Cancer Risk for Patients Using Thiazolidinediones for Type 2 Diabetes: A Meta-Analysis

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Key Words. Cancer • Diabetes • Meta-analysis • Oral antidiabetic therapy • Pioglitazone • Thiazolidinedione

Learning Objectives

Evaluate the risk of cancer as well as cardiovascular and renal disease in the use of oral antidiabetics.

Define and adequately quantify the effect of TZD on the risk of bladder cancer, other selected cancers, and all neoplasms.

ABSTRACT

Objective. To clarify and quantify the effect of thiazolidinediones (TZDs; e.g., pioglitazone, rosiglitazone) on the risk of bladder cancer, other selected cancers, and overall cancer in patients with type 2 diabetes, we performed a systematic review and meta-analysis of observational studies.

Methods. A PubMed/MEDLINE search was conducted for studies published in English up to June 30, 2012. Random-effect models were fitted to estimate summary relative risks (RR).

Results. Seventeen studies satisfying inclusion criteria (3 case-control studies and 14 cohort studies) were considered. Use of TZDs was not associated to the risk of cancer overall (summary RR: 0.96; 95% confidence interval [CI]: 0.91–1.01). A modest excess risk of bladder cancer was reported in pioglitazone (RR: 1.20; 95% CI: 1.07–1.34 from six studies) but not in rosiglitazone

(RR: 1.08; 95% CI: 0.95–1.23 from three studies) users. The RRs of bladder cancer were higher for longer duration (RR: 1.42 for >2 years) and higher cumulative dose of pioglitazone (RR: 1.64 for >28,000 mg). Inverse relations were observed with colorectal cancer (RR: 0.93; 95% CI: 0.90–0.97 from six cohort studies) and liver cancer (RR: 0.65; 95% CI: 0.48–0.89 from four studies), whereas there was no association with pancreatic, lung, breast, and prostate cancers.

Conclusions. Adequate evidence excludes an overall excess cancer risk in TZD users within a few years after starting treatment. However, there is a modest excess risk of bladder cancer, particularly with reference to pioglitazone. Assuming that this association is real, the potential implications on the risk-benefit analysis of TZD use should be evaluated. *The Oncologist* 2013;18:148–156

Implications for Practice: This comprehensive meta-analysis of available epidemiological evidence on thiazolidinediones (TZDs) and cancer risk provides convincing reassurance that TZD use in subjects with type 2 diabetes is not associated with overall cancer risk. The summary relative risks (RR) were close to, or below, unity for all cancers combined and for major cancer sites considered, including colorectum, liver, pancreas, lung, breast, and prostate. A modest excess RR was apparent for bladder cancer, particularly among pioglitazone users. Thus, cancer risk has no major implications in clinical practice for TZD use. However, the benefits-risk of TZD use should be critically evaluated in subjects at high risk of bladder cancer, i.e., those with pre-neoplastic bladder lesions, family history of bladder cancer, and heavy smokers. TZDs have been available for 15 years or less in most countries, thus their potential long-term implications on cancer risk remain undefined.

INTRODUCTION

Diabetes mellitus affects a large and growing number of people worldwide—approximately 350 million patients in 2008 [1]. Diabetes has been associated with an increased risk of liver, pancreatic, and endometrial cancers, as well as (to a lesser extent) colon, postmenopausal breast, and bladder

cancers [2–4]. The association between diabetes and the risk of selected cancers has been related to insulin and insulin-like growth factor (IGF)-1 in cancer promotion; overexpression of the IGF-1 receptor has been detected in several cancers [2].

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Thiazolidinediones (TZDs; e.g., pioglitazone and rosiglitazone), which increase insulin sensitivity in peripheral tissues, may also interfere with insulin and IGF pathways. A few observational studies suggested an increased risk of bladder cancer, whereas data are scattered and appear inconclusive for other cancer sites.

Medications prescribed for the treatment of type 2 diabetes have also been suggested to influence the risk of cancer [2, 5–6]. Thus, insulin, insulin analogues and secretagogues, which increase the circulating levels of insulin, have been associated with increased cancer risk [7–9]; metformin, which reduces the levels of both circulating glucose and insulin in patients with insulin resistance, has been associated with a reduced risk of cancer, mainly of the colorectum and pancreas [10, 11].

