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SYSTEMATIC REVIEW

The impact of sodium-glucose cotransporter-2 inhibitors on breast cancer and cancer-related mortality: a systematic review and meta-analysis of randomized controlled trials

Mohammad Amin Karimi[1†], Razieh Khadem[2†], Alireza Haraj[3], Mehdi Azizabadi Farahani[4], Pardis Charehsaz Avari Firouzeh[5], Arash Azizinezhad[6], Hasti Kianpour Raki[7], Mohaddeseh Belbasi[8], Melika Arab Bafrani[9*], Niloofar Deravi[7*], Yaser Khakpour[10], Ali Faghih Habibi[11] and Vahid Aghsaghloo[11]

Abstract

Background SGLT-2 inhibitors (SGLT-2i) lower blood glucose levels in type 2 diabetes by inhibiting renal glucose reabsorption. While the relationship between SGLT-2i and breast cancer remains inconclusive, emerging evidence suggests potential anticancer properties. This systematic review and meta-analysis compares the effects of SGLT-2i and DPP-4i on breast cancer incidence and related mortality to clarify current conflicting evidence.

Methods An extensive literature search was conducted using MeSH terms and relevant keywords related to SGLT-2 inhibitors, breast cancer, and mortality across PubMed, Scopus, and Google Scholar up to August 12, 2023. Additionally, reference lists of the included studies were manually screened to identify further eligible articles. Data on the impact of SGLT-2 inhibitors on breast cancer and its associated mortality were extracted from the included studies. Findings were presented using hazard ratios (HR) with 95% confidence intervals (CI) displayed in a forest plot. At the same time, heterogeneity was assessed using the I^2 statistic, applying a random-effects model for significant heterogeneity.

Results Seven cohort studies involving 408,026 individuals were included. SGLT-2 inhibitors were not associated with a significant difference in breast cancer risk compared to DPP-4 inhibitors (HR = 1.03, 95% CI: 0.82–1.30, $p > 0.05$), but

† Mohammad Amin Karimi and Razieh Khadem contributed to this work equally.

*Correspondence:
Melika Arab Bafrani
Melika.arab92@gmail.com
Niloofar Deravi
niloofarderavi@sbmu.ac.ir

Full list of author information is available at the end of the article

were linked to a 30% reduction in breast cancer–specific mortality and improved overall survival (HR = 0.71, 95% CI: 0.65–0.77, $p < 0.05$).

Conclusions The impact of SGLT-2 inhibitors and DPP-4 inhibitors on breast cancer incidence appears to be comparable. However, SGLT-2 inhibitors may confer a greater reduction in breast cancer–related mortality and potentially improve overall patient survival compared to DPP-4 inhibitors. Given the observed heterogeneity among existing studies, larger, high-quality randomized controlled trials are warranted to validate these findings.

Keywords SGLT-2i, DPP-4i, Breast cancer, Diabetes, Mortality, Cancer, Meta-analysis

Background

Breast cancer is the most common cancer in women worldwide and ranks as the second leading cause of cancer-related mortality among women globally. Despite significant advances in treatment, breast cancer continues to be a major cause of mortality, particularly in cases of advanced metastatic disease [1–4]. Breast cancer is a highly heterogeneous disease with distinct molecular subtypes, each exhibiting unique clinical behaviors and progression pathways. These subtypes rely on various metabolic and signaling mechanisms, such as aerobic glycolysis, to sustain tumor growth and survival [5]. Breast cancer cells primarily rely on aerobic glycolysis for energy production to sustain their growth and survival; they employ strategies to increase glucose uptake and utilization to boost adenosine triphosphate (ATP) production [6–8]. This underscores the critical role of glucose metabolism in cancer cell survival, further highlighting the therapeutic potential of Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) in breast and other cancers.

SGLT-2i and DPP-4i are two distinct classes of oral antidiabetic medications, each with unique mechanisms of action contributing to their efficacy in managing type 2 diabetes mellitus (T2DM). SGLT-2 inhibitors function by inhibiting the SGLT-2 protein in the renal proximal tubules, thereby reducing glucose reabsorption and promoting its excretion through urine [9]. SGLT-2 inhibitors have demonstrated the ability to suppress cancer cell growth in renal, liver, and colon cancers by inhibiting glucose uptake. This mechanism aligns with recent evidence highlighting the crucial role of SGLT-2 in cancer development. In breast cancer, the overexpression of SGLT-2 has been confirmed, further suggesting a potential link between SGLT-2 activity and tumor progression [10–16].

Recent studies on the cancer-related risks associated with SGLT-2 and DPP-4 inhibitors have yielded conflicting evidence. A meta-analysis suggests that canagliflozin, an SGLT-2 inhibitor, may offer protective effects against gastrointestinal cancers. In contrast, empagliflozin has been linked to a higher risk of bladder cancer. Retrospective data from Taiwan showed that SGLT-2 inhibitor use was associated with lower cancer-related mortality compared to DPP-4 inhibitors. Other studies also indicate a reduced risk of urinary tract and hematological cancers among SGLT-2 inhibitor users [17]. On the other hand, in a population-based study, SGLT-2 inhibitors significantly lower the risks of hepatocellular carcinoma (HCC) compared to DPP-4 inhibitors in patients with T2DM. SGLT-2 inhibitors exhibited protective effects by reducing inflammation, fat accumulation, and liver disease progression, thereby decreasing cancer-related and all-cause mortality [18].

In contrast, DPP−4 inhibitors exert their therapeutic effects by inhibiting the enzyme dipeptidyl peptidase−4, which degrades incretin hormones such as glucagon-like peptide−1 (GLP−1). By prolonging the action of these hormones, DPP−4 inhibitors enhance glucose-dependent insulin secretion and suppress glucagon release, thereby improving glycemic control [19]. While early studies suggested a potential link between DPP−4 inhibitors and increased risks of pancreatic and thyroid cancers, recent meta-analyses show no significant association with overall cancer incidence [20]. DPP−4 inhibitors may impair postoperative outcomes in colorectal cancer patients by promoting epithelial-to-mesenchymal transition (EMT) and fostering a tumor-permissive immune environment, thus reducing disease-free survival rates [21]. Similarly,some studies have linked DPP−4 inhibitors to increased risks of liver, kidney, and bladder cancers, as well as melanoma. However, other studies report no significant association across different drug subclasses [17]. Conversely, sitagliptin, a DPP−4 inhibitor, has been reported to reduce breast cancer risk in women with T2DM [20].

