Thiazolidinediones and the Risk of Lung, Prostate, and Colon Cancer in Patients With Diabetes

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ABSTRACT

Purpose
Peroxisome proliferator-activated receptor gamma (PPARγ) mediates cell cycle arrest and adipocyte differentiation; has tumor suppressor activity in liposarcoma, lung, and prostate cancers; and suppresses colonic polypl formation in adenomatous polyposis coli (APC)min/+ mice. To assess the influence of thiazolidinediones (TZDs), which are PPARγ ligands used to treat diabetes mellitus, a retrospective analysis of a database from 10 Veterans Affairs medical centers was conducted.

Patients and Methods
Data on male patients 40 years and older diagnosed to have diabetes mellitus between 1997 and 2003 were obtained from the Veterans Integrated Services Network 16 (VISN 16) data warehouse. Subsequent diagnoses of colorectal, lung, and prostate cancer and use of TZD, other antidiabetic agents, and insulin were identified. Cox regression with time-dependent covariates was used to estimate the association between TZD use and cancer risk. Relative risks were adjusted for confounders (age, race/ethnicity, body mass index, use of insulin, and other oral antidiabetic agents).

Results
Of 87,678 individuals, 1,137 had colorectal cancer, 3,246 had prostate cancer, and 1,371 had lung cancer. We observed a 33% reduction in lung cancer risk among TZD users compared with nonusers after adjusting for confounder interactions (relative risk, 0.67; 95% CI, 0.51 to 0.87). The cancer risk reduction for colorectal and prostate cancers did not reach statistical significance.

Conclusion
TZD use was associated with reduced risk of lung cancer. Further studies are warranted to confirm our findings.

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INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are members of a super family of nuclear receptors. The PPAR subfamily has three isotypes: alpha (α), beta/delta (β/δ), and gamma (γ), which are ligand-activated transcription regulators important in cellular homeostasis.1-3 Stimulation of PPARγ induces cell cycle arrest and has a role in the terminal differentiation of adipocytes. PPARγ agonists bind to the DNA only in the PPARRXR (retinoid X receptor) heterodimer form. PPARγ agonists induce cell cycle arrest and apoptosis of lung cancer cell lines in vitro.4,5 The metabolites of arachidonic acid, 15-HETE [15(s)-hydroxyeicosatetraenoic acid] and linoleic acid, 13-HODE [13(s)-hydroxododecanedioic acid], are ligands for either PPARγ or mitogen-activated protein (MAP) kinase and may mediate the pathogenesis of prostate cancer.6 In the normal prostate gland, activation of MAP kinase induces phosphorylation of PPARγ, which in turn suppresses differentiation and de-represses growth. Thiazolidinediones (TZDs) suppress MAP kinase activation and, hence, the phosphorylation of PPARγ, and in turn induce differentiation and growth repression. TZDs increase the number of intestinal polyplys in adenomatous polyposis coli (APC)min/+ mice in small doses, but have the opposite effect at higher doses and are not tumorigenic in wild-type mice.7-10 Some of the antineoplastic actions of TZDs may be mediated by antiangiogenic effects.11,12

TZDs (glitazones) are synthetic ligands for PPARγ that are used to treat diabetes mellitus. There are insufficient clinical data regarding the protective effects of glitazones on cancer.1,9,13 To assess whether the glitazones have a cancer preventive effect, we conducted a retrospective analysis of a database from 10 Veteran Affairs medical centers aged 40 years and older.
The objective of the study was to assess whether there was a difference in the risk of development of three malignancies—lung, prostate, and colorectal cancer—that are common in the veteran population and for whom published preclinical data provided a possible rationale for a role for TZD action.

**PATIENTS AND METHODS**

**Study Population**

The population for this retrospective study was derived from an electronic database covering 10 Veterans’ Affairs (VA) hospitals (Alexandria, LA; Biloxi, MS; Fayetteville, AR; Houston, TX; Jackson, MS; Little Rock, AR; Muskogee, OK; New Orleans, LA; Oklahoma City, OK; and Shreveport, LA) that comprise the Veterans Integrated Services Network 16 (VISN 16). All of the data in the database, such as diagnosis, laboratory values, and treatment, were entered into the electronic patient charts, which in turn were exported to the VISN 16 and the VA national database. The protocol was approved by the institutional review board of the University of Arkansas for Medical Sciences and the VA administration. Male patients aged 40 years or older who were newly diagnosed with diabetes mellitus between October 1997 and September 2003 were eligible. Cancer diagnosis dates were collected through September 2003, and patient contact dates (visits, laboratory test dates) were collected through December 2, 2004. The diabetic subjects were identified using the International Classification of Diseases (ICD) code 250.XX (XX: all patients with diabetes mellitus type 1, type 2, with and without complications, were identified). Those who had a diagnosis of cancer at the time of diagnosis of diabetes mellitus were excluded. ICD-9 codes were used to identify the diagnosis of lung cancer (162.9), colorectal cancer (153.9 and 153.10), and prostate cancer (185.0).

