Sodium–glucose cotransporter 2 inhibitors and risk of cancer in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

Running title: SGLT2 inhibitors and risk of cancer

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Abstract

Aims/hypothesis The association between Sodium-glucose cotransporter 2 (SGLT2) inhibitors and risk of cancer in patients with type 2 diabetes remains uncertain. This study aimed to evaluate the cancer risk associated with SGLT2 inhibitors.

Methods We systematically searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to February 15, 2017 to identify eligible randomized controlled trials (RCTs) that report cancer events in type 2 diabetes patients 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 their odds ratios (ORs) and 95% confidence intervals (CIs).

Results In total, 580 cancer cases among 34,569 patients were identified from 46 independent RCTs with a mean trial duration of 61 weeks. When compared to comparators (placebo or other active anti-diabetic treatments), SGLT2 inhibitors were not significantly associated with increased risk of overall cancer (OR 1.14 [95% CI 0.96, 1.36]). For pre-specified cancer types, SGLT2 inhibitors might increase risk of bladder cancer (OR 3.87 [95% CI 1.48, 10.08]), especially for 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 type 2 diabetes patients 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.

Keywords SGLT2 inhibitors; Type 2 diabetes; Cancer; Meta-analysis; randomized controlled trials

Abbreviations

CENTRAL Cochrane Central Register of Controlled Trials

CI confidence interval

RCTs randomized controlled trials

SGLT2 Sodium glucose cotransporter 2

SUCRA surface under the cumulative ranking curve

Introduction

Growing evidence suggests that patients with type 2 diabetes are at elevated risk for cancer [1, 2]. Though the clear mechanisms remain unknown, several carcinogenic processes involving the pathophysiology of type 2 diabetes may explain increased cancer risk with type 2 diabetes. Certain diabetes risk factors (e.g., obesity) play a significant role in increasing cancer risk [3]. Furthermore, several antidiabetic drugs have the potential to affect cancer risk [1]. For example, metformin therapy has been shown to decrease the risk of cancer, while other such drugs may increase the risk of specific cancers [4]. Recently, concern was raised about a potential link between thiazolidinedione (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 antidiabetic 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 hypoglycemic effects, SGLT2 inhibitors also offer additional benefits for weight loss and reduction of blood pressure [10]. In clinical practice, SGLT2 inhibitors are recommended combination with metformin and/or other agents as second-line or third-line choices after not achieving the target level of glycemic control of one or more other agents [11].

In 2011, a regulatory submission presented to the U.S. Food and Drug Association (FDA) raised concerns regarding the risk of bladder cancer and breast cancer associated with dapagliflozin [12]. An imbalance between dapagliflozin and comparators in the risk of bladder cancer 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 randomization rather than a causal relationship[13]. No elevated risk of bladder or breast cancer was reported for other SGLT2 inhibitors in humans[14] , although it was indicated that they might induce tumors in rats [15] and male mice [16]. Given conflicting results regarding possible associations with rare cancers, individual trials were 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 randomized controlled trials (RCTs) data to test the hypothesis that SGLT2 inhibitors affect cancer risk by comparing SGLT2 inhibitors with placebo in patients with type 2 diabetes. We also carried out a network meta-analysis to evaluate the comparative effects of SGLT2 inhibitors on cancer risk using combination of direct and indirect evidence based on a common comparator (e.g., placebo).

Methods

This network meta-analysis was performed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care 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 February 15, 2017 to identify eligible RCTs using the following search terms: random*, RCTs, sodium–glucose cotransporter, SGLT2, SGLT-2, and the names of 10 individual SGLT2 inhibitors. No restrictions were applied in terms of language, date, or publication.

In addition, we also 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 on **ESM Table 1**. Furthermore, we reviewed the submission documents provided to the U.S. 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 antidiabetic treatments in adult patients with type 2 diabetes; 2) trial durations ≥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 due to lack of detailed information on the trials' characteristics, definition of outcome, and trial quality.

Data extraction and quality assessment Two reviewers (HT and WS) independently extracted the following data: first author, publication year, study characteristics (country of origin, funding, and follow-up), characteristics of patients (inclusion criteria, background treatments, mean age, proportion of men, duration of type 2 diabetes, baseline HbA1c%, and body mass index [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 patients (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 (HT and WS) 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 their odds ratios (ORs) and 95% confidence intervals (CIs) of overall cancer or pre-specified types of cancer. All meta-analyses were performed with STATA (Version 14; Stata Corp., College Station, TX).

