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Cohort Study of Pioglitazone and Cancer Incidence in Patients with Diabetes Mellitus Extended Follow-up (1997-2009)

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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 severely restricted.

Pioglitazone (ACTOS®) is a PPARγ ligand used in the treatment of type 2 diabetes. It is indicated as an adjunct to diet and exercise to improve glycemic control. It is generally not used as a first line therapy (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). Recent findings suggest that synthetic PPARγ ligands may affect cell growth independent of the presence of PPARγ (6,7). Clinical trial and epidemiologic data on TZDs and cancer risk are limited and results from the few studies conducted to date have been conflicting (8-10), (11), (12-14).

Based on preclinical data provided to us by Takeda Pharmaceuticals North America (TPNA), the question has arisen 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. An 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 (15). 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.

In 2006, the European Medicines Agency (EMA) requested an investigation of the potential association between use of pioglitazone and risk of several other malignancies. A new study was designed to conduct exploratory analyses of 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).

Summary of the results of the initial KPNC study of pioglitazone and risk of incident cancer at multiple sites with follow-up from 1997 to 2005

In the initial study, we followed for cancer endpoints 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, endometrial and non-Hodgkin's lymphoma). For the 10 most common cancer sites, the number of cases ranged from a low of 373 for melanoma to a high of 2,105 for prostate cancer.

In Cox regression models adjusted for age, gender, 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. There also was little evidence of increasing risk with increasing dose, duration, or time since first use.

There were 25 other cancer sites with at least 1 case exposed to pioglitazone. HRs for these sites 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 (HR=0).

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, and felt that in several years time, perhaps 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.

Extension and expansion of original study

Study 1. In 2008 we received approval from the EMA on 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, which will provide a minimum and maximum follow-up of 6.5 years and 15.5 years, respectively.

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 interim report for both Study 1 and Study 2, we present results with follow-up from 1997 through 2009.

The proposed 5-year extension study continues to be a collaboration between Investigators at the Division of Research of Kaiser Permanente and Investigators at Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine. Members of our original Advisory Board (Drs. Barrett-Connor, Herring, McDonald, Suissa, and Weiss) have all agreed to stay on for the extension and they have provided 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 (16) and other previous observational studies (8-10,17) of TZD use among diabetic patients 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 study was conducted in a large cohort of diabetic patients, in the previous analyses with follow-up from January 1, 1997 to December 31, 2005 we had relatively few pioglitazone-exposed cancer cases at most sites, limiting our precision, especially for risk estimates associated with duration, dose, and latency.

The **aim** of this interim report is to evaluate whether treatment with pioglitazone was associated with risk of incident cancer at the 10 most common sites (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma [NHL], pancreas, kidney/renal pelvis, rectal, and melanoma) in a cohort of patients with recognized diabetes that was followed from January 1, 1997 to December 31, 2009.

The mean follow-up for the cohort has increased from the 1,436 days available for the initial analyses(16) to 2,183 days for this interim report.

1. B. METHODS

a. Study population and data sources

The study population is the same as in 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.

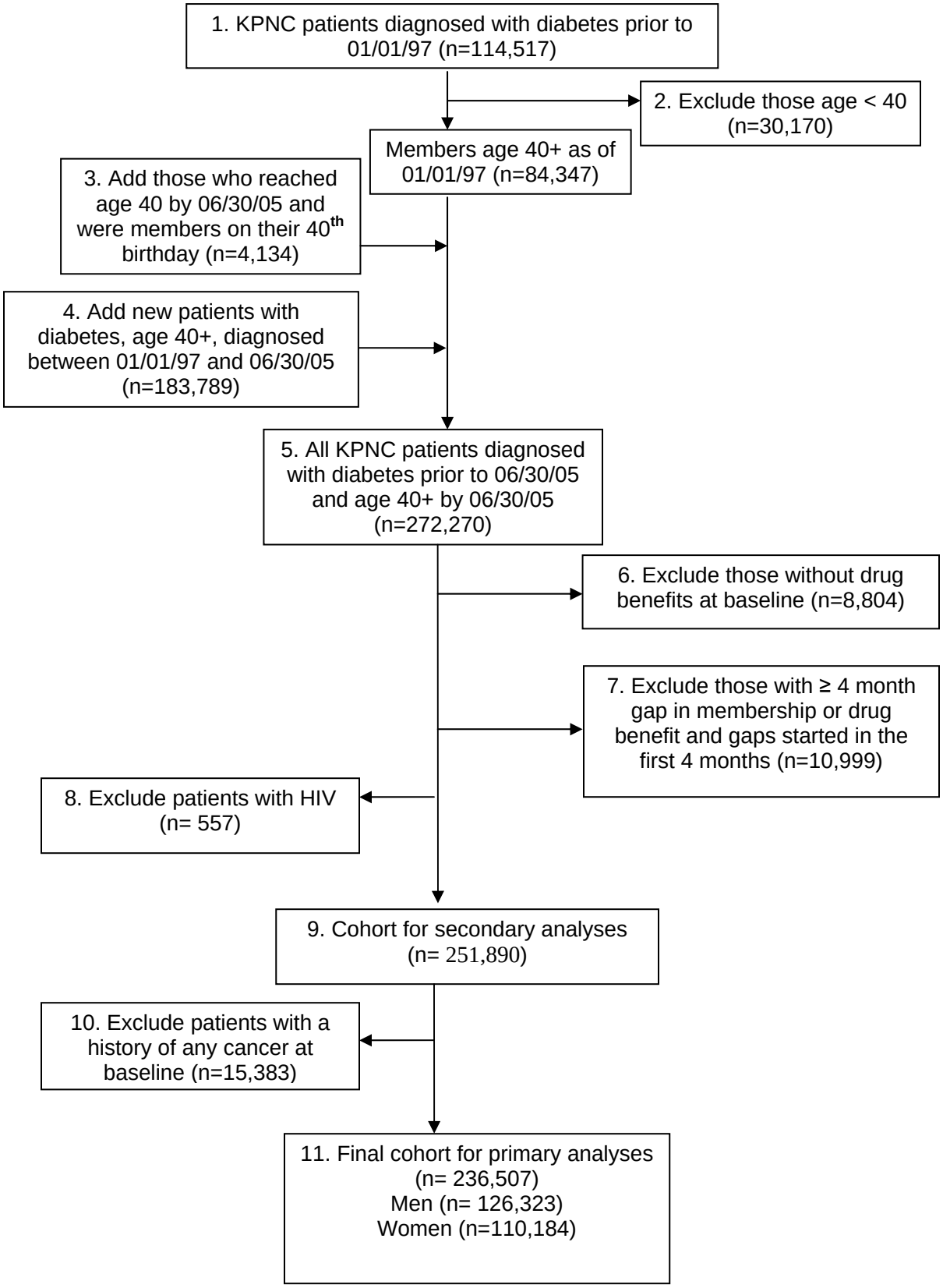
c. Cohort Exclusion Criteria

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 endometrial cancer, 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 at baseline, i.e., all participants ever diagnosed with cancer other than non-melanoma skin cancer (n= 15,383).

In secondary analyses, only those patients with a history of the cancer of interest were excluded. This allowed for comparisons with the results for the initial study, which used this same exclusion criterion.

Figure 1.1 Study population inclusion and exclusion criteria common to all analyses; Northern California Kaiser Permanente Diabetes registry 1997-2009.



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 cancer prior to baseline**. The 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 are first identified as having diabetes and were 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, for all outcomes except pancreatic cancer. For pancreatic cancer, follow-up started at 12 months after entry into the cohort since new onset diabetes can be an early sign of pancreatic cancer. This longer lag period should help reduce inclusion of patients with prevalent, but undiagnosed, pancreatic cancer at the start of follow-up.

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 (December 31, 2009).

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 December 31, 2009 (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 members of the cohort we identified all prescriptions for diabetes medications from the date of entry into the cohort through December 31, 2009 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), metformin, insulin, sulfonylureas, and other oral agents (e.g., miglitol, acarbose, nataglinide, repaglinide). 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 36,250 (15.3%) patients who never had any DM medication prescriptions during the study period and 9,979 (4.2%) 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 second pioglitazone prescription among patients who ever used pioglitazone. Time since initiation was categorized as never user, < 2 years, 2-3 years, 4-5 years, and 6 or more years.

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, and 36+ months of use.

Cumulative dose of pioglitazone was calculated in a similar fashion. 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 duration of use was categorized as never user, 1-12,000 mg, 12,001-30,000 mg, and 30,001 or more mg.

g. Potential confounders and their data sources

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. Gender was also obtained from the membership file. Race-ethnicity was obtained from several databases and was categorized as follows: non-Hispanic white, African American, Asian/Pacific Islanders, Hispanic, other and missing race/ethnicity data.

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.

