Original Investigation

Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes

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IMPORTANCE Studies suggest pioglitazone use may increase risk of cancers.

OBJECTIVE To examine whether pioglitazone use for diabetes is associated with risk of bladder and 10 additional cancers.

DESIGN, SETTING, AND PARTICIPANTS Cohort and nested case-control analyses among persons with diabetes. A bladder cancer cohort followed 193 099 persons aged 40 years or older in 1997-2002 until December 2012; 464 case patients and 464 matched controls were surveyed about additional confounders. A cohort analysis of 10 additional cancers included 236 507 persons aged 40 years or older in 1997-2005 and followed until June 2012. Cohorts were from Kaiser Permanente Northern California.

EXPOSURES Ever use, duration, cumulative dose, and time since initiation of pioglitazone as time dependent.

MAIN OUTCOMES AND MEASURES Incident cancer, including bladder, prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, pancreas, kidney/renal pelvis, rectum, and melanoma.

RESULTS Among 193 099 persons in the bladder cancer cohort, 34 181 (18%) received pioglitazone (median duration, 2.8 years; range, 0.2-13.2 years) and 1261 had incident bladder cancer. Crude incidences of bladder cancer in pioglitazone users and nonusers were 89.8 and 75.9 per 100 000 person-years, respectively. Ever use of pioglitazone was not associated with bladder cancer risk (adjusted hazard ratio [HR], 1.06; 95% CI, 0.89-1.26). Results were similar in case-control analyses (pioglitazone use: 19.6% among case patients and 17.5% among controls; adjusted odds ratio, 1.18; 95% CI, 0.78-1.80). In adjusted analyses, there was no association with 8 of the 10 additional cancers; ever use of pioglitazone was associated with increased risk of prostate cancer (HR, 1.13; 95% CI, 1.02-1.26) and pancreatic cancer (HR, 1.41; 95% CI, 1.16-1.71). Crude incidences of prostate and pancreatic cancer in pioglitazone users vs nonusers were 453.3 vs 449.3 and 81.1 vs 48.4 per 100 000 person-years, respectively. No clear patterns of risk for any cancer were observed for time since initiation, duration, or dose.

CONCLUSIONS AND RELEVANCE Pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded. The increased prostate and pancreatic cancer risks associated with ever use of pioglitazone merit further investigation to assess whether they are causal or are due to chance, residual confounding, or reverse causality.

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Thiazolidinedione agonists of peroxisome proliferators-activated receptors have been used to treat up to 26% of persons with diabetes mellitus.[1] Their history includes controversy in regard to safety. Marketing of troglitazone was discontinued because of hepatotoxicity,[2] and use of rosiglitazone was temporarily restricted because of concerns in regard to cardiovascular disease.[3,4] Pioglitazone is the only thiazolidinedione commonly used worldwide today.

Safety concerns with pioglitazone include a possible association with bladder cancer. A higher incidence of bladder cancer was observed in premarketing studies of pioglitazone in male rats, but not in female rats or mice of either sex.[5] Dual peroxisome proliferators-activated receptor-α and -γ agonists also caused bladder neoplasia in animal models.[6]

In 2003, the US Food and Drug Administration and the manufacturer agreed to this 10-year observational study to evaluate the potential risk of bladder cancer with pioglitazone use in humans. Shortly thereafter, the European Medicines Agency requested a second postmarketing investigation of pioglitazone use and risk of cancer at other sites.

A 5-year interim analysis showed no increased risk of bladder cancer overall. However, persons receiving more than 2 years of pioglitazone treatment had a small but statistically significant 1.4-fold elevated risk of bladder cancer (hazard ratio [HR], 1.4; 95% CI, 1.0-2.0),[7] a finding that was reproduced in most, but not all, other studies.[8] Subsequently, both the European Medicines Agency and Food and Drug Administration requested updates to the product safety information and allowed continued marketing of pioglitazone.[9]

Interim analyses of 10 other cancers (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, pancreas, kidney/renal pelvis, rectum, and melanoma) showed no statistically significant association between pioglitazone and any cancer, although there was a suggestion that ever use of pioglitazone was associated with an increased risk of melanoma and non-Hodgkin lymphoma and decreased risk of kidney/renal pelvis cancers.[10] However, there were relatively few cancers in pioglitazone-exposed persons, the maximum duration of follow-up after initiation of pioglitazone was fewer than 6 years, and the ability to examine cancer risk associated with 2 or more years of pioglitazone use or 2 or more years since initiation was limited.[6] As such, the European Medicines Agency requested that follow-up be extended. Here we report the results for the extended follow-up for both investigations.

Methods

The study methods were reported previously[7,10] and are further described in the eMethods in the Supplement. The study was conducted within Kaiser Permanente Northern California (KPNC), using electronic health records.[11] The source population was the KPNC diabetes registry, which identifies persons with type 1 and type 2 diabetes on the basis of hospital and physician diagnoses, prescription medications, and laboratory tests.[11] The protocols were approved by institutional review boards at the Kaiser Foundation Research Institute and the University of Pennsylvania. Persons were eligible for the cohorts if they met any of the following criteria: received a diagnosis of diabetes as of January 1, 1997, were aged 40 years or older, and were members of KPNC; had received a diagnosis of diabetes, were aged 40 years between January 1, 1997, and December 31, 2002, for the bladder cancer analyses or December 31, 2005, for the 10 cancer analyses and were KPNC members on their 40th birthday; or had diabetes and were aged 40 years or older when they joined KPNC between January 1, 1997, and December 31, 2002, for the bladder cancer analyses or June 30, 2005, for the 10 cancer analyses. Persons without prescription benefits on entry into the cohort or with a greater than 4-month gap in prescription or membership benefits starting within 4 months of entering the cohort were excluded.

Persons receiving a diagnosis of bladder cancer before cohort entry or within 6 months of joining KPNC were excluded from the bladder cancer cohort, and persons with a diagnosis of any cancer before cohort entry were excluded from the 10-cancer cohort.

Follow-up started when the inclusion criteria were first met and ended with the first of the following: gap of greater than 4 months in membership or prescription benefits, incident bladder cancer for the bladder cancer analyses or any cancer for the 10 cancer analyses, death, or December 31, 2012, for the bladder cancer analyses or June 30, 2012, for the 10-cancer analyses.

Ever use of pioglitazone and other diabetes medications was defined as having filled 2 prescriptions for the drug within a 6-month period. Once a patient met the exposure definition, he or she was considered exposed from that point forward.

Site-specific cancer diagnoses were identified from the KPNC cancer registry, which reports to the California Cancer Registry and the National Cancer Institute's Surveillance, Epidemiology and End Results program of registries. During implementation of the nested case-control study, bladder cancer case identification was supplemented through surveillance of new electronic pathology reports.

Potential confounders other than smoking were derived from electronic health records data recorded on or before the start of follow-up. In the bladder cancer cohort analyses, the following variables were treated as time-updating covariates: use of other diabetes medications, use of statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, or medications for benign prostatic hypertrophy, urinary incontinence, urinary tract infection or pyelonephritis, urolithiasis, other bladder conditions, prostate-specific antigen testing, hemoglobin A_{1c} concentration, and complications of diabetes. Data on smoking status and diabetes duration were derived by combining data from the electronic health record and surveys previously completed by 34% of the bladder cancer cohort. Smoking status and diabetes duration could be determined for 96% and 79% of persons, respectively. See the eMethods in the Supplement for additional details.

