Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone

Interim report of a longitudinal cohort study

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OBJECTIVE—Some preclinical in vivo studies and limited human data suggest a possible increased risk of bladder cancer with pioglitazone therapy. This is an interim report of an ongoing cohort study examining the association between pioglitazone therapy and the risk of bladder cancer in patients with diabetes.

RESEARCH DESIGN AND METHODS—This study includes 193,099 patients in the Kaiser Permanente Northern California diabetes registry who were ≥40 years of age between 1997 and 2002. Those with prior bladder cancer were excluded. Ever use of each diabetes medication (defined as two or more prescriptions within 6 months) was treated as a time-dependent variable. Cox regression–generated hazard ratios (HRs) compared pioglitazone use with nonpioglitazone use adjusted for age, sex, race/ethnicity, diabetes medications, A1C, heart failure, household income, renal function, other bladder conditions, and smoking.

RESULTS—The group treated with pioglitazone comprised 30,173 patients. There were 90 cases of bladder cancer among pioglitazone users and 791 cases of bladder cancer among nonpioglitazone users. Overall, ever use of pioglitazone was not associated with risk of bladder cancer (HR 1.2 [95% CI 0.9–1.5]), with similar results in men and women (test for interaction $P = 0.8$). However, in the a priori category of >24 months of therapy, there was an increased risk (1.4 [1.03–2.0]). Ninety-five percent of cancers diagnosed among pioglitazone users were detected at early stage.

CONCLUSIONS—In this cohort of patients with diabetes, short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for more than 2 years was weakly associated with increased risk.

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Peroxisome proliferator–activated receptor (PPAR)γ has been detected in normal uroepithelial tissue by some but not all investigators and is generally detectable in bladder tumors (1–3). Thiazolidinedione (TZD) PPARγ ligands have been shown to alter cell proliferation rates and differentiation in human cancer cell lines, including bladder cancer cells (1–7).

Pioglitazone (ACTOS) is a thiazolidinedione PPARγ ligand used in the treatment of type 2 diabetes. It is indicated as an adjunct to diet and exercise to improve glycemic control. However, it is not generally used as a first-line therapy (8). In preclinical studies, male rats treated with pioglitazone developed more bladder tumors than male rats treated with placebo. This was not observed with female rats at the same dose or with mice of either sex at higher doses (9). However, bladder tumors have also been reported in laboratory animals taking experimental drugs with dual PPARα and PPARγ activity (10).

Others have reported on potential associations between treatment with TZDs and risk of cancer at other sites (11–14). However, there are limited data in humans to address this question. The data available mostly come from the PROactive study, which found a nonsignificant excess of bladder tumors among patients treated with pioglitazone (15). In 2003, the U.S. Food and Drug Administration (FDA) requested that the manufacturer of pioglitazone conduct a safety study to assess whether therapy with pioglitazone increases the risk of bladder cancer. The authors of this study drafted the initial protocol that was subsequently reviewed by the FDA and revised accordingly. At the request of the FDA, the study was planned to be conducted over 10 years. This report describes the results of the planned midpoint interim analysis.

RESEARCH DESIGN AND METHODS

Data source

Kaiser Permanente Northern California (KPNC) provides comprehensive health care services to approximately 3.2 million members, representing approximately 30% of the population of the geographic area (16). The KPNC pharmacy database includes information on each outpatient prescription dispensed at a KPNC pharmacy. Approximately 95% of KPNC members with pharmacy benefits fill all of their prescriptions at KPNC pharmacies (16).

The source population was identified from the KPNC diabetes registry. The diabetes registry gathers data from various components of the KPNC electronic medical record (EMR) and related clinical databases to build and follow the registry cohort across time. These data include cancer registries, pharmacy records, laboratory records, and inpatient and outpatient medical diagnoses. The registry

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identifies patients with diabetes primarily from four data sources: primary hospital discharge diagnoses of diabetes, two or more outpatient-visit diagnoses of diabetes, any prescription of a diabetes-related medication, or any record of A1C >6.7%. These data have been widely used in prior epidemiology studies (16).