For pairwise meta-analysis, Peto’s method was used to calculate the ORs for direct comparisons between therapeutic regimens due to low event rate [19]. An I^2 statistic was used to evaluate the presence of between-study heterogeneity, with 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 added on therapy); 5) race/ethnicity (White *vs.* Asian); 6) mean age (≥ 60 years *vs.* < 60 years); 7) mean BMI (≥ 30 *vs.* < 30 kg/m^2); and 8) mean percentage of male subjects (≥ 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 (odds ratio *vs.* risk ratio), 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 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 $\chi 2$ 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 2,450 citations were retrieved through electronic search, and then 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 datasets for two different comparisons, respectively, 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 summarized in **ESM Table 3**. Totaling 34,569 patients from 46 independent trials were randomly assigned to one of three SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) or comparators (placebo or other active anti-diabetic treatments). Sample sizes of individual trials were between 180 and 7,020 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 summarized as follows (**ESM Fig. 3**): 36 RCTs

reported adequate random sequence generation; 33 RCTs reported adequate allocation concealment; masking conditions were high in 3 RCTs, of which 2 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 patients (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 patients with 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 (p all > 0.05). There was low heterogeneity among studies (I^2 ranged from 0 to 36.1%). 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 analyzed, 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 versus comparators (OR 4.49 [95% CI 1.21, 16.73]). Canagliflozin was significantly associated with lower risk of gastrointestinal cancers than comparators (OR 0.15 [95% CI 0.04, 0.60]). 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 3.57 [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 ranged from 0 to 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]) was significantly associated with increased risk of overall cancer; the incidence of overall cancer was similar among these three SGLT2 inhibitors. We generated hierarchies of treatment effects based on the SUCRA probabilities, canagliflozin was ranked the lowest risk for over 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 analyzed (**ESM Figs 10 to 16),** canaglifozin was significantly associated with decreased risk of gastrointestinal cancers as 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]), respectively **(ESM Fig. 11)**, and canagliflozin was placed as the safest intervention among these interventions for its largest SUCRA probability and lowest mean rank (**ESM Table 5**). In contrast to the results from pairwise meta-analysis, empaglifozin was not significantly associated with increased risk of bladder cancer as 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 cases among 34,569 patients with type 2 diabetes. We found that SGLT2 inhibitors were not significantly associated with increased risk of overall cancer during the mean trial duration of 61 weeks. Our meta-regression analysis identify none of pre-specified factors significantly influenced the sizes of treatment effects. However, there was some evidence suggested that SGLT2 inhibitors might increase this risk in obese patients (BMI ≥ 30 kg/m^2). For

pre-specified cancer types, SGLT2 inhibitors might significantly increase bladder cancer risk, particularly for empagliflozin. The increased risk was observed in the trials with duration ≥ 52 weeks and obese patients (BMI ≥ 30 kg/m^2). Interestingly, there was suggestive evidence that canagliflozin was significantly associated with decreased risk of gastrointestinal cancers. However, given the short term RCTs clinical trials, 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 indicated no elevated risk of overall cancer associated with SGLT2 inhibitors. Our results were 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 the 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, the results from pre-clinical studies found no increased hyperplasia or neoplasia in the urinary bladder mucosa, urogenital tract, or kidney in SGLT2 knockout mice compared with those with wild type [75]. However, our results included only 580 cases from 46 short term RCTs with a mean trial duration of 61 weeks (range: 24 weeks to 160 weeks). Also, we observed a non-significant risk increase among patients 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 possibilities of cancer risk. Our findings are needed to be confirmed by future

large trials including CANVAS (cannagliflozin; NCT01032629) and DECLARE-TIMI58 (dapagliflozin; NCT01730534) as well as long term observational studies.