Despite these findings and the contradictory evidence regarding the cancer-related risks of SGLT−2 and DPP−4 inhibitors, significant uncertainty persists about their comparative associations with the incidence of various cancers. Given the widespread use of these medications, this review aims to evaluate the impact of SGLT−2 inhibitors relative to DPP−4 inhibitors on the risk of breast cancer in patients with T2DM.

Method

Registration and reporting

In this systematic review and meta-analysis, we aimed to investigate the impact of Sodium-glucose cotransporter-2 inhibitors on breast cancer and cancer-related mortality. The current investigation followed the guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) to conduct a thorough systematic review and meta-analysis [22]. The design protocol for our study was appropriately registered in the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/ZHCTD).

Literature search

The first phase involved identifying pertinent keywords using Medical Subject Headings (MeSH) terminology. Following this, an in-depth investigation was conducted until August 12, 2023. The inquiry incorporated the databases PubMed, Scopus, and Google Scholar. Searches included article titles, abstracts, and keywords using advanced database filters. To increase the precision of the search, the strategy comprised three main subgroups of keywords and MeSH terms: one subgroup included terms related to the generic, brand, and premarketing titles of distinct SGLT-2 inhibitors; the other two included keywords and terminology related to breast cancer and mortality, respectively. These subgroups were combined using the 'AND' operator.

Additionally, we analyzed reference lists of included investigations to identify potentially qualifying studies. No explicit limitations or restrictions were imposed regarding the date, publication type, or language. The search approach employed in this study is shown in Table 1.

Study selection

This study investigates the inclusion and exclusion criteria employed in the research design. The researchers utilized specified criteria for inclusion and exclusion to discover appropriate publications. The study's inclusion criteria encompassed the following:

1. The study design needed to include either observational cohort studies (including retrospective and prospective), randomized controlled trials, or early-phase clinical trials published in peer-reviewed publications and accompanied by comprehensive analysis.
2. The trials included in the examination must have examined using SGLT−2 inhibitors as an intervention for breast cancer.
3. The present study incorporated research investigations that examined the comparative efficacy of SGLT−2 inhibitors concerning placebo, active therapies, or no intervention among adults aged 18 years or older.
4. Our study encompassed investigations documenting at least one instance of breast cancer or one fatality attributed to breast cancer.
5. The outcomes of breast cancer incidence or cancer-related mortality must be reported in clinical trials. This includes documented breast cancer cases, cancer-related deaths, and pertinent data required for calculating the effect magnitude (such as hazard ratios, relative risks, or odds ratios).

The exclusion criteria encompassed the following:

1. The survey population was restricted to breast cancer patients, excluding those with other types of cancer.
2. Excluded from the analysis were studies that evaluated outcomes that were considered irrelevant.
3. Only observational cohort studies (including retrospective and prospective), randomized controlled trials, or early-phase clinical trials that were adequately designed were included in this analysis. Studies that utilized other methods, were conducted on animal models, had biases, or employed different study designs were excluded.

Data extraction

The present analysis exclusively included observational cohort studies, encompassing retrospective and prospective designs and randomized controlled trials. Furthermore, we considered early-phase clinical trials published in peer-reviewed journals and conducted extensive evaluations. The main aim of our study was to examine academic literature that explored the impact of SGLT-2 inhibitors on breast cancer and cancer-related mortality. After conducting an extensive search, removing any duplicate entries, and retrieving pertinent articles, two researchers meticulously examined the titles and abstracts of the chosen studies. When inconsistencies emerged, a third author was engaged to help the settlement process through deliberation. Following this, the subsequent phase involved thoroughly analyzing the full text of the identified articles to determine their exact compliance with the established inclusion criteria. All studies that met the predetermined inclusion criteria were included in the analysis, and if any inconsistencies arose, a third reviewer was responsible for resolving them. The two reviewers systematically gathered pertinent study data using a pre-established data collection table. The researchers collected relevant data about the study, encompassing details such as the author's identification, study methodology, year of publication, sample size, duration, and patient group characteristics. Furthermore, the researchers collected several patient

Table 1 Characteristic features of included studies

The first author (year)	Country	Participants (female)	SGLT-2i Type	Outcome	Glycemic Control	Changes in body weight	Study findings
Chung (2023) [17]	Hong Kong	Total: 60,112 (43.64%) SGLT-2i (18167) DPP-4i (41945)	● Canagliflozin: 24.89% ● Dapagliflozin: 58.1% ● Empagliflozin: 20.8% ● Ertugliflozin: 13.9%	Breast cancer mortality	● Metformin ● Sulfonylurea ● GLP–1RA ● Acarbose ● Insulin ● Thiazolidinedione	NM	SGLT-2i may have potential benefits in reducing mortality, cancer-related risks, and lowering the probability of breast cancer compared to placebo.
Sütő (2021) [26]	Hungary	Total: 37,116 (NM) SGLT-2i (18583) DPP-4i (18583)	NM	Breast cancer mortality	● Metformin ● Sulfonylurea ● GLP–1RA ● Metiglinides ● Glitazones ● Acarbose ● Insulin	NM	SGLT-2i show potential for reducing all-cause mortality and improving cardiovascular outcomes, supported by CVOTs and RWE.
Chung (2022) [27]	Taiwan	Total: 106,528 (44.12%) SGLT-2i (53264) DPP-4i (53264)	● Canagliflozin: 1.11% ● Dapagliflozin: 55.44% ● Empagliflozin: 43.43%	Breast cancer mortality	● Metformin ● GLP–1RA ● Insulin	NM	SGLT-2i may potentially reduce all-cause mortality, with consistent benefits across subgroups, compared to other glucose-lowering drugs.
Suissa (2019) [28]	The U.K	Total: 46,569 (100%) SGLT-2i (9938) DPP-4i (36631)	● Canagliflozin: 17.4% ● Dapagliflozin: 54.6% ● Empagliflozin: 27.9%	Breast cancer risk	● Metformin ● Sulfonylureas ● Thiazolidinedione ● Meglitinides ● alpha-glucosidase inhibitors ● GLP–1 RA ● Insulin	NM	There is no significant association between SGLT-2i and an increased probability of breast cancer risk.
Heerspink (2021) [29]	386 sites in 21 countries	Total: 4304 (33.10%) SGLT-2i (2152) Placebo (2152)	● Dapagliflozin: 100%	Breast cancer risk	NM	NM	Dapagliflozin can potentially reduce all-cause mortality by 31%, especially in deaths from infections and malignancies
Perkovic (2019) [30]	690 sites in 34 countries	Total: 4401 (33.94%) SGLT-2i (2202) Placebo (2199)	● Canagliflozin: 100%	Breast cancer risk	● Sulfonylurea ● GLP–1RA ● Biguanides ● Insulin ● Thiazolidinediones ● Alpha glucosidase inhibitors	A reduction in body weight by 0.80 kg (95% CI, 0.69 to 0.92)	Canagliflozin potentially lowers the risks of renal complications, cardiovascular events, and hospitalization for heart failure.
Wiviott (2019) [31]	882 sites in 33 countries	17,160 (37.42%) SGLT-2i (8582) Placebo (8578)	● Dapagliflozin: 100%	Breast cancer mortality	● Metformin ● Sulfonylurea ● Insulin	A reduction in body weight by 1.8 kg (95% CI, 1.7 to 2.0)	Dapagliflozin may reduce the probability of cardiovascular death and heart failure hospitalization, but with an increased risk of diabetic ketoacidosis and serious infections.

