Diabetology & Metabolic Syndrome

REVIEW

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Comparative risk of cancer associated with SGLT inhibitors and DPP-4 inhibitors in patