Article

SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials

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Received: 16 March 2017 / Accepted: 2 June 2017

Abstract

Aims/hypothesis The association between sodium–glucose cotransporter 2 (SGLT2) inhibitors and the risk of cancer in individuals with type 2 diabetes remains uncertain. This study aimed to evaluate the risk of cancer associated with SGLT2 inhibitor treatment of type 2 diabetes.

Methods We systematically searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov from inception to 15 February 2017 to identify eligible randomised controlled trials (RCTs) that report cancer events in individuals with type 2 diabetes treated with SGLT2 inhibitors for at least 24 weeks. We performed pairwise and network meta-analyses as well as a cumulative meta-analysis to calculate ORs and 95% CIs.

Results In total, 580 incidences of cancer among 34,569 individuals were identified from 46 independent RCTs with a mean trial duration of 61 weeks. When compared with comparators (placebo or other active glucose-lowering treatments), SGLT2 inhibitors were not significantly associated with an increased risk of overall cancer (OR 1.14 [95% CI 0.96, 1.36]). For pre-specified cancer types, the risk of bladder cancer might be increased with SGLT2 inhibitors (OR 3.87 [95% CI 1.48, 10.08]), especially empagliflozin (OR 4.49 [95% CI 1.21, 16.73]). Interestingly, canagliflozin might be protective against gastrointestinal cancers (OR 0.15 [95% CI 0.04, 0.60]).

Conclusions/interpretation Current evidence from short-term RCTs did not indicate a significantly increased risk of overall cancer among individuals with type 2 diabetes using SGLT2 inhibitors. Given the short-term trial durations and uncertainty of evidence, future long-term prospective studies and post-marketing surveillance studies are warranted.

Key words

Cancer, Meta-analysis, Randomised controlled trials, SGLT2 inhibitors, Systematic review, Type 2 diabetes

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
RCT	Randomised controlled trial
SGLT2	Sodium–glucose cotransporter 2
SUCRA	Surface under the cumulative ranking curve

Introduction

Growing evidence suggests that people with type 2 diabetes are at elevated risk for cancer [1, 2]. Though the mechanisms remain unknown, several carcinogenic processes involving the pathophysiology of type 2 diabetes may explain the increased cancer risk in these individuals. Certain diabetes risk factors (e.g. obesity) play a significant role in increasing cancer risk [3]. Furthermore, several glucose-lowering drugs have the potential to affect cancer risk [1]. For example, metformin therapy has been shown to decrease the risk of cancer, while other drugs may increase the risk of specific cancers [4]. Recently, concern was raised about a potential link between thiazolidinediones (e.g. pioglitazone) and bladder cancer [5]. However, no clear conclusions have been drawn regarding a causal relationship [6].

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral glucose-lowering drugs for treating type 2 diabetes [7]. They decrease plasma glucose levels by selectively inhibiting renal glucose reabsorption and increasing urinary glucose excretion [8, 9]. In addition to their hypoglycaemic effects, SGLT2 inhibitors also offer additional benefits for weight loss and reduction of BP [10]. In clinical practice, SGLT2 inhibitors are recommended in combination with metformin and/or other agents as second- or third-line therapy if an individual fails to achieve the target level of glycaemic control with one or more other agents [11].

In 2011, a regulatory submission presented to the US Food and Drug Association (FDA) raised concerns regarding the risk of bladder and breast cancer associated with dapagliflozin [12]. An imbalance between dapagliflozin and comparators in the risk of bladder and breast cancer was observed in the 2011 report [12]. However, a recent pooled analysis of 21 clinical trials suggested that the increased risk of bladder and breast cancers might be an absence of detailed diagnosis prior to randomisation rather than a causal relationship [13]. An elevated risk of bladder or breast cancer has not been reported for other SGLT2 inhibitors in humans [14], although it was indicated that they might induce tumours in rats [15] and male mice [16]. Given conflicting results regarding possible associations with rare cancers, individual trials are not powerful enough to clarify the cancer risk associated with the use of SGLT2 inhibitors. We therefore performed a pairwise meta-analysis of all available head-to-head randomised controlled trial (RCT) data to test the hypothesis that SGLT2 inhibitors affect cancer risk by comparing SGLT2 inhibitors with placebo in individuals with type 2 diabetes. We also carried out a network meta-analysis to evaluate the comparative effects of SGLT2 inhibitors on cancer risk using a combination of direct and indirect evidence based on a common comparator (e.g. placebo).

Methods

The network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions [17] and was registered with PROSPERO (number CRD42016045707).

Search strategy and study selection We comprehensively searched PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 15 February 2017 to identify eligible RCTs using the following search terms: random*, RCTs, sodium–glucose cotransporter, SGLT2, SGLT-2 and the names of ten individual SGLT2 inhibitors. No restrictions were applied in terms of language, date or publication. In addition, we identified other published and unpublished trials by manually searching the references of included trials and relevant meta-analyses as well as ClinicalTrials.gov. Detailed information about our search strategy is presented in the electronic supplementary material (ESM) Table 1. Furthermore, we reviewed the submission documents provided to the US FDA or European Medicines Agency (EMA) for more data. Two reviewers independently selected the studies according to the following inclusion criteria: (1) RCTs that compared SGLT2 inhibitors with placebo or other active glucose-lowering treatments in adults with type 2 diabetes; (2) trial duration ≥24 weeks; and (3) studies reporting any cancer as an outcome. Our primary outcome measure was risk of overall cancer and the secondary outcomes included risk of pre-specified cancer types including skin, breast, respiratory, gastrointestinal, bladder, prostate and renal (ESM Table 2). Any cancer event was reported by investigators as a serious adverse event identified in the database using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA). Conference abstracts were excluded because of the lack of detailed information on the trials' characteristics, definition of outcome and trial quality.

Data extraction and quality assessment Two reviewers (H. Tang and W. Shi) independently extracted the following data: first author, publication year, study characteristics (country of origin, funding and follow-up), characteristics of participants (inclusion criteria, background treatments, mean age, proportion of men, duration of type 2 diabetes, baseline HbA_{1c} [%] and BMI), interventions (type and dose of SGLT2 inhibitors), comparators and the incidence of cancer.

If multiple reports from the same population were retrieved, only the most complete and/or most recently reported data were used. If cancer events were not reported in the manuscripts, data from regulatory submissions or the 'Serious adverse events' section on the ClinicalTrials.gov were extracted. In addition, if pre-specified cancer outcomes were not reported on ClinicalTrials.gov, the incidence of the events was assumed to be zero. If two different comparison groups of non-overlapping participants (i.e. A vs B and C vs D) were included in the same report, each comparison was considered separately. If three arms (i.e. A vs B vs A+B) were evaluated in the RCTs, only two arms (A vs B) were included.

The Cochrane risk of bias tool was used to assess the quality of RCTs based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) [18]. Two reviewers (H. Tang and W. Shi) independently reviewed and judged each domain as low risk of bias, high risk of bias or unclear risk of bias.

Statistical analysis Both pairwise and network meta-analyses were performed to calculate the ORs and 95% CIs of overall cancer or pre-specified types of cancer. All meta-analyses were performed with STATA (version 14; Stata, College Station, TX, USA).

For the pairwise meta-analysis, Peto's method was used to calculate the ORs for direct comparisons between therapeutic regimens to account for low event rates [19]. An I^2 statistic was used to evaluate the presence of between-study heterogeneity, with an I^2 of <25%, ≥25 and <75%, and ≥75% indicating low, medium and high heterogeneity, respectively [20]. The source of heterogeneity was further explored in the following pre-specified subgroups: (1) type of SGLT2 inhibitors (canagliflozin vs dapagliflozin vs empagliflozin); (2) type of control groups (placebo vs other active treatment); (3) length of trial duration (<52 vs ≥52 weeks); (4) mode of therapy (SGLT2 inhibitor monotherapy vs SGLT2 inhibitor add-on therapy); (5) race/ethnicity (white vs Asian); (6) mean age (≥60 years vs <60 years); (7) mean BMI (≥30 kg/m^2 vs <30 kg/m^2); and (8) mean percentage of male participants (≥50% vs <50%). Additionally, a meta-regression was performed to explore whether the above variables influenced the size of intervention effects. A sensitivity analysis was carried out by comparing two statistical methods (Peto vs Manthel–Haenszel method), comparing two effect measures (OR vs RR) or excluding the largest trial (EMPA-REG OUTCOME Trial) [21]. In addition, a cumulative meta-analysis was performed to explore the evolution of the evidence with the accumulation of data over time. Finally, potential publication bias was assessed by the Begg's and Egger's tests, as well as visual inspection of the funnel plots.

For indirect and mixed comparisons, a network meta-analysis with a random-effects model using the 'mvmeta' command and programmed STATA routines was used to compare different interventions [22, 23]. For zero-event RCT, a 0.5 zero-cell correction was applied before meta-analysis [24]. To rank the SGLT2 inhibitors for a specified outcome, we estimated the relative ranking probabilities of each treatment using the surface under the cumulative ranking curve (SUCRA) and mean ranks. For incidence of cancer, large SUCRA probability and lower mean rank indicate a safer intervention [25]. The heterogeneity variance (tau) estimated by a restricted maximum likelihood method was employed to investigate between-study heterogeneity in the network meta-analysis [26].

To check for the presence of inconsistency, a loop inconsistency–specific approach was introduced to evaluate the difference between direct and indirect estimates for a specific comparison [27]. To check the assumption of consistency in the entire network, a design-by-treatment interaction model using

the χ^2 test was used [28]. In addition, a comparison-adjusted funnel plot was used to assess small-study effects within a network of interventions [29].

Results

Study selection and study characteristics A total of 2450 citations were retrieved through electronic search. Of which, 201 potentially eligible reports were identified by reviewing study titles and abstracts. After fully reviewing the potential trials and searching lists of references and ClinicalTrials.gov. Finally, 45 articles with 46 independent RCTs were eligible and included in this meta-analysis [21, 30-73] (ESM Fig. 1). Two articles provided two independent data sets for two different comparisons which we considered separately [42, 58]. Because data from two trials were presented together on ClinicalTrials.gov, we included the combined data as one independent trial [70, 71].

The study characteristics are summarised in ESM Table 3. In total, 34,569 participants from 46 independent trials were randomly assigned to one of three SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) or comparators (placebo or other active glucose-lowering treatment). Sample sizes of individual trials were between 180 and 7020 participants, and the mean trial duration was 61 weeks (range 24–160 weeks). The spread of trial duration for each SGLT2 inhibitors is presented on ESM Fig. 2.

The risk of bias for the 46 RCTs is summarised as follows (ESM Fig. 3): 36 RCTs reported adequate random sequence generation; 33 RCTs reported adequate allocation concealment; masking conditions were high in three RCTs, of which two RCTs were open-label in their extended periods and one RCT set one arm with open-label; finally, all RCTs were judged as unclear for selective reporting because none included cancer events as outcomes of interest. All of the trials were funded by industrial companies.

Pairwise meta-analysis Forty-six trials reported the incidence of overall cancer with a total of 580 events among 34,569 participants (a crude event rate of 1.68%). Cancer rates were 1.78% in the SGLT2 inhibitor treatment groups and 1.55% in the comparator groups. The results of overall and subgroup pairwise meta-analysis are presented in Fig. 1. There was no significant difference between SGLT2 inhibitors and comparators in overall cancer risk (OR 1.14 [95% CI 0.96, 1.36]), with low statistical heterogeneity (I^2=19.2%) (ESM Fig. 4). The pre-specified subgroup analyses showed that SGLT2 inhibitors were significantly associated with increased risk of overall cancer only in obese participants with a mean BMI ≥30 kg/m^2 (OR 1.23 [95% CI 1.02, 1.48]) (Fig. 1). We found no significant difference between SGLT2 inhibitors and placebo (OR 1.17 [95% CI 0.96, 1.41]) and between SGLT2 inhibitors and other active treatments (OR 1.03 [95% CI 0.67, 1.57]). Our meta-regression analysis indicated that none of the pre-specified factors, significantly influenced the sizes of treatment effects (all p>0.05). There was low heterogeneity among studies (I^2 range 0–53.1%). Our

cumulative meta-analysis based on publication year showed that SGLT2 inhibitors were not significantly associated with increased risk of overall cancer (Fig. 2).

In the sensitivity analysis, the results remained robust to different pairwise meta-analysis methods and the exclusion of the largest trial (EMPA-REG OUTCOME Trial) (OR 1.03 [95% CI 0.81, 1.33]) (ESM Table 4 and ESM Fig. 5). Moreover, our analysis yielded no evidence of substantial publication bias, based on the Egger's test (p=0.31), Begg's test (p=0.72), and a visual inspection of the funnel plot (ESM Fig. 6).

When pre-specified types of cancer were analysed, SGLT2 inhibitors were significantly associated with increased risk of bladder cancer (OR 3.87 [95% CI 1.48, 10.08]), particularly in the comparison of empagliflozin vs comparators (OR 4.49 [95% CI 1.21, 16.73]) (Fig. 3). Canagliflozin was significantly associated with lower risk of gastrointestinal cancers than comparators (OR 0.15 [95% CI 0.04, 0.60]) (Fig. 3). No significant differences between SGLT2 inhibitors and comparators were observed in the risks of other pre-specified cancer types (Fig. 3). For bladder cancer risk, a further subgroup analysis indicated a significantly increased risk in the trials with durations ≥52 weeks (OR 4.80 [95% CI 1.74, 13.29]), mean BMI ≥30 kg/m^2 (OR 4.65 [95% CI 1.40, 15.48]), or mean age ≥60 years (OR 3.57 [95% CI 1.09, 11.66]) (ESM Fig. 7). In addition, there was low to medium heterogeneity among studies (I^2 range 0–52.1%).

Network meta-analysis The trial network plot and the results of network meta-analysis for overall cancer risk are presented in ESM Fig. 8 and Fig. 4, respectively. Compared with placebo, none of canagliflozin (OR 0.74 [95% CI 0.35, 1.55]), dapagliflozin (OR 1.02 [95% CI 0.68, 1.53]) and empagliflozin (OR 1.03 [95% CI 0.65, 1.64]) were significantly associated with increased risk of overall cancer; the incidence of overall cancer was similar among these three SGLT2 inhibitors. In the generated hierarchies of treatment effects based on the SUCRA probabilities, canagliflozin was ranked the lowest risk for overall cancer among these SGLT2 inhibitors (ESM Table 5). There was low between-study heterogeneity (tau = 0.25) (ESM Table 6), no inconsistency between direct and indirect estimates (all 95% CIs across zero) (ESM Table 7) and no global inconsistency within any network (p=0.83) (ESM Table 8). In addition, the comparison-adjusted funnel plot indicated the absence of small-study effects (ESM Fig. 9).

When different types of cancer were analysed (ESM Figs 10–16), canagliflozin was significantly associated with a decreased risk of gastrointestinal cancer compared with placebo (OR 0.31 [95% CI 0.11, 0.88]), empagliflozin (OR 0.25 [95% CI 0.08, 0.75]) or other active treatments (OR 0.28 [95% CI 0.09, 0.88]) (ESM Fig. 11), and canagliflozin was placed as the safest intervention among these medications for its largest SUCRA probability and lowest mean rank (ESM Table 5). In contrast to the results from pairwise meta-analysis, empagliflozin was not significantly associated with an increased risk of bladder cancer compared with placebo (OR 0.52 [95% CI 0.14, 1.90]) (ESM Fig.

12). There was low between-study heterogeneity (tau ≈ 0) (ESM Table 6), no inconsistency between direct and indirect estimates (all 95% CIs across zero) (ESM Table 7) and no global inconsistency within any network (p>0.05) (ESM Table 8).

Discussion

Our meta-analysis included 46 RCTs that reported 580 incidences of cancer among 34,569 people with type 2 diabetes. We found that SGLT2 inhibitors were not significantly associated with an increased risk of overall cancer during a mean trial duration of 61 weeks. Our meta-regression analysis identified that none of pre-specified factors significantly influenced the sizes of treatment effects. However, there was some evidence to suggest that SGLT2 inhibitors might increase the cancer risk in obese participants (BMI ≥30 kg/m^2). For pre-specified cancer types, SGLT2 inhibitors might significantly increase bladder cancer risk, particularly empagliflozin. The increased risk was observed in the trials with a duration ≥52 weeks and in obese participants (BMI ≥30 kg/m^2). Interestingly, there was suggestive evidence that canagliflozin was significantly associated with decreased risk of gastrointestinal cancer. However, given the short durations of the included RCTs, estimates of cancer caused by longer exposure to SGLT2 inhibitors are not possible. Thus, our results should be interpreted with caution.

Our meta-analysis of current available evidence from RCTs indicates that SGLT2 inhibitor treatment is not associated with a significantly increased risk of overall cancer. Our results are consistent with one previous meta-analysis of data from regulatory submissions and scientific reports, which also showed no effect on risk of cancer [74]. One pooled analysis of 21 phase 2b/3 clinical trials showed that the overall incidence of malignancies was balanced between a dapagliflozin group and comparator groups [13]. Additionally, the overall incidence of bladder, breast and renal cancers was not increased by canagliflozin relative to comparators in a pooled analysis of eight phase 3 clinical trials [14]. Furthermore, preclinical studies did not find increased hyperplasia or neoplasia in the urinary bladder mucosa, urogenital tract or kidney in SGLT2 knockout mice compared with wild-type mice [75]. However, our results included only 580 incidences from 46 short-term RCTs with a mean trial duration of 61 weeks (range 24–160 weeks). Furthermore, we observed a non-significant risk increase among individuals using SGLT2 inhibitors with a lower border of CI of 0.96 (OR 1.17 [95% CI 0.96, 1.41]). We cannot completely rule out the possibility of an increased cancer risk. Our findings need to be confirmed in large trials such as CANVAS (canagliflozin; NCT01032629) and DECLARE-TIMI58 (dapagliflozin; NCT01730534), as well as in long-term observational studies.

