

Article

Association Between Thiazolidinediones and Solid Tumors in Patients with Diabetes: Evidence from the US Veteran Healthcare System

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Abstract

Introduction: Previous research has suggested thiazolidinediones (TZDs) may be associated with certain solid tumors. We examined incidence rates over time for patients with solid tumors who received TZD treatment for diabetes. **Methods:** We identified medication use and diagnosis codes that were aggregated to phecode disease classifications derived from the nationwide Veterans Administration Health Record System from 2000 to 2021. We identified 148,139 patients who had ≥ 2 diabetes diagnoses and had no previous cancer diagnosis. Among these, 8981 subjects had ≥ 4 years of TZD exposure. We then identified subjects with ≥ 2 diagnosis codes for solid tumors including bladder ($n = 3987$), breast ($n = 632$), colorectal ($n = 5139$), esophageal ($n = 482$), glioma ($n = 591$), lung ($n = 5142$), melanoma ($n = 1896$), pancreatic ($n = 726$), prostate ($n = 11,884$), renal ($n = 3145$), testicular ($n = 369$), and thyroid ($n = 513$). We used multivariable Cox proportional hazards regressions to measure associations between TZD use and cancer incidence. TZD use was modeled as a time-varying covariate from the first to last prescription of TZD medication, and analyses were adjusted for age at diabetes diagnosis, self-reported race, self-reported ethnicity, sex, body mass index, and cancer site-specific polygenic risk scores. **Results:** Long-term (≥ 4 years) exposure to TZDs was significantly associated with increased risk of developing prostate cancer ($HR = 1.24, p < 0.001$) and decreased risk of developing lung ($HR = 0.58, p < 0.001$), bladder ($HR = 0.51, p < 0.001$), and renal cancer ($HR = 0.75, p = 0.003$). **Conclusions:** Decreased risk of developing several solid tumors (lung, bladder, and renal) indicate that TZDs may be strong candidates for drug repurposing strategies to manage these types of cancer. These results warrant replication attempts in external datasets.

Keywords: drug repurposing; thiazolidinediones; pioglitazone; rosiglitazone; cancer; bladder cancer



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1. Introduction

Cancer remains a significant public health burden around the world [1]. In 2026, an estimated 2,114,850 new cases and 626,140 deaths are projected in the United States [2]. Cancer drug development is typically a long and expensive process, with in-depth and expensive preclinical research required before clinical trials can even begin. Drug repurposing is a promising strategy that may allow for a more efficient process of drug discovery. Drug repurposing explores new therapeutic applications for drugs that have already been approved by the Food & Drug Administration (FDA), thus decreasing the time and expense needed for drug development because certain aspects, such as safety assessment, have already been performed [3,4].

Cancer and diabetes share certain risk factors, such as age, obesity, activity level, and alcohol use [5], as well as certain biological pathways, such as the PI3K-AKT signaling pathway and the insulin/IGF axis [5–7]. Additionally, epidemiological studies have shown that individuals with diabetes are more likely to develop some forms of cancer [5,7,8]. These shared factors have caused researchers to explore diabetes medications as drug repurposing candidates for cancer therapy [8]. Thiazolidinediones (TZDs), particularly pioglitazone and rosiglitazone, have been studied extensively in relation to the incidence of solid tumors in many different potential cancer sites [9]. However, the results of these studies have been inconsistent, with some studies finding a decrease in the incidence of certain cancers in those using TZDs and some finding no association [10–30]. The most consistent result has been a moderate association between pioglitazone use and bladder cancer, resulting in an FDA warning against its use in those with active bladder cancer [31]. TZDs also contain a black-box warning for congestive heart failure because they may cause fluid retention which can exacerbate heart failure in susceptible patients [32]. The otherwise-inconsistent results in relation to cancer incidence likely result from a combination of factors, including heterogeneity in study design, differences among study populations, and various confounders that were insufficiently controlled for. Additionally, some studies assess TZDs as a drug class while others assess a particular TZD (e.g., pioglitazone or rosiglitazone).

