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Cohort Study of Pioglitazone and Cancer Incidence in Patients with Diabetes Mellitus, Follow-up 1997-2012

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Executive Summary - Study 1

Background

In addition to an ongoing study at Kaiser Permanente Northern California (KPNC) to examine whether the risk of bladder cancer in patients with diabetes is associated with pioglitazone use, in 2006 the EMEA requested an investigation of the potential association between use of pioglitazone and risk of several other malignancies. It was recognized from the onset, that this was a hypothesis generating study, not a hypothesis testing study.

Objectives

This study was designed to conduct exploratory analyses of the potential association between treatment with pioglitazone and risk of cancer at sites other than bladder.

Methods

Study population. The source population was identified from the Kaiser Diabetes Registry. Several data items from KPNC databases (including the membership database, medication benefit database, hospitalization and surgery procedures databases, cancer registry database) were merged with data in the Diabetes Registry in order to restrict the study population to individuals with diabetes who are eligible based on study inclusion (e.g. diabetes, 40 years of age or older) and exclusion (e.g. no medication benefits, history of cancer other than non-melanoma skin cancer prior to cohort entry) criteria.

Outcome identification. Among the eligible study population, we identified all incident cancers (for all sites) by linkage with the KPNC cancer registry. The KPNC cancer registry is a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program registry and KPNC registry's data are of comparable accuracy and completeness to that of SEER. We focused on the 10 cancers with the highest incidence rates reported in the general population as measured in the Northern California SEER registry database (prostate, breast, lung and bronchus, colon, non-Hodgkin's lymphoma, corpus uteri, pancreatic, kidney/renal pelvis, melanoma, and rectal).

Exposure assessment. For members of the cohort, we identified all prescriptions for diabetes medications from the date of entry into the cohort (January 1, 1997 at the earliest) to June 30, 2012 by linkage with the KPNC Pharmacy Information Management System. Eligible cohort members were categorized as "ever exposed" to pioglitazone at the time they received at least two prescriptions for pioglitazone within a 6-month period. We examined whether duration, dose, and time since initiation supported a potential causal association; for these analyses, cohort members were categorized as exposed to pioglitazone at the time of the first prescription.

Analysis. Cox regression modeling was used to provide point and interval estimates of the relative hazard of the 10 most common cancers associated with ever use of pioglitazone and time since first use, cumulative duration, and dose. In all regression analyses, these measures of exposure to pioglitazone were treated as time-dependent covariates. Follow-up began 6 months after cohort entry and time since entry into the cohort was the time scale.

Results

The eligible cohort included 236,507 men and women with diabetes aged 40 years and older. At the end of follow-up, there were 38,190 patients who were exposed to pioglitazone. Large numbers of patients developed one of the cancers of interest, ranging from 629 for rectal cancer to 3,783 for prostate cancer.

In models adjusted for age, year of cohort entry, use of other diabetes medications, sex, race, income, current smoking, baseline HbA1c, diabetes duration, new diabetes diagnosis, creatinine, and congestive heart failure, the HRs for risk of 8 of the 10 cancers associated with ever use of pioglitazone ranged from 0.81 to 1.15 and all 95% CIs included 1.0. Ever use of pioglitazone was associated with a small increase in the risk of prostate cancer [HR=1.13 (95% CI 1.02-1.26)], however, no clear pattern was observed with increasing time since initiation, duration or dose of pioglitazone. There was possibility of an increased risk of pancreatic cancer associated with ever use of pioglitazone [HR= 1.41 (95% CI 1.16-1.71)], although no consistent trend of increasing risk was observed with increasing duration of use, cumulative dose or time since first use of

pioglitazone. The association with increased risk of pancreatic cancer was the strongest in the first year of pioglitazone therapy and an increased risk of pancreatic cancer was also observed for ever use of other medications used to treat hyperglycemia (i.e. metformin, insulin and sulfonylureas), suggesting reverse causality. For the other 8 cancers, there was also no consistent trend of increased risk associated with increasing duration of use, cumulative dose or time since first use of pioglitazone.

Discussion

In this hypothesis generating study we found no evidence of an association between use of pioglitazone and risk of cancer. As in previous reports, a different pattern was observed for pancreatic cancer, likely in part due to diabetes being an early symptom of this disease. In addition, the association did not increase further with extended duration of use of this drug, cumulative dose, or with time since first use.

There are several limitations that should be considered when interpreting our results. Pioglitazone was only approved for use in the US in 1999 and there were few prescriptions for this medication among our cohort prior to 2000. We therefore were only able to examine the association between relatively recent and intermediate-term use (median 5.4 years) of pioglitazone and cancer risk, albeit with longer use and follow-up than in the previously published studies. The latency period for many carcinogens is often many years or even decades. Thus, this study of intermediate-term use could miss effects that require longer term exposure or follow-up in order to become evident. While the study was conducted in a large cohort of diabetics, we had relatively few pioglitazone-exposed cancer cases at some sites, limiting our precision, especially for risk estimates associated with duration, dose, and latency. Given the above limitations, particularly our inability to examine longer-term use only, additional follow-up of this cohort would allow for the examination of longer-term use and latency.

Executive Summary - Study 2

Background
When the study of pioglitazone therapy and risk of the 10 most common cancers was extended in 2008, a second study of diabetes and cancer risk was requested by the sponsor.

Objectives
This companion study was designed to: 1) estimate the rates of the 10 most common cancers among KPNC members with and without diabetes and 2) estimate the relative risk of each of 10 most common cancers associated with recognized diabetes.

Methods
Members of the KPNC with and without diabetes who were age 40 or older between January 1, 1997 and June 30, 2011 and had no prior diagnosis of any cancers (except non-melanoma skin cancer) were included in analyses. Members with diabetes were identified by the Kaiser Diabetes Registry and members without diabetes were identified by the KPNC membership database (i.e. those who were not included in the Kaiser Diabetes Registry). Data on age and sex were obtained from the electronic databases.

A similar analysis was conducted among members with recognized diabetes who completed the Kaiser Diabetes Registry Survey in 1994-1996 and among a random sample of KPNC members who completed a similar survey, the Member Health Survey, in 1996, 1999, 2002 and 2005 who did not have recognized diabetes. Survey responders had additional information on potential confounders, such as age, smoking, alcohol consumption, education, race/ethnicity, and BMI.

Among the eligible study population, we identified all incident cancers (prostate, breast, lung and bronchus, colon, non-Hodgkin's lymphoma, corpus uteri, pancreatic, kidney/renal pelvis, melanoma, and rectal) by linkage with the KPNC cancer registry.

Analysis. For each cancer site, age- and sex-specific incidence rates and interval estimates were calculated, stratified by diabetes status, using the direct method with the 2000 U.S. Census as the standard. Cox proportional hazards regression modeling was used to provide point and interval estimates of the relative hazard of the 10 most common cancers associated with diabetes (time-varying), with control for available potential confounders. Cox regression techniques were similarly used to estimate the association between diabetes and cancer risk among the cohort of survey responders, with adjustment for additional potential confounders.

Results
At baseline, there were 156,174 persons identified by the Kaiser Diabetes Registry who had recognized diabetes and 2,474,492 persons identified in the KPNC membership file who did not have recognized diabetes. By the end of follow-up, there were 332,017 members with diabetes and 2,298,649 members without diabetes. For the analysis of survey responders, there were 62,053 KPNC members in the diabetes group and 54,551 in the non-diabetic comparison group.

In the full membership, standardized cancer rates were higher among those with diabetes for six cancer sites (colon, uterine, kidney/renal pelvis, NHL, pancreas, rectal), cancer rates were lower among those with diabetes for two sites (prostate, melanoma), and similar among those with and without diabetes for two sites (breast, lung). Standardized rates were generally similar in the survey responders. In the full membership, the age- and sex-adjusted HRs suggested an increased risk of cancer at some sites (colon, corpus uteri, pancreas, kidney/renal pelvis, and rectal) and a decreased risk at other sites (prostate and melanoma); similar age- and sex-adjusted HR estimates were obtained in the cohort of survey responders. In analyses conducted among the survey responders, there was evidence of a modest amount of positive confounding by BMI for uterine cancer and for kidney cancer.

Discussion

A diagnosis of diabetes appears to be associated with an increased risk of several common cancers and a decreased risk of a smaller number of others. For most cancer sites, this association does not appear to be confounded by race/ethnicity, smoking, BMI, education, or alcohol consumption.

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of transcription factors whose activities are regulated by high affinity binding of small lipophilic ligands such as steroid hormones (1). A class of diabetic drugs, the thiazolidinediones (TZDs), has been developed to bind to the γ subtype of the PPARs. These medications have proved to be a valuable new therapy for type 2 diabetes mellitus. Three TZDs have been approved for marketing within the United States; two, Actos (pioglitazone) and Avandia (rosiglitazone), are currently available, albeit use of rosiglitazone is now severely restricted. Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control. It is generally not used as a first line therapy (2).

PPARγ agonists have been shown to induce apoptosis in several malignant cell lines (3,4) and to inhibit colon and breast cancers' cells invasive activity, as well as liver metastasis, in animal and in vitro studies. 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 (5). Evidence suggests that synthetic PPARγ ligands may affect cell growth independent of the presence of PPARγ (6,7). A recent meta-analysis of pioglitazone use and cancer risk in patients with type 2 diabetes (8) reported no association between ever use of pioglitazone and colorectal cancer (pooled RR= 0.97, 95% CI 0.90-1.04), lung cancer (pooled RR= 0.95, 95% CI 0.88-1.02), breast cancer (pooled RR= 0.93, 95% CI 0.85-1.01), prostate cancer (pooled RR= 1.00, 95% CI 0.82-1.22), or renal cancer (pooled RR= 0.89, 95% CI 0.76-1.04), but concluded that further evaluation was needed, as few studies have been conducted to date.

Bladder Cancer Study

Based on preclinical data provided to us by Takeda Pharmaceuticals North America (TPNA), the question arose as to whether pioglitazone use could be associated with *bladder cancer* risk. As a result, we are currently conducting a study among members of the Kaiser Permanente of Northern California (KPNC) Diabetes Registry to test the hypothesis that the risk of bladder cancer in patients with diabetes who receive pioglitazone differs from that of patients who do not receive pioglitazone, after adjustment for potentially confounding variables. The study was approved by the United States Food and Drug Administration (FDA) in 2004 and also reviewed and approved by the European Medicines Agency (EMA) in 2004. The investigation has two components: a cohort study using data from KPNC electronic records and a nested case-control study that involves the primary collection of additional data on confounding variables. A 5-year interim analysis showed only a modest increase [HR= 1.4 (95% CI 1.03-2.0)] in the risk of bladder cancer associated with use of pioglitazone for 24 months or more (9). A subsequent 8-year interim analysis observed a weaker association between 48 months or more of pioglitazone exposure and bladder cancer risk that did not reach statistical significance [HR= 1.30 (95% CI 0.91-1.86)]. A final analysis is currently under way.

Study of Multiple Cancers (other than Bladder)

In 2006, the European Medicines Agency (EMA) requested an investigation of the potential association between use of pioglitazone and risk of several other malignancies. Subsequently, another study was designed to examine the potential association between treatment with pioglitazone and risk of cancer at sites other than bladder using information available from a variety of KPNC electronic data sources, including the diabetes registry, the cancer registry, the pharmacy database and a variety of other laboratory and clinical databases. The study was approved by the European Medicines Agency (EMA).

Incident cancers were identified in a cohort of 252,467 male and female members of Kaiser Permanente of Northern California (KPNC) who had diabetes and were aged 40 years and older from January 1 1997 to December 31, 2005 (see results in the attached paper published in Diabetes Care). Briefly, at the end of follow-up, there were 26,364 patients who were exposed to pioglitazone. There were a total of 9,082 patients diagnosed with at least one of the 10 most common cancers (lung, colon, rectal, breast, prostate, pancreatic, melanoma, renal, corpus uteri and non-Hodgkin's lymphoma), ranging from a low of 373 cases of melanoma to a high of 2,105 cases of prostate cancer.

In Cox regression 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% confidence intervals including 1.0. There was a suggestion of an increased risk of melanoma [HR= 1.3 (95% CI 0.9-2.0)] and non-Hodgkin lymphoma (NHL) [HR= 1.3 (95% CI 1.0-1.8)] and a decreased risk of kidney/renal pelvis cancers [HR= 0.7 (95% CI 0.4-1.1)] associated with ever use of pioglitazone. For each of the 10 common cancer sites, there was little evidence of increasing risk with increasing dose, duration, or time since first use of pioglitazone.

There were 25 other types of cancer diagnosed in at least 1 patient exposed to pioglitazone. HRs for these other cancer types ranged from 0.4 to 4.0; there were 12 cancers with HRs that were above 1.0, 9 cancers with HRs below 1.0, and 3 cancers with HR =1.0. All 95% CI for these HRs included 1.0, and the HRs were therefore within the limits of chance. In addition, there were seven cancer sites for which there were no exposed cases.

After reviewing and discussing these results at an in-person meeting on January 28, 2008, the Advisory Board provided recommendations about the possible need for further research to the Principal Investigators and Sponsor. Specifically, the Advisory Board (Drs. Barrett-Connor, Herring, McDonald, Suissa, and Weiss) noted that the limitations of the study related almost entirely to the recent introduction of pioglitazone into medical practice. As a result, there were relatively few persons in the study population who had developed cancer. The ability to examine cancer risk associated with more than 24 months of pioglitazone use, or more than 24 months since initiation, was particularly limited. The Advisory Board also noted that these limitations could be addressed by enlarging the study, recommending that in 3-6 years, it would be reasonable to redo the primary analyses to include additional incident cancers that occurred in members of the original cohort after December 31, 2005. The Advisory Board did not recommend evaluation of the less frequent cancers at a later time.

Extension and expansion of study of pioglitazone and multiple cancers (other than bladder)

Study 1. In 2008 we received EMA approval of our protocol describing the **continuation of our initial study of the association of pioglitazone therapy with risk of the 10 most common cancers** in the United States. The study population and methods for this continuation are similar to the original, but with follow-up through June 30, 2012 (original ended December 31, 2005).

Study 2. This protocol also included a second study **of diabetes and cancer risk**. The aims of this second study are to: 1) estimate rates of the 10 most common cancers among KPNC members with and without diabetes, and 2) estimate the relative risks of each of 10 most common cancers associated with a diagnosis of diabetes.

In this final report, we present results with follow-up from 1997 through 2012 for study 1, and results with follow-up from 1997 to 2011 for study 2 (complete Diabetes Registry data available only through 2011).

The extension and expansion of the multi-cancer study continues to be a collaboration between Investigators at the Division of Research of Kaiser Permanente and Investigators at the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine. All members of our original Advisory Board (Drs. Barrett-Connor, Herring, McDonald, Suissa, and Weiss) agreed to stay on for the extension and provide input for this report.

STUDY 1: COHORT STUDY OF PIOGLITAZONE AND CANCER INCIDENCE IN PATIENTS WITH DIABETES MELLITUS

1.A. BACKGROUND AND SPECIFIC AIMS

In our previous analyses (10), as well as the other observational studies and randomized trials (8,11-15) of TZD use and cancer risk, the most important limitation was the very short-term exposure to pioglitazone. Studies of relatively short-term use could miss effects that require longer-term exposure or follow-up to become evident. While our initial study was conducted in a large cohort of patients with diabetes, follow-up was from January 1, 1997 to December 31, 2005 and we had relatively few pioglitazone-exposed cancer cases at most sites, limiting our precision, especially for risk estimates associated with certain categories of duration, dose, and latency.

In this final report, we provide results of analyses on the association between treatment with pioglitazone and risk of incident cancer at the 10 most common sites except bladder (prostate, female breast, lung/bronchus, corpus uteri, colon, non-Hodgkin lymphoma [NHL], pancreas, kidney/renal pelvis, rectal, and melanoma) in a cohort of patients with recognized diabetes that was followed from January 1, 1997 to June 30, 2012. The mean follow-up for the cohort has increased from the 4 years available for the initial analyses (10) to 6 years for the interim report to 7.3 years for this final report.

1. B. METHODS

a. Study population and data sources

The extension was conducted in the same population as the initial study. The source population was identified from the KPNC Diabetes Registry, which was first constructed in 1993 and has been updated annually since then. The registry identifies patients primarily from four data sources: primary hospital discharge diagnoses of diabetes mellitus (since 1971); two or more outpatient visit diagnoses of diabetes (since 1995); any prescription for a diabetes-related medication (since 1994); or any record of an abnormal HbA1c test (>6.7%) (since 1991).

A number of additional variables were obtained from a variety of Kaiser databases, including membership, medication benefit, hospitalizations, and surgical procedures, and cancer, in order to restrict the study population to individuals with diabetes who are eligible for this study based on inclusion and exclusion criteria that were described in the original proposal. These criteria are listed below (see Figure 1 below).

b. Cohort Inclusion Criteria

Men and women with diabetes were eligible for the study cohort if they met any of the following criteria:

1) they had been in the KPNC diabetes registry (DM registry), were aged 40 years or older, and were members of KPNC as of January 1, 1997, or
2) they had been in the DM registry, reached aged 40 years between January 1, 1997 and June 30, 2005, and were KPNC members on their 40th birthday, or
3) they joined KPNC after January 1, 1997 and were aged 40 years or older when they were identified by the DM registry between January 1, 1997 and June 30, 2005. (This group includes both patients who joined KPNC and already had a diagnosis of DM, and patients who had a diagnosis of DM after joining KPNC.)