Thiazolidinediones (TZDs; e.g., pioglitazone and rosiglitazone), which increase insulin sensitivity in peripheral tissues, may also interfere with insulin and IGF pathways. A few observational studies suggested an increased risk of bladder cancer [12–17], whereas data are scattered and appear inconclusive for other cancer sites [18–29]. In particular, clinical trials of pioglitazone on cardiovascular diseases [30–32] and a study from the U.S. Food and Drug Administration adverse reporting system [33] raised some concerns on adverse effects of pioglitazone on bladder cancer. No significant relationship with bladder cancer was reported in a meta-analysis of clinical studies on rosiglitazone [34]. An interim report of a cohort study from the Kaiser Permanente Northern California registry [12], which was requested by the European Medicines Agency on the basis of such concerns, reported a nonsignificant 20% increased risk of bladder cancer in relation to pioglitazone use, with a significant trend of increasing risk with duration of use (relative risk [RR]: 1.4 for more than 2 years), but not with cumulative dose. Subsequently, three cohort studies reported a 20%–30% increased risk [14–16] and one reported an 80% increased risk [13] of bladder cancer in pioglitazone (but not rosiglitazone) users, with increasing trends in risk with duration and cumulative dose. However, a nested case-control study based on a Taiwan health insurance database [26] did not find an association between either pioglitazone or rosiglitazone and bladder cancer. To clarify and quantify the effect of TZDs on the risk of cancer as a whole and of bladder and other site-specific tumors in patients with type 2 diabetes, we performed a systematic review and meta-analysis of available observational studies.

MATERIALS AND METHODS

We carried out a PubMed/MEDLINE search for observational studies published in English up to June 30, 2012 that investigated the association between TZDs and the risk of cancer. The following key words were used: (thiazolidinediones OR glitazones OR pioglitazone OR rosiglitazone) AND (neoplasms OR cancer) AND risk. We retrieved and assessed potentially relevant articles and checked the reference lists of all papers of interest to identify additional relevant publications.

Studies were included if they included original data from case-control or cohort studies; investigated exposure to TZDs;

specifically mentioned that participants were affected by type 2 diabetes mellitus; assessed either the risk of cancer as a whole or the risk of cancer at specific sites, with the exclusion of studies including recurrent cancer cases; and reported crude or adjusted estimates of the association between the exposure and outcome of interest (i.e., RR, odds ratio, hazard or rate ratio, and the corresponding 95% confidence interval [CI] or *p* value), or provided raw data to allow their estimation. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis only the most recent or informative one. Unpublished data were not considered. We did not assign quality scores to studies and did not exclude a priori any study for weakness of design or data quality. Two readers (D.B. and V.R.) independently reviewed and cross-checked the data; disagreements were resolved by consensus.

For each study, we extracted details on study design, country, publication year, number of cancer cases and corresponding controls (or persons at risk for cohort studies), exposure and reference therapy (e.g., no use of TZDs), cancer site, and RR (or other association measures) with the corresponding 95% CI.

Statistical Methods

For all neoplasms combined, and for specific cancer sites for which there were at least three independent studies, we derived summary estimates of the RR for the exposure to TZDs—both overall and separately for case-control and cohort studies—using both fixed-effects models (i.e., as weighted averages on the inverse of the variance of the log RR) and random-effects models (i.e., as weighted averages on the sum of the inverse of the variance of the log RR and the moment estimator of the variance between studies) [35]. Only the results from the latter models were presented to take into account the heterogeneity of risk estimates and being more conservative. Heterogeneity between study-specific estimates was tested using the *Q* statistic [36] and measured with the *I*² statistic [37], which represents the percentage of the total variation across studies attributable to heterogeneity rather than chance. In some studies, to obtain a single estimate for TZD use, we pooled the RRs for different types of TZDs (pioglitazone and rosiglitazone) or for combinations of TZDs with other antidiabetic medications using fixed-effects models. When possible, we pooled adjusted estimates from the original studies; otherwise, we used raw data and computed crude RRs. Publication bias was evaluated through funnel plot visual analysis and with the Egger's and Begg's test [38, 39]. The corresponding calculations and graphical visualizations of forest and funnel plots were carried out using STATA Software Program Version 9 (STATA, College Station, TX).