These previous studies, though, were unable to adjust their analyses for the impact of genetic predisposition to cancer. In this study, we examine incidence over time of twelve types of cancer in patients who received TZD treatment for diabetes in a large, nationwide healthcare system. In addition to adjusting our analyses for standard variables (race, sex, etc.), we also adjust for the individual polygenic risk scores (PRSs) of each participant for each of the studied cancer types [33]. Cancer epidemiologic studies are essential to evidence-informed framework, as they identify risk factors and inform population-level prevention and management strategies needed to address the growing burden across resource setting [34]. To our knowledge, this is the first study to analyze risk of developing cancers in those receiving TZD treatment that accounts for the impact of an individual's genetic predisposition to cancer.

2. Materials and Methods

2.1. Data Source

We studied individuals who participated in the Million Veteran Program (MVP), a large genetic biorepository containing genetic data for ~650,000 Veterans [35]. All information regarding patient demographic and clinical characteristics, including age at diabetes diagnosis, sex, race, Hispanic ethnicity, body mass index, and medication use was collected from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW), which was accessed through the VA Informatics and Computing Infrastructure (VINCI). Electronic health records between 2000 and 2021 were included. PRSs were calculated from Release4 of MVP, in which missing variants are imputed using data from the Trans-Omics

for Precision Medicine (TopMed) [36,37]. When calculating PRS, each genetic variant has a beta value that identifies its association to a cancer of interest. For each patient those scores are aggregated to calculate the risk for the specific cancer. This study was approved by the VA Central Institutional Review Board and the Research and Development Committee at the Salt Lake City VA Healthcare System. MVP participants provided informed consent and Health Insurance Portability and Accountability Act authorization to analyze and link their EHR data with the results of genetic testing.

2.2. Study Population

We identified all Veterans with a diagnosis of type 2 diabetes (T2D) between 2000 and 2021. To ensure a true disease diagnosis, we required at least two diagnosis codes on different dates in the medical record for each disease category we analyzed. Among patients with T2D, we identified those with at least two diagnosis codes on distinct dates of the following solid tumors: bladder, breast, colorectal, endometrial, esophageal, glioma, lung, melanoma, oral, ovarian, pancreatic, prostate, renal, testicular, and thyroid. Both diabetes and cancer diagnoses were identified using diagnosis codes aggregated to phecode disease classifications [38] (Supplemental Table S1). We identified patients with exposure to TZDs (i.e., pioglitazone, rosiglitazone, or troglitazone [discontinued in 2000] [39]) by the presence of an OMOP concept identifier consistent with TZDs and a diabetes diagnosis prior to their first TZD prescription. Subjects with a diagnosis of both diabetes and a solid tumor at cancer sites are listed in Table 1.

Table 1. Demographic and clinical variables describing the analyzed cohort.

	Stratified by TZD Use		
	<4 Years	≥4 Years	<i>p</i>
Total participants	139,158	8981	--
TZD use ≥ 8years (%)	0 (0.0)	3322 (37.0)	<0.001
Age at diabetes (mean [SD])	58.95 (9.79)	56.62 (8.64)	<0.001
BMI (mean [SD]) (%)	32.58 (6.39)	33.56 (6.51)	<0.001
Male sex	131,986 (94.8)	8667 (96.5)	<0.001
Race			
Asian (%)	21 (0.0)	1 (0.0)	1
Black (%)	34,796 (25.0)	1810 (20.2)	<0.001
Native American (%)	954 (0.7)	42 (0.5)	0.017
Native Hawaiian/Pacific Islander (%)	234 (0.2)	23 (0.03)	0.07
White (%)	100,968 (72.6)	6956 (77.5)	<0.001
Other (%)	678 (0.5)	35 (0.4)	0.224
Unknown (%)	1507 (1.1)	114 (1.3)	0.111
Ethnicity			0.074
Hispanic (%)	1416 (1.0)	89 (1.0)	
Not Hispanic (%)	136,667 (98.2)	8803 (98.0)	
Unknown (%)	1075 (0.8)	89 (1.0)	
Cancer-specific PRS			
Bladder PRS (mean [SD])	0.58 (0.11)	0.59 (0.11)	0.02

Table 1. Cont.