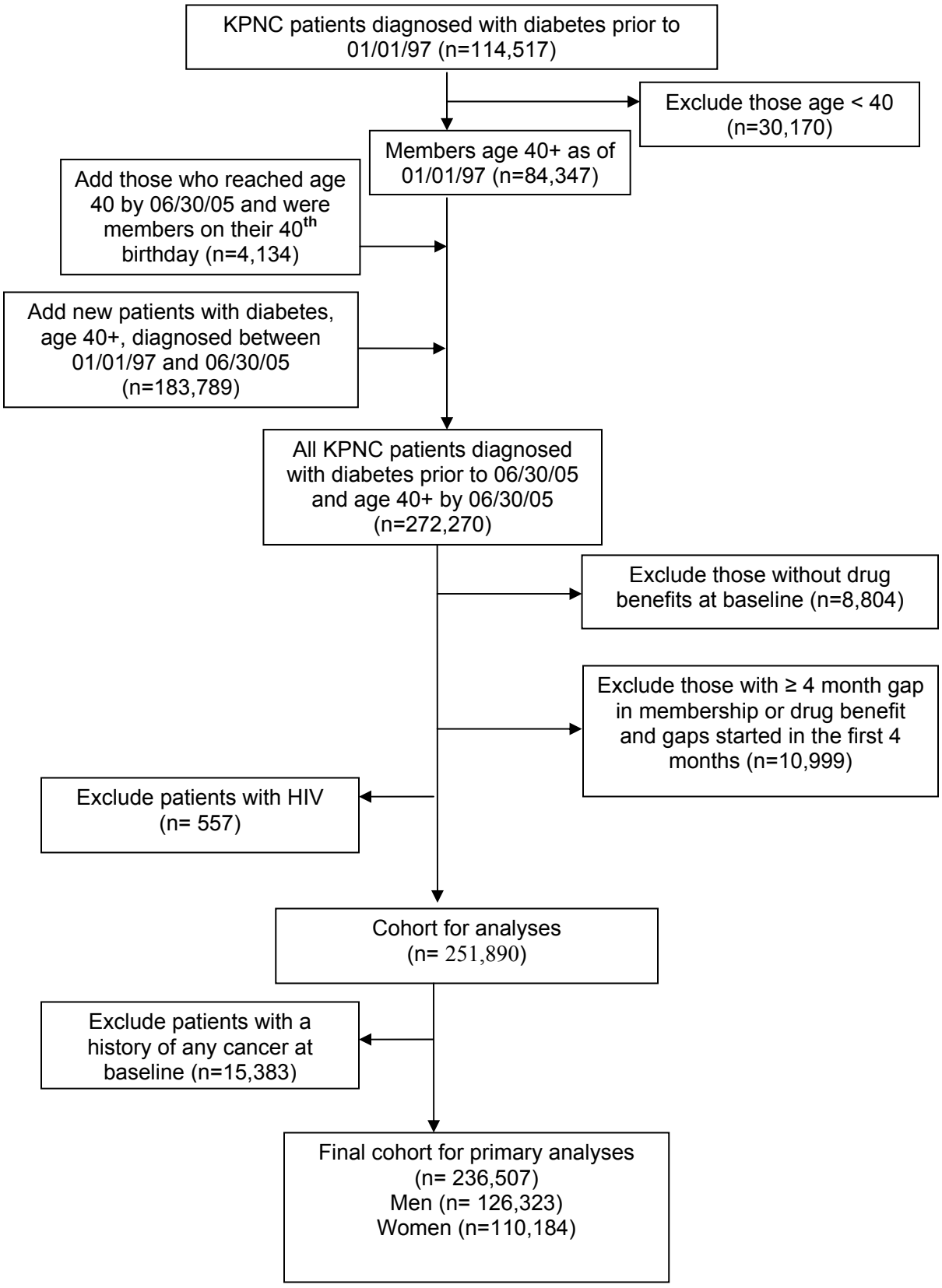
c. Cohort Exclusion Criteria

Individuals were excluded from the cohort for the following:

1. Age < 40 years as of June 30, 2005. The lower age limit of 40 years helps to exclude patients with type 1 diabetes who are much less likely to be treated with TZDs. Moreover, cancer is rare prior to age 40. For each of the cancers of interest, fewer than 5% occur in those aged < 40 years
2. No KPNC medication benefits at the time of entry into the cohort (baseline) or gap in medication benefit ≥4 months that started in the first 4 months after entering in the cohort. Patients without KPNC medication benefits may have filled prescriptions outside the Kaiser pharmacies and therefore their complete medication use may not be captured by KPNC's pharmacy database. This would lead to possible misclassification of the exposure of interest. Only 5% of KPNC members do not have medication benefits; therefore the exclusion of these people does not materially impact our study power (n=8,804).
3. Gap in KPNC membership ≥ 4 months that started in the first 4 months after entering in the cohort (n=10,999).
4. Patient with a diagnosis of HIV (n= 577).
5. For some cancer sites, selected surgeries. Women with evidence of a hysterectomy prior to baseline were excluded from the analysis of pioglitazone and cancer of the corpus uteri, and men with evidence of a complete prostatectomy prior to baseline were excluded from the analysis of pioglitazone and prostate cancer. Men and women with evidence of complete or subtotal surgical removal of the colon were excluded from the analysis of pioglitazone and colon or rectal cancer.
6. History of cancer other than non-melanoma skin cancer at prior to entering the cohort (n= 15,383).

The final cohort that resulted from application of these inclusion and exclusion criteria is depicted in Figure 1.01.

Figure 1.01 Study population inclusion and exclusion criteria common to all analyses; Northern California Kaiser Permanente Diabetes registry 1997-2012.



d. Baseline and follow-up time and their data sources

The eligible study population included **236,507 persons with recognized diabetes and without a history of any cancer at baseline**. Baseline was defined as the date of entry into the cohort (i.e. the first date that the inclusion criteria were met: on January 1, 1997, or a subsequent date when they had diabetes and turned 40 years of age or were first identified as having diabetes and were already 40 years of age or older).

Follow-up started at 6 months (T_0) after entry into the cohort, regardless of length of membership in the health plan.

Follow-up ended at the earliest of the following events: 1) a gap of 4 months or greater in either membership or prescription benefits, 2) a new diagnosis of any invasive cancer, 3) death from any cause, or 4) end of the study (June 30, 2012).

e. Outcomes and their data sources

Among the eligible study population, we identified all those with a history of cancer prior to baseline and all those with incident cancer after baseline through June 30, 2012 (all sites) by linkage with the KPNC cancer registry.

The KPNC cancer registry is a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program registry and KPNC registry's data are of comparable accuracy and completeness to that of SEER. All medical facilities in California are required by law to report all newly diagnosed cases of cancer to the California Cancer Registry (CCR), through a network of 10 regional registries that together capture the cancer incidence experience of the entire state. All registries follow SEER practices in verifying and coding incident cancers. SEER requirements include categorization of histopathology, invasiveness, tumor size, extension, and lymph node involvement. All cancers are staged according to SEER guidelines as local, regional, distant, or undetermined.

f. Diabetes medications and exposure definitions

For each member of the cohort, we identified all prescriptions for diabetes medications from the date of entry into the cohort through June 30, 2012 by linkage with the KPNC Pharmacy Information Management System (PIMS). Records in PIMS include the patient member number, the drug name and strength, treatment regimen, date dispensed, and days' supply.

Diabetes medications were categorized as pioglitazone, other TZDs (almost exclusively troglitazone, as rosiglitazone was not part of the KPNC pharmacy formulary), metformin, insulin, sulfonylureas, and other oral agents (e.g., miglitol, acarbose, nataglinide, repaglinide, GLP-1 agonists, DPP4 inhibitors). Assessment of exposure to diabetes medications started at entry into the cohort (baseline).

The primary exposure of interest in this study was treatment with pioglitazone. Eligible cohort members were categorized as "ever exposed" to pioglitazone at the time they received at least two prescriptions for pioglitazone within a 6-month period. Requiring the second prescription helps to exclude the small fraction of patients who may fill a prescription but never actually take the medication. Filling two prescriptions within a reasonably brief period (6 months) seems, almost certainly, to be an indication that the medication is being used. Exposure to each of the other diabetes medications was classified in a similar fashion. Eligible cohort members were categorized as "ever exposed" to another diabetes medication at the time they received at least two prescriptions for that medication within a 6-month period.

In addition, indicator variables were created separately for patients who had not received any diabetes medication prescriptions and for those who did not fill at least two prescriptions for the same medication within a 6-month period. Each of these was considered as a separate variable.

Exposure to each DM medication, and indicator variables for "never use of any DM medication" and 'never filled two prescriptions of the same medication within 6 months' were all treated as time-varying variables. There were 33,525 (14.2%) patients who never had any DM medication prescriptions during the study period and 9,667 (4.1%) patients who never had two or more prescriptions for the same DM medication within a 6 month period.

Our secondary definitions of exposure to pioglitazone were defined according to time since first use, duration, and dose. **All measures (except never use) of exposure to pioglitazone defined below were applied only to those meeting the definition of ever use.**

Time since initiation of pioglitazone was calculated by counting the interval in days since the date of the first pioglitazone prescription among patients who ever used pioglitazone. Time since initiation was categorized as never user, <12 months, 12-23 months, 24-35 months, 36-47 months, 48-83 months, and 84 or more months.

Cumulative duration of pioglitazone use was measured by counting the days' supply for each prescription, starting with first prescription. 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. Cumulative duration of use was categorized as never user, <12 months, 12-23 months, 24-35 months, 36-59 months, and 60 or more months of use.

Cumulative dose of pioglitazone was calculated in a similar fashion, starting from the first prescription. For any prescription that was dispensed prior to an event date (including the first prescription), 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 except when a prescription's days' supply extended beyond the date of an event. In this instance, the total consumed dose was reduced to reflect the cumulative dose consumed on the date of the event. Cumulative dose was categorized as never user, 1-9,000 mg, 9,001-25,000 mg, 25,001-50,000 mg, and 50,001 or more mg.

g. Potential confounders and their data sources

KPNC Electronic Databases
Information on several potential confounders was obtained from electronic databases as shown in **Table 1**.

We considered potential confounders to be those variables associated or potentially associated with the risk of cancer (e.g., age, sex, smoking history, socioeconomic status), and variables that could also be associated with the likelihood of being prescribed pioglitazone (e.g., diabetes duration, HbA1c level, congestive heart failure, renal insufficiency, and use of other diabetes medications). Several of these latter variables also may be confounders for cancer sites for which diabetes or severity of diabetes is a risk factor (e.g., prostate).

Age at baseline was calculated from the birth date available in the KPNC membership file. Sex was also obtained from the membership file. Race-ethnicity was obtained from several databases and was categorized as follows: non-Hispanic white (reference), African American, Asian/Pacific Islanders, Hispanic, other and missing.

Median annual household income in the census block group of residence was used as a measure of socioeconomic status. We dichotomized this measure as high or low, based on whether the census block group median annual household income was above or below the average census block median income for the cohort ($59,000).

Glycemic control at baseline was defined according to HbA1c levels measured prior to or within one month of the baseline date. If more than one test was performed, the test closest to the baseline date was selected.

Renal insufficiency at baseline was determined on the basis of measured creatinine concentrations prior to or within one month after the baseline date. If more than one test was performed, the test closest to the baseline date was selected. We elected to use the sex-specific threshold levels suggested as contraindication to metformin therapy to define renal insufficiency (≥1.5 mg/dL in males and ≥1.4 mg/dL in females).

Congestive heart failure at baseline was considered present if patients had a diagnosis in the inpatient or outpatient electronic medical record any time prior to the baseline date.

Smoking status was categorized as current or not current. Data on smoking have been recorded in the electronic databases since the middle of 1998. For patients who entered the cohort prior to this time, electronic smoking data are incomplete. To account for this, we also used data on smoking from a patient survey that was completed during the years 1994 to 1996 by members of the diabetes registry (see below). Thus, patients were categorized as smokers if they were identified as current smokers in the electronic database or by the survey. For 19,652 people, we classified current smoking status by using electronic or survey data. For the remaining 216,855 people, 25,678 people were categorized as current smokers during the follow-up using electronic data. Smoking status was not treated as time-varying, but was fixed throughout the follow-up period.

Table 1.01. Potential confounders available from electronic data sources

Variable	Operational definition	Data source
Age at baseline and sex	Age (5-year intervals), sex (male, female)	Membership file
Race/ethnicity*	White, Asian, African American, Hispanic, Other and missing	Several survey databases, inpatient and cancer registry databases
Socioeconomic status at baseline	Low income defined as median household income in census block below the cohort average ($59,000)	From 2000 U.S. Census block group SES data.
Glycemic control as measured by HbA1c* at baseline	categorized as HbA1c <7.0, 7.0-7.9, 8.0-8.9, 9.0-9.9, ≥10%, and missing	Laboratory files
Duration of diabetes at baseline*	categorized as 0-4 yrs, 5-9 yrs, 10+ yrs and missing	For those who responded to the survey in 1994-1996 and those who were identified by the DM registry after 1 year of being enrolled in KPNC
Renal insufficiency at baseline*	Creatinine ≥1.4 for women, ≥1.5 for men, and missing	Laboratory files
Congestive heart failure at baseline*	Presence of diagnosis (yes/no)	From outpatient and inpatient diagnostic data
Current Smoking status	Yes, no and missing anytime during the follow-up	Available as “current” smoker in outpatient diagnostic database, and for those who responded to the 1995-1996 survey available as current, past, never and cigarette/day
Other DM medications	Ever use (2 prescription within 6 months) of other TZD, metformin, insulin, sulfonylureas, or other oral agents. Each treated as time varying variable	Pharmacy database:

* Incompletely recorded in electronic data; used to the extent available

Diabetes Registry Survey

Between 1994 and 1996, a 4-page survey was mailed to all health plan members with recognized diabetes who were age 18 years and older and were current KPNC members. The principal aim of the survey was to obtain information on race/ethnicity, duration of diabetes, body mass index (BMI), education, alcohol intake, and smoking. Using this source, we obtained diabetes duration at the baseline (or date of entry in the cohort) for 43,865 people. For the remaining 192,642 people we attempted to calculate diabetes duration at baseline using the date of entry in the diabetes registry. We were successful for 146,174 diabetes registry members who had been in the health plan for at least one year prior to the date of entry in the diabetes registry. For the remaining 46,468 people who had been in the health plan for less than one year before the date of entry in the diabetes registry, we were unable to assess diabetes duration and these patients were considered to have missing data on diabetes duration. This classification of diabetes duration was used for adjustment in analyses conducted among the full cohort.

Among survey responders, BMI, as calculated from weight and height self-reported on the diabetes registry survey, was categorized as <20 kg/m^2, 20-24 kg/m^2 (reference), 25-29 kg/m^2, 30-34 kg/m^2, and ≥35 kg/m^2. Alcohol intake was categorized as: 0 drinks per week (reference), <7 drinks per week, ≥7 drinks per week, and missing. Smoking was categorized as 0 total packs smoked (reference), 1-5,000 total packs smoked, ≥5,001 total packs smoked and missing.

h. Statistical analysis

Cox proportional hazards regression modeling was used to provide point and interval estimates of the relative hazard of the 10 most common cancers associated with ever use of pioglitazone and time since first use, cumulative duration, and dose. In all regression analyses, these measures of exposure to pioglitazone were treated as time-dependent covariates and time since entry into the cohort was the time scale.

Point and interval estimates of hazard ratios for each cancer site of interest associated with each measure of pioglitazone use were obtained with control for two different sets of covariates as specified below. Categorical variables were treated as such in all regression models (i.e., as a set of indicator variables).

Adjusted Models included the pioglitazone exposure measure, age at cohort entry (categorized in 5-yr age groups), use of other diabetes medications (ever vs. never, time dependent), year of entry into the cohort (categorized as calendar year), sex, race/ethnicity, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine, and history of congestive heart failure (yes vs. no). We also included interaction terms between categories of baseline HbA1c level and "newly captured in DM registry at cohort entry" (e.g., captured 30 days or less prior to baseline). We added this interaction term because we previously observed that HbA1c values were higher among newly identified diabetic patients (these include newly diagnosed diabetic patients as well as previously diagnosed patients who were newly enrolled in the Kaiser Permanente Northern California health plan). [Note: Similarly adjusted models were presented as 'Model 2' in the 2011 interim report.]

Subgroup and sensitivity analyses

All sensitivity and sub-analyses are based on the cohort included in the primary analyses (e.g., without a history of any cancer at baseline and with censoring at the diagnosis of any invasive cancer).

The following subgroup analyses were conducted:

1) Restricted to KPNC members with complete information on pioglitazone prescriptions (i.e. those who entered the cohort in January 1, 1997 or were captured by the Diabetes Registry after January 1, 1997 but had ≥2 years of KPNC membership prior to being identified by the Registry), n= 196,401.

