Cohort Study of Pioglitazone and Cancer Incidence in Patients With Diabetes

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OBJECTIVE—To explore whether treatment with pioglitazone was associated with risk of incident cancer at the 10 most common sites (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma [NHL], pancreas, kidney/renal pelvis, rectal, and melanoma).

RESEARCH DESIGN AND METHODS—A cohort study of 252,467 patients aged ≥40 years from the Kaiser Permanente Northern California Diabetes Registry was conducted. All prescriptions for diabetes medications were identified by pharmacy records. Cox proportional hazards models were used to examine the association between risk of incident cancer and ever use, duration, dose, and time since initiation of pioglitazone (modeled as time-dependent variables).

RESULTS—In models adjusted for age, sex, year of cohort entry, race/ethnicity, income, smoking, glycemic control, diabetes duration, creatinine levels, congestive heart failure, and use of other diabetes medications, the hazard ratio (HR) for each cancer associated with ever use of pioglitazone ranged from 0.7 to 1.3, with all 95% CIs including 1.0. There was a suggestion of an increased risk of melanoma (HR 1.3 [95% CI 0.9–2.0]) and NHL (1.3 [1.0–1.8]) and a decreased risk of kidney/renal pelvis cancers (0.7 [0.4–1.1]) associated with ever use of pioglitazone. These associations were unaltered with increasing dose, duration, or time since first use.

CONCLUSIONS—We found no clear evidence of an association between use of pioglitazone and risk of the incident cancers examined. Because the maximum duration of follow-up was fewer than 6 years after the initiation of pioglitazone, longer-term studies are needed.

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The thiazolidinediones (TZDs) bind to the γ subtype of peroxisome proliferator–activated receptors (PPARs). Pioglitazone (ACTOS) is a PPARγ ligand used in the treatment of type 2 diabetes. It is indicated as an adjunct to diet and exercise to improve glycemic control. It is generally not used as a first-line therapy (1).

PPARγ agonists have been shown to induce apoptosis in several malignant cell lines (2,3) and to inhibit the invasive activity of colon and breast cancers cells (4–7). In contrast, animal toxicity studies have suggested a possible increased cancer risk in multiple organs in association with a wide variety of PPARγ and dual PPARα/γ agonists (8). Recent findings suggest that synthetic PPARγ ligands may affect cell growth independent of the presence of PPARγ (9,10). Clinical trial and epidemiologic data on TZDs and cancer risk are limited and results from the few studies conducted to date have been conflicting (11–17).

Because of the concern of a possible association between pioglitazone and bladder cancer risk (15–17), the European Medicines Agency requested that Takeda, the manufacturer of pioglitazone, undertake an epidemiologic study of pioglitazone use and the risk of cancer at several sites. The authors of this article developed the study protocol, which was approved by the European Medicines Agency. Because we were already conducting a study of pioglitazone use and bladder cancer risk, the aim of this study was to explore whether pioglitazone treatment is associated with the risk of incident cancer at the 10 sites, excluding the bladder, with the highest incidence in the U.S.: prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma (NHL), pancreas, kidney/renal pelvis, rectal, and melanoma.

RESEARCH DESIGN AND METHODS—The source population was identified from the Kaiser Permanente Northern California (KPNC) Diabetes Registry (18,19), which identifies patients from four data sources: primary hospital discharge diagnoses of diabetes, two or more outpatient visit diagnoses of diabetes, any prescription for a diabetes-related medication, or any record of an abnormal HbA$_{1c}$ test (>6.7%).

Men and women with diabetes were eligible for the cohort if they met any of the following criteria: *1*) were in the KPNC Diabetes Registry, aged ≥40 years and members of KPNC as of 1 January 1997; *2*) were in the diabetes registry, reached age 40 years between 1 January 1997 and 30 June 2005, and were KPNC members on their 40th birthday; or *3*) joined KPNC after 1 January 1997 and were aged ≥40 years when they were identified by the diabetes registry between 1 January 1997 and 30 June 2005.

Individuals were excluded from the cohort if they *1*) were <40 years of age between 1 January 1997 and 30 June 2005; *2*) had no KPNC medication benefits at the time of cohort entry (baseline); *3*) had a gap in benefits or KPNC membership for ≥4 months that started in the 4 months following cohort entry; or *4*) had evidence in the registry of a cancer diagnosis prior to cohort entry.