Interestingly, our meta-analysis of direct and indirect evidence showed that canagliflozin was significantly associated with decreased risk of gastrointestinal cancers. SGLT1 was found to be overexpressed in many cancers [76], and SGLT2 is functionally expressed in pancreatic and prostate adenocarcinomas [77]. SGLT, especially SGLT1, has been demonstrated to play an important role in cancer cell survival by taking up glucose [77]. Canagliflozin is a potent SGLT2 inhibitor but possesses potent SGLT1 inhibitory activity [76]. SGLT1 is expressed mainly in the gastrointestinal tract, but is also expressed in kidney and heart, while SGLT2 is highly selectively expressed in kidney and less so in the gastrointestinal tract [78]. Therefore, it suggests that canagliflozin may protect against gastrointestinal cancers by suppressing the expression of SGLT1 and SGLT2 in the gastrointestinal tract. In human colon cancer cells not expressing UGT1A9, which encodes the enzyme for metabolizing SGLT2 inhibitors, dapagliflozin significantly reduced the number of colon cells [79]. However, our meta-analysis did not detect any decreased risk of gastrointestinal cancers with the use of dapagliflozin or empagliflozin. This might be explained by the fact that empagliflozin and dapagliflozin exhibited higher selectivity for SGLT2 versus SGLT1 than canagliflozin [76], or small number of gastrointestinal cancer cases included. Further prospective studies are needed to determine the potential effects of SGLT2 inhibitors on risk of gastrointestinal cancers.

Risk of increased 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, though this was not

confirmed in the network meta-analysis. Most bladder cases were identified from the EMPA-REG OUTCOME Trial (empagliflozin: 6 cases of bladder cancer, 2 cases of bladder transitional cell carcinoma, and one case of bladder cancer recurrent; placebo: 0 cases) [21]. An increased risk of bladder cancer was observed in the patients taking empagliflozin as compared with placebo in this trial [21], which was consistent with the findings on dapagliflozin in the regulatory report submitted to the U.S. FDA [12]. However, our meta-analysis did not find that dapagliflozin significantly increase the risk of bladder cancer, nor was this risk affected by use of canagliflozin. One pooled analysis of eight phase-3 clinical trials based on regulatory submissions (canagliflozin: 5 cases; comparators: 4 cases) showed that the incidence of bladder cancer was no higher in the canagliflozin group than in other groups [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 the glycosuria and urinary tract infection related to SGLT2 inhibitor use may be responsible for that increased risk [14]. We found a significantly increased risk of bladder cancer among the obese patients (BMI ≥ 30 kg/m^2) or the trials with duration ≥ 52 weeks. On the other hand, our meta-analysis did not detect a significantly increased risk of breast cancer with the use of SGLT2 inhibitors as compared with comparators. However, the possibility of increased these risks cannot be excluded, as the short duration of RCTs is probably insufficient to address these questions. Future large long-term RCTs and real-world data are required to clarify the association between SGLT2 inhibitor and risk of pre-specified cancer types (especially for SGLT2 inhibitors and bladder cancer risk).

Several pre-specified risk factors (e.g., ethnicity, gender, BMI, and age) were further explored in our meta-regression analysis. However, none of the results were significant. In the subgroup analysis, we found that SGLT2 inhibitors as compared with comparators were significantly associated with increased risk of overall cancer or bladder cancer in obese patients (BMI ≥ 30 kg/m^2) but not in normal weight/overweight subgroup. The 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 weights to the overall results and even more weights 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 risk of overall cancer in obese patients; (2) SGLT2 inhibitors (especially empagliflozin) might increase risk of bladder cancer; and (3) canagliflozin might have a protective effect against gastrointestinal cancers. Furthermore, 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 also included; and (4) multiple subgroup analyses,

meta-regression, and sensitivity analysis 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 due to lack of data on incidence of cancer, though additional data on ClinicalTrials.gov and regulatory reports submitted to U.S. FDA and EMA were searched and retrieved to minimize publication bias and outcome-reporting bias. The data of canagliflozin and empagliflozin from regulatory submissions were not included due to only total number of cases reported from several trials, which made it difficult to assign these outcomes to each trial. However, these results were compared in the discussion. Second, The exposure or follow-up time in most trials (mean trial durations: 61 weeks; range: 24 to 160 weeks) were not long enough 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 of carcinogenesis. Third, the quality of our evidence were relatively low due to indirect comparisons, inadequate power, and wide CIs according to the GRADE system [82]. Also, we cannot rule out any heterogeneity and inconsistency due to sparse cancer events among the trials. It is premature to apply our results from the analyses to clinical practice and guideline development. Fourth, background treatments and patient characteristics varied among the RCTs and might contribute to heterogeneity, although multiple subgroup analyses were performed to minimize clinical heterogeneity. Finally, the risk of cancer associated with other novel SGLT2 inhibitors remains uncertain due to lack of RCT data.

