Protocol for the 5-year extension

Cohort Study of Pioglitazone and Cancer Incidence in Patients with Diabetes Mellitus

Kaiser Permanente Division of Research

Assiamira Ferrara, MD, Ph.D.

Laurel A. Habel, Ph.D.

Stephen K. Van Den Eeden, Ph.D.

Charles P. Quesenberry Jr., Ph.D.

University of Pennsylvania

James D. Lewis, MD, MSCE

Brian L. Strom, MD, MPH

This protocol amendment describes the **continuation of our original 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 will be similar to the original, but with follow-up through June 30, 2012. This will, provide a minimum and maximum follow-up of 6.5 years and 15.5 years, respectively.

This protocol also describes an expansion of the original study. The expansion will include **an epidemiological study of diabetes and cancer risk** to: 1) estimate rates of the 10 most common cancers among Kaiser Permanente members with and without diabetes, and 2) estimate the relative risks of each of 10 most common cancers associated with a diagnosis of diabetes.

The proposed 5-year extension study will continue 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 have all agreed to stay on for the extension and we will continue to have regular meetings with them.

I. Continuation of original study

A. Summary of the results of the 2-year study

In the original 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 Final Report). Briefly, at the end of follow-up, there were 26,364 patients who were exposed to pioglitazone. There were a total of 11,977 cohort members diagnosed with at least one cancer and 9,082 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 cancers, there are a considerable number of cases, ranging from 373 for melanoma to 2,105 for prostate cancer.

In our basic analytic models adjusted only for age, year of cohort entry, and use of other diabetes medications, the hazard ratios (HRs) for the risk of each of the 10 most common cancers associated with ever use of pioglitazone ranged from 0.7 to 1.5 and all 95% confidence intervals included 1.0. There was a suggestion of a slightly increased risk of melanoma and non-Hodgkin lymphoma (NHL) associated with ever use of pioglitazone (HR =1.5, 95% CI 1.0-2.1 for melanoma; HR=1.4, 95% CI 1.0-1.9 for NHL), although these did not increase further with dose, duration, or time since first use. Further adjustment for gender, race-ethnicity, income, current smoking, baseline glycemic control, diabetes duration, creatinine levels and congestive heart failure did not materially change the results.

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 (AB) 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 AB 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 observed and expected cancers that occurred in members of the original cohort after December 31, 2005.

B. Protocol for the 5-year extension study

1. Study population: The extension will include Kaiser members who were eligible for our original study and will again utilize only electronic data available within the numerous databases of Kaiser Permanente. The source population for the original study was health plan members captured by the Kaiser Diabetes Registry, which was first constructed in 1993 and has been updated annually. Data from several other electronic files were merged with data from the Diabetes Registry in order to restrict the study population to individuals meeting the inclusion and exclusion criteria (see criteria below). We identified 252,467 Kaiser members meeting these eligibility criteria.

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 they were aged 40 years or older when they were identified by the DM registry between January 1, 1997 and June 30, 2005.

Cohort Exclusion Criteria

Individuals were excluded from the cohort for the following:

1. Age < 40 years during study period.
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.
3. Gap in KPNC membership >= 4 months that started in the first 4 months after entering in the cohort.
4. All prevalent cancers at baseline, i.e. all participants ever diagnosed with cancer other than non-melanoma skin cancer. [For comparison with initial results, we will also conduct secondary analyses where these prevalent cases are not excluded].

2. Baseline and follow-up time: As in the original study, the baseline date will be defined as the first date that the inclusion criteria were met. Follow-up for outcomes will begin 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 will begin at 12 months after entry into the cohort to account for prodromic diabetes symptoms related to their pancreatic cancer.

Follow-up for the extension will end at the earliest of: 1) diagnosis of the outcome of interest, 2) diagnosis of another cancer (eg, for breast cancer analyses, follow-up time will be censored at diagnosis of non-breast cancer) [for primary analyses only, will not be censored in secondary

analyses], 3) death, 4) a gap of greater than 4 months in either membership or prescription benefits, or 5) the end of the study period (June 30, 2012). In selected analyses, patients will be censored at the time of a surgery (for indications other than cancer) that significantly reduce or preclude cancer development at that organ site (e.g., hysterectomy in analyses of endometrial cancer).