Patients were eligible for the overall study cohort if they met any of the following criteria: *1*) as of 1 January 1997, they had been diagnosed with diabetes, were age ≥40 years and were members of KPNC; *2*) they had been diagnosed with diabetes, reached age 40 years between 1 January 1997 and 31 December 2002, and were KPNC members on their 40th birthday; or *3*) they had diabetes and were age ≥40 years when they joined KPNC between 1 January 1997 and 31 December 2002. From this cohort of 207,389, we excluded 823 patients with a diagnosis of bladder cancer prior to entry in the cohort or within 6 months of joining KPNC to avoid misclassification of prevalent bladder cancers as incident diagnoses. Likewise, patients without prescription benefits at the time of entry into the cohort (n = 6,674) or those with a gap of >4 months in prescription or membership benefits where the gap started within the first 4 months of entering the cohort (*n* = 6,782) were excluded. This analysis included data from 1 January 1997 to 30 April 2008.

Exposure definition

Ever use of a diabetes medication was defined as having filled at least two prescriptions for the drug within a 6-month period according to the KPNC pharmacy database. Diabetes medications were categorized as pioglitazone, other TZDs, metformin, sulfonylureas, insulin, and other (e.g., miglitol and acarbose). Separate indicator variables were created for patients who had not received any diabetes medication prescriptions and for those who received at least one prescription but had not met the definition of exposure.

Time since initiation of pioglitazone was calculated by counting the interval, in days, since the date of the second pioglitazone prescription. Cumulative duration of exposure to pioglitazone was measured by counting the number of days between prescriptions. If the next prescription was filled within 30 days of the expected end date of the previous prescription, we assumed that therapy was uninterrupted. However, if there were no refills within the 30 days after the expected end date of the previous prescription, we assumed a gap in therapy starting 30 days after the date that the previous prescription should have ended. The cumulative duration variable was a time-varying sum of all periods of exposure even if there were gaps in treatment.

Cumulative dose of pioglitazone was calculated in a similar fashion. For any prescription that was completed prior to an event date, the total prescribed dose (i.e., number of pills in the prescription multiplied by the dose of the pills) was assumed to have been consumed. For prescriptions that were still active on the date of an event, the total consumed dose was reduced to reflect the proportion of pills expected to have been consumed by that date.

Primary outcome

Follow-up started on the first date that the inclusion criteria were met. Follow-up ended on 30 April 2008 or when any of the following occurred: *1*) a gap of greater than 4 months in either membership or prescription benefits, *2*) a new diagnosis of bladder cancer, or *3*) death from any cause.

Incident bladder cancers were identified from the KPNC cancer registry, one of several sites that submit data to the Surveillance, Epidemiology, and End Results (SEER) program, from 1 January 1997 to 30 April 2008. This was supplemented by case identification through surveillance of electronic pathology reports within KPNC from 1 January 2005 to 30 April 2008. We did not make any distinction regarding the histology of the bladder cancer and included patients diagnosed with in situ bladder cancer and papillary urethral neoplasm of low malignant potential from 2005 onward (17,18). Cancer stage was categorized according to SEER guidelines as local, regional, distant, or undetermined.

Confounder variables

Variables considered as potential confounders are included in Table 1. Data on potential confounders were extracted from the EMR. Possible confounders, such as congestive heart failure, were identified by searching the related ICD-9 codes in the hospital and outpatient databases. Other confounders, such as renal insufficiency and glycemic control, were identified in the clinical laboratory database. Demographic variables were identified from administrative data. For smoking and duration of diabetes, the EMR data were supplemented with data from member surveys. We selected as potential confounders variables believed to be associated with one or more of the following: the risk of bladder cancer (e.g., age, race, sex, smoking, and socioeconomic status), the possibility of detection of bladder cancer (e.g., urinary diseases or symptoms, including urinary tract infections, urinary incontinence, urolithiasis, and prior history of other cancers), or the likelihood of being prescribed pioglitazone (e.g., diabetes duration, A1C levels, congestive heart failure, and renal insufficiency). With the exception of smoking, all confounders were measured using data recorded on or before the start of follow-up.

