pioglitazone in new patients on June 10, 2011.¹⁶ Tunisia and Mauritius followed the footsteps of France by suspending and withdrawing the use of pioglitazone.¹⁶

The CHMP summoned a meeting to discuss the bladder cancer risk associated with pioglitazone on June 20–23, 2011, but no conclusion or recommendation was made after this meeting.¹⁷ The decision of the CHMP was postponed until July 21, 2011, with a recommendation that "benefit-risk balance remains positive in a limited population of type 2 diabetics" and pioglitazone is contraindicated in patients with current bladder cancer or a history of bladder cancer.¹⁸

Taiwanese observations

By using the reimbursement databases of the National Health Insurance (NHI), we recently demonstrated that diabetic patients in Taiwan have a higher risk of bladder cancer incidence than people without diabetes.¹⁹ In addition, we showed that male sex, nephropathy, and urinary tract diseases including infections and stones were significant risk factors for bladder cancer.¹⁹ After adjustment, use of TZDs (including rosiglitazone and pioglitazone) were actually associated with a lower, though insignificant, risk of bladder cancer; and among 422 patients using pioglitazone, none had developed bladder cancer during the short observation period of 3 years.¹⁹ Because the main purpose of that study was to investigate the link between diabetes and bladder cancer risk, we did not consider the cumulative dose or duration of exposure for TZDs.¹⁹

It is interesting that we observed a decreasing risk of bladder cancer with longer duration of diabetes, which is in contrary to an increasing risk observed by Mackenzie and colleagues.²⁰ It should be noted that the design of the study by Mackenzie and colleagues was case-control, and they adjusted only for age, sex, smoking, body mass index and urinary tract infection in multivariable models.²⁰ Some of the comorbidities that might be associated with both diabetes duration and bladder cancer (thus can be a confounder), such as renal disease, as shown in our study,¹⁹ were not considered for adjustment by Mackenzie and colleagues.²⁰ It is easy to explain the decreasing risk of bladder cancer with longer duration of diabetes observed in the Taiwanese study¹⁹: with prolonged diabetes duration, the impact of age and chronic complications (especially nephropathy and urinary tract diseases) may set in and attenuate the association.

According to the National Reporting System of Adverse Drug Reactions in Taiwan (supported by the Department of Health of Taiwan), no case of bladder cancer associated with pioglitazone use has ever been reported.²¹ However, under-reporting is possible before the issue of such a link has been brought into public attention by the media following the French suspension of pioglitazone in June 2011.¹⁵

The Taiwan FDA summoned a meeting to discuss on the issue of pioglitazone and bladder cancer risk on June 22, 2011. The current recommendation of the Taiwan FDA followed those of the USFDA and a labeling of warnings in the Chinese package insert has also been requested.²²

Discussion

Results from currently available studies on the link between pioglitazone and bladder cancer are not consistent. Whether the positive link in patients using pioglitazone in some studies could be due to the drug *per se*, or due to the underlying disease of diabetes, the interactions with other concomitant drugs, the inherent flaws associated with study designs and statistical analyses, or the different ethnicities between studies, are worthy of discussion.

Diabetes

Diabetes *per se* may increase the risk of cancer, probably via the activation of the Ras/Raf/mitogen-activated protein kinase pathway in association with a reduction of the expression of epidermal growth factor receptor.²³ In fact, epidemiologic studies also suggest an increased risk of bladder cancer in diabetic patients,^{19,24,25} independent of the commonly used oral antidiabetic agents or insulin.¹⁹ Therefore, if without appropriate adjustment and consideration of the severity and duration of diabetes, an association between bladder cancer and any of the anti-diabetic agents may only reflect an effect of the disease *per se* or an indication bias associated with the use of the medication due to the severity of the disease.