Stratified by TZD Use			
	<4 Years	≥4 Years	<i>p</i>
Breast PRS (mean [SD])	0.40 (0.02)	0.40 (0.02)	0.243
Colorectal PRS (mean [SD])	0.51 (0.04)	0.51 (0.04)	0.107
Endometrial PRS (mean [SD])	0.40 (0.05)	0.40 (0.05)	0.158
Esophageal PRS (mean [SD])	0.55 (0.12)	0.55 (0.12)	0.89
Glioma PRS (mean [SD])	0.64 (0.10)	0.64 (0.10)	<0.001
Lung PRS (mean [SD])	0.42 (0.04)	0.42 (0.04)	0.002
Melanoma PRS (mean [SD])	0.36 (0.11)	0.37 (0.11)	<0.001
Oral PRS (mean [SD])	0.64 (0.14)	0.65 (0.14)	0.178
Ovarian PRS (mean [SD])	0.56 (0.08)	0.56 (0.09)	0.126
Pancreatic PRS (mean [SD])	0.58 (0.09)	0.57 (0.09)	<0.001
Prostate PRS (mean [SD])	0.52 (0.03)	0.52 (0.03)	0.868
Renal PRS (mean [SD])	0.48 (0.15)	0.47 (0.15)	0.002
Testicular PRS (mean [SD])	0.55 (0.08)	0.55 (0.08)	<0.001
Thyroid PRS (mean [SD])	0.62 (0.15)	0.62 (0.15)	0.688
Cancer diagnosis			
Bladder (%)	3670 (2.6)	317 (3.5)	<0.001
Breast (%)	589 (0.4)	43 (0.5)	0.485
Colorectal (%)	4772 (3.4)	367 (4.1)	0.001
Endometrial (%)	63 (0.0)	4 (0.0)	1
Esophageal (%)	461 (0.3)	21 (0.2)	0.14
Glioma (%)	555 (0.4)	36 (0.4)	1
Lung (%)	4785 (3.4)	357 (4.0)	0.008
Melanoma (%)	1702 (1.2)	194 (2.2)	<0.001
Oral (%)	25 (0.0)	1 (0.0)	0.95
Ovarian (%)	74 (0.1)	1 (0.0)	0.14
Pancreatic (%)	673 (0.5)	53 (0.6)	0.186
Prostate (%)	11,051 (7.9)	833 (9.3)	<0.001
Renal (%)	2906 (2.1)	239 (2.7)	<0.001
Testicular (%)	347 (0.2)	22 (0.2)	1
Thyroid (%)	473 (0.3)	40 (0.4)	0.12

2.3. Study Design and Endpoint

The primary endpoint of this retrospective cohort study was diagnosis of a solid tumor, defined as time from first diabetes diagnosis to first diagnosis of a particular solid tumor, censored at the date of last VA follow-up. Solid-tumor incidence was evaluated based on time exposed to TZDs (<4 years, ≥4 years).

2.4. Statistical Analysis

We compared distributions of baseline clinical and demographic information using *t*-tests for continuous variables and Chi-squared tests for categorical variables.

Multivariable Cox proportional hazards regressions for time-dependent covariates were used to measure the associations between TZD use and incidence of different cancers using hazard ratios (HRs). Cox proportional hazards analysis was conducted over a 17-year period. Cancer sites with <100 subjects were not analyzed due to lower statistical power. TZD use was modeled as a time-varying covariate from the beginning of TZD medication use. Patients were considered not on TZDs until their first administration of TZDs and then were considered in the TZD group for the rest of follow-up. Analyses were adjusted for age at diabetes, self-identified race, self-identified ethnicity, sex, body mass index at the time of diabetes diagnosis, and cancer site-specific polygenic risk scores. Cancer site-specific PRSs were computed from previously published beta estimates external to MVP [33].

Because 12 cancer sites were tested, a Bonferroni multiple-testing threshold of $p < 0.004$ ($p < 0.05/12$) was used to establish significance for TZD exposure influencing cancer outcomes.