Abbreviations: SGLT–2i: Sodium-Glucose Co-Transporter 2 inhibitors; DPP–4i: Dipeptidyl Peptidase–4 inhibitors; GLP–1RA: Glucagon-like peptide–1 receptor agonists; NM: Not Mentioned; CVOTs: Cardiovascular outcome trials; RWE: Real-world evidence; T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; CI: Confidence interval characteristics, including gender, age, starting measures, ethnicity, and outcomes.

Study quality assessment

Two reviewers employed the critical appraisal checklists for cohort, case-control, and analytical cross-sectional studies established by the Joanna Briggs Institute (JBI) (https://jbi.global/critical-appraisal-tools). If there were any discrepancies, a third author was involved in the process.

Statistical analysis

For the data analysis in this study, the software utilized was STATA 13.1, developed by StataCorp LP, a company based in College Station, Texas, United States. The findings were presented as HRs and a 95% CI graphically represented in a forest plot. The heterogeneity among the eligible studies was assessed using the I2 statistic [23]. The random effects model was employed in cases of considerable heterogeneity (I2 > 50%) [24]. In addition, a sensitivity analysis was performed in which individual studies were systematically excluded one at a time, followed by repeating the meta-analysis. This allowed us to ascertain the consistency and reliability of our results. We employed visual inspection methods of funnel plot symmetry and Egger's regression analysis to examine the possibility of publication bias [25].

Result

Studyon selecti

A total of 433 records were identified through a systematic search of electronic databases, including PubMed (n = 92), Scopus (n = 156), along with Google Scholar (n = 170) and manual reference screening (n = 15). After the removal of 40 duplicate entries, the titles and abstracts of 393 studies were screened. Of these, 386 studies were excluded based on the inclusion and exclusion criteria following title, abstract, and full-text assessment. Ultimately, seven studies met the eligibility criteria and were included in this systematic review and meta-analysis. The detailed selection process is illustrated in the PRISMA flow diagram (Fig. 1). Google Scholar (n = 170) Google Scholar (n = 170).

Study characteristics

All the studies included in this article were published in English between 2019 and 2023. The total number of participants included 276,190 diabetic patients, of whom 112,888 (40.87%), 150,423 (54.46%), and 12,929 (4.68%) were treated with SGLT-2i, DPP-4i [17, 26–28] and placebo [29–31], respectively. The most frequent subtypes of SGLT-2i were dapagliflozin [17, 27–29, 31], and other subtypes included canagliflozin [17, 27, 28, 30], empagliflozin [17, 27, 28], and ertugliflozin [17]. These studies were conducted in different countries, including China [17], Hungary [26], Taiwan [27], Germany [30], the U.K [28]., and multiple countries [29, 31]. Four studies compared the mortality due to breast cancer between SGLT-2i versus DPP-4i/placebo, while others compared the risk of breast cancer (Table 1).

SGLT−2i and the cancer-related mortality/risk of breast cancer.

Reporting of the relationship between SGLT−2 inhibitors and cancer-related mortality in 4 studies (2 studies reported separated between SGLT−2 inhibitors subtypes) showed a pooled HR of 0.71 (HR = 0.71, 95% CI: 0.65–0.77, $p = 0.000$, $I^2 = 0.00\%$). Our analysis revealed that diabetic patients using SGLT−2 inhibitors experienced a 30% risk reduction compared to those using DPP−4 inhibitors (Fig. 2). Leave-One-Out Sensitivity analysis was performed by sequentially removing one study at a time and recalculating the summary effect size and corresponding confidence interval. Overall, the sensitivity analysis results were consistent with our main findings, with no single study significantly influencing the overall effect size estimate.

Conversely, three studies showed that SGLT−2 inhibitors in diabetes mellitus (DM) patients, in comparison with DPP−4 inhibitors, imply an equal hazard of breast cancer in these 2 groups (HR = 1.03, 95% CI: 0.82–1.30, $p = 0.78$, $I^2 = 0.00\%$) (Fig. 3).

Publication bias and sensitivity analysis

We assess publication bias through Begg's test and a visualized funnel plot. The funnel plot (Fig. 4) for both breast cancer risk and mortality was symmetrical, indicating no publication bias. Moreover, Begg's test showed no significant bias ($P > 0.05$).

