Thiazolidinedione use and cancer incidence in type 2 diabetes: A systematic review and meta-analysis

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Abstract

Aims. — Evidence suggests thiazolidinediones (TZDs) may modify the relationship between type 2 diabetes and cancer incidence. We aimed to summarize data from randomized controlled trials (RCTs) and observational studies to examine risk of overall and site-specific cancers with TZD use in individuals with type 2 diabetes.

Methods. — We searched 12 key biomedical databases and seven grey literature sources up to June 2011, without language restrictions. We performed separate meta-analyses according to cancer site and study design, comparing ever-use to never-use of TZDs, and pioglitazone alone.

Results. — The search yielded 1338 unique citations; we included four RCT, seven cohort and nine nested case-control studies, contributing data from 2.5 million people. Estimates from observational studies suggested any TZD use was associated with a decreased risk of colorectal (pooled RR: 0.93, 95%CI 0.87–1.00, P = 0.04, I² = 30%), lung (pooled RR: 0.91, 95%CI 0.84–0.98, P = 0.02, heterogeneity (I²) = 35%) and breast (pooled RR: 0.89, 95%CI 0.81–0.98, P = 0.02, I² = 44%) cancer. Risk of overall cancer with TZD use was not significantly modified in RCTs (pooled RR: 0.92, 95%CI 0.79–1.07, P = 0.26, I² = 0%) or observational studies (pooled OR: 0.95, 95%CI 0.78–1.16, P = 0.63, I² = 70%). Pioglitazone use was, however, associated with a decreased risk of overall cancer (colorectal, lung, breast, prostate and renal sub-sites combined) in observational studies (pooled OR: 0.95, 95%CI 0.91–0.99, P = 0.009, I² = 0%).

Conclusions. — Our findings suggest that use of TZDs is associated with a modest but significantly decreased risk of lung, colorectal and breast cancers. Results were limited by the paucity of studies designed to answer our research question. Further evaluation of TZD use, cancer risk factors and potential confounders is required.

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Keywords: Type 2 diabetes; Cancer; Thiazolidinediones; Pioglitazone; Rosiglitazone; Review; Meta-analysis; Pharmacoepidemiology

Résumé


Contexte. — Certaines données suggèrent que les thiazolidinediones (TZDs) pourraient modifier les relations diabète type 2 (DT2) et cancer. Nous avons passé en revue les résultats provenant des essais contrôlés randomisés (ECR) et des études observationnelles afin d’examiner l’association éventuelle entre le risque de cancer, global et par site spéciﬁque, avec l’utilisation des TZDs chez les patients atteints de DT2.

Méthodes. — La recherche bibliographique a été fondée sur 12 bases de données biomédicales et sept sources de littérature grise jusqu’à juin 2011, sans restriction de langue. Les méta-analyses ont été réalisées par site de cancer et par type d’étude, en fonction ou non de la prise de TZDs.

Résultats. — La recherche bibliographique a donné 1338 citations uniques ; nous avons inclus quatre ECR, sept études de cohorte et neuf études cas-témoins, soit les données de 2,5 millions de patients. Les estimations provenant d’études observationnelles suggèrent que la prise de TZDs est associée à une diminution du risque de cancer colorectal (RR combiné : 0,93, IC à 95 % 0,87–1,00, P = 0,04, I² = 30 %), de cancer du poumon (RR combiné : 0,91, IC 95 % 0,84–0,98, P = 0,02, hétérogénéité (I²) = 35 %) et de cancer du sein (RR combiné : 0,89, IC 95 % 0,81–0,98, P = 0,02, I² = 44 %). Il n’y avait pas de modification significative du risque total de cancer global par la prise de TZDs en ECR (RR combiné : 0,92, IC 95 % 0,79–1,07, P = 0,26, I² = 0 %) ou en études d’observation (OR combiné : 0,95, IC 95 % 0,78–1,16, P = 0,63, I² = 70 %). La prise de pioglitazone était cependant associée à une réduction du risque global de cancer (dont cancer colorectal, du poumon, du sein, de la prostate, et du rein combiné) dans les études observationnelles (RR combiné : 0,95, IC 95 % 0,91–0,99, P = 0,009, I² = 0 %).

