Systematic Review/Meta-analysis

Thiazolidinediones and risk of colorectal cancer in patients with diabetes mellitus: A meta-analysis

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Abstract

Background/Aims: A growing body of evidence has suggested that thiazolidinediones (TZDs) potentially reduce the risk of colorectal cancer (CRC). This study aimed to evaluate the effect of TZDs on CRC risk in patients with diabetes mellitus (DM).

Patients and Methods: A systematic search of electronic databases was performed for studies evaluating the exposure to TZDs and reporting CRC risk in diabetic patients. Pooled estimates with 95% confidence intervals (CIs) were estimated using fixed or random effects models.

Results: A total of 10 observational studies reporting more than 18,972 CRC cases in 2,470,768 DM patients were included. Meta-analysis showed a 9% reduction in CRC risk associated with TZDs use in all studies [relative risk (RR) =0.91, 95% CI = 0.84–0.99, P = 0.03] and cohort studies (RR = 0.89, 95% CI = 0.80–0.99, P = 0.04), respectively. However, such effect was not shown in case–control studies. In subgroup analyses, lower CRC risk was found in Asian population (RR = 0.40, 95% CI = 0.29–0.53, P = 0.00), and a trend toward lower CRC risk was observed in US population (RR = 0.94, 95% CI = 0.88–1.01, P = 0.08). CRC risk was significantly modified with non-pioglitazone TZD use (RR = 0.88, 95% CI = 0.82–0.95, P = 0.00), but not with pioglitazone use (RR = 0.95, 95% CI = 0.89–1.01, P = 0.11). No significant difference was observed with cancer site (colon or rectum). There was considerable inherent heterogeneity across studies, partly explained by study location.

Conclusions: This meta-analysis supports a protective association between TZDs use and CRC risk in patients with DM. Future well-designed prospective studies with larger cohorts would be needed to understand this association better.

Keywords: Colorectal cancer, diabetes mellitus, meta-analysis, thiazolidinediones

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide with both prevalence and mortality increasing.[1] Diabetes mellitus (DM) is considered as an independent risk factor for CRC, with an approximately 30–40% higher risk as compared to non-DM patients.[2,3] Diabetes promotes the development of CRC carcinogenesis through complex processes. The mechanisms underlying may possibly be related to hyperinsulinemia, hyperglycemia, or an obesity-associated chronic inflammation, which may contribute to an increased cellular proliferation and tumor

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formation.[4-6] Besides, high concentrations of insulin-like growth factor-1 (IGF-1) and the accumulation of β-catenin are also believed to play important roles in colorectal carcinogenesis in diabetes.[7-9]

Several preclinical studies have demonstrated that antidiabetic medications (ADMs) may modify the risk of multiple cancers. The insulin sensitizer thiazolidinediones (TZDs), known as peroxisome proliferator-activated receptors gamma (PPAR-γ) agonists, serve as one of the ADMs options to directly reduce insulin resistance in patients with DM. PPAR-γ belongs to the nuclear hormone receptor superfamily, which forms heterodimers with retinoid X receptor to bind to DNA response elements to exert its effects.[10] PPAR-γ is expressed at high levels in colon mucosa, adenocarcinoma, and human colon cancer cell lines.[11,12] Previous studies have suggested that PPAR-γ agonists induce the differentiation and apoptosis of CRC cells, though some tumor suppression pathways, such as mTOR and LKB-1,[13,14] reduce tumor growth *in vitro* and *in vivo*.[15-19] In addition to antiproliferative effects in CRC, TZDs may sensitize tumor cells to anticancer therapies.[20]

Although cancer-modifying effects are biologically plausible, data on the potential effect of TZDs are inconsistent. In earlier studies, some have shown an association between TZDs use and lower cancer risk among DM patients,[21,22] while others have shown no beneficial effect.[23,24]

Given the current evidence, there remains a lack of consensus regarding the effect of TZDs use on CRC risk. Thus, we performed a meta-analysis to examine the potential role of TZDs in influencing CRC susceptibility.

