Review

Association between pioglitazone use and bladder cancer: A systematic review

Sujatha Baddam[1], Amulya Varshini Banka[2], Shravani Divity[3], Maharshikumar Sandesara[4], Yethindra Vityala[5]*

[1]Department of General Medicine, Huntsville Hospital, Huntsville, Alabama, 35801 United States
[2]Department of General Medicine, Dalian Medical University, Dalian, Liaoning, 116044 China
[3]Department of General Medicine, Government Medical College Mahabubnagar, Mahabubnagar, Telangana, 509001 India
[4]Department of General Medicine, C.U. Shah Medical College and Hospital, Surendranagar, 363001 India
[5]Department of Pathology, International Higher School of Medicine, Bishkek, 720054 Kyrgyzstan

Abstract

Background: Bladder cancer (BC) remains a significant global health concern, and its incidence is influenced by a wide array of factors, including geography, sex, and socioeconomic status. **Objective:** This systematic review evaluated the potential association between pioglitazone use and the risk of BC. We sought to determine whether pioglitazone, used in diabetes management, is associated with an increased risk of BC by reviewing recent studies. **Methods:** A comprehensive search was conducted in the PubMed, Scopus, and Web of Science databases for relevant studies published between January 31, 2018 and July 31, 2024. From an initial pool of 212 articles, 176 were excluded due to failure to meet the inclusion criteria, 24 were removed for inadequate data or unclear conclusions, and six were eliminated due to inaccessibility. Ultimately, six eligible studies were included in the final review. **Results:** Of the included studies, two suggested a potential association between pioglitazone use and an increased risk of BC, whereas four reported no statistically significant correlation. **Conclusion:** These mixed findings highlight the need for further research that accounts for confounding factors, such as treatment duration and patient demographics. This systematic review emphasizes the importance of cautious interpretation regarding the safety profile of pioglitazone in relation to BC risk.

Keywords: Bladder cancer, Drug safety, Pioglitazone, Systematic review, Type 2 diabetes

1. INTRODUCTION

Bladder cancer (BC) represents a significant global health concern, ranking as the 10th most common cancer worldwide. Its incidence and mortality rates are markedly higher in men than in women [1]. Geographical variations in BC prevalence are conspicuous, with the highest incidence being observed among men in Southern and Western Europe, North America, and parts of Northern Africa and Western Asia [2]. In Egypt, a notable shift has occurred in the predominant histological type of BC, transitioning from squamous cell carcinoma to transitional cell carcinoma, particularly in the Kotour District [3]. Although women are less likely to develop BC, they tend to experience poorer prognoses and higher mortality rates than men, even after adjusting for stage and tumor characteristics [4].

Socioeconomic factors also influence BC incidence and higher rates were found in individuals with low socioeconomic status in Canada, with growing income- and education-related disparities [5]. In China, the incidence of BC increased from 1998 to 2007, followed by a decline through 2015, along with a decrease in mortality rate [6]. In the Netherlands, shifts in classification and reporting systems have significantly impacted the trends in BC incidence [7].

The epidemiology of BC is subject to geography, sex, socioeconomic status, and variations in medical classification and reporting systems. While smoking is commonly associated with lung cancer, it is also a significant and preventable risk

***Corresponding author:**
Yethindra Vityala (yethindravityala10@gmail.com)

Received: 18 September 2024; Revision received: 05 November 2024; Accepted: 13 November 2024; Published: 17 December 2024

How to cite this article: Baddam S, Banka AV, Divity S, Sandesara M, Vityala Y. Association between pioglitazone use and bladder cancer: A systematic review. *Bladder*. 2024;11(4):e21200023. DOI: 10.14440/bladder.2024.0039

factor for BC. Other potential contributors include genetic predisposition, occupational exposure to carcinogens, and the use of chronic medications [8]. Renal transplant recipients have a higher incidence of BC [9], and the condition is also prevalent in patients with upper urinary tract tumors [10].

Age is a key factor involved in BC development. BC is typically diagnosed between the ages of 57 and 64 years [11], with a significant prevalence among individuals aged >40 years [12]. The risk of BC increases with age, with most lesions being superficial [12]. Notably, there is a significant sex disparity in BC incidence, with men being more frequently afflicted than women. Male-to-female ratios in BC reportedly ranged from 4:1 to 6.2:1 [11].

The association between pioglitazone use and BC has been extensively studied. In 2016, the United States Food and Drug Administration further evaluated pioglitazone and reported a potential association with an increased risk of BC [13]. However, studies investigating this link have yielded mixed results. Colmers *et al.* [14] reported a 40% higher BC risk among pioglitazone users, whereas Piccinni *et al.* [15] emphasized the importance of addressing confounding factors, such as smoking, that could influence the results. Lewis *et al.* [16] found no significant increase in BC risk with short-term pioglitazone use but noted a higher risk with use exceeding 2 years. Filipova *et al.* [17] found no significant difference in BC incidence between pioglitazone users and non-users, suggesting that long-term use may not directly correlate with BC risk, with smoking potentially being a more significant factor.

In this systematic review, we evaluated the association between pioglitazone use and BC and synthesized evidence to clarify the safety profile of pioglitazone. By reviewing recent studies on the effects of pioglitazone, we aimed to determine whether its use in diabetes management is associated with an increased risk of BC.

2. MATERIALS AND METHODS

This review comprehensively assessed the existing literature to evaluate the association between pioglitazone use and BC occurrence. This analysis was conducted in accordance with the guidelines for systematic reviews and meta-analyses outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [18].

The methodology involved a systematic search of the PubMed, Scopus, and Web of Science electronic databases for studies published in English from January 31, 2018, to July 31, 2024. A comprehensive search strategy included the combination use of the Medical Subject Headings terms "pioglitazone," "urinary bladder," "risk factors," "diabetes mellitus," association," and "prevalence." Boolean operators "AND," "OR," and "NOT" were employed to connect these terms, arranged as follows: "(((pioglitazone) AND (urinary bladder) AND (cancer)) AND (relationship))."

The inclusion criteria for the studies were: (i) English language publications; (ii) studies evaluating the association between pioglitazone use and BC occurrence; (iii) clinical trials involving human participants; (iv) original research, and (v) studies published within the past 6 years. The exclusion criteria included: (i) insufficient data; (ii) irrelevant results; (iii) theses and other repository documents; (iv) systematic reviews, case reports, meta-analyses, and qualitative studies; (v) duplicate studies; and (vi) inaccessible full texts, despite efforts to obtain them.

Titles and abstracts from the search results were initially screened for eligibility based on the inclusion and exclusion criteria. Full text was then reviewed to confirm that they had the necessary components for inclusion in this study.

All authors participated in the data extraction across the databases to ensure consistency and minimize potential bias. The extracted information encompassed the study design, population characteristics, evaluated parameters, and key findings. Reference management involved importing citations into RefWorks 2.0 (RefWorks-COS, United States) for duplicate removal, followed by transfer to DistillerS (Evidence Partners Incorporated, Canada) for screening titles and abstracts, as well as full-text analysis. RefWorks served as the citation management tool, whereas DistillerS facilitated the systematic review process, enabling efficient data extraction and comprehensive screening.

To ensure consistency and minimize bias, three independent reviewers (SP, KC, and MN) conducted the screening process. They reviewed all titles, abstracts, and full texts, resolving discrepancies through discussion and consensus. The review protocol was registered in the Prospective Register of Systematic Reviews (registration number: CRD42024600742).

3. RESULTS

The initial literature search yielded 212 results, which were filtered according to specific inclusion and exclusion criteria. Of these, 176 articles were excluded due to lack of open access. Despite efforts to locate alternative resources, limited availability hindered these attempts, potentially introducing bias. This event underscores the need for greater accessibility to ensure a comprehensive literature review. The remaining 36 articles were further analyzed after 24 were removed for inadequate data or unclear conclusions. Of the 12 remaining articles, full-text access could not be obtained for six, despite multiple retrieval attempts, leaving six studies eligible for the systematic review [19-24]. The selection process is illustrated

in Figure 1, and Table 1 provides details of the six studies included in the review.

This systematic review aimed to explore the potential association between pioglitazone use and BC risk. The six selected studies presented a complex array of findings, revealing both consensus and discrepancies, which emphasizes the necessity of a cautious and nuanced interpretation of the evidence.

Riaz *et al.* [19] examined individuals aged ≥40 years with a 2-year history of type 2 diabetes mellitus (T2DM). Group A consisted of patients who had been using pioglitazone for at least 2 years, whereas Group B comprised patients using either oral hypoglycemic agents or insulin. In groups, the majority of participants were male, with a mean age of 47.01 ± 8.27 years in Group A and 58.97 ± 8.14 years in Group B. The average duration of T2DM was 8.65 ± 3.72 years in Group A, against 10.86 ± 4.48 years in Group B. The mean duration of pioglitazone use was 6.92 ± 2.28 years. Notably, none of the participants were diagnosed with BC during the study period.

Garry *et al.* studied 247,356 medicare patients aged >65 years who began treatment with pioglitazone (n = 38,700), dipeptidyl peptidase 4 inhibitors (DPP-4s) (n = 82,552), or sulfonylureas (n = 126,104) between 2007 and 2014 [20]. Over a mean follow-up of 1.2 years, 727 patients developed BC. Pioglitazone users had higher incidence rates of BC per 100,000 person-years (n = 308) compared to DPP-4s (n = 204) or sulfonylurea (n = 231) users. The adjusted hazard ratio (aHR) for pioglitazone use versus DPP-4s was 1.57 (95% confidence interval [CI]: 1.23–2.00), and the aHR for pioglitazone use versus sulfonylureas was 1.32 (95% CI: 1.02–1.70), with an elevated risk observed within the first 2 years of therapy. However, the risk of developing BC decreased in patients who discontinued pioglitazone within 2 years (aHR 0.89, 95% CI: 0.61–1.28) compared to those who were on treatment for over 2 years (aHR 1.45, 95% CI: 0.93–2.26), relative to DPP-4 users.

Bhushan *et al.* [21] reported a global association between pioglitazone and adverse drug reactions, with BC being the most common (43%). Metformin was frequently co-administered, appearing in 25% of all individual case safety reports involving pioglitazone, and in 40% of BC-specific case safety reports. Suspected pioglitazone-related BC was reported across 27 countries, with 8,548 severe cases, 1,858 fatalities, and an information component value of 9.15. The Americas had the highest proportion of suspected BC cases in pioglitazone safety reports (53%), whereas the prevalence in India was considerably lower (2%).

Agrawal *et al.* [22] investigated the association between pioglitazone use and BC risk in 4170 patients with T2DM, of whom 50% were taking pioglitazone. The patients underwent symptom questionnaires, urinalysis, cystoscopy, and bladder biopsies when necessary. The study found no increased risk of BC in pioglitazone users, nor any correlation between cumulative dose or duration and cancer development, indicating that pioglitazone is an effective and safe treatment for managing blood sugar levels in T2DM patients.

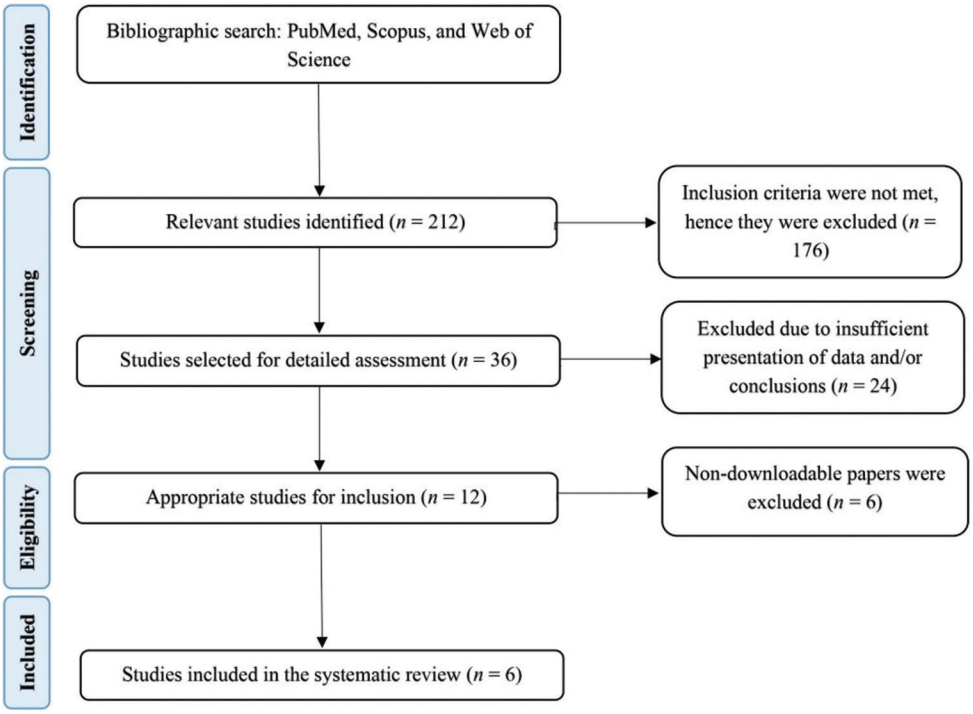

Figure 1. Flow diagram of literature search and study selection for systematic review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart).

Table 1. Characteristics of the studies selected to investigate the association between pioglitazone use and bladder cancer

Researchers	Study type and population	Parameters evaluated	Main results	Conclusion
Riaz *et al*. [19]	A comparative study of 1,168 patients with T2DM aged >40 years (584 patients in each of Groups A and B). In Group A, the average duration of T2DM was 8.65±3.72 years, while in Group B, it was 10.86±4.48 years. In Group A, 11.99% (*n*=70) were smokers, whereas in Group B, 21.75% (*n*=127) were smokers.	Use of pioglitazone.	None of the patients in either group were diagnosed with BC (0%).	No significant association between pioglitazone use and BC was found.
Garry *et al*. [20]	A comparative study of 38,700 patients with T2DM aged >65 years who began pioglitazone treatment, of whom 3334 (8.6%) were smokers.	Pioglitazone use and administration time	Overall RR for BC was 1.32 (95% CI: 1.02–1.70); RR for 24 months of treatment was 1.32 (95% CI: 0.98–1.78); RR for >24 months of treatment was 1.29 (95% CI: 0.76–2.18).	Pioglitazone use was significantly associated with BC risk; however, no significant dose-dependent relationship was identified.
Bhushan *et al*. [21]	A retrospective study investigating 16.9 million individual case safety reports for various medications, including 19,904 reports specifically related to pioglitazone use.	Distribution by sex, regional location, and age group	This study identified a higher prevalence of BC in men (37%) than in women (30%). The United States registered the highest number of cases (*n*=8158, 95%), whereas India recorded the fewest case numbers (*n*=3, 0.03%). Patients aged 45–64 years were most affected, while those aged 18–44 years were least affected.	Pioglitazone use was associated with a higher risk of BC, particularly among men, individuals residing in the United States, and those aged 45 years or older.
Agrawal *et al*. [22]	This retrospective study examined 4170 patients with T2DM, including 2085 pioglitazone users and 2,085 non-users.	Users and non-users of pioglitazone	Of the 2085 individuals treated with pioglitazone, cancer was detected in five patients (four women and one man). In contrast, no cancer cases were observed in the non-user group.	Pioglitazone exposure did not increase the risk of BC.
Li *et al*. [23]	This retrospective study examined 97,024 patients with T2DM.	Use of pioglitazone.	RR 0.70 (95% CI: 0.54–0.92)	Pioglitazone use was not found to be a significant risk factor for BC.
Malhotra *et al*. [24]	This case–control study examined 6440 patients with T2DM, dividing them into two groups: 1056 patients using pioglitazone (Group A) and 5384 patients not using pioglitazone (Group B). The mean duration of T2DM was 12.7 years in Group A and 10.6 years in Group B.	Users and non-users of pioglitazone	Users: RR 1.29 (95% CI: 0.83–2.00); non-users: RR 0.94 (95% CI: 0.834–1.061) (*p*=0.207)	No significant association between pioglitazone use and BC incidence was observed.

BC: Bladder cancer, CI: Confidence interval, RR: Relative risk, T2DM: Type 2 diabetes mellitus.

Li *et al.* [23] studied 97,024 patients with T2DM to assess the incidence of newly diagnosed BC in patients using a combination of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and pioglitazone. The patients were grouped according to their medication regimens: both drugs (Group 1), SGLT-2 inhibitors only (Group 2), pioglitazone only (Group 3), and non-study drugs (Group 4). Over a mean follow-up of 2.8 years, no new cases of BC were observed in Group 1, and overall mortality was significantly reduced (aHR: 0.70, 95% CI: 0.54–0.92) compared with the control group. Groups 2 and 3 showed no increase in BC risk and exhibited a decrease in all-cause mortality compared to the control group.

Malhotra *et al.* [24] analyzed 6440 patients with T2DM, categorizing them into pioglitazone users (Group A, $n = 1056$; 16.3%) and non-users (Group B, $n = 5384$; 83.6%). BC incidence did not significantly differ between the groups (odds ratio [OR] 1.29, 95% CI: 0.83–2.00 for users; OR 0.94, 95% CI 0.834–1.061 for non-users; $p = 0.207$). However, BC was significantly associated with hematuria in pioglitazone users, older age, and smoking history in the entire cohort. Among all participants, 3.5% of men and 4.6% of women developed cancer. Multivariate forward regression analysis revealed a significant correlation between age and the presence of BC (OR 1.036, 95% CI: 1.022–1.051; $p = 0.00$).

4. DISCUSSION

The 2022 World Health Organization classification categorizes BC into conventional urothelial carcinoma, urothelial carcinoma subtypes, and non-urothelial tumors with divergent differentiation [25]. Investigating the associations between pioglitazone and these subtypes is essential, as the varying histopathological features of BC often correlate with poorer outcomes and require tailored treatment strategies [25,26]. Recognizing specific subtypes can help elucidate the carcinogenic mechanisms of pioglitazone and support more accurate risk evaluation and treatment decisions.

Identifying variant histopathology, such as micropapillary or plasmacytoid carcinoma, is crucial, as these are typically associated with aggressive disease and reduced survival, particularly in muscle-invasive BC [27,28]. These findings highlight the importance of thorough pathological evaluation in patients using pioglitazone. A better understanding of variant histopathology may improve risk classification and facilitate more effective multidisciplinary treatment approaches. Given that non-muscle-invasive BC with visible hematuria exhibits distinct clinical features, future research should include histopathological evaluations to accurately define the risks associated with pioglitazone use [29].

The inconsistent findings regarding BC risk in relation to pioglitazone use necessitate comprehensive assessments that account for factors such as patient demographics, smoking history, dosage, and treatment duration. Understanding the subtypes of BC may further clarify pioglitazone's safety profile and assist in managing diabetes while considering potential oncogenic risks [25,28].

Of the six studies included in this review, two, by Garry *et al.* and Bhushan *et al.* [20,21], identified a significant association between pioglitazone use and increased BC risk, particularly in men, older adult patients, and those on prolonged treatment regimens. Garry *et al.* [20] reported a 32% higher risk of BC (relative risk [RR] 1.32, 95% CI: 1.02–1.70), which may be linked to initial exposure to pioglitazone. Bhushan *et al.* [20,21] observed a slight but significant increase in BC incidence (RR 1.13, 95% CI: 1.03–1.25), with more pronounced effects found in specific demographic groups. In contrast, four studies, by Riaz *et al.*, Agrawal *et al.*, Malhotra *et al.*, and Li *et al.* [19,22-24], failed to find a significant correlation between pioglitazone use and BC risk, suggesting minimal or no effect in the broader populations. Notably, Li *et al.* [24] observed a potential protective effect (RR 0.70, 95% CI: 0.54–0.92), indicating that other factors, such as coexisting health conditions or concurrent medications, might influence BC risk more than pioglitazone.

Studies on the effects of pioglitazone on BC risk have yielded inconsistent results, with RR estimates ranging from 0.70 to 1.32. Garry *et al.* and Bhushan *et al.* [20,21] suggested a higher risk within the first 2 years of use, particularly among older adult patients and men. In contrast, Agrawal *et al.* and Malhotra *et al.* reported no significant dose-related effects, suggesting that patient-specific factors might be more influential [22,23].

Studies by Garry *et al.* and Bhushan *et al.* [20,21], which controlled for smoking, identified pioglitazone as a significant predictor of BC, implying that its effect may be independent of smoking. Conversely, studies by Riaz *et al.* and Li *et al.* [19,24] lacked consistent adjustments for potential confounders, which may have biased their outcomes. These inconsistencies, along with variations in patient characteristics, contributed to the divergent findings.

Given the uncertainty surrounding the effect of pioglitazone on BC development, health-care providers should exercise caution, particularly when treating high-risk individuals. An individualized risk-benefit assessment is crucial to balance the benefits of pioglitazone in blood sugar management with the potential, though not definitively proven, risk of BC.

Factors affecting Bacillus Calmette-Guérin (BCG) therapy for non-muscle-invasive BC include immunocompromised status due to infection risks [30], limited access to relevant health-care services in rural areas or high costs [31], and contraindications related to severe kidney or heart conditions. Diabetes may impair immune function, reducing the effectiveness of BCG therapy [32,33], while adaptive immune resistance, indicated by programmed death-ligand 1 expression, may result in a poor response to BCG [34]. Alterations in bladder tissue due to these conditions may hinder BCG absorption and local efficacy [32,34]. In addition, irregular treatment schedules due to socioeconomic factors may further decrease the therapy's effectiveness [35]. Genetic factors, such as single-nucleotide polymorphisms in autophagy-related genes, may also influence BCG outcomes, as autophagy is crucial for BCG-induced trained immunity [36]. Addressing these limitations through policy changes, increased funding, personalized treatment plans incorporating immune markers, and combining BCG with other therapies, such as checkpoint inhibitors, could improve BCG therapy outcomes in patients with BC [35].

Meta-analyses by Ripamonti *et al.* and Davidson *et al.* [37,38] indicated an association between protracted pioglitazone use and increased BC risk (RR 1.28, 95% CI: 1.08–1.53). However, the dose was not significantly associated with BC risk (RR 1.21, 95% CI: 0.85–1.73). Age and smoking history may have influenced the observed risk findings.

Yan *et al.* and Garry *et al.* [20,23] investigated the dosage of pioglitazone as a potential risk factor; however, their results were not statistically significant (RR 1.29, 95% CI: 0.75–2.22 and RR 1.29, 95% CI: 0.76–2.18, respectively), which are consistent with the findings reported by Li *et al.* [39]. Conversely, Riaz *et al.* [19] found no cases of BC among 1,168 patients with diabetes aged >40 years who were using pioglitazone, and Agrawal *et al.* [22] reported no increased BC risk in a study of 2085 patients. Similarly, Malhotra *et al.* [24] found no significant association in their case–control study (RR 0.94, 95% CI: 0.834–1.061; $p = 0.207$).

Adil *et al.* [40] conducted a meta-analysis of 2,470,397 patients with T2DM and found a significant association between pioglitazone use and BC risk. Observational studies indicated an increased risk of BC

(RR 1.20, 95% CI: 1.09–1.31; $p < 0.001$), although this risk emerged only after 12 months of continuous pioglitazone use (RR 1.43, 95% CI: 1.10–1.71), except in studies where pioglitazone (28 mg) had been prescribed. Ramezannezhad *et al.* [41] reported that using pioglitazone for more than five years increased cancer risk (RR 1.24, 95% CI: 1.09–1.41), particularly in the 60–69-year age group (RR 1.20, 95% CI: 1.04–1.38). This observation contrasts with the findings of Bhushan *et al.* [21], who examined 16.9 million cases and reported an increased cancer risk associated with age ≥45 years, male sex, and residency in the Americas.

Sinha *et al.* [42] reported no significant association between pioglitazone use and BC risk in a study involving 10,890 patients with diabetes (RR 1.56, 95% CI: 0.79–3.05), the result being consistent with the findings of Tang *et al.* [43].

Kaga *et al.* [44] also found no link between pioglitazone and BC but identified a significant association between insulin use and BC risk. Conversely, Lewis *et al.* [45] observed no association between pioglitazone and BC but did report increased risks for prostate and pancreatic cancers. Systematic reviews and meta-analyses by Ferwana *et al.* and Zhu *et al.* [46,47] investigated the risk of BC among pioglitazone users. Clyne *et al.* and Tuccori *et al.* [48,49] further supported the association between prolonged use or higher doses with an increased BC risk. While some studies reported no significant association, other studies suggested an elevated risk with long-term tobacco use. These findings emphasize the importance of considering patient history and risk factors when prescribing pioglitazone and underscore the need for further research to clarify potential risks. Nevertheless, many studies have found a correlation between BC and factors such as the quantity and duration of drug use, along with other factors, including age, sex, and a history of hematuria.

In a risk-benefit analysis of pioglitazone for managing patients with T2DM, pioglitazone, as an insulin sensitizer, offered significant benefits. It improved glycemic control, reduced hemoglobin A1c levels, and enhanced lipid profiles by lowering triglycerides and increasing high-density lipoprotein-cholesterol levels [50-53]. A meta-analysis has shown that pioglitazone reduced major adverse cardiovascular events in individuals with insulin resistance, pre-diabetes, and T2DM, especially in those with a history of cardiovascular issues [53]. In the treatment of non-alcoholic fatty liver disease, pioglitazone decreased hepatic fat levels, improved liver enzyme profiles, and demonstrated histological improvements in liver tissue [50,52].

However, there are risks associated with pioglitazone use. It could cause dose-dependent weight gain [51,54] and increase the risk of heart failure [53-55], as well as the likelihood of bone fractures, particularly in post-menopausal women [54,55]. In addition, the relationship between long-term pioglitazone use and BC remains controversial [51]. In rare cases, it may also cause liver damage, requiring regular monitoring of liver function [50]. While pioglitazone provides significant benefits for glycemic control and cardiovascular health in the treatment of T2DM, its potential risks must be carefully considered. An individualized patient assessment and continuous monitoring are essential to the optimization of treatment efficacy and minimization of adverse effects, emphasizing the importance of integrating pioglitazone into a comprehensive T2DM management strategy.

Several limitations complicate the interpretation of studies examining the association between pioglitazone use and BC risk, including confounding variables, such as smoking, which render it difficult to isolate the effect of pioglitazone on BC risk. In addition, many of these studies were of retrospective observational designs, which are prone to bias and hinder the establishment of causal relationships. The heterogenicity of study populations also raises concerns regarding the generalizability of the results. Furthermore, variability in the duration of pioglitazone administration and the dosage used across trials led to inconsistent findings, likely due to differences in the study design, patient adherence, and cumulative drug exposure. Moreover, some studies suffered from small sample sizes and inadequate follow-up periods, which compromised their statistical power and potentially resulted in inaccurate risk estimates.

5. CONCLUSION

Current research on the association between pioglitazone use and BC incidence remains inconclusive, with only 50% of studies reporting an association. However, significant associations have been identified with the duration of use (>12 months), cumulative dosage (>10.5 g), age (≥60 years), male sex, a history of hematuria, and smoking. Further studies are required to definitively establish the relationship between pioglitazone use and the incidence of BC.

ACKNOWLEDGMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Sujatha Baddam, Amulya Varshini Banka, Yethindra Vityala

Writing – original draft: Shravani Divity, Maharshikumar Sandesara, Yethindra Vityala
Writing – review & editing: All authors

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

Data are available from the corresponding author upon reasonable request.

REFERENCES

1. Izzah SU, Susilo I. Clinicopathological profile of urothelial carcinoma of the bladder: A five-year retrospective study. *Ro J Med Pract*. 2023;18(3):147-151. doi: 10.37897/RJMP.2023.3.8
2. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: A global overview and recent trends. *Eur Urol*. 2017;71(1):96-108. doi: 10.1016/j.eururo.2016.06.010
3. Fedewa SA, Soliman AS, Ismail K, *et al.* Incidence analyses of bladder cancer in the Nile delta region of Egypt. *Cancer Epidemiol*. 2009;33(3-4):176-181. doi: 10.1016/j.canep.2009.08.008
4. Scosyrev E, Trivedi D, Messing E. Female bladder cancer: Incidence, treatment, and outcome. *Curr Opin Urol*. 2010;20(5):404-408. doi: 10.1097/MOU.0b013e32833c7a9b
5. Densmore R, Hajizadeh M, Hu M. Trends in socio-economic inequalities in bladder cancer incidence in Canada: 1992-2010. *Can J Public Health*. 2019;110(6):722-731. doi: 10.17269/s41997-019-00227-y
6. Li HZ, Zheng RS, Du LB, *et al.* Bladder cancer incidence, mortality and temporal trends in China. *Zhonghua Zhong Liu Za Zhi*. 2021;43(3):293-298. doi: 10.3760/cma.j.cn112152-20200421-00362
7. Kiemeney LA, Coebergh JW, Koper NP, *et al.* Bladder cancer incidence and survival in the south-eastern part of The Netherlands, 1975-1989. *Eur J Cancer*. 1994;30A(8):1134-1137. doi: 10.1016/0959-8049(94)90472-3
8. Seisen T, Labban M, Lipsitz SR, *et al.* Assessment of the ecological association between tobacco smoking exposure and bladder cancer incidence over the past half-century in the United States. *Curr Oncol*. 2023;30(2):1986-1998. doi: 10.3390/curroncol30020154
9. Buzzeo BD, Heisey DM, Messing EM. Bladder cancer in renal transplant recipients. *Urology*. 1997;50(4):525-528. doi: 10.1016/S0090-4295(97)00305-1
10. Tashiro K, Torii S, Iwamuro S, *et al.* A clinical study of the renal pelvis and ureteral cancer. *Nihon Hinyokika Gakkai Zasshi*. 1990;81(3):439-446. doi: 10.5980/jpnjurol1989.81.439
11. Ray D, Mondal R, Achryya S, Mondal S. A retrospective study of bladder cancer and the impact of age, sex, and smoking habits with related clinicopathological correlations in the tribal population of Bankura, WB, India. *IOSR-JDMS.* 2013;10:29-32. doi: 10.9790/0853-1042932
12. Ponnaboina DM, Perumandal S, Sreelakshmi I. Correlation of HER2 with p53 and p63 in urothelial bladder carcinoma. *Cureus*. 2023;15(4):e38018. doi: 10.7759/cureus.38018
13. FDA Drug Safety Communication: Updated FDA Review Concludes that Use of Type 2 Diabetes Medicine Pioglitazone may be linked to an Increased Risk of Bladder Cancer. United States: Food and Drug Administration. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-updated-fda-review-concludes-use-type-2-diabetes-medicine-pioglitazone [Last accessed on 2024 Jul 22].
14. Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: A meta-analysis. *CMAJ*. 2012;184(12):E675-E683. doi: 10.1503/cmaj.112102
15. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care*. 2011;34(6):1369-1371. doi: 10.2337/dc10-2412
16. Lewis JD, Ferrara A, Peng T, *et al*. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. *Diabetes Care*. 2011;34(4):916-922. doi: 10.2337/dc10-1068
17. Filipova E, Uzunova K, Kalinov K, Vekov T. Pioglitazone and the risk of bladder cancer: A meta-analysis. *Diabetes Ther*. 2017;8(4):705-726. doi: 10.1007/s13300-017-0273-4
18. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. doi: 10.1186/2046-4053-4-1
19. Riaz A, Khan K, Afreen B, Kazmi I. Bladder cancer in patients with type 2 diabetes treated with pioglitazone, a comparative study. *J Ayub Med Coll Abbottabad*. 2018;30(3):356-359.
20. Garry EM, Buse JB, Lund JL, Pate V, Stürmer T. Comparative safety of pioglitazone versus clinically meaningful treatment alternatives concerning the risk of bladder cancer in older US adults with type 2 diabetes. *Diabetes Obes Metab*. 2018;20(1):129-140. doi: 10.1111/dom.13049
21. Bhushan S, Ray RS, Prakash J, Singh GN. Global versus Indian perspective of pioglitazone-induced adverse drug reactions including bladder cancer: A comparative retrospective pharmacovigilance analysis. *Clin Ther*. 2019;41(11):2252-2262.