In 1994-1996, approximately 19% of the cohort was invited to participate in a postal survey that obtained detailed information on duration of diabetes, race/ethnicity, education, weekly alcohol intake, total cigarette packs smoked, and body mass index. In this subset, we examined whether any of these variables were confounders of the association between pioglitazone use and risk of the 10 cancers, and thus whether there could be residual confounding in the full cohort because of less detailed information in the electronic health record.

Bladder Cancer Nested Case-Control Analyses

Because the electronic health record data are incomplete for race/ethnicity, smoking history, diabetes duration, and occupational exposures, a survey of the bladder cancer cases and matched controls was conducted nested within the cohort. From the source cohort, all persons with an incident bladder cancer diagnosis from October 1, 2002, to March 23, 2012, were identified. The index date was the date of bladder cancer diagnosis.

For each bladder cancer case, one cohort member who was alive, under follow-up, and without bladder cancer at the case patient's diagnosis was randomly selected as a control after matching on sex, age (±2.5 years), and time from entry into the diabetes registry to index date (±6 months). When a control could not be reached for interview or refused to participate, additional controls were selected until a matched control could be enrolled (see the eMethods in the Supplement for details).

The case's index date served as the index date for its matched control. Additional information on diabetes duration, smoking history, occupational exposures, indwelling catheter use, and frequency of urinary tract infections was collected up to the index date through computer-assisted telephone interviews with a standardized questionnaire. For 46 case patients and 30 controls who were unable to complete the full interview, a shorter interview was completed by a proxy (see the eMethods in the Supplement for details).

Cigarette smoking was categorized according to total pack-years consumed before index date. Diabetes duration was categorized as less than or equal to 5 years, 6 to 10 years, more than 10 years, and unknown. Employment as a painter, driver, or hairdresser[12-14] was a composite dichotomous variable. Previous urinary tract infection was categorized as 0, 1 to 2, or greater than 2 previous infections.

Statistical Analyses

For the cohort analyses, Cox regression was used to calculate the adjusted relative hazard (HR) of bladder or other cancers associated with ever use of pioglitazone. The reference group for all analyses was never use of pioglitazone (time-varying), which included persons receiving no diabetes medications, with fewer than 2 pioglitazone prescription fills in a 6-month period, and with use of diabetes medications other than pioglitazone. Follow-up for ever use began with the second of 2 prescriptions defining ever use. Identical methods were used to calculate HRs associated with ever use of other categories of diabetes medications.

The most fully adjusted models for the bladder cancer analysis included the following covariates: age at cohort entry, sex, race/ethnicity, other diabetes medications, smoking, other bladder conditions, median household income, congestive heart failure, cancer other than bladder, renal insufficiency, hemoglobin A_{1c} concentration, the interaction of hemoglobin A_{1c} concentration with new diagnosis of diabetes, diabetes duration, year of cohort entry, and proteinuria testing[15] (see the eMethods in the Supplement for additional details). For analyses of the other 10 cancers, the models were similar but did not include proteinuria testing and other bladder conditions.

Time since initiation, dose, and duration were computed starting at the first of 2 prescriptions defining exposure. Sensitivity analyses were conducted by computing these same variables starting at the second prescription defining exposure. Variables were categorized into tertiles and treated as time-varying. Potential effect modification of the pioglitazone-bladder cancer association by sex or smoking history was examined by the addition of interaction terms in regression models.

Test for linear trends was included in all models to assess whether the risk of each cancer increased or decreased with increasing time since initiation, dose, and duration of pioglitazone use.

Post hoc analyses focusing on examinations of possible bias in the associations between pioglitazone use and risk of any of the cancers of interest are described in detail in the eMethods. Additional post hoc analyses to examine the potential for detection bias in the analyses of prostate cancer are also described in the eMethods.

Case-control analyses for bladder cancer were similar to the cohort analyses except that conditional logistic regression was used to calculate odds ratios (ORs). Confounders were defined as variables that changed the unadjusted OR for pioglitazone use by greater than or equal to 10%.

Analyses were conducted with SAS version 9.3, with 2-sided $P < .05$ defining statistical significance.

Results

Pioglitazone Use and the Risk of Bladder Cancer

The final cohort included 193 099 persons with diabetes, of whom 34 181 received pioglitazone during follow-up. The cohort included 59 070 persons who had received a new diagnosis of diabetes between January 1, 1997, and December 31, 2002. During 1 624 308 person-years of follow-up, 51 927 (26.9%) cohort members died of causes other than bladder cancer, 74 285 (38.5%) had a lapse in membership or drug benefits, 1261 (0.65%) received a diagnosis of bladder cancer, and 65 626 (34.0%) were without bladder cancer and were members of KPNC at the end of follow-up. The latter group included 55% of the pioglitazone-exposed persons and 29% of the persons never exposed to it.

Covariates other than female sex differed by pioglitazone use, but the magnitude of the differences was small for most variables (**Table 1**). Persons who ever used pioglita-

Table 1. Characteristics of the Bladder Cancer Cohort According to Pioglitazone Use at Any Time During Follow-up[a]

	Use of Pioglitazone, %	
	Ever (n = 34 181)	Never (n = 158 918)
Age at baseline, y		
40-49	29.2	22.1
50-59	33.0	25.6
60-69	25.7	26.2
≥70	12.0	26.1
Female sex	46.5	46.5
Race/ethnicity		
White	51.3	52.3
Black	10.2	10.8
Asian	14.8	12.8
Hispanic	13.4	10.6
Other	5.9	5.7
Missing data	4.3	7.8
Current smoker	20.4	17.4
Renal function at baseline, creatinine level		
Normal	77.4	77.1
Elevated[b]	4.0	8.7
Missing data	18.6	14.1
Congestive heart failure at baseline	3.0	6.9
Income		
Low[c]	47.8	50.6
High	42.8	40.5
Missing data	9.4	9.0
Baseline hemoglobin A_{1c}, %		
<7	17.1	28.6
7-7.9	18.3	19.3
8-8.9	12.8	10.4
9-9.9	9.7	7.0
≥10	23.9	17.1
Missing data	18.1	17.5
Diabetes diagnosed at start of follow-up[d]	50.8	57.9
Diabetes duration at baseline, y		
0-4	60.1	62.8
5-9	9.2	6.0
≥10	9.1	10.9
Missing data	21.6	20.4
Other cancer before baseline	3.1	5.3
Statin use	88.9	58.7
ACE inhibitors or ARB	92.3	69.6
BPH medications[e]	27.8[f]	19.9[f]
Urinary incontinence	7.4	5.4
Urinary tract infection/pyelonephritis	35.3	29.7
Urolithiasis	8.1	5.0
Other bladder conditions[g]	34.8	26.1
Prostate-specific antigen testing[f]	91.5	71.1
Proteinuria testing	97.7	77.6
Diabetes complications[h]	94.7	81.6
Diabetic retinopathy	52.9	32.5
Peripheral neuropathy[i]	75.0	54.9
Proteinuria[j]	77.1	59.8
Diabetic nephropathy[k]	26.6	21.2
Coronary artery disease	50.0	46.1
Ever use of pioglitazone but no other diabetes medications	5.2	0
Ever use of other diabetes medications[l]		
Other thiazolidinediones	8.2	1.5
Metformin	84.8	45.9
Sulfonylureas	89.8	61.2
Other oral hypoglycemic drugs	6.4	1.4
Insulin	52.7	29.4
None[m]	0	14.3
Time since starting pioglitazone, median (range), y[n]	6.1 (0.2-13.3)	
<4.5	34.5	
4.5-8.0	33.7	
>8	31.8	
Duration of therapy, median (range), y[n]	2.8 (0.2-13.2)	
<1.5	30.5	
1.5-4.0	33.6	
>4.0	35.8	
Cumulative dose, median (range), mg[n]	24 000 (450-156 000)	
1-14 000	34.2	
14 001-40 000	33.1	
>40 000	32.7	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

[a] All variables are at any time during follow-up except for some baseline variables noted. All comparisons $P < .01$ except female sex ($P = .99$).