PATIENTS AND METHODS

Study identification

This study was performed according to the standard guidelines for meta-analyses and systematic reviews of observational studies.[25] PubMed, EMBASE, Cochrane Library, ISI Web of Knowledge were searched through April 2017 for observational studies investigating the association between TZDs and CRC risk, using the terms "thiazolidinediones," "glitazones," "troglitazone," "pioglitazone," "rosiglitazone," "colorectal," "colon," "rectum," "cancer," "neoplasm," and "risk." The reference lists were also inspected for relevant studies.

Study selection and quality assessment

Eligible studies were included in the meta-analysis if they met the following criteria: (1) Full-text observational studies published in English, including cohort studies and case–control studies; (2) to compare TZDs with placebo or drugs other than TZDs; (3) with raw data on the association of TZDs use and CRC risk in DM patients, or report crude/adjusted estimates; (4) when multiple reports were published on the same population, the most recent/comprehensive publication was selected.

The quality of observational studies was assessed by Newcastle-Ottawa Scale (NOS), which included eight items scored by star. In this scale, observational studies were scored across three categories: selection of study groups, comparability of study groups, and ascertainment of the outcome of interest.[26]

Data extraction and synthesis

Study selections were performed independently by two of the authors (Y Liu and PP Jin). Disagreements were resolved by consensus. The following information were extracted: First author, publication year, study duration, study location, study design, cancer site, intervention, number of patients, and cancer incidence. The strength of the associations between treatments and outcomes was estimated by relative risk (RR) and 95% confidence interval (CI). Summary estimates of the RRs were derived using fixed-effects models (Mantel–Haenszel method) or random-effects models (DerSimonian and Laird method).[27] Adjusted estimates were pooled from the original studies if possible; otherwise, raw data were used to compute crude RRs. Heterogeneity between studies was assessed by Cochran Q-test. A P value of >0.10 for the Q-test indicated a lack of heterogeneity. I^2 statistic value of <30%, 30–60%, 61–75%, and >75% was suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[28] Heterogeneity was further explored by performing meta-regression analyses using method of moments, with $P < 0.10$ considered statistically significant.[29] Sensitivity analysis was performed by exclusion of each study. The presence of publication bias was assessed by Begg and Mazumdar adjusted rank correlation test ($P < 0.05$ indicated publication bias).[30] The Duval and Tweedie's trim and fill method was used for the estimation of results after correction for publication bias.[31] All meta-analyses were performed using STATA version 12.0 (Stata Corporation, Texas).

RESULTS

Eligible studies and quality assessment

A total of 10 full-text observational studies reporting more than 18,972 CRC cases in 2,470,768 patients with DM were included in the final analysis (7 cohort studies, 3 case–control studies).[23,24,32-39] Figure 1 shows the selection

procedure. Table 1 presents the main details of the selected studies. The NOS scores for observational studies ranged from 6 to 9 stars. The overall methodological quality of evidence was high.

CRC risk in diabetic patients using TZDs

The main results of the meta-analysis are shown in Table 2. On meta-analysis of all observational studies that evaluated the risk of CRC with TZDs exposure in DM patients, the association was statistically significant (RR = 0.91, 95% CI = 0.84–0.99, P = 0.03) [Figure 2]. Considerable heterogeneity was found across studies ($P_{heterogeneity}$ = 0.00, I^2 = 82.1%). Results were unchanged in cohort studies (n = 7 studies, more than 14,278 CRC cases in 2,223,780 patients with DM; RR = 0.89, 95% CI = 0.80–0.99, P = 0.04, I^2 = 86.9%).[24,32,35-39] However, such effects were not shown in case–control studies (n = 3 studies, 4,666 CRC cases in 246,988 patients with DM; RR = 0.94, 95% CI = 0.84–1.05, P = 0.28, I^2 = 31.9%).[23,33,34]