**Covariate Data**

Dates of first use of TZD, other oral antidiabetic agents, and insulin; age; race/ethnicity; sex; height; weight; and hemoglobin (Hgb) A1C measures were extracted from the database. The information extracted was current as of the date of data extraction in March 2005. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). The duration of TZD prescription for each patient was obtained from the database from the dates of first and last prescription. The duration of TZD exposure for each patient was estimated from the database from the dates of first and last prescription and from the amounts dispensed at each prescription. Under the assumption that dispensed amounts were to be taken at one tablet per day, some prescriptions were for 90 or 180 days, but a large majority were for 30 days. Accordingly, 30 days plus the number of days between first and last prescription dates was taken as a crude estimate of TZD exposure duration.

**Statistical Analyses**

Cox proportional hazards regression with time-dependent covariates for drug exposures was used to estimate the association between TZD use and cancer risk. The relative risk (RR) of development of cancer was defined as the hazard ratio for time to cancer development in patients who became exposed to TZD, other oral agents, insulin, or combinations of the three, compared with that for patients not yet exposed to these drugs. Risk increases and reductions with TZD exposure were computed as the absolute value of |RR - 1| and expressed as percentages. RRs were estimated unadjusted, adjusted for only age and race/ethnicity, and adjusted for all available confounders. In the analyses, the response variables were times to cancer, defined as the times from date of diabetes diagnosis to date of diagnosis of colorectal, lung, or prostate cancer. Study participants who reached their last follow-up without a diagnosis for a particular cancer were censored for that cancer at the last follow-up date. The Cox regressions modeled TZD, insulin, and other oral antidiabetic agents as time-dependent covariates using first drug-use dates to mark the onset of exposure, with time-dependent drug-drug interactions for patients who began a second drug, with stratification to control for age and race/ethnicity, and with covariate adjustment to control for BMI and HgbA1C.

SAS version 9.1 (SAS Institute, Cary, NC) was the statistical software package used to perform the computations presented. P values less than .05 were considered to be statistically significant despite the multiple comparisons so as not to inflate type II error in this hypothesis-generating observational study.

Eighty-seven thousand six hundred seventy-eight patients met the study inclusion criteria, of whom 72,323 had nonmissing data for height, weight, and HgbA1C. Eleven thousand two hundred eighty-nine patients were treated with TZD, and 76,389 were never prescribed a TZD. The median duration of TZD exposure was 364 days. Table 1 presents characteristics of the study population. Age was equally distributed between TZD users and nonusers, with equal medians, equal lower quartiles, and nearly equal upper quartiles. The race/ethnicity breakdown for TZD users was 62% white, 12% African American, and 26% unknown, compared with 57% white, 17% African American, and 26% unknown for TZD nonusers. The imbalance was considered modest for a study population of this magnitude. The higher median BMI, higher use of insulin and other oral antidiabetic agent use among those who use a TZD compared with those who did not use a TZD are in accordance with the prescribing tendency of TZD for more advanced and refractory diabetes. A median HgbA1C level, a measure of control of diabetes, was also higher among TZD users than among nonusers.

During the study period, 1,137 patients were diagnosed with colorectal cancer, 3,246 with prostate cancer, and 1,371 with lung cancer (Table 2). The unadjusted risk reduction for lung cancer among TZD users was 29%, as was the age- and race-adjusted risk reduction for this cancer. After adjusting for all available covariates (age, race/ethnicity, BMI, HgbA1C, insulin use, use of other oral agents, and drug-drug interactions), we observed a 33% reduction in lung cancer risk among TZD users compared with nonusers (RR, 0.67; 95% CI, 0.51 to 0.87; P = .0033). Although we observed mild trends toward risk reduction with TZD use for prostate cancer (RR, 0.86; 95% CI, 0.64 to 1.14; P = .30) and colorectal cancer (RR, 0.88; 95% CI, 0.74 to 1.05; P = .16) after adjusting for all available covariates, they did not attain statistical significance.