Information on diabetes duration at baseline was also available from a patient survey that was completed during the years1995-1996 by members of the diabetes registry. 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 the baseline using the date of entry in the diabetes registry. We were able to do so for the 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. However, 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 thus these patients were considered to have missing data on diabetes duration.

Table 1.1. Potential confounders available from electronic data sources

Variable	Operational definition	Data source
Age at baseline and gender	Age (5-year intervals), gender (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 1995-1996 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

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 anytime 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. Thus, patients were categorized as smokers if they were identified as current smokers in the electronic database or by the survey. We were able to classify current smoking status at the baseline or prior to baseline for 19,652 people by using electronic and 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.

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 (primary analysis) and time since first use, cumulative duration, and dose (secondary analyses). 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).

Model 1 (Basic): Included pioglitazone exposure measure, age at cohort entry (categorized in 5-yr age groups), use of other diabetes medications (ever vs. never, time dependent), and year of entry into the cohort (categorized as calendar year).

Model 2: Included all variables in Model 1, plus gender, race/ethnicity, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine, and history of congestive heart failure (yes vs. no).

In Model 2, 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).

Primary analyses

Our primary analyses were based on the cohort of 236,507 diabetic patients with diabetes without a history of cancer at baseline. In the primary analyses, 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 (December 31, 2009).

Secondary analyses

Our secondary analyses were based on the cohort of 251,890 diabetic patients with diabetes who may have had any type of cancer at baseline. In the secondary analyses, only patients with a history of cancer at the site of interest were excluded and 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 cancer at the anatomic site of interest, 3) death from any cause, or 4) end of the study (December 31, 2009).

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 cancer at baseline and with censoring at the diagnosis of any invasive cancer).

1. C. RESULTS

Characteristics of study population, by pioglitazone use (Table 1.2)

Compared to never users, the proportion of persons aged 50 to 59 and 60 to 69 years was greater among ever users of pioglitazone (Table 1.2). Patients treated with pioglitazone were less likely to have high creatinine levels and to have congestive heart failure at the time of entry into the cohort. Compared to patients who never received pioglitazone, patients who ever used pioglitazone were less likely to have a baseline HbA1c lower than 7% and more likely to have a baseline HbA1c greater than 10%. Approximately 60% of the ever users of pioglitazone and approximately 70% 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 gender, race-ethnicity, and current smoking were similar among ever users and never users of pioglitazone.

Exposure to pioglitazone (Tables 1.3-1.4)

There were few diabetic patients that had a first prescription of pioglitazone prior to 2000 (Table 1.3). The number of people 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. At the end of follow-up, there were 36,071 patients who were exposed to pioglitazone (Table 1.4). Among pioglitazone users, the median time from the first prescription to the end of follow-up was 3.7 years (range 0.2- 10.1 years). The median duration of therapy was 27.6 months (range 2.4- 122.4 months). The median dose of pioglitazone was 19,500 mg (range 450- 230,010 mg).

Cancer incidence (Table 1.5)

Table 1.5 provides the number of new primary invasive cancers diagnosed among the study cohort during follow-up and the age and sex-standardized incidence rates (2000 US Census) for each of 42 cancers sites, irrespective of drug exposure. For the 10 most common cancers, there are a considerable number of cases, ranging from 590 for melanoma to 3,236 for prostate cancer.

Hazard ratios for the 10 most common cancers (tables 1.6-1.15)

Tables 1.6 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 most common cancers. For each cancer site we reported results for both the primary analyses and the secondary analyses.

Primary analyses (Tables 1.6 to 1.16)

Results from our basic models, i.e., adjusted only for age, year of cohort entry, and use of other diabetes medications (Model 1) were very similar to the results obtained from our multivariate adjusted model, i.e., adjusted for all the variables in model 1 plus gender, race/ethnicity, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine, and CHF (Model 2). In Model 2, the HRs for the risk of each of the 10 most common cancers associated with ever use of pioglitazone ranged from 0.9 to 1.3 and all 95% CI included 1.0 except for pancreatic cancer. For pancreatic cancer, the HR was 1.3 (95% CI 1.1-1.7) (Table 1.12). In this model, ever use of metformin, insulin, or sulfonylureas also were associated with slight to modestly increased risk of pancreatic cancer (Table 1.16).

There was no clear pattern of increasing risk with increasing time since initiation, duration of use, or cumulative dose of pioglitazone for any of the 10 most common cancers (tables 1.6-1.15), although elevated HRs were observed for some exposure measures at some cancer sites. In analyses with follow-up starting at 12 months after cohort entry, risk of pancreatic cancer was elevated in the lowest category of time since

initiation (<12 months) of pioglitazone (HR= 2.1; 95% CI = 1.5-3.0), and in the lowest category of duration (<12 months) of pioglitazone (HR= 1.5; 95% CI = 1.1-2.0), and then decreased with increasing time since pioglitazone initiation and duration. The risk of pancreatic cancer was also increased in the highest category of cumulative dose (> 25,000 mg) of pioglitazone (HR= 1.5; 95% CI = 1.0-2.1).

Secondary analyses (Tables 1.6 to 1.15)

Results from the secondary analyses (which excluded only patients with a history at baseline of invasive cancer at the anatomic site of interest) were similar to those obtained from the primary analyses (which excluded patients with any prevalent invasive cancer at baseline).

Subgroup and sensitivity analyses

Since results obtained from the primary and secondary analyses were similar, we performed the subgroup and sensitivity analyses among the cohort of diabetic patients used for the primary 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 166,209 (70.3% of the full cohort) patients who had been KPNC members before January 1, 1997 and were newly diagnosed with diabetes after January 1, 1997. Similar results were observed in this subgroup and in the full cohort, except for pancreatic cancer.

2. Sub-analyses among those with complete information on prescriptions of diabetes medications

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 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 DM Registry and were newly diagnosed with DM after January 1, 1997. Results obtained in this sub-analyses were similar to those obtained in our primary analysis, suggesting that there was little residual confounding in our primary analyses which also included patients who had been diagnosed with diabetes before they joined the KPNC or had diabetes diagnosed at KPNC before 1995 (i.e., before the pharmacy data became available). In this sub-cohort, risk of pancreatic cancer was no longer elevated among those who used pioglitazone for less than 12 months (HR= 1.1; 95% CI = 0.6-1.9), but there was a suggestion that it was elevated among those who used pioglitazone for more than 2 years. Those who used it for 24-35 months had an HR of 1.8 (95% CI = 0.9-3.7) and use 36 months or longer had an HR= 1.5 (95% CI = 0.7-2.9). The risk of pancreatic cancer remained elevated among those whose cumulative dose of pioglitazone was > 25,000 mg (HR= 2.0; 95% CI = 1.1-3.4).

3. Sub-analyses among those for whom DM 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 1995-1996 and provided information on date of DM diagnosis. 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 DM 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 significant association between DM duration and cancer at any of the sites other than pancreas. For pancreatic cancer the risk was decreased among those who had a DM duration 5 to 9 years or 10+ years as compared with those with DM duration less than 5 years [HR (95% CI): 0.6 (0.4-0.8) and 0.6 (0.4-0.8), respectively]. In this sub-cohort, we continued to see associated with ever use of pioglitazone an increased risk of pancreatic cancer 1.4 (95% CI 1.1-1.8) and patterns relating time since initiation, duration, and dose of pioglitazone to the risk of pancreatic cancers were similar to those observed in the primary analyses.

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

Approximately 20% of the cohort participated in the 1995/1996 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, year of entry in the cohort, and ever use of other medications (Model 1). When BMI was added to the models, the point estimates for the association between ever pioglitazone use and risk of cancer did not appreciably change. These results indicate that we can conduct analyses in the full cohort with confidence that BMI is not confounding the pioglitazone and cancer relationship.

Of note, as shown by previous studies, in the multiple adjusted models higher BMI was associated with increased risk of colon cancer, cancer of the corpus uteri, and kidney cancer.

1. D. DISCUSSION

We found no suggestion of an association between the use of pioglitazone and an increased risk of incident cancer at 9 of the 10 sites. Use of pioglitazone was associated with an increased risk of pancreatic cancer [HR (95% CI) = 1.3 (1.1-1.7)]. However, in the same model, ever use of metformin, insulin or sulfonylureas were all associated with increased risk of pancreatic cancer [HR (95% CI) = 1.3 (1.1- 1.6), 2.5 (2.1- 3.0) and 1.6 (1.3-1.9), respectively]. The results for pancreatic cancer are difficult to interpret because an early manifestation of this cancer is hyperglycemia (18).

The results obtained in this interim report with follow-up from January 1, 1997 to December 31, 2009 are largely similar to those obtained in our previous report with follow-up from January 1, 1997 to December 31, 2005. As expected, the confidence limits around our HR estimates for each of the exposure categories of interest are narrower with the longer follow-up. With longer follow-up, however, we no longer find suggestions that ever vs never use of pioglitazone is associated with a small increase in the risk of melanoma and NHL and a small decrease in the risk of cancer of the kidney/renal pelvis. Associations with time since initiation, duration, and dose for these cancer sites were also attenuated with longer follow-up.