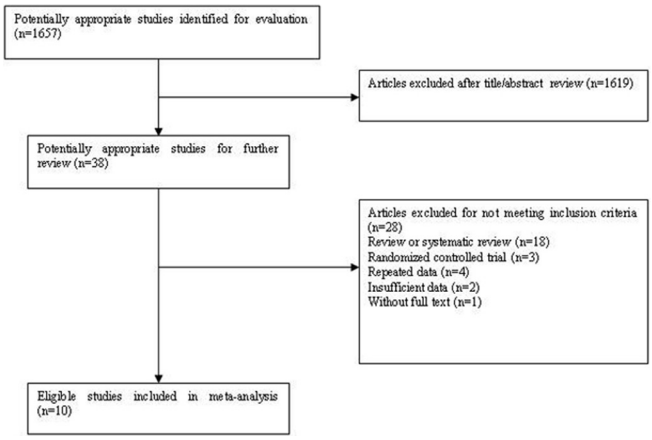

Figure 1: Flowchart of literature search

Subgroup analyses/sensitivity analyses

Subgroup analysis on study location did not show cancer-modifying effect of TZDs in Europe (n = 2 studies, more than 1,650 CRC cases in 361,722 patients with DM; RR = 0.96, 95% CI = 0.89–1.04, P = 0.34).[35,37] A trend of protective effect was found in United States (US) (n = 7 studies, 16,971 CRC cases in 2,076,155 patients with DM; RR = 0.94, 95% CI = 0.88–1.01, P = 0.08),[23,24,32-34,38,39] although the association was not statistically significant. Only a cohort study from Asia showed a significant result (351 CRC cases in 32,891 patients with DM; RR = 0.40, 95% CI = 0.29–0.53, P = 0.00).[36] When referred to drug type, non-pioglitazone TZD showed a modest protective effect on CRC risk in diabetic patients (n = 2 studies, 12,268 CRC cases in 1,737,613 patients with DM; RR = 0.88, 95% CI = 0.82–0.95, P = 0.00);[37,38] however, such effect was not found in pioglitazone group (n = 3 studies, 14,969 CRC cases in 1,974,120 patients with DM; RR = 0.95, 95% CI = 0.89–1.01, P = 0.11).[33,37,38] No significant difference was noted based on cancer site (For colon: n = 4 studies, more than 3,742 CRC cases in 660,664 patients with DM;[23,33,35,38] RR = 1.00, 95% CI = 0.99–1.02, P = 0.61. For rectum: n = 3 studies, more than 1,017 CRC cases in 598,229 patients with DM;[33,35,38] RR = 0.98, 95% CI = 0.96–1.01, P = 0.23) [Table 2].

Due to significant heterogeneity, apart from using the random-effects model, further sensitivity analysis was performed. Exclusion of any study did not considerably alter the magnitude of summary estimate [Figure 3].

The meta-regression analysis evaluating the regression of study location on log risk ratio showed significant result (Z = −2.08, P = 0.09); however, publication year (Z = 0.03,