doi: 10.1016/j.clinthera.2019.08.018
22. Agrawal P, Jain A, Gautam A, Nigam AK, Pursnani N, Farooqui M. A retrospective study to assess the risk of bladder cancer in type-2 diabetic patients treated with pioglitazone. *Perspect Clin Res*. 2021;12(1):9-13. doi: 10.4103/picr.PICR_192_18
23. Li YR, Liu CH, Sun WC, *et al.* The risk of bladder cancer in type 2 diabetes mellitus with combination therapy of SGLT-2 inhibitors and pioglitazone. *J Pers Med*. 2021;11(9):828. doi: 10.3390/jpm11090828
24. Malhotra B, Hiteshi P, Khalkho P, *et al.* Bladder cancer with pioglitazone: A case-control study. *Diabetes Metab Syndr*. 2022;16(11):102637. doi: 10.1016/j.dsx.2022.102637
25. Netto GJ, Amin MB, Berney DM, *et al.* The 2022 World Health Organization Classification of tumors of the urinary system and male genital organs-part B: Prostate and urinary tract tumors. *Eur Urol*. 2022;82(5):469-482. doi: 10.1016/j.eururo.2022.07.002
26. Claps F, van de Kamp MW, Mayr R, *et al.* Prognostic impact of variant histologies in urothelial bladder cancer treated with radical cystectomy. *BJU Int*. 2023;132(2):170-180. doi: 10.1111/bju.15984
27. Stroman L, Nair R, Russell B, *et al*. The impact of non-urothelial variant histology on oncological outcomes following radical cystectomy. *BJU Int*. 2019;124(3):418-423. doi: 10.1111/bju.14704
28. Claps F, Biasatti A, Di Gianfrancesco L, *et al*. The prognostic significance of histological subtypes in patients with muscle-invasive bladder cancer: An overview of the current literature. *J Clin Med*. 2024;13(15):4349. doi: 10.3390/jcm13154349
29. Sanguedolce, F., Calò, B., Mancini, V., *et al*. Non-muscle invasive bladder cancer with variant histology: Biological features and clinical implications. *Oncology*. 2021;99(6):345-358. doi: 10.1159/000514759
30. Pérez-Jacoiste Asín MA, Fernández-Ruiz M, López-Medrano F, *et al.* Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: Incidence, risk factors, and outcome in a single-institution series and review of the literature. *Medicine (Baltimore)*. 2014;93(17):236-254. doi: 10.1097/MD.0000000000000119
31. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder cancer: A review. *JAMA*. 2020;324(19):1980-1991. doi: 10.1001/jama.2020.17598
32. Jiang S, Redelman-Sidi G. BCG in bladder cancer immunotherapy. *Cancers* (*Basel*). 2022;14(13):3073. doi: 10.3390/cancers14133073
33. Benn CS, Fisker AB, Whittle HC, Aaby P. Revaccination with live attenuated vaccines confers additional beneficial nonspecific effects on overall survival: A review. *EBioMedicine*. 2016;10:312-317. doi: 10.1016/j.ebiom.2016.07.016
34. De Jong FC, Laajala TD, Hoedemaeker RF, *et al.* Non-muscle-invasive bladder cancer molecular subtypes predict differential response to intravesical Bacillus Calmette-Guérin. *Sci Transl Med*. 2023;15(697):eabn4118. doi: 10.1126/scitranslmed.abn4118
35. Kamat AM, Shore N, Hahn N, *et al.* KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Fut Oncol*. 2020;16(10):507-516. doi: 10.2217/fon-2019-0817
36. Buffen K, Oosting M, Quintin J, *et al.* Autophagy controls BCG-induced trained immunity and the response to intravesical BCG therapy for bladder cancer. *PLoS Pathog*. 2014;10(10):e1004485. doi: 10.1371/journal.ppat.1004485
37. Ripamonti E, Azoulay L, Abrahamowicz M, Platt RW, Suissa S. A systematic review of observational studies of the association between pioglitazone use and bladder cancer. *Diabet Med*. 2019;36(1):22-35. doi: 10.1111/dme.13854
38. Davidson MB, Pan D. An updated meta-analysis of pioglitazone exposure and bladder cancer and comparison to the drug's effect on cardiovascular disease and non-alcoholic steatohepatitis. *Diabetes Res Clin Pract*. 2018;135:102-110. doi: 10.1016/j.diabres.2017.11.002
39. Yan H, Xie H, Ying Y, *et al*. Pioglitazone use in patients with diabetes and risk of bladder cancer: A systematic review and meta-analysis. *Cancer Manag Res*. 2018;10:1627-1638. doi: 10.2147/CMAR.S164840
40. Adil M, Khan RA, Ghosh P, Venkata SK, Kandhare AD, Sharma M. Pioglitazone and risk of bladder cancer in type 2 diabetes mellitus patients: A systematic literature review and meta-analysis of observational studies using real-world data. *CEGH*. 2018;6(2):61-68. doi: 10.1016/j.cegh.2017.08.002
41. Ramezannezhad P, Khosravifarsani M. The association between pioglitazone consumption and incidence of bladder cancer in type II diabetic patients: A systematic review and meta-analysis of observational studies. *J Nephropathol*. 2023;12(2):e21443. doi: 10.34172/jnp.2023.21443
42. Sinha B, Ghosal S. Assessing the need for pioglitazone in the treatment of patients with type 2 diabetes: A meta-analysis of its risks and benefits from prospective trials. *Sci Rep.* 2020;10(1):15781. doi: 10.1038/s41598-020-72967-8
43. Tang H, Shi W, Fu S, *et al.* Pioglitazone and bladder cancer risk: A systematic review and meta-analysis. *Cancer Med*. 2018;7(4):1070-1080. doi: 10.1002/cam4.1354
44. Kaga K, Araki K, Kanesaka M, *et al.* Does pioglitazone increase the risk of bladder cancer in Japanese diabetic patients? *Med Surg Urol*. 2014;4:1-3. doi: 10.4172/2168-9857.1000147
45. Lewis JD, Habel LA, Quesenberry CP, *et al.* Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA*. 2015;314(3):265-277. doi: 10.1001/jama.2015.7996
46. Ferwana M, Firwana B, Hasan R, *et al.* Pioglitazone and risk of bladder cancer: A meta-analysis of controlled studies. *Diabet*