Nested case-control study

Because of incomplete or missing EMR data on potential confounders including race/ethnicity, smoking history, duration of diabetes, and occupational exposures, we supplemented the cohort study with a case-control study nested within the study cohort to assess whether there was residual confounding by these variables in the cohort study. From the source cohort, we identified all incident diagnoses of bladder cancer from 1 October 2002 to 30 April 2008. The index date was defined as the date of bladder cancer diagnosis.

For each individual with bladder cancer, one control was randomly selected after matching for sex, age (±2.5 years), and time from entry into the KPNC diabetes registry to index date (±6 months). In addition, no control subjects could be diagnosed with bladder cancer or be censored from the cohort for other reasons as of the date of first diagnosis with bladder cancer of the matched case subject.

The date that the case subject was first diagnosed with bladder cancer served as the reference date for both the case subject and the matched control. The additional data for the case-control study (e.g., duration of diabetes, smoking, use of indwelling catheters, frequency of urinary tract infections, and occupational exposures) were collected up to the reference date through telephone interviews using a standardized questionnaire administered by trained interviewers.

Statistical analyses

Continuous and categorical variables were compared with the Wilcoxon rank-sum test and χ^2 test or Fisher's exact test, respectively. Exposure to pioglitazone

and exposure to all other diabetes medications were treated as unidirectional time–dependent variables; i.e., all follow-up time from entry into the cohort until the date that the patient first met the definition of ever use was attributed to the never-use group and once a patient met the definition of ever use the patient was considered exposed from that point forward, even if the patient discontinued the medication. Cox proportional hazards models were used for all calculations of the hazard ratio (HR) of bladder cancer with pioglitazone, adjusted for the covariates. The reference group for calculation of the HR associated with ever use of pioglitazone (with or without other diabetes medications) was never use of pioglitazone at that point of time, which by definition included those treated with any diabetes medications other than pioglitazone and those with only dietary therapy. Identical methods were used to determine relative HRs associated with exposure to other categories of diabetes medications. Because the large number of cases of bladder cancer made overfitting the statistical model unlikely, we included all potential confounders listed in Table 1 in the fully adjusted Cox regression models for ever exposure.

Analysis of the case-control study was conducted in a similar fashion except that conditional logistic regression was used to calculate odds ratios (ORs) (95% CIs).

RESULTS—After application of the exclusion criteria, the final cohort included 193,099 patients with diabetes. Patients who ever used pioglitazone during the study period (n = 30,173) were less likely to be age ≥70 years and were more likely to have a baseline A1C >10% than patients who never used pioglitazone (Table 1). They were also more likely to have been treated with metformin, sulfonylureas, and insulin prior to, after, or along with pioglitazone. Among patients who ever used pioglitazone, the median time from the first prescription to the end of follow-up was 3.3 years (range 0.2–8.5 years), and the median duration of therapy among pioglitazone-treated patients was 2.0 years (0.2–8.5 years) (Table 1). The median follow-up time from cohort entry was 6.2 years (0.1–11.3) in those never treated with pioglitazone and 9.3 years (0.1–11.3) in those ever exposed to pioglitazone (including follow-up before, during, and after pioglitazone therapy).

Table 1—*Demographics of the study cohort according to ever use of pioglitazone: the KPNC diabetes registry, 1997–2008*