Each patient's baseline was defined as the date of cohort entry (i.e., the first date that inclusion criteria were met). For all

outcomes except pancreatic cancer, follow-up started 6 months after cohort entry to allow sufficient time for patients to fill at least two prescriptions of diabetes medication. For pancreatic cancer, follow-up began 12 months after cohort entry to minimize an association between the initiation of diabetes medication and incident cancer that was due to prodromic hyperglycemia that often precedes the diagnosis of pancreatic cancer (20).

Follow-up ended at the first occurrence of one of the following events: *1*) a gap of ≥4 months in either membership or prescription benefits, *2*) a diagnosis of site specific cancer, *3*) death from any cause, or *4*) end of the study (31 December 2005).

We identified all prevalent and incident invasive cancers (for all sites) by linkage with the KPNC Cancer Registry. The KPNC Cancer Registry is a contributor to the Surveillance, Epidemiology, and End Results (SEER) program. All invasive cancers are staged according to SEER guidelines as local, regional, distant, or undetermined.

For all cohort members, we identified all prescriptions for diabetes medications from the pharmacy clinical database. Diabetes medications were categorized as pioglitazone, other TZDs (almost exclusively troglitazone), metformin, insulin, sulfonylureas, and other oral agents (e.g., miglitol, acarbose, nataglinide, repaglinide). Cohort members were categorized as "ever users" of pioglitazone when they had filled two prescriptions for pioglitazone in a 6-month period. Exposure to other diabetes medications was similarly classified. Separate variables were created to indicate never having received any prescriptions for diabetes medication and never having filled at least two prescriptions for the same medication within 6 months.

Time since the initiation of pioglitazone was calculated by counting the interval, in days, since the date of the second pioglitazone prescription. Cumulative duration of pioglitazone use was measured by counting the days supply for each prescription, starting with the first prescription. If the subsequent prescription was filled within 30 days of the expected end date for the previous prescription, we assumed that therapy was uninterrupted. If there were no refills within 30 days of 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

Table 1—Characteristics of 252,467 patients with diabetes by pioglitazone use: KPNC Diabetes Registry, 1997–2005

	Ever user of pioglitazone†	Never user of pioglitazone§
n	26,364	226,103
Total person-years in each age-group*		
40–49	7,733 (11.6%)	134,484 (14.4%)
50–59	19,588 (29.3%)	242,792 (26.0%)
60–69	21,029 (31.4%)	253,584 (27.2%)
≥70	18,533 (27.7%)	302,526 (32.4%)
Female	12,438 (47.2%)	105,165 (46.5%)
Income		
Low‡	14,100 (53.5%)	121,581 (53.8%)
High	11,821 (44.8%)	99,038 (43.8%)
Missing	443 (1.7%)	5,484 (2.4%)
Race/ethnicity		
Non-Hispanic white	12,628 (47.9%)	106,267 (47.0%))
African American	2,286 (8.7%)	21,086 (9.3%)
Asian or Pacific Islander	2,895 (11.0%)	26,018 (11.5%)
Hispanic	2,717 (10.3%)	19,304 (8.5%)
Other	1,479 (5.6%)	11,660 (5.1%)
Missing	4,359 (16.5%)	41,768 (18.5%)
Current smoking		
Yes	5,105 (19.4%)	41,197 (18.2%)
No	21,259 (80.6%)	178,245 (78.8%)
Missing	0 (0.0%)	6,661 (2.9%)
Renal function		
Normal creatinine	19,750 (74.9%)	178,677 (79.0%)
Elevated creatinine**	1,262 (4.8%)	19,109 (8.5%)
Missing	5,352 (20.3%)	28,317 (12.5%)
Congestive heart failure	970 (3.7%)	14,542 (6.4%)
Baseline HbA$_{1c}$ (%)		
<7.0%	4,184 (15.9%)	72,576 (32.1%)
7.0–7.9%	4,384 (16.6%)	39,661 (17.5%)
8.0–8.9%	3,273 (12.4%)	20,597 (9.1%)
9.0–9.9%	2,568 (9.7%)	14,068 (6.2%)
≥10.0%	5,928 (22.5%)	34,108 (15.1%)
Missing	6,027 (22.9%)	45,093 (19.9%)
Time since diabetes diagnosis (years)		
0–4	13,793 (52.3%)	154,915 (68.5%)
5–9	2,684 (10.2%)	10,980 (4.9%)
≥10	2,796 (10.6%)	19,311 (8.5%)
Missing	7,091 (26.9%)	40,897 (18.1%)
Other TZDs†	2,772 (10.5%)	2,803 (1.2%)
Metformin†	20,418 (77.5%)	89,384 (39.5%)
Sulfonylureas†	21,550 (81.7%)	111,725 (49.4%)
Other oral agents†	1,217 (4.6%)	2,003 (0.9%)
Insulin†	9,880 (37.5%)	41,631 (18.4%)
Estrogen† only***	2,478 (19.9%)	14,492 (13.8%)
Estrogen† plus progestin† ***	1,682 (13.5%)	7,729 (7.4%)
Pioglitazone use during follow-up		
Time since starting pioglitazone (months)		
Median (range)	28.8 months (2.4–74.4)	N/A
<12 months	6,698 (25.4%)	N/A
12–23 months	4,938 (18.7%)	N/A
24–35 months	4,391 (16.7%)	N/A
36–47 months	3,992 (15.1%)	N/A
48+ months	6,345 (24.1%)	N/A

Table 1—*Continued*

	Ever user of pioglitazone†	Never user of pioglitazone§
Duration of therapy (months)		
Median (range)	19.2 months (2.4–74.4)	N/A
<12 months	8,898 (33.8%)	N/A
12–23 months	6,782 (25.7%)	N/A
24–35 months	4,439 (16.8%)	N/A
36+ months	6,245 (23.7%)	N/A
Cumulative dose (mg)		
Median (range)	15,000 mg (450–90,000)	N/A
1–9,000 mg	9,167 (34.8%)	N/A
9,001–25,000 mg	8,899 (33.7%)	N/A
>25,000 mg	8,298 (31.5%)	N/A

Data are *n* (%) unless otherwise indicated. N/A, not applicable. †Filled at least two prescriptions within a 6-month period. *With pioglitazone use treated as a time-varying variable. **Creatinine ≥1.4 for women and ≥1.5 for men. ‡Low income defined as median household income in census block below the cohort average ($59,000). ***Data from 12,438 women treated with pioglitazone and 105,165 women never treated with pioglitazone. §All comparisons between ever user of pioglitazone and never user of pioglitazone have *P* values <0.05 except use of estrogen only (*P* = 0.06).

have ended. To calculate cumulative dose of pioglitazone, we used any prescription that was dispensed prior to an event date (including the first prescription) and 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. However, when a prescriptions' days supply extended beyond the date of an event, the total consumed dose was reduced to reflect the cumulative dose consumed by the event date.

Information on the confounders shown in Table 1 was obtained from electronic medical records. For smoking, the electronic medical record data were supplemented with data from a postal survey. With the exception of smoking, all confounders were measured using data recorded at or before baseline. In addition, approximately 19% of the cohort had been invited to participate in a postal survey conducted in 1994–1996, which obtained information on the following potential confounders: duration of diabetes, smoking, race/ethnicity, and BMI.

Cox proportional hazards regression models were used to provide point and interval estimates of the relative hazard of the 10 cancers associated with ever use of pioglitazone, time since first use, cumulative duration, and cumulative dose. In all regressions, these measures of pioglitazone exposure, along with measures of other diabetes medications and indicator variables for "never use of any diabetes medication" and "never filled two prescriptions of the same medication within 6 months," were treated as time-dependent covariates with time since cohort entry as the time scale. Specifically, all follow-up time from entry 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 he/she discontinued the medication. The reference group for calculation of the hazard ratios (HRs) 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.

Analyses of each cancer site were conducted with control for two sets of covariates. Model 1 included the pioglitazone exposure measure, age at cohort entry, use of other diabetes medications, and calendar year of entry into the cohort. Model 2 included all the Model 1 covariates along with sex, race/ethnicity, baseline HbA_{1c}, diabetes duration, renal function, and history of congestive heart failure. Results in Model 1 and Model 2 were very similar, and as such we report only the results from the fully adjusted models (Models 2). Among women, we ran additional models adjusting for hormone therapy, which was treated as time-varying. All covariates were categorized as shown in Table 1 and included a missing category.