Medications

TZDs are usually used as a second or a third line drug for the treatment of diabetes. Its use always indicates a more severe disease stage of diabetes, which may be associated with older age, longer diabetes duration, poorer glycemic control, higher prevalence of comorbidities, and the use of multiple drugs. All of these can have an impact on the development of bladder cancer. Therefore, if without appropriate adjustment, indication bias associated with pioglitazone use in patients with a late stage of diabetes may result in biased estimates, which may reverse a lack of association or even a protective effect to a higher risk related to the use of the drug.

Because metformin may prevent some cancer and sulfonylureas/insulin may be associated with a higher risk of cancer,^{26,27} the interaction between pioglitazone and other therapeutic agents used in the diabetic patients is important and requires further clarification. For example, in the KPNC study, pioglitazone users had significantly higher rates of using sulfonylureas (87.2% vs. 58.6%) and insulin (43.5% vs. 25.4%). These agents should have been used for a long duration before pioglitazone was added. Therefore, pioglitazone could also be a scapegoat or an accomplice while the real culprit was not interrogated intensively at the same time. If sulfonylureas/insulin did increase the risk of bladder cancer, they must have already

posed a greater risk to the using patients and this should be investigated simultaneously.

It is worthy to note that the daily dose of pioglitazone used in the PROactive study was 45 mg,⁶ which was higher than a daily dose of 30 mg commonly used in Taiwan. Therefore, it is an interesting issue to explore whether the higher dose used in Caucasians could possibly explain the higher risk of bladder cancer among pioglitazone users.¹³

Study designs and analyses

In clinical trials, confounders can always be controlled and bias can be avoided by using a randomized, double-blind, and placebo-control design. The temporal sequence of cause and effect is easily discerned and is always correct. However, it is unethical and impractical to conduct a clinical trial for evaluating cancer risk associated with the use of a medication. Observational epidemiologic studies remain the mainstay in answering this kind of questions, but causal inference from observational studies is always a great challenge.

The PROactive study is the only clinical trial that has provided an inconclusive hint for a possible link between pioglitazone and bladder cancer. However, the small case number of bladder cancer monitored as a safety profile did not provide sufficient statistical power for causal inference. The results from the US KPNC¹³ and the French CNAMTS¹⁴ studies similarly show a possible small increase in bladder cancer risk associated with pioglitazone use. However, both may suffer from bias and confounding associated with the inherent limitations of observational studies, and may not confirm a causal relationship based on all stringent epidemiologic criteria, including strength, consistency, specificity, temporality, biologic gradient, plausibility, and coherence.²⁸

Cigarette smoking and occupational or environmental exposure to carcinogenic chemicals, such as aniline dyes, cyclophosphamide, aromatic amines, and arsenic, are well-recognized risk factors for bladder cancer.^{20,29,30} However, these were not satisfactorily adjusted for either in the KPNC study, the French CNAMTS study, or the other observational studies. With regard to smoking, only information on current smokers was reported in the KPNC study; therefore, cigarette smoking was only partially adjusted. It is not known how accurately this information was collected and whether information bias could exist. The CNAMTS or other observational studies did not adjust for smoking.

The study by Tseng¹⁹ in Taiwan was not primarily aimed at evaluating the association between the use of antidiabetic drugs and bladder cancer. Therefore, the case number of pioglitazone users was too small to provide sufficient statistical power. However, the Taiwanese study confirmed that nephropathy and urinary tract diseases, including stones and infection, are important risk factors for bladder cancer.¹⁹ Diabetic patients may also have a higher prevalence of these risk factors and they may also use more medications than nondiabetic individuals because of a higher prevalence of other comorbidities. If these potential confounders are not adequately adjusted, biased estimation of the associated risk even in an opposite direction would result. For example, if we only

considered an adjustment for age, sex, and hypertension by using the NHI database, a higher but insignificant risk of bladder cancer could be seen in patients using TZDs (January 2011).