Discussion

SGLT-2 inhibitors, initially designed for managing hyperglycemia in diabetic patients, have demonstrated notable anticancer potential, particularly in breast cancer treatment [32, 33]. Canagliflozin, a widely studied SGLT-2 inhibitor, has demonstrated efficacy in suppressing breast cancer cell proliferation by inhibiting mitochondrial complex I. This disruption impairs cellular respiration and lipogenesis, contributing to its antitumor effects. This inhibition subsequently increases the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK), leading to a metabolic shift that hinders cancer cell proliferation [34, 35]. Additionally, research has revealed that dapagliflozin and canagliflozin induce cell cycle arrest and apoptosis by activating AMPK, while simultaneously reducing oxidative phosphorylation and decreasing ATP levels within cancer cells, further contributing to their antiproliferative effects [16, 33].

A critical mechanism behind these effects is the inhibition of glutamine utilization, which is crucial

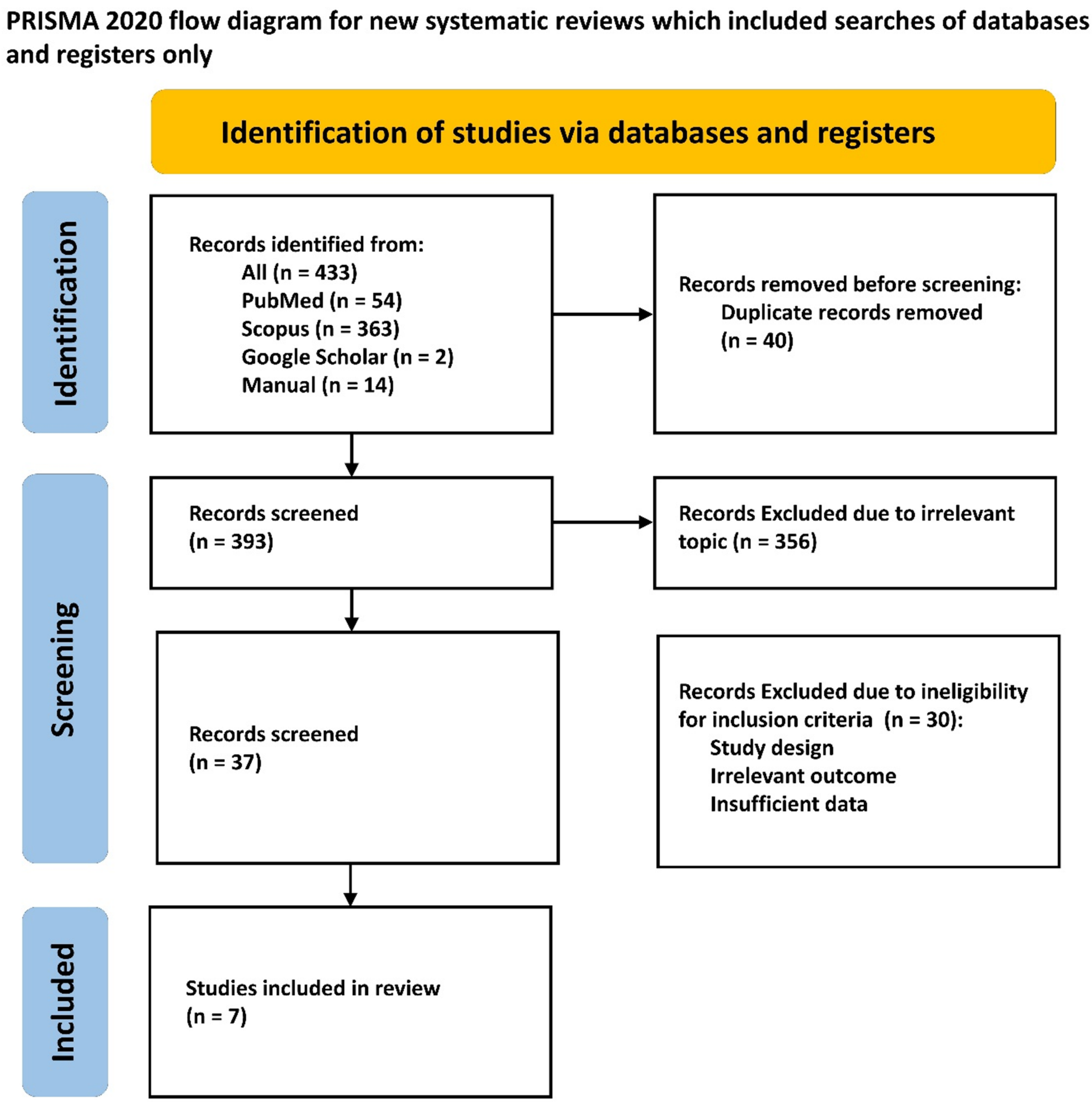

Fig. 1 PRISMA diagram of current systematic review and meta-analysis

for ATP production and cellular respiration in cancer cells. Canagliflozin's ability to block this pathway disrupts the energy supply of tumor cells, thereby suppressing their growth [36, 37]. Ipragliflozin has also been reported to exert antiproliferative effects by limiting the entry of glucose and sodium into breast cancer cells, leading to mitochondrial destabilization and cellular membrane hyperpolarization [15, 38]. These mechanisms collectively highlight the broad anticancer potential of SGLT-2i beyond their role in diabetes management.

The anticancer effects of SGLT-2 inhibitors are not restricted to breast cancer alone. Studies have shown that these drugs exhibit activity against various other cancer types, including lung, thyroid, hepatocellular, pancreatic cancers, and even osteosarcoma [39–43]. This broad-spectrum efficacy is likely due to the reliance of many cancer cells on glucose uptake for energy production and biosynthesis, a process that SGLT-2 inhibitors directly target. These drugs effectively cut off the fuel supply needed for tumor growth and metastasis by inhibiting glucose transport into cancer cells.

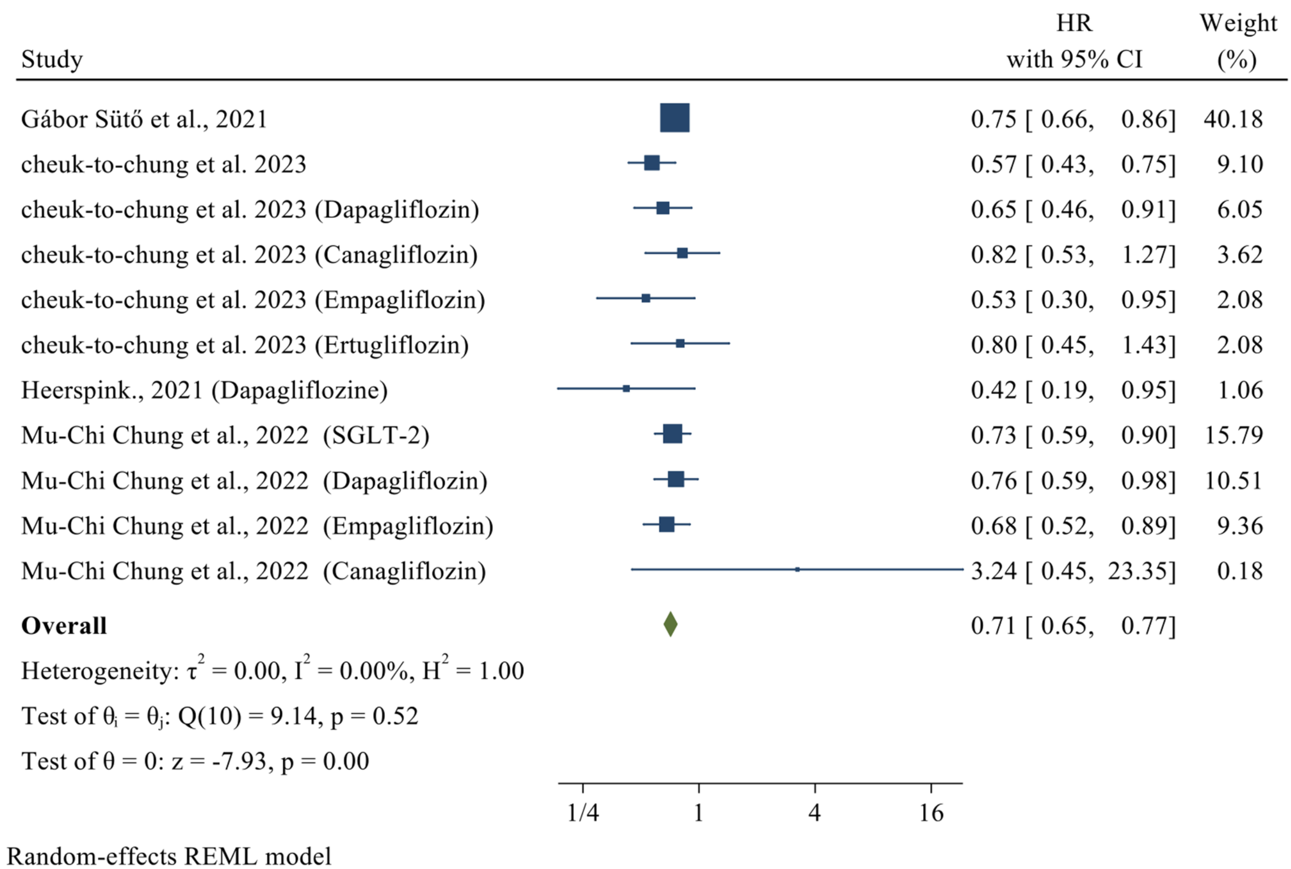

Fig. 2 Forest plot related to SGLT-2i impact on breast cancer mortality

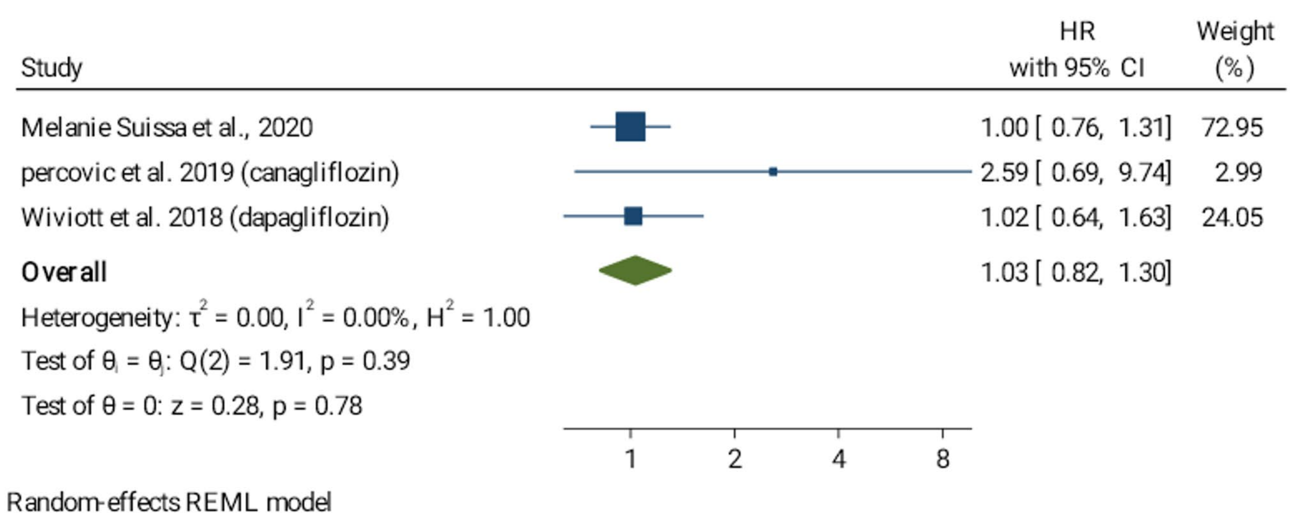

Fig. 3 Forest plot of the risk of breast cancer influenced by SGLT-2i

Despite encouraging preclinical outcomes, the clinical application of SGLT-2 inhibitors in oncology remains underexplored and warrants further comprehensive investigation. Clinical trials are necessary to determine the safety, optimal dosage, and potential side effects of using these drugs in cancer patients, particularly when combined with conventional therapies like chemotherapy and radiotherapy [33]. Additionally, identifying biomarkers that predict the responsiveness to SGLT-2 inhibitors will be crucial in optimizing their therapeutic application, particularly in aggressive breast cancer subtypes such as