The study was approved by the Kaiser Permanente and University of Pennsylvania Institutional Review Boards.

RESULTS—The characteristics of the study population, by pioglitazone use, are shown in Table 1. By the end of follow-up, 26,364 patients had been exposed to pioglitazone. The mean follow-up time for patients who ever used pioglitazone and patients who never used pioglitazone was 2.54 years (range 0.1–6.2) and 3.7 years (0.01–8.5), respectively. There were 9,082 cohort members diagnosed with an incident cancer at 1 or more of the 10 sites of interest, ranging from 373 patients diagnosed with melanoma to 2,105 with prostate cancer. Table 2 provides adjusted HR estimates for the association between ever use of pioglitazone and site-specific cancer risk. The HRs associated with ever use of pioglitazone ranged from 0.7 to 1.3, with all 95% CIs including 1.0. There was a suggestion of an increased risk of melanoma and NHL associated with ever use of pioglitazone (HR 1.3 [95% CI 0.9–2.0] and 1.3 [1.0–1.8], respectively), and a decreased risk of cancers of the kidney and renal pelvis (0.7 [0.4–1.1]). For melanoma, we observed a similar increase with the use of sulfonylureas (1.3 [0.9–1.8]). For NHL, we observed an increase with the use of other hypoglycemic medications, which included miglitol, acarbose, nataglinide, and repaglinide (1.7 [1.0–3.1]).

Ever use of sulfonylureas and ever use of insulin were associated with an increased risk of pancreatic cancer (HR 2.3 [95% CI 1.7–3.2] and 3.1 [2.4–4.0], respectively), whereas ever use of insulin was associated with a decreased risk of prostate cancer (0.8 [0.7–0.9]). Metformin was not associated with either a decrease or an increase in the risk of the cancers studied; only a small increased risk in pancreatic cancer was observed in association with ever use of metformin.

In general, we saw little evidence of linear trends for time since initiation, duration or dose of pioglitazone use, and risk of cancer at any site (Table 3). For cancer of the corpus uteri, we did see a statistically significant trend (*P* = 0.049) of increasing risk with increasing time since initiation of pioglitazone. For NHL, there was a statistically significant trend (*P* = 0.048) for dose (although the HR for the highest dose was lower than for the intermediate dose). For NHL, the HRs for pioglitazone use initiated 1–2 years prior, 1–2 years of cumulative pioglitazone use, and cumulative dose of pioglitazone of 9,001–25,000 mg were 1.8 (95% CI 1.1–2.9), 1.6 (1.0–2.7), and 1.8 (1.2–2.8), respectively. HRs for longer

Table 2—Adjusted HRs* (95% CI) for ever use of pioglitazone and risk of cancer of the prostate, female breast, lung/bronchus and colon, NHL, corpus uteri, pancreas, kidney/renal pelvis, and rectum and melanoma: KPNC Diabetes Registry, 1997–2005