A recently published *Letter to the Editor*³¹ argued against the use of time-dependent pioglitazone usage in Cox models for the possibility of wrong conclusion on its association with cancer risk. Analyses using time-varying incidence of cancer may also lead to detection bias.³² Both the KPNC study¹³ and the CNAMTS study¹⁴ used time-dependent pioglitazone exposure for analyses. It is not known whether this would have led to biased or incorrect estimates in the studies.

Overfitting of regression models may also lead to a bias against the null.^{33,34} Whether including too many variables in the full models in the KPNC study may also lead to such a bias is not known (although it was claimed to be unlikely).¹³ Multiple comparisons in the KPNC study might also have led to an incorrect rejection of the null hypothesis among a set of statistical inferences just by chance. Therefore, a stronger level of significance or a smaller *p* value should be observed to make an inference of significant association between pioglitazone use and bladder cancer in the KPNC study.¹³

The KPNC study suffered from severe incomparability in baseline characteristics between the pioglitazone ever-users and never-users and the rates of missing data are very high in most of the baseline characteristics, which could have resulted from the use of self-reported personal history and the incompleteness of the insurance databases. Although the investigators tried their best to correct for these potential biases, it should be noted that biases may not always be corrected after data collection. It is also interesting to note that the rate of congestive heart failure in the pioglitazone users was significantly lower than nonusers in the KPNC study (3.2% vs. 6.8%, *p* < 0.001). This is somewhat against our common sense that pioglitazone is associated with such a risk.^{6,35} Although pioglitazone users might be younger and therefore less prone to congestive heart failure in the KPNC study, a careful look into the possibility of selection and information bias is required.

According to French regulation, a personal medical database can only be stored for a maximum of 4 years; therefore, the investigators could only analyze the databases within a short period of time from 2006 to 2009. Furthermore, the findings derived from a retrospective study, the lack of an appropriate adjustment for potential confounders (such as smoking, renal function, or urinary tract disease), and the potential selection and information bias associated with the CNAMTS study should better be confirmed with more evidence.

It should also be noted that the evidence for cardiovascular risk associated with rosiglitazone leading to its withdrawal in Europe was mainly derived from clinical trials.⁴ However, the current evidence for the link between pioglitazone and bladder cancer was mainly derived from observational studies. The level of evidence from observational studies is always lower than that from clinical trials. Therefore, a meta-analysis using all available clinical trials to compare the bladder cancer risk between pioglitazone and its comparators is urgently needed.

Different ethnicities and sexes

According to the Taiwan Cancer Registry, the age-standardized (to the World Health Organization 2000 standard population) bladder cancer incidence in the year 2007 was 10.5 and 4.2 per 100,000 people for Taiwanese men and women, respectively.^{36,37} In the United States, the incidence rates among different ethnicities differ markedly, with Caucasians having the highest incidence, followed by blacks, and the other ethnicities.³⁸ In 2007, Caucasian men and women showed an age-adjusted incidence of approximately 27 and 6.5 per 100,000 people, respectively.³⁸ Whether the different incidences between our Taiwanese population¹⁹ and Caucasians^{13,14} could be explained by the different genetic backgrounds remains to be answered. It is possible that differences in dietary components and socioeconomic and cultural backgrounds between different ethnicities could play some role on the different link.

Universally, men have a higher risk of bladder cancer than women in various ethnicities.^{19,38} Therefore, factors related to sex, either genetically or environmentally linked, can play some role on the development of bladder cancer. The French CNAMTS study showed that the link between pioglitazone and bladder cancer was only observed in men but not in women, but the U.S. KPNC study suggested a lack of interaction between sexes. Therefore, these contradictory findings with regard to sex^{13,14} require further exploration.