Table 1: Main characteristics of the included studies

First author (Year)	Study location	Study design	Cancer site	Medication		No. of cases/persons at risk	RR	95% CI	NOS
				Exposure	Comparison				
Htoo (2016)	U.S.	Cohort	Colorectum	TZD	DPP-4i	167/65120	0.92*	0.68–1.26	9
Lewis (2015)	U.S.	Case-control	Colon	PIO	No PIO	2074/236507	0.91	0.78–1.05	9
			Rectum	PIO	No PIO	627/236507	0.81	0.60–1.08	
Sehdev (2015)	U.S.	Case-control	Colorectum	TZD	No TZD	1557/8046	0.92	0.81–1.06	8
Valent (2015)	Italy	Cohort	Colon	TZD	No TZD	n/r/109255	1.00	0.99–1.02	8
			Rectum	TZD	No TZD	n/r/109255	0.98	0.96–1.01	
Lin (2014)	Taiwan	Cohort	Colorectum	TZD	Other ADMs	295/28225	0.43	0.29–0.64	9
			Colorectum	TZD	No ADMs	84/11822	0.35	0.22–0.56	
Neumann (2012)	France	Cohort	Colorectum	PIO	No PIO	10618/1485146	0.97	0.90–1.05	8
			Colorectum	ROSI	No ROSI	10618/1485146	0.88	0.82–0.95	
Ferrara (2011)	U.S.	Cohort	Colon	PIO	No PIO	1260/252467	0.90	0.70–1.10	8
			Colon	Non-PIO TZD	No non-PIO TZD	1260/252467	1.10	0.80–1.50	
			Rectum	PIO	No PIO	390/252467	1.20	0.80–1.80	
			Rectum	Non-PIO TZD	No non-PIO TZD	390/252467	0.70	0.40–1.50	
Oliveria (2008)	U.S.	Cohort	Colorectum	TZD	No TZD	383/191223	1.08	0.86–1.36	7
Govindarajan (2007)	U.S.	Cohort	Colorectum	TZD	No TZD	1137/87678	0.88	0.74–1.05	6
Koro (2007)	U.S.	Case-control	Colon	TZD	No TZD	408/2435	1.15	0.88–1.49	7

TZD: Thiazolidinedione; ROSI: Rosiglitazone; PIO: Pioglitazone; DPP-4i: dipeptidyl-peptidase-4 inhibitors; ADMs: Anti-DM drugs; NOS: Newcastle-Ottawa Scale; RR: Relative risk; CI: Confidence interval; n/r: Not reported; *RR not adjusted

Table 2: Subgroup analysis of studies comparing the association between TZDs and CRC

Outcome	No. of studies	RR (95% CI)	*P*	$P_{heterogeneity}$	I^2 (%)
All observational studies	10	0.91 (0.84, 0.99)	0.03	0.00	82.1
Study design					
Cohort studies	7	0.89 (0.80, 0.99)	0.04	0.00	86.9
Case-control studies	3	0.94 (0.84, 1.05)	0.28	0.23	31.9
Study location					
Western	9	0.96 (0.91-1.01)	0.08	0.06	46.8
US	7	0.94 (0.88-1.01)	0.08	0.52	0.0
Europe	2	0.96 (0.89-1.04)	0.34	0.01	87.2
Asia	1	0.40 (0.29-0.53)	0.00	-	-
Cancer site					
Colon	4	1.00 (0.99-1.02)	0.61	0.41	0.0
Rectum	3	0.98 (0.96-1.01)	0.23	0.41	0.0
Drug					
PIO	3	0.95 (0.89-1.01)	0.11	0.63	0.0
Non-PIO TZD	2	0.88 (0.82-0.95)	0.00	0.65	0.0

RR: Relative risk; CI: confidence interval; ROSI: Rosiglitazone; PIO: Pioglitazone

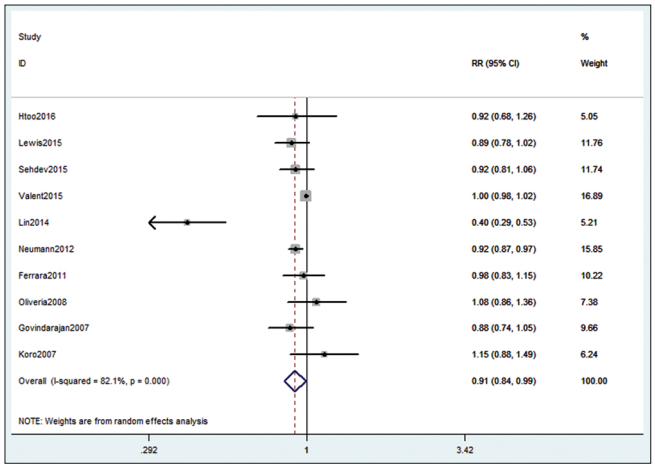

Figure 2: Forest plot showing individual and pooled RRs (95% CIs) in studies comparing CRC risk in patients with DM on TZDs and controls