3. Exposure assessment: As in the original study, medication exposures will be determined based on filled prescriptions from the date of entry into the cohort through the end of follow-up by linkage with the KPNC Pharmacy Information Management System. The primary definition of exposure is "ever exposed", defined as receipt of at least two prescriptions for pioglitazone within a 6-month period. Secondary exposure definitions will include: 1) time since initiation of pioglitazone, 2) cumulative duration of pioglitazone use, and 3) cumulative dose of pioglitazone.

4. Outcome identification: Prevalent and incident cancers (for all sites) will be identified by linkage with the KPNC cancer registry, a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program registry. In the primary analyses we will exclude all prevalent cancers, while for the secondary analyses we will exclude only the prevalent cases of the cancer of interest. Primary analyses will focus on the 10 cancers other than bladder with the highest incidence rates reported in the general population from the Northern California SEER registry database; bladder cancer is the focus of a different protocol. These cancers include: lung, colon, rectal, breast, prostate, pancreatic, melanoma, renal, endometrial and non-Hodgkin's lymphoma. Exploratory analyses will examine less common cancers. These will be limited to cancers that occurred in at least 3 patients exposed to pioglitazone.

5. Selection of confounders: As in the original study, data on the following potential confounders are available within the KPNC electronic data: age, ever use of other DM medications categorized by class, year of entry in the cohort, gender, race, income based on census block, current smoking, baseline HbA1c, DM duration, new DM diagnosis, baseline creatinine and a history of congestive heart failure. Use of statins and different classes of hypertension medications were not proposed as confounders in the initial protocol but will be examined in this extension. Hormone replacement therapy will be examined among women as a potential confounder. Exposure definition for the confounders that are medications will be the same as our primary exposure definition for pioglitazone.

6. Statistical analysis: After excluding all prevalent cancers, we will examine the association between diabetes medication and incidence of each of the 10 most common cancers that occurred between July 1 1997 and June 30, 2012. Cox proportional hazards regression modeling will be 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 will be treated as time-dependent covariates and time since entry into the cohort was the time scale. We will include age, sex (for non-sex specific cancer sites), and all categories of diabetes medications as time-dependent covariates in all regression models. Additional potential confounders, will be assessed by determining if model inclusion appreciably changes the point estimates for the pioglitazone exposure measure under consideration (>10%). Because HbA1c is expected to be increased at the time of diagnosis, we will include an interaction term between HbA1c levels and whether the measurement coincides with a new diagnosis of diabetes based on the patient newly entering the diabetes registry (this could include true incident diagnosis of diabetes or a patient with diabetes who newly registers with Kaiser Permanente). Any variable that meets this criterion will be included in the final model. Finally, we will explore the possibility of joint confounding by

including all potential confounder variables in a single model. We will assess for departures from model assumptions via diagnostic plots of weighted residuals and tests for interaction between exposure and time. The above analyses will be repeated without excluding prevalent cancers. Additionally, we will compare use of pioglitazone at cohort entry among prevalent cancer patients to use among other members of the cohort (adjusted for age and sex).

The following subgroup analyses are planned: 1) among those for whom DM duration is known (i.e. prior diabetes survey responders and patients with at least 2 years of Kaiser membership before being captured by the Diabetes Registry) 2) among patients with at least 2 years of membership and newly diagnosed with DM since January 1995 (ie, with complete information on DM prescriptions because electronic pharmacy records started in 1995), and 3) among those for whom BMI is known (i.e. prior diabetes survey responders). The longer follow-up period in the extension (and therefore the increased number of events) will provide substantially greater power for these sub analyses.

For those cancer sites, if any, with an observed increased risk associated with pioglitazone use, we will examine whether risk varies by stage at cancer diagnosis.

In exploratory models of less common cancers, we will adjust only for age and year of cohort entry. If there are sufficient numbers of subjects with the cancer, we will adjust for gender in non-sex specific cancers.