2) Restricted to KPNC members with complete information on all diabetes prescriptions (i.e. diagnosed with diabetes after January 1, 1997 and ≥2 years of KPNC membership prior to being identified by the Diabetes Registry), n= 120,255.
3) Restricted to KPNC members for whom diabetes duration is known (i.e. survey responders and those with ≥2 years of KPNC membership prior to being identified by the Diabetes Registry), n= 182,661.
4) Restricted to KPNC members for whom BMI is known (i.e. survey responders), n= 48,425.

1. C. RESULTS

Characteristics of study population, by pioglitazone use (Table 1.02)

Compared to never users, the proportion of persons aged 60 to 69 years was greater among ever users of pioglitazone (**Table 1.02**). Patients treated with pioglitazone were less likely to have elevated creatinine levels and to have congestive heart failure at the time of entry into the cohort. Compared to patients who never used pioglitazone, patients who ever used pioglitazone less frequently had a baseline HbA1c lower than 7% and more frequently had a baseline HbA1c greater than 10%. Approximately 60% of the ever users of pioglitazone and approximately 68% of the never users of pioglitazone were diagnosed with diabetes for less than 5 years before the start of follow-up. As expected, pioglitazone treated patients were commonly treated with metformin, sulfonylureas, and insulin prior to, following, and/or simultaneous with pioglitazone. The distributions of sex, race-ethnicity, and current smoking were similar among ever users and never users of pioglitazone.

Exposure to pioglitazone (Tables 1.03-1.04)

There were few cohort members with a first prescription of pioglitazone prior to 2000 (**Table 1.03**). The number with a first prescription of pioglitazone started to decrease in 2007, likely because after June 2005 new patients did not enter the study cohort and as such, new starters were limited to patients already included in the cohort. Further decreases in new starters of pioglitazone observed in 2011 and 2012 might be related to the decreases in pioglitazone use observed in throughout the United States due to concern for heart failure, cardiovascular disease, and more recently, bladder cancer. At the end of follow-up, there were 38,190 patients who were ever exposed to pioglitazone (**Table 1.04**). Among pioglitazone users, the median time from the first prescription to the end of follow-up was 5.4 years (range 0.2- 12.6 years). The median duration of therapy was 30.9 months (range 2.0- 150.4 months). The median dose of pioglitazone was 22,500 mg (range 450- 290,550 mg).

Cancer incidence (Table 1.05)

Table 1.05 provides the number of incident invasive cancers diagnosed among the study cohort during follow-up and the age and sex-standardized incidence rates (2000 US Census) for each cancers site, irrespective of drug exposure. For the 10 most common cancers, there are a considerable number of cases, ranging from 696 for melanoma to 3,783 for prostate cancer.

Hazard ratios for the 10 most common cancers (Tables 1.06-1.15)

Results from the Full Cohort

Tables 1.06 to 1.15 provide HR estimates for the association of each of our measures of pioglitazone use (ever vs. never, time since initiation, duration, and dose) and the risk of each of the 10 common cancers.

Among the full cohort, in models adjusted for age, other diabetes medications, year of cohort entry, sex, race/ethnicity, income, current smoking, baseline HbA1c, diabetes duration, new diabetes diagnosis, creatinine, history of congestive heart failure and interaction terms for new diabetes diagnoses and baseline HbA1c, the HRs for the risk of individual cancer types associated with ever use of pioglitazone ranged from 0.81 to 1.15 and all 95% CI included 1.00, except for pancreatic cancer [HR=1.41(95% CI 1.16-1.71)] and prostate cancer [HR=1.13 (95% CI 1.02-1.26)].

For each of the cancers, there was no clear pattern of increasing risk with increasing time since initiation, duration of use, or cumulative dose of pioglitazone (**Tables 1.06-1.15**), although elevated HRs were observed for some exposure measures at some cancer sites. For example, for prostate cancer (**Table 1.06**), the intermediate categories for time since initiation (36-47 months), duration (12-23 months), and dose (9,001-25,000 mg) were associated with increased risk, with HRs of 1.36 (95% CI 1.07-1.71), 1.30 (95% CI 1.08-1.57) and 1.24 (95% CI 1.06-1.46), respectively. For breast cancer (**Table 1.07**), the longest category of time since initiation (84+ months ago) was associated with increased risk [HR= 1.38 (95% CI 1.06-1.80)]. For colon cancer (**Table 1.09**), the shortest category of time since initiation (< 12 months ago) and one intermediate category of duration of pioglitazone use (36-59 months) were associated with decreased risk [HR= 0.62 (95% CI 0.41-0.92) and HR= 0.66 (95% CI 0.46-0.94), respectively]. For melanoma (**Table 1.15**), an intermediate category of duration of pioglitazone use (12-23 months) was associated with increased risk [HR= 1.59 (95% CI 1.08-2.330].

As in the previous report, a different pattern was observed for pancreatic cancer, likely in part due to diabetes being an early symptom of this disease. For pancreatic cancer, the HR for ever use of pioglitazone was 1.41 (95% CI 1.16-1.71) (**Table 1.12**). In this model, ever use of metformin, insulin or sulfonylureas were also associated with slight to modestly increased risk of pancreatic cancer (**Table 1.16**), with HRs of 1.21 (95% CI 1.02-1.43), 2.34 (95% CI 1.97-2.78), and 1.49 (95% CI 1.22-1.81), respectively. Although there was not a clear pattern for increasing risk of pancreatic cancer with increasing time since initiation, duration and dose of pioglitazone, risk of pancreatic cancer was elevated in the lowest category of time since initiation (<12 months) of pioglitazone [HR= 2.27 (95% CI 1.61-3.20)], and in several categories of duration of use: <12 months of pioglitazone use [HR= 1.48 (95% CI 1.12-1.95)], 36-59 months of pioglitazone use [HR= 1.63 (95% CI 1.15-2.31)] and 60+ months of pioglitazone use [HR= 1.53 (95% CI 1.00-2.33)]. The risk of pancreatic cancer was also increased for several categories of cumulative dose of pioglitazone: 1-9,000 mg, 25,001-50,000 mg and > 50,001 mg [HR= 1.50 (95% CI 1.14-1.98); HR= 1.46 (95% CI 1.04-2.06); and HR= 1.61 (95% CI 1.10-2.35), respectively].

In post-hoc analyses, we found no statistically significant linear trends in increasing or decreasing risk associated with time since initiation, duration and dose for any cancer site, except for a statistically significant decrease in the risk of pancreatic cancer with increasing time since initiation.

Subgroup and sensitivity analyses

1. Analyses restricted to KPNC members with complete information on pioglitazone prescriptions

In order to assess whether our results were biased by the possibility that we did not correctly measure duration of pioglitazone use among patients who joined KPNC and had already been treated with pioglitazone outside KPNC, analyses of pioglitazone therapy, time since initiation, duration and dose and cancer risk were repeated among 196,401 (83% of the full cohort) patients who entered the cohort in January 1, 1997 or were captured by the Diabetes Registry after January 1, 1997 but had ≥2 years of KPNC membership prior to being identified by the Registry. Similar results were observed in this subgroup and in the full cohort.

2. Sub-analyses among those with complete information on prescriptions of diabetes medications (analyses restricted to those with diabetes diagnosed after 2 years of KPNC membership and after 1997)

Because the risk of cancer may be related to the previous use of other diabetes medications, we repeated the analyses among a sub-cohort of 120,255 patients (51% of the full cohort) who had complete information on all prescriptions for diabetes medications. This sub-cohort comprised patients with at least 2 years of membership before they were identified by the KPNC Diabetes Registry and were newly diagnosed with DM after January 1, 1997 (i.e. newly diagnosed with diabetes at cohort entry). Results of analyses in this sub-cohort with and without adjustment for other diabetes medications were almost identical, suggesting little if any confounding by other diabetes medications. Results obtained in this sub-analyses were generally similar to those obtained in the full cohort. However, for the higher categories of pioglitazone exposure, we observed somewhat more elevated risks for some cancer sites (i.e., prostate and breast); for some, the risk was lower (i.e., NHL).

3. Sub-analyses among those for whom diabetes duration is known (i.e., survey responders and patients with at least 2 years of KPNC membership before being identified by the Diabetes Registry)

Approximately 19% of the cohort was invited to participate in a survey conducted in 1994-1996 and provided information on date of diabetes diagnoses. An additional 59% of the cohort were identified by the Kaiser Diabetes Registry at least 2 years after they joined the health plan; for these patients we assumed that they were diagnosed with diabetes on the same day they were identified by the Diabetes Registry (see protocol for description of registry inclusion criteria). The remaining 22% of the cohort joined the health plan less than 2 years prior to being identified by the Diabetes Registry or were not part of the survey. Note that we have required that cohort members had been with the health plan for 2 years before being identified by the diabetes registry (instead of one year as we did for the definition of duration as an adjustment variable) to ensure that diabetes duration was better defined in this subanalysis.

Among the subset of 182,661 patients for whom we were able to calculate diabetes duration at baseline, there was no suggestion of an association between diabetes duration and risk of cancer at sites other than pancreas. For pancreatic cancer, the risk was decreased among those who had a longer DM duration, such as patients with DM durations of 5 to 9 years or 10+ years as compared with those with DM duration less than 5 years [HR (95% CI): 0.55 (0.39-0.77) and 0.64 (0.48-0.85), respectively]. Patterns relating time since initiation, duration, and dose of pioglitazone to the risk of pancreatic and other cancers were similar to those observed in the full cohort.

4. Sub-analyses among those for whom BMI is known (i.e., subcohort of survey responders)

Approximately 20% of the cohort participated in the 1994-1996 survey and provided information on height and weight in order to calculate body mass index (BMI) and classify individuals according to the following BMI categories: < 20.0, 20.0-24.9 (reference), 25.0-29.9, 30.0-34.9, and 35.0+. Among this subset (n= 48,425), we first calculated HRs for cancer risk associated with ever use of pioglitazone adjusted for age, other diabetes medications, year of cohort entry, sex, race/ethnicity, income, current smoking, baseline HbA1c, diabetes duration, new diabetes diagnosis, creatinine, history of congestive heart failure and interaction terms for new diabetes diagnoses and baseline HbA1c. When BMI was added to the models, point estimates for the association between ever pioglitazone use and risk of cancer were unaltered. Likewise, point estimates were unaltered with additional adjustment for education, alcohol consumption and smoking (i.e. in the fully adjusted models). These results suggest that we can conduct analyses in the full cohort and BMI is unlikely to be an important confounder of the pioglitazone and cancer relationship. Of note, as shown by previous studies, in the fully adjusted models, higher BMI was associated with increased risk of colon cancer, cancer of the corpus uteri, and kidney cancer.

Although, again, in general, we observed little evidence of increasing cancer risk with increasing time since initiation, duration or dose, some patterns of risk did differ, somewhat, from the full cohort. For example, for breast cancer, 60+ months duration of pioglitazone use had a HR of 1.25 for the full cohort and 1.07 for the subcohort of survey responders. For NHL, these HRs were 0.89 and 1.91, respectively.

1. D. DISCUSSION

In this expansion of our earlier study, conducted to address safety concerns related to the risk of cancer following treatment with pioglitazone, we did not observe an association between ever use of pioglitazone and an increased risk of incident cancer at 8 of the 10 sites of interest. We also saw little evidence of increasing cancer risk with increasing time initiation, duration or dose of pioglitazone.

Overall, fewer statistically significant associations were observed than would have been expected by chance alone. Ever use of pioglitazone was associated with a small increase in the risk of prostate cancer [HR=1.13 (95% CI 1.02-1.26)], however, no clear pattern was observed with increasing time since initiation, duration or dose of pioglitazone. Ever use of pioglitazone was associated with an increased risk of pancreatic cancer [HR= 1.41 (95% CI 1.16-1.71)], as was ever use of metformin, insulin and sulfonylureas. No clear patterns of risk were observed with increasing time since initiation, duration or dose of pioglitazone. In addition, the results for pancreatic cancer are difficult to interpret because an early manifestation of this cancer is hyperglycemia (16).

The results obtained in this report with follow-up from January 1, 1997 to June 30, 2012 are largely similar to those obtained in our previous report with follow-up from January 1, 1997 to December 31, 2005 (10). With follow-up of this cohort through June 30, 2012, we have gained increased precision of our estimates. This report includes an additional 2,762 patients who used pioglitazone for at least 3-5 years and an additional 7,893 patients who used pioglitazone for at least 5 years, as well as an additional 652,622 person-years of follow-up. As expected, the confidence limits around our HR estimates for each of the exposure categories of interest are narrower. Notably, the prior signal of a potential increase in the risk of melanoma and NHL and a small decrease in the risk of cancer of the kidney/renal pelvis were attenuated.

There are several limitations that should be considered when interpreting our results. Pioglitazone was approved for use in the US in 1999 and there were few prescriptions for this medication among our cohort prior to 2000. Although we now have an additional 6.5 years of follow-up on the majority of the cohort, the length of follow up may still be too short to observe effects that require longer latencies or exposures. The latency period for many carcinogens is estimated to be decades. In addition, associations observed should be interpreted with caution due to the large number of comparisons.

We lacked complete information on several potentially important confounders in the full cohort. Fortunately, in analyses restricted to individuals who completed a postal survey and who self-reported information on race/ethnicity, height and weight, and alcohol and smoking, we found little evidence of confounding by these factors. There is also likely to be some misclassification on duration of diabetes. We measured diabetes duration based on the available data in the database. However, in analyses restricted to individuals with information on duration of diabetes, there was little evidence of confounding by this factor. Indeed, there was also little evidence that diabetes duration was associated with any of the cancers of interest. This is an important consideration for future studies of cancer risk associated with diabetes therapies.

There are several major strengths of this cohort study. First, enrollees of Kaiser Permanente receive virtually all of their health care from this pre-paid, integrated health plan. In addition, the Kaiser Permanente diabetes registry includes a large population of patients available for analysis of exposure to medications and cancer outcomes. The diabetes registry employs active surveillance based on diagnoses, laboratory tests and pharmacy data, and as such is able to also identify persons with diabetes who are not treated with medications. We used the Kaiser Permanente cancer registry to identify patients with cancer. This cancer registry, which contributes data to SEER, is well established and is held to SEER's very high quality standards.

This study is also strengthened by the availability of the Kaiser Permanente pharmacy data. Pharmacoepidemiology studies require accurate data on medication consumption. By requiring patients to fill two prescriptions within a six-month period, we have minimized misclassification of unexposed patients as exposed. Finally, the large number of patients who have been prescribed pioglitazone is a major strength of the study.

Conclusions

Concern over an increased risk of bladder cancer among patients treated with pioglitazone prompted regulators from the European Union to request this epidemiological assessment of the risk of other common cancers. In this cohort of more than 38,000 users of pioglitazone, including more than 9,000 with greater than 5 years of use, the largest and longest observational study of pioglitazone and common cancers to date, we did not observe an increased incidence of any of the other 10 most common cancers within the United States, with the exception of pancreatic cancer and prostate cancer. The association with increased risk of pancreatic cancer was the strongest in the first year of therapy and was commonly shared by other medications used to treat hypergycemia, suggesting reverse causality. The major limitation of this study remains the relatively short duration of follow-up. Given this limitation, additional follow-up of this cohort would allow for the examination of longer-term use and latency. However, acknowledging this limitation, we conclude that short to intermediate duration of therapy with pioglitazone does not increase the incidence of common malignancies over a median of 5.4 years of follow-up.

Table 1.02 Selected characteristics of study cohort of 236,507 diabetic patients by pioglitazone use; Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 – June 30, 2012.

	Ever User of Pioglitazone† (n=38,190) Number (%)	Never User of Pioglitazone (n=198,317) Number (%)
Total person-years in each age group*		
40-49	18,508 (9.0%)	188,000 (12.9%)
50-59	57,776 (28.2%)	376,456 (25.9%)
60-69	67,304 (32.9%)	401,581 (27.6%)
≥ 70	61,243 (29.9%)	489,681 (33.6%)
Female sex	17,632 (46.2%)	92,552 (46.7%)
Income		
Low‡	20,379 (53.4%)	107,007 (54.0%)
High	17,125 (44.8%)	86,384 (43.6%)
Missing	686 (1.8%)	4,926 (2.5%)
Race/Ethnicity		
Non-Hispanic white	18,717 (49.0%)	99,641 (50.2%)
African American	3,667 (9.6%)	19,931 (10.1%)
Asian or Pacific Islander	5,695 (14.9%)	26,637 (13.4%)
Hispanic	5,144 (13.5%)	21,554 (10.9%)
Other	2,129 (5.6%)	10,549 (5.3%)
Missing	2,838 (7.4%)	20,005 (10.1%)
Current smoking	7,929 (20.8%)	37,401 (18.9%)
Renal function		
Normal creatinine	29,476 (77.2%)	156,510 (78.9%)
Elevated creatinine**	1,495 (3.9%)	16,234 (8.2%)
Missing	7,219 (18.9%)	25,573 (12.9%)
Congestive Heart Failure	1,070 (2.8%)	12,602 (6.4%)
Baseline HbA1c		
< 7.0%	6,832 (17.9%)	63,867 (32.2%)
7.0-7.9%	6,594 (17.3%)	34,579 (17.4%)
8.0-8.9%	4,514 (11.8%)	17,971 (9.1%)
9.0-9.9%	3,451 (9.0%)	12,342 (6.2%)
≥10.0%	8,390 (22.0%)	29,836 (15.0%)
Missing	8,409 (22.0%)	39,722 (20.0%)
Time since diabetes diagnosis◊		
0-4 years	22,835 (59.8%)	134,209 (67.7%)
5-9 years	3,148 (8.2%)	9,554 (4.8%)
≥ 10 years	2,993 (7.8%)	17,300 (8.7%)
Missing	9,214 (24.1%)	37,254 (18.8%)

Table 1.02 (continued) Selected characteristics of study cohort of 236,507 diabetic patients by pioglitazone use; Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 – June 30, 2012.