[b] Creatinine level ≥1.4 mg/dL for women and ≥1.5 mg/dL for men.

[c] Low = median household income in census block below the cohort average ($59 000).

[d] Includes persons with newly diagnosed diabetes mellitus and those who newly enrolled in Kaiser Permanente with an existing diagnosis of diabetes.

[e] Medications to treat benign prostatic hypertrophy (BPH).

[f] Number and percentage among men.

[g] Other bladder conditions include hematuria, retention, urgency, neurogenic bladder, catheter, and other bladder/urethral symptoms.

[h] Diabetes complications include diabetic retinopathy, peripheral neuropathy, proteinuria, diabetic nephropathy, and coronary artery disease.

[i] Includes diabetic neuropathy, foot ulcer, or amputation.

[j] Includes microalbuminuria or macroalbuminuria.

[k] Creatinine level ≥2.0 mg/dL for both men and women.

[l] Includes use of any other diabetes medications during follow-up.

[m] Never received ≥2 prescriptions for a diabetes medication within a 6-month period.

[n] Reported as of the end of follow-up but were time updating in all analyses. All pioglitazone users contributed follow-up time to the lowest categories; those with cumulative exposure in the middle and highest categories contributed follow-up time to the middle category; only those with cumulative exposure in the highest category contributed follow-up time to the highest category.

zone were younger and more commonly had a baseline hemoglobin A_{1c} concentration greater than or equal to 10% and had been treated with metformin, sulfonylureas, and insulin (Table 1).

The median duration of follow-up was 7.2 years (range, 0.1-16.0 years) among persons who never received pioglitazone. Among those who received pioglitazone, the median duration of therapy was 2.8 years (range, 0.2-13.2 years) during a median follow-up of 6.1 years (range, 0.2-13.3 years). By the end of follow-up, 31.8% of persons who received pioglitazone had begun receiving it greater than 8 years earlier, 35.8% had greater than 4 years of use, and 32.7% had received greater than 40,000 mg.

The crude incidence of bladder cancer was 89.8 and 75.9 per 100 000 person-years in pioglitazone users and nonusers, respectively. Cancer stage did not differ between pioglitazone users and nonusers (eTable 1 in the Supplement; $P = .16$, excluding undetermined stage). In the most fully adjusted model, there was no association between ever use of pioglitazone and bladder cancer risk (HR, 1.06; 95% CI, 0.89-1.26) (**Table 2**). Similarly, ever use of other diabetes medications, such as metformin, sulfonylureas, insulin, and other thiazolidinediones (troglitazone and rosiglitazone), was not statistically significantly associated with bladder cancer risk in the most fully adjusted model, with HRs ranging from 0.91 to 1.09 (eTable 2 in the Supplement). None of the categories of time since initiation of pioglitazone, duration of therapy, or cumulative dose, or tests for linear trend across these categories, were statistically significantly associated with the risk of bladder cancer (Table 2). Crude incidence rates (per 100 000 person-years) and HRs for the highest categories were greater than 8 years since initiation, 125.8 (HR, 1.20; 95% CI, 0.83-1.75), greater than 4 years' duration, 113.7 (HR, 1.16; 95% CI, 0.87-1.54), and greater than 40 000 mg cumulative dose, 101.4 (HR, 1.07; 95% CI, 0.79-1.44). Tests for an interaction of pioglitazone with sex and with smoking were not statistically significant (eTable 3 in the Supplement).

Additional analyses were conducted to explore differences between the 5-year interim results[7] and the results with extended follow-up (eTables 4-8 in the Supplement). Analyses using the dose and duration categories from the interim report and finer gradation of long-term use produced results similar to those of the extended follow-up analyses (eTable 4 in the Supplement). The highest HR observed for duration of use was for a post hoc category of 4.1 to 6 years of use (HR, 1.29; 95% CI, 0.91-1.82), although this was not statistically significant, nor was use for greater than 2 years (HR, 1.09; 95% CI, 0.88-1.36). A post hoc category of cumulative dose between 28 000 and 40 000 mg reached statistical significance (HR, 1.53; 95% CI,

Table 2. Crude Incidence Rate and Hazard Ratios for the Association Between Pioglitazone Use and Risk of Bladder Cancer Among 193 099 Persons

	Pioglitazone											
	User		Years									
			Time Since Starting			Duration of Use			Cumulative Dose, mg			
	Never	Ever	<4.5	4.5-8.0	>8.0	<1.5	1.5-4.0	>4.0	1-14 000	14 001-40 000	>40 000	
Cases of bladder cancer	1075	186	88	65	33	60	69	57	66	69	51	
Person-years of follow-up time	1 417 196	207 112	129 017	58 247	26 234	88 839	78 059	50 145	95 534	71 198	50 310	
Bladder cancer incidence, per 100 000 person-years	75.9 (71.3-80.4)	89.8 (76.9-102.7)	68.2 (54.0-82.5)	111.6 (84.5-138.7)	125.8 (82.9-168.7)	67.5 (50.4-84.6)	88.4 (67.5-109.3)	113.7 (84.2-143.2)	69.1 (52.4-85.8)	96.9 (74.0-119.8)	101.4 (73.5-129.2)	
Hazard ratios (95% CI)												
Unadjusted	1 [Reference]	0.99 (0.84-1.16)	0.81 (0.65-1.01)	1.15 (0.89-1.49)	1.20 (0.84-1.73)	0.80 (0.61-1.04)	0.97 (0.76-1.24)	1.13 (0.86-1.49)	0.80 (0.63-1.03)	1.05 (0.82-1.35)	1.03 (0.77-1.37)	
Model 1[a]	1 [Reference]	1.09 (0.92-1.29)[b]	0.93 (0.75-1.17)	1.30 (1.00-1.68)	1.29 (0.90-1.86)	0.95 (0.73-1.24)	1.09 (0.85-1.40)	1.22 (0.92-1.61)	0.95 (0.74-1.22)	1.17 (0.91-1.50)	1.14 (0.85-1.52)	
Model 2[c]	1 [Reference]	1.09 (0.92-1.30)	0.94 (0.75-1.17)	1.30 (1.00-1.68)	1.29 (0.90-1.87)	0.95 (0.73-1.23)	1.09 (0.85-1.40)	1.23 (0.93-1.62)	0.95 (0.74-1.22)	1.17 (0.91-1.50)	1.14 (0.85-1.53)	
Model 3[d]	1 [Reference]	1.10 (0.92-1.31)	0.93 (0.74-1.17)	1.26 (0.97-1.65)	1.22 (0.84-1.78)	0.93 (0.71-1.22)	1.08 (0.83-1.39)	1.19 (0.89-1.58)	0.94 (0.73-1.22)	1.15 (0.89-1.49)	1.09 (0.81-1.47)	
Model 4[e]	1 [Reference]	1.06 (0.89-1.26)	0.89 (0.71-1.12)	1.21 (0.93-1.59)	1.20 (0.83-1.75)	0.88 (0.68-1.16)	1.03 (0.80-1.33)	1.16 (0.87-1.54)	0.90 (0.69-1.16)	1.10 (0.85-1.42)	1.07 (0.79-1.44)	

[a] Adjusted for age, sex, and year of cohort entry.

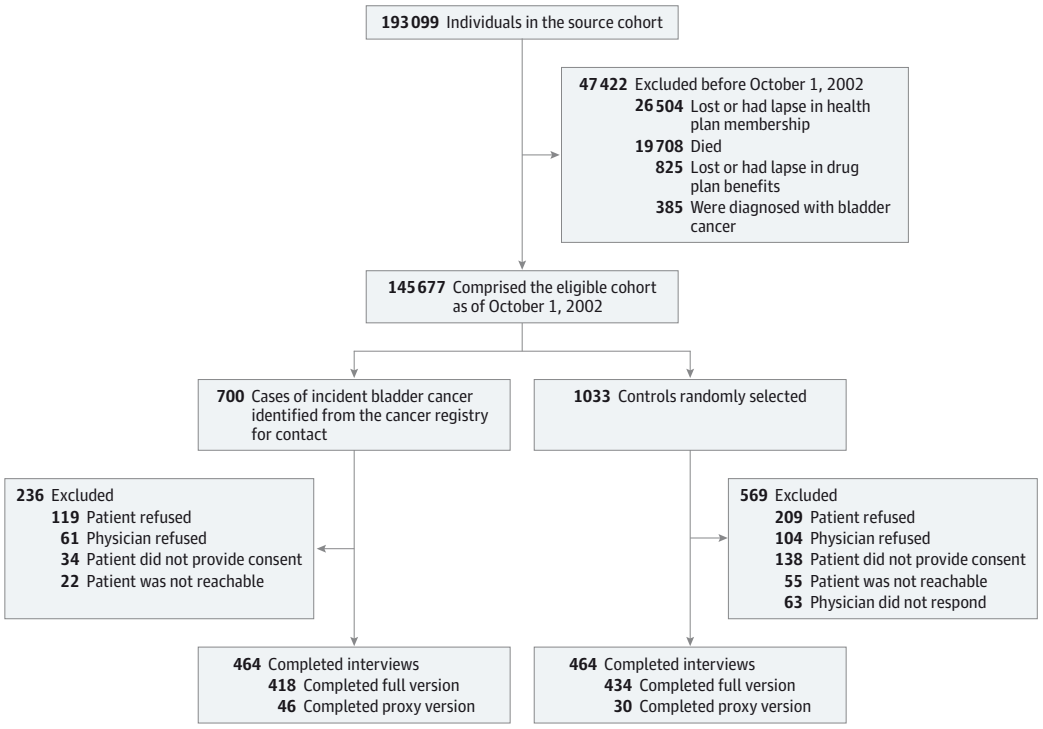
[b] Also adjusted for use of other diabetes medication.

[c] Adjusted for variables in model 1 and smoking.

[d] Adjusted for variables in model 2 and race/ethnicity, other diabetes medications, other bladder conditions, median household income, congestive heart failure, cancer other than bladder cancer, renal insufficiency, hemoglobin A_{1c} concentration and the interaction with new diagnosis of diabetes, and duration of diabetes.

[e] Adjusted for variables in model 3 and the 3-level time-updated proteinuria testing variable (no testing, negative and positive testing result for proteinuria), excluding same-day test for hematuria. Test for trend: time since initiation of therapy, $P = .32$; duration of therapy, $P = .51$; cumulative dose, $P = .64$.

Figure. Creation of the Study Population for the Nested Case-Control Study



1.07-2.18) but greater than 40,000 mg did not (HR, 1.07; 95% CI, 0.79-1.44) (eTable 4 in the Supplement). In the subset of persons receiving a new diagnosis of diabetes at cohort entry (n = 59 070), there was no evidence of increased risk of bladder cancer with short- or long-term pioglitazone use (eTable 5 in the Supplement). Analyses truncating follow-up when persons discontinued pioglitazone (eTable 6 in the Supplement), using finer age adjustment (eTable 7 in the Supplement), excluding the first 6 months after cohort entry, or using alternative methods to compute dose and duration (eTable 8 in the Supplement) produced results similar to those of the primary analyses.

Case-Control Analyses for Bladder Cancer

Between October 1, 2002, and March 23, 2012, there were 700 eligible persons from the source cohort with a new diagnosis of bladder cancer. Among case patients and controls who could be contacted and were deemed able to provide consent, participation rates were 80% and 69%, respectively (**Figure**). The proportion of nonparticipants with pioglitazone use before the index date was 16% for both case patients and controls, although the distribution was skewed toward pioglitazone use among refusers for the controls and toward nonparticipation for other reasons for the case patients (eTable 9 in the Supplement). Participants were slightly younger than nonparticipants. The case patients were more likely than controls to have a history of heavy smoking (23% vs 13%), to have occupations associated with bladder cancer (44% vs 34%), and to be non-Hispanic white (73% vs 58%) (**Table 3**).

In analyses accounting for matching variables only, the association between ever use of pioglitazone and bladder cancer was similar to that observed in the cohort analysis (OR, 1.14; 95% CI, 0.79-1.65) (**Table 4**). After adjusting for self-reported race/ethnicity, smoking history, occupations associated with bladder cancer, frequency of urinary tract infections, and hemoglobin A_{1c} levels, the OR was 1.18 (95% CI, 0.78-1.80). There were no clear patterns of increasing risk with increasing time since initiation, duration of use, or cumulative dose of pioglitazone. Unadjusted and adjusted ORs were generally similar, although for pioglitazone use of 1.5 to 4 years' duration, adjustment for the confounders met our definition of a greater than or equal to 10% change in the OR (unadjusted OR, 1.55; adjusted OR, 1.78). None of the categories of time since initiation, duration, or dose of pioglitazone exposure were statistically significantly associated with increased bladder cancer risk (Table 4).