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

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Duality of interest

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

Contribution statement

HT, YS, JH designed the study. HT and SW identified and acquired reports of trials and extracted data. HT, QD, SW, SZ, YS, and JH performed all data analyses, checked for statistical inconsistency, and interpreted data. HT, QD, SW, SZ, YS, and JH contributed to data interpretation. HT drafted the report, and all other authors (QD, SW, SZ, YS, and JH) critically reviewed the report.

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Figure Legends:

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

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

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

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

Figure1

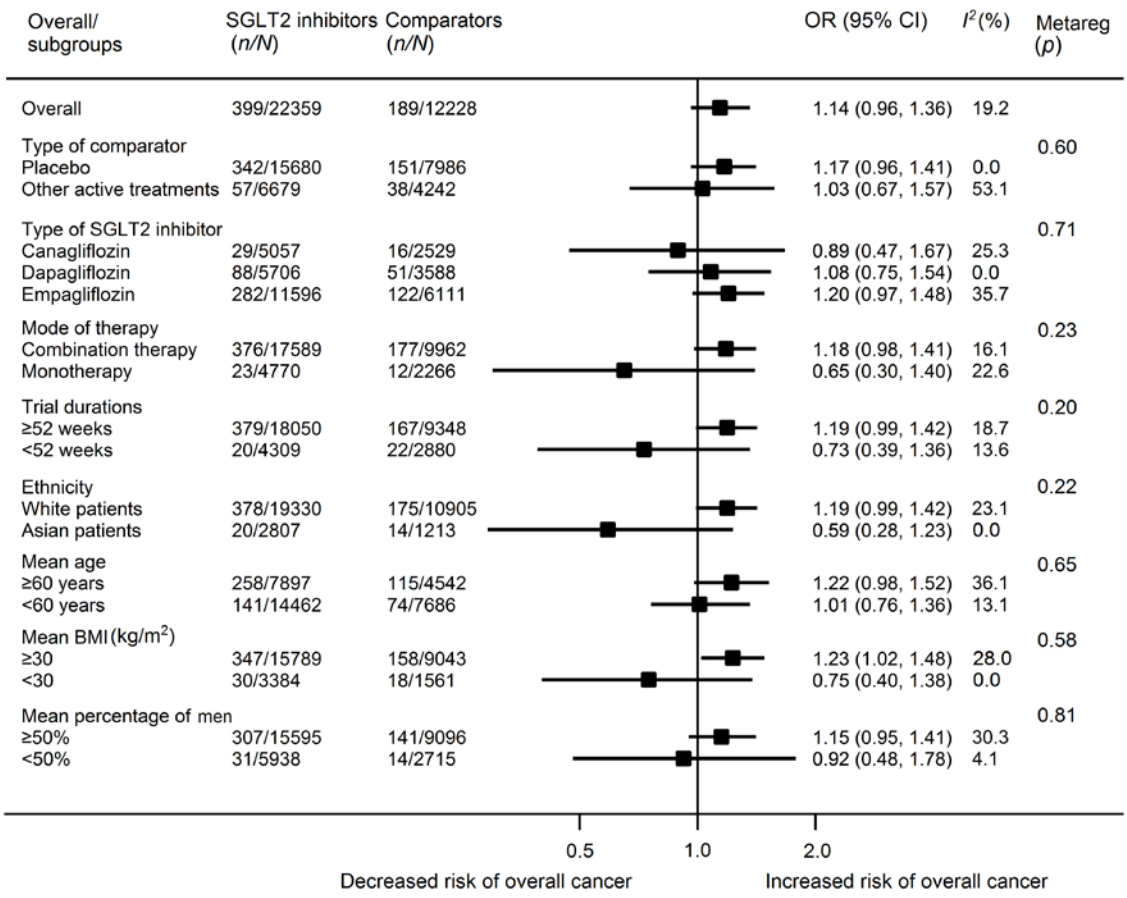

Overall/ subgroups
SGLT2 inhibitors (n/N)
Comparators (n/N)
OR (95% CI)
I²(%)
Metareg (p)
Overall 399/22359 189/12228 1.14 (0.96, 1.36) 19.2
Type of comparator 0.60
Placebo 342/15680 151/7986 1.17 (0.96, 1.41) 0.0
Other active treatments 57/6679 38/4242 1.03 (0.67, 1.57) 53.1
Type of SGLT2 inhibitor 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