	Ever use of pioglitazone*	Never use of pioglitazone*
N	30,173	162,926
Age (years)		
40–49	8,612 (28.5)	36,452 (22.4)
50–59	9,945 (33.0)	41,962 (25.8)
60–69	7,799 (25.8)	42,691 (26.2)
≥70	3,817 (12.7)	41,821 (25.7)
Sex (female)	14,157 (46.9)	75,686 (46.5)
Race/ethnicity		
White	14,768 (48.9)	80,777 (49.6)
Black	2,823 (9.4)	16,731 (10.3)
Asian	3,834 (12.7)	18,877 (11.6)
Hispanic	3,320 (11.0)	14,430 (8.9)
Other	1,691 (5.6)	8,876 (5.4)
Missing	3,737 (12.4)	23,235 (14.3)
Current smoker	6,052 (20.1)	28,023 (17.2)
Renal function		
Normal creatinine	23,174 (76.8)	125,879 (77.3)
Elevated creatinine†	1248 (4.1)	13,993 (8.6)
Missing	5,751 (19.1)	23,054 (14.2)
Bladder condition‡	3,686 (12.2)	25,581 (15.7)
Congestive heart failure	969 (3.2)	11,038 (6.8)
Income		
Low§	14,413 (47.8)	82,270 (50.5)
High	12,825 (42.5)	66,133 (40.6)
Missing	2,935 (9.7)	14,523 (8.9)
Baseline A1C (%)		
<7	4,873 (16.2)	46,407 (28.5)
7–7.9	5,455 (18.1)	31,517 (19.3)
8–8.9	3,921 (13.0)	17,060 (10.5)
9–9.9	2,979 (9.9)	11,524 (7.1)
≥10	7,330 (24.3)	28,017 (17.2)
Missing	5,615 (18.6)	28,401 (17.4)
Newly diagnosed with diabetes at the start of follow-up¶	14,687 (48.7)	94,739 (58.1)
Duration of diabetes (years)		
0–5	17,363 (57.5)	102,916 (63.2)
5–9	2,983 (9.9)	9,671 (5.9)
≥10	2,956 (9.8)	17,432 (10.7)
Missing	6,871 (22.8)	32,907 (20.2)
Other cancer prior to baseline	1,186 (3.9)	8,762 (5.4)
Other diabetes medications		
Other TZDs	2,754 (9.1)	2,470 (1.5)
Metformin	24,797 (82.2)	70,956 (43.6)
Sulfonylureas	26,311 (87.2)	95,429 (58.6)
Other oral hypoglycemic drugs	1,482 (4.9)	1,865 (1.1)
Insulin	13,123 (43.5)	41,337 (25.4)
Pioglitazone use during follow-up		
Time since starting pioglitazone (months)	39.5 (1–102)	N/A
<18	7,245 (24.0)	N/A
18–36	6,681 (22.1)	N/A
>36	16,247 (53.8)	N/A
Duration of therapy (months)	24.1 (1–102)	N/A
<12	7,332 (24.3)	N/A
12–24	7,677 (25.4)	N/A
>24	15,164 (50.3)	N/A

Table 1—*Continued*

	Ever use of pioglitazone*	Never use of pioglitazone*
Cumulative dose (mg)	17,670 (450–179,000)	N/A
1–10,500	10,281 (34.1)	N/A
10,501–28,000	9,667 (32.0)	N/A
>28,000	10,225 (33.9)	N/A

Data are *n* (%) or median (range) unless otherwise indicated. N/A, not applicable. *All comparisons have *P* values <0.01 except female sex ($P = 0.46$). †Creatinine ≥1.4 mg/dL for women and ≥1.5 mg/dL for men. ‡History of urinary tract infections, urolithiasis, incontinence, and other bladder or urethral conditions. §Low income defined as median household income in census block below the cohort average ($59,000). ¶Includes newly diagnosed patients and patients who newly enrolled in KPNC with an existing diagnosis of diabetes.

During the follow-up period, there were 881 cases of newly diagnosed bladder cancer cases: 90 among patients who ever used pioglitazone and 791 among patients who never used pioglitazone. The unadjusted bladder cancer incidence rates per 100,000 person-years for ever use of pioglitazone and never use of pioglitazone were 81.5 and 68.8, respectively. By comparison, in SEER, the annual incidence per 100,000 person-years in those aged ≥50 years ranged from 70.6 to 75.3 during the years 2000–2007 (19). After adjustment for only age, sex, and use of other categories of diabetes medications, there was a slightly elevated but not significant association of ever use of pioglitazone with bladder cancer risk (HR 1.2 [95% CI 0.9–1.5]). The fully adjusted model provided nearly identical results (Table 2). The pioglitazone use–bladder cancer association did not differ by sex (men 1.1 [0.9–1.5)] and women 1.4 [0.8–2.6]; test for interaction $P = 0.81$). Analyses from the case-control study revealed the absence of residual confounding due to variables that were incompletely measured (smoking and race/ethnicity) or not measured (occupation) in the cohort study (data not shown).