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 short-term use (median 27.6 months) 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.

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 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 duration of diabetes.

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 diabetic 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, one that will be even more valuable if follow-up time is extended.

With additional follow-up of this cohort through June 30, 2012, we will have increased precision in estimation of the association between pioglitazone use and the risk of cancer.

Table 1.2 Selected characteristics of study cohort of 236,507 diabetic patients by pioglitazone use; Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 - December 31, 2009.

	Ever User of Pioglitazone† (n=36,071) Number (%)	Never User of Pioglitazone (n=200,436) Number (%)
Total person-years in each age group*		
40-49	15,747 (10.5%)	178,085 (14.0%)
50-59	44,049 (29.5%)	337,089 (26.5%)
60-69	47,690 (31.9%)	346,874 (27.3%)
≥ 70	41,853 (28.0%)	409,623 (32.2%)
Female sex	16,703 (46.3%)	93,481 (46.6%)
Income		
Low‡	19,322 (53.6%)	108,064 (53.9%)
High	16,101 (44.6%)	87,408 (43.6%)
Missing	648 (1.8%)	4,964 (2.5%)
Race/Ethnicity		
Non-Hispanic white	17,843 (49.5%)	100,515 (50.1%)
African American	3,466 (9.6%)	20,132 (10.0%)
Asian or Pacific Islander	5,264 (14.6%)	27,068 (13.5%)
Hispanic	4,816 (13.4%)	21,882 (10.9%)
Other	2,022 (5.6%)	10,656 (5.3%)
Missing	2,660 (7.4%)	20,183 (10.1%)
Current smoking	7,460 (20.7%)	37,870 (18.9%)
Renal function		
Normal creatinine	27,687 (76.8%)	158,299 (79.0%)
Elevated creatinine**	1,442 (4.0%)	16,287 (8.1%)
Missing	6,942 (19.2%)	25,850 (12.9%)
Congestive Heart Failure	1,046 (2.9%)	12,626 (6.3%)
Baseline HbA1c		
< 7.0%	6,240 (17.3%)	64,459 (32.2%)
7.0-7.9%	6,183 (17.1%)	34,990 (17.5%)
8.0-8.9%	4,316 (12.0%)	18,169 (9.1%)
9.0-9.9%	3,294 (9.1%)	12,499 (6.2%)
≥10.0%	7,999 (22.2%)	30,227 (15.1%)
Missing	8,039 (22.3%)	40,092 (20.0%)
Time since diabetes diagnosis		
0-4 years	21,165 (58.7%)	135,879 (67.8%)
5-9 years	3,068 (8.5%)	9,634 (4.8%)
≥ 10 years	2,938 (8.1%)	17,355 (8.7%)
Missing	8,900 (24.7%)	37,568 (18.7%)
Other TZDs†	2,801 (7.8%)	2,569 (1.3%)
Metformin†	29,933 (83.0%)	91,727 (45.8%)

Sulfonylureas[†]	31,178 (86.4%)	107,738 (53.8%)
Other oral agents[†]	1,929 (5.3%)	2,259 (1.1%)
Insulin[†]	15,486 (42.9%)	44,892 (22.4%)

[†] Filled at least two prescriptions within a 6-month period;
* With pioglitazone use treated as a time-varying variable;
** Creatinine $\geq$1.4 for women and $\geq$1.5 for men;
[‡] Low income defined as median household income in census block below the cohort average ($59,000);

Table 1.3 Calendar year of first prescription for pioglitazone among diabetic patients in the study cohort; Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 - December 31, 2009.

Year of 1st Pioglitazone Prescription	N*	Percent	Cumulative Frequency
1999	165	0.43	165
2000	5243	13.58	5,408
2001	4675	12.11	10,083
2002	4752	12.30	14,835
2003	4099	10.61	18,934
2004	3954	10.24	22,888
2005	4655	12.05	27,543
2006	4277	11.07	31,820
2007	3630	9.40	35,450
2008	1948	5.04	37,398
2009	1221	3.16	38,619

*Individuals

Table 1.4 Pioglitazone exposure (as of the end of follow-up); Kaiser Permanente Northern California Diabetes Registry: January 1, 1997 - December 31, 2009.

Category	
Ever exposed, n	36,071
Time since starting pioglitazone, yrs	
Median (range)	3.7 yrs (0.2- 10.1)
<1 yrs (n, %)	4,687 (13.0%)
1.0-1.9 yrs (n, %)	4,333 (12.0%)
2.0-2.9 yrs (n, %)	5,496 (15.2%)
3.0-3.9 yrs (n, %)	4,597 (12.7%)
4+ yrs (n, %)	16,958 (47.0%)
Duration of therapy, months	
Median (range)	27.6 months (2.4- 122.4)
<12 months (n, %)	8,316 (23.1%)
12-23 months (n, %)	7,865 (21.8%)
24-35 months (n, %)	6,197 (17.2%)
36+ months (n, %)	13,693 (38.0%)
Cumulative dose, mg	
Median (range)	19,500 mg (450- 230,010)
1 – 9000 mg (n, %)	9,933 (27.5%)
9001 – 25000 mg (n, %)	11,260 (31.2%)
>25000 mg (n, %)	14,878 (41.3%)

Table 1.5. 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	3236	447.8	291.1
2. Breast	2393	357.6	285.4
3. Lung/Bronchus	2206	155.8	107.4
4. Colon	1764	125.5	93.3
5. Urinary Bladder	941	66.6	46.4
6. Non-Hodgkin Lymphoma	801	56.6	43.6
7. Corpus Uteri	750	119.1	103.3
8. Pancreatic	662	50.8	36.0
9. Kidney/Renal Pelvis	651	46.0	36.1
10. Melanoma	590	41.7	32.4
11. Rectum/Rectosigmoid	550	39.1	30.6
12. Liver/Intrahep.Bile Duct	488	37.4	28.9
13. Stomach	411	29.0	22.8
14. Multiple Myeloma	258	18.2	13.2
15. Lip,Tongue/Other Mouth	247	17.4	12.8
16. Lymphocytic Leukemia	246	17.4	13.0
17. Ovary	227	33.8	29.9
18. Esophagus	201	14.2	9.9
19. Myeloid Leukemia	199	14.1	10.7
20. Thyroid	159	11.2	11.8
21. Brain	133	9.4	7.2
22. Larynx	104	7.3	5.2
23. Nasopharynx, Tonsil, Oropharynx/Other Oral Cavity/	103	7.3	6.2
24. Soft Tissue/Heart	86	6.1	4.9
25. Other Biliary	81	5.7	4.1
26. Vagina & Vulva	67	10.0	8.3
27. Small Intestine	64	4.5	3.3
28. Hodgkin Lymphoma	61	4.3	3.5
29. Gallbladder	54	3.8	3.0
30. Cervix Uteri	54	8.6	10.1
31. Anus/Anal Canal/Anorectum	47	3.3	2.5
32. Retroperitoneum & Peritoneum/Omentum/Mesentery	35	2.5	2.0
33. Salivary Glands	33	2.3	2.0
34. Nose/Nasal Cavity/Middle Ear	29	2.0	2.0
35. Monocytic Leukemia & Other Leukemia	28	2.0	1.4
36. Ureter	25	1.8	1.2
37. Other Endocrine/Thymus	16	1.1	0.9
38. Penis	15	2.0	1.3
39. Bones/Joints	13	0.9	0.9
40. Testis	11	1.5	2.2
41. Eye And Orbit	5	0.4	0.2
42. Pleura	4	0.3	0.2
43. Other Nervous System	4	0.3	0.3

* Cancer site based on SEER classification, bladder includes in-situ
**Age adjusted to the 2000 U.S. population of age 40 or above.