	Prostate	Female breast	Lung/bronchus	Colon	NHL	Corpus uteri	Pancreas	Kidney/renal pelvis	Rectum	Melanoma
Persons with cancer (n)	2,105	1,561	1,637	1,260	569	552	431	430	390	373
Ever pioglitazone†	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.9 (0.7–1.1)	1.3 (1.0–1.8)	1.1 (0.8–1.5)	1.2 (0.8–1.7)	0.7 (0.4–1.1)	1.2 (0.8–1.8)	1.3 (0.9–2.0)
Ever other TZD	1.0 (0.7–1.3)	0.9 (0.7–1.2)	0.9 (0.6–1.3)	1.1 (0.8–1.5)	0.7 (0.4–1.2)	1.2 (0.8–1.9)	1.0 (0.6–1.8)	1.3 (0.7–2.3)	0.7 (0.4–1.5)	1.0 (0.5–1.8)
Ever metformin	1.0 (0.9–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	1.0 (0.8–1.2)	0.9 (0.8–1.2)	1.2 (1.0–1.5)	1.3 (1.0–1.6)	0.9 (0.7–1.2)	0.8 (0.6–1.1)
Ever insulin	0.8 (0.7–0.9)	1.0 (0.9–1.2)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	3.1 (2.4–4.0)	1.3 (0.9–1.7)	1.0 (0.7–1.4)	1.1 (0.8–1.5)
Ever sulfonylureas	1.0 (0.8–1.1)	1.0 (0.8–1.1)	1.2 (1.0–1.4)	1.0 (0.9–1.2)	1.1 (0.9–1.5)	1.1 (0.9–1.4)	2.3 (1.7–3.2)	1.1 (0.8–1.4)	1.2 (0.9–1.7)	1.3 (0.9–1.8)
Ever other OHA	1.2 (0.8–1.8)	0.7 (0.4–1.3)	0.9 (0.6–1.5)	1.0 (0.6–1.7)	1.7 (1.0–3.1)	1.0 (0.5–2.1)	1.2 (0.6–2.4)	0.6 (0.2–1.9)	0.5 (0.1–1.9)	0.9 (0.3–2.3)
Never diabetes drug prescription	0.8 (0.7–1.0)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.7–1.4)	0.8 (0.6–1.1)	0.9 (0.6–1.4)	1.2 (0.8–1.7)	0.9 (0.6–1.4)	1.1 (0.7–1.7)
Never two same drug prescriptions	1.2 (0.9–1.5)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	1.0 (0.7–1.4)	1.2 (0.7–1.9)	0.8 (0.5–1.4)	2.3 (1.4–4.0)	0.8 (0.4–1.5)	0.9 (0.5–1.6)	1.7 (1.0–2.9)

OHA, oral hypoglycemic agent. *HRs are adjusted for age, ever use of other diabetes medications, year of cohort entry, sex, race/ethnicity, income, current smoking, baseline HbA_{1c}, diabetes duration, new diabetes diagnosis, creatinine, and congestive heart failure. †Never use of pioglitazone as reference group. Identical method was used to determine the HR of other diabetes medications.

lengths of time since initiation, longer durations of use, and higher dose of pioglitazone were lower, but the number of exposed cases was also small. Compared with never users of pioglitazone, the risk of melanoma was approximately twofold higher among those who initiated pioglitazone therapy 1–2 years prior and among those whose duration of pioglitazone therapy was 1–2 years. HRs for longer times since initiation and duration were lower, although the numbers of exposed cases were small.

In order to assess whether our results were biased by incorrectly measuring time since first use, duration, and dose of pioglitazone use among patients who joined KPNC after pioglitazone was first available, analyses were repeated among 180,203 patients who had been KPNC members before 1 January 1997. Therefore, in this analysis only new users of pioglitazone were included in the exposed group. Similar results were observed in this subgroup and in the full cohort in relation to the association of time since first use, duration, and dose of pioglitazone with risk of cancer at each site (data not shown).

We further examine the associations between pioglitazone use and risk of melanoma, NHL, and kidney/renal pelvis cancers by assessing the stage of cancer at diagnosis. Specifically, the distribution of local, regional, distant, or undetermined stages at the diagnosis in patients who ever used pioglitazone and in patients who never used pioglitazone for melanoma was 86, 6, 8, and 0 vs. 85, 6, 5, and 3%, respectively (P = 0.67); for NHL the distribution was 28, 16, 54, and 2 vs. 33, 16, 48, and 3%, respectively (P = 0.88); and for kidney/renal pelvis cancers the distribution was 55, 18, 18, and 9 vs. 58, 19, 21, and 2%, respectively (P = 0.29).

Results were similar among the 117,603 women, both before and after adding use of hormone therapy to the fully adjusted model (data not shown).

Among the 52,331 patients for whom survey data were available on height and weight, diabetes duration, smoking history, and race/ethnicity, inclusion of BMI and other survey variables in the models did not appreciably alter point estimates for the association between ever use of pioglitazone and the risk of cancer (data not shown).