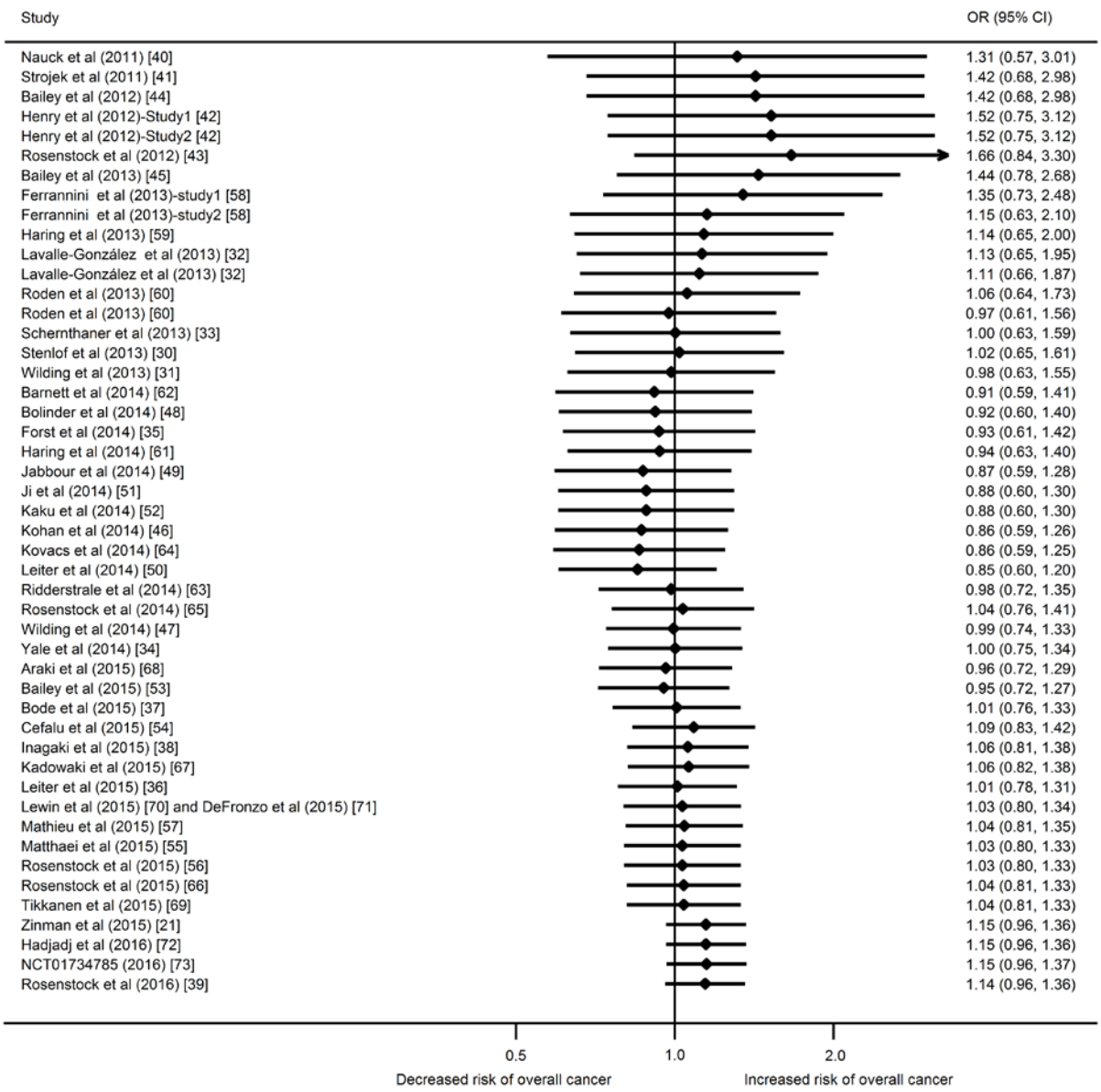

Study
OR (95% CI)
Nauck et al (2011) [40]
1.31 (0.57, 3.01)
Strojek et al (2011) [41]
1.42 (0.68, 2.98)
Bailey et al (2012) [44]
1.42 (0.68, 2.98)
Henry et al (2012)-Study1 [42]
1.52 (0.75, 3.12)
Henry et al (2012)-Study2 [42]
1.52 (0.75, 3.12)
Rosenstock et al (2012) [43]
1.66 (0.84, 3.30)
Bailey et 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

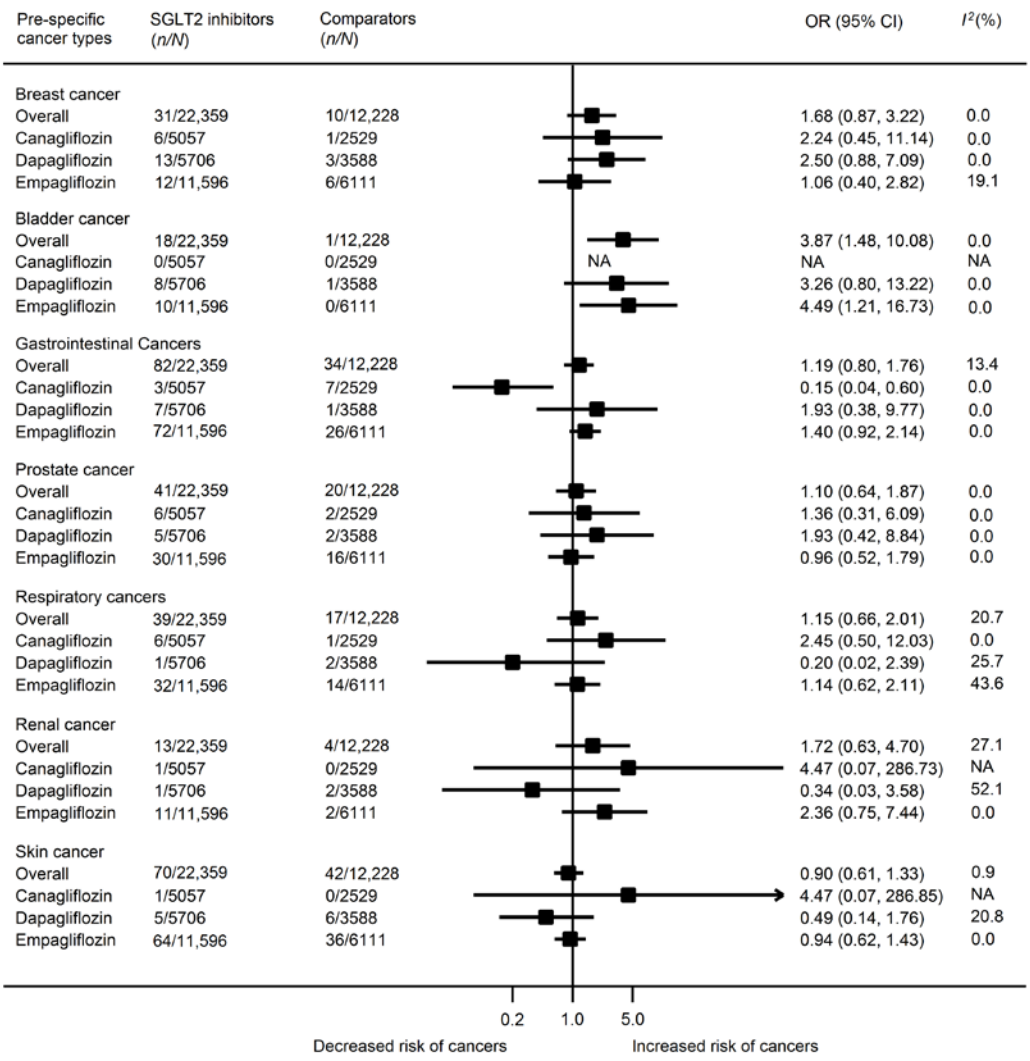
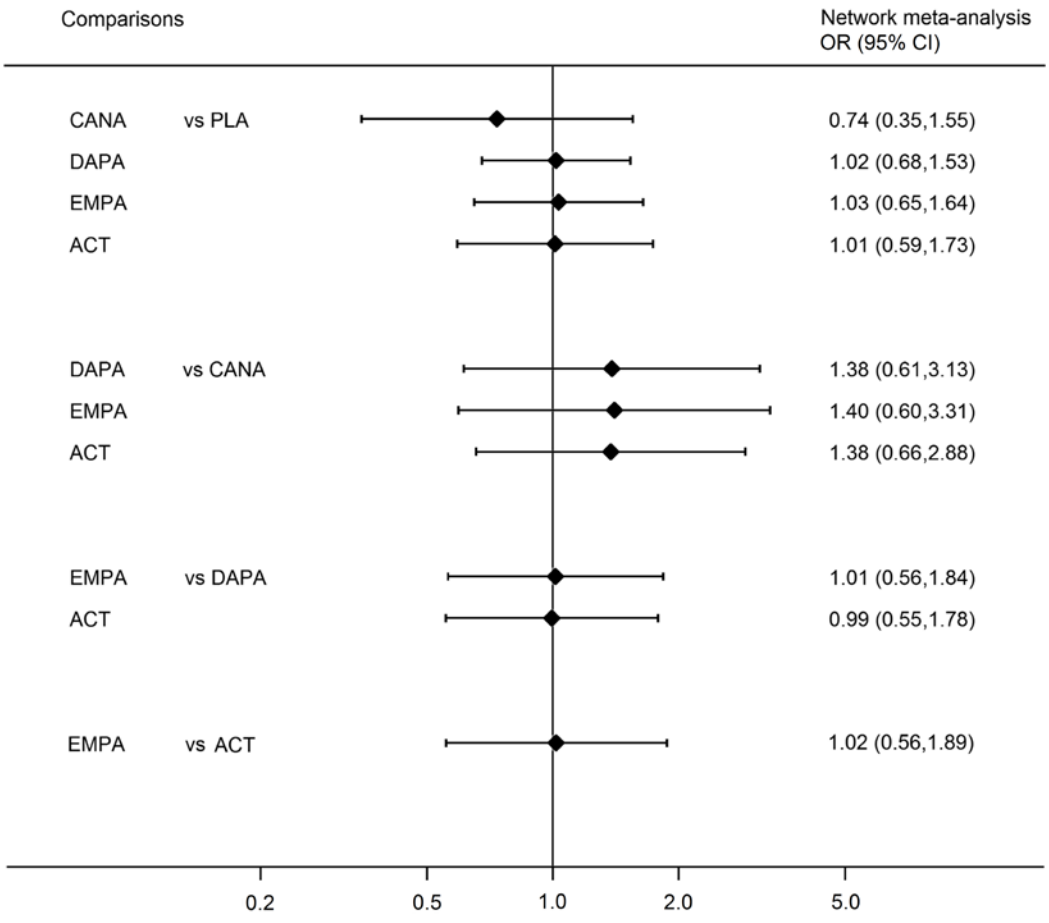