Table 1.6 Hazard Ratios for **PROSTATE** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	340/18957	1.0 (0.9- 1.2)	1.1 (0.9- 1.2)	365/19565	1.0 (0.9- 1.2)	1.1 (1.0- 1.2)
TIME SINCE INITIATION						
< 12 months ago	68/2489	1.0 (0.7- 1.2)	1.0 (0.8- 1.2)	69/2507	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
12-23 months ago	67/2410	1.1 (0.8- 1.4)	1.1 (0.9- 1.4)	74/2438	1.1 (0.9- 1.4)	1.1 (0.9- 1.4)
24-35 months ago	59/2941	1.1 (0.8- 1.4)	1.1 (0.9- 1.5)	63/3036	1.1 (0.9- 1.4)	1.1 (0.9- 1.5)
36-47 months ago	47/2496	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)	49/2556	1.1 (0.8- 1.4)	1.1 (0.8- 1.5)
48+ months ago	99/8620	1.0 (0.8- 1.3)	1.1 (0.8- 1.3)	110/9027	1.1 (0.9- 1.3)	1.1 (0.9- 1.3)
DURATION OF PIO						
< 12 months	91/4067	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	96/4144	0.9 (0.7- 1.1)	0.9 (0.8- 1.1)
12-23 months	93/3986	1.2 (1.0- 1.5)	1.2 (1.0- 1.5)	101/4122	1.2 (1.0- 1.5)	1.2 (1.0- 1.5)
24-35 months	52/3359	0.9 (0.7- 1.2)	1.0 (0.7- 1.3)	55/3456	0.9 (0.7- 1.2)	1.0 (0.7- 1.3)
36+ months	104/7544	1.2 (0.9- 1.4)	1.2 (1.0- 1.5)	113/7842	1.2 (1.0- 1.4)	1.2 (1.0- 1.5)
DOSE OF PIO						
1-9,000 mg	100/4795	1.0 (0.8- 1.2)	1.0 (0.8- 1.2)	105/4942	1.0 (0.8- 1.2)	1.0 (0.8- 1.2)
9,001-25,000 mg	125/5843	1.1 (0.9- 1.4)	1.2 (1.0- 1.4)	134/6004	1.2 (1.0- 1.4)	1.2 (1.0- 1.4)
>25,000 mg	115/8318	1.0 (0.8- 1.2)	1.0 (0.8- 1.3)	126/8618	1.0 (0.8- 1.2)	1.1 (0.9- 1.3)

†Never use of pioglitazone as reference group for all analyses.
°Primary analyses exclude those with a history of <u>any</u> cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

Table 1.7 Hazard Ratios for **FEMALE BREAST** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	237/16643	1.0 (0.9- 1.2)	1.0 (0.9- 1.2)	251/17278	1.0 (0.9- 1.1)	1.0 (0.9- 1.1)
TIME SINCE INITIATION						
< 12 months ago	52/2175	1.0 (0.8- 1.4)	1.1 (0.8- 1.4)	55/2182	1.1 (0.8- 1.4)	1.1 (0.8- 1.4)
12-23 months ago	36/1896	0.8 (0.6- 1.1)	0.8 (0.6- 1.1)	38/1931	0.8 (0.6- 1.1)	0.8 (0.6- 1.1)
24-35 months ago	42/2480	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)	44/2547	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
36-47 months ago	25/2025	0.8 (0.5- 1.2)	0.8 (0.5- 1.2)	28/2115	0.9 (0.6- 1.2)	0.9 (0.6- 1.2)
48+ months ago	82/8067	1.1 (0.9- 1.4)	1.1 (0.9- 1.4)	86/8503	1.1 (0.8- 1.4)	1.1 (0.8- 1.3)
DURATION OF PIO						
< 12 months	78/4160	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	84/4259	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)
12-23 months	59/3779	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	63/3906	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)
24-35 months	40/2761	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)	42/2877	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
36+ months	60/5943	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	62/6236	1.0 (0.7- 1.3)	1.0 (0.7- 1.3)
DOSE OF PIO						
1-9,000 mg	79/5037	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	84/5215	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)
9,001-25,000 mg	81/5273	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	84/5442	1.0 (0.8- 1.2)	1.0 (0.8- 1.2)
>25,000 mg	76/6332	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	82/6620	1.1 (0.8- 1.3)	1.0 (0.8- 1.3)

†Never use of pioglitazone as reference group for all analyses.
° Primary analyses exclude those with a history of any cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

Table 1.8 Hazard Ratios for **LUNG AND BRONCHUS** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	207/36074	1.0 (0.9- 1.2)	1.0 (0.9- 1.2)	236/38528	1.0 (0.8- 1.1)	1.0 (0.8- 1.1)
TIME SINCE INITIATION						
< 12 months ago	39/4687	0.9 (0.7- 1.3)	0.9 (0.7- 1.3)	44/4735	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
12-23 months ago	42/4333	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)	47/4490	1.0 (0.8- 1.4)	1.0 (0.8- 1.4)
24-35 months ago	43/5498	1.3 (1.0- 1.8)	1.3 (1.0- 1.8)	48/5819	1.2 (0.9- 1.7)	1.2 (0.9- 1.6)
36-47 months ago	22/4597	0.8 (0.5- 1.3)	0.8 (0.5- 1.3)	25/4902	0.8 (0.5- 1.2)	0.8 (0.5- 1.2)
48+ months ago	61/16958	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)	72/18581	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
DURATION OF PIO						
< 12 months	67/8316	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	71/8694	0.8 (0.6- 1.0)	0.8 (0.6- 1.0)
12-23 months	51/7865	1.1 (0.8- 1.4)	1.0 (0.8- 1.4)	60/8336	1.1 (0.8- 1.4)	1.0 (0.8- 1.4)
24-35 months	36/6198	1.1 (0.8- 1.6)	1.1 (0.8- 1.6)	42/6649	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
36+ months	53/13694	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	63/14848	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)
DOSE OF PIO						
1-9,000 mg	74/9950	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	81/10547	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)
9,001-25,000 mg	66/11266	1.0 (0.7- 1.2)	1.0 (0.8- 1.2)	74/11964	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
>25,000 mg	67/14856	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	81/16016	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)

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

° Primary analyses exclude those with a history of <u>any</u> cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.

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

Table 1.9 Hazard Ratios for **COLON** cancer associated with ever use, time since initiation, duration, and dose of pioglitazone.

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	167/35879	0.9 (0.8- 1.1)	0.9 (0.8- 1.1)	187/38103	0.9 (0.7- 1.0)	0.9 (0.7- 1.0)
TIME SINCE INITIATION						
< 12 months ago	23/4677	0.6 (0.4- 0.9)	0.6 (0.4- 0.9)	28/4712	0.7 (0.5- 1.0)	0.7 (0.5- 1.0)
12-23 months ago	36/4327	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)	39/4471	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)
24-35 months ago	35/5466	1.2 (0.9- 1.7)	1.2 (0.8- 1.7)	37/5770	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
36-47 months ago	22/4575	0.9 (0.6- 1.4)	0.9 (0.6- 1.4)	24/4849	0.9 (0.6- 1.3)	0.8 (0.6- 1.3)
48+ months ago	51/16833	0.8 (0.6- 1.1)	0.8 (0.6- 1.1)	59/18300	0.8 (0.6- 1.1)	0.8 (0.6- 1.1)
DURATION OF PIO						
< 12 months	62/8287	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)	71/8616	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)
12-23 months	41/7824	0.9 (0.7- 1.3)	0.9 (0.7- 1.3)	44/8249	0.9 (0.7- 1.2)	0.9 (0.6- 1.2)
24-35 months	28/6161	1.0 (0.7- 1.4)	0.9 (0.6- 1.4)	29/6576	0.9 (0.6- 1.2)	0.8 (0.6- 1.2)
36+ months	36/13606	0.7 (0.5- 1.0)	0.7 (0.5- 1.0)	43/14661	0.7 (0.5- 1.0)	0.7 (0.5- 1.0)
DOSE OF PIO						
1-9,000 mg	60/9901	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	69/10426	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)
9,001-25,000 mg	54/11218	0.9 (0.7- 1.2)	0.9 (0.7- 1.1)	57/11862	0.8 (0.6- 1.0)	0.8 (0.6- 1.0)
>25,000 mg	53/14758	0.9 (0.6- 1.1)	0.8 (0.6- 1.1)	61/15814	0.8 (0.6- 1.1)	0.8 (0.6- 1.1)

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

° Primary analyses exclude those with a history of any cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	89/36072	1.1 (0.8- 1.4)	1.0 (0.8- 1.3)	105/38508	1.1 (0.9- 1.3)	1.1 (0.8- 1.3)
TIME SINCE INITIATION						
< 12 months ago	20/4687	1.2 (0.8- 1.9)	1.2 (0.7- 1.8)	24/4737	1.3 (0.8- 1.9)	1.2 (0.8- 1.9)
12-23 months ago	24/4333	1.6 (1.0- 2.4)	1.5 (1.0- 2.3)	25/4493	1.4 (0.9- 2.1)	1.4 (0.9- 2.1)
24-35 months ago	15/5496	1.1 (0.6- 1.8)	1.1 (0.6- 1.8)	16/5808	1.0 (0.6- 1.7)	1.0 (0.6- 1.6)
36-47 months ago	9/4598	0.8 (0.4- 1.6)	0.8 (0.4- 1.6)	11/4901	0.9 (0.5- 1.6)	0.8 (0.5- 1.5)
48+ months ago	21/16957	0.8 (0.5- 1.2)	0.7 (0.5- 1.2)	29/18568	0.9 (0.6- 1.3)	0.8 (0.6- 1.3)
DURATION OF PIO						
< 12 months	29/8316	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)	34/8686	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)
12-23 months	27/7865	1.4 (0.9- 2.0)	1.4 (0.9- 2.0)	29/8341	1.3 (0.9- 1.9)	1.3 (0.9- 1.8)
24-35 months	14/6197	1.0 (0.6- 1.7)	1.0 (0.5- 1.7)	16/6644	1.0 (0.6- 1.6)	0.9 (0.6- 1.6)
36+ months	19/13693	0.8 (0.5- 1.3)	0.8 (0.5- 1.2)	26/14836	0.9 (0.6- 1.4)	0.9 (0.6- 1.3)
DOSE OF PIO						
1-9,000 mg	29/9950	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)	34/10543	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)
9,001-25,000 mg	35/11266	1.2 (0.9- 1.7)	1.2 (0.8- 1.7)	38/11959	1.1 (0.8- 1.6)	1.1 (0.8- 1.6)
>25,000 mg	25/14854	0.8 (0.6- 1.3)	0.8 (0.5- 1.3)	33/16005	1.0 (0.7- 1.4)	0.9 (0.6- 1.3)