Risk of bladder cancer versus benefits in cardiovascular disease

Pioglitazone reduces the risk of all-cause mortality, nonfatal myocardial infarction, or stroke as secondary endpoints by 16% (*p* = 0.027),⁶ prevents recurrent fatal/nonfatal myocardial infarction by 28% (*p* = 0.0453),³⁵ and reduced fatal or nonfatal stroke by 47% (*p* = 0.0085)⁷ in the PROactive study. Pioglitazone is also effective to postpone the permanent use of insulin,⁶ to improve lipid profile, and to further reduce blood glucose level when metformin and/or sulfonylurea fail.³⁹

Weighing the beneficial effects of pioglitazone on cardiovascular disease and glycemic control against the yet unconfirmed possible risk of bladder cancer, it may not be the best option to withdraw pioglitazone before the small bladder cancer risk is confirmed. To abruptly discontinue its use under panic in the diabetic patients is not recommended, because this can probably lead to an uncontrollable blood glucose level and unpredictable risk of cardiovascular events. The repository for changing to other oral antidiabetic agents in patients who have been put on pioglitazone as a third line treatment is actually limited. Insulin may be needed to control hyperglycemia after the withdrawal from pioglitazone. However, it should also be stressed that neither insulin nor sulfonylurea has been proved to be safe without risk of cancer development.^{26,40,41}

More evidence on mechanisms needed

It would also be interesting to know whether another medication of the same class, i.e., rosiglitazone, would

Table 1. Main findings from human observations of pioglitazone or TZD use and bladder cancer risk

Year [Reference]	Name of source of study	Study design	Numbers of cases/follow-up duration	Relative risk estimates (95% CI)	Other remarks
2005 [6]	PROspective pioglitazone Clinical Trial in macroVascular Events study	Report of serious adverse events in a clinical trial	Case numbers for pioglitazone users and placebo users were 2,605 and 2,633, respectively. Average follow-up: 34.5 mos.	Bladder cancer cases (percentage) in pioglitazone group versus placebo group: 14 (0.5%) versus 6 (0.2%) ($p > 0.05$).	After excluding bladder cancer cases probably attributed to other etiology, the Data and Safety Monitoring Committee concluded that bladder cancer might not be related to pioglitazone.
2008 [11]	U.S. pharmacy claims study	Retrospective cohort study using U.S. population-based pharmacy claims databases	178 bladder cancer cases among 191,223 diabetic patients; median follow-up: 3.9 yrs.	TZD: 1.05 (0.71–1.54)	The adjusted relative risk was estimated for TZD use (not specifically for pioglitazone) after excluding patients exposed to insulin alone.
2011 [12]	USFDA Adverse Event Reporting System analysis	A spontaneous adverse event reporting system for medications from January 2004 to December 2009	Among 86,987 reports of adverse events, there were 37,841 reports concerning pioglitazone. Among 93 reports of bladder cancer, 31 concerning pioglitazone.	4.30 (2.82–6.52)	Significantly higher risk of bladder cancer in pioglitazone users. However, reporting bias should be considered.
2014 [13]	Kaiser Permanente Northern California study (interim report)	Prospective cohort study using Kaiser Permanente Northern California diabetes registry	Among 193,099 diabetic patients, 30,173 were ever treated with pioglitazone. Bladder cancer cases among ever users and nonusers were 90 and 294, respectively, with estimated incidence of 81.5 and 68.8 per 100,000 person-yrs, respectively. Median follow-up from cohort entry: 9.2 (range: 0.1–11.3) and 6.2 (0.1–11.3) yrs, respectively.	1.2 (0.9–1.5)	No overall significantly increased risk observed, but a significant 40% higher risk can be seen for use of pioglitazone >2 yrs.
2011 [14]	French CNAMTS study	Retrospective cohort study using the French health insurance databases within a 4-year period from 2006 to 2009	Among 1,491,060 patients with diabetes, 455,535 were pioglitazone users and 1,335,525 were non-users. The bladder cancer cases were 175 and 1,841, respectively.	1.22 (1.05–1.43)	Dose-response relationship was observed but sex-specific analyses showed significant risk in men only, with relative risk of 1.28 (1.09–1.51).