CONCLUSIONS—We found no suggestion of an association between the use

Table 3—Adjusted HRs* (95% CI) for time since initiation of pioglitazone, duration of pioglitazone use, and dose of pioglitazone used and risk of cancer at 10 sites: KPNC Diabetes Registry, 1997–2005

	Prostate	Female breast	Lung/bronchus	Colon	NHL	Corpus uteri	Pancreas	Kidney/renal pelvis	Rectum	Melanoma
Patients with cancer (n)	2,105	1,561	1,637	1,260	569	552	431	430	390	373
Time since initiation (months)										
Never used	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
12	0.9 (0.7–1.3)	1.1 (0.8–1.6)	1.0 (0.7–1.4)	0.5 (0.3–0.9)	1.3 (0.8–2.2)	1.0 (0.6–1.7)	0.8 (0.5–1.5)	0.7 (0.3–1.5)	0.7 (0.3–1.6)	1.1 (0.5–2.2)
12–23	0.8 (0.6–1.2)	0.7 (0.5–1.2)	1.0 (0.7–1.5)	1.0 (0.6–1.6)	1.8 (1.1–2.9)	1.5 (0.7–3.1)	1.0	0.4 (0.1–1.2)	1.4 (0.7–2.9)	2.0 (1.1–3.6)
24–35	1.2 (0.8–1.7)	1.0 (0.7–1.7)	1.2 (0.7–1.9)	1.2 (0.7–1.9)	1.3 (0.7–2.5)	0.9 (0.4–1.7)	0.5 (0.2–1.4)	1.0 (0.4–2.2)	1.5 (0.7–3.5)	1.7 (0.8–3.6)
36–47	1.1 (0.7–1.8)	0.8 (0.4–1.6)	1.3 (0.9–2.0)	1.2 (0.7–2.0)	0.8 (0.3–2.2)	0.6 (0.2–2.0)	0.6 (0.2–2.0)	0.7 (0.2–2.1)	1.6 (0.6–4.4)	1.5 (0.6–3.7)
48+	0.7 (0.4–1.5)	1.6 (1.0–2.8)	1.0 (0.5–1.9)	0.9 (0.4–1.8)	1.2 (0.4–3.4)	3.0 (1.6–5.8)	0.6 (0.2–2.3)	0.8 (0.3–2.7)	1.8 (0.5–6.0)	0.7 (0.2–3.0)
Test for trend	0.821	0.672	0.996	0.961	0.200	0.049	0.052	0.217	0.154	0.103
Duration of use (months)										
Never	1.0	1.0	1.0	1.0	1.0	1.0	0.9 (0.5–1.7)	1.0	1.0	1.0
<12	0.8 (0.6–1.1)	1.0 (0.7–1.3)	0.9 (0.6–1.2)	0.8 (0.6–1.2)	1.3 (0.8–1.9)	1.2 (0.8–1.8)	1.4 (0.7–2.8)	0.5 (0.2–1.0)	1.0 (0.4–2.2)	1.2 (0.7–2.2)
12–23	0.9 (0.6–1.3)	0.9 (0.6–1.4)	1.0 (0.7–1.5)	0.8 (0.5–1.3)	1.6 (1.0–2.7)	1.0 (0.5–1.8)	1.0	0.7 (0.3–1.6)	1.0 (0.4–2.2)	2.0 (1.1–3.6)
24–35	1.3 (0.9–1.8)	1.1 (0.6–1.8)	1.4 (0.9–2.1)	1.1 (0.6–1.8)	1.3 (0.7–2.7)	0.8 (0.3–1.9)	0.7 (0.2–2.1)	0.8 (0.3–2.1)	1.5 (0.6–3.7)	1.6 (0.7–3.6)
36+	1.3 (0.9–2.0)	1.2 (0.7–2.1)	0.8 (0.4–1.5)	0.8 (0.4–1.5)	1.1 (0.4–2.7)	1.6 (0.8–3.3)	0.6 (0.2–2.3)	1.1 (0.4–2.7)	0.8 (0.2–3.3)	0.9 (0.3–2.9)
Test for trend	0.465	0.833	0.884	0.351	0.126	0.523	0.137	0.314	0.786	0.094
Dose (mg)										
Never used	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1–9,000	0.9 (0.7–1.2)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.9 (0.6–1.3)	1.1 (0.7–1.7)	1.3 (0.9–1.9)	1.0 (0.6–1.8)	0.5 (0.2–1.0)	1.0 (0.5–1.8)	1.4 (0.9–2.4)
9,001–25,000	1.0 (0.7–1.3)	0.8 (0.6–1.2)	1.0 (0.7–1.4)	0.9 (0.6–1.3)	1.8 (1.2–2.8)	0.9 (0.5–1.6)	1.5 (0.8–2.9)	0.7 (0.3–1.4)	1.3 (0.7–2.5)	1.5 (0.9–2.7)
>25,000	1.1 (0.8–1.5)	1.4 (0.9–2.1)	1.0 (0.7–1.6)	0.8 (0.4–1.3)	1.2 (0.6–2.3)	1.2 (0.6–2.2)	1.0	0.9 (0.4–2.1)	1.4 (0.6–3.3)	1.3 (0.6–2.9)
Test for trend	0.964	0.795	0.909	0.195	0.047	0.710	0.341	0.211	0.433	0.076