Pre-specific cancer types
SGLT2 inhibitors (n/N)
Comparators (n/N)
OR (95% CI)
I²(%)
Breast cancer
Overall 31/22,359 10/12,228 1.68 (0.87, 3.22) 0.0
Canagliflozin 6/5057 1/2529 2.24 (0.45, 11.14) 0.0
Dapagliflozin 13/5706 3/3588 2.50 (0.88, 7.09) 0.0
Empagliflozin 12/11,596 6/6111 1.06 (0.40, 2.82) 19.1
Bladder cancer
Overall 18/22,359 1/12,228 3.87 (1.48, 10.08) 0.0
Canagliflozin 0/5057 0/2529 NA NA
Dapagliflozin 8/5706 1/3588 3.26 (0.80, 13.22) 0.0
Empagliflozin 10/11,596 0/6111 4.49 (1.21, 16.73) 0.0
Gastrointestinal Cancers
Overall 82/22,359 34/12,228 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 72/11,596 26/6111 1.40 (0.92, 2.14) 0.0
Prostate cancer
Overall 41/22,359 20/12,228 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 30/11,596 16/6111 0.96 (0.52, 1.79) 0.0
Respiratory cancers
Overall 39/22,359 17/12,228 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 32/11,596 14/6111 1.14 (0.62, 2.11) 43.6
Renal cancer
Overall 13/22,359 4/12,228 1.72 (0.63, 4.70) 27.1
Canagliflozin 1/5057 0/2529 4.47 (0.07, 286.73) NA
Dapagliflozin 1/5706 2/3588 0.34 (0.03, 3.58) 52.1
Empagliflozin 11/11,596 2/6111 2.36 (0.75, 7.44) 0.0
Skin cancer
Overall 70/22,359 42/12,228 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 64/11,596 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