Interestingly, our meta-analysis of direct and indirect evidence showed that canagliflozin was significantly associated with a decreased risk of gastrointestinal cancer. SGLT1 has been found to be overexpressed in many cancers [76] and SGLT2 is functionally expressed in pancreatic and prostate adenocarcinomas [77]. SGLTs, especially SGLT1, have been shown to play an important role in

cancer cell survival through glucose uptake [77]. Canagliflozin is not only a potent SGLT2 inhibitor but also possesses potent SGLT1 inhibitory activity [76]. SGLT1 is expressed mainly in the gastrointestinal tract, but also in the kidneys and heart, while SGLT2 is highly selectively expressed in the kidneys and less so in the gastrointestinal tract [78]. Therefore, these findings suggest that canagliflozin may protect against gastrointestinal cancer by suppressing the expression of both SGLT1 and SGLT2 in the gastrointestinal tract. In a study of human colon cancer cells not expressing UGT1A9, which encodes the enzyme for metabolising SGLT2 inhibitors, dapagliflozin significantly reduced the number of colon cells [79]. However, our meta-analysis did not detect a decreased risk of gastrointestinal cancer with the use of dapagliflozin or empagliflozin. This might reflect the higher selectivity for SGLT2 vs SGLT1 exhibited by empagliflozin and dapagliflozin compared with canagliflozin [76], or the small number of incidences of gastrointestinal cancer observed. Further prospective studies are needed to determine the potential effects of SGLT2 inhibitors on the risk of gastrointestinal cancer.

An increased risk of bladder and breast cancer remains a safety issue associated with SGLT2 inhibitors. Our pairwise meta-analysis showed that SGLT2 inhibitors (particularly empagliflozin) were significantly associated with bladder cancer; although this was not confirmed in the network meta-analysis. Most incidences of bladder cancer were identified from the EMPA-REG OUTCOME Trial (empagliflozin: six incidences of bladder cancer, two incidences of bladder transitional cell carcinoma and one incidence of bladder cancer recurrent; placebo: zero incidences) [21]. An increased risk of bladder cancer was observed in the individuals taking empagliflozin compared with placebo in this trial [21], which was consistent with the findings on dapagliflozin in the regulatory report submitted to the US FDA [12]. However, our meta-analysis did not find a significantly increased risk of bladder cancer with dapagliflozin or canagliflozin. One pooled analysis of eight phase 3 clinical trials based on regulatory submissions (canagliflozin: five incidences; comparators: four incidences) showed that the incidence of bladder cancer was no higher with canagliflozin than with comparators [14]. The mechanisms underlying the elevated risk of bladder cancer associated with SGLT2 inhibitors remain unclear. Diabetes and obesity are indeed risk factors for bladder cancer, and increased rates of glycosuria and urinary tract infections related to SGLT2 inhibitor use may be responsible for the observed increased risk [14]. We found a significantly increased risk of bladder cancer among obese participants (BMI $\geq$30 kg/m^2) or the trials with a duration $\geq$52 weeks. Our meta-analysis did not detect a significantly increased risk of breast cancer with the use of SGLT2 inhibitors compared with comparators. However, the possibility of an increased risk cannot be excluded, as the duration of the included RCTs is probably insufficient to address these safety issues conclusively. Future large long-term RCTs and real-world data are required to clarify the association between SGLT2 inhibitors and the risk of pre-specified cancer types (especially bladder cancer).

Several pre-specified risk factors (e.g. ethnicity, sex, BMI and age) were further explored in our meta-regression analysis. None of the results were significant. However, in the subgroup analysis, we found that, compared with comparators, SGLT2 inhibitors were significantly associated with an increased risk of overall cancer and bladder cancer in obese participants (BMI ≥30 kg/m^2) but not in normal weight/overweight participants. These disparate findings may be explained by imbalanced sample sizes. It should be noted that the significantly increased risk was largely driven by EMPA-REG OUTCOME Trial [21], which contributed over 50% of the weight to the overall results and even more weight to the subgroup results. Overweight and obesity are risk factors for several types of cancer (e.g. bladder cancer) [80, 81]. Future prospective studies are needed to clarify the subgroup findings. Compared with the null finding regarding overall cancer risk in one previously published meta-analysis [74], our meta-analysis not only showed a non-significantly increased risk of overall cancer associated with SGLT2 inhibitors, but also suggests some novel and important findings: (1) SGLT2 inhibitors in general might increase the risk of overall cancer in obese individuals; (2) SGLT2 inhibitors (especially empagliflozin) might increase the risk of bladder cancer; and (3) canagliflozin might have a protective effect against gastrointestinal cancer.

Our meta-analysis has several advantages: (1) our research question was specific regarding incidence of cancer, including both overall cancer and pre-specific cancer types; (2) this is the first network meta-analysis to comprehensively assess the comparative effects of SGLT2 inhibitors on cancer risk; (3) RCTs from electronic databases were systematically searched and additional data from Clinicaltrials.gov were included; and (4) multiple subgroup analyses, meta-regression and sensitivity analyses were performed to test the robustness of our findings. However, several limitations of our study merit consideration. First, a large number of potentially eligible trials were not included in the meta-analysis because of lack of data on incidence of cancer; however, additional data on ClinicalTrials.gov and regulatory reports submitted to the US FDA and EMA were searched and retrieved to minimise publication bias and outcome-reporting bias. The data for canagliflozin and empagliflozin from regulatory submissions were not included because they only reported the total number of incidences from several trials, which made it difficult to assign these outcomes to each trial. However, these results were considered in the discussion. Second, the exposure or follow-up time in most trials (mean trial duration 61 weeks, range 24–160 weeks) were not adequate to detect incidence of cancer given the long latency period of cancer. The evidence at this point is far from convincing and, therefore, it is likely that the observed associations may be caused by chance and may reflect their effects on late stage carcinogenesis. Third, the quality of our evidence is relatively low as a result of indirect comparisons, inadequate power and wide CIs according to the GRADE system [82]. Furthermore, we cannot rule out any heterogeneity and inconsistency due to sparse cancer events among the trials. It is premature to apply the results of the analyses to clinical practice

and guideline development. Fourth, background treatments and participant characteristics varied among the RCTs and might contribute to heterogeneity, although multiple subgroup analyses were performed to minimise clinical heterogeneity. Finally, the risk of cancer associated with other novel SGLT2 inhibitors remains uncertain as RCT data are lacking.