	Ever User of Pioglitazone† (n=38,190) Number (%)	Never User of Pioglitazone (n=198,317) Number (%)
Other TZDs†	2,834 (7.4%)	2,537 (1.3%)
Metformin†	32,209 (84.3%)	93,719 (47.3%)
Sulfonylureas†	33,539 (87.8%)	109,723 (55.3%)
Other oral agents†	2,211 (5.8%)	2,423 (1.2%)
Insulin†	18,166 (47.6%)	48,089 (24.2%)

† 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;
◊ Diabetes duration from survey or date of entry in the diabetes registry for those who had been in the health plan for at least one year;‡ Low income defined as median household income in census block below the cohort average ($59,000);

Table 1.03 Calendar year of first prescription for pioglitazone among diabetic patients in the study cohort; Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 - June 30, 2012.

Year of 1st Pioglitazone Prescription	N*	Percent	Cumulative Frequency
1999	153	0.40	153
2000	4918	12.88	5,071
2001	4402	11.53	9,473
2002	4464	11.69	13,937
2003	3881	10.16	17,818
2004	3720	9.74	21,538
2005	4387	11.49	25,925
2006	3981	10.42	29,906
2007	3370	8.82	33,276
2008	1844	4.83	35,120
2009	1480	3.88	36,600
2010	989	2.59	37,589
2011	551	1.44	38,140
2012	50	0.13	38,190

*Individuals

Table 1.04 Pioglitazone exposure (as of the end of follow-up); Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 - June 30, 2012.

Category	
Ever exposed, n	38,190
Time since starting pioglitazone, yrs	
Median (range)	5.4 yrs (0.2-12.6)
<1 year (n, %)	2,959 (7.7%)
1.0-1.9 yrs (n, %)	3,678 (9.6 %)
2.0-2.9 yrs (n, %)	3,659 (9.6%)
3.0-3.9 yrs (n, %)	3,647 (9.6%)
4.0-6.9 yrs (n, %)	11,829 (31.0%)
7+ yrs (n, %)	12,418 (32.5%)
Duration of therapy, months	
Median (range)	30.9 months (2.0- 150.4)
<12 months (n, %)	8,124 (21.3%)
12-23 months (n, %)	7,622 (20.0%)
24-35 months (n, %)	5,544 (14.5%)
36-59 months (n, %)	7,784 (20.4%)
60+ months (n, %)	9,116 (23.9%)
Cumulative dose, mg	
Median (range)	22,500 mg (450- 290,550)
1 – 9000 mg (n, %)	9,621 (25.2%)
9001 – 25000 mg (n, %)	10,891 (28.5%)
25001 – 50000 mg (n, %)	8,786 (23.0%)
>50000 mg (n, %)	8,892 (23.3%)

Table 1.05. Number and incidence rates of invasive cancers among study cohort of n=236,507 diabetic patients, after excluding those with a history of any cancer at baseline and censoring at diagnosis of any cancer, irrespective of exposure to pioglitazone.

Cancer Site*	Number of cases	Crude Incidence Rate (per 100,000 person-yrs)	Age-Adj** Incidence Rate (per 100,000 person-yrs)
1. Prostate	3783	450.7	287.1
2. Breast	2798	357.1	280.3
3. Lung/Bronchus	2582	156.2	104.6
4. Colon	2077	126.7	91.6
5. Urinary Bladder	1139	69.1	46.6
6. Non-Hodgkin Lymphoma	959	58.0	43.6
7. Corpus Uteri	917	124.8	107.3
8. Pancreatic	812	52.8	36.4
9. Kidney/Renal Pelvis	800	48.4	37.3
10. Melanoma	696	42.1	31.9
11. Rectum/Rectosigmoid	629	38.4	29.7

* Cancer site based on SEER classification, bladder includes in-situ

**Age adjusted to the 2000 U.S. population of age 40 or above.

Table 1.06 Multiple Adjusted Hazard Ratios for **PROSTATE** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 124,378)	**Complete info on pioglitazone** (n= 103,033)	**Complete info on all diabetes prescriptions** (n= 63,550)	**Diabetes duration is known** (n= 95,988)	**Subcohort of Survey Responders** (n= 24,879)	**Adjusted for BMI** (n= 24,879)	**Adjusted[a] for BMI, education and behaviors** (n= 24,879)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	476	1.13 (1.02-1.26)*	1.14 (1.02-1.28)*	1.19 (1.01-1.41)*	1.16 (1.03-1.30)*	1.12 (0.92-1.36)	1.12 (0.93-1.36)	1.12 (0.93-1.36)
TIME SINCE INITIATION								
< 12 months ago	55	0.92 (0.73-1.17)	0.93 (0.71-1.20)	0.91 (0.62-1.35)	0.92 (0.70-1.20)	0.88 (0.57-1.37)	0.88 (0.57-1.37)	0.88 (0.57-1.37)
12-23 months ago	82	1.18 (0.94-1.47)	1.22 (0.96-1.55)	1.13 (0.79-1.63)	1.24 (0.97-1.59)	1.14 (0.76-1.73)	1.14 (0.75-1.73)	1.14 (0.76-1.73)
24-35 months ago	76	1.21 (0.96-1.52)	1.06 (0.81-1.39)	1.06 (0.71-1.58)	1.09 (0.82-1.43)	1.44 (0.98-2.13)	1.44 (0.98-2.13)	1.44 (0.98-2.13)
36-47 months ago	75	1.36 (1.07-1.71)*	1.36 (1.05-1.75)*	1.59 (1.11-2.27)*	1.42 (1.09-1.84)*	1.49 (1.00-2.23)	1.49 (1.00-2.23)	1.50 (1.00-2.24)
48-83 months ago	119	1.04 (0.86-1.26)	1.16 (0.95-1.42)	1.38 (1.03-1.84)*	1.18 (0.96-1.45)	0.85 (0.60-1.22)	0.85 (0.60-1.22)	0.85 (0.60-1.22)
84+ months ago	69	1.23 (0.95-1.59)	1.23 (0.93-1.63)	1.30 (0.80-2.10)	1.17 (0.87-1.58)	1.15 (0.77-1.72)	1.16 (0.78-1.73)	1.16 (0.77-1.73)
DURATION OF PIO								
< 12 months	118	1.00 (0.84-1.19)	0.99 (0.82-1.20)	1.06 (0.80-1.40)	0.99 (0.82-1.21)	0.88 (0.63-1.22)	0.88 (0.63-1.23)	0.89 (0.64-1.23)
12-23 months	121	1.30 (1.08-1.57)*	1.32 (1.07-1.61)*	1.39 (1.04-1.87)*	1.32 (1.07-1.63)*	1.20 (0.85-1.70)	1.20 (0.85-1.69)	1.19 (0.85-1.68)
24-35 months	72	1.07 (0.84-1.35)	1.01 (0.77-1.32)	1.22 (0.84-1.77)	1.07 (0.82-1.40)	1.03 (0.67-1.57)	1.03 (0.67-1.57)	1.03 (0.67-1.57)
36-59 months	99	1.18 (0.96-1.45)	1.22 (0.97-1.52)	1.22 (0.86-1.72)	1.25 (1.00-1.57)	1.24 (0.88-1.76)	1.25 (0.88-1.77)	1.25 (0.88-1.77)
60+ months	66	1.16 (0.90-1.50)	1.30 (1.00-1.69)	1.44 (0.94-2.20)	1.26 (0.95-1.66)	1.21 (0.82-1.79)	1.22 (0.82-1.80)	1.22 (0.82-1.80)
DOSE OF PIO								
1-9,000 mg	129	1.08 (0.91-1.27)	1.05 (0.87-1.26)	1.11 (0.86-1.45)	1.04 (0.86-1.26)	0.90 (0.65-1.25)	0.90 (0.65-1.26)	0.91 (0.65-1.26)
9,001-25,000 mg	167	1.24 (1.06-1.46)*	1.24 (1.04-1.48)*	1.38 (1.07-1.77)*	1.28 (1.07-1.53)*	1.24 (0.93-1.65)	1.23 (0.93-1.65)	1.23 (0.92-1.64)
25,001-50,000 mg	109	1.12 (0.92-1.37)	1.18 (0.96-1.46)	1.28 (0.93-1.75)	1.20 (0.97-1.50)	1.13 (0.81-1.58)	1.13 (0.81-1.59)	1.13 (0.81-1.58)
≥50,001 mg	71	1.00 (0.78-1.28)	1.07 (0.83-1.39)	1.06 (0.68-1.64)	1.06 (0.81-1.39)	1.09 (0.75-1.58)	1.09 (0.75-1.59)	1.10 (0.75-1.59)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.07 Multiple Adjusted Hazard Ratios for **BREAST** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 110,183)	**Complete info on pioglitazone** (n= 91,112)	**Complete info on all diabetes prescriptions** (n= 55,675)	**Diabetes duration is known** (n= 84,596)	**Subcohort of Survey Responders** (n= 22,619)	**Adjusted for BMI** (n= 22,619)	**Adjusted[a] for BMI, education and behaviors** (n= 22,619)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	320	1.00 (0.88-1.13)	1.01 (0.88-1.16)	0.95 (0.77-1.17)	1.00 (0.87-1.16)	1.00 (0.79-1.25)	0.99 (0.79-1.24)	0.98 (0.78-1.24)
TIME SINCE INITIATION								
< 12 months ago	42	1.00 (0.76-1.31)	0.92 (0.67-1.25)	0.66 (0.39-1.12)	0.95 (0.69-1.31)	1.09 (0.67-1.75)	1.08 (0.67-1.74)	1.07 (0.67-1.73)
12-23 months ago	42	0.84 (0.62-1.14)	0.89 (0.64-1.24)	1.03 (0.66-1.60)	0.92 (0.66-1.29)	0.71 (0.39-1.30)	0.71 (0.39-1.29)	0.70 (0.38-1.28)
24-35 months ago	47	1.04 (0.77-1.39)	1.04 (0.75-1.43)	1.14 (0.73-1.78)	1.04 (0.75-1.45)	0.85 (0.47-1.51)	0.84 (0.47-1.50)	0.83 (0.47-1.49)
36-47 months ago	31	0.77 (0.54-1.10)	0.83 (0.57-1.21)	0.92 (0.54-1.57)	0.87 (0.60-1.28)	0.64 (0.32-1.30)	0.64 (0.31-1.29)	0.63 (0.31-1.28)
48-83 months ago	91	1.03 (0.83-1.28)	1.05 (0.83-1.34)	0.94 (0.64-1.38)	1.04 (0.81-1.33)	1.24 (0.86-1.78)	1.23 (0.85-1.77)	1.21 (0.84-1.75)
84+ months ago	67	1.38 (1.06-1.80)*	1.44 (1.08-1.92)*	1.43 (0.86-2.37)	1.30 (0.96-1.78)	1.18 (0.75-1.84)	1.16 (0.74-1.82)	1.15 (0.74-1.80)
DURATION OF PIO								
< 12 months	88	0.84 (0.69-1.03)	0.84 (0.67-1.05)	0.74 (0.52-1.05)	0.83 (0.66-1.05)	0.95 (0.68-1.34)	0.95 (0.67-1.33)	0.94 (0.67-1.33)
12-23 months	75	1.07 (0.84-1.35)	1.01 (0.77-1.32)	0.90 (0.59-1.37)	0.99 (0.75-1.31)	0.91 (0.58-1.43)	0.90 (0.57-1.42)	0.89 (0.57-1.41)
24-35 months	47	1.01 (0.75-1.35)	1.04 (0.76-1.43)	1.15 (0.73-1.83)	1.12 (0.81-1.54)	0.98 (0.58-1.66)	0.97 (0.58-1.64)	0.97 (0.57-1.63)
36-59 months	61	1.06 (0.82-1.38)	1.21 (0.92-1.58)	1.15 (0.75-1.77)	1.23 (0.93-1.63)	1.09 (0.69-1.71)	1.08 (0.69-1.69)	1.07 (0.68-1.67)
60+ months	49	1.25 (0.93-1.68)	1.29 (0.94-1.77)	1.52 (0.93-2.50)	1.17 (0.83-1.65)	1.09 (0.66-1.82)	1.08 (0.65-1.80)	1.07 (0.64-1.78)
DOSE OF PIO								
1-9,000 mg	92	0.89 (0.73-1.08)	0.86 (0.69-1.07)	0.84 (0.61-1.17)	0.82 (0.65-1.04)	0.84 (0.58-1.20)	0.83 (0.58-1.19)	0.82 (0.57-1.19)
9,001-25,000 mg	98	0.95 (0.77-1.17)	0.99 (0.79-1.24)	0.90 (0.64-1.28)	1.03 (0.82-1.30)	0.98 (0.68-1.41)	0.97 (0.67-1.40)	0.97 (0.67-1.40)
25,001-50,000 mg	77	1.15 (0.91-1.46)	1.19 (0.92-1.54)	1.01 (0.66-1.56)	1.21 (0.92-1.57)	1.30 (0.88-1.92)	1.29 (0.87-1.90)	1.27 (0.86-1.88)
≥50,001 mg	53	1.19 (0.89-1.57)	1.28 (0.95-1.72)	1.60 (1.02-2.53)*	1.22 (0.89-1.68)	0.98 (0.59-1.62)	0.97 (0.59-1.61)	0.96 (0.58-1.60)

†Never use of pioglitazone as reference group for all analyses.

In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.08 Multiple Adjusted Hazard Ratios for **LUNG AND BRONCHUS** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	282	1.00 (0.87-1.15)	1.04 (0.90-1.21)	1.13 (0.91-1.40)	1.06 (0.91-1.24)	1.01 (0.80-1.28)	1.02 (0.81-1.30)	1.03 (0.81-1.31)
TIME SINCE INITIATION								
< 12 months ago	32	0.82 (0.59-1.14)	0.80 (0.56-1.15)	0.71 (0.40-1.25)	0.82 (0.56-1.20)	0.90 (0.52-1.57)	0.91 (0.52-1.59)	0.91 (0.52-1.58)
12-23 months ago	48	1.12 (0.84-1.50)	1.23 (0.90-1.67)	1.45 (0.96-2.21)	1.28 (0.94-1.76)	1.18 (0.71-1.96)	1.19 (0.72-1.98)	1.19 (0.72-1.98)
24-35 months ago	45	1.13 (0.84-1.53)	1.20 (0.87-1.65)	1.29 (0.81-2.04)	1.22 (0.87-1.70)	1.24 (0.75-2.07)	1.26 (0.76-2.09)	1.26 (0.76-2.10)
36-47 months ago	37	1.04 (0.75-1.45)	1.06 (0.74-1.52)	1.41 (0.88-2.27)	1.09 (0.75-1.58)	0.93 (0.51-1.71)	0.94 (0.51-1.73)	0.94 (0.51-1.73)
48-83 months ago	75	0.95 (0.74-1.20)	1.03 (0.80-1.33)	1.00 (0.67-1.49)	1.09 (0.84-1.42)	0.98 (0.66-1.46)	0.99 (0.66-1.48)	1.00 (0.67-1.50)
84+ months ago	45	0.96 (0.70-1.31)	0.94 (0.66-1.33)	0.75 (0.37-1.53)	0.86 (0.58-1.26)	0.91 (0.56-1.49)	0.93 (0.57-1.52)	0.95 (0.58-1.55)
DURATION OF PIO								
< 12 months	83	0.90 (0.73-1.12)	0.94 (0.75-1.19)	1.13 (0.82-1.57)	0.93 (0.73-1.19)	0.68 (0.44-1.05)	0.69 (0.45-1.06)	0.71 (0.46-1.09)
12-23 months	60	0.98 (0.75-1.27)	1.04 (0.78-1.38)	1.11 (0.74-1.67)	1.05 (0.78-1.41)	1.12 (0.73-1.72)	1.13 (0.74-1.74)	1.13 (0.74-1.73)
24-35 months	41	0.96 (0.70-1.31)	1.07 (0.77-1.49)	0.76 (0.42-1.38)	1.18 (0.84-1.64)	1.44 (0.92-2.25)	1.45 (0.93-2.28)	1.47 (0.94-2.30)
36-59 months	56	1.06 (0.81-1.40)	1.15 (0.86-1.54)	1.19 (0.76-1.87)	1.17 (0.86-1.58)	1.22 (0.80-1.88)	1.24 (0.81-1.90)	1.24 (0.81-1.90)
60+ months	42	1.12 (0.81-1.54)	1.01 (0.70-1.45)	1.21 (0.68-2.17)	1.05 (0.72-1.53)	0.83 (0.48-1.45)	0.85 (0.49-1.48)	0.84 (0.48-1.46)
DOSE OF PIO								
1-9,000 mg	90	0.98 (0.80-1.21)	0.99 (0.79-1.24)	1.27 (0.94-1.72)	1.05 (0.84-1.33)	0.73 (0.48-1.12)	0.74 (0.48-1.13)	0.75 (0.49-1.14)
9,001-25,000 mg	81	0.91 (0.73-1.15)	1.04 (0.82-1.32)	0.91 (0.62-1.33)	1.00 (0.77-1.29)	1.17 (0.82-1.67)	1.18 (0.83-1.69)	1.20 (0.84-1.72)
25,001-50,000 mg	61	0.97 (0.75-1.26)	1.07 (0.81-1.41)	1.01 (0.64-1.59)	1.14 (0.86-1.51)	1.15 (0.76-1.74)	1.17 (0.77-1.76)	1.17 (0.78-1.77)
≥50,001 mg	50	1.12 (0.84-1.50)	1.02 (0.73-1.43)	1.13 (0.64-1.97)	1.02 (0.71-1.45)	1.01 (0.63-1.63)	1.03 (0.64-1.66)	1.02 (0.63-1.63)

†Never use of pioglitazone as reference group for all analyses.