†Never use of pioglitazone as reference group for all analyses.
° Primary analyses exclude those with a history of any cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	83/15572	1.0 (0.8- 1.2)	1.0 (0.7- 1.2)	86/16452	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
TIME SINCE INITIATION						
< 12 months ago	18/2063	1.0 (0.6- 1.5)	1.0 (0.6- 1.5)	19/2070	0.9 (0.6- 1.5)	0.9 (0.6- 1.5)
12-23 months ago	17/1798	1.0 (0.6- 1.7)	1.0 (0.6- 1.6)	17/1870	0.9 (0.6- 1.5)	0.9 (0.6- 1.5)
24-35 months ago	7/2336	0.5 (0.2- 1.1)	0.5 (0.2- 1.1)	7/2440	0.5 (0.2- 1.0)	0.4 (0.2- 0.9)
36-47 months ago	14/1898	1.3 (0.7- 2.2)	1.3 (0.7- 2.2)	15/2006	1.2 (0.7- 2.1)	1.2 (0.7- 2.1)
48+ months ago	27/7477	1.1 (0.7- 1.7)	1.1 (0.7- 1.6)	28/8066	1.0 (0.7- 1.6)	1.0 (0.7- 1.5)
DURATION OF PIO						
< 12 months	36/3952	1.2 (0.8- 1.6)	1.1 (0.8- 1.6)	37/4083	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
12-23 months	19/3548	0.9 (0.6- 1.5)	0.9 (0.6- 1.5)	21/3732	0.9 (0.6- 1.4)	0.9 (0.6- 1.4)
24-35 months	10/2570	0.8 (0.4- 1.4)	0.8 (0.4- 1.4)	10/2745	0.7 (0.4- 1.3)	0.7 (0.4- 1.3)
36+ months	18/5502	0.9 (0.5- 1.5)	0.9 (0.5- 1.4)	18/5892	0.8 (0.5- 1.3)	0.8 (0.5- 1.3)
DOSE OF PIO						
1-9,000 mg	35/4744	1.1 (0.8- 1.6)	1.1 (0.8- 1.6)	36/4957	1.1 (0.8- 1.5)	1.1 (0.8- 1.5)
9,001-25,000 mg	29/4927	1.0 (0.7- 1.5)	1.0 (0.7- 1.5)	31/5207	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)
>25,000 mg	19/5900	0.7 (0.5- 1.2)	0.7 (0.4- 1.1)	19/6288	0.7 (0.4- 1.1)	0.7 (0.4- 1.0)

†Never use of pioglitazone as reference group for all analyses.
° Primary analyses exclude those with a history of any cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.
In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	114/35605	1.3 (1.0- 1.6)	1.3 (1.1- 1.7)	122/38111	1.2 (1.0- 1.5)	1.3 (1.0- 1.6)
TIME SINCE INITIATION						
< 12 months ago	31/4220	2.0 (1.4- 2.9)	2.1 (1.4- 3.0)	34/4276	2.0 (1.4- 2.9)	2.1 (1.5- 3.0)
12-23 months ago	20/4333	1.3 (0.8- 2.0)	1.3 (0.8- 2.1)	20/4481	1.2 (0.7- 1.8)	1.2 (0.8- 1.9)
24-35 months ago	14/5497	1.0 (0.6- 1.7)	1.0 (0.6- 1.8)	15/5826	1.0 (0.6- 1.7)	1.0 (0.6- 1.7)
36-47 months ago	13/4597	1.0 (0.6- 1.8)	1.1 (0.6- 1.9)	15/4907	1.1 (0.6- 1.9)	1.1 (0.6- 1.9)
48+ months ago	36/16958	1.1 (0.7- 1.6)	1.1 (0.8- 1.6)	38/18621	1.0 (0.7- 1.4)	1.0 (0.7- 1.5)
DURATION OF PIO						
< 12 months	42/7991	1.4 (1.1- 2.0)	1.5 (1.1- 2.0)	48/8231	1.4 (1.1- 1.9)	1.5 (1.1- 1.9)
12-23 months	21/7723	1.1 (0.7- 1.6)	1.1 (0.7- 1.7)	23/8342	1.0 (0.6- 1.5)	1.0 (0.6- 1.5)
24-35 months	13/6198	0.9 (0.5- 1.6)	0.9 (0.5- 1.6)	15/6663	0.9 (0.5- 1.6)	1.0 (0.6- 1.6)
36+ months	35/13693	1.5 (1.0- 2.1)	1.5 (1.0- 2.2)	36/14875	1.3 (0.9- 1.9)	1.4 (1.0- 2.0)
DOSE OF PIO						
1-9,000 mg	39/9647	1.4 (1.0- 1.9)	1.4 (1.0- 2.0)	46/10201	1.4 (1.0- 1.9)	1.4 (1.1- 1.9)
9,001-25,000 mg	29/11111	1.0 (0.7- 1.5)	1.0 (0.7- 1.5)	32/11865	1.0 (0.7- 1.4)	1.0 (0.7- 1.4)
>25,000 mg	43/14846	1.4 (1.0- 2.0)	1.5 (1.0- 2.1)	44/16045	1.3 (0.9- 1.8)	1.3 (1.0- 1.9)

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

° Primary analyses exclude those with a history of any cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.

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

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	78/36069	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	89/38491	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)
TIME SINCE INITIATION						
< 12 months ago	11/4686	0.7 (0.4- 1.4)	0.7 (0.4- 1.3)	13/4730	0.7 (0.4- 1.3)	0.7 (0.4- 1.3)
12-23 months ago	9/4333	0.6 (0.3- 1.2)	0.6 (0.3- 1.2)	11/4475	0.6 (0.3- 1.1)	0.6 (0.3- 1.1)
24-35 months ago	13/5497	1.1 (0.6- 1.9)	1.1 (0.6- 1.9)	14/5821	1.0 (0.6- 1.7)	1.0 (0.6- 1.6)
36-47 months ago	13/4597	1.3 (0.7- 2.3)	1.3 (0.7- 2.3)	15/4900	1.3 (0.7- 2.1)	1.2 (0.7- 2.1)
48+ months ago	32/16955	1.2 (0.8- 1.8)	1.2 (0.8- 1.7)	36/18564	1.1 (0.8- 1.6)	1.1 (0.7- 1.6)
DURATION OF PIO						
< 12 months	26/8315	0.9 (0.6- 1.4)	0.9 (0.6- 1.4)	28/8676	0.8 (0.6- 1.2)	0.8 (0.6- 1.2)
12-23 months	13/7865	0.7 (0.4- 1.3)	0.7 (0.4- 1.2)	17/8337	0.8 (0.5- 1.3)	0.8 (0.5- 1.3)
24-35 months	9/6197	0.7 (0.4- 1.4)	0.7 (0.4- 1.4)	10/6648	0.7 (0.4- 1.3)	0.7 (0.4- 1.2)
36+ months	30/13691	1.4 (0.9- 2.0)	1.3 (0.9- 2.0)	34/14829	1.3 (0.9- 1.9)	1.3 (0.9- 1.8)
DOSE OF PIO						
1-9,000 mg	24/9950	0.9 (0.6- 1.3)	0.9 (0.6- 1.3)	28/10532	0.8 (0.6- 1.2)	0.8 (0.6- 1.2)
9,001-25,000 mg	23/11264	0.9 (0.6- 1.4)	0.9 (0.6- 1.3)	25/11958	0.8 (0.5- 1.2)	0.8 (0.5- 1.2)
>25,000 mg	31/14853	1.1 (0.8- 1.7)	1.1 (0.7- 1.6)	36/16000	1.1 (0.8- 1.6)	1.1 (0.7- 1.5)

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

° Primary analyses exclude those with a history of <u>any</u> cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.