RESULTS

From the original literature search, we identified and screened 161 publications; of these, 32 were considered of interest on the basis of the title and abstract, and their full text was retrieved for detailed evaluation (supplemental online Fig. 1). Four additional studies were identified through the references of the retrieved papers; 19 papers were subsequently excluded, including 14 editorials or reviews, 1 cross-sectional study, 1 study on adverse effect databases, 2 studies not specifically focused on diabetics, and 1 study not providing an es-

Table 1. Main findings of epidemiological studies on thiazolidinediones and cancer risk in patients with type 2 diabetes

Study	Country	Cancer site	n of cases	n of controls/ persons at risk	Drug	Reference category	RR	95% CI	Adjustment variables	Comments
Case-control studies										
Li et al. [18]	U.S.	Pancreas	259	109	TZD	Never TZD	1.55	0.78–3.07	Age, sex, race, smoking, alcohol, family history of cancer, BMI, duration of diabetes, insulin	No significant association in never users of insulin (RR: 1.22) or with duration of diabetes (RR: 1.65 for >2 yrs)
Monami et al. [19]	Italy	Any site	195	195	TZD	No TZD	2.00	0.29–22.55 ^a	Age, sex, duration of diabetes, HbA1c, BMI, comorbidity score, smoking, alcohol abuse, other hypoglycemic drugs	No significant association with duration of exposure (RR: 1.61 for ≥1 yr; RR: 1.05 for ≥3 yrs)
Hassan et al. [20]	U.S.	Liver	122	86	TZD	No TZD	0.3	0.1–0.7	Age, sex, race, education, alcohol, smoking, family history of cancer, hepatitis C, and hepatitis B	
Cohort studies										
Govindarajan et al. [21]	U.S.	Colorectum	1,137	87,678	TZD	No TZD	0.88	0.74–1.05	Age, race, BMI, HbA1c, insulin, other oral agents, drug interactions	
		Lung	1,371		TZD	No TZD	0.67	0.51–0.87		
		Prostate	3,246		TZD	No TZD	0.86	0.64–1.14		
Koro et al. [22]	U.S.	Colon	408	2,027	TZD	Untreated or other antidiabetics	1.15 ^a	0.88–1.49 ^a		Nested case-control study
		Breast	513	2,557	TZD	Untreated or other antidiabetics	0.92 ^a	0.70–1.19 ^a		
		Prostate	643	3,176	TZD	Untreated or other antidiabetics	1.02 ^a	0.81–1.26 ^a		
Oliveria et al. [23]	U.S.	Colorectum	383	191,223	TZD monotherapy/ combination therapy	No TZD	1.08	0.86–1.36	Age, sex, history of polyps, ulcerative colitis, Crohn's disease	
		Liver	39		TZD monotherapy/ combination therapy	No TZD	0.79	0.34–1.81	Age, sex, alcoholism, hepatitis B, hepatitis C, cirrhosis	
		Pancreas	102		TZD monotherapy/ combination therapy	Non TZD	0.76	0.46–1.24	Age, sex, alcoholism, hepatitis B, hepatitis C history of polyps, partial gastrectomy, chronic pancreatitis, deep venous thrombosis, dermatomyositis/polymyositis	
		Bladder	178		TZD monotherapy/ combination therapy	No TZD	0.94	0.66–1.34	Age, sex, schistosomiasis, pelvic radiation	
Bodmer et al. [24]	U.K.	Breast	305	22,621	TZD	No TZD	1.76	0.84–3.68	Age, sex, general practice, calendar time, BMI, smoking, duration of diabetes, other antidiabetic drugs, prandial glucose regulator, HbA1c, acarbose, postmenopausal estrogens	Nested case-control study
Ferrara et al. [25]	U.S.	Colon	1,260	252,467	Pioglitazone	Never pioglitazone	0.9	0.7–1.1	Age, sex, race/ethnicity, year of cohort entry, smoking, income, duration of diabetes, new diabetes diagnosis, other diabetes medications, HbA1C, creatinine, congestive heart failure	
		Rectum	390		Pioglitazone	Never pioglitazone	1.1	0.8–1.5		
		Pancreas	431		Pioglitazone	Never pioglitazone	1.2	0.8–1.8		
		Lung/bronchus	1,637		Pioglitazone	Never pioglitazone	0.7	0.4–1.5		
					Pioglitazone	Never pioglitazone	1.2	0.8–1.7		
					Pioglitazone	Never pioglitazone	1.0	0.6–1.8		
					Pioglitazone	Never pioglitazone	1.0	0.8–1.3		
		Melanoma	373		Pioglitazone	Never pioglitazone	0.9	0.6–1.3		
					Pioglitazone	Never pioglitazone	1.3	0.9–2.0		
					Pioglitazone	Never pioglitazone	1.0	0.5–1.8		
		Breast	1,561		Pioglitazone	Never pioglitazone	1.0	0.8–1.3		
					Pioglitazone	Never pioglitazone	0.9	0.7–1.2		
		Corpus uteri	552		Pioglitazone	Never pioglitazone	1.1	0.8–1.5		
					Pioglitazone	Never pioglitazone	1.2	0.8–1.9		
		Prostate	2,105		Pioglitazone	Never pioglitazone	1.0	0.8–1.2		
					Pioglitazone	Never pioglitazone	1.0	0.7–1.3		
		Kidney/renal pelvis	430		Pioglitazone	Never pioglitazone	0.7	0.4–1.1		
					Pioglitazone	Never pioglitazone	1.3	0.7–2.3		
		Non Hodgkin lymphoma	569		Pioglitazone	Never pioglitazone	1.3	1.0–1.8		
Lewis et al. [12]	U.S.	Bladder	881	193,099	Pioglitazone	Never pioglitazone	0.7	0.4–1.2	Age, sex, race/ethnicity, income, smoking, newly diagnosed with diabetes, hemoglobin A1C, other cancer prior to baseline, duration of diabetes, other diabetes medications, renal function, bladder condition, congestive heart failure	Significant trend with duration (RR: 1.4 for >2 yrs) but not with cumulative dose