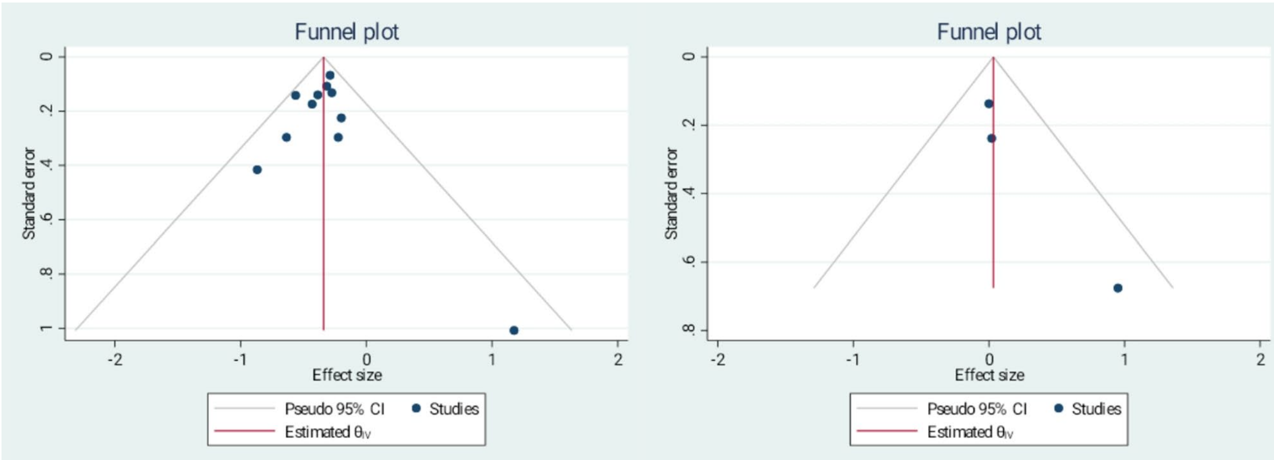

Fig. 4 Funnel plots for the impact of SGLT-2i on breast cancer risk (Left) and the mortality related to breast cancer (Right)

triple-negative breast cancer (TNBC), where treatment options remain limited [35].

In this systemic review and meta-analysis, we investigated the impact of SGLT-2 inhibitors on breast cancer and cancer-related mortality versus DPP-4 inhibitors. This study included 408,026 Participants from 7 studies. Our findings indicate that people with DM who use SGLT-2 inhibitors have a lower risk of cancer-related mortality compared to those who use DPP-4 inhibitors. In contrast, our data revealed that SGLT-2 inhibitors in people with DM, when compared to DPP-4 inhibitors, have the same level of risk for developing breast cancer.

This meta-analysis revealed that taking SGLT-2 inhibitors resulted in a 30% reduction in cancer-related mortalities (HR = 0.71, 95% CI: 0.65–0.77, $p = 0.000$, I^2 = 0.00%). Chung et al. [27] investigated the correlation between SGLT-2 inhibitors and reduced mortality rates in individuals with T2DM. They reported that the use of SGLT-2 inhibitors in patients with T2DM was significantly linked to a reduced mortality risk compared to DPP-4 inhibitors in a nationwide cohort study. Their findings showed a 34% decrease in the risk of all-cause mortality associated with SGLT-2 inhibitors. They identified a 0.73-fold reduction in the probability of cancer death among individuals who SGLT-2 inhibitors. The benefits of using SGLT-2 inhibitors for reducing the risk of death were consistent across all subgroups [27]. Another study by Chung et al. [17] compared the impact of SGLT-2 inhibitors and DPP-4 inhibitors on various newly developed cancers in 60,112 patients diagnosed with T2DM. They discovered that SGLT-2 inhibitors are associated with a lower risk of all-cause death, cancer-related mortality, and the development of total cancer when compared to DPP-4 inhibitors.

Moreover, SGLT-2 inhibitors are linked to a decreased likelihood of developing breast cancer. Both dapagliflozin and ertugliflozin exhibit a reduced chance of developing new cancer cases, with dapagliflozin notably showing a decreased risk for breast cancer [17]. Consistent with the mentioned studies, a Hungarian nationwide study assessed the mortality risk in T2DM treated with SGLT-2 and/or DPP-4 inhibitors. Sütő et al. [26] illustrated that individuals using SGLT-2 inhibitors, as opposed to DPP-4 inhibitors, experienced a reduction in all-cause mortality by 13% and a 25% decrease in cancer-related mortalities [26]. Heerspink et al. examined the effectiveness of dapagliflozin on mortality rates among chronic kidney disease patients. Their results showed that dapagliflozin effectively increased the lifespan of individuals with chronic kidney disease, regardless of whether they had T2DM. Additionally, the group of participants who received dapagliflozin experienced a lower number of fatalities caused by cancer compared to those who were given a placebo [26].

On the other hand, our study's findings revealed that SGLT-2 inhibitors in patients with DM have a similar risk of developing breast cancer compared to DPP-4 inhibitors (HR = 1.03, 95% CI: 0.82–1.30, $p = 0.78$, I2 = 0.00%). Suissa et al. [28] undertook a comprehensive cohort study to investigate the probability of breast cancer incidence among British women diagnosed with T2DM. Their research encompassed 9,938 patients who initiated SGLT-2 inhibitors and 36,631 individuals who began DPP-4 inhibitors therapy. Over approximately 2.6 years, the incidence rates of breast cancer among individuals using SGLT-2 inhibitors and DPP-4 inhibitors were 2.8 and 3.7 per 1,000 person-years, respectively. The comprehensive findings of this investigation suggest that the utilization of SGLT-2 inhibitors does not demonstrate a higher susceptibility to breast cancer than DPP-4 inhibitors [28]. Moreover, other studies examining the impact of canagliflozin [30] and dapagliflozin [31] on individuals with T2DM did not observe a significant incidence of breast cancer throughout their investigations.

This systematic review and meta-analysis employed an extensive search across various databases, thereby enhancing the probability of locating pertinent papers and reducing the potential for biased selection. Before the publication of this study, there existed a notable absence of comprehensive research assessing the impact of SGLT-2 inhibitors versus DPP-4 inhibitors on breast cancer incidence and cancer-related mortality.