3. Results

3.1. Subjects

We identified 148,139 patients with at least two T2D diagnoses occurring on different dates between 2000 and 2021, without a cancer diagnosis before their first diabetes diagnosis. Within the cohort, 4.4% ($n = 7486$) were female, and the cohort included 36,786 (24.8%) Black patients and 1505 (1.0%) patients of Hispanic or Latino ethnicity. The mean age at first diagnosis of diabetes in the cohort was 57.7 years (SD = 9.2 years).

From the study population, we identified 8981 subjects with exposure to TZDs for at least 4 years without a cancer diagnosis. Comparing patients with 4 years of TZD use to those with less than 4 years of TZD use, patients with 4 years of TZD use were on average younger (56.62 years vs. 58.95 years) at diabetes diagnosis and had higher BMI. There were fewer Black patients in the TZD category, and there were more women in the TZD category.

We identified participants with at least two diagnoses of the following solid tumors (with possible overlaps): bladder ($n = 3987$), breast ($n = 632$), colorectal ($n = 5139$), esophageal ($n = 482$), glioma ($n = 591$), lung ($n = 5142$), melanoma ($n = 1896$), pancreatic ($n = 726$), prostate ($n = 11,884$), renal ($n = 3145$), testicular ($n = 369$), and thyroid ($n = 513$) (Table 1). Because fewer than 100 participants had endometrial, oral, and ovarian cancers, these sites were not analyzed.

3.2. Cancer Site-Specific Cox Proportional Hazard Analysis

Among solid-tumor sites with at least 1000 subjects, we observed statistically significant decreased risk of developing bladder cancer (HR = 0.51, $p < 0.001$), lung cancer (HR = 0.58, $p < 0.001$), and renal cancer (HR = 0.75, $p = 0.003$) in those with ≥ 4 years of TZD exposure and a nominally significant decreased risk of developing for colorectal cancer among the same group (HR = 0.81, $p = 0.006$) (Table 2). Of note, among these cancer sites, we observed an increased risk of developing prostate cancer (HR = 1.24, $p < 0.001$) and melanoma (HR = 1.21, $p = 0.056$), although the latter was not statistically significant. Cumulative incidence plots for these cancer sites appear in Figure 1. Solid-tumor sites with <1000 subjects had notably lower statistical power and we did not observe statistically significant outcomes for these. However, we did observe a non-significant protective effect for esophageal cancer (HR = 0.58, $p = 0.048$), glioma (HR = 0.83, $p = 0.370$), pancreatic cancer (HR = 0.64, $p = 0.047$), testicular cancer (HR = 0.68, $p = 0.198$), and thyroid cancer (HR = 0.97, $p = 0.876$). Among these tumor sites, we observed non-significant increased risk of developing breast cancer (HR = 1.03, $p = 0.891$).

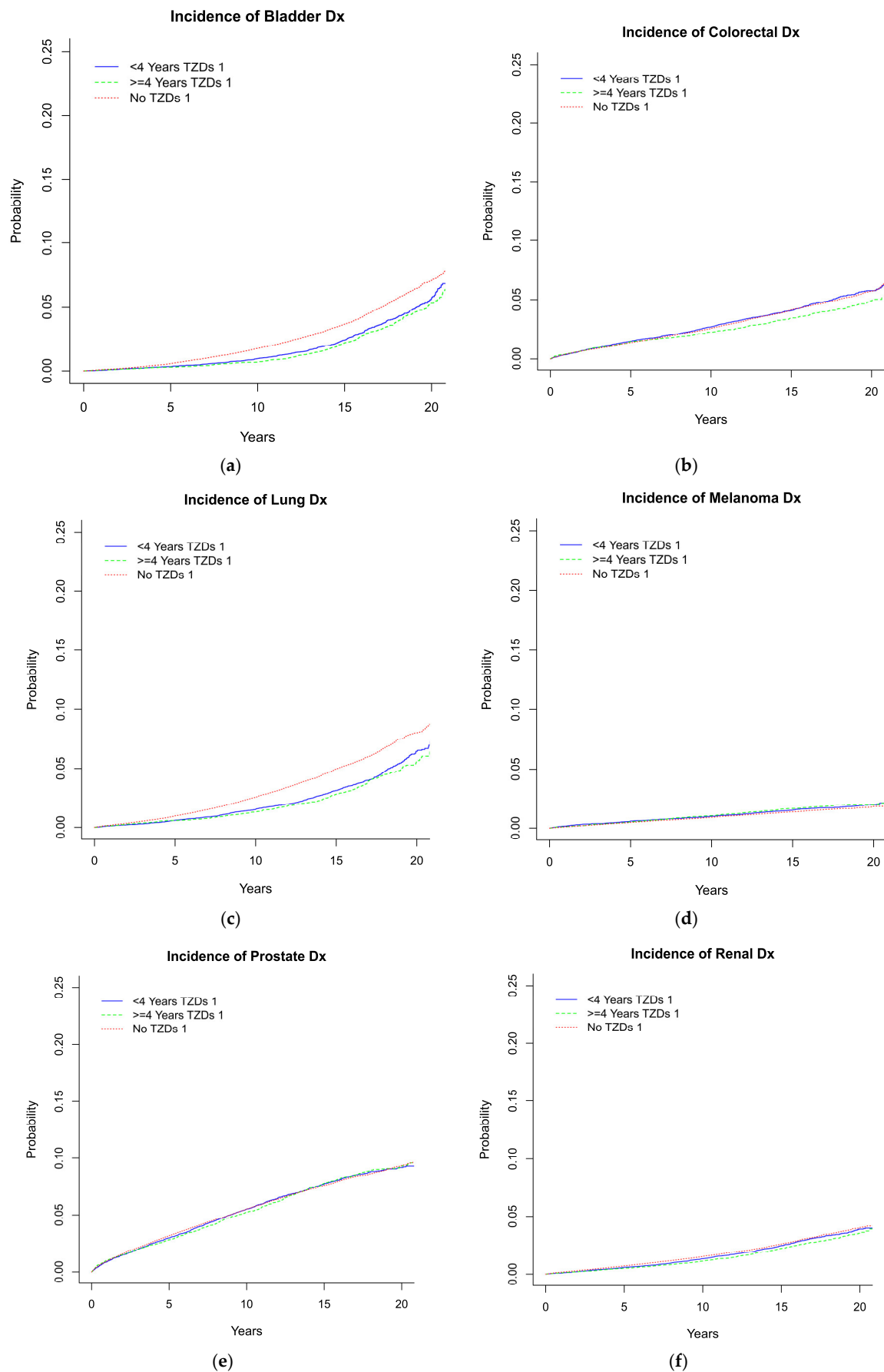


Figure 1. Cumulative incidence of solid tumors with $n > 1000$ subjects. (a) Bladder, (b) colorectal, (c) lung, (d) melanoma, (e) prostate, (f) renal.

Table 2. Time-dependent Cox models for cancer sites with ≥ 1000 subjects.

	Bladder			Colorectal			Lung		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age at diabetes	1.06	(1.06, 1.07)	<0.001	1.03	(1.02, 1.03)	<0.001	1.03	(1.03, 1.04)	<0.001
Ethnicity not Hispanic	1.00	(0.74, 1.35)	0.996	1.00	(0.75, 1.32)	0.977	1.03	(0.78, 1.35)	0.844
Ethnicity unknown	0.34	(0.18, 0.66)	0.001	0.99	(0.64, 1.52)	0.948	0.87	(0.56, 1.34)	0.522
BMI	1.01	(1.00, 1.01)	0.027	1.00	(0.99, 1.00)	0.611	0.97	(0.97, 0.97)	<0.001
Black race	0.62	(0.56, 0.69)	<0.001	1.17	(1.09, 1.25)	<0.001	0.92	(0.84, 0.99)	0.021
Sex	0.33	(0.24, 0.46)	<0.001	0.87	(0.74, 1.01)	0.075	0.89	(0.76, 1.05)	0.166
Site-specific PRS	1.21	(1.17, 1.25)	<0.001	1.18	(1.15, 1.22)	<0.001	1.14	(1.10, 1.17)	<0.001
TZD exposure	0.51	(0.41, 0.62)	<0.001	0.81	(0.70, 0.94)	0.006	0.58	(0.49, 0.69)	<0.001
	Melanoma			Prostate			Renal		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age at diabetes	1.03	(1.03, 1.04)	<0.001	1.05	(1.04, 1.05)	<0.001	1.03	(1.02, 1.03)	<0.001
Ethnicity not Hispanic	0.92	(0.59, 1.43)	0.708	1.08	(0.86, 1.35)	0.521	1.14	(0.78, 1.67)	0.487
Ethnicity unknown	0.99	(0.51, 1.90)	0.968	0.97	(0.68, 1.37)	0.846	0.96	(0.53, 1.73)	0.892
BMI	1.00	(0.99, 1.01)	0.575	0.99	(0.99, 1.00)	0.002	1.02	(1.02, 1.03)	<0.001
Black race	0.14	(0.11, 0.19)	<0.001	2.51	(2.40, 2.63)	<0.001	1.07	(0.98, 1.17)	0.135
Sex	0.73	(0.54, 0.99)	0.046	0.00	(0.00, 0.02)	<0.001	0.51	(0.40, 0.66)	<0.001
Site-specific PRS	1.36	(1.30, 1.43)	<0.001	1.37	(1.34, 1.40)	<0.001	1.06	(1.02, 1.10)	0.002
TZD exposure	1.21	(0.99, 1.48)	0.056	1.24	(1.12, 1.36)	<0.001	0.75	(0.62, 0.91)	0.003

4. Discussion

We performed time-to-event survival analysis for TZD exposure and incidence of solid tumors among subjects with T2D and TZD exposure. Within the MVP dataset, TZD exposure was significantly protective for several cancers (bladder, lung, renal, and colorectal [nominally significant]) and significantly contributed to risk for two others (prostate and melanoma [nominally significant]). Our analysis used VA subjects who had genomic data available, allowing us to include a PRS score for each subject for each cancer site in our survival models, a strategy that did reduce overall sample sizes for each tumor site, but likely also added precision to the survival models.

The results of the current study clearly suggest that cancers at different tissue sites do not uniformly respond to TZD exposure, which is unsurprising in the context of previous research. The cancer site with the lowest risk estimate in this dataset was bladder cancer (HR = 0.51, 95% CI: 0.41, 0.62). This result contradicts previous studies where several meta-analyses involving sample sizes sometimes exceeding 200K subjects have yielded increased risk estimates for bladder cancer with TZD exposure [12,13,21,40] with ORs ranging from 1.20 to 1.66. In fact, as noted earlier and reported by Hampp et al., discrepant findings among studies of TZDs and bladder cancer led the FDA to issue a warning against the use of pioglitazone in patients with active bladder cancer [31]. The result from the MVP dataset is a clear outlier for this cancer site, though it is unclear how differences between these studies or populations might contribute to this discrepancy. Certain methodological limitations might contribute to this unexpected result. For instance, this analysis does not examine different TZDs separately and the cancer risk may be different for pioglitazone and rosiglitazone. As stated earlier, meta-analyses have found an increased incidence of

bladder cancer in patients exposed to pioglitazone, but the results of studies examining the association between rosiglitazone and bladder cancer have been more mixed [41,42]. Another possibility is that due to the documented safety concerns physicians may have been less likely to prescribe pioglitazone to individuals at higher risk for bladder cancer. Our analysis did not adjust for smoking status, which is a major risk factor for bladder cancer [43]. Additionally, the Veteran population is primarily older and male, two other major risk factors for bladder cancer, which may have influenced prescribing patterns [44].

TZD use was also associated with a lower risk of lung cancer (HR = 0.58, 95% CI: 0.49, 0.69) and renal cancer (HR = 0.75, 95% CI: 0.62, 0.91). Previous research in individuals with TZD exposure includes several studies reporting lower risk for lung cancer (with HRs from 0.34 to 0.67) [11,22,27], a meta-analysis reporting overall reduced risk (pooled RR = 0.91) [16], and no studies reporting higher risk. Previous research for renal cancer includes two cohort studies, both reporting reduced risk of renal cancer (HRs from 0.29 to 0.70) [18,22]. We also observed a nominally significant protective effect for colorectal cancer (HR = 0.81, 95% CI: 0.70, 0.94). Previous reports of this cancer site include two meta-analyses (RRs from 0.93 to 0.91) and two cohort studies by Chang et al. and Lin et al. (OR = 0.86 and HR = 0.31, respectively), all showing protective effects [13,14,22,24].

In this dataset, TZD exposure was associated with an increased risk for prostate cancer (HR = 1.24, 95% CI: 1.12, 1.36). Previous studies of the association between TZD exposure and prostate cancer give conflicting results: two meta-analyses report a protective effect (ORs from 0.55 to 0.88) [10,45], one cohort study also reports a protective effect (HR = 0.12) [22], and another cohort study reports a risk effect (HR = 1.13) [17]. TZD exposure had a nominally significant association with increased risk for melanoma (HR = 1.21, 95% CI: 0.99, 1.48). Previous studies reporting the effect of TZD exposure on melanoma include two cohort studies by Ferrara et al. and Oliveria et al. that report conflicting effects (HR = 1.3 and RR = 0.67, respectively) [18,29].

Strengths and Limitations

A major strength of the present study is the access to the VHA longitudinal health record data that supplies a consistent medical record across the entire analyzed cohort, allowing us to analyze a homogeneously curated set of data. Furthermore, unlike other studies, we have included participants' cancer genetic risk with the inclusion of cancer site-specific PRSs as covariates in the time-to-event survival analyses. We were thus able to account for individual subjects' cancer predisposition for that cancer site [33], which in turn removed noise from the model. However, there are also some limitations. Some Veterans may have increased cancer risk due to military exposure such as to Agent Orange or other combat-related exposure. We did not include metformin in this analysis, though most Veterans in the VA national population who are prescribed TZDs have had previous exposure to metformin. Currently, military exposure data in the VHA is self-report and determination of exposures increase service-connection coverage so there are incentives to self-report exposures. Therefore, military exposures were not included in the analysis. VHA is currently working to obtain reliable unbiased sources of deployment-related military exposures from the Department of War. The absence of key socioeconomic variables—such as education and income may limit our ability to account for social determinants that influence cancer incidence. Higher total pack years also significantly increase the risk of several cancers, including bladder, kidney, lung, and prostate cancer. However, smoking status within VA data is self-reported as current, former, and never; because of the lack of precision within this data, smoking status was not included in the analysis. Among MVP participants, 75% report a current or former smoking status. Furthermore, other

medications may mediate cancer risk. Due to limitations in access to data, this analysis was limited to TZD.

5. Conclusions

A practical implication of the overall findings is that drug repurposing, as a general strategy, can be a cost-effective way to gain knowledge about the safety and economic utility of drugs with a high degree of prior clinical use [3,4]. The findings of the current study argue that for some cancer sites treatment with TZDs should be considered and future direct studies on their efficacy are warranted [8]. With the notable exception of bladder cancer, our findings largely align with previous research, though not for some cancers. These findings from the analysis of the VA clinical and genomic data comprise another data point supporting a role for TZDs in cancer treatment.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/diabetology7070127/s1>, Table S1: Number of subjects identified and pcode/medication codes for categories analyzed.

Author Contributions: C.C.T. participated in methodology, formal analysis, investigation, data curation, writing—original draft, and writing—review and editing. T.J.N. participated in methodology, visualization, formal analysis, investigation, writing—original draft, and writing—review and editing. K.M.P. participated in writing—original draft, and writing—review and editing. F.Y.A. participated in writing—original draft, and writing—review and editing. M.G. participated in writing—review and editing. A.D.S. participated in writing—review and editing. K.G.B. participated in writing—review and editing. H.J.F. participated in writing—review and editing. R.L.H. participated in writing—review and editing, supervision, project administration, and funding acquisition. J.A.L. participated in conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, supervision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the VA Central Institutional Review Board (protocol code 1613697-1, date of approval 3 May 2019) and the Research and Development Committee at the Salt Lake City VA Healthcare System (date of approval 1 January 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Patient-level data are accessible to all VA researchers with appropriate IRB approvals.

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