Abbreviations: RCT, Randomized Control Trial; TZD, thiazolidinedione.
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Conclusions. — Nos résultats suggèrent que la prise des TZD est associée à une diminution modeste mais significative du risque de cancers pulmonaire, colorectal et mammaire. Ces résultats sont limités par la rareté des études qui visent à répondre à la question posée dans cette étude. Il est nécessaire d’évaluer de manière plus poussée, les effets de la prise des TZDs, les facteurs de risque de cancer et les facteurs de confusion potentiels.

Mots clés : Diabète de type 2 ; Cancer ; Thiazolidinediones ; Pioglitazone ; Rosiglitazone ; Revue générale ; Méta-analyse ; Pharmaco-épidémiologie

1. Introduction

Epidemiologic evidence indicates that individuals with diabetes are at an increased risk of developing and dying from various types of cancer [1,2]. Hyperinsulinaemia is a leading hypothesis underlying the association between type 2 diabetes and cancer, whereby elevated insulin levels in type 2 diabetes stimulate insulin receptors on cancer cells, promoting cell division and growth [3–5]. Various glucose-lowering agents (i.e., metformin, sulfonylureas and exogenous insulin) are thought to further modify this association with cancer [4].

Over the past decade, thiazolidinediones (TZDs; namely pioglitazone and rosiglitazone) have been added as a third line glycaemic control option for type 2 diabetes [6]. TZDs exert their glucose-lowering effects by binding to peroxisome proliferator activated receptor-gamma (PPARγ), which increases glucose uptake [7]. Although the mechanisms are not fully understood, PPARγ can activate potent tumor suppression pathways such as LKB-1 and mTOR; as well, TZDs have been noted to have PPARγ-independent anti-cancer effects [8–11]. Cellular experiments and animal studies have shown promise for TZDs in preventing or reducing various cancers [8], and clinical trials are now testing TZDs as a possible therapy for lung, breast and other cancers [12–14].

Recent international attention surrounding pioglitazone use and bladder cancer prompted us to compile a systematic review and meta-analysis on TZD use and bladder cancer in individuals with type 2 diabetes [15]. In this previous review, we observed an increased risk of bladder cancer associated with TZD use (pooled RR: 1.15, 95%CI 1.04–1.26), which in subgroup analyses was significantly associated with pioglitazone use, but not rosiglitazone use, suggesting that TZD analogues may differ in their association with any given cancer [15].

Aside from the recent focus on bladder cancer, a number of studies report on TZD use and other cancers in people with type 2 diabetes [16–19]. Therefore, our objective was to systematically gather, summarize and appraise evidence from randomized controlled trials (RCTs), cohort and case-control studies to explore the effects of TZDs on the risk of overall and site-specific cancers in people with type 2 diabetes. We hypothesized TZD use was associated with a decreased risk of overall and site-specific cancer incidence in individuals with type 2 diabetes.

2. Methods

2.1. Search strategy and selection criteria

The protocol for this study was developed a priori and is available from authors upon request. We conducted a comprehensive search of the following key electronic biomedical databases from inception through June 2011: Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Conference Proceedings Citation Index – Science, Cochrane Library, Pubmed (cancer subset, limited to adults), Toxnet and Scopus. We did not apply any study design filters or language restrictions to our search. The search strategy was created with the assistance of a librarian experienced in systematic reviews and a sample search is provided in Appendix A.

We also searched the following seven sources of grey literature: conference proceedings from five international conferences of major diabetes and diabetes-related organizations from 2008 onward (International Society of Pharmacoepidemiology, American Diabetes Association, Canadian Diabetes Association, European Association for the Study of Diabetes and Canadian Association of Population Therapeutics); Google Scholar; clinical trials registries (clinicaltrials.gov and International Clinical Trials Registry Platform [ICTRP]); databases of international drug safety surveillance agencies (Food and Drug Administration [FDA], Health Canada, and European Medicines Agency [EMA]); hand searching from reference lists of relevant studies; consultation with experts in the field; and contacting authors of studies for additional unpublished information.

Primary outcomes for this study were overall and site-specific cancer incidence. When calculating overall cancer incidence for TZD use, we included studies reporting any and all cancer types; however we excluded bladder cancer as a site-specific outcome, as we previously summarized this evidence [15]. A checklist developed a priori was used to assess whether studies met our inclusion criteria for population (individuals with type 2 diabetes), exposure (ever-use of any TZD therapy), comparison group (never-use of any TZD therapy), and outcome (any report on our primary outcomes as listed above, even if it was not a primary or secondary outcome of the included study) and study design (RCTs, cohort and case-control studies).