Med. 2013;30(9):1026-1032.
doi: 10.1111/dme.12144
47. Zhu Z, Shen Z, Lu Y, Zhong S, Xu C. Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract*. 2012;98(1):159-163. doi: 10.1016/j.diabres.2012.05.006
48. Clyne M. Bladder cancer: Pioglitazone increases risk of bladder cancer. *Nat Rev Urol*. 2012;9(7):353. doi: 10.1038/nrurol.2012.131
49. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: Population-based cohort study. *BMJ*. 2016;352:i1541. doi: 10.1136/bmj.i1541
50. Cusi K, Orsak B, Bril F, *et al*. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: A randomized trial. *Ann Intern Med*. 2016;165(5):305-315. doi: 10.7326/M15-1774
51. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. *Diab Vasc Dis Res*. 2019;16(2):133-143. doi: 10.1177/1479164118825376
52. Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: A meta-analysis. *Front Endocrinol* (*Lausanne*). 2021;12:615409. doi: 10.3389/fendo.2021.615409
53. Zhou Y, Huang Y, Ji X, Wang X, Shen L, Wang Y. Pioglitazone for the primary and secondary prevention of cardiovascular and renal outcomes in patients with or at high risk of type 2 diabetes mellitus: A meta-analysis. *J Clin Endocrinol Metab*. 2020;105(5):dgz252. doi: 10.1210/clinem/dgz252
54. Liao HW, Saver JL, Wu YL, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: A systematic review and meta-analysis. *BMJ Open*. 2017;7(1):e013927. doi: 10.1136/bmjopen-2016-013927
55. Kernan WN, Viscoli CM, Furie KL, *et al.* Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374(14):1321-1331. doi: 10.1056/NEJMoa1506930