7. Power calculation: Given the expected additional person-years accrued with follow-up extended through June 2012, and cancer incidence rate estimates from the previous study (see Final Report), the expected total number of cancer cases at the 10 most common sites in the cohort of 242,467 diabetics is approximately twice that observed in the previous study, ranging from approximately 650 (rectal) to 4,000 (prostate) with exclusion of cases with a previous cancer at another site.

Table 1: Expected number of cancer cases among the cohort of 242,467 diabetes, 1/1/97 – 6/30/12.

Cancer Site		**N cases after exclusion of cases with a previous cancer at another site**
Prostate		4067
Female Breast		3038
Lung and Bronchus		2987
Colon		2473
Corpus Uteri		1076
Non-Hodgkin Lymphoma		1056
Pancreas		855
Kidney/ Renal Pelvis		843
Rectal		652
Melanoma		790

We present minimum detectable relative hazards for each cancer site of interest based on the likelihood ratio test and a Cox proportional hazards regression analysis, as presented by Self[1] and as implemented in the software package EGRET[2]. These estimates account for varying length of follow-up due to cohort accrual period, end of study, and estimated pattern of termination of Health Plan membership and mortality. In the previous study, approximately 10% of the cohort was exposed to pioglitazone. With the additional 6.5 years of follow-up, we expect the proportion exposed to increase and therefore present power calculations assuming a range in pioglitazone use from 10% to 20%. We have sufficient power (.80) to detect associations of

modest strength across the range in expected number of cancers cases and proportion exposed to pioglitazone.

Table 2. Minimum detectable relative hazards of cancer associated with pioglitazone use (2 sided test, α = .05, power =.80)

Proportion exposed to pioglitazone	Expected number of cancer cases			
	650	1000	2500	4000
10%	1.40	1.32	1.20	1.16
20%	1.30	1.24	1.15	1.12

II. Epidemiological study of diabetes and cancer risk.

A. Background and specific aims

As noted above, we found weak associations between pioglitazone use and risk of melanoma and NHL in our original study. Although we controlled for indicators of diabetes severity such as HbA1c levels, diabetes duration, and use of other diabetes medications, it is possible that the observed associations between pioglitazone use and risk of melanoma and NHL, or associations with other cancers that may appear in our extended follow-up, actually reflect associations between diabetes severity (based on indicators we were not able to control for) and cancer risk.

It is also possible that diabetes, independent of severity, is associated with risk of cancer at some sites. At least one previous study found that diabetes was associated with an approximately 20-40% increased risk of cancer mortality[3]. While other studies[4-6] have found no association between diabetes and cancer risk, these studies were often underpowered because of the small number of subjects with diabetes. A recent meta-analysis[7] of studies of diabetes and risk of NHL reported that although the results from prospective studies suggested a positive association between diabetes and NHL, the evidence is inconclusive because of limitations in the studies conducted to date. These limitations include the definition of diabetes (often based on self report) and the inability to adequately control for potential confounders such as obesity. In a recent study[8] conducted in Northern Sweden, the risk of melanoma increased with increasing levels of fasting plasma glucose. A twofold increase (95% CI 1.14-4.35) in the risk of malignant melanoma was observed for both men and women in the highest quartile of fasting plasma glucose levels as compared to men and women in the lowest quartile.

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. While the question of cancer risk and diabetes severity can be addressed among the diabetic cohort, analyses limited to patients with diabetes do not allow an examination of whether patients with the least severe diabetes have an increased risk of a given cancer relative to those without diabetes.

Takeda has requested that we conduct a study of the relation between diabetes and cancer risk. Of course all analyses from this study will be interpreted and qualified by the consideration that any associations observed could be due to the underlying disease or its therapies.

We propose the following specific aims:

1. To estimate the age-, gender- and calendar-specific incidence rates for each of the 10 most common cancers, stratified by the presence or absence of diabetes (full KPNC membership).