2.2. Data collection

Two trained and independent reviewers (INC and SLB) conducted study selection, data abstraction, and risk of bias assessment. All discrepancies between reviewers were resolved through discussion and consensus and by a third reviewer (JAJ) if consensus was not reached. Risk of bias was evaluated as low, unclear or high using the Cochrane Risk of
Bias Tool for RCTs [20]. Cohort and case-control studies were assessed using a modified version of the Newcastle-Ottawa Scale that accorded a maximum of eight points to each study, with five or less points indicating high risk of bias [21].

2.3. Synthesis of data

We tabulated pertinent descriptive data from included studies, stratified by study design. In our primary analysis we examined the risk of overall or site-specific cancer incidence with any TZD exposure (± other therapies). If studies reported more than one estimate for a given outcome, we used the estimate adjusted for the most potential confounders. Where more than one exposure subgroup was reported (i.e., rosiglitazone and pioglitazone use separately), we abstracted both estimates and included them in our meta-analysis without adjustment for multiple comparisons. Our systematic review included both RCTs, cohort and case-control studies, to provide as broad an evidence base as possible [22–25]. We nonetheless performed separate meta-analyses for RCTs and observational studies, to allow for comparison of the estimates from different study designs. For observational studies, we combined cohort studies and nested case-control studies (only), to focus on those studies with prospectively collected exposure information.

We used inverse variance calculations (for observational studies) and unadjusted risk ratios using Mantel-Haenszel calculations (for RCTs), to estimate pooled risk ratios within our two study design categories. Under the rare disease assumption, which applies to incident cancer, we used the odds ratios reported in nested case-control studies to approximate the risk ratio. For RCTs and observational studies reporting only raw numbers [26,27], we calculated risk ratios or odds ratios [28]. For study arms with zero events, a value of 0.5 was imputed to avoid computing errors. Given the variation in underlying study populations, adjusted risk estimates were pooled in a random effects model and were analyzed in RevMan version 5.1 (Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark).

As criteria for meta-analyzing data, we considered a minimum of three studies, and a maximum heterogeneity of $I^2 \leq 75\%$, from studies of the same design (i.e., RCT or observational), reporting the same site-specific cancer incidence. Heterogeneity was assessed as low ($\leq 25\%$), moderate ($>25–50\%$), and high ($>50–75\%$); we explored possible sources of heterogeneity for $I^2 > 25\%$. Due to a limited number of reports in each meta-analytic category, we were unable to assess publication bias for site-specific cancers [29]. We did, however, construct a funnel plot by study design for all cancer outcomes reported (Appendix B).

In post hoc exploratory analyses, we examined the association between ever-use of pioglitazone and site-specific cancer incidence (with the exception of bladder cancer, which has been published elsewhere) [15]. For this analysis we maintained the study design and site-specific cancer groupings, but permitted meta-analysis of two or more studies.

3. Results

3.1. Study selection

Our search of 12 biomedical databases and seven sources of grey literature returned 1338 results, once duplicates were removed. After screening all titles and abstracts for possibility of meeting the inclusion criteria, 49 studies were considered for further evaluation. Studies were subsequently excluded for the following reasons: no report of cancer incidence ($n = 18$); duplicate reports of the same study ($n = 5$); no thiazolidinedione (TZD) exposure reported for type 2 diabetes (T2DM) patients ($n = 2$); no relevant comparison group ($n = 2$); and ineligible study design ($n = 2$) (Fig. 1).

3.2. Study characteristics

Sixteen full text publications and four unpublished studies were included in our review, comprising four RCTs, seven cohort studies, and nine case-control studies (Table 1) and (Table S1; see supplementary material associated with this article online) [16–19,26,27,30–43]. One study was published in French [34]. One publication [44] reported previously unpublished cancer outcomes from two randomized control trials (RCTs) that were included in this review (ADOPT [31] and RECORD [32]). We constructed a funnel plot of any/all cancer outcomes by study design (Appendix B). One cohort study reporting overall cancer in rosiglitazone ever vs. never exposure [27] and one case-control study reporting liver cancer in TZD ever vs. never exposure [40], fell outside the 95% confidence interval range. The plot showed no other signs of outliers.