Pioglitazone Use and the Risk of Cancer at 10 Sites Other Than the Bladder

Selected characteristics of the cohort of 236 507 persons are displayed in **Table 5**. By the end of follow-up, 16% (n = 38 190) had ever been treated with pioglitazone. The mean follow-up time for persons who ever received pioglitazone and persons who never received it was 5.4 years (range, 0.2-12.6 years) and 6.5 years (range, 0.2-15.3 years), respectively. There were 15 992 cohort members who received a diagnosis of an incident cancer at one or more of the 10 sites, ranging from 629 with rectal cancer to 3777 with

Table 3. Characteristics of Bladder Cancer Case Patients and Matched Controls

	No. (%)	
	Case Patients (n = 464)	Controls (n = 464)
Age at reference date, y		
40-59	18 (3.9)	19 (4.1)
60-69	118 (25.4)	126 (27.2)
70-79	210 (45.3)	210 (45.3)
≥80	118 (25.4)	109 (23.5)
Female sex	70 (15.1)	70 (15.1)
Time in registry, y		
0-5	127 (27.4)	122 (26.3)
6-10	165 (35.6)	172 (37.1)
>10	172 (37.1)	170 (36.6)
Race/ethnicity		
Non-Hispanic, white	340 (73.3)	270 (58.2)
Non-Hispanic, black, or African American	31 (6.7)	51 (11)
Hispanic	32 (6.9)	57 (12.3)
Asian or Pacific Islander	19 (4.1)	52 (11.2)
Other	40 (8.6)	30 (6.5)
Missing data	2 (0.4)	4 (0.9)
Cigarette smoking history, pack-year		
Never	155 (33.4)	200 (43.1)
≤20	87 (18.8)	111 (23.9)
21-40	93 (20)	66 (14.2)
>40	106 (22.8)	61 (13.1)
Missing data	23 (5)	26 (5.6)
Pipe or cigar smoker		
No	329 (70.9)	341 (73.5)
Yes	84 (18.1)	91 (19.6)
Missing data	51 (11)	32 (6.9)
Renal function		
Normal	384 (82.8)	368 (79.3)
Elevated creatinine[a]	23 (5)	28 (6)
Missing data	57 (12.3)	68 (14.7)
Urinary tract infections		
None	284 (61.2)	312 (67.2)
1-2	64 (13.8)	60 (12.9)
>3	43 (9.3)	41 (8.8)
Missing data	73 (15.7)	51 (11)
Urinary incontinence		
No	357 (76.9)	353 (76.1)
Yes	57 (12.3)	75 (16.2)
Missing data	50 (10.8)	36 (7.8)
Catheter use		
No	394 (84.9)	415 (89.4)
Yes	22 (4.7)	17 (3.7)
Missing data	48 (10.3)	32 (6.9)
Manufacturing industry	123 (26.5)	110 (23.7)
High-risk occupation[b]	204 (44)	157 (33.8)
Congestive heart failure	21 (4.5)	13 (2.8)
Annual household income, $		
<40 000	177 (38.1)	154 (33.2)
40 000-74 000	172 (37.1)	159 (34.3)
≥75 000	91 (19.6)	114 (24.6)
Missing data	24 (5.2)	37 (8)
Baseline hemoglobin A_{1c}, %		
<7	176 (37.9)	167 (36)
7-7.9	80 (17.2)	104 (22.4)
8-8.9	53 (11.4)	42 (9.1)
≥9	90 (19.4)	79 (17)
Missing data	65 (14)	72 (15.5)
Newly diagnosed diabetes at cohort entry	288 (62.1)	287 (61.9)
Diabetes duration, y		
0-5	95 (20.5)	92 (19.8)
6-10	103 (22.2)	118 (25.4)
>10	204 (44)	209 (45)
Missing data	62 (13.4)	45 (9.7)
Ever use of diabetes medications		
Pioglitazone	91 (19.6)	81 (17.5)
Other thiazolidinedione	14 (3)	10 (2.2)
Any thiazolidinedione	96 (20.7)	88 (19)
Metformin	258 (55.6)	252 (54.3)
Sulfonylureas	313 (67.5)	296 (63.8)
Insulin	107 (23.1)	123 (26.5)
Other oral hypoglycemic agent	11 (2.4)	9 (1.9)
Never received any diabetes drugs	71 (15.3)	66 (14.2)
None of the above	17 (3.7)	15 (3.2)
Time since starting pioglitazone, y		
Nonuser	373 (80.4)	383 (82.5)
<4.5	46 (9.9)	36 (7.8)
4.5-8.0	32 (6.9)	26 (5.6)
>8.0	13 (2.8)	19 (4.1)
Total duration of pioglitazone use, y		
None	373 (80.4)	383 (82.5)
<1.5	25 (5.4)	24 (5.2)
1.5-4.0	39 (8.4)	27 (5.8)
>4.0	27 (5.8)	30 (6.5)
Total dose of pioglitazone, mg		
None	373 (80.4)	383 (82.5)
<14 000	31 (6.7)	27 (5.8)
14 001-40 000	33 (7.1)	27 (5.8)
>40 000	27 (5.8)	27 (5.8)

[a] Creatinine level >1.4 mg/dL for women and >1.5 mg/dL for men.

[b] High-risk occupation includes painter, driver, or barber.

Table 4. Odds Ratios for the Association of Pioglitazone Treatment and Bladder Cancer in the Nested Case-Control Study (Kaiser Permanente Northern California Diabetes Registry)

	Cases (n = 464)	Controls (n = 464)	Odds Ratio (95% CI)	
			Unadjusted	Adjusted[a]
Never use of pioglitazone	373	383	1 [Reference]	1 [Reference]
Ever exposed	91	81	1.14 (0.79-1.65)	1.18 (0.78-1.80)
Time since starting pioglitazone, y				
<4.5	46	36	1.36 (0.84-2.21)	1.42 (0.80-2.52)
4.5-8.0	32	26	1.33 (0.75-2.36)	1.20 (0.62-2.32)
>8.0	13	19	0.65 (0.29-1.43)	0.70 (0.27-1.78)
Duration of therapy, y				
<1.5	25	24	1.10 (0.62-1.96)	1.16 (0.59-2.25)
1.5-4.0	39	27	1.55 (0.90-2.67)	1.78 (0.93-3.40)
>4.0	27	30	0.94 (0.54-1.64)	0.81 (0.42-1.55)
Cumulative dose, mg				
1-14 000	31	27	1.19 (0.70-2.03)	1.26 (0.69-2.33)
14 001-40 000	33	27	1.27 (0.75-2.15)	1.27 (0.68-2.36)
>40 000	27	27	1.06 (0.59-1.88)	0.98 (0.50-1.93)

[a] Adjusted for other diabetes medications, race, smoking history, high-risk occupations, urinary tract infections, and hemoglobin A_{1c} concentration.

prostate cancer. Crude cancer incidence rates are displayed in eTable 10 in the Supplement.

Adjusted HR estimates for the association between ever use of pioglitazone and each of the 10 cancers are presented in **Table 6**. Ever use of pioglitazone was associated with an increased risk of prostate cancer (HR, 1.13; 95% CI, 1.02-1.26) and an increased risk of pancreatic cancer (HR, 1.41; 95% CI, 1.16-1.71). Hazard ratios for the association of cancers other than prostate and pancreas with ever use of pioglitazone ranged from 0.81 to 1.15, with 95% CIs including 1.0.

Elevated HRs were observed for some categories of time since initiation, duration, or dose of pioglitazone at some cancer sites. However, no clear pattern of increasing or decreasing risk with increasing exposure emerged, and there was no evidence of linear trends for any cancer site, except for a decrease in the risk of pancreatic cancer with increasing time since initiation (Table 6).

eTable 11 in the Supplement shows the associations between ever use of other diabetes medication and risk of cancer at 10 sites. Ever use of insulin was associated with a decreased risk of prostate cancer (HR, 0.90; 95% CI, 0.81-0.99). Ever use of metformin (HR, 1.21; 95% CI, 1.02-1.43), insulin (HR, 2.34; 95% CI, 1.97-2.78), and sulfonylureas (HR, 1.49; 95% CI, 1.22-1.81) and never having 2 prescriptions of a diabetes medication from the same class within 6 months (HR, 1.55; 95% CI, 1.02-2.36) were each associated with increased risk of pancreatic cancer.

Several sensitivity analyses were conducted. To examine whether associations with pioglitazone were stronger if exposure was restricted to current use, follow-up was censored at discontinuation of pioglitazone; estimates were largely unchanged (eTable 12 in the Supplement). To assess whether the results might have been biased by incomplete assessment of pioglitazone exposure before KPNC membership, analyses were repeated among the persons with complete information on pioglitazone prescriptions. There were 196 401 patients who had been KPNC members before January 1, 1997 (ie, before the introduction of pioglitazone), or had greater than or equal to 2 years of KPNC membership before being identified by the Diabetes Registry (ie, with newly diagnosed diabetes). Estimates were largely unchanged, although the weak linear trends for increasing breast cancer risk with increasing pioglitazone cumulative dose and duration of use became statistically significant (eTable 13 in the Supplement). Subgroup analyses were conducted among the 48 425 persons with postal survey data on body mass index, education, weekly alcohol intake, and total packs smoked; results suggested little unmeasured confounding by these variables in the full cohort (eTable 14 in the Supplement). Sensitivity analyses in which cumulative dose and duration were computed from the first prescription instead of from the second one produced results similar to those from the primary analysis (eTable 15 in the Supplement). Results of analyses of prostate cancer risk adjusted for prostate-specific antigen testing were similar to those of the primary analysis, whereas adjusting for benign prostatic hypertrophy diagnosis and treatment produced slightly lower HRs that were not statistically significant (ever use of pioglitazone: HR, 1.08; 95% CI, 1.00-1.17) (eTable 16 in the Supplement). When starting follow-up at a first prostate-specific antigen test during the study period (among the 80 079 men with at least 1 test), use of pioglitazone was not associated with a statistically significant increased prostate cancer risk (HR, 1.08; 95% CI, 0.97-1.22).

Users of pioglitazone more commonly had local-stage prostate cancer and less commonly had local-stage pancreatic cancer. For pancreatic cancer, the proportion of local, regional, distant, or undetermined stages among persons who ever used vs never used pioglitazone was 5.5%, 26.2%, 60.4%, and 7.9% vs 11.6%, 21.6%, 57.3%, and 9.6%, respectively (P = .05, comparison of cancer stage by pioglitazone use after excluding the undetermined). For prostate cancer, the distributions were 89.3%, 4.8%, 4.2%, and 1.7% vs 82.3%, 7.2%, 6.2%, and 4.3%, respectively (use P = .03, comparison

Table 5. Characteristics of 236 507 Diabetic Persons Included in the 10-Cancer Cohort According to Pioglitazone Use at Any Time During Follow-up[a]

	Use of Pioglitazone, %	
	Ever (n = 38 190)[b]	Never (n = 198 317)[c]
Year of cohort entry		
1997	42.6	34.4
1998	7.0	6.4
1999	7.7	7.6
2000	7.8	7.6
2001	9.2	10.4
2002	8.9	9.5
2003	6.9	8.9
2004	6.4	9.4
2005	3.6	5.8
Total person-years in each age group[d]		
40-49	9.0	12.9
50-59	28.2	25.9
60-69	32.9	27.6
≥70	29.9	33.6
Female sex	46.2	46.7
Income		
Low[e]	53.4	54.0
High	44.8	43.6
Missing data	1.8	2.5
Race/ethnicity		
Non-Hispanic, white	49.0	50.2
Black	9.6	10.1
Asian or Pacific Islander	14.9	13.4
Hispanic	13.5	10.9
Other	5.6	5.3
Missing data	7.4	10.1
Current smoking	20.8	18.9
Renal function at baseline, creatinine level		
Normal	77.2	78.9
Elevated[f]	3.9	8.2
Missing data	18.9	12.9
Congestive heart failure at baseline	2.8	6.4
Baseline hemoglobin A_{1c}, %		
<7.0	17.9	32.2
7.0-7.9	17.3	17.4
8.0-8.9	11.8	9.1
9.0-9.9	9.0	6.2
≥10.0	22.0	15.0
Missing data	22.0	20.0
Newly diagnosed diabetes at start of follow-up[g]	57.8	66.8
Diabetes duration at baseline, y		
0-4	59.8	67.7
5-9	8.2	4.8
≥10	7.8	8.7
Missing data	24.1	18.8
Ever use of other diabetes medications[b]		
Other thiazolidinediones	7.4	1.3
Metformin	84.3	47.3
Sulfonylureas	87.8	55.3
Other oral agents	5.8	1.2
Insulin	47.6	24.2
Pioglitazone use during follow-up[h]		
Time since starting pioglitazone, y		
Median (range)	5.4 (0.2-12.6)	
<1	7.7	
1.0-1.9	9.6	
2.0-2.9	9.6	
3.0-3.9	9.6	
4.0-6.9	31.0	
≥7	32.5	
Duration of pioglitazone use, mo		
Median (range)	30.9 (2.0- 150.4)	
<12	21.3	
12-23	20.0	
24-35	14.5	
36-59	20.4	
≥60	23.9	
Cumulative dose of pioglitazone, mg		
Median (range)	22 500 (450-290 550)	
1-9000	25.2	
9001-25 000	28.5	
25 001-50 000	23.0	
>50 000	23.3	

[a] All variables are at any time during follow-up, except for some baseline variables noted.

[b] Filled at least 2 prescriptions within a 6-mo period.

[c] All comparisons between ever users and never users have $P < .05$, except for female sex ($P = .07$).

[d] With pioglitazone use treated as a time-varying variable.

[e] Low = median household income in census block below the cohort average ($59 000).

[f] Creatinine level ≥1.4 mg/dL for women and ≥1.5 mg/dL for men.

[g] Includes persons with newly diagnosed diabetes mellitus and those who newly enrolled in Kaiser Permanente with an existing diagnosis of diabetes.

[h] Time since starting pioglitazone, duration of use, and cumulative dose are reported as of the end of follow-up but were time updating in all analyses. All users of pioglitazone contributed follow-up time to the lowest categories; those with cumulative exposure in the middle and highest categories contributed follow-up time to the middle category; only participants with cumulative exposure in the highest category contribute follow-up time to the highest category.