(continued)

timate of TZD use versus no use. A total of 17 studies were thus considered in the present meta-analysis (3 case-control and 14 cohort studies; Table 1).

Figure 1 shows the study-specific RRs of all cancers combined in users of TZDs compared to nonusers, as well as the summary estimates overall and by study design. Figure 2 gives

Table 1. (Continued)

Study	Country	Cancer site	n of cases	n of controls/ persons at risk	Drug	Reference category	RR	95% CI	Adjustment variables	Comments
Azoulay et al. [13]	U.K.	Bladder	376	6,699	Pioglitazone	Never use of any TZD	1.83	1.10–3.05	Year of birth, year of cohort entry, sex, duration of follow-up (matching variables), alcohol, obesity, smoking status, hemoglobin A1C, previous bladder conditions, previous cancer, Charlson comorbidity score, and use of other antidiabetic agents	Nested case-control study. Significant trend with cumulative duration (RR: 1.99 for >2 yrs) and cumulative dose (RR: 2.54 for >28,000 mg) for pioglitazone
					Rosiglitazone	Never use of any TZD	1.14	0.78–1.68		
					Pioglitazone/Rosiglitazone	Never use of any TZD	0.78	0.18–3.29		
Chang et al. [26]	Taiwan	Colorectum	7,200	28,712	Pioglitazone	No pioglitazone	1.04	0.91–1.20	Other antidiabetic drugs, number of oral antidiabetic drugs, statins, aspirin, beta-blockers, calcium channel blockers, chronic lung, liver or kidney disease, nephropathy, cerebro- or cardiovascular disease plus neuropathy, retinopathy, depression, ACE inhibitors (for colorectum), retinopathy, angiotensin receptor blockers, alpha-glucosidase inhibitors (for lung), neuropathy, and ACE inhibitors (for bladder)	Nested case-control study. For liver cancer, trend with cumulative dose and duration, and stronger inverse association in patients with chronic liver diseases. No clear dose-duration-risk relationships for other neoplasms
		Liver	10,741	41,847	Rosiglitazone	No rosiglitazone	0.86	0.76–0.96		
					Pioglitazone	No pioglitazone	0.83	0.72–0.95		
		Lung	5,361	21,313	Rosiglitazone	No rosiglitazone	0.73	0.65–0.81		
					Pioglitazone	No pioglitazone	1.14	0.95–1.37		
		Bladder	1,583	6,308	Pioglitazone	No pioglitazone	1.12	0.90–1.39		
Lai et al. [28]	Taiwan	Liver	224	19,349	TZD	No TZD	0.56	0.37–0.84	Age, sex, comorbidities (including cirrhosis, alcoholic liver damage, hepatitis B and C)	
Lai et al. [27]	Taiwan	Lung	129	19,624	TZD	No TZD	0.55	0.32–0.94	Age, sex, pulmonary tuberculosis, chronic obstructive pulmonary disease, and propensity score	
Neumann et al. [14]	France	Colorectum	10,618	1,485,146	Pioglitazone	No pioglitazone	0.97	0.90–1.05	Age, sex, exposure to glucose-lowering drugs	For pioglitazone and bladder cancer, higher risk in men (RR: 1.28) than in women (RR: 0.78) and significant trend with cumulative duration (RR: 1.36 for ≥2 yrs) and with cumulative dose (RR: 1.75 for ≥28,000 mg)