2011 [19]	Taiwanese study	Retrospective cohort study using National Health Insurance reimbursement databases	Among 388,235 individuals without diabetes and 115,731 with diabetes, 362 and 227 incident bladder cancer cases during a 3-year follow-up were observed, respectively.	TZD: 0.80 (0.34-1.96)	The relative risk was estimated for TZD users (including rosiglitazone and pioglitazone) versus non-users because no bladder cancer incident case was observed among 422 patients using pioglitazone.
2011 [21]	National Reporting System of Adverse Drug Reactions in Taiwan	A spontaneous adverse event reporting system for medications supported by the Department of Health, Taiwan.	No case of bladder cancer related to pioglitazone use has ever been reported. However, under-reporting is possible.		

CI = confidence interval; TZD = thiazolidinedione.

have any effect on bladder cancer. According to our recently published papers,^{19,42} a lower but insignificant risk of bladder cancer¹⁹ and prostate cancer⁴² was observed for either rosiglitazone or pioglitazone. A meta-analysis, including 80 clinical trials using rosiglitazone with a duration >24 weeks, suggested that rosiglitazone use was associated with a significantly lower risk of cancer incidence than the control group (0.23 versus 0.44 per 100 person-years, $p < 0.05$).⁴³ However, this study did not specifically analyze bladder cancer.

Actually, TZDs with PPAR γ agonistic activity may show anticancer effects in *in vitro* studies,⁴⁴ and there is no evidence supporting an increased cancer risk related to PPAR γ agonism. If pioglitazone does increase the risk of bladder cancer, a mechanism other than PPAR γ activation might be responsible, as shown in animals.⁴⁵ In rats, the prevention of pioglitazone-induced bladder tumor by acidifying the urine is not due to an effect on PPAR γ agonism or mitogenic potential, but probably related to drug-induced compositional changes in the urine.⁴⁵

The urinary bladder of diabetic patients with poor glycemic control would be exposed to high levels of glucose excreted from the urine. One of the mechanisms related to a possible increased risk of bladder cancer in the diabetic patients is the glucose-induced carcinogenicity. If this is the case, long-term glycemic control *per se* will be a significant risk factor for bladder cancer and should be considered for adjustment in future studies. Taking into account the recent warning of increased bladder cancer risk associated with the use of sodium-dependent glucose cotransporter 2 inhibitors (a class of oral antidiabetic drugs under development with a novel mechanism of inhibiting glucose reabsorption from the kidney),⁴⁶ a glucose-induced mechanism on bladder cancer cannot be excluded.

Summary

The main findings from human observations on the issue of pioglitazone use and bladder cancer risk as discussed in this article are summarized in Table 1. In humans, bladder cancer incidence differs among different ethnicities, and men consistently show a higher risk than their female counterparts within the same ethnicities. Caucasians have significantly higher incidence of bladder cancer than other ethnicities, including blacks and Asians. Clinical trials aimed at evaluating the link between pioglitazone use and bladder cancer risk are lacking but will not be practical or feasible for future study. However, a meta-analysis using all available clinical trials to compare the bladder cancer risk between pioglitazone and its comparators will be helpful. Observational epidemiologic studies remain the main source for providing evidence, but currently available analyses neither confirm nor exclude such a possible link. Because both diabetes *per se* and comorbidities highly prevalent in diabetic patients can be significant risk factors for bladder cancer, causal inferences from observational studies without considering the representativeness of study subjects or adequate adjustment for confounders may result in biased estimates, which may even be in the opposite direction. Furthermore, findings from studies conducted in Caucasians who have a higher risk of

developing bladder cancer and may probably have different risk factors should not be immediately generalized to other ethnicities without sufficient evidence. Because the link between therapeutic agents and cancer risk is always of high concern to the public, a clarification of the link between pioglitazone use and bladder cancer risk in different ethnicities is urgently needed.

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