In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.09 Multiple Adjusted Hazard Ratios for **COLON** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	233	0.91 (0.78-1.05)	0.93 (0.79-1.09)	0.83 (0.63-1.08)	0.92 (0.78-1.09)	1.00 (0.79-1.28)	1.00 (0.78-1.27)	1.00 (0.79-1.28)
TIME SINCE INITIATION								
< 12 months ago	22	0.62 (0.41-0.92)*	0.64 (0.41-0.98)*	0.60 (0.31-1.17)	0.61 (0.39-0.97)*	0.63 (0.31-1.28)	0.63 (0.31-1.27)	0.63 (0.31-1.28)
12-23 months ago	30	0.79 (0.55-1.14)	0.74 (0.49-1.12)	0.65 (0.34-1.26)	0.72 (0.47-1.11)	0.76 (0.39-1.48)	0.76 (0.39-1.47)	0.76 (0.39-1.48)
24-35 months ago	47	1.35 (1.00-1.81)	1.31 (0.95-1.82)	1.22 (0.73-2.05)	1.33 (0.95-1.86)	1.31 (0.79-2.18)	1.30 (0.78-2.17)	1.31 (0.79-2.18)
36-47 months ago	26	0.81 (0.55-1.19)	0.82 (0.53-1.25)	0.37 (0.14-1.00)	0.83 (0.54-1.29)	1.44 (0.88-2.37)	1.44 (0.87-2.36)	1.44 (0.88-2.37)
48-83 months ago	71	0.97 (0.76-1.24)	1.02 (0.78-1.33)	1.05 (0.67-1.62)	0.97 (0.74-1.29)	0.96 (0.64-1.44)	0.95 (0.63-1.43)	0.96 (0.64-1.44)
84+ months ago	37	0.79 (0.56-1.12)	0.89 (0.62-1.26)	0.82 (0.38-1.77)	0.96 (0.67-1.37)	0.96 (0.60-1.53)	0.94 (0.59-1.51)	0.95 (0.60-1.52)
DURATION OF PIO								
< 12 months	72	0.86 (0.68-1.08)	0.87 (0.68-1.13)	0.81 (0.54-1.22)	0.83 (0.64-1.09)	0.93 (0.63-1.37)	0.93 (0.63-1.37)	0.93 (0.63-1.38)
12-23 months	48	0.88 (0.66-1.18)	0.82 (0.59-1.15)	0.81 (0.49-1.37)	0.82 (0.58-1.15)	0.81 (0.48-1.36)	0.80 (0.47-1.35)	0.81 (0.48-1.36)
24-35 months	40	1.03 (0.75-1.42)	1.12 (0.80-1.57)	0.73 (0.38-1.42)	1.13 (0.80-1.60)	1.26 (0.78-2.04)	1.25 (0.77-2.03)	1.26 (0.78-2.04)
36-59 months	33	0.66 (0.46-0.94)*	0.68 (0.47-0.99)*	0.68 (0.36-1.29)	0.70 (0.48-1.02)	0.79 (0.47-1.32)	0.78 (0.47-1.31)	0.79 (0.47-1.32)
60+ months	40	1.05 (0.76-1.46)	1.14 (0.81-1.60)	0.92 (0.45-1.87)	1.18 (0.83-1.66)	1.33 (0.85-2.08)	1.31 (0.84-2.05)	1.32 (0.84-2.07)
DOSE OF PIO								
1-9,000 mg	72	0.87 (0.69-1.10)	0.89 (0.69-1.14)	0.79 (0.52-1.19)	0.88 (0.68-1.15)	1.02 (0.70-1.49)	1.01 (0.69-1.48)	1.02 (0.70-1.48)
9,001-25,000 mg	70	0.86 (0.68-1.10)	0.86 (0.66-1.13)	0.82 (0.54-1.27)	0.83 (0.62-1.10)	0.80 (0.52-1.23)	0.80 (0.52-1.22)	0.80 (0.52-1.23)
25,001-50,000 mg	56	0.97 (0.74-1.27)	0.96 (0.71-1.29)	0.73 (0.41-1.30)	0.98 (0.72-1.33)	1.02 (0.66-1.57)	1.01 (0.65-1.56)	1.02 (0.66-1.57)
≥50,001 mg	35	0.79 (0.56-1.12)	0.91 (0.64-1.30)	0.79 (0.39-1.61)	0.95 (0.66-1.35)	1.21 (0.78-1.88)	1.20 (0.77-1.86)	1.21 (0.78-1.87)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.10 Multiple Adjusted Hazard Ratios for **NON-HODGKIN LYMPHOMA** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	120	1.00 (0.81-1.23)	1.00 (0.79-1.26)	0.77 (0.52-1.14)	0.99 (0.77-1.26)	1.39 (0.98-1.97)	1.38 (0.98-1.96)	1.38 (0.98-1.96)
TIME SINCE INITIATION								
< 12 months ago	21	1.15 (0.75-1.76)	1.22 (0.77-1.93)	1.08 (0.53-2.19)	1.18 (0.73-1.92)	1.58 (0.80-3.13)	1.58 (0.80-3.11)	1.58 (0.80-3.12)
12-23 months ago	26	1.44 (0.97-2.14)	1.57 (1.03-2.39)*	1.00 (0.47-2.13)	1.70 (1.11-2.60)*	2.04 (1.09-3.81)*	2.02 (1.08-3.78)*	2.03 (1.09-3.79)*
24-35 months ago	16	0.92 (0.56-1.53)	0.86 (0.49-1.54)	0.91 (0.40-2.06)	0.79 (0.42-1.48)	1.01 (0.41-2.50)	1.01 (0.41-2.48)	1.01 (0.41-2.48)
36-47 months ago	12	0.79 (0.44-1.40)	0.64 (0.32-1.29)	0.36 (0.09-1.46)	0.61 (0.29-1.29)	1.05 (0.42-2.59)	1.04 (0.42-2.57)	1.04 (0.42-2.57)
48-83 months ago	24	0.70 (0.46-1.06)	0.67 (0.42-1.08)	0.51 (0.22-1.17)	0.65 (0.40-1.08)	0.98 (0.50-1.91)	0.97 (0.50-1.89)	0.97 (0.50-1.90)
84+ months ago	21	0.98 (0.61-1.56)	0.98 (0.59-1.63)	0.55 (0.17-1.78)	0.98 (0.57-1.68)	1.45 (0.75-2.81)	1.43 (0.74-2.78)	1.44 (0.74-2.79)
DURATION OF PIO								
< 12 months	35	0.93 (0.66-1.29)	0.83 (0.57-1.23)	0.71 (0.39-1.31)	0.81 (0.54-1.22)	1.17 (0.67-2.04)	1.16 (0.66-2.03)	1.16 (0.66-2.03)
12-23 months	32	1.25 (0.87-1.80)	1.46 (1.00-2.12)	0.96 (0.49-1.89)	1.55 (1.06-2.27)*	2.02 (1.17-3.49)*	2.01 (1.16-3.47)*	2.03 (1.18-3.51)*
24-35 months	20	1.08 (0.69-1.70)	1.01 (0.60-1.70)	0.77 (0.32-1.89)	1.03 (0.60-1.77)	1.30 (0.60-2.81)	1.29 (0.59-2.78)	1.28 (0.59-2.77)
36-59 months	17	0.72 (0.44-1.18)	0.72 (0.42-1.24)	0.76 (0.34-1.73)	0.68 (0.38-1.21)	0.81 (0.35-1.87)	0.80 (0.35-1.84)	0.80 (0.35-1.85)
60+ months	16	0.89 (0.53-1.49)	0.93 (0.53-1.61)	0.20 (0.03-1.41)	0.88 (0.48-1.59)	1.95 (1.03-3.70)*	1.92 (1.01-3.65)*	1.91 (1.01-3.64)*
DOSE OF PIO								
1-9,000 mg	34	0.92 (0.66-1.29)	0.87 (0.60-1.27)	0.90 (0.52-1.55)	0.88 (0.60-1.31)	0.94 (0.51-1.76)	0.94 (0.50-1.74)	0.94 (0.51-1.75)
9,001-25,000 mg	44	1.16 (0.85-1.59)	1.21 (0.86-1.70)	0.80 (0.43-1.47)	1.18 (0.82-1.69)	1.63 (0.98-2.71)	1.62 (0.98-2.69)	1.62 (0.98-2.69)
25,001-50,000 mg	28	1.02 (0.69-1.51)	1.00 (0.65-1.55)	0.67 (0.29-1.51)	1.10 (0.71-1.70)	1.68 (0.95-2.99)	1.67 (0.94-2.96)	1.67 (0.94-2.97)
≥50,001 mg	14	0.66 (0.38-1.13)	0.74 (0.42-1.30)	0.17 (0.02-1.21)	0.62 (0.33-1.19)	1.55 (0.80-3.00)	1.54 (0.79-2.97)	1.53 (0.79-2.96)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.11 Multiple Adjusted Hazard Ratios for **CORPUS UTERI** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 105,484)	**Complete info on pioglitazone** (n= 86,639)	**Complete info on all diabetes prescriptions** (n= 52,558)	**Diabetes duration is known** (n= 80,323)	**Subcohort of Survey Responders** (n= 21,718)	**Adjusted for BMI** (n= 21,718)	**Adjusted[a] for BMI, education and behaviors** (n= 21,718)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	118	0.88 (0.71-1.09)	0.85 (0.68-1.08)	0.71 (0.49-1.01)	0.86 (0.68-1.10)	1.01 (0.70-1.47)	0.98 (0.67-1.42)	0.97 (0.67-1.42)
TIME SINCE INITIATION								
< 12 months ago	14	0.91 (0.58-1.43)	0.91 (0.56-1.49)	1.25 (0.68-2.28)	0.99 (0.61-1.62)	0.80 (0.32-1.96)	0.77 (0.31-1.90)	0.77 (0.31-1.90)
12-23 months ago	20	0.97 (0.62-1.53)	0.92 (0.56-1.51)	0.84 (0.39-1.78)	0.93 (0.56-1.57)	1.03 (0.45-2.37)	1.00 (0.44-2.29)	1.00 (0.44-2.28)
24-35 months ago	12	0.65 (0.37-1.16)	0.57 (0.29-1.10)	0.53 (0.20-1.41)	0.55 (0.27-1.10)	0.93 (0.37-2.29)	0.89 (0.36-2.21)	0.89 (0.36-2.21)
36-47 months ago	15	0.90 (0.54-1.52)	0.77 (0.42-1.41)	0.74 (0.30-1.80)	0.83 (0.45-1.52)	0.43 (0.11-1.75)	0.42 (0.10-1.70)	0.41 (0.10-1.69)
48-83 months ago	36	0.99 (0.70-1.41)	1.02 (0.71-1.49)	0.79 (0.42-1.46)	1.05 (0.71-1.54)	1.31 (0.73-2.36)	1.26 (0.70-2.28)	1.26 (0.70-2.26)
84+ months ago	21	0.94 (0.59-1.51)	1.02 (0.63-1.66)	0.47 (0.15-1.49)	0.93 (0.55-1.60)	1.25 (0.62-2.51)	1.19 (0.59-2.39)	1.18 (0.59-2.38)
DURATION OF PIO								
< 12 months	43	1.01 (0.75-1.35)	1.04 (0.76-1.42)	1.14 (0.73-1.78)	1.11 (0.81-1.53)	0.95 (0.54-1.66)	0.93 (0.53-1.63)	0.92 (0.53-1.61)
12-23 months	24	0.83 (0.55-1.25)	0.77 (0.49-1.23)	0.81 (0.42-1.59)	0.76 (0.47-1.24)	0.96 (0.47-1.98)	0.92 (0.44-1.89)	0.92 (0.44-1.89)
24-35 months	19	0.97 (0.61-1.55)	0.89 (0.53-1.50)	0.80 (0.35-1.80)	0.85 (0.49-1.48)	0.84 (0.34-2.07)	0.79 (0.32-1.97)	0.80 (0.32-1.98)
36-59 months	19	0.78 (0.49-1.24)	0.75 (0.45-1.25)	0.44 (0.16-1.18)	0.77 (0.46-1.30)	0.93 (0.42-2.03)	0.90 (0.41-1.97)	0.90 (0.41-1.97)
60+ months	13	0.73 (0.42-1.29)	0.75 (0.42-1.35)	0.17 (0.02-1.19)	0.70 (0.37-1.33)	1.41 (0.69-2.92)	1.35 (0.65-2.78)	1.33 (0.65-2.75)
DOSE OF PIO								
1-9,000 mg	43	1.02 (0.76-1.37)	1.02 (0.74-1.40)	1.12 (0.72-1.74)	1.09 (0.79-1.50)	0.97 (0.55-1.70)	0.94 (0.54-1.64)	0.94 (0.54-1.64)
9,001-25,000 mg	38	0.90 (0.64-1.25)	0.88 (0.61-1.27)	0.84 (0.48-1.44)	0.87 (0.60-1.28)	1.06 (0.59-1.89)	1.02 (0.57-1.83)	1.02 (0.57-1.83)
25,001-50,000 mg	19	0.67 (0.42-1.06)	0.66 (0.40-1.09)	0.49 (0.20-1.20)	0.58 (0.33-1.02)	0.55 (0.22-1.37)	0.53 (0.21-1.32)	0.53 (0.21-1.31)
≥50,001 mg	18	0.87 (0.54-1.42)	0.82 (0.48-1.40)	0.15 (0.02-1.09)	0.86 (0.49-1.48)	1.51 (0.78-2.93)	1.46 (0.75-2.82)	1.43 (0.74-2.77)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.12 Multiple Adjusted Hazard Ratios for **PANCREAS** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	164	1.41 (1.16-1.71)*	1.48 (1.20-1.82)*	1.51 (1.11-2.04)*	1.48 (1.19-1.84)*	1.23 (0.87-1.74)	1.21 (0.86-1.72)	1.22 (0.86-1.73)
TIME SINCE INITIATION								
< 12 months ago	33	2.27 (1.61-3.20)*	2.39 (1.66-3.43)*	2.43 (1.48-3.99)*	2.41 (1.65-3.50)*	1.38 (0.64-2.97)	1.36 (0.63-2.95)	1.37 (0.63-2.96)
12-23 months ago	22	1.31 (0.85-2.01)	1.44 (0.91-2.26)	1.14 (0.56-2.32)	1.47 (0.92-2.34)	1.33 (0.61-2.87)	1.32 (0.61-2.85)	1.32 (0.61-2.86)
24-35 months ago	18	1.13 (0.71-1.82)	1.29 (0.79-2.10)	1.41 (0.72-2.76)	1.38 (0.85-2.26)	0.94 (0.38-2.32)	0.93 (0.38-2.30)	0.93 (0.38-2.31)
36-47 months ago	19	1.28 (0.80-2.04)	1.29 (0.78-2.15)	1.59 (0.81-3.13)	1.22 (0.71-2.10)	0.94 (0.38-2.33)	0.93 (0.38-2.31)	0.94 (0.38-2.33)
48-83 months ago	41	1.14 (0.82-1.60)	1.22 (0.85-1.74)	1.45 (0.86-2.43)	1.17 (0.80-1.70)	1.03 (0.58-1.84)	1.02 (0.57-1.82)	1.03 (0.57-1.84)
84+ months ago	31	1.39 (0.93-2.07)	1.29 (0.82-2.01)	0.43 (0.10-1.77)	1.34 (0.85-2.12)	1.53 (0.85-2.76)	1.52 (0.84-2.73)	1.53 (0.85-2.75)
DURATION OF PIO								
< 12 months	54	1.48 (1.12-1.95)*	1.56 (1.16-2.10)*	1.40 (0.90-2.19)	1.59 (1.17-2.15)*	1.39 (0.85-2.28)	1.38 (0.84-2.26)	1.38 (0.84-2.27)
12-23 months	28	1.19 (0.82-1.73)	1.25 (0.84-1.87)	1.15 (0.63-2.13)	1.20 (0.79-1.85)	0.93 (0.45-1.92)	0.92 (0.45-1.90)	0.93 (0.45-1.91)
24-35 months	18	1.03 (0.64-1.66)	1.18 (0.72-1.94)	2.00 (1.11-3.60)*	1.28 (0.78-2.10)	0.46 (0.15-1.46)	0.45 (0.14-1.44)	0.46 (0.14-1.45)
36-59 months	36	1.63 (1.15-2.31)*	1.68 (1.15-2.45)*	1.57 (0.84-2.91)	1.59 (1.06-2.38)*	1.57 (0.88-2.80)	1.54 (0.87-2.76)	1.56 (0.87-2.78)
60+ months	25	1.53 (1.00-2.33)	1.50 (0.94-2.38)	1.54 (0.67-3.55)	1.62 (1.02-2.58)*	1.49 (0.78-2.81)	1.46 (0.77-2.77)	1.48 (0.78-2.81)
DOSE OF PIO								
1-9,000 mg	52	1.50 (1.14-1.98)*	1.66 (1.24-2.22)*	1.48 (0.96-2.29)	1.69 (1.25-2.27)*	1.45 (0.89-2.37)	1.44 (0.88-2.35)	1.44 (0.88-2.35)
9,001-25,000 mg	39	1.10 (0.79-1.53)	1.09 (0.76-1.57)	1.19 (0.71-1.99)	1.07 (0.73-1.57)	0.71 (0.35-1.40)	0.70 (0.35-1.39)	0.70 (0.35-1.40)
25,001-50,000 mg	38	1.46 (1.04-2.06)*	1.55 (1.07-2.24)*	1.71 (0.98-2.98)	1.62 (1.12-2.36)*	1.36 (0.76-2.42)	1.34 (0.75-2.38)	1.36 (0.77-2.42)
≥50,001 mg	32	1.61 (1.10-2.35)*	1.61 (1.06-2.43)*	1.85 (0.93-3.68)	1.55 (1.00-2.40)	1.44 (0.79-2.62)	1.42 (0.78-2.57)	1.43 (0.79-2.61)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.13 Multiple Adjusted Hazard Ratios for **KIDNEY/ RENAL PELVIS** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	110	0.95 (0.76-1.18)	0.92 (0.72-1.18)	0.84 (0.58-1.22)	0.92 (0.71-1.19)	0.85 (0.56-1.27)	0.83 (0.55-1.24)	0.82 (0.54-1.22)
TIME SINCE INITIATION								
< 12 months ago	12	0.75 (0.43-1.30)	0.72 (0.38-1.35)	0.88 (0.39-1.98)	0.63 (0.31-1.26)	0.37 (0.09-1.51)	0.37 (0.09-1.50)	0.37 (0.09-1.49)
12-23 months ago	10	0.59 (0.32-1.11)	0.65 (0.34-1.27)	0.73 (0.30-1.78)	0.63 (0.31-1.28)	0.39 (0.10-1.57)	0.38 (0.09-1.54)	0.38 (0.09-1.54)
24-35 months ago	18	1.14 (0.71-1.83)	1.07 (0.62-1.83)	1.24 (0.61-2.53)	1.17 (0.68-2.01)	0.61 (0.19-1.94)	0.60 (0.19-1.90)	0.59 (0.19-1.88)
36-47 months ago	17	1.16 (0.71-1.90)	0.83 (0.44-1.56)	0.86 (0.35-2.10)	0.92 (0.49-1.73)	0.84 (0.31-2.30)	0.82 (0.30-2.24)	0.81 (0.30-2.22)
48-83 months ago	35	1.01 (0.71-1.44)	1.08 (0.74-1.58)	0.80 (0.42-1.54)	1.10 (0.73-1.64)	1.19 (0.68-2.07)	1.15 (0.66-2.00)	1.13 (0.65-1.98)
84+ months ago	18	0.90 (0.55-1.50)	0.97 (0.57-1.66)	0.55 (0.17-1.78)	0.86 (0.46-1.58)	1.00 (0.45-2.21)	0.96 (0.44-2.13)	0.94 (0.43-2.09)
DURATION OF PIO								
< 12 months	32	0.92 (0.65-1.30)	0.96 (0.66-1.40)	0.79 (0.44-1.43)	0.96 (0.64-1.42)	0.91 (0.48-1.70)	0.90 (0.48-1.68)	0.89 (0.48-1.67)
12-23 months	20	0.81 (0.52-1.27)	0.90 (0.56-1.45)	0.95 (0.48-1.86)	0.78 (0.46-1.34)	0.52 (0.19-1.41)	0.51 (0.19-1.38)	0.50 (0.18-1.36)
24-35 months	17	0.96 (0.59-1.57)	0.83 (0.46-1.48)	1.07 (0.50-2.28)	0.92 (0.51-1.64)	0.51 (0.16-1.60)	0.49 (0.16-1.56)	0.49 (0.15-1.56)
36-59 months	23	0.99 (0.64-1.52)	0.88 (0.53-1.44)	0.99 (0.48-2.04)	0.98 (0.60-1.62)	0.89 (0.43-1.87)	0.86 (0.41-1.80)	0.85 (0.41-1.78)
60+ months	18	1.03 (0.63-1.68)	1.01 (0.59-1.73)	0.40 (0.10-1.61)	0.93 (0.51-1.69)	1.31 (0.66-2.63)	1.26 (0.63-2.53)	1.24 (0.62-2.48)
DOSE OF PIO								
1-9,000 mg	28	0.83 (0.57-1.19)	0.93 (0.64-1.37)	0.98 (0.58-1.67)	0.96 (0.65-1.43)	0.69 (0.33-1.41)	0.68 (0.33-1.39)	0.67 (0.33-1.39)
9,001-25,000 mg	37	1.03 (0.73-1.44)	0.95 (0.64-1.40)	0.93 (0.53-1.64)	0.87 (0.56-1.33)	0.69 (0.33-1.43)	0.68 (0.33-1.40)	0.67 (0.32-1.38)
25,001-50,000 mg	23	0.86 (0.56-1.32)	0.78 (0.48-1.28)	0.76 (0.36-1.63)	0.83 (0.50-1.38)	0.73 (0.33-1.58)	0.70 (0.32-1.53)	0.70 (0.32-1.52)
≥50,001 mg	22	1.05 (0.67-1.64)	1.02 (0.63-1.68)	0.50 (0.16-1.58)	1.05 (0.62-1.77)	1.42 (0.76-2.65)	1.37 (0.74-2.56)	1.34 (0.72-2.51)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.14 Multiple Adjusted Hazard Ratios for **RECTAL** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	59	0.81 (0.60-1.08)	0.84 (0.61-1.14)	0.72 (0.44-1.19)	0.84 (0.60-1.16)	1.06 (0.66-1.70)	1.07 (0.66-1.72)	1.07 (0.67-1.73)
TIME SINCE INITIATION								
< 12 months ago	8	0.67 (0.34-1.29)	0.62 (0.29-1.32)	0.62 (0.20-1.94)	0.58 (0.26-1.31)	0.48 (0.12-1.95)	0.48 (0.12-1.96)	0.48 (0.12-1.97)
12-23 months ago	8	0.65 (0.32-1.31)	0.57 (0.26-1.29)	0.67 (0.21-2.09)	0.63 (0.28-1.42)	0.79 (0.25-2.52)	0.80 (0.25-2.53)	0.80 (0.25-2.54)
24-35 months ago	11	1.02 (0.56-1.86)	1.22 (0.66-2.23)	0.75 (0.24-2.37)	1.22 (0.64-2.30)	1.93 (0.83-4.49)	1.94 (0.83-4.52)	1.95 (0.84-4.53)
36-47 months ago	12	1.27 (0.71-2.27)	1.28 (0.67-2.42)	1.38 (0.56-3.41)	1.41 (0.75-2.68)	1.53 (0.55-4.27)	1.54 (0.56-4.29)	1.55 (0.56-4.31)
48-83 months ago	12	0.60 (0.33-1.08)	0.61 (0.32-1.17)	0.42 (0.13-1.33)	0.48 (0.23-1.04)	0.93 (0.39-2.21)	0.94 (0.40-2.23)	0.95 (0.40-2.25)
84+ months ago	8	0.87 (0.42-1.81)	1.06 (0.50-2.24)	0.73 (0.17-3.02)	1.23 (0.58-2.61)	1.33 (0.50-3.59)	1.35 (0.50-3.62)	1.36 (0.50-3.65)
DURATION OF PIO								
< 12 months	21	0.87 (0.57-1.33)	0.87 (0.55-1.39)	0.93 (0.47-1.84)	0.90 (0.56-1.46)	0.99 (0.48-2.06)	1.00 (0.48-2.07)	1.00 (0.48-2.08)
12-23 months	13	0.78 (0.45-1.37)	0.95 (0.54-1.66)	0.83 (0.34-2.04)	0.89 (0.49-1.64)	1.20 (0.52-2.77)	1.20 (0.52-2.79)	1.21 (0.52-2.81)
24-35 months	9	0.80 (0.41-1.56)	0.86 (0.42-1.74)	0.75 (0.24-2.35)	0.95 (0.47-1.94)	1.19 (0.43-3.28)	1.19 (0.43-3.30)	1.20 (0.43-3.32)
36-59 months	8	0.58 (0.29-1.18)	0.52 (0.23-1.18)	0.62 (0.19-1.95)	0.59 (0.26-1.33)	0.44 (0.11-1.83)	0.45 (0.11-1.85)	0.45 (0.11-1.85)
60+ months	8	0.89 (0.43-1.82)	0.91 (0.42-1.97)	NA	0.74 (0.30-1.83)	1.60 (0.66-3.88)	1.62 (0.67-3.92)	1.63 (0.67-3.95)
DOSE OF PIO								
1-9,000 mg	20	0.84 (0.54-1.30)	0.82 (0.51-1.33)	1.02 (0.53-1.94)	0.85 (0.52-1.39)	0.76 (0.33-1.75)	0.76 (0.33-1.76)	0.77 (0.33-1.77)
9,001-25,000 mg	18	0.76 (0.47-1.23)	0.87 (0.53-1.42)	0.57 (0.23-1.41)	0.85 (0.50-1.43)	1.38 (0.71-2.71)	1.39 (0.71-2.72)	1.40 (0.72-2.74)
25,001-50,000 mg	12	0.75 (0.42-1.34)	0.76 (0.40-1.44)	0.73 (0.27-1.99)	0.77 (0.39-1.51)	0.77 (0.28-2.14)	0.77 (0.28-2.16)	0.78 (0.28-2.16)
≥50,001 mg	9	0.82 (0.41-1.61)	0.87 (0.42-1.79)	0.30 (0.04-2.16)	0.87 (0.40-1.88)	1.42 (0.59-3.42)	1.43 (0.59-3.45)	1.43 (0.59-3.45)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