(continued)

Table 6. Adjusted Hazard Ratios (95% CIs) for Ever Use of Pioglitazone, Time Since Initiation of Pioglitazone, Duration of Pioglitazone Use, and Dose of Pioglitazone Used and Risk of Cancer at 10 Sites

	Hazard Ratios (95% CI)[a]									
	Prostate	Female Breast	Lung/Bronchus	Colon	NHL	Corpus Uteri	Pancreas	Kidney/Renal Pelvis	Rectum	Melanoma
Persons with cancer, No.	3777	2797	2574	2074	955	916	811	795	627	694
Used pioglitazone, person-years, No.										
Never	734 668	687 798	1 448 685	1 437 413	1 448 431	646 149	1 337 529	1 448 616	1 437 440	1 448 633
Ever	105 006	96 005	204 551	203 004	204 542	88 745	202 326	204 523	203 012	204 544
Ever use of pioglitazone										
Never	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Ever	1.13 (1.02-1.26)	1.00 (0.88-1.13)	1.00 (0.87-1.15)	0.91 (0.78-1.05)	1.00 (0.81-1.23)	0.88 (0.71-1.09)	1.41 (1.16-1.71)	0.95 (0.76-1.18)	0.81 (0.60-1.08)	1.15 (0.91-1.46)
Time Since Initiation, mo										
Never used pioglitazone	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
<12	0.92 (0.73-1.17)	1.00 (0.76-1.31)	0.82 (0.59-1.14)	0.62 (0.41-0.92)	1.15 (0.75-1.76)	0.91 (0.58-1.43)	2.27 (1.61-3.20)	0.75 (0.43-1.30)	0.67 (0.34-1.29)	1.03 (0.60-1.76)
12-23	1.18 (0.94-1.47)	0.84 (0.62-1.14)	1.12 (0.84-1.50)	0.79 (0.55-1.14)	1.44 (0.97-2.14)	0.97 (0.62-1.53)	1.31 (0.85-2.01)	0.59 (0.32-1.11)	0.65 (0.32-1.31)	1.37 (0.85-2.21)
24-35	1.21 (0.96-1.52)	1.04 (0.77-1.39)	1.13 (0.84-1.53)	1.35 (1.00-1.81)	0.92 (0.56-1.53)	0.65 (0.37-1.16)	1.13 (0.71-1.82)	1.14 (0.71-1.83)	1.02 (0.56-1.86)	1.02 (0.57-1.83)
36-47	1.36 (1.07-1.71)	0.77 (0.54-1.10)	1.04 (0.75-1.45)	0.81 (0.55-1.19)	0.79 (0.44-1.40)	0.90 (0.54-1.52)	1.28 (0.80-2.04)	1.16 (0.71-1.90)	1.27 (0.71-2.27)	1.45 (0.87-2.40)
48-83	1.04 (0.86-1.26)	1.03 (0.83-1.28)	0.95 (0.74-1.20)	0.97 (0.76-1.24)	0.70 (0.46-1.06)	0.99 (0.70-1.41)	1.14 (0.82-1.60)	1.01 (0.71-1.44)	0.60 (0.33-1.08)	0.96 (0.62-1.47)
≥84	1.23 (0.95-1.59)	1.38 (1.06-1.80)	0.96 (0.70-1.31)	0.79 (0.56-1.12)	0.98 (0.61-1.56)	0.94 (0.59-1.51)	1.39 (0.93-2.07)	0.90 (0.55-1.50)	0.87 (0.42-1.81)	1.47 (0.91-2.36)
Test for trend, *P*	.58	.16	.85	.97	.24	.39	.03	.18	.81	.69
Duration of Use, mo										
Never used pioglitazone	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
<12	1.00 (0.84-1.19)	0.84 (0.69-1.03)	0.90 (0.73-1.12)	0.86 (0.68-1.08)	0.93 (0.66-1.29)	1.01 (0.75-1.35)	1.48 (1.12-1.95)	0.92 (0.65-1.30)	0.87 (0.57-1.33)	1.06 (0.73-1.54)
12-23	1.30 (1.08-1.57)	1.07 (0.84-1.35)	0.98 (0.75-0.96)	0.88 (0.66-1.18)	1.25 (0.87-1.80)	0.83 (0.55-1.25)	1.19 (0.82-1.73)	0.81 (0.52-1.27)	0.78 (0.45-1.37)	1.59 (1.08-2.33
24-35	1.07 (0.84-1.35)	1.01 (0.75-1.35)	0.96 (0.70-1.31)	1.03 (0.75-1.42)	1.08 (0.69-1.70)	0.97 (0.61-1.55)	1.03 (0.64-1.66)	0.96 (0.59-1.57)	0.80 (0.41-1.56)	1.06 (0.62-1.81)
36-59	1.18 (0.96-1.45)	1.06 (0.82-1.38)	1.06 (0.81-1.40)	0.66 (0.46-0.94)	0.72 (0.44-1.18)	0.78 (0.49-1.24)	1.63 (1.15-2.31)	0.99 (0.64-1.52)	0.58 (0.29-1.18)	0.80 (0.46-1.37)
≥60	1.16 (0.90-1.50)	1.25 (0.93-1.68)	1.12 (0.81-1.54)	1.05 (0.76-1.46)	0.89 (0.53-1.49)	0.73 (0.42-1.29)	1.53 (1.00-2.33)	1.03 (0.63-1.68)	0.89 (0.43-1.82)	1.46 (0.91-2.35)
Test for trend, *P*	.91	.14	.16	.59	.30	.39	.78	.60	.58	.90
Cumulative Dose, mg										
Never used pioglitazone	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-9000	1.08 (0.91-1.27)	0.89 (0.73-1.08)	0.98 (0.80-1.21)	0.87 (0.69-1.10)	0.92 (0.66-1.29)	1.02 (0.76-1.37)	1.50 (1.14-1.98)	0.83 (0.57-1.19)	0.84 (0.54-1.30)	1.20 (0.84-1.72)
9001-25 000	1.24 (1.06-1.46)	0.95 (0.77-1.17)	0.91 (0.73-1.15)	0.86 (0.68-1.10)	1.16 (0.85-1.59)	0.90 (0.64-1.25)	1.10 (0.79-1.53)	1.03 (0.73-1.44)	0.76 (0.47-1.23)	1.26 (0.88-1.81)
25 001-50 000	1.12 (0.92-1.37)	1.15 (0.91-1.46)	0.97 (0.75-1.26)	0.97 (0.74-1.27)	1.02 (0.69-1.51)	0.67 (0.42-1.06)	1.46 (1.04-2.06)	0.86 (0.56-1.32)	0.75 (0.42-1.34)	1.03 (0.66-1.62)
≥50 001	1.00 (0.78-1.28)	1.19 (0.89-1.57)	1.12 (0.84-1.50)	0.79 (0.56-1.12)	0.66 (0.38-1.13)	0.87 (0.54-1.42)	1.61 (1.10-2.35)	1.05 (0.67-1.64)	0.82 (0.41-1.61)	1.14 (0.70-1.85)
Test for trend, *P*	.12	.12	.48	.41	.22	.30	.59	.51	.73	.74

Abbreviation: NHL, non-Hodgkin lymphoma.

[a] Hazard ratios are adjusted for age, ever use of other diabetes medications, year of cohort entry, sex, race/ethnicity, income, current smoking, baseline hemoglobin A_{1c} concentration, new diabetes diagnosis, hemoglobin A_{1c} concentration and the interaction with new diagnosis of diabetes, diabetes duration, creatinine level, and congestive heart failure. Never use of pioglitazone is the reference group.

of cancer stage by pioglitazone after excluding the undetermined). Pioglitazone users less commonly had well or moderately differentiated prostate cancers (0.4% and 53.2%) compared with never users (1.6% and 58.2%; $P = .002$ after excluding the undetermined).