One unpublished RCT [33] was assessed to be at a high risk of bias due to potential for bias introduced in the methods. Two RCTs [31,32] were at a high risk of bias due to important differential losses to follow-up (Table 1). We could not estimate the impact of differential losses on cancer incidence in these trials, however we assessed the impact of adding a “would-be” case to either the TZD or non-TZD groups to explore the robustness of the estimates. This test of robustness revealed estimates from RCTs to be unstable. For example, the maximum change in the calculated risk ratio was for pancreatic cancer in the ADOPT trial [31], which dropped from 21.86 (95%CI 1.21–395.13) to 9.94 (95%CI 1.16–85.02) when adding one case to the control group and increased to 25.84 (95%CI 1.46–458.36) when the case was instead added to the exposed group. In the RECORD trial [32], the maximum change was for leukemia, where adding one case to the TZD group increased the risk estimate from 4.01 (95%CI 0.45–35.87) to 5.02 (95%CI 0.59–42.90). Three estimates (for gastrointestinal, hematological and renal cancers in the ADOPT trial) reversed their direction of association if one case was added to either the exposed or the control group.

3.3. Systematic review of cancer incidence

3.3.1. Randomized trials

Four RCTs reported incident cancer, comprising 14,422 participants with type 2 diabetes and 691 incident cancers
Table 1
Summary of study characteristics included in review (abridged).

<table>
<thead>
<tr>
<th>Source (Country)</th>
<th>Study period</th>
<th>Mean F/U (ys)</th>
<th>Study sample size</th>
<th>Risk of bias</th>
<th>Exposure vs. comparison</th>
<th>Incident cancer sites reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized control trials</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dormandy 2005 (PROactive Study, Multi-Centre) [30]</td>
<td>2001–2004</td>
<td>2.9</td>
<td>5238</td>
<td>Unclear</td>
<td>PIO vs. no TZD use</td>
<td>Overall, breast, colorectal, gastric, haematological, lung, ovarian/uterine, pancreatic, prostate, renal, skin</td>
</tr>
<tr>
<td>Kahn 2006 (ADOPT, Multi-Centre) [31]</td>
<td>2000–2006</td>
<td>3.4</td>
<td>4351</td>
<td>High</td>
<td>ROSI® vs. (Met® or Glib®)</td>
<td>Overall, breast, colorectal, endocrine, gastric, haematological, intestinal, liver (hepato-biliary), lung, melanoma, nasal/faryngeal, nervous system, non-melanoma skin, oral/esophageal, ovarian, pancreatic, prostate, renal, sarcoma, testicular, uterine/cervical</td>
</tr>
<tr>
<td>Home 2009 (RECORD, Multi-Centre) [32]</td>
<td>2001–2008</td>
<td>5.5</td>
<td>4447</td>
<td>High</td>
<td>ROSI plus (SU or Met) vs. No TZD (SU + Met)</td>
<td>Overall, breast, endometrial, gastric, gastrointestational, genitourinary, haematological, head and neck, leukemia, liver (liver/gall bladder/biliary), lung, lymphoma, melanoma, neurological, non-melanoma skin, ovarian, pancreatic, prostate, renal, uterine</td>
</tr>
<tr>
<td>Sanofi-Aventis 2009 (Multi-centre, USA)</td>
<td>2006–2008</td>
<td>n/a</td>
<td>386</td>
<td>High</td>
<td>TZD plus Ins and (SU or Met) vs. Ins + Met + SU</td>
<td>Breast, prostate</td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNAMTS 2011 (national health insurance, France) [34]</td>
<td>2006–2009</td>
<td>2.4 (exposed grp)</td>
<td>1,491,060</td>
<td>7</td>
<td>PIO vs. no PIO or ROSI vs. No ROSI</td>
<td>Breast, colorectal, ear/mouth/nose/throat, lung, kidney</td>
</tr>
<tr>
<td>Ferrara 2011 (Kaiser Permanente, Northern California, USA) [16]</td>
<td>1997–2005</td>
<td>3.6</td>
<td>252,467</td>
<td>6</td>
<td>PIO vs. no PIO or non-PIO TZD vs No non-PIO TZD</td>
<td>Breast, colon, endometrial, lung, melanoma, non-hodgkin, lymphoma, pancreatic, prostate, rectal, renal</td>
</tr>
<tr>
<td>Govindarajan 2007 (Veterans Affairs VISN-16, USA) [17]</td>
<td>1997–2003</td>
<td>n/r</td>
<td>87,678</td>
<td>7</td>
<td>TZD vs. No TZD</td>
<td>Colorectal, lung, prostate</td>
</tr>
<tr>
<td>Oliveria 2008 (Source not reported, USA) [35]</td>
<td>2000–2004</td>
<td>3.9</td>
<td>191,223</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Colorectal, liver, pancreatic</td>
</tr>
<tr>
<td>Tseng 2011 (National Health Insurance, Taiwan) [36]</td>
<td>2003–2005</td>
<td>n/r</td>
<td>204,741</td>
<td>6</td>
<td>PIO vs. no PIO or ROSI vs. No ROSI</td>
<td>Prostate</td>
</tr>
<tr>
<td>Yang 2010 (Diabetes Registry, Hong Kong) [27]</td>
<td>1996–2005</td>
<td>4.82</td>
<td>6103</td>
<td>7</td>
<td>PIO vs. no PIO or ROSI vs. No ROSI</td>
<td>Overall</td>
</tr>
<tr>
<td>Zhang 2009 (GPRD, UK) [37]</td>
<td>1987–2008</td>
<td>7.8</td>
<td>63,826</td>
<td>6</td>
<td>PIO vs. no PIO or ROSI vs. No ROSI</td>
<td>Overall</td>
</tr>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bodmer 2010 (GPRD, UK) [38]</td>
<td>1994–2005</td>
<td>n/r</td>
<td>1458</td>
<td>7</td>
<td>TZD vs. No TZD</td>
<td>Breast</td>
</tr>
<tr>
<td>El-Serag 2009 (Veterans Affairs, USA) [39]</td>
<td>2000–2002</td>
<td>n/a</td>
<td>6515</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Liver cancer (hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Hassan 2010 (MDACC Texas, USA) [40]</td>
<td>2000–2008</td>
<td>n/a</td>
<td>1524</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Liver cancer (hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Koro 2007 (Integrated Health Information Services, USA) [18]</td>
<td>1997–2004</td>
<td>1.8</td>
<td>126,971</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Breast, colon, prostate</td>
</tr>
<tr>
<td>Lewis 2008 (Kaiser Permanente, Northern California, USA) [19]</td>
<td>1994–2005</td>
<td>n/r</td>
<td>14,086</td>
<td>7</td>
<td>TZD vs. No TZD</td>
<td>Colon</td>
</tr>
<tr>
<td>Li 2009 (MDACC Texas, USA) [41]</td>
<td>2004–2008</td>
<td>n/a</td>
<td>1,836</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>Mannucci 2010 (Diabetes Clinic, University of Florence, Italy) [26]</td>
<td>1998–2008</td>
<td>2.3</td>
<td>482</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Overall</td>
</tr>
<tr>
<td>Wright 2009 (King County Washington, USA) [43]</td>
<td>2002–2005</td>
<td>n/a</td>
<td>1943</td>
<td>6</td>
<td>TZD vs. No TZD</td>
<td>Prostate</td>
</tr>
</tbody>
</table>