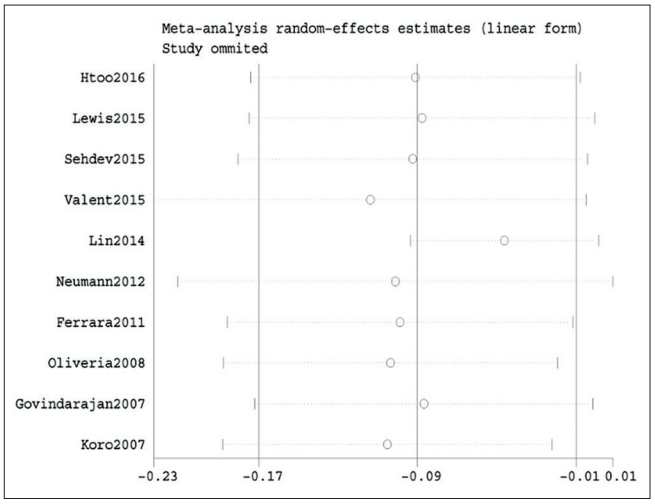

Figure 3: Sensitivity plot showing the effect of exclusion of any study on the magnitude of the summary estimate

$P = 0.98$), study design ($Z = -0.22$, $P = 0.83$), cancer site ($Z = 1.06$, $P = 0.34$), drug type ($Z = -0.96$, $P = 0.38$), CRC cases > 1000 ($Z = 0.37$, $P = 0.73$), or NOS score >6 ($Z = -0.55$, $P = 0.60$) showed no significant results.

Publication bias

Begg's funnel plot was performed to assess the publication bias. The shape of the funnel plot did not reveal any evidence of asymmetry ($P = 0.86$) [Figure 4]. Using nonparametric Duval and Tweedie's trim and fill method, we found no additional undisclosed trials need be performed (data not shown).

DISCUSSION

In this comprehensive meta-analysis of 10 observational studies analyzing the cancer-modifying effect of TZDs in more than two million diabetic patients, we found TZDs were associated with a modest, yet statistically significant, protective association (an estimated 9% reduction) in CRC risk as compared to non-users of TZDs. The consistency of the results as shown in the sensitivity analysis and the lack of publication bias strengthened the results of this meta-analysis.

When restricting to the analysis on study population, we found the antineoplastic association of TZDs use and CRC risk was more pronounced in Asia than US (with a 60% reduction in Asia and a 6% reduction trend in US, respectively). The differences observed between the two regions should be interpreted with caution. First, different dietary habits and cultural behaviors may lead to the differential association in the two populations. Besides, a higher prevalence of central obesity is exhibited in some Asian populations, who are supposed to be more insulin resistant and more responsive to TZDs treatment as compared to Caucasians.[40-42] Moreover, only one study from Taiwan with 351 CRC cases in 32,891 DM patients was represented as an Asian population.[36] The results of other studies based on the Taiwan National Health Insurance Research Database (NHIRD) did not provide

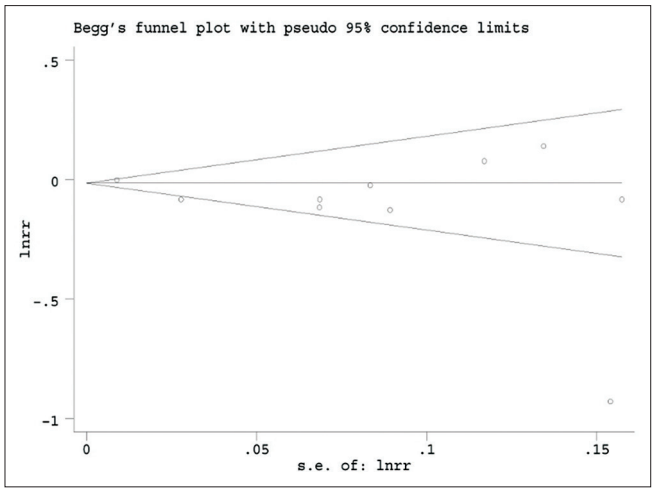

Figure 4: Begg's funnel plot of publication bias test

clear evidence of anti-CRC effect of TZDs.[22,43-45] In view of the above-mentioned facts, more population-based studies assessing the effects of TZDs use on CRC risk in other Asian populations are needed to definitively clarify this issue.