		Lung	9,298	1,493,472	Rosiglitazone	No rosiglitazone	0.88	0.82–0.95		
					Pioglitazone	No pioglitazone	0.94	0.87–1.02		
		Breast	6,820	671,510	Rosiglitazone	No rosiglitazone	0.91	0.84–0.99		
					Pioglitazone	No pioglitazone	0.91	0.83–1.00		
		Bladder	2,016	1,491,060	Rosiglitazone	No rosiglitazone	0.80	0.73–0.88		
					Pioglitazone	No pioglitazone	1.22	1.05–1.43		
		Kidney	2,861	1,495,787	Rosiglitazone	No rosiglitazone	1.08	0.92–1.26		
					Pioglitazone	No pioglitazone	0.91	0.79–1.06		
		Head and neck	2,868	1,495,411	Rosiglitazone	No rosiglitazone	0.98	0.86–1.13		
Tseng et al. [15]	Taiwan	Bladder	165	54,928	Pioglitazone	No pioglitazone	0.85	0.73–0.99	Age, sex, region of residence, occupation, diabetes duration, previous cancer, nephropathy, urinary tract disease, hypertension, chronic obstructive pulmonary disease, cerebrovascular disease, ischemic heart disease, peripheral arterial disease, eye disease, dyslipidemia, heart failure, statin, fibrate, ACE inhibitors/angiotensin receptor blocker, calcium channel blocker, and other antidiabetic drugs	No trend with duration or cumulative dose
					Rosiglitazone	No rosiglitazone	0.79	0.67–0.92		
Wei et al. [16]	UK	Bladder	869	207,714	Pioglitazone	Other oral hypoglycemic drugs	1.22	0.80–1.84	Propensity matched analysis for age, sex, smoking status, BMI, and duration of diabetes	
Yang et al. [29]	China	Lung	270	6,074	TZD	No TZD	0.17	0.04–0.71	Age, sex, smoking, alcohol, employment status, BMI, duration of diabetes, HbA1c, other antidiabetic drugs, blood pressure, cholesterol indicators, statins, fibrates, renin-angiotensin system inhibitors	Dose-response relationship

^aComputed from raw data.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CI, confidence interval; Hb, hemoglobin; NHL, non-Hodgkin lymphoma; NR, not reported; RR, relative risk; TZD, thiazolidinedione.

the corresponding RR estimates for cancers of the colorectum, liver, pancreas, lung, breast, and prostate; Figure 3 illustrates the corresponding RR estimates for bladder cancer. The summary RR of all cancers (Fig. 1) was 0.88 (95% CI: 0.25–3.15) in three case-control studies [18–20], 0.96 (95% CI: 0.91–1.01) in 14 cohort studies [12–16, 21–29],

and 0.96 (95% CI: 0.91–1.01) overall. There was, however, a significant heterogeneity between both case-control and cohort studies.

With reference to colorectal cancer (Fig. 2), the summary RR for six cohort studies was 0.93 (95% CI: 0.90–0.97) [14, 21–23, 25–26]. Most information came from a large French study

Figure 1. Study-specific and summary relative risk estimates for use of thiazolidinediones (vs. no use of TZDs) and overall cancer risk. Abbreviations: CI, confidence interval; NHL, non-Hodgkin lymphoma; RR, relative risk; TZD, thiazolidinedione.

reporting a significant reduced risk [14], but the estimates from other studies were not heterogeneous.