2. To estimate the age-, gender-standardized (standardized to 2000 US Census) rates for each of the 10 most common cancers, stratified by the presence or absence of diabetes (full KPNC membership).
3. To estimate the relative risk of each of 10 most common cancers associated with diabetes (time-varying), while adjusting for confounding variables available on the full KPNC membership (age, gender, calendar year).
4. To explore potential confounding by variables not available on the full membership by estimating the relative risk of each of 10 most common cancers associated with diabetes (treated as time-varying) using two approaches. We will explore confounding among subsets of the KPNC membership with survey information on additional potential confounders (race, BMI, smoking, alcohol).

B. Methods

1. Study population: The study population for aims 1, 2, and 3 will include all Kaiser members who were aged 40+ years between 1997 and 2011. The study population for aim 4 will include all Kaiser members aged 40+ between 1997 and 2011 who took the 1996/7 diabetes survey, plus members who took the Member Health Survey (MHS) in calendar years 1993, 1996, 1999, 2001 or 2003.

2. Diabetes status: For aims 1, 2, and 3, a member will be considered to have diabetes on the date that they are captured by the Diabetes Registry. This classification will be time-varying and members who are not diabetic at cohort entry may be later classified as diabetic at the time they are captured by the diabetes registry.

For aim 4, members with diabetes will include those aged 40+ years who completed the 1996/7 diabetes survey, plus members who took the MHS (1993, 1996, 1999, 2001 or 2003) and were also identified as diabetic via the Diabetes Registry). The non-diabetic comparison group will be members who took the MHS (1993, 1996, 1999, 2001 or 2003) and were not identified by the DM registry as being diabetic at the time of the MHS. For those who later are identified as diabetic by the DM registry, follow-up time will be censored at DM diagnosis. We recognize that these individuals will have had diabetes for some period of time prior to diagnosis.

3. Outcome identification: As in the original study, prevalent and incident cancers (for all sites) will be identified by linkage with the KPNC cancer registry, a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program registry. Primary analyses will focus on the 10 cancers other than bladder with the highest incidence rates reported in the general population from the Northern California SEER registry database; bladder cancer is the focus of a different protocol. These cancers include: lung, colon, rectal, breast, prostate, pancreatic, melanoma, renal, endometrial and non-Hodgkin's lymphoma. Exploratory analyses will examine less common cancers.

4. Subset of KPMCP Members that Responded to the Surveys (aim 4 only):
Diabetes Survey. Between 1995 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 KPMCP 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 77,726 members who responded to the survey, approximately 3% stated that they did not have diabetes and therefore, were excluded from the diabetic cohort.

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, 2001 and 2003 to random samples of KPMCP members, age 18 years and above, stratified by age and KPMCP facility.

Members who responded to both the MHS and to the Diabetes Registry survey will be included in the diabetic cohort and data on potential confounders will be taken from the Diabetes Survey. Persons who stated on the MHS that they had diabetes but they did not respond to the diabetes survey will be excluded from both groups, given the lack of information on diabetes-specific covariates. Persons who responded to the survey but were no longer members of KPMCP at the time they filled-out the surveys will also be excluded.

5. Follow-up: The beginning of follow-up for aims 1, 2 and 3 will be similar to that for our original study. Follow-up will begin at the first time all three of the following criteria are met: January 1, 1997, aged 40 years or older, and KPNC member for at least 6 months.

For aim 4, members will begin follow-up on the date of their survey. If a member completed multiple MHS surveys, follow-up will begin on the date of their earliest MHS survey. For example, members who completed both the 1993 and the 1996 MHS will begin contributing person time in 1993. Data on potential confounders will also be obtained from the earliest survey completed.

Follow-up will end at the earliest of: 1) diagnosis of the outcome of interest, 2) death, 3) a gap of greater than 4 months in either membership, or 4) the end of the study period (June 30, 2012). In selected analyses, patients will be censored at the time of a surgery (for indications other than cancer) that significantly reduce or preclude cancer development at that organ site (e.g., hysterectomy in analyses of endometrial cancer).

6. Statistical analyses: In analyses of each cancer of interest, we will exclude KP cohort members with a diagnosis of that cancer prior to the baseline date of January 1, 1997 or when they become eligible to enter the cohort (i.e. KP members who reached 40 years of age or new KP members aged 40 or older).