F/U: Follow-Up (in years); PIO: pioglitazone; ROSI: rosiglitazone; TZD: thiazolidinedione (any); MET: metformin; SU: sulfonylurea; INS: insulin; GLIB: glibenclamide.

Additional information (risk estimates, adjustment, etc.) available in online appendix.

* 12-week trial with 10% loss to follow-up.
* Unpublished work.
* Drug monotherapy.
* Nested case-control study design.
The incidence rate for overall cancer was 11.3 per 1000 person-years in the TZD arms of studies and 11.6 per 1000 person-years in the non-TZD arms of the trials.

3.3.2. Observational studies

Seven cohort and nine case-control studies reported incident cancers among 2,232,290 and 321,073 individuals, respectively (Table S1; see supplementary material associated with this article online). There was insufficient information in the reports to tabulate the total number of cancers or calculate an overall cancer incidence rate.

3.4. Meta-analysis of risk of thiazolidinediones use and overall and site-specific cancers

Meta-analysis was possible using all four RCTs and 12 of the 13 eligible observational (cohort and nested case-control) studies, reporting incident cancers of the following sites: overall, breast, colon/rectum, gastric/intestine, hematologic, kidney, lung, pancreas and prostate (Figs. 2 and 3) (Table S2; see supplementary material associated with this article online).

One eligible observational study [39] reported a cancer site where we had less than three reports and we therefore did not include it in a meta-analysis. We did not include non-nested case-control studies in the meta-analysis.