Table 1.15 Multiple Adjusted Hazard Ratios for **MELANOMA** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses		Sensitivity Analyses			Survey Responders		
	n cases exposed	**Full Cohort** (n= 236,507)	**Complete info on pioglitazone** (n= 196,401)	**Complete info on all diabetes prescriptions** (n= 120,255)	**Diabetes duration is known** (n= 182,661)	**Subcohort of Survey Responders** (n= 48,425)	**Adjusted for BMI** (n= 48,425)	**Adjusted[a] for BMI, education and behaviors** (n= 48,425)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever Pioglitazone†	102	1.15 (0.91-1.46)	1.14 (0.88-1.47)	1.09 (0.73-1.62)	1.17 (0.90-1.53)	1.22 (0.82-1.82)	1.21 (0.81-1.80)	1.21 (0.81-1.80)
TIME SINCE INITIATION								
< 12 months ago	10	1.03 (0.60-1.76)	1.09 (0.61-1.94)	0.96 (0.39-2.35)	1.15 (0.64-2.05)	1.24 (0.50-3.06)	1.23 (0.50-3.05)	1.23 (0.50-3.05)
12-23 months ago	18	1.37 (0.85-2.21)	1.37 (0.81-2.30)	1.44 (0.67-3.08)	1.45 (0.86-2.45)	1.30 (0.56-2.99)	1.29 (0.56-2.98)	1.29 (0.56-2.98)
24-35 months ago	12	1.02 (0.57-1.83)	0.90 (0.46-1.75)	0.94 (0.35-2.54)	0.96 (0.49-1.87)	0.91 (0.33-2.51)	0.91 (0.33-2.50)	0.91 (0.33-2.49)
36-47 months ago	16	1.45 (0.87-2.40)	1.50 (0.87-2.58)	1.57 (0.69-3.57)	1.38 (0.77-2.48)	1.72 (0.78-3.77)	1.70 (0.77-3.74)	1.69 (0.77-3.72)
48-83 months ago	24	0.96 (0.62-1.47)	0.87 (0.53-1.41)	0.77 (0.34-1.77)	0.84 (0.50-1.41)	0.79 (0.37-1.68)	0.78 (0.37-1.66)	0.78 (0.37-1.65)
84+ months ago	22	1.47 (0.91-2.36)	1.52 (0.91-2.56)	2.03 (0.86-4.81)	1.72 (1.02-2.90)*	1.52 (0.73-3.15)	1.50 (0.72-3.10)	1.49 (0.72-3.08)
DURATION OF PIO								
< 12 months	25	1.06 (0.73-1.54)	0.93 (0.60-1.45)	0.70 (0.33-1.49)	0.96 (0.61-1.50)	1.14 (0.60-2.14)	1.13 (0.60-2.13)	1.13 (0.60-2.14)
12-23 months	29	1.59 (1.08-2.33)*	1.59 (1.04-2.43)*	1.59 (0.83-3.03)	1.58 (1.02-2.46)*	1.53 (0.79-2.98)	1.52 (0.78-2.95)	1.51 (0.78-2.94)
24-35 months	14	1.06 (0.62-1.81)	1.17 (0.66-2.05)	1.35 (0.59-3.07)	1.16 (0.65-2.09)	0.78 (0.28-2.14)	0.77 (0.28-2.13)	0.77 (0.28-2.13)
36-59 months	14	0.80 (0.46-1.37)	0.74 (0.40-1.37)	1.12 (0.49-2.56)	0.80 (0.44-1.48)	0.68 (0.27-1.70)	0.67 (0.27-1.69)	0.66 (0.26-1.67)
60+ months	20	1.46 (0.91-2.35)	1.47 (0.87-2.47)	1.51 (0.61-3.77)	1.62 (0.96-2.73)	1.77 (0.89-3.54)	1.75 (0.88-3.49)	1.74 (0.87-3.48)
DOSE OF PIO								
1-9,000 mg	28	1.20 (0.84-1.72)	1.04 (0.68-1.58)	0.68 (0.32-1.46)	1.07 (0.70-1.64)	1.52 (0.86-2.69)	1.50 (0.85-2.66)	1.52 (0.86-2.68)
9,001-25,000 mg	34	1.26 (0.88-1.81)	1.39 (0.95-2.03)	1.51 (0.87-2.64)	1.36 (0.92-2.02)	1.04 (0.53-2.01)	1.03 (0.53-2.00)	1.02 (0.53-1.99)
25,001-50,000 mg	21	1.03 (0.66-1.62)	0.94 (0.56-1.57)	1.48 (0.75-2.92)	1.02 (0.61-1.71)	0.71 (0.31-1.66)	0.71 (0.30-1.64)	0.70 (0.30-1.63)
≥50,001 mg	19	1.14 (0.70-1.85)	1.13 (0.67-1.93)	1.03 (0.38-2.84)	1.25 (0.73-2.13)	1.38 (0.70-2.73)	1.37 (0.69-2.70)	1.36 (0.69-2.69)

†Never use of pioglitazone as reference group for all analyses.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. All models adjusted for age, ever use of other DM medications, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.
[a]Additional adjustment for BMI, education, and behaviors (weekly alcohol intake and total packs smoked [instead of current smoking]).

TABLE 1.16 Hazard Ratios and 95% confidence intervals for the association between cancer at the ten most common sites and ever use of diabetes medication versus never use.