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

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	47/35883	0.9 (0.7- 1.2)	0.9 (0.6- 1.2)	57/38068	0.9 (0.7- 1.2)	0.9 (0.6- 1.2)
TIME SINCE INITIATION						
< 12 months ago	7/4679	0.6 (0.3- 1.3)	0.6 (0.3- 1.3)	7/4712	0.5 (0.2- 1.1)	0.5 (0.2- 1.1)
12-23 months ago	10/4329	1.0 (0.5- 1.9)	1.0 (0.5- 1.9)	13/4471	1.1 (0.6- 1.9)	1.1 (0.6- 1.9)
24-35 months ago	10/5466	1.2 (0.7- 2.3)	1.2 (0.6- 2.3)	11/5767	1.1 (0.6- 2.1)	1.1 (0.6- 2.0)
36-47 months ago	7/4575	1.1 (0.5- 2.3)	1.0 (0.5- 2.2)	8/4840	1.0 (0.5- 2.0)	1.0 (0.5- 2.0)
48+ months ago	13/16833	0.8 (0.5- 1.5)	0.8 (0.4- 1.4)	18/18277	0.8 (0.5- 1.4)	0.8 (0.5- 1.3)
DURATION OF PIO						
< 12 months	17/8289	0.9 (0.6- 1.5)	0.9 (0.6- 1.5)	18/8616	0.8 (0.5- 1.3)	0.8 (0.5- 1.3)
12-23 months	11/7826	0.9 (0.5- 1.6)	0.9 (0.5- 1.6)	14/8240	0.9 (0.5- 1.6)	0.9 (0.5- 1.6)
24-35 months	8/6161	0.9 (0.4- 1.8)	0.8 (0.4- 1.8)	12/6572	1.1 (0.6- 2.0)	1.1 (0.6- 2.0)
36+ months	11/13606	0.8 (0.4- 1.5)	0.8 (0.4- 1.4)	13/14639	0.7 (0.4- 1.3)	0.7 (0.4- 1.2)
DOSE OF PIO						
1-9,000 mg	16/9904	0.9 (0.5- 1.4)	0.9 (0.5- 1.4)	16/10415	0.7 (0.5- 1.2)	0.7 (0.5- 1.2)
9,001-25,000 mg	16/11219	0.9 (0.5- 1.5)	0.9 (0.5- 1.5)	21/11854	1.0 (0.6- 1.5)	1.0 (0.6- 1.5)
>25,000 mg	15/14758	0.9 (0.5- 1.5)	0.9 (0.5- 1.5)	20/15798	0.9 (0.6- 1.5)	0.9 (0.5- 1.4)

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

° Primary analyses exclude those with a history of <u>any</u> cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest.In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

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

	Primary Analyses°			**Secondary Analyses°**		
	n cases exposed/n exposed	Basic Model	Fully adjusted	n cases exposed/n exposed	Basic Model	Fully adjusted
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Never Pioglitazone		1.0	1.0		1.0	1.0
Ever Pioglitazone†	77/36071	1.2 (0.9- 1.6)	1.1 (0.9- 1.5)	88/38449	1.3 (1.0- 1.6)	1.2 (0.9- 1.5)
TIME SINCE INITIATION						
< 12 months ago	11/4686	0.9 (0.5- 1.6)	0.9 (0.5- 1.6)	14/4727	1.0 (0.6- 1.8)	1.0 (0.6- 1.7)
12-23 months ago	17/4333	1.5 (0.9- 2.4)	1.4 (0.9- 2.3)	17/4484	1.4 (0.8- 2.2)	1.3 (0.8- 2.1)
24-35 months ago	16/5496	1.6 (1.0- 2.7)	1.5 (0.9- 2.6)	17/5812	1.6 (1.0- 2.6)	1.5 (0.9- 2.4)
36-47 months ago	8/4597	1.0 (0.5- 1.9)	0.9 (0.4- 1.8)	10/4897	1.1 (0.6- 2.0)	1.0 (0.5- 1.9)
48+ months ago	25/16958	1.2 (0.8- 1.9)	1.1 (0.7- 1.8)	30/18528	1.3 (0.9- 2.0)	1.2 (0.8- 1.8)
DURATION OF PIO						
< 12 months	22/8315	1.1 (0.7- 1.7)	1.1 (0.7- 1.6)	25/8669	1.0 (0.7- 1.6)	1.0 (0.7- 1.5)
12-23 months	22/7865	1.4 (0.9- 2.2)	1.4 (0.9- 2.2)	22/8335	1.3 (0.8- 2.0)	1.2 (0.8- 2.0)
24-35 months	14/6197	1.3 (0.8- 2.3)	1.2 (0.7- 2.1)	15/6641	1.3 (0.8- 2.2)	1.2 (0.7- 2.1)
36+ months	19/13693	1.1 (0.7- 1.8)	1.0 (0.6- 1.6)	26/14803	1.4 (0.9- 2.2)	1.2 (0.8- 1.9)
DOSE OF PIO						
1-9,000 mg	23/9949	1.2 (0.8- 1.7)	1.2 (0.8- 1.7)	26/10535	1.1 (0.7- 1.6)	1.1 (0.7- 1.6)
9,001-25,000 mg	27/11265	1.3 (0.8- 1.9)	1.2 (0.8- 1.8)	28/11939	1.2 (0.8- 1.8)	1.1 (0.8- 1.7)
>25,000 mg	27/14855	1.2 (0.8- 1.9)	1.1 (0.7- 1.6)	34/15974	1.5 (1.0- 2.1)	1.3 (0.9- 1.8)

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

° Primary analyses exclude those with a history of <u>any</u> cancer at the baseline; secondary analyses exclude only patients with a history at baseline of the cancer of interest. In all models, pioglitazone use and other medications are time-varying variables, time since the start of follow-up is the time scale. Basic Model adjusted for age, ever use of other DM medications and year of entry in the cohort; Fully Adjusted Model adjusted for age, ever use of other DM medications, year of entry in the cohort, gender, race, income, current smoking, baseline HbA1c, DM duration, new DM diagnosis, creatinine and CHF.

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 from the fully adjusted models of the primary analyses.

	Prostate	Female Breast	Lung/ Bronchus	Colon	NHL[a]	Corpus Uteri	Pancreas	Kidney/ Renal Pelvis	Rectal	Melanoma
Pioglitazone										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	1.1 (0.9- 1.2)	1.0 (0.9- 1.2)	1.0 (0.9- 1.2)	0.9 (0.8- 1.1)	1.1 (0.8- 1.3)	1.0 (0.7- 1.2)	1.3 (1.1- 1.7)	1.0 (0.8- 1.3)	0.9 (0.6- 1.2)	1.1 (0.9- 1.5)
Other TZD										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)	0.9 (0.7- 1.2)	1.1 (0.8- 1.5)	1.1 (0.7- 1.7)	1.3 (0.8- 1.9)	1.4 (0.9- 2.0)	1.1 (0.7- 1.7)	0.6 (0.3- 1.3)	1.3 (0.8- 2.0)
Metformin										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	1.0 (1.0- 1.1)	0.9 (0.8- 1.0)	0.9 (0.8- 1.0)	1.0 (0.8- 1.1)	1.1 (0.9- 1.3)	1.0 (0.8- 1.2)	1.3 (1.1- 1.6)	1.0 (0.9- 1.3)	1.0 (0.8- 1.2)	0.9 (0.7- 1.1)
Insulin										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	0.8 (0.7- 0.9)	1.1 (0.9- 1.2)	1.2 (1.1- 1.4)	1.0 (0.9- 1.1)	0.9 (0.7- 1.1)	0.9 (0.7- 1.1)	2.5 (2.1- 3.0)	1.1 (0.9- 1.4)	0.9 (0.7- 1.2)	1.0 (0.8- 1.3)
Sulfonylureas										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	0.9 (0.8- 1.0)	1.0 (0.9- 1.1)	1.1 (0.9- 1.2)	1.0 (0.9- 1.2)	1.0 (0.8- 1.2)	1.0 (0.9- 1.3)	1.6 (1.3- 1.9)	1.0 (0.8- 1.3)	1.0 (0.8- 1.3)	1.2 (1.0- 1.6)
OHA										
Never use	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	0.9 (0.7- 1.3)	0.6 (0.4- 1.0)	1.0 (0.7- 1.4)	0.9 (0.6- 1.4)	1.5 (0.9- 2.5)	0.8 (0.4- 1.6)	1.0 (0.6- 1.8)	0.9 (0.5- 1.8)	0.4 (0.1- 1.4)	1.3 (0.7- 2.4)

[a] Non-Hodgkin Lymphoma

STUDY 2: Epidemiologic study of diabetes and cancer risk

2.A. BACKGROUND AND SPECIFIC AIMS

As requested by Takeda, we are conducting a second study 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 are as follows:

1. To estimate the age- and gender- 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 gender-standardized incidence rates (standardized to the 2000 U.S. Census) within the full KPNC membership for each of the 10 most common cancers, stratified by the presence or absence of diabetes.