When we examined the association between bladder cancer incidence and increasing levels of pioglitazone exposure (Table 2), the risk of bladder cancer slightly increased with increasing dose and duration of pioglitazone use. After adjustment for only age and sex, the risk of bladder cancer was 30% higher among those whose duration of pioglitazone therapy was 12–24 months (HR 1.3 [95% CI 0.9–2.0]) and 50% higher among those with >24 months of exposure (1.5 [1.1–2.0]) than that among never users of pioglitazone. The fully adjusted models provided similar results (>24 months of exposure 1.4 [1.03–2.0]). There were no clear patterns between increasing time since initiation of pioglitazone and bladder cancer risk.

Among men, after adjustment for age there was a significant increase in the relative hazard of bladder cancer with more than 24 months of exposure (HR 1.6 [95% CI 1.2–2.3]) and with a >28,000-mg cumulative dose (1.8 [1.2–2.6]). Because there were only 14 women treated with pioglitazone who were diagnosed with bladder cancer, estimates of dose and duration were unstable and are not reported.

In a post hoc analysis to assess whether the increased incidence of bladder cancer was greater with even longer duration of exposure, we further subdivided the category of >24 months of exposure. This analysis demonstrated an additional increase in the relative hazard of bladder cancer with longer duration of therapy. Among 6,670 patients with >48 months of pioglitazone exposure, the age- and sex-adjusted HR was 1.7 (95% CI 1.1–2.9), and the fully adjusted hazard ratio was 1.6 (0.96–2.7). The age- and sex-adjusted point estimates compared with those of unexposed subjects went from 0.8 for <12 months of use to 1.3 for 12–24 months, 1.3 for 24–36 months, 1.5 for 36–48 months, and 1.7 for >48 months (test for trend treating duration of exposure as an ordinal variable with levels 0 [no exposure] to 5 [>48 months of exposure], $P = 0.01$ in age- and sex-adjusted and $P = 0.02$ in fully adjusted models).

There were proportionately more in situ cancers among the pioglitazone users (data not shown). Only 3% of bladder cancers in the patients who ever used pioglitazone were of regional or advanced stage at the time of diagnosis. In contrast, 9% of bladder cancers in the patients who never used pioglitazone had regional or advanced stage disease at the time of diagnosis (two-sided Fisher's exact $P = 0.10$ excluding 2% of pioglitazone-exposed cancers and 4% of nonpioglitazone-exposed cancers with undetermined stage).

CONCLUSIONS—We describe the interim results of an ongoing cohort study being conducted at the request of the FDA in response to animal studies suggesting a possible increased risk of bladder cancer among patients treated with pioglitazone. This association was initially observed in male rats but not in female rats or in mice of either sex (9). Subsequent research suggested that this effect in male rats can be prevented with dietary modification, suggesting a mechanism related to the bladder anatomy and acid milieu of urine in male rats (20). However, a more recent study in a different animal model, hydroxybutyl(butyl)nitrosamine (OH-BBN), proposed that rosiglitazone, another TZD, may be a tumor promoter even in late stages of bladder cancer development (21). At the time of this interim report, we did not observe a significant association between any pioglitazone exposure and bladder cancer risk in our cohort study overall. However, we observed an increased risk of bladder cancer among patients with the longest exposure to pioglitazone. A post hoc analysis suggests further increased risk with even longer exposure periods. Finally, there was no evidence of a stage shift to more advanced bladder cancer among the pioglitazone-exposed patients.