In incidence rate calculations, individuals will contribute person-time to the denominator until one of four events occurred: 1) the end of the study, 2) a diagnosis of the cancer of interest, 3) death or 4) termination of membership in KPMCP (via electronic KPMCP membership files), which ever occurred first. Cohort members with an incident cancer diagnosis at a given site during follow-up will remain at risk and contribute person-time for follow-up for cancer at other sites.

For each cancer site of interest, age (categorized in 5 year intervals), gender and calendar year specific incidence rates (and 95% confidence intervals) will be 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, will be calculated using the direct method (2000 US Census as standard), with further stratification on calendar year (**Aim 2**).

The association between diabetes and each cancer outcome will be assessed using Cox proportional hazards regression models, providing point and interval estimates of the relative

hazard of each cancer outcome associated with DM status (time-dependent covariate), with control for potential confounders available on the full KPNC membership: age (categorical variable with 5 year intervals), gender, calendar year (**Aim 3**). Assessment of departures from model assumptions will include diagnostic plots of weighted residuals and tests for interaction between exposure and time.

Similarly, we will use Cox regression techniques to examine the association between DM status and cancer risk with adjustment for potential confounding variables in the survey respondent cohort (**Aim 4**). First, we will compare 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 RRs are similar, we will then explore three models, defined by sequential blocks of covariates: Model 1: age, gender, calendar year and race-ethnicity; Model 2: Model 1 covariates and smoking; Model 3: Model 2 covariates, BMI, education and alcohol consumption. For each of the three sets of covariates, model inclusion for each covariate will be based on a change-in-estimate strategy, which compares the exposure-outcome (DM- cancer) association with and without adjustment for the covariate under consideration for model inclusion. Potential confounding will be assessed by determining if model inclusion of a covariate appreciably changes the relative hazard for cancer associated with diabetes (>10%).

7. Power calculation

Given preliminary data, approximately 3,392,000 Health Plan members will meet cohort inclusion criteria during the cohort accrual period (1/1/1997 – 12/31/2011), with approximately 1,262,000 entering the cohort in 1997. Given expected cohort accrual patterns and annual rates of drop-out due to death and membership termination, estimated via a length of membership enrollment database, we will observe approximately 30,324,000 person-years of follow-up for event ascertainment through 6/30/2012. Given data from our previous pioglitazone study, we expect approximately 10% of the full cohort will have a diabetes diagnosis ascertained via the KPNC registry (either at cohort entry, or during follow-up). Given current KPNC cancer registry data, the expected number of incident cancer cases among the 10 most common sites ranges from approximately 4,700 (pancreas) to 39,000 (prostate) [Table 3].

Table 3: Expected number of cancer cases among the cohort of 3,392,000 KP Health Plan members, 1/1/97 – 6/30/12.

Cancer Site	Number of cases
Prostate	38,922
Female Breast	33,502
Lung and Bronchus	24,003
Colon	15,038
Corpus Uteri	6,567
Non-Hodgkin Lymphoma	8,589
Pancreas	4,693
Kidney/ Renal Pelvis	5,498
Rectal	5,691
Melanoma	8,445

Using methods as outlined for power calculations in our original study, we present minimum detectable relative hazards for cancer associated with diabetes across the range in expected number of incident cancer cases. We have sufficient power (.80) to detect associations of modest strength.

Table 4. Minimum detectable relative hazards of cancer associated with diabetes (2 sided test, α = .05, power =.80)

Expected number of cancer cases				
4,700	8,500	15,000	25,000	40,000
1.14	1.11	1.08	1.06	1.05

Given that detectable effect sizes are quite small in this large cohort, it will be essential to focus on point and interval estimates of relative risk, rather than statistical significance. This study will have statistical power to detect relative risks which are not in the range of clinical significance, and also well within the range of estimated effect sizes that could be explained entirely by lack of control of unmeasured confounding variables.

8. Timeline for interim and final reports: This extension of the initial protocol will parallel the ongoing study of bladder cancer. As such, we will plan for an interim report to be completed by December 31, 2011 including data on cancers that have been diagnosed as of June 30, 2009. A final report will be available by December 31, 2013 that will include data on cancers that have been diagnosed as of June 30, 2012.

Reference List

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