3. To estimate the relative risk of the 10 most common cancers associated with diabetes within the full KPNC membership, while adjusting for available confounding variables (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 available for the full membership by estimating the relative risk of the 10 most common cancers associated with diabetes using two approaches. We explore confounding 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 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, 2009 and had no prior diagnosis of the cancer of interest. At baseline, there were 147,198 persons identified by the Kaiser Diabetes Registry who had recognized diabetes and

2,309,004 persons identified in the KPNC membership file who were not included in the Kaiser Diabetes Registry (i.e. did not have recognized 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 62,926 adults with recognized diabetes who completed the Kaiser Diabetes Registry Survey in 1996-1997 and among a random sample of KPNC members that completed a similar survey, the Member Health Survey (MHS), in 1993, 1996, 1999, 2002, or 2005 (68,839 for all five 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, 2009 and had no prior diagnosis of the cancer. 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 questionnaires related to these items and used in the Diabetes Registry survey and in the MHS were identical.

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.

e. Diabetes Registry Survey

Between 1996 and 1997, 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, current diabetes therapy, type of diabetes, 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.

f. Assembly of the cohort of Diabetes Registry responders

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 2009 were excluded, leaving 63,111 members in the diabetes group.

g. Member Health Surveys (MHS)

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 1993 survey had 19,753 responders (57%), 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%).

h. Assembly of the cohort of Member Health Survey (MHS) responders

The non-diabetic comparison group 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 also mentioned above).

Finally, those who were under 40 years of age or not a member of KPNC between 1997 and 2009 were excluded, as were those who had developed diabetes prior to entering the cohort, leaving 68,839 members in the non-diabetic comparison group.

i. Follow-up time

The beginning of follow-up for aims 1, 2, 3, and 4 matched that of our study of pioglitazone use and cancer risk (Study 1). Follow-up began at cohort entry, or 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. Covariate data came from the MHS and Diabetes Registry survey. 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. If a member completed multiple surveys, data on potential confounders were obtained from the earliest survey completed.

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 (June 30, 2009). 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 (e.g., hysterectomy in analyses of endometrial cancer).

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). In the analyses that treated diabetes as a time varying exposure variable, those who responded to the MHS and were later identified as by 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 for the diabetes group. In the analyses that treated diabetes status as fixed, 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.

j. Covariates

In addition to the potential confounding variables age and gender, 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, African American, Hispanic, Asian or Pacific Islander, other, and missing), education (some high school or high school graduate, some college, college graduate or post-college, and

missing), alcohol consumption (never, past, current, and missing), smoking (never, past, current, and missing), and obesity. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

k. Statistical Analyses

For incidence rate calculations, individuals contributed person-time to the denominator until one of four events occurred: 1) a diagnosis of the cancer of interest, 2) death, 3) termination of membership in KPNC, or 4) the end of the study (December 31, 2009), whichever occurred first.

For each cancer site of interest, age (categorized in 10 year intervals), gender, and calendar year-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, calendar year intervals, and potentially change diabetes status during follow-up. Age-and gender-adjusted incidence rates, stratified by diabetes status, were calculated using the direct method (2000 U.S. Census as standard), with further stratification on calendar year (Aim 2).

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), gender, 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, gender, 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 potential confounding in the following models: Model 1: age, gender, 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 follow-up time by age, gender, and diabetes status are presented in Table 2.1. Among members without diabetes, those less than 60 years of age contributed over 50% of the person-time. 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

There were approximately equal numbers of patients in the DM and MHS surveys (Table 2.2). Those with diabetes were more frequently older. They also were more commonly non-white and more commonly obese (BMI= 30+). Those with DM were less commonly current alcohol drinkers, never smokers, or college graduates.

Age- and sex- <u>standardized cancer rates</u> – full KPNC membership

The age- and gender-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, colorectal, and lung.

For seven cancer sites, rates were higher among those with diabetes (colon, uterine, kidney/renal pelvis, NHL, ovary, pancreas, rectum). In contrast, rates among patients with diabetes were lower for breast, lung, melanoma, and prostate.

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

The age- and gender-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 above, 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). However, there was evidence of a modest amount of positive confounding by BMI for uterine cancer (age-, sex-, calendar year-, and smoking-adjusted HR=2.0 vs. HR=1.4 with same variables plus BMI) and for kidney cancer (HRs =1.4 vs. 1.2, respectively). See Table 2.4 for the age- and gender-adjusted HRs (column 3) and the HRs from the fully adjusted model with age, year of cohort entry, gender, 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 approximately 2.5 million adults aged 40 years and older, we found that the age- and sex-adjusted rates of several cancers (colorectal, pancreatic, uterine, kidney/renal, and NHL) were slightly to moderately higher among patients with diabetes than among those without diabetes. In contrast, rates of melanoma and prostate were lower and rates of lung and ovary 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(19), both with respect to standardized cancer rates among the non-DM patients, and with respect to associations of DM 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.

We also examined potential confounding by several factors unavailable on the full membership but available on two separate survey populations. Importantly, the age- and gender-standardized cancer rates and the age- and gender-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 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 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 2.1 Age of full KP cohort (n=2,456,202), by gender and diabetes status during follow up (1997-2009)

Age	Never DM (n=2,156,227)				Ever DM (n=299,975)			
	Female (n=1,128,057)		Male (n=1,028,170)		Female (n=137,107)		Male (n=162,868)	
	Pr-yrs	%(col)	Pr-yrs	%(col)	Pr-yrs	%(col)	Pr-yrs	%(col)
40-44	1,300,068	18.40	1,221,767	20.41	88,772	8.01	114,346	9.00
45-49	1,227,673	17.38	1,109,944	18.54	122,988	11.10	153,484	12.08
50-54	1,114,495	15.78	985,304	16.46	154,238	13.92	188,564	14.84
55-59	931,092	13.18	807,727	13.49	161,729	14.60	198,714	15.64
60-64	711,383	10.07	600,719	10.03	148,542	13.41	181,045	14.25
65-69	528,728	7.48	428,392	7.16	134,671	12.16	155,338	12.22
70-74	438,664	6.21	332,176	5.55	119,165	10.76	125,501	9.87
75-79	358,268	5.07	247,262	4.13	91,220	8.23	86,564	6.81
80-84	250,075	3.54	154,668	2.58	54,924	4.96	46,267	3.64
85+	204,371	2.89	99,103	1.66	31,595	2.85	21,085	1.66
All (%row)	7,064,817	45.78	5,987,062	38.80	1,107,844	7.18	1,270,908	8.24

* Person years was calculated by censoring at first invasive cancer

Table 2.2 Characteristics of survey sub-cohort* (n=119,770) by gender and diabetes (DM) status (1997-2009)

	Never DM (n=58,316)				Ever DM (n=61,454)			
	Female (n=32,382)		Male (n=25,934)		Female (n=28,706)		Male (n=32,748)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	%
Age (person-years)**								
40-44	26,866	11.74	18,727	10.59	9,850	4.06	9,598	3.63
45-49	29,751	13.00	21,707	12.28	16,995	7.01	17,300	6.54
50-54	29,274	12.79	22,101	12.50	25,312	10.44	28,041	10.60
55-59	26,636	11.64	20,798	11.76	31,025	12.80	37,062	14.01
60-64	22,114	9.66	18,210	10.30	33,907	13.99	40,975	15.49
65-69	19,672	8.59	16,344	9.25	35,362	14.59	40,661	15.37
70-74	20,714	9.05	16,998	9.61	35,066	14.47	38,078	14.39
75-79	23,178	10.13	18,908	10.70	28,803	11.88	29,578	11.18
80-84	19,175	8.38	15,121	8.55	17,063	7.04	16,385	6.19
85+	11,522	5.03	7,873	4.45	9,018	3.72	6,858	2.59
Race								
White	23,307	71.98	19,052	73.46	15,661	54.56	19,158	58.50
Black	1,886	5.82	1,248	4.81	4,089	14.24	3,552	10.85
Hispanic	2,506	7.74	1,891	7.29	3,929	13.69	4,249	12.97
Asian/PI	3,706	11.44	2,839	10.95	3,665	12.77	4,393	13.41
Other	671	2.07	593	2.29	891	3.10	972	2.97
Missing	306	0.94	311	1.20	471	1.64	424	1.29
Alcohol								
Current	22,127	68.33	19,879	76.65	10,893	37.95	18,399	56.18
Former	4,291	13.25	3,126	12.05	6,900	24.04	7,541	23.03
Never	4,577	14.13	2,292	8.84	7,697	26.81	3,487	10.65
Missing	1,387	4.28	637	2.46	3,216	11.20	3,321	10.14
Education								
HS Graduate	8,633	26.66	6,115	23.58	12,691	44.21	11,510	35.15
Some college	12,884	39.79	9,320	35.94	8,615	30.01	9,475	28.93
College graduate	10,622	32.80	10,265	39.58	5,042	17.56	8,840	26.99
Missing	243	0.75	234	0.90	2,358	8.21	2,923	8.93
Smoking								
Current	3,349	10.34	3,136	12.09	2,851	9.93	3,780	11.54
Former	8,113	25.05	9,065	34.95	7,916	27.58	14,075	42.98
Never	20,354	62.86	13,331	51.40	15,617	54.40	11,880	36.28
Missing	566	1.75	402	1.55	2,322	8.09	3,013	9.20
BMI								
<19	1,263	3.90	293	1.13	280	0.98	199	0.61
19-24	15,175	46.86	9,245	35.65	4,982	17.36	6,041	18.45
25-29	8,737	26.98	11,591	44.69	7,461	25.99	12,537	38.28
30-34	3,690	11.40	3,220	12.42	6,239	21.73	6,913	21.11
35+	2,075	6.41	819	3.16	6,426	22.39	3,806	11.62
Missing	1,442	4.45	766	2.95	3,318	11.56	3,252	9.93