3.4.1. Overall cancer incidence

Six studies reported eight estimates of overall cancer incidence; we observed no difference in the overall cancer risk with TZD use in three RCTs [30–32] (pooled RR: 0.92, 95% confidence interval (CI) 0.79–1.07, \( P = 0.26, n = 3 \), heterogeneity \( (I^2) = 0\% \)) and observational studies [26,27,37] (pooled RR: 0.95, 95%CI 0.78–1.16, \( P = 0.63, n = 5, I^2 = 70\% \)) (Fig. 2) and (Fig. S1; see supplementary material associated with this article online).

The higher heterogeneity among observational studies may be due to differences in weighting and adjusted covariates. One of the pooled studies [37] accounted for 95.5% of the weighting and only this study reported an adjusted risk estimate. The remaining estimates were not adjusted. Removing this disproportionately weighted study [37] reduced the risk estimate to 0.19 (95%CI 0.08–0.49) and heterogeneity to 0%. Alternatively, heterogeneity in the estimate from observational studies may be due to the study by Yang et al. (2010) study [27], which differs from the other studies in terms of the population, and suffers from immortal time bias [45]. Removing this study reduced heterogeneity to 1%, although the pooled estimate remained non-significant (pooled RR: 1.04, 95%CI 0.98–1.10).
3.4.2. Site-specific cancer incidence

We meta-analyzed reports of the following site-specific incident cancers: colorectal, lung, breast, prostate, pancreas, renal, gastrointestinal, skin (melanoma and non-melanoma), and hematological (Fig. 2). TZD use was significantly associated with a decreased risk of colorectal cancer (six observational studies [16–19,34,35] reporting ten estimates, pooled RR: 0.93, 95%CI 0.87–1.00, \( P = 0.04, I^2 = 30\% \)). The risk of lung cancer was decreased with TZD use among observational studies (three studies [16,17,34] reporting five estimates, pooled RR: 0.91, 95%CI 0.84–0.98, \( P = 0.02, I^2 = 35\% \)), but was not associated with TZD use among RCTs (pooled RR, 1.14, 95%CI 0.70–1.88, \( P = 0.68, I^2 = 0\% \)). Risk of breast cancer was reduced in RCTs, although the wide confidence intervals crossed 1.0 (pooled RR, 0.68, 95%CI 0.37–1.24, \( P = 0.21, n = 4, I^2 = 11\% \)), but was significantly decreased in observational studies (four studies [16,18,34,38] reporting six estimates, pooled RR: 0.89, 95%CI 0.81–0.98, \( P = 0.02, I^2 = 44\% \)).

Heterogeneity in observational studies reporting lung cancer may be due to differences in population demographics. One study [17] was conducted using a database comprised of 99% males; eliminating this study reduced heterogeneity.
to 0% (pooled RR: 0.93, 95% CI 0.88–0.98, n = 4, P = 0.009). Heterogeneity among observational studies reporting colorectal cancer may be due to differences between the cohort and nested case-control study designs; removing nested case-control study estimates [18,19] reduced heterogeneity to 18% (pooled RR: 0.94, 95% CI 0.88–1.00, n = 8, P = 0.04). Further variation may be due to disproportionate weighting, adjustment for potential confounders (i.e., use of other glucose-lowering agents, socioeconomic status and clinical variables [such as BMI and A1c]) and differences in risk of bias. Exploring these possible sources of heterogeneity did not reduce $I^2$, and in the case of the latter, heterogeneity increased to 54% when excluding studies with risk of bias lower than seven [16,18,35]. Heterogeneity in the pooled observational estimate for breast cancer remained high when we excluded studies based on study design (i.e. nested case-control or cohort studies), adjustment for clinical variables (e.g., A1c and smoking status) and risk of bias score; excluding the study with the highest weighting [34] reduced heterogeneity to 8% (pooled RR: 0.96, 95% CI 0.82–1.11, n = 4, P = 0.56), and excluding studies conducted outside of America [34,38] reduced heterogeneity to 0% (pooled RR: 0.93, 95% CI 0.80–1.08, n = 3, $P = 0.34$).