There are several major strengths of this study. The KPNC diabetes registry includes a large population of individuals with diabetes. The diabetes registry uses active surveillance based on diagnoses, laboratory tests, and pharmacy data and as such is also able to identify individuals with diabetes who are not treated with medications. We used the KPNC cancer registry to identify patients with bladder cancer. The cancer registry, which contributes data to SEER, is held to SEER's very high quality standards. Another strength is the availability of the KPNC pharmacy data. By requiring patients to fill two prescriptions within a 6-month period, we have minimized misclassification of unexposed patients as exposed. Patients who filled only a single pioglitazone prescription ($n = 4,679$) or who filled two or more prescriptions that were never within 6 months of each other ($n = 580$) were not categorized as exposed according to our definition. Some of these patients may have actually been exposed to pioglitazone. However, this misclassification is

Table 2—*Incidence rate and HR of bladder cancer with pioglitazone use: the KPNC diabetes registry, 1997–2008*

	Median (range) bladder cancer incidence rate (per 100,000 person-years)	HR (95% CI) adjusted for age and sex	Fully adjusted HR (95% CI)*
Never use of pioglitazone	68.8 (64.1–73.6)	Ref.	Ref.
Ever use of pioglitazone†	81.5 (64.7–98.4)	1.2 (0.9–1.5)‡	1.2 (0.9–1.5)
Time since starting pioglitazone (months)†			
<18	67.1 (41.8–92.4)	1.1 (0.8–1.6)	1.2 (0.8–1.7)
18–36	85.2 (51.8–118.6)	1.3 (0.9–2.0)	1.4 (0.9–2.1)
>36	93.1 (63.5–122.7)	1.3 (0.9–1.8)	1.3 (0.9–1.8)
P_{trend}	—	0.04	0.07
Duration of therapy (months)†			
<12	48.4 (29.0–67.8)	0.8 (0.5–1.2)	0.8 (0.6–1.3)
12–24	86.7 (52.0–121.4)	1.3 (0.9–2.0)	1.4 (0.9–2.1)
>24	102.8 (71.7–133.8)	1.5 (1.1–2.0)	1.4 (1.03–2.0)
P_{trend}	—	0.02	0.03
Cumulative dose (mg)†			
1–10,500	59.7 (39.0–80.4)	1.0 (0.7–1.4)	1.0 (0.7–1.5)
10,501–28,000	76.8 (48.3–105.2)	1.1 (0.8–1.6)	1.2 (0.8–1.8)
>2,8000	105.9 (68.0–143.8)	1.5 (1.1–2.2)	1.4 (0.96–2.1)
P_{trend}	—	0.05	0.08

*Includes all potential confounders listed in Table 1 in the statistical model. †Never use of pioglitazone was the reference group for the calculation of the HR associated with ever use of pioglitazone and time, duration, and dose of pioglitazone use. ‡Also adjusted for use of other diabetes medications.

unlikely to be important given that such a small duration of therapy would be unlikely to change the risk of cancer. Furthermore, because these patients represented a small proportion of those who filled at least one pioglitazone prescription and an even smaller proportion of the population categorized as unexposed, their potential impact on the estimated HR is limited. Finally, the large number of patients who have been prescribed pioglitazone and that >50% of these have taken the medication for >2 years are major strengths of the study.

Considering potential limitations, our cohort study had incomplete or missing data on several variables known to be associated with bladder cancer, such as smoking and occupational exposures. However, our nested case-control study demonstrated that these unmeasured or incompletely measured confounders known to be associated with bladder cancer were unlikely to have influenced our cohort study results. In addition, in the case-control analysis we were able to more precisely categorize smoking according to cumulative exposure in pack-years. Despite this, smoking was not a confounder of the pioglitazone-bladder cancer analysis. Our analysis of the stage of cancer allows us to consider the potential for detection bias. Stage at diagnosis of bladder cancer was not significantly different between the pioglitazone-treated patients and those not treated with pioglitazone. However, there were proportionately more in situ cancers among the pioglitazone users. This might be observed if pioglitazone-treated patients underwent greater surveillance for bladder cancer or if pioglitazone increases the risk of bladder cancer by its effect on the early stages of development. To account for the possibility of increased surveillance, we adjusted for recorded bladder conditions that might prompt increased testing. Furthermore, we cannot determine whether there were patients with undiagnosed bladder cancer at the start of follow-up. However, this should not have been differential between those who did and those who did not receive treatment with pioglitazone. Further, the positive associations that we observed were with long-term exposure. Therefore, it is unlikely that this would be explained by an imbalance in prevalent yet undiagnosed cancer at the time of cohort entry.