Table 2.3 Age- and sex-standardized incidence rates (SIR)~~SIRs~~ for the 10 most common cancers, by DM status ((1997-2009)

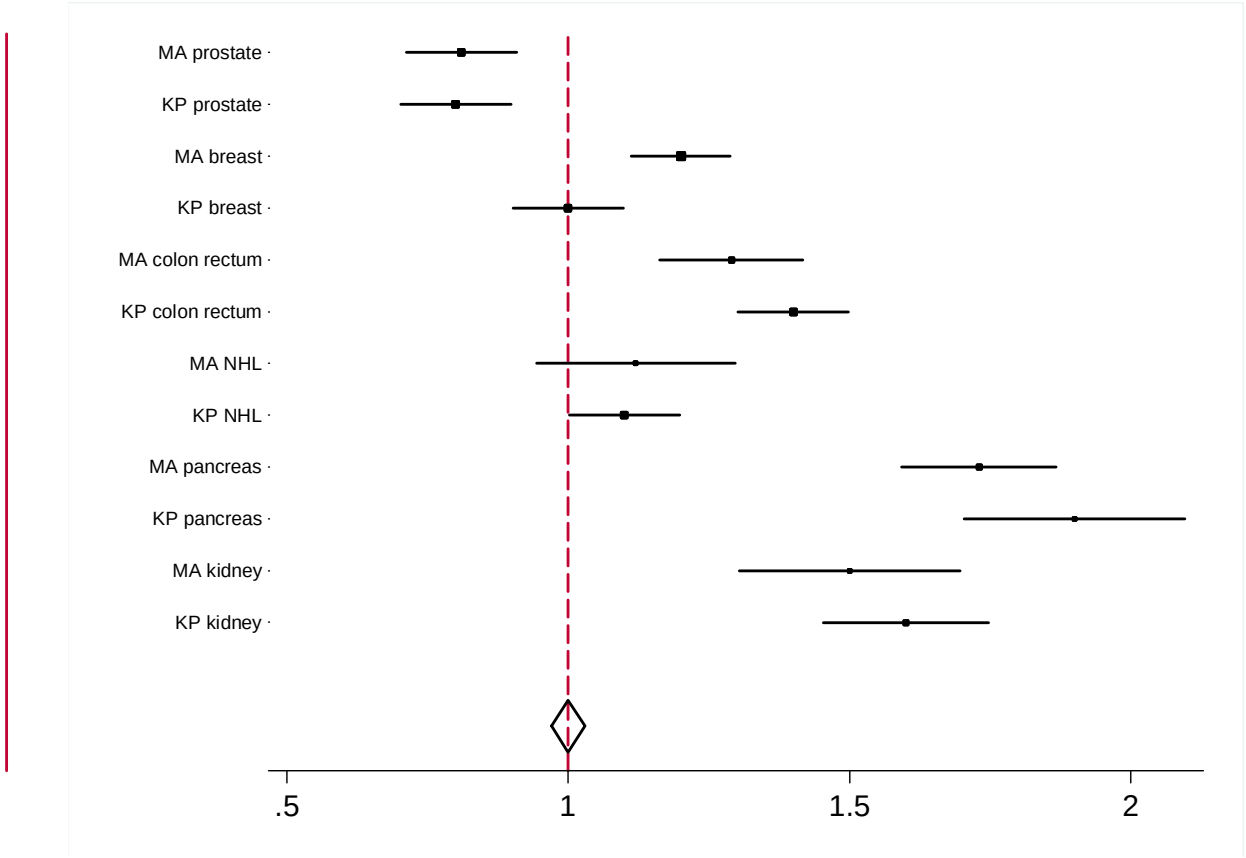
		Full KPNC cohort			Survey Sub-cohort		
Cancer Site	**DM**	**Number of Cases**	**SIR**	**95% CI**	**Number of Cases**	**SIR**	**95% CI**
Breast	No	21,805	**293.3**	289.3 - 297.2	913	**325.9**	304.0 - 347.7
	Yes	2,870	**290.1**	278.4 - 301.8	946	**290.9**	268.5 - 313.3
Colon	No	9,244	**70.3**	68.9 - 71.8	469	**70.7**	63.9 - 77.6
	Yes	2,266	**95.4**	91.2 - 99.7	811	**98.2**	90.6 - 105.8
Corpus uteri	No	3,950	**54.3**	52.6 - 56.0	154	**54.2**	45.4 - 63.1
	Yes	993	**111.1**	103.3 - 119.0	329	**106.9**	92.9 - 120.9
Kidney/renal pelvis	No	3,168	**22.6**	21.8 - 23.4	147	**22.8**	18.7 - 26.9
	Yes	888	**37.9**	35.1 - 40.8	271	**32.8**	27.6 - 38.1
Lung/bronchus	No	15,321	**113.3**	111.5 - 115.1	819	**117.2**	108.7 - 125.8
	Yes	2,917	**111.4**	107.1 - 115.7	972	**105.1**	97.5 - 112.7
Melanoma	No	5,812	**41.0**	39.9 - 42.1	286	**48.5**	42.3 - 54.7
	Yes	729	**30.6**	28.1 - 33.2	253	**32.6**	26.4 - 36.7
NHL	No	5,427	**39.5**	38.5 - 40.6	251	**39.4**	34.1 - 44.8
	Yes	1,090	**46.3**	43.2 - 49.4	364	**44.8**	39.0 - 50.6
Ovary	No	2,124	**28.1**	26.9 - 29.3	96	**30.5**	24.2- 36.8
	Yes	290	**31.3**	27.2 - 35.4	93	**33.0**	23.8 - 42.2
Pancreatic	No	2,464	**18.4**	17.7 - 19.1	128	**17.3**	14.1 - 20.5
	Yes	1,179	**47.4**	44.5 - 50.4	317	**37.2**	32.2 - 42.2
Prostate	No	22,835	**379.3**	374.3 - 384.3	1,134	**428.3**	402.2 - 454.5
	Yes	4,080	**308.5**	298.7 - 318.3	1,287	**284.4**	267.4 - 301.3
Rectum/rectosigmoid	No	3,433	**24.9**	24.0 - 25.7	142	**25.0**	20.5 - 29.4
	Yes	737	**31.9**	29.3 - 34.5	249	**33.1**	27.6 - 38.6

Table 2.4 Hazard Ratios for risk of 10 common cancers associated with DM 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	0.8 (0.8-0.8)	0.7 (0.7-0.8)	0.7 (0.7-0.8)
Female Breast	1.0 (1.0-1.1)	0.9 (0.8-1.0)	0.9 (0.8-1.1)
Lung/Bronchus	1.0 (1.0-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.1)
Colon	1.4 (1.3-1.4)	1.4 (1.2-1.6)	1.3 (1.1-1.5)
NHL	1.2* (1.1-1.2)	1.1 (0.9-1.3)	1.1 (0.9-1.4)
Corpus Uteri	1.9 (1.7-2.0)	1.9 (1.5-2.3)	1.5 (1.2-1.9)
Pancreas	2.6 (2.4-2.8)	2.3 (1.8-3.0)	2.2 (1.7-2.9)
Kidney/Renal Pelvis	1.5 (1.4-1.7)	1.3 (1.0-1.6)	1.1 (0.8-1.4)
Rectal	1.3 (1.2-1.4)	1.6 (1.2-2.1)	1.7 (1.3-2.2)
Melanoma	0.8 (0.7-0.8)	0.8 (0.6-0.9)	1.0 (0.8-1.2)

[1]Basic Model: adjusted for age, year of cohort entry, and gender
[2]Fully Adjusted Model: adjusted for age, year of cohort entry, gender, race, 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

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