In conclusion, the current evidence from RCTs does not show a significant association between SGLT2 inhibitors and an increased risk of overall cancer. There is some evidence suggesting that SGLT2 inhibitors (especially empagliflozin) might increase the risk of bladder cancer, while canagliflozin might offer a protective effect against gastrointestinal cancer. However, given the relatively short-term design of the RCTs include in the analysis, the long-term effects of SGLT2 inhibitors on cancer remain uncertain. Future long-term prospective studies and post-marketing surveillance studies are warranted.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding The project described was supported by the Indiana University Health–Indiana University School of Medicine Strategic Research Initiative.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement HT, YS and JH designed the study. HT and WS identified and acquired reports of trials and extracted data. HT, QD, WS, SZ, YS and JH performed all data analyses, checked for statistical inconsistency, and interpreted data. HT, QD, WS, SZ, YS and JH contributed to data interpretation. HT drafted the report and all other authors critically reviewed the report. JH is the guarantor of this work.

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Fig. 1 Pairwise meta-analysis of the effects of SGLT2 inhibitors on the risk of overall cancer. *n*/*N*, number of incidences/number of participants; metareg, meta-regression analysis

Fig. 2 Cumulative meta-analysis of the effects of SGLT2 inhibitors on the risk of overall cancer

Fig. 3 Pairwise meta-analysis of the effects of SGLT2 inhibitors on the risk of pre-specified cancer types. *n*/*N*, number of incidences/number of participants

Fig. 4 Network meta-analysis of the effects of SGLT2 inhibitors on the risk of overall cancer. Common heterogeneity between studies was low (tau = 0.25). ACT, other active treatments; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; PLA, placebo

Figure 1

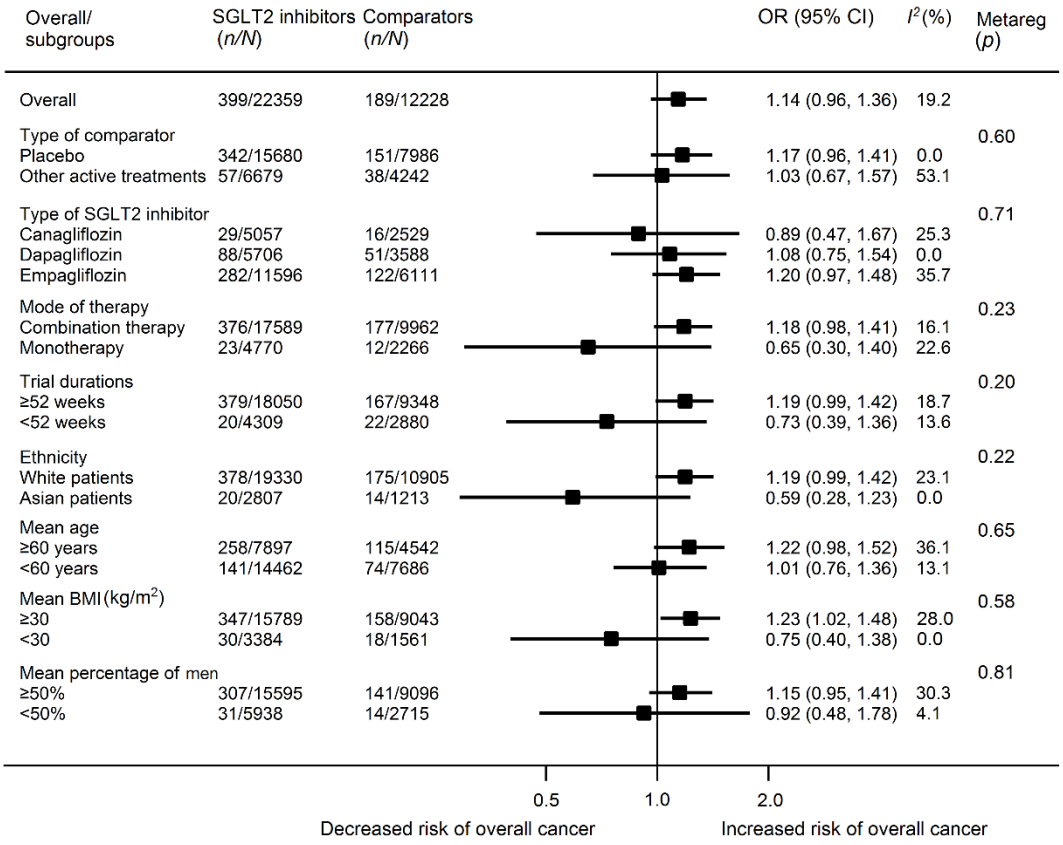

Overall/ subgroups
SGLT2 inhibitors (n/N)
Comparators (n/N)
OR (95% CI)
I²(%)
Metareg (p)
Overall 399/22359 189/12228 1.14 (0.96, 1.36) 19.2
Type of comparator 0.60
Placebo 342/15680 151/7986 1.17 (0.96, 1.41) 0.0
Other active treatments 57/6679 38/4242 1.03 (0.67, 1.57) 53.1
Type of SGLT2 inhibitor 0.71
Canagliflozin 29/5057 16/2529 0.89 (0.47, 1.67) 25.3
Dapagliflozin 88/5706 51/3588 1.08 (0.75, 1.54) 0.0
Empagliflozin 282/11596 122/6111 1.20 (0.97, 1.48) 35.7
Mode of therapy 0.23
Combination therapy 376/17589 177/9962 1.18 (0.98, 1.41) 16.1
Monotherapy 23/4770 12/2266 0.65 (0.30, 1.40) 22.6
Trial durations 0.20
≥52 weeks 379/18050 167/9348 1.19 (0.99, 1.42) 18.7
<52 weeks 20/4309 22/2880 0.73 (0.39, 1.36) 13.6
Ethnicity 0.22
White patients 378/19330 175/10905 1.19 (0.99, 1.42) 23.1
Asian patients 20/2807 14/1213 0.59 (0.28, 1.23) 0.0
Mean age 0.65
≥60 years 258/7897 115/4542 1.22 (0.98, 1.52) 36.1
<60 years 141/14462 74/7686 1.01 (0.76, 1.36) 13.1
Mean BMI (kg/m²) 0.58
≥30 347/15789 158/9043 1.23 (1.02, 1.48) 28.0
<30 30/3384 18/1561 0.75 (0.40, 1.38) 0.0
Mean percentage of men 0.81
≥50% 307/15595 141/9096 1.15 (0.95, 1.41) 30.3
<50% 31/5938 14/2715 0.92 (0.48, 1.78) 4.1
0.5
1.0
2.0
Decreased risk of overall cancer
Increased risk of overall cancer