Eight percent of patients ever exposed to pioglitazone were documented to have received their first prescription within 4 months of entry into the cohort. For this small group, we may have underestimated the cumulative duration of exposure. However, this would potentially overestimate the relative risk of short- and intermediate-term exposure if long-term use of pioglitazone is associated with an increased risk of bladder cancer. Thus, any misclassification from this left censoring is unlikely to have changed the results.

Although several studies have suggested an increased risk of bladder cancer among patients with diabetes irrespective of medication exposure (22), there are limited controlled data on the relative risk of bladder cancer among patients treated with pioglitazone. The PROactive study included 2,605 patients treated with pioglitazone and 2,633 treated with placebo, and there was a nonsignificant excess of bladder tumors among patients treated with pioglitazone (14 vs. 6) (15). In that study, average follow-up time was 34.5 months, yet much of the excess in bladder cancer incidence (eight pioglitazone versus three placebo) occurred in the first year of follow-up. After the first year, there were six cases of cancer in the pioglitazone arm versus three in the placebo arm. In 4 years of observational follow-up of the PROactive population after the end of the randomized phase of the study, the relative incidence of bladder cancer among the patients treated with pioglitazone during the initial clinical trial phase has not increased further. However, most subjects did not receive any TZDs during the observational follow-up period (I. Ahmad, personal communication). In our study, the HRs were 0.8 for

<1 year and 1.4 for both 1–2 years and >2 years of therapy. In a post hoc analysis, the HR was even higher for those with >36 months of exposure and >48 months of exposure, with a significant test for trend for increasing risk with increasing duration of exposure. Although these longer durations were not statistically significant in the fully adjusted models, this may have been due to low statistical power because the results were similar to the age- and sex-adjusted model. A recent observational cohort study using claims data did not observe an increased risk of bladder cancer with TZD exposure. However, that study was limited by a small number of bladder cancer cases and reliance on administrative data to establish the diagnosis of bladder cancer, did not distinguish between pioglitazone and rosiglitazone, and, perhaps most importantly, did not report data on duration of exposure (11).

It is possible that any increased risk of bladder cancer observed with pioglitazone could be attributed to other diabetes medications that reduce the risk of bladder cancer. Some research suggests that metformin use is associated with a reduced risk for various cancers (23,24); others have suggested that insulin use might increase the risk of cancer (24,25). However, we did not observe any association between ever use of other diabetes medications and bladder cancer risk. In addition, we could not compare pioglitazone with other TZDs because there had been little use of the latter in this cohort.

In summary, we did not observed a statistically significant increased risk of bladder cancer among patients treated with pioglitazone for <2 years. However, the analyses addressing increasing exposure to pioglitazone observed a weak increased risk with longer-term therapy. Additional follow-up is planned to explore this association. Regardless, it is reassuring that only 3 of the 90 patients diagnosed with bladder cancer and treated with pioglitazone were at advanced stage.

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J.D.L. and A.F. designed the study, interpreted data, and drafted and edited the manuscript. T.P. collected, analyzed, and interpreted data and edited the manuscript. M.H. collected, analyzed, and interpreted data; edited the manuscript; and provided administrative support. W.B.B., C.P.Q., and D.J.V. designed the study, interpreted data, and edited the manuscript. L.N. interpreted data, edited the manuscript, and provided administrative support. J.S. and B.L.S. designed the study, interpreted data, and edited the manuscript.

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