	Prostate		Female Breast		Lung/Bronchus		Colon		NHL[a]	
	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)
Pioglitazone										
Never use	3,307	1.00	2,478	1.00	2,300	1.00	1,844	1.00	839	1.00
Ever use	476	1.13 (1.02-1.26)*	320	1.00 (0.88-1.13)	282	1.00 (0.87-1.15)	233	0.91 (0.78-1.05)	120	1.00 (0.81-1.23)
Other TZD										
Never use	3,708	1.00	2,731	1.00	2,528	1.00	2,025	1.00	932	1.00
Ever use	75	0.90 (0.71-1.14)	67	0.94 (0.73-1.21)	54	0.90 (0.68-1.19)	52	1.06 (0.80-1.41)	27	1.11 (0.75-1.66)
Metformin										
Never use	2,062	1.00	1,510	1.00	1,561	1.00	1,176	1.00	515	1.00
Ever use	1,721	1.07 (0.99-1.16)	1,288	0.94 (0.86-1.04)	1,021	0.89 (0.81-0.98)*	901	0.92 (0.83-1.03)	444	1.07 (0.91-1.26)
Insulin										
Never use	3,092	1.00	2,111	1.00	1,962	1.00	1,589	1.00	747	1.00
Ever use	691	0.90 (0.81-0.99)*	687	1.08 (0.97-1.21)	620	1.21 (1.08-1.35)*	488	1.03 (0.90-1.16)	212	0.91 (0.76-1.10)
Sulfonylureas										
Never use	1,577	1.00	1,248	1.00	1,0,75	1.00	808	1.00	404	1.00
Ever use	2,206	0.95 (0.86-1.04)	1,550	0.98 (0.88-1.08)	1,507	1.11 (0.99-1.24)	1,269	1.10 (0.96-1.24)	555	0.98 (0.82-1.18)
Other oral agents										
Never use	3,739	1.00	2,771	1.00	2,543	1.00	2,051	1.00	935	1.00
Ever use	44	0.83 (0.61-1.12)	27	0.60 (0.41-0.88)*	39	1.08 (0.78-1.49)	26	0.82 (0.55-1.21)	24	1.67 (1.10-2.52)*

[a] Non-Hodgkin Lymphoma

Models adjusted for age, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

TABLE 1.16 (continued) Hazard Ratios and 95% confidence intervals for the association between cancer at the ten most common sites and ever use of diabetes medication versus never use.

	Corpus Uteri		Pancreas		Kidney/ Renal Pelvis		Rectal		Melanoma	
	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)	n cases	HR (95% CI)
Pioglitazone										
Never use	799	1.00	648	1.00	690	1.00	570	1.00	594	1.00
Ever use	118	0.88 (0.71-1.09)	164	1.41 (1.16-1.71)*	110	0.95 (0.76-1.18)	59	0.81 (0.60-1.08)	102	1.15 (0.91-1.46)
Other TZD										
Never use	884	1.00	778	1.00	774	1.00	618	1.00	672	1.00
Ever use	33	1.31 (0.91-1.88)	34	1.31 (0.92-1.89)	26	1.34 (0.89-2.02)	11	0.81 (0.44-1.49)	24	1.28 (0.83-1.97)
Metformin										
Never use	426	1.00	373	1.00	403	1.00	353	1.00	383	1.00
Ever use	491	1.06 (0.90-1.25)	439	1.21 (1.02-1.43)*	397	1.07 (0.90-1.28)	276	1.00 (0.82-1.22)	313	0.95 (0.79-1.15)
Insulin										
Never use	681	1.00	516	1.00	599	1.00	505	1.00	534	1.00
Ever use	236	1.00 (0.84-1.20)	296	2.34 (1.97-2.78)	201	1.11 (0.91-1.35)	124	0.95 (0.75-1.21)	162	0.99 (0.80-1.23)
Sulfonylureas										
Never use	361	1.00	251	1.00	330	1.00	251	1.00	294	1.00
Ever use	556	1.09 (0.91-1.30)	561	1.49 (1.22-1.81)*	470	1.02 (0.84-1.23)	378	1.14 (0.90-1.44)	402	1.07 (0.86-1.32)
Other oral agents										
Never use	904	1.00	792	1.00	787	1.00	622	1.00	684	1.00
Ever use	13	0.76 (0.44-1.32)	20	1.11 (0.71-1.74)	13	0.97 (0.56-1.70)	7	0.83 (0.39-1.76)	12	1.10 (0.62-1.96)

Models adjusted for age, year of entry in the cohort, sex, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

STUDY 2: Epidemiologic study of diabetes and cancer risk

2.A. BACKGROUND AND SPECIFIC AIMS

As requested by Takeda, our expansion includes a second study, the goal of which is to examine the association between diabetes and cancer risk in the KPNC membership. Once diagnosed, type 2 diabetes is usually treated with oral hypoglycemic agents and/or insulin. Therefore, disentangling risks associated with the disease from risks associated with treatment for the disease is nearly impossible.

With this understanding, our specific aims were as follows:

1. To estimate the age- and sex- specific incidence rates within the full KPNC membership for each of the 10 most common cancers among those with diabetes and among those without diabetes.

2. To estimate the age- and sex-standardized incidence rates (standardized to the 2000 U.S. Census) within the full KPNC membership for each of the 10 most common cancers besides bladder cancer among those with and those without diabetes

3. To estimate the relative risk of the 10 most common cancers associated with diabetes within the full KPNC membership, while adjusting for age, gender, and calendar year. In primary analyses, diabetes status was treated as time-varying. In sensitivity analyses, diabetes status was fixed at baseline (with censoring at diabetes diagnosis during follow-up).

4. To explore potential confounding by variables that are not consistently available for the full membership by estimating the relative risk of the 10 most common cancers associated with diabetes. Analyses were conducted among subsets of the KPNC membership with survey information on additional potential confounders (race, BMI, smoking, and alcohol). Diabetes status was treated as time-varying in primary analyses and was fixed at baseline in sensitivity analyses.

2.B. METHODS

a. Study population and data sources

This study utilized electronic health and administrative records available within the databases of KPNC, as well as data from surveys sent to health plan members with and without diabetes.

b. Inclusion Criteria

Individuals were eligible for cohort entry the first time all three of the following criteria were met: January 1, 1997, 40 years of age or older, they were members of KPNC for at least 6 months and had no prior diagnosis of the cancer of interest.

c. Analyses within the Full KPNC Membership (Aims 1, 2 and 3)

A retrospective longitudinal cohort study design was used to investigate the incidence of cancer at 10 sites (prostate, female breast, lung/bronchus, corpus uteri, colon, Non-Hodgkin lymphoma, pancreas, kidney/renal pelvis, rectum and melanoma) by diabetes status among members of the KPNC who were age 40 or older between January 1, 1997 and June 30, 2011 and had no prior diagnosis of the cancer of interest. At baseline, there were 156,174 persons identified by the Kaiser Diabetes Registry who had recognized diabetes and 2,474,492 persons identified in the KPNC membership file who were not included in the Kaiser Diabetes

Registry (i.e. did not have recognized diabetes). By the end of follow-up, there were 332,017 members with diabetes and 2,298,649 members without diabetes.

d. Subset of KPNC Members who responded to the Surveys (Aim 4)

A similar retrospective longitudinal cohort study design was used to investigate the incidence of cancer at 10 sites among 62,053 adults with recognized diabetes who completed the Kaiser Diabetes Registry Survey in 1994-1996 and among a random sample of KPNC members who completed a similar survey, the Member Health Survey (MHS), in 1996, 1999, 2002, or 2005 (54,551 for all four surveys combined) who did not have recognized diabetes (i.e., were not included in the Kaiser Diabetes Registry and did not report having been diagnosed with diabetes on the MHS); all were age 40 or older between January 1, 1997 and June 30, 2011and had no prior diagnosis of the cancer of interest. Both those persons with recognized diabetes and those without provided information on potential confounders, such as age, smoking, ethnicity, weight, and height, by responding to these surveys. The questions related to these items were similar in the Diabetes Registry and MHS surveys.

Persons who were no longer members of KPNC at the time they completed either the Diabetes Registry survey or the MHS were excluded. Members who responded to both the MHS and the Diabetes Registry survey were included in the diabetes group and data on potential confounders were obtained from the Diabetes Registry survey. Those who participated in the MHS and reported they had diabetes (and were in the Diabetes Registry), but did not participate in the Diabetes Registry survey, were included in the diabetes group and their covariate data were obtained from the MHS. MHS responders identified in the Diabetes Registry at the time of their MHS who did not indicate they had diabetes on the MHS were excluded, as were those reporting diabetes on the MHS who were not found in the Diabetes Registry.

d.1. Diabetes Registry Survey (Aim 4)

Between 1994 and 1996, a 4-page survey was mailed to all health plan members with recognized diabetes who were age 18 years and older and were current KPNC members. The principal aim of the survey was to obtain information on race/ethnicity, duration of diabetes, body mass index (BMI), education, alcohol intake, and smoking. Of the 76,447 members who responded to the survey, approximately 1% stated that they did not have diabetes and therefore, were excluded from the diabetes group.

d.2. Assembly of the cohort of Diabetes Registry responders (Aim 4)

Initially, 76,447 members were identified by the Diabetes Registry survey. Those who stated on the Diabetes Registry survey that they did not have diabetes were excluded first, followed by those who were not in the Diabetes Registry by the end of 1997 and those who were not members of Kaiser Permanente at the time of the Diabetes Registry survey. This left 65,016 members.

A total of 2,715 members stated on the MHS that they had diabetes and were in the Diabetes Registry at the time of the MHS, but they were not included in the Diabetes Registry survey. These 2,715 members were added to the diabetes group (n= 67,731). Finally, members who were under 40 years of age or not a member of Kaiser Permanente between 1997 and 2011 were excluded, as were those ≥4 months gap in membership the first 4 months after cohort entry leaving 62,053 members in the diabetes group. An additional 3,752 members developed diabetes during follow-up; after excluding those with prevalent cancer, there were 60,856 members with diabetes. (Table 2.1b)

d.3. Member Health Surveys (MHS) (Aim 4)

The principal aim of the MHS was to obtain data on race and ethnicity, chronic disease prevalence, health practices, functional status, and health behaviors, such as alcohol and smoking. Questionnaires were mailed out in 1993, 1996, 1999, 2002, and 2005 to random samples of KPMCP members, age 18 and above, stratified by age and KPMCP facility. The MHS did not begin obtaining permission for using these data for research until 1996; therefore, the 1993 survey data are not included in this report.

The 1996 survey had 17,735 responders (53%), the 1999 survey had 18,937 responders (50%), the 2002 survey had 18,604 responders (47%), and the 2005 survey had 18,733 responders (45%).

d.4. Assembly of the cohort of Member Health Survey (MHS) responders (Aim 4)

The non-diabetic comparison group initially contained health plan members who responded to the MHS in 1993, 1996, 1999, 2002, or 2005. For those who completed more than one MHS (i.e., multiple survey years), data from the earliest MHS completed were included. This was a total of 91,345 MHS responders.

As noted above, MHS responders found in the Diabetes Registry survey were excluded, as were those who were no longer members of the health plan at the time of the MHS, leaving 85,757 potential cohort members. Members who denied having diabetes on the MHS but who were found in the Diabetes Registry were excluded, as were those who reported having diabetes on the MHS but were not found in the Diabetes Registry at the time of the MHS (leaving 84,791).

Members who reported having diabetes on the MHS who were also in the Diabetes Registry at the time of MHS were excluded from the non-diabetic comparison group (and included in the diabetes group, as mentioned above).

Those who were under 40 years of age or not a member of KPNC between 1997 and 2011 were excluded, as were those who had developed diabetes prior to entering the cohort, and those ≥4 months gap in membership the first 4 months after cohort entry. Lastly, the 1993 MHS responders were excluded, leaving 54,551 members in the non-diabetic comparison group. After excluding those with a history of cancer at baseline, there were 50,211 members in the non-diabetic comparison group at cohort entry. As previously noted, 3,572 members developed diabetes over the course of follow-up.

e. Follow-up time

The beginning of follow-up for aims 1, 2, and 3 matched that of our study of pioglitazone use and cancer risk (Study 1). Follow-up began at cohort entry, defined as the first time all three of the following criteria are met: January 1, 1997, aged 40 years or older, and enrollment in KPNC for at least 6 months. For aim 4, the earliest start of follow-up was January 1, 1997. For those who completed surveys after January 1, 1997, follow-up began at the later of the two dates: the date of survey completion or cohort entry (as defined for aims 2-3).

Follow-up ended at the earliest of: 1) diagnosis of the outcome of interest, 2) death, 3) a gap of greater than 4 months in membership, or 4) the end of the study period (December 31, 2011). In selected analyses, patients were censored at the time of a surgery (for indications other than cancer) that significantly reduced or precluded cancer development at that organ site (prostatectomy, oophorectomy, hysterectomy, colectomy, mastectomy).

f. Covariates

In addition to the potential confounding variables age and sex, which were available from the electronic databases on the full membership, the following potential confounding variables were collected in the surveys: race-ethnicity [non-Hispanic white (reference), African American, Hispanic, Asian or Pacific Islander, other, and missing], education [some high school or high school graduate (reference), some college, college graduate or post-college, and missing], alcohol consumption [abstain (reference), <7 drinks per week, ≥7 drinks per week, and missing], smoking [0 (reference), 1-5,000 total packs smoked, ≥ 5,001 total packs smoked and missing], and self-reported body mass index [BMI; <19 kg/m^2, 19-24 kg/m^2 (reference), 25-29 kg/m^2, 30-34 kg/m^2, and ≥35 kg/m^2].

g. Statistical Analyses

In primary analyses, diabetes status was treated as time-varying. Those who responded to the MHS and were later identified by the Diabetes Registry were considered to have diabetes at the date they were identified by

the Diabetes Registry, at which time they started to contribute to the follow-up time to the diabetes group. In sensitivity analyses, diabetes status was fixed at baseline (with censoring at diabetes diagnosis during follow-up). In these analyses, those who responded to the MHS and were later identified as having diabetes by Diabetes Registry had their follow-up time censored at the time of the diabetes diagnosis.

For each cancer site of interest, prevalent cases of that cancer were excluded from analyses. For each cancer site, age (categorized in 10 year intervals) and sex-specific incidence rates (and 95% confidence intervals) were calculated, stratified by diabetes status (Aim 1), with attention to the proper allocation of at-risk person-time as cohort members move through age categories and potentially change diabetes status during follow-up. Age-and sex-standardized incidence rates, stratified by diabetes status, were calculated using the direct method (2000 U.S. Census as standard).

The association between diabetes and risk of each of the 10 most common cancers among the full KPNC membership was assessed using Cox proportional hazards regression models, providing point and interval estimates of the relative hazard of each cancer outcome associated with diabetes status (time-dependent covariate), with control for available potential confounders: age (categorical variable with 5 year intervals), sex, calendar year (Aim 3).

Similarly, we used Cox regression techniques to examine the association between diabetes status and cancer risk among the survey responder cohort, with adjustment for additional potential confounding variables (Aim 4). First, we compared the estimate of relative hazard for each cancer associated with diabetes adjusted for age, sex, and calendar year in the survey respondent cohort to that obtained in analysis of the full KPNC membership cohort. If HRs were similar, we examined additional potential confounding in the following models: Model 1: age, sex, calendar year; Model 2: Model 1 covariates plus race/ethnicity; Model 3: Model 2 covariates plus smoking; Model 4: Model 3 covariates plus BMI, education, and alcohol consumption. Model 4 was considered the fully adjusted model.

2. C. RESULTS

Characteristics of the study population – full KPNC membership

The distributions of person-years by age, sex, and diabetes status are presented in **Table 2.1a** for the full KPNC cohort and **Table 2.1b** for the cohort survey responders. Among members without diabetes, those less than 60 years of age contributed 66% of the person-time in the full cohort and 47% of the person-time in the cohort of survey responders. Among members with diabetes, those less than 60 years of age contributed approximately 43% of the person-time in the full cohort and approximately 33% of the person-time in the cohort of survey responders. As expected, the age distribution was slightly older among those with diabetes. Among those without diabetes, there was more follow-up for females; the opposite was true for those with diabetes.

Characteristics of the DM and MHS sub-cohort

More DM patients had survey data than non-DM patients (60,856 vs. 46,639, respectively; **Table 2.2**). Those with diabetes were more commonly non-white and more commonly obese (BMI= 30+). Those with DM were less commonly current or heavy alcohol drinkers, never smokers, or college graduates.

Age- and sex- standardized cancer rates – full KPNC membership

The age- and sex-standardized rates of the 10 most common cancers among those with diabetes and among those without diabetes are presented in **Table 2.3**. The total number of cancers and the standardized rates were highest for breast, prostate, and lung.

For six cancer sites (colon, uterine, kidney/renal pelvis, NHL, pancreas, rectum), rates were higher among those with diabetes. In contrast, for melanoma and prostate, rates among patients with diabetes were lower. No difference in standardized incidence rates by diabetes status were observed for lung cancer and breast cancer.

Age- and sex- standardized cancer rates – survey sub-cohort

The age- and sex-standardized rates of the 10 most common cancers among those with diabetes and among those without diabetes are presented in **Table 2.3**. Standardized rates were generally very similar to those in the full KPNC membership. However, in DM patients the rates of pancreatic and prostate cancer were lower in the survey sub-cohort compared to the full KPNC membership. In non-DM patients, the rate of prostate cancer was higher in the survey sub-cohort compared to the full KPNC membership.

Age- and sex- adjusted hazard ratios associated with DM – full KPNC membership

The age- and sex-adjusted hazard ratios (HR) for the 10 most common cancers associated with diabetes are presented in **Table 2.4** (see column 2). As expected based on the standardized rates, the HRs associated with diabetes (time-varying) were elevated for several sites. Note, HRs were virtually identical when diabetes status was fixed at baseline (not shown).

Age- and sex- adjusted hazard ratios associated with DM – survey sub-cohort

The age- and sex-adjusted HRs for the 10 most common cancers associated with diabetes (time-varying) among the survey cohorts are presented in **Table 2.4** (see column 3). The HRs were similar to those for the full KPNC membership. Similar results were obtained when diabetes was fixed at baseline (not shown).