Figure 2

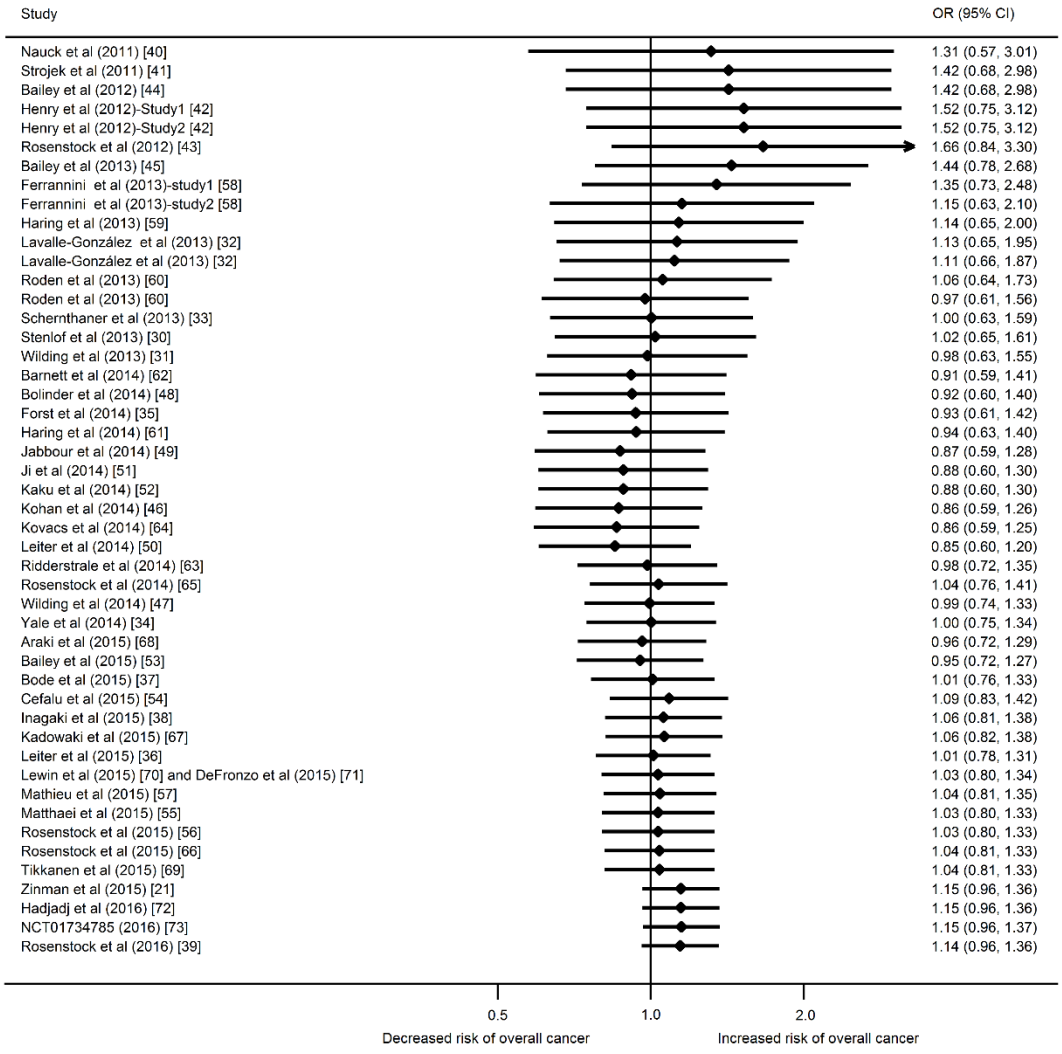

Study
OR (95% CI)
Nauck et al (2011) [40] 1.31 (0.57, 3.01)
Strojek et al (2011) [41] 1.42 (0.68, 2.98)
Bailey et al (2012) [44] 1.42 (0.68, 2.98)
Henry et al (2012)-Study1 [42] 1.52 (0.75, 3.12)
Henry et al (2012)-Study2 [42] 1.52 (0.75, 3.12)
Rosenstock et al (2012) [43] 1.66 (0.84, 3.30)
Bailey et al (2013) [45] 1.44 (0.78, 2.68)
Ferrannini et al (2013)-study1 [58] 1.35 (0.73, 2.48)
Ferrannini et al (2013)-study2 [58] 1.15 (0.63, 2.10)
Haring et al (2013) [59] 1.14 (0.65, 2.00)
Lavalle-González et al (2013) [32] 1.13 (0.65, 1.95)
Lavalle-González et al (2013) [32] 1.11 (0.66, 1.87)
Roden et al (2013) [60] 1.06 (0.64, 1.73)
Roden et al (2013) [60] 0.97 (0.61, 1.56)
Schernthaner et al (2013) [33] 1.00 (0.63, 1.59)
Stenlof et al (2013) [30] 1.02 (0.65, 1.61)
Wilding et al (2013) [31] 0.98 (0.63, 1.55)
Barnett et al (2014) [62] 0.91 (0.59, 1.41)
Bolinder et al (2014) [48] 0.92 (0.60, 1.40)
Forst et al (2014) [35] 0.93 (0.61, 1.42)
Haring et al (2014) [61] 0.94 (0.63, 1.40)
Jabbour et al (2014) [49] 0.87 (0.59, 1.28)
Ji et al (2014) [51] 0.88 (0.60, 1.30)
Kaku et al (2014) [52] 0.88 (0.60, 1.30)
Kohan et al (2014) [46] 0.86 (0.59, 1.26)