TZD use was not associated with risk of prostate cancer in RCTs (pooled RR: 0.99, 95% CI 0.63–1.55, $P = 0.96$, n = 4, $I^2 = 0\%$) or observational studies (four studies [16–18,36] reporting six estimates, pooled RR: 0.98, 95% CI 0.87–1.10, $P = 0.74$, $I^2 = 0\%$). Pooled observational studies suggested no significant risk of pancreatic cancer with TZD use (three studies reporting four estimates, pooled RR: 1.04, 95% CI 0.76–1.43, $P = 0.81$, $I^2 = 36\%$); heterogeneity among RCT estimates for pancreatic cancer was too high to allow pooling ($I^2 = 89\%$). Pooled RCT estimates were not significantly associated with the risk of renal cancer (pooled RR: 0.81, 95% CI 0.38–1.72, $P = 0.59$, n = 3, $I^2 = 0\%$), gastrointestinal cancer (pooled RR: 0.78, 95% CI 0.53–1.16, $P = 0.22$, n = 3, $I^2 = 0\%$), melanoma and non-melanoma skin cancers (pooled RR: 1.21, 95% CI 0.58–2.51, $P = 0.61$, n = 3, $I^2 = 46\%$) and hematological cancer (pooled RR: 0.89, 95% CI 0.46–1.71, $P = 0.73$, n = 3, $I^2 = 0\%$). Forest plots of pooled studies are available in the (Fig. S2; see supplementary material associated with this article online).

3.5. Subgroup analysis of pioglitazone use and risk of site-specific cancers

One RCT [30] and five cohort studies [16,27,34,36,37] reported incident cancers among pioglitazone users. From these, we were able to combine data for five site-specific cancers reported by three cohort studies in our subgroup analysis (Fig. 3) and (Fig. S3; see supplementary material associated with this article online).

We observed no association between pioglitazone use and colorectal (pooled RR: 0.97, 95% CI 0.90–1.04, $P = 0.39$, n = 3, lung (pooled RR: 0.95, 95% CI 0.88–1.02, $P = 0.15$, n = 2, $I^2 = 0\%$), breast (pooled RR: 0.93, 95% CI 0.85–1.01, $P = 0.08$, n = 2, $I^2 = 0\%$), prostate (pooled RR: 1.00, 95% CI 0.82–1.22, $P = 0.98$, n = 2, $I^2 = 0\%$), or renal (pooled RR: 0.89, 95% CI 0.76–1.04, $P = 0.13$, n = 2, $I^2 = 0\%$) cancers. Interestingly, however, pioglitazone use was associated with a significantly decreased risk when all five cancer sub-sites were combined (summary RR: 0.95, 95% CI 0.91–0.99, $P = 0.009$, n = 3, $I^2 = 0\%$) (Fig. 3).

4. Discussion

We identified 20 studies in our systematic review of overall and site-specific cancer incidence and TZD use, of which 16 were included in meta-analyses. Among observational studies, we observed modest, but significantly decreased risks of lung (9%), colorectal (7%) and breast cancers (11%). Summary estimates from RCTs were consistent with those from observational studies for colorectal (gastrointestinal) and breast cancers, but not for lung cancer, although the confidence interval from RCTs for site-specific cancers spanned the confidence interval from observational studies in all instances. Overall cancer risk in randomized and observational studies was lower in TZD-users, but was not statistically significant.

Pioglitazone and rosiglitazone differ in effectiveness, potency and risk profiles [46,47] and in a previous systematic review, we observed a significantly increased risk of bladder cancer with pioglitazone, but not rosiglitazone use [15]. Given these observed differences, we conducted an exploratory subgroup analysis of pioglitazone use to explore possible associations with other cancer sites. Use of pioglitazone was not associated with risk of any cancer site, and when sites (other than bladder) were pooled, the summary estimate showed a modest but significant 5% overall risk reduction. When the estimate for bladder cancer with pioglitazone use [15] is added to the pooled estimate, the effect becomes a non-significant 3% overall decrease in cancer risk.

Studies suggest that PPARγ is involved in known tumor suppression pathways, such as those involving mTOR and LKB-1 [8,9,11], yet mechanisms linking TZDs with the suppression of site-specific cancers, such as lung, colorectal and breast, have not been fully elucidated. Several clinical studies testing TZDs in the treatment of various cancers, including lung and breast cancers, are underway [12–14]. Differences at the biologic level between pioglitazone and rosiglitazone, and differences in cancer morphologies may contribute to the observed discrepancies between TZD use and pioglitazone (only) use for site-specific cancers.