Discussion

These studies were conducted to address safety concerns related to the risk of cancer after treatment with pioglitazone. After extension of follow-up of the cohorts, no statistically significant associations were observed between ever use of pioglitazone and increased risk of bladder cancer or cancer at 8 of the other 10 sites of interest (female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, kidney/renal pelvis, rectal, and melanoma). However, ever use of pioglitazone was associated with an increase in the risk of prostate cancer and pancreatic cancer. Other diabetes medications were also associated with an increased risk of pancreatic cancer, suggesting reverse causality because an early manifestation of this cancer is hyperglycemia.[11] This interpretation is supported by the observation that the increased risk of pancreatic cancer was attenuated with increasing time since initiation. There was little evidence of increasing risk of other cancers with increasing time since initiation of pioglitazone. For all cancers, including bladder, there were no clear patterns of increasing risk with increasing duration or dose in the primary analysis. However, in a sensitivity analysis restricted to persons with complete information on pioglitazone use, statistically significant trends emerged in the associations of cumulative dose and duration with increased risk of female breast cancer.

Risk of Bladder Cancer

There has been controversy in regard to pioglitazone and the risk of bladder cancer.[16-19] Initially suggested in animal data, in 2005 the Proactive study provided the first signal in humans of a possible association between pioglitazone and bladder cancer.[20] Most other studies, including our own interim analysis, and meta-analyses of these studies have observed an increased risk of bladder cancer among persons treated with pioglitazone for greater than or equal to 2 years.[8] These studies led clinicians to question the role of pioglitazone for treatment of diabetes, led regulators to issue warnings in some countries and suspend marketing in others, and spurred litigation over presumed harm.[16-19] In the current analyses, with up to 16 years of follow-up, no statistically significant association was observed between bladder cancer risk and ever use of pioglitazone or increasing duration of therapy. This contrasts with our interim analysis,[7] which showed no association with ever use but an increased risk of bladder cancer with greater than or equal to 2 years of use.

Most cancers, including bladder cancer, are thought to develop during long periods. To our knowledge, until now, all studies examining the risk of bladder cancer among persons receiving pioglitazone have examined short-term exposures.[8,21] Although a duration-response relationship was observed in these earlier studies (ie, greater risk with ≥2 years of use), the magnitude of risk associated with longer-term therapy was unknown. New data from our extended follow-up, which included more than 12 000 persons with more than 4 years of pioglitazone use, did not show an increased risk of bladder cancer with any duration of pioglitazone use. Although this study cannot address risks associated with even longer latencies or durations of pioglitazone use, these data provide reassurance to patients, clinicians, and regulators.

A key question is why the extended follow-up results and interim results of the bladder cancer analyses differ. Because the methods were nearly identical, differences were not due to changes in methodology. The categories of dose and duration were updated in the final analyses to maintain balance in the size of the groups. However, results when the original categories were used were also not statistically significant. Although publicity surrounding this controversy could have changed physicians' prescribing and screening behavior, most users began receiving pioglitazone before publication of our first report, and our analyses were adjusted for key bladder cancer risk factors and proteinuria testing, which could act as a bladder cancer screening test in persons with diabetes.[15] Chance is an unlikely cause of the observed 40% increased risk of bladder cancer with greater than 2 years of pioglitazone exposure in the interim analysis[7] because these findings were repeatedly reproduced.[8] However, one cannot rule out temporal changes in an unmeasured confounder. Finally, according to the upper limit of the 95% CI of the 1.16 HR for greater than 4 years of pioglitazone use, this study cannot exclude up to a 54% increased risk of bladder cancer.

Risk of Cancer at Sites Other Than the Bladder

As in previous studies,[22-33] including interim analyses of this study, there was no statistically significant association between ever use of pioglitazone and an increased risk of cancer of the breast, lung/bronchus, endometrium, colon, rectum, or kidney/renal pelvis, or increased risk of non-Hodgkin lymphoma or melanoma. Our finding of modestly increasing breast cancer risk with increasing duration and dose in one sensitivity analysis has not been observed in previous studies and was not observed in our other sensitivity analyses.[34] To our knowledge, the only other report of increased prostate cancer risk with pioglitazone comes from the analysis of Proactive participants with extended follow-up (ie, mean follow-up 8.7 years after randomization); a statistically significant 65% increased risk of prostate cancer was observed for those in the pioglitazone arm.[22,34] Other studies have observed decreased risk of prostate cancer in pioglitazone users compared with insulin users.[35] To further evaluate the small (13%) increased risk of prostate cancer among persons treated with pioglitazone in the primary analysis of the current study, which may be due to chance, the stage and differentiation of the tumors were examined in a post hoc analysis. Persons treated with piogli-

tazone were slightly more likely to have local-stage disease, suggesting the possibility that differential screening for asymptomatic prostate cancer contributed to observed differences. Adjustment for prostate-specific antigen testing did not meaningfully alter the association. Adjusting for benign prostatic hypertrophy diagnosis and treatment attenuated the association of ever use of pioglitazone with prostate cancer, although some categories of duration and dose of use remained statistically significant. If pioglitazone use increases the risk of prostate cancer, particularly early-stage disease, it must be put into the context that prostate cancer is common but often not fatal, even without treatment.[36]

The study also provided estimates of the risk of cancer with ever use of other diabetes medications. Most diabetes medication-cancer associations were not statistically significant. However, the risk of lung cancer was increased among ever users of insulin and decreased among ever users of metformin.

The study has several important strengths beyond the long follow-up. The KPNC cancer registry is held to Surveillance, Epidemiology and End Results' high quality standards. Analyses of bladder cancer were adjusted for proteinuria screening.[15] Time-updating exposures were used to avoid immortal time bias.[37] Numerous sensitivity analyses were conducted, including truncating follow-up after discontinuation of pioglitazone and restricting to persons with newly diagnosed diabetes. Finally, the nested case-control analyses examined potential unmeasured confounding in the bladder cancer cohort, particularly by race/ethnicity, diabetes duration, smoking history, and occupational exposures, whereas the analyses among survey participants suggested little unmeasured confounding by diabetes duration, smoking and alcohol consumption, and body mass index in the full cohort. This study also has several potential limitations. As an observational study, there is the potential for unmeasured confounding; however, it would be infeasible to conduct a long-term and adequately powered randomized clinical trial to assess the risk of each cancer, given the extremely large sample size required. Even in our large cohorts there was limited statistical power for subgroup analyses related to time since initiation, dose, and duration. Similarly, statistical power was reduced in the subgroups with more complete data on potential confounders. An additional limitation includes the inability to exclude all persons with type 1 diabetes, but this was minimized by restricting to persons aged 40 years or older.

Conclusions

There was no statistically significant increased risk of bladder cancer associated with pioglitazone use. However, a small increased risk, as previously observed, could not be excluded. The increased prostate and pancreatic cancer risks associated with ever use of pioglitazone merit further investigation to assess whether the observed associations are causal or due to chance, residual confounding, or reverse causality.

ARTICLE INFORMATION

Author Contributions: Drs Habel and Ferrara had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lewis and Ferrara contributed equally to the conduct of the bladder cancer study. Dr Ferrara directed the study of other common cancers.

Study concept and design: Lewis, Habel, Quesenberry, Strom, Mamtani, Van Den Eeden, Ferrara.
Acquisition, analysis, or interpretation of data: Lewis, Habel, Quesenberry, Peng, Hedderson, Ehrlich, Mamtani, Bilker, Vaughn, Nessel, Van Den Eeden, Ferrara.
Drafting of the manuscript: Lewis, Habel, Quesenberry, Peng, Ferrara.
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Study supervision: Strom, Hedderson, Ferrara.

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