Kovacs et al (2014) [64] 0.86 (0.59, 1.25)
Leiter et al (2014) [50] 0.85 (0.60, 1.20)
Ridderstrale et al (2014) [63] 0.98 (0.72, 1.35)
Rosenstock et al (2014) [65] 1.04 (0.76, 1.41)
Wilding et al (2014) [47] 0.99 (0.74, 1.33)
Yale et al (2014) [34] 1.00 (0.75, 1.34)
Araki et al (2015) [68] 0.96 (0.72, 1.29)
Bailey et al (2015) [53] 0.95 (0.72, 1.27)
Bode et al (2015) [37] 1.01 (0.76, 1.33)
Cefalu et al (2015) [54] 1.09 (0.83, 1.42)
Inagaki et al (2015) [38] 1.06 (0.81, 1.38)
Kadowaki et al (2015) [67] 1.06 (0.82, 1.38)
Leiter et al (2015) [36] 1.01 (0.78, 1.31)
Lewin et al (2015) [70] and DeFronzo et al (2015) [71] 1.03 (0.80, 1.34)
Mathieu et al (2015) [57] 1.04 (0.81, 1.35)
Matthaei et al (2015) [55] 1.03 (0.80, 1.33)
Rosenstock et al (2015) [56] 1.03 (0.80, 1.33)
Rosenstock et al (2015) [66] 1.04 (0.81, 1.33)
Tikkanen et al (2015) [69] 1.04 (0.81, 1.33)
Zinman et al (2015) [21] 1.15 (0.96, 1.36)
Hadjadj et al (2016) [72] 1.15 (0.96, 1.36)
NCT01734785 (2016) [73] 1.15 (0.96, 1.37)
Rosenstock et al (2016) [39] 1.14 (0.96, 1.36)
0.5
1.0
2.0
Decreased risk of overall cancer
Increased risk of overall cancer

Figure 3

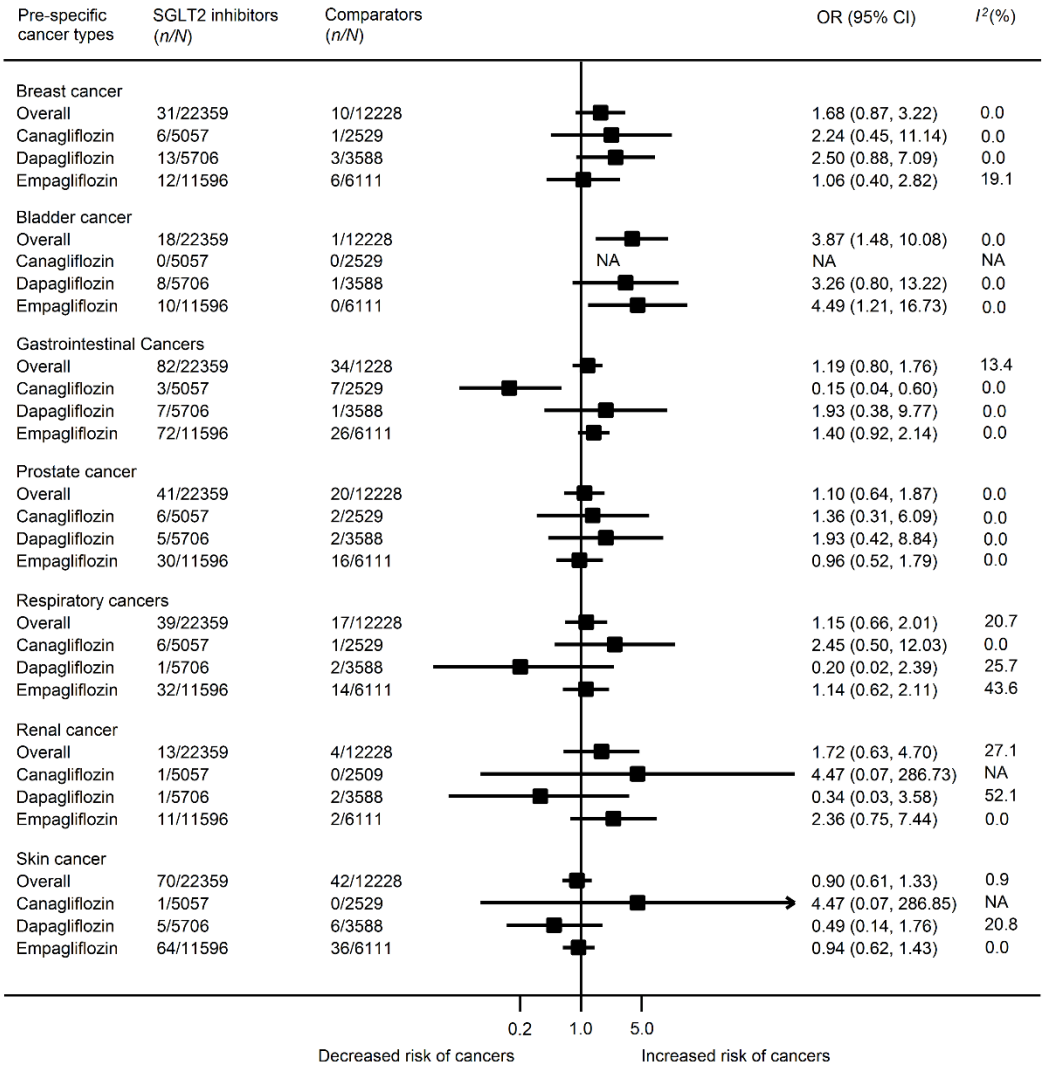
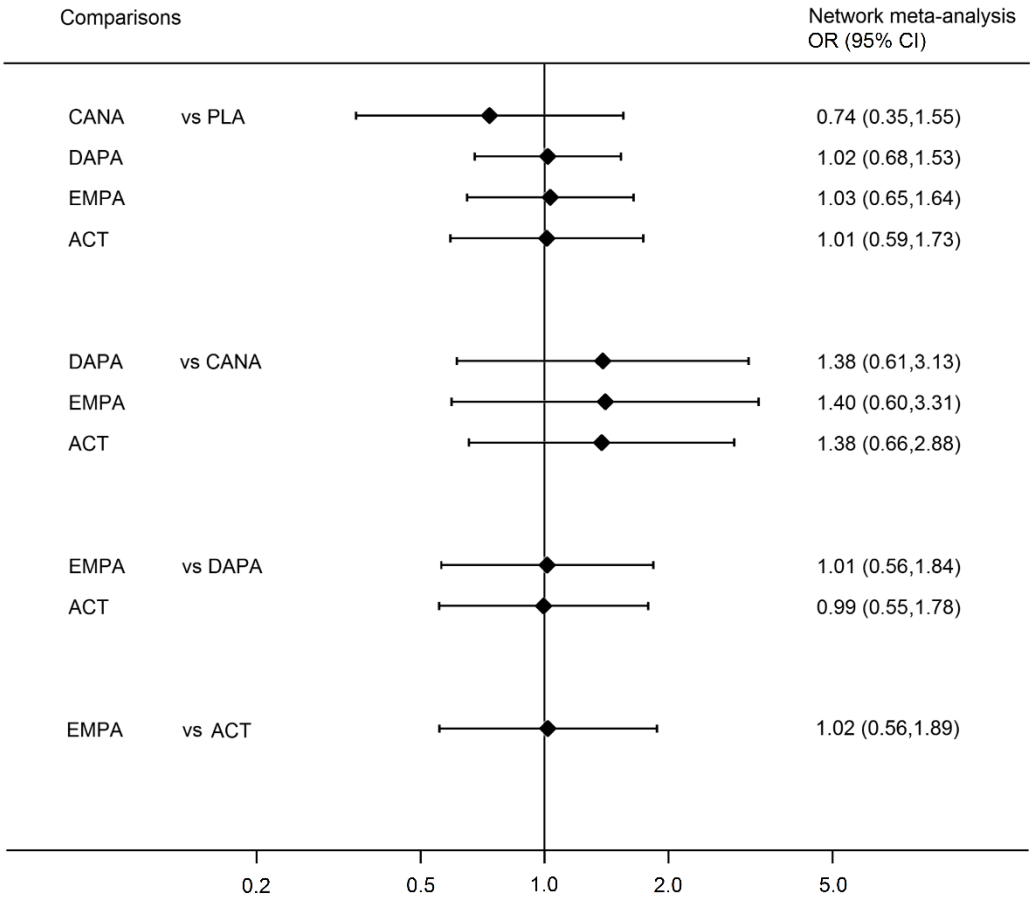