As far as drug type is concerned, the apparent protection from malignancy conferred by non-pioglitazone TZD use (mainly rosiglitazone) was detectable in our study (a 12% reduction in CRC risk). On the other hand, pioglitazone did not protect from malignancy. The observed discrepancies between the two types of TZDs may be due to the differences at biologic level. Pharmacologically, rosiglitazone has PPAR-γ activity, which has shown antiproliferative, apoptotic-inducing, and differentiation-stimulating effects in different malignancies,[10] whereas pioglitazone has dual PPAR-α-γ activities, which have shown carcinogenic effects in animal models, especially for bladder cancer.[46-49] The mediation of cancer initiation and progression through various pathways may also differ between the two TZDs.[50]

Pioglitazone continues to be recommended in current diabetes guidelines,[51] because concerns over bladder cancer conferred by pioglitazone have largely been allayed by recent evidence.[52-54] The side effects of rosiglitazone have limited its use, including weight gain, bone fracture, chronic edema, and heart failure.[55] Considering the positive consequences on CRC risk, the potential implications on the risk/benefit analysis of non-pioglitazone TZDs use should be revaluated.

We could not establish whether TZDs are differentially associated with risk of colon or rectal cancer. Comparisons that have been made for different cancer sites on CRC risk were not statistically significant.

The high statistical heterogeneity observed across studies could be partly explained by differences in study location. However, it could not be accounted for study design, cancer site, drug type, CRC cases, NOS score, or publication year. Besides, substantial heterogeneity was observed in European regions ($P_{heterogeneity}$ = 0.01, I^2 = 87.2%), which may lead to some degree of detection bias.

Nevertheless, generally speaking, our meta-analysis should be interpreted with caution. First, patients in the comparator group (no TZDs) received a variety of ADMs, including insulin, insulin analogs, sulfonylureas, metformin, or other hypoglycemia agents, which may have inherent cancer-modifying effects. For example, insulin or sulfonylurea has been reported to be associated with an increased risk of CRC, whereas metformin may be correlated with a decreased CRC risk.[56] This may result in an overestimation or underestimation of the magnitude of effect on CRC. Second, all studies did not adjust for the same confounders, such as body mass index, dietary habits, or physical activity, which are all major risk factors for CRC. Besides, although many confounders can be controlled and adjusted for in the analysis, most of the included observational studies were based on retrospectively historical medical data. Thus, a complete elimination of bias on details was impossible. Third, pioglitazone and rosiglitazone are two different drugs for cancer risk. Pooling them together creates an obvious lack of drug-specific observational study. Fourth, this meta-analysis was based on published full-text articles; it may be affected by incomplete disclosure, with missing information on a lack of publication with opposite results. Fifth, this meta-analysis did not include randomized controlled trials (RCTs). Due to the small number of CRC cases and the short follow-up duration, previously published RCTs were not adequately powered to detect a significant association of TZDs use and CRC risk.[57,58]

CONCLUSION

In summary, this meta-analysis indicated that the use of TZDs is associated with a significantly decreased risk of CRC. TZDs might be considered as a novel approach in cancer adjuvant therapy. Considering the observed magnitude of CRC risk reduction associated with TZDs use was relatively modest, the number needed in order to treat to prevent one case of CRC would be large. Meanwhile, careful management of individual risk/benefit profiles is needed to limit the exposure to adverse effects of TZDs use. In the future, well-designed studies with larger cohorts are warranted to confirm the potential anti-neoplastic benefit for individuals with diabetes on TZDs treatment.

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Conflicts of interest

There are no conflicts of interest.

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