The summary RR of liver cancer (Fig. 2) was 0.65 (95% CI: 0.48–0.89) from four studies [20, 23, 26–27]. All studies reported inverse associations, which were significant in three studies [20, 26–27]; there was no evidence of heterogeneity across them.

One case-control study [18] and two cohort studies [23, 25] on pancreatic cancer reported a summary RR of 1.06 (95% CI: 0.76–1.48; Fig. 2). Only one study reported an increased risk of pancreatic cancer (RR: 1.55) in relation to TZD use, but the estimate was not significant [18]. Moreover, no significant trend with duration was identified in that study.

For lung cancer (Fig. 2), the overall RR was 0.90 (95% CI: 0.76–1.06) from five cohort studies [14, 21, 25–27]. The study-specific estimates were, however, significantly heterogeneous, with three studies reporting significant inverse associations [14, 21, 27] and other two studies reporting no meaningful association [25, 26].

Four cohort studies examined the RR of breast cancer (Fig. 2) and gave a summary RR of 0.91 (95% CI: 0.80–1.03) [14, 22, 24, 25]. One study reported a nonsignificant increased risk of 1.76 [24]; however, it was not significantly heterogeneous from the estimates of other two studies reporting no association [22, 25].

The summary RR of prostate cancer (Fig. 2) was 0.98 (95% CI: 0.87–1.11) from three cohort studies [21, 22, 25], all reporting RRs around unity.

With reference to bladder cancer (Fig. 3), seven cohort studies provided information on the association with TZD use, with a summary RR of 1.13 (95% CI: 1.05–1.23) [12–16, 23, 26]. The RR was 1.08 (95% CI: 0.95–1.23) for rosiglitazone, based on three studies [13, 14, 26] and 1.20 (95% CI: 1.07–1.34) for pioglitazone, based on six studies [12–16, 26]. The summary RR was 0.94 for <12 months of pioglitazone use, 1.36 for 12–24 months of use, and 1.42 for >24 months of use [12–14, 26]; the RR was 1.11 for <10,500 mg of cumulative dose of pioglitazone, 1.22 for 10,500–28,000 mg, and 1.64 for >28,000

Figure 2. Study-specific and summary relative risk estimates for use of thiazolidinediones (vs. no use) and risk of selected cancer sites. Abbreviations: CI, confidence interval; RR, relative risk; TZD, thiazolidinedione.

mg [12–14]. Only one study provided information on dose and duration-risk relationships for rosiglitazone, without any meaningful trend in risk [26].

There was no evidence of publication bias (Fig. 4), as indicated by visual inspection of the funnel plot on the overall

studies on TZD and cancer and confirmed by the Egger's and Begg's tests ($p = .25$ and $.96$, respectively; data not shown).

DISCUSSION

The present meta-analysis indicates that there is no overall association between TZDs and cancer risk in diabetic patients. There is, however, an overall 20% excess risk of bladder cancer in relation to pioglitazone use, with somewhat higher risks for longer duration of use (RR: 1.4 for >2 years) and for higher cumulative dose (RR: 1.6 for $>28,000$ mg). An inverse relationship was observed between TZD and colorectal and liver cancers, whereas there was no meaningful association with pancreatic, lung, breast and prostate cancers.

TZDs are peroxisome proliferator-activated receptors (PPAR)- γ antagonists, which have shown growth inhibitory actions in tissue culture systems [40–43]. However, the pharmacological profile of pioglitazone is comparable to that of dual α - and γ -PPAR antagonists, which have shown carcinogenic effects in animals [44–46]. Animal studies have also reported an increased incidence of bladder cancers in male rats,

The present meta-analysis indicates that there is no overall association between TZDs and cancer risk in diabetic patients. There is, however, an overall 20% excess risk of bladder cancer in relation to pioglitazone use, with somewhat higher risks for longer duration of use (RR: 1.4 for >2 years) and for higher cumulative dose (RR: 1.6 for $>28,000$ mg). An inverse relationship was observed between TZD and colorectal and liver cancers, whereas there was no meaningful association with pancreatic, lung, breast and prostate cancers.

Figure 3. Study-specific and summary relative risk estimates for thiazolidinediones (use vs. no use and dose-response analyses) and risk of bladder cancer.
Abbreviations: CI, confidence interval; RR, relative risk; TZD, thiazolidinedione.