Pre-specific cancer types
SGLT2 inhibitors (n/N)
Comparators (n/N)
OR (95% CI)
I²(%)
Breast cancer
Overall 31/22359 10/12228 1.68 (0.87, 3.22) 0.0
Canagliflozin 6/5057 1/2529 2.24 (0.45, 11.14) 0.0
Dapagliflozin 13/5706 3/3588 2.50 (0.88, 7.09) 0.0
Empagliflozin 12/11596 6/6111 1.06 (0.40, 2.82) 19.1
Bladder cancer
Overall 18/22359 1/12228 3.87 (1.48, 10.08) 0.0
Canagliflozin 0/5057 0/2529 NA NA NA
Dapagliflozin 8/5706 1/3588 3.26 (0.80, 13.22) 0.0
Empagliflozin 10/11596 0/6111 4.49 (1.21, 16.73) 0.0
Gastrointestinal Cancers
Overall 82/22359 34/1228 1.19 (0.80, 1.76) 13.4
Canagliflozin 3/5057 7/2529 0.15 (0.04, 0.60) 0.0
Dapagliflozin 7/5706 1/3588 1.93 (0.38, 9.77) 0.0
Empagliflozin 72/11596 26/6111 1.40 (0.92, 2.14) 0.0
Prostate cancer
Overall 41/22359 20/12228 1.10 (0.64, 1.87) 0.0
Canagliflozin 6/5057 2/2529 1.36 (0.31, 6.09) 0.0
Dapagliflozin 5/5706 2/3588 1.93 (0.42, 8.84) 0.0
Empagliflozin 30/11596 16/6111 0.96 (0.52, 1.79) 0.0
Respiratory cancers
Overall 39/22359 17/12228 1.15 (0.66, 2.01) 20.7
Canagliflozin 6/5057 1/2529 2.45 (0.50, 12.03) 0.0
Dapagliflozin 1/5706 2/3588 0.20 (0.02, 2.39) 25.7
Empagliflozin 32/11596 14/6111 1.14 (0.62, 2.11) 43.6
Renal cancer
Overall 13/22359 4/12228 1.72 (0.63, 4.70) 27.1
Canagliflozin 1/5057 0/2509 4.47 (0.07, 286.73) NA
Dapagliflozin 1/5706 2/3588 0.34 (0.03, 3.58) 52.1
Empagliflozin 11/11596 2/6111 2.36 (0.75, 7.44) 0.0
Skin cancer
Overall 70/22359 42/12228 0.90 (0.61, 1.33) 0.9
Canagliflozin 1/5057 0/2529 4.47 (0.07, 286.85) NA
Dapagliflozin 5/5706 6/3588 0.49 (0.14, 1.76) 20.8
Empagliflozin 64/11596 36/6111 0.94 (0.62, 1.43) 0.0
0.2
1.0
5.0
Decreased risk of cancers
Increased risk of cancers

Figure 4


Comparisons
Network meta-analysis
OR (95% CI)
CANA vs PLA
0.74 (0.35,1.55)
DAPA
1.02 (0.68,1.53)
EMPA
1.03 (0.65,1.64)
ACT
1.01 (0.59,1.73)
DAPA vs CANA
1.38 (0.61,3.13)
EMPA
1.40 (0.60,3.31)
ACT
1.38 (0.66,2.88)
EMPA vs DAPA
1.01 (0.56,1.84)
ACT
0.99 (0.55,1.78)
EMPA vs ACT
1.02 (0.56,1.89)
0.2
0.5
1.0
2.0
5.0