*HRs are adjusted for age, ever use of other diabetes medications, and year of cohort entry. Never use of pioglitazone is reference group for all cancers except pancreatic cancer.

of pioglitazone and risk of incident cancer at 7 of the 10 sites. There was some suggestion that use of pioglitazone was associated with an increased risk of melanoma and NHL and a decreased risk of the kidney/renal pelvis cancers, but the sizes of the observed risk increases and decreases were small (30%) and the confidence intervals all included unity. In addition, the associations did not increase with extended duration of use, cumulative dose, or time since first use of pioglitazone, which makes a causal association less likely. However, our power was somewhat limited given the relatively small number of cases for NHL, kidney/renal pelvis cancers, and melanoma. Lastly, these possible associations need to be interpreted with caution given the large number of comparisons that were performed in this study.

Several limitations should be considered when interpreting our results. Pioglitazone was approved for use in the U.S. in 1999, so there were few prescriptions for this medication in our cohort prior to 2001. Therefore, we were only able to examine recently initiated therapy and short-term use (median 1.6 years) of pioglitazone, albeit with longer use and follow-up than in previously published studies (11–13). However, the latency period for many carcinogens is often many years or even decades. It is also possible that there is some residual confounding from some variables we have not measured, and we also lacked complete information on several potentially important confounders for the full cohort. However, in analyses restricted to individuals with information on race/ethnicity, BMI, and diabetes duration, we found little evidence of confounding by these factors. Finally, it is important to consider the possibility that any increased or decreased risk of cancer observed in association with pioglitazone use could in fact be due to other diabetes medications reducing or increasing the cancer risk. Some research has suggested that metformin use is associated with a reduced risk for various cancers (21), and others have suggested that insulin use might be associated with increased cancer risk (22). However, we did not observe any significant association between ever use of metformin or insulin and the risk of melanoma, NHL, and kidney/renal pelvis cancer.

There are several major strengths to be noted. First, enrollees of KPNC receive virtually all of their health care from this prepaid, integrated health plan. The

KPNC Cancer Registry is also well established and as a contributor to SEER, held to high standards of quality. This study is also strengthened by the availability of the KPNC pharmacy database. By requiring two prescriptions within a 6-month period, we have minimized misclassification of unexposed patients as exposed.

Previous observational studies (11–13,23) of TZD use among diabetic patients and cancer risk addressed only a small number of cancers and had several important limitations, including only very short-term exposure to pioglitazone, no analyses for dose or duration of pioglitazone use, and missing data on important confounders such as race/ethnicity and smoking. Previous studies have not identified signals of increased cancer incidence. In our study, we observed possible weak signals for NHL and melanoma, two cancers that were not examined in the prior studies. We did not confirm the decreased risk of lung cancer and colon or rectal cancer, as was suggested by Govindarajan et al. (12).

We found no clear evidence of an association between use of pioglitazone and risk of the incident cancer at the sites examined. This study of relatively short-term use could miss effects that require longer-term exposure or follow-up to become evident. Although the study was conducted in a large cohort of diabetic patients, we had relatively few pioglitazone-exposed cancer cases at most sites, limiting our precision, especially for risk estimates associated with duration, dose, and latency. Studies with longer follow-up are needed before any firm conclusions can be reached regarding pioglitazone and cancer risk. A longer follow-up study in this cohort is ongoing.

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