Figure 4. Funnel plot for the studies on thiazolidinediones and cancer risk.
Abbreviation: RR, relative risk.

but not in female rats or in mice [44, 47–50], treated with pioglitazone. This has been related to chronic bladder irritation rather than to the PPAR signaling [45, 51], although this hypothesis needs to be confirmed. More importantly, it is unclear whether these mechanisms are relevant in humans. Thus, there are no clear biological mechanisms that can explain the apparent increase in bladder cancer risk in pioglitazone users. Moreover, our findings indicate that the association between pioglitazone and bladder cancer is mod-

est and can therefore be due to other sources of bias or residual confounding in observational studies.

We observed a modest risk reduction of colorectal cancer in relation to TZDs, largely influenced by a large French study reporting an inverse association particularly with rosiglitazone [14]. This could be related to the ability of PPAR- γ to inhibit tumor growth and colon carcinogenesis [52–54]. Similarly, there is some animal evidence of anticancer activity of PPAR- γ and TZDs in the liver [55, 56]. The overall reduced risk of liver cancer found in TZD users, however, may be explained by possible confounding by indication. TZDs are generally not recommended for patients with diabetes and liver diseases, although a study showed a dose-risk relationship which supports the hypothesis of a real causal association [26].

With reference to other neoplasms, the evidence is largely inconsistent. A U.S. case-control study reported a 50% excess risk of pancreatic cancer in TZD users [18], which was not confirmed in two cohort studies [23, 25]. A nonsignificant increased risk of breast cancer in relation to TZDs was reported in a nested case-control study within the U.K. General Practice Research Database (GPRD) [24], but no meaningful association was found in two other larger studies [22, 25]. For lung cancer, some inverse association emerged from two cohort

studies [21, 27], but not from two other larger investigations [25, 26]. Thus, the overall evidence—although still limited—does not indicate any relevant role of TZD use on pancreatic, breast, and lung cancers.

TZDs were introduced in the market in the late 1990s. Consequently, we were able to evaluate short-term exposures only, with limited information on the relationship with duration and cumulative dose. Among other limitations of this meta-analysis are the possible biases of the original observational studies. These include in particular confounding by indication because patients with diabetes who are treated with TZDs may have different baseline socioeconomic and clinical characteristics as compared with those treated with other antidiabetic medications [57]. Even allowing for a large number of covariates, it is not possible to completely rule out some residual bias by indication or other unmeasured sources of confounding [5, 58].

A cohort study based on the U.K. GPRD, in which various antidiabetic medications were compared to metformin, showed a reduced risk of cancer for TZDs after a few months of treatment only. Therefore, patients treated with TZDs may have a different underlying cancer risk respect to patients treated with metformin [59]. Moreover, because TZDs are used for patients with refractory disease to other antiglycemic agents, the severity of the underlying disease may confound an apparent relationship between TZD use and subsequent cancer diagnosis.

The nature of the comparison group may also influence the associations investigated. Patients not using TZDs may be or have been on treatment with other antidiabetic treatments, which in turn may influence the risk of developing cancer [2, 5–6]. Further, giving the frequent subsequent or concomitant use of several antidiabetic treatments, there are difficulties in measuring the separate role of each single drug, although many studies mutually adjusted the estimates for various treatments. In particular, metformin may reduce the risk of selected cancer sites, whereas no material association was found for sulfonylurea [11]. None of the other antidiabetic treatments, however, have been meaningfully related to bladder cancer.

Moreover, several studies were based on health prescription databases. Although these studies were able to investigate drug use in the clinical practice on large population

samples and should be relatively free from selection and information bias, they may be limited by the lack of data on important confounders, the inclusion of prescriptions (which might not well reflect real drug use), and the inclusion of both new and prevalent antidiabetic users. Differences in cancer sites, comparison groups, study population and design, and covariates allowed for in the analyses may explain part of the heterogeneity observed between studies. With regard to publication bias, both the graphical display of funnel plots and the statistical tests did not indicate any major bias when considering all neoplasms, but data were too limited to assess publication bias for single cancer sites.

CONCLUSION

Adequate evidence now exists to exclude an overall increased cancer risk in TZD users within a few years after starting treatment. However, there is a modestly increased risk of bladder cancer, particularly with use of pioglitazone, with some indication of duration and dose-risk relationships. Assuming that this association is real, the potential implications on the risk-benefit analysis of TZD use should be evaluated.

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