Although our study offers valuable insights, several limitations must be acknowledged. The studies included in our systematic review applied various methods to adjust for potential confounding factors, such as age, sex, and baseline characteristics. Some studies employed propensity score matching to adjust for variables such as age, sex, comorbidities, and medication history [26, 27], while others utilized stratified analyses based on factors like age and kidney function [29]. In some instances, adjustments were made for age, sex, and estimated glomerular filtration rate (eGFR) to account for variations in kidney function and demographic factors [30]. Additional studies accounted for age, sex, and cardiovascular risk factors [31]. These diverse adjustment strategies may have contributed to the variability in outcomes observed across the studies. Moreover, the relatively high heterogeneity in breast cancer risk reported in the included studies represents another limitation. As a result, further research is required to validate these findings and provide more robust, statistically significant conclusions.

Conclusion

In conclusion, the cancer-related mortality rate in patients who were taking SGLT-2 inhibitors was lower than that of those taking DPP-4 inhibitors. Nevertheless, the risk of developing breast cancer did not differ significantly among these medication categories. The significant heterogeneity among studies concerning breast cancer risk highlights the need for further studies to validate and enhance these results, providing a more thorough comprehension of the influence of these drugs on cancer-related outcomes in diabetic populations.

Abbreviations

SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
DPP-4i	Dipeptidyl peptidase-4 inhibitor
GLP-1RA	Glucagon-like peptide-1 receptor agonist
AMPK	5′ adenosine monophosphate-activated protein kinase
CI	Confidence interval
DM	Diabetes mellitus
HR	Hazard ratios
mTOR	Mammalian target of rapamycin
MeSH	Medical subject headings
OSF	Open science framework
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
T2DM	Type 2 diabetes mellitus
NM	Not mentioned
CVOTs	Cardiovascular outcome trials
RWE	Real-world evidence
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
EMT	Epithelial-to-mesenchymal transition
GLP-1	Glucagon-like peptide-1

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Author contributions
Conception and study design: N.D, M.A.K; Protocol: P.CAF; Systematic search: M.A.K, study selection: A.H, R.K; Data extraction: M.AF, P.CAF; Quality assessment: H.H, M.B; Data analysis: M.AB; Drafting the manuscript: M.A.K, R.K, A.A, A.H; critical revision: AF, M.A.K, A.F.H, Y.Kh, A.A. All authors approved the submitted version of the manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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Author details
[1]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Amol Faculty of Paramedical Sciences, Mazandaran University of Medical Sciences, Sari, Iran
[5]Institute of Biology and Medicine of Taras, Shevchenko National University of Kyiv, Kyiv, Ukraine
[6]Universal Scientific Education and Research Network (USERN), Tehran, Iran
[7]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran 19839-63113, Iran
[8]Student Research Committee, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran
[9]Students Scientific Research Center (SSRC), Tehran University of Medical Sciences, 16 Azar St., Enghelab Square, Tehran 14179-35840, Iran
[10]Faculty of Medicin, Guilan University of Medical Sciences, Rasht, Iran
[11]Otorhinolaryngology Research Center, Department of Otolaryngology and Head and Neck Surgery, School of Medicine, Amiralmomenin Hospital, Guilan University of Medical Sciences, Rasht, Iran

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References

1. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444–57.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2021;71(3):209–49.

3. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global increase in breast Cancer incidence: risk factors and preventive measures. Biomed Res Int. 2022;2022:9605439.
4. Dawoud MM, Abdelaziz KK-E, Alhanafy AM, Ali MS-d, Elkhouly EAB. Clinical significance of immunohistochemical expression of neuropeptide Y1 receptor in patients with breast cancer in Egypt. Appl Immunohistochem Mol Morphology. 2021;29(4):277–86.
5. Nagy Á, Munkácsy G, Győrffy B. Pancancer survival analysis of cancer hallmark genes. Sci Rep. 2021;11(1):6047.
6. Jiang X-P, Elliott RL, Head JF. Exogenous normal mammary epithelial mitochondria suppress glycolytic metabolism and glucose uptake of human breast cancer cells. Breast Cancer Res Treat. 2015;153(3):519–29.
7. Shahruzaman S, Mustafa M, Ramli S, Maniam S, Fakurazi S. The cytotoxic effect and glucose uptake modulation of Baeckea frutescens on breast cancer cells. BMC Complement Altern Med. 2019;19(1):1–10.
8. Nakagawa T, Lanaspa MA, Millan IS, Fini M, Rivard CJ, Sanchez-Lozada LG, et al. Fructose contributes to the Warburg effect for cancer growth. Cancer Metabolism. 2020;8(1):1–12.
9. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
10. Kuang H, Liao L, Chen H, Kang Q, Shu X, Wang Y. Therapeutic effect of sodium glucose co-transporter 2 inhibitor Dapagliflozin on renal cell carcinoma. Med Sci Monitor: Int Med J Experimental Clin Res. 2017;23:3737.
11. Jojima T, Wakamatsu S, Kase M, Iijima T, Maejima Y, Shimomura K, et al. The SGLT2 inhibitor Canagliflozin prevents carcinogenesis in a mouse model of diabetes and non-alcoholic steatohepatitis-related hepatocarcinogenesis: association with SGLT2 expression in hepatocellular carcinoma. Int J Mol Sci. 2019;20(20):5237.
12. Nasiri AR, Rodrigues MR, Li Z, Leitner BP, Perry RJ. SGLT2 Inhibition slows tumor growth in mice by reversing hyperinsulinemia. Cancer Metabolism. 2019;7(1):1–13.
13. Crunkhorn S. Repurposing SGLT2 inhibitors. Nat Rev Drug Discovery. 2019;18(1):18.
14. Srivastava SP, Goodwin JE. Cancer biology and prevention in diabetes. Cells. 2020;9(6):1380.
15. Komatsu S, Nomiyama T, Numata T, Kawanami T, Hamaguchi Y, Iwaya C, et al. SGLT2 inhibitor Ipragliflozin attenuates breast cancer cell proliferation. Endocr J. 2020;67(1):99–106.
16. Zhou J, Zhu J, Yu S-J, Ma H-L, Chen J, Ding X-F, et al. Sodium-glucose co-transporter–2 (SGLT–2) Inhibition reduces glucose uptake to induce breast cancer cell growth arrest through AMPK/mTOR pathway. Biomed Pharmacother. 2020;132:110821.
17. Chung CT, Lakhani I, Chou OHI, Lee TTL, Dee EC, Ng K, et al. Sodium-glucose cotransporter 2 inhibitors versus dipeptidyl peptidase 4 inhibitors on new-onset overall cancer in type 2 diabetes mellitus: A population-based study. Cancer Med. 2023;12(11):12299–315.
18. Chou OHI, Ning J, Chiu Chan RN, Chung CT, Huang H, Ng K et al. Lower risks of sodium glucose cotransporter 2 (SGLT2) inhibitors compared to dipeptidyl peptidase–4 (DPP4) inhibitors for new-onset non-alcoholic fatty liver disease and hepatocellular carcinoma in type 2 diabetes mellitus: A population-based study. medRxiv. 2022:2022.08.16.22278847.
19. Aroda VR. A review of GLP–1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials. Diabetes Obes Metab. 2018;20(Suppl 1):22–33.
20. Dicembrini I, Nreu B, Montereggi C, Mannucci E, Monami M. Risk of cancer in patients treated with dipeptidyl peptidase–4 inhibitors: an extensive meta-analysis of randomized controlled trials. Acta Diabetol. 2020;57(6):689–96.
21. Saito A, Kitayama J, Horie H, Koinuma K, Kawashima R, Ohzawa H, et al. Dipeptidyl peptidase (DPP)–4 inhibitor impairs the outcomes of patients with type 2 diabetes mellitus after curative resection for colorectal Cancer. Cancer Res Commun. 2021;1(2):106–14.
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
24. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials. 2007;28(2):105–14.
25. Sterne JAC, Harbord R. Funnel plots in meta-analysis. Stata J. 2004;4(2):127–41.
26. Sütő G, Molnár GA, Rokszin G, Fábián I, Kiss Z, Szekanecz Z et al. Risk of morbidity and mortality in patients with type 2 diabetes treated with sodium-glucose cotransporter–2 inhibitor and/or dipeptidyl peptidase–4 inhibitor: a nationwide study. BMJ Open Diabetes Res Care. 2021;9(1).
27. Chung MC, Hsu HT, Chang CH, Hung PH, Hsiao PJ, Wu LY, et al. Association of SGLT2 inhibitors with lower incidence of death in type 2 diabetes mellitus and causes of death analysis. Sci Rep. 2022;12(1):10147.
28. Suissa M, Yin H, Yu OHY, Wong SM, Azoulay L. Sodium-Glucose cotransporter 2 inhibitors and the Short-term risk of breast Cancer among women with type 2 diabetes. Diabetes Care. 2021;44(1):e9–11.
29. Heerspink HJ, Sjöström CD, Jongs N, Chertow GM, Kosiborod M, Hou FF, et al. Effects of Dapagliflozin on mortality in patients with chronic kidney disease: a pre-specified analysis from the DAPA-CKD randomized controlled trial. Eur Heart J. 2021;42(13):1216–27.
30. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.
31. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
32. Dabour Mohamed S, George Mina Y, Daniel Mary R, Blaes Anne H, Zordoky Beshay N. The cardioprotective and anticancer effects of SGLT2 inhibitors. JACC: CardioOncology. 2024;6(2):159–82.
33. Sun M, Sun J, Sun W, Li X, Wang Z, Sun L, Wang Y. Unveiling the anticancer effects of SGLT–2i: mechanisms and therapeutic potential. Front Pharmacol. 2024;15.
34. Villani LA, Smith BK, Marcinko K, Ford RJ, Broadfield LA, Green AE, et al. The diabetes medication Canagliflozin reduces cancer cell proliferation by inhibiting mitochondrial complex-I supported respiration. Mol Metabolism. 2016;5(10):1048–56.
35. Naeimzadeh Y, Tajbakhsh A, Nemati M, Fallahi J. Exploring the anti-cancer potential of SGLT2 inhibitors in breast cancer treatment in pre-clinical and clinical studies. Eur J Pharmacol. 2024;978:176803.
36. Papadopoli D, Uchenunu O, Palia R, Chekkal N, Hulea L, Topisirovic I, et al. Perturbations of cancer cell metabolism by the antidiabetic drug Canagliflozin. Neoplasia. 2021;23(4):391–9.
37. Dutka M, Bobiński R, Francuz T, Garczorz W, Zimmer K, Ilczak T et al. SGLT–2 inhibitors in Cancer Treatment-Mechanisms of action and emerging new perspectives. Cancers (Basel). 2022;14(23).
38. Basak D, Gamez D, Deb S. SGLT2 inhibitors as potential anticancer agents. Biomedicines. 2023;11(7).
39. Li H, Tong CW-S, Leung Y, Wong M-H, To KK-W, Leung K-S. Identification of clinically approved drugs indacaterol and Canagliflozin for repurposing to treat epidermal growth factor tyrosine kinase inhibitor-resistant lung cancer. Front Oncol. 2017;7:288.
40. Wu W, Zhang Z, Jing D, Huang X, Ren D, Shao Z, Zhang Z. SGLT2 inhibitor activates the STING/IRF3/IFN-β pathway and induces immune infiltration in osteosarcoma. Cell Death Dis. 2022;13(6):523.
41. Wang Y, Yang L, Mao L, Zhang L, Zhu Y, Xu Y, et al. SGLT2 Inhibition restrains thyroid cancer growth via G1/S phase transition arrest and apoptosis mediated by DNA damage response signaling pathways. Cancer Cell Int. 2022;22(1):1–16.
42. Nakano D, Kawaguchi T, Iwamoto H, Hayakawa M, Koga H, Torimura T. Effects of Canagliflozin on growth and metabolic reprograming in hepatocellular carcinoma cells: Multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT). PLoS ONE. 2020;15(4):e0232283.
43. Xu D, Zhou Y, Xie X, He L, Ding J, Pang S, et al. Inhibitory effects of Canagliflozin on pancreatic cancer are mediated via the downregulation of glucose transporter–1 and lactate dehydrogenase A. Int J Oncol. 2020;57(5):1223–33.

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