The effect of TZD was also analyzed in a subgroup analysis by race/ethnicity (Table 3). For both white and African American patients, there was a reduction in the incidence of lung cancer among those who were prescribed TZD. After adjustment for age, BMI, HgbA1C, insulin use, and the use of other oral antidiabetics, the TZD-associated risk reduction for lung cancers was 26% among white (RR, 0.74; 95% CI, 0.58 to 0.95; P = .02) and 62% among African American patients (RR, 0.38; 95% CI, 0.15 to 0.93; P = .03). The covariate-adjusted colorectal cancer risk with TZD use fell 2% in white (RR, 0.98; 95% CI, 0.80 to 1.21; P = .85) but 47% in African American patients (RR, 0.53; 95% CI, 0.31 to 0.93; P = .03), consistent with the lower risk reduction for white patients noted earlier. In contrast, the covariate-adjusted race-specific risk of prostate cancer showed increases with TZD use of 18% in African American (RR, 1.18; 95% CI, 0.94 to 1.50; P = .16) and 15% in white patients (RR, 1.15; 95% CI, 1.02 to 1.31; P = .03).
Our data provide a strong association between the use of TZD and reduced risk of lung cancer. Published preclinical studies suggest several possible mechanisms that may explain the association between the reduction in lung cancer risk and exposure to TZD. TZD and other PPARγ ligands induce apoptosis of non–small-cell lung cancer cell lines H841, A549, and PC14; arrest A549 non–small-cell lung cancer cells in G0/G1 phase; induce growth arrest and DNA-damage inducible 45 genes (GADD45); and, in addition, induce Early growth response-1 gene leading to apoptosis. RXR, also a member of the nuclear-receptor family, is a common binding partner for PPARγ. The resulting functional complex, a heterodimer of one RXR molecule with one PPARγ molecule, is a target for TZD as well as other drugs. Heterodimerization of PPARγ with RXR in response to ligand stimulation may be a mechanism of action in lung cancer risk reduction. In vitro studies have shown downregulation of PSA antigen expression in vitro and inhibition of proliferation of prostate cancer cell lines such as LNCaP in response to exposure to PPARγ ligands such as TZD and BRL 49653. Troglitazone, a TZD, induces growth arrest and differentiation of colon cancer cell line HT-29 in a dose-dependent manner. When APCmin mice are exposed to TZD, the number of polyps decreased with increasing TZD dose, although the number of polyps may increase at a very small dose. This response is limited to mice expressing tumor suppressor gene APCmin and is not seen in those with wild-type genes. Ligands for PPARγ dose dependently suppress growth and differentiation of human umbilical vein endothelial cells that express PPARγ mRNA. TZD may also influence tumor growth and development through an antiangiogenic mechanism. PPARγ ligand 15d-PGJ2 inhibits the angiogenic effect of vascular endothelial growth factor in the rat cornea model. PPARγ is highly expressed in vascular endothelial cells and is lost on exposure to TZD, suggesting that the antiangiogenic properties of PPARγ ligands may play a role in inducing an antineoplastic effect. The effective concentration of

Table 1. Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TZD Users</th>
<th>%</th>
<th>TZD Nonusers</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11,289</td>
<td>76,389</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>Median 67</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR 58-75</td>
<td>58-76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>White 7,012</td>
<td>62.1</td>
<td>43,925</td>
<td>57.5</td>
</tr>
<tr>
<td>African American 1,389</td>
<td>12.3</td>
<td>12,810</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Other/undeclared* 2,888</td>
<td>25.6</td>
<td>19,654</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>Median 31.2</td>
<td>29.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR 27.6-35.6</td>
<td>26-33.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin use</td>
<td>6,628</td>
<td>45.2</td>
<td>20,265</td>
<td>26.3</td>
</tr>
<tr>
<td>Other oral agents</td>
<td>9,593</td>
<td>85</td>
<td>47,887</td>
<td>62</td>
</tr>
<tr>
<td>HgbA1C</td>
<td>Median 7.8</td>
<td>6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR 6.7-9.3</td>
<td>6.1-8.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of TZD exposure, days</td>
<td>Median 364</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQR 148-685</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TZD, thiazolidinedione; IQR, interquartile range; Hgb, hemoglobin; NA, not applicable.
*Hispanic, Native American, Asian/Pacific Islanders, n = 1,501; undeclared, n = 21,041.

Table 2. Relative Risk of Cancer Development Among Diabetics Treated With TZD

<table>
<thead>
<tr>
<th>Cancer Diagnosis</th>
<th>Events</th>
<th>HR</th>
<th>P</th>
<th>95% CI</th>
<th>Race/Ethnicity and Age Adjusted*</th>
<th>Events</th>
<th>HR</th>
<th>P</th>
<th>95% CI</th>
<th>Covariate Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>1,137</td>
<td>0.90</td>
<td>.33</td>
<td>0.74 to 1.11</td>
<td>0.91</td>
<td>.35</td>
<td>0.74 to 1.11</td>
<td>999</td>
<td>0.88</td>
<td>.16</td>
</tr>
<tr>
<td>Prostate</td>
<td>3,246</td>
<td>0.95</td>
<td>.43</td>
<td>0.84 to 1.07</td>
<td>0.98</td>
<td>.70</td>
<td>0.86 to 1.10</td>
<td>2,849</td>
<td>0.86</td>
<td>.30</td>
</tr>
<tr>
<td>Lung</td>
<td>1,371</td>
<td>0.71</td>
<td>.0009</td>
<td>0.58 to 0.87</td>
<td>0.71</td>
<td>.0012</td>
<td>0.58 to 0.88</td>
<td>1,110</td>
<td>0.67</td>
<td>.0033</td>
</tr>
</tbody>
</table>

NOTE. The incidence of lung, colorectal, and prostate cancers among diabetic patients using TZD compared with those not using TZD. P values are not adjusted for multiple comparisons, so as not to inflate type II error.
Abbreviations: TZD, thiazolidinedione; HR, hazard ratio.
*Adjusted for age and race/ethnicity. The patient denominator for this analysis was 87,678.
†Adjusted for age, race/ethnicity, body mass index, hemoglobin A1C, insulin, other oral agents, and drug-drug interactions. The patient denominator for this analysis was 72,323.
the glitazones in in vitro studies ranged from 20 to 50 μmol/L, in keeping with the clinical concentration of glitazone one might expect from therapeutic dosing.22,23 Although the laboratory data indicate that TZDs act as ligands for PPARγ and, in turn, have an effect on the growth and differentiation of prostate cancer cells, success has been limited to serum prostate-specific antigen (PSA) stabilization and downregulation of PSA expression.6,22 Likewise, a phase II trial treating patients with metastatic colorectal cancer with troglitazone did not produce any measurable effect.23 Nonetheless, this data set provided an excellent opportunity to perform a hypothesis-generating study to better refine the clinical area and conditions appropriate for further exploration regarding the impact of TZD use on malignant diseases.

The veteran population is a select group of subjects who utilize a single system for their medical needs. We chose diabetics because this the only group of patients treated with TZD. The incidence of certain types of cancer has been reported to be higher in diabetics as opposed to nondiabetics.24-26 This should not influence the results on the risk of cancer development. If TZD users is probably mediated by RXR-α receptor–mediated pathways. The incidence of colorectal and prostate cancers was not influenced by TZD usage when the population was analyzed as a whole, but there was an increase in the incidence of prostate cancer among white and African American patients. There was a decrease in the incidence of colon cancer among African American patients (Table 3). The difference in the racial incidence of prostate and colorectal cancers is difficult to explain, and may have to do with the statistical power of detection as well as a hypothetical difference in the participation population to provide adequate statistical power to detect a statistically significant level of risk reduction.

This study evaluates the role of TZD in reducing the incidence of lung cancer in a clinical setting. This study includes a large number of patients supporting preclinical data on the protective effect of PPARγ ligands on carcinogenesis. VISN 16 has a large database that is a reliable source of patient data because patients in this database are all treated within a single system. This database is extracted from the electronic medical record used by all the clinicians to enter the patient information in an ongoing basis and is an excellent source of clinical data that can be used to ask questions and generate hypothesis for future clinical trials. However, this study, being retrospective in nature, has several limitations. Smoking history was not collected for the vast majority of patients. Racial information was not available for 24% of patients. The information was obtained from a database that is not a research tool, that has the data entered by various clinical services, and that is not designed as a research tool to collect prospective data. The duration of therapy with TZD is not taken into the analysis because the study was not designed to analyze the association between the duration of exposure to TZD and the impact on the incidence of cancer. All patients who had a diagnosis of cancer after the date of exposure to TZD have been taken into account, irrespective of the fact that the duration of therapy with TZD might not be sufficient to have a meaningful impact on cancer development. This could have a negative impact on our study resulting from under-reporting of the impact of TZD on the risk of cancer development. It is possible that some patients treated with TZD might have developed cancer that was not diagnosed and entered into the database at the time of the study, which could lead to over-reporting of the impact of TZD on the risk of cancer development.

Nonetheless, we believe that this study has several strengths that tend to offset these limitations. All inclusion and exclusion criteria were implemented using computer programming statements

| Table 3. TZD Use and Cancer Risk Stratified by Race/Ethnicity in Men With Diabetes |
|-----------------------------------------|-----------------|-----------------|-----------------|
| Cancer Diagnosis                  | Unadjusted   | Covariate Adjusted* |
|-----------------------------------------|-----------------|-----------------|-----------------|
| Events | HR | P | 95% CI | Events | HR | P | 95% CI |
| White                                      | 50,937†       | 42,596†        |
| Colorectal                                  | 745 0.94 .62 0.74 to 1.20 | 659 0.98 .85 0.80 to 1.21 |
| Prostate                                    | 1,881 1.01 .90 0.87 to 1.18 | 1,659 1.15 .27 1.02 to 1.31 |
| Lung                                        | 934 0.72 .0068 0.57 to 0.91 | 774 0.74 .019 0.58 to 0.95 |
| African American                            | 11,664†       |
| Colorectal                                  | 211 0.75 .36 0.41 to 1.38 | 185 0.53 .27 0.31 to 0.93 |
| Prostate                                    | 718 0.99 .95 0.73 to 1.34 | 622 1.18 .16 0.94 to 1.50 |
| Lung                                        | 260 0.26 .0028 0.11 to 0.63 | 196 0.38 .034 0.15 to 0.93 |

NOTE. P values are not adjusted for multiple comparisons, so as not to inflate type II error.
Abbreviations: TZD, thiazolidinedione; HR, hazard ratio.
†Adjusted for age, body mass index, hemoglobin A1C, insulin, and other oral agents.
‡Patient denominators for the unadjusted analyses by race/ethnicity.
§Patient denominators for the covariate-adjusted analyses by race/ethnicity.
trials. This is a hypothesis-generating, rather than a hypothesis-when he did not use them. These features, we believe, are enough to subject before his first use of TZD would properly be associated with description. In this manner, a cancer that occurred in a TZD-using dependent covariates that, for each subject, changed status from drug exposures were modeled in the Cox regressions as time-

insulin often commenced well after his entry into the risk set, the Because a patient’s exposure to TDZ, other oral antidiabetics, and insulin often commenced well after his entry into the risk set, the drug exposures were modeled in the Cox regressions as time-
dependent covariates that, for each subject, changed status from “unexposed” to “exposed” on the date of the subject’s first prescription. In this manner, a cancer that occurred in a TZD-using subject before his first use of TZD would properly be associated with when he did not use them. These features, we believe, are enough to give our study credibility despite the limitations noted herein.

This is a single large database that can be a potential source to get preliminary data to support the conduct of further clinical trials. This is a hypothesis-generating, rather than a hypothesis-testing study. To better understand the role of TZD use on lung cancer development, two studies designs have the potential to provide useful information. One study could answer the question of protective effect of TZD on lung cancer would be a randomized study to look at the incidence of bronchial dysplasia in high-risk individuals (smokers). Another option is to study the effect of TZD in prevention of second cancers among patients with stage IB and IIA lung cancers postresection in a randomized, placebo-controlled study.

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Acknowledgment

We thank Melody Darbe and Sam Barnhart for data extraction from the VISN database.

In the References section, the citation for reference 3 was incorrect, and should have read: Michalik L, Desvergne B, Wahli W: Peroxisome-proliferator-activated receptors and cancers: Complex stories. Nat Rev Cancer 4:61-70, 2004


In the June 20, 2007, Supplement, the abstract by Galili et al entitled, “Prognostic value of low platelets in MDS patients with del(5q)” (J Clin Oncol 25, 2007 [abstr 7078]) contained an error in the spelling of A. Siddiki. It was originally published as A. Siddiqui and should have been A. Siddiki.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2007.15.0508


The Title should not have included the word “Cancer,” and should have read: “Clinical Benefit With Docetaxel Plus Fluorouracil and Cisplatin Compared With Cisplatin and Fluorouracil in a Phase III Trial of Advanced Gastric or Gastroesophageal Adenocarcinoma: The V-325 Study Group”

In Table 2, the last footnote was given as:
“§Defined as the first opioid intake for grade > 3 cancer pain or death if death was the reason for treatment discontinuation; percent of assessable patients with an event is shown in parenthesis.”

While it should have read:
“§Defined as the first opioid intake for grade > 3 cancer pain or death if death was the reason for treatment discontinuation.”

In the Author Contributions section, all authors should have been acknowledged for “Collection and assembly of data.”

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2007.15.0516