Potential confounding by variables not available on the full KPNC membership

In analyses conducted among the survey sub-cohort, there was no evidence of confounding by race-ethnicity or smoking for any of the 10 most common cancers (i.e., HRs did not change when these variables were added, one at a time, to models; data not shown). However, there was evidence of a modest amount of positive confounding by BMI for uterine cancer (age-, sex-, year of cohort entry-, race-ethnicity and smoking-adjusted HR=1.82 vs. HR=1.26 with same variables plus BMI) and for kidney cancer (HRs =1.41 vs. 1.23, respectively). See **Table 2.4** for HRs from models adjusted for age, year of cohort entry, and sex (column 3) and the HRs from the fully adjusted model with age, year of cohort entry, sex, race, smoking, education, alcohol consumption, and BMI (column 4).

Comparisons with other studies

A comparison of the HRs for six cancer sites among the KPNC membership with HRs from meta-analyses of studies of these same cancer sites are presented in **Figure 2.1**. For all sites but breast, the HRs are fairly similar and have overlapping confidence limits. In contrast to the meta-analysis result for breast, we found no increase in cancer risk associated with diabetes.

2. D. DISCUSSION

In our study of over 2.5 million adults aged 40 years and older, we found that the age- and sex- adjusted rates of several cancers (colon, NHL, uterine, pancreatic, kidney/renal, and rectal) were slightly to moderately higher among patients with diabetes than among those without diabetes. In contrast, rates of prostate and melanoma were lower and rates of breast and lung were similar among those with and without diabetes.

The patterns observed in the full KPNC membership were generally quite similar to what has been reported by others (17), both with respect to standardized cancer rates among the non-DM patients, and with respect to associations of diabetes with cancer risk (i.e., HRs). There was a slight difference in the association of diabetes with breast cancer risk in our study (HR=1.0) compared to the meta-analysis (HR=1.2). This could be due to chance alone or to differences between the study populations, such as race/ethnicity or use of cancer screening modalities.

We also examined potential confounding by several factors unavailable on the full membership but available on two separate survey populations. Importantly, the age- and sex-standardized cancer rates and the age- and sex-adjusted HRs for cancer associated with diabetes were, in general, quite similar to those observed in the full KPNC membership. We found very little evidence of confounding by race/ethnicity or smoking. However, there was evidence of a modest amount of positive confounding by BMI for uterine and kidney cancer.

This study has several strengths and limitations. The study was population-based, with sufficient size and follow-up time such that our point estimates for most cancer sites were fairly precise. Our study was conducted among members of a large, prepaid health plan and therefore may not be generalizable to all settings. However, our cancer rates and our estimates of risk associated with diabetes are generally quite similar to those reported by others. Although we did not have information on several potentially important confounding variables on the full cohort, we were able to examine confounding by many of these variables in sub-cohorts that appeared to be representative of the general membership and diabetes registry.

In conclusion, a diagnosis of diabetes appears to be associated with an increased risk of several common cancers and a decreased risk of a smaller number of others. For most cancer sites, this association does not appear to be confounded by race/ethnicity, smoking, BMI, education, or alcohol consumption.

Table 2.1a: Total person-years* by age, sex and diabetes status among the full KPNC cohort° (n=2,630,666).

Total person-years in each age group *	NO DM (n=2,474,492‡)						DM (n=332,017‡)					
	Female (n=1,281,864)		Male (n=1,192,628)		Combined		Female (n=151,884)		Male (n=180,133)		Combined	
	Person-years	% (col)	Person-years	% (col)	Person-years	% (col)	Person-years	% (col)	Person-years	% (col)	Person-years	% (col)
40-44	1,531,588	17.93	1,454,388	19.86	2,985,976	18.82	57,610	6.23	72,676	6.87	130,286	6.58
45-49	1,462,738	17.12	1,341,755	18.33	2,804,493	17.68	82,684	8.95	105,119	9.94	187,803	9.48
50-54	1,341,345	15.70	1,204,255	16.45	2,545,600	16.05	112,079	12.13	138,721	13.12	250,800	12.66
55-59	1,138,017	13.32	1,002,145	13.69	2,140,161	13.49	131,561	14.24	160,959	15.22	292,520	14.76
60-64	893,659	10.46	764,884	10.45	1,658,543	10.45	131,179	14.20	160,712	15.20	291,891	14.73
65-69	656,876	7.69	538,258	7.35	1,195,134	7.53	119,727	12.96	141,473	13.38	261,199	13.18
70-74	533,621	6.25	406,618	5.55	940,239	5.93	109,302	11.83	118,654	11.22	227,956	11.51
75-79	430,339	5.04	299,000	4.08	729,339	4.60	87,729	9.49	86,145	8.15	173,874	8.78
80-84	301,754	3.53	187,226	2.56	488,980	3.08	56,718	6.14	48,672	4.60	105,390	5.32
85+	253,537	2.97	122,999	1.68	376,536	2.37	35,482	3.84	24,089	2.28	59,570	3.01
All (%row)	8,543,473	47.87	7,321,528	41.03	15,865,001	88.90	924,070	5.18	1,057,218	5.92	1,981,288	11.10

* Person years calculated by censoring at first invasive cancer.

° Excludes those with any prevalent cancer, except non-melanoma skin cancer, at cohort entry.

‡ n=175,843 who contributed person-time to both the No DM and the DM groups.

Table 2.1b: Total person-years* by age, sex and diabetes status among the cohort of survey responders° (n= 107,495).

Total person-years in each age group *	NO DM (n=50,211‡)						DM (n=60,856‡)					
	Female(n=27,663)		Male (n=22,548)		Combined		Female (n=28,445)		Male (n=32,411)		Combined	
	Person-years	%(col)	Person-years	%(col)	Person-years	%(col)	Person-years	%(col)	Person-years	%(col)	Person-years	%(col)
40-44	23,265	11.32	16,290	10.22	39,555	10.84	9,461	3.77	9,079	3.33	18,540	3.54
45-49	25,588	12.45	18,500	11.61	44,087	12.08	16,570	6.59	16,545	6.07	33,114	6.32
50-54	25,126	12.22	18,918	11.87	44,043	12.07	25,015	9.96	27,331	10.02	52,346	9.99
55-59	23,731	11.54	18,386	11.54	42,117	11.54	31,367	12.48	37,275	13.67	68,642	13.10
60-64	20,430	9.94	16,690	10.47	37,120	10.17	35,342	14.07	42,501	15.58	77,843	14.86
65-69	18,086	8.80	15,358	9.64	33,444	9.16	36,758	14.63	42,541	15.60	79,299	15.13
70-74	18,552	9.02	15,468	9.71	34,021	9.32	36,654	14.59	39,928	14.64	76,582	14.62
75-79	20,979	10.20	17,325	10.87	38,303	10.50	30,541	12.16	31,367	11.50	61,908	11.81
80-84	18,353	8.93	14,503	9.10	32,856	9.00	18,954	7.54	18,060	6.62	37,014	7.06
85+	11,471	5.58	7,923	4.97	19,394	5.31	10,591	4.22	8,101	2.97	18,692	3.57
All (%row)	205,581	23.13	159,359	17.93	364,940	41.05	251,252	28.26	272,726	30.68	523,979	58.95

* Person years was calculated by censoring at first invasive cancer.

° Excludes those with any prevalent cancer, except non-melanoma skin cancer, at cohort entry.

‡ n=3,572 who contributed person-time to both the No DM and DM groups.

Table 2.2 Characteristics of survey sub-cohort (n=107,495) by diabetes (DM) status (1997-2011)

	Never DM (n= 46,639)		**Ever DM** (n= 60,856)	
Characteristic	n	%	n	%
Race-ethnicity				
White	33,449	71.72	34,388	56.51
Black	2,561	5.49	7,606	12.50
Hispanic	3,727	7.99	8,144	13.38
Asian/Pacific Islander	5,493	11.78	8,015	13.17
Other	905	1.94	1,823	3.00
Missing	504	1.08	880	1.45
Alcohol				
Never	5,508	11.81	11,080	18.21
Former	6,201	13.30	14,377	23.62
Current	33,178	71.14	28,860	47.42
Missing	1,752	3.76	6,539	10.75
Education				
High School Graduate	11,711	25.11	23,989	39.42
Some college	17,578	37.69	17,830	29.30
College graduate	16,979	36.41	13,756	22.60
Missing	371	0.80	5,281	8.68
Smoking				
Current	4,940	10.59	6,512	10.70
Former	13,700	29.37	21,765	35.76
Never	27,195	58.31	27,243	44.77
Missing	804	1.72	5,336	8.77
BMI				
<19	1,242	2.66	481	0.79
19-24	19,037	40.82	10,909	17.93
25-29	16,333	35.02	19,716	32.40
30-24	5,706	12.23	13,021	21.40
35+	2,416	5.18	10,164	16.70
Missing	1,905	4.08	6,565	10.79

Table 2.2 (continued) Characteristics of survey sub-cohort (n=107,495) by diabetes (DM) status (1997-2011)

	Never DM (n= 46,639)		**Ever DM** (n= 60,856)	
Characteristic	n	%	**Characteristic**	n
Alcohol (drinks/week)				
0	11,711	25.11	25,480	41.87
<7	20,613	44.20	22,099	36.31
≥7	9,101	19.51	4,758	7.82
Missing	5,214	11.18	8,519	14.00
Smoking (total packs)				
0	25,379	54.42	27,100	44.53
1-5000	6,563	14.07	8,738	14.36
≥5001	8,285	17.76	16,240	26.69
Missing	6,412	13.75	8,778	14.42

Table 2.3 Age- and sex-standardized incidence rates for the 10 most common cancers, by diabetes status (1997-2011).

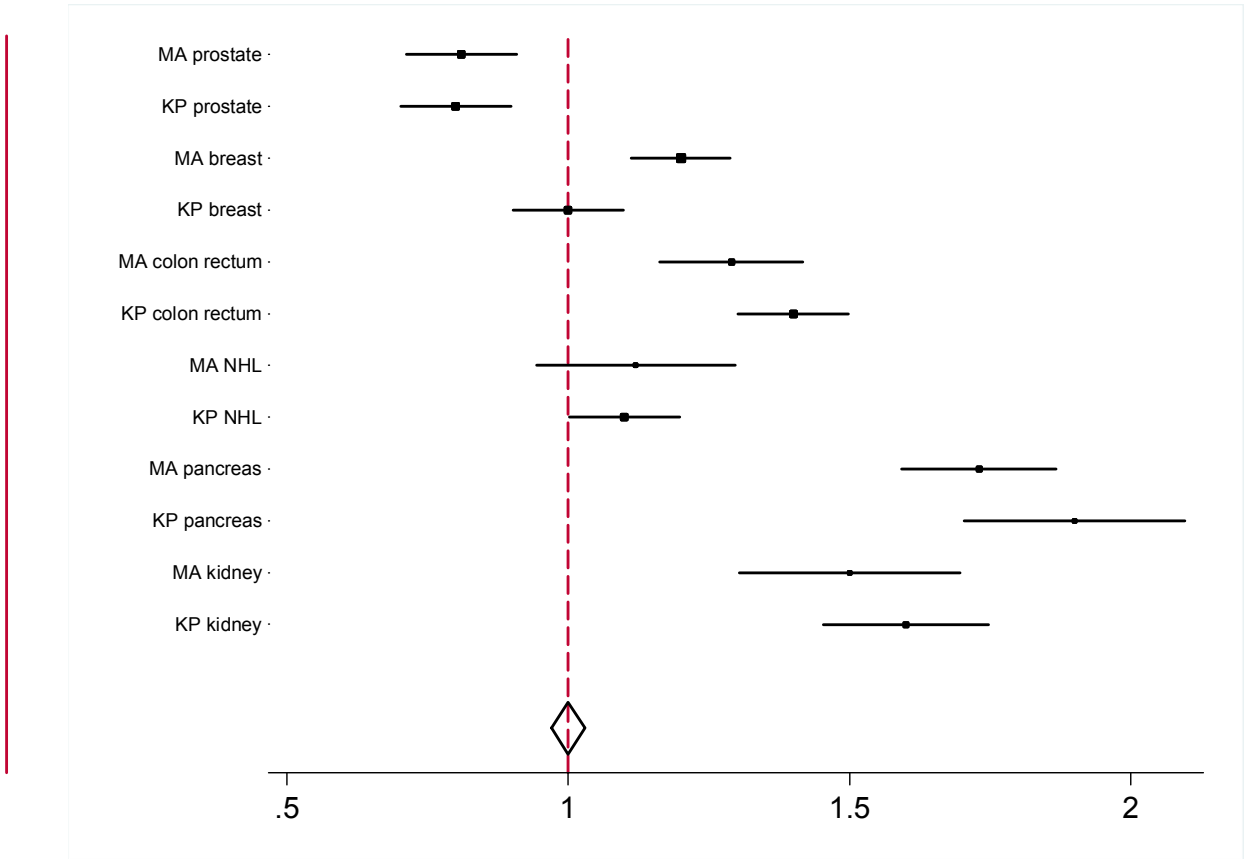
		Full KPNC cohort			Survey Sub-cohort		
Cancer Site	DM	Number of Cases	Sex-standardized incidence rates	95% CI	Number of Cases	Sex-standardized incidence rates	95% CI
Prostate	No	26,560	380.2	375.6 - 384.9	957	421.9	393.6 - 450.2
	Yes	4,902	308.0	299 - 316.9	1,393	281.9	265.7 - 298.2
Female Breast	No	25,140	291.8	288.2 - 295.5	757	310.7	287.6 - 333.8
	Yes	3,442	286.9	276.3 - 297.5	1,022	287.9	266.1 - 309.6
Lung/Bronchus	No	17,463	111.3	109.7 – 113.0	729	116.1	107.0 - 125.3
	Yes	3,462	108.8	104.9 - 112.6	1,070	105.9	98.5 - 113.2
Colon	No	10,590	69.1	67.8 - 70.5	445	75.5	67.9 - 83.1
	Yes	2,699	93.5	89.7 - 97.3	894	97.3	90.1 - 104.5
NHL	No	6,305	39.5	38.5 - 40.5	225	40.6	34.6 - 46.6
	Yes	1,318	45.6	42.8 - 48.4	392	43.2	37.7 - 48.6
Corpus uteri	No	4,720	55.9	54.3 - 57.5	144	59.7	49.6 - 69.8
	Yes	1,209	112.1	104.9 - 119.2	356	106.2	92.7 - 119.6
Pancreas	No	2,924	18.8	18.1 - 19.5	117	18.5	14.9 - 22.1
	Yes	1,433	47.3	44.6 - 49.9	350	37.1	32.3 - 41.9
Kidney/Renal Pelvis	No	3,808	23.5	22.7 - 24.2	126	21.5	17.2 - 25.7
	Yes	1,124	39.5	36.8 - 42.2	304	34.5	29.0 - 40.0
Rectal	No	3,951	24.6	23.8 - 25.4	134	26.7	21.7 - 31.7
	Yes	860	31.1	28.7 - 33.4	261	31.9	26.6 - 37.2
Melanoma	No	6,953	42.5	41.5 - 43.5	288	55.8	48.5 - 63.0
	Yes	891	30.6	28.2 - 32.9	281	31.7	26.8 - 36.7

Table 2.4 Hazard Ratios for risk of 10 common cancers associated with DM (time-dependent) in the full KPNC membership and the sub-cohort of survey responders

Cancer	Full KPNC cohort	Sub-cohort of Survey Responders	
	Basic Model[1] HR (95% CI)	Basic Model[1] HR (95% CI)	Fully Adjusted Model[2] HR (95% CI)
Prostate	0.81 (0.78-0.83)	0.77 (0.68- 0.86)	0.78 (0.69- 0.88)
Female Breast	1.01 (0.98-1.05)	0.98 (0.86- 1.12)	0.99 (0.86- 1.14)
Lung/Bronchus	0.99 (0.96-1.03)	0.84 (0.74- 0.96)	0.88 (0.77- 1.01)
Colon	1.36 (1.31-1.42)	1.18 (1.01- 1.38)	1.13 (0.96- 1.33)
NHL	1.14 (1.07-1.21)	1.06 (0.85- 1.33)	1.04 (0.82- 1.32)
Corpus Uteri	1.82 (1.71- 1.95)	1.67 (1.28- 2.18)	1.43 (1.08- 1.90)
Pancreas	2.50 (2.35- 2.67)	2.38 (1.78- 3.18)	2.30 (1.71- 3.10)
Kidney/Renal Pelvis	1.56 (1.46- 1.67)	1.37 (1.04- 1.82)	1.16 (0.87- 1.56)
Rectal	1.25 (1.16-1.35)	1.41 (1.05- 1.89)	1.48 (1.09- 2.00)
Melanoma	0.73 (0.68-0.79)	0.69 (0.55- 0.86)	0.91 (0.72- 1.15)

[1]Basic Model: adjusted for age, year of cohort entry, and sex
[2]Fully Adjusted Model: adjusted for age, year of cohort entry, sex, race-ethnicity, smoking, education, alcohol consumption, and BMI

Figure 2.1 Comparison of HRs for cancer risk associated with diabetes in KP membership and meta-analyses



MA = meta-analysis
KP = Kaiser Permanente Northern California study
Diamond represents the null, no summary measure was calculated

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