Eight observational studies, but no RCTs, assessed TZD use and cancer incidence as their primary analysis [16–19,34,37,42]. Therein lies a major limitation for the different study designs to address this question, that is, risk of cancer as an adverse event. Although the RCTs were able to balance known and unknown confounders through randomization, the high risk of bias in three of four studies, and the observed instability of risk estimates for cancer from RCTs (due to the small numbers of site-specific cancer events during follow-up time) reduce the level of evidence from this study design. Pooled estimates from RCTs are nonetheless useful in corroborating trends observed in pooled estimates from observational studies designs [22,24]. Only one of 16 observational studies was considered at a high
risk of bias. Nearly all observational studies controlled for potential confounders, including age, sex and use of at least one other glucose-lowering drug; however, most observational studies lacked information on potentially important covariates, such as body mass index (BMI), A1c and smoking habits. Cohort and, by association, case-control studies nested within cohorts, can provide strong evidence in assessing latent or rare outcomes such as incident cancer or assessing safety of pharmacotherapies, due to their longer duration and prospective collection of information [22–24,48,49].

Despite the benefits of meta-analysis, our work has several limitations. First, our ever vs. never definitions for TZD use created comparable exposure groups; however the comparison groups differed between studies. Our pooled risk estimates may have been distorted due to possible associations between other glucose-lowering agents and site-specific cancers. This bias likely occurs in a non-differential manner, however, as TZD-users were also exposed to a combination of glucose-lowering agents [4]. Second, we observed modest, statistically significant differences in the risk of cancer in pooled cohort studies, which may be partly due to the large number of individuals (1.5 million) included in one cohort study [34]. However, when this study was removed from the meta-analyses, the TZD-cancer association retained a similar trend (results not shown). Third, heterogeneity in pooled results – lung cancer, breast cancer and colorectal cancer in particular – suggest that there is a moderate amount of variation in our estimates that is attributable to the differences between studies. We were able to explore and identify possible sources of heterogeneity for each cancer comparison, which we attributed to variation in study populations, design and precision of estimates (reflected in weighting). In other results, particularly those pooled from RCTs, low heterogeneity (i.e., $I^2 = 0\%$) generally reflected underpowered individual risk estimates, rather than indicating agreement among well-powered results. Fourth, many of the observational studies lacked potentially important clinical variables in their data (such as BMI, A1c, physical activity and smoking status) and we were unable to control for these confounders at the meta-analytic level. These are all potential confounders in the association between choice of drug therapy and cancer risk in people with type 2 diabetes. Finally, the majority of observational studies did not specifically exclude individuals with type 1 diabetes. Given the population-based source of information for these studies, type 2 diabetes will comprise 90% or more of the individuals with diabetes [50] and, since TZDs are rarely, if ever, prescribed to individuals with type 1 diabetes, it is unlikely this would significantly impact our results. Given inherent limitations, caution should be used when interpreting pooled results from this meta-analysis.

Our systematic review and meta-analysis rigorously summarized research from an exhaustive search of published and unpublished literature in all languages. We used both randomized and observational studies to assess incident cancer by specific organ sites, which allowed examination of possible associations with finer granularity and comparison of results across study designs. Additional subgroup analyses among pioglitazone users highlighted the possibility of differential associations of drugs within the TZD class and cancer at different organ sites. Further research is required to properly assess and clarify the association, if any, between TZD use and site-specific cancer, and should consider using large population-based cohort studies, using a clearly defined reference group(s), examine site-specific (rather than overall) cancers, assess pioglitazone and rosiglitazone separately, and have a long duration of follow-up in order to sufficiently attribute outcome to exposure [51]. Additional consideration must be given to controlling for (time-varying) confounding and bias [51].

In summary, we observed TZD use to be associated with a modest, but significantly decreased risk of lung, colorectal and breast cancers, and a trend towards a decrease in overall risk of cancer. Our results identify gaps in understanding the association between TZDs and site-specific cancers in individuals with type 2 diabetes. This summary can be used to direct and strengthen further research and inform policies around TZD use.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

5. Contribution statement

All authors (INC, SLB, JAJ) contributed to:

- conception and design of the study;
- analysis and interpretation of data;
- drafting of the manuscript or revising it critically for important intellectual content, and;
- final approval of the version to be published.

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Appendix A. Sample MEDLINE search strategy

Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

1. thiazoles/or thiazolidinediones/
2. rosiglitazone.mp.
3. pioglitazone.mp.
4. troglitazone.mp.
Appendix B. Funnel Plot of any reported cancer outcome, by study design

Appendix C. Supplementary material

Supplementary material (Fig. S1-S3, Tables S1-S2) associated with this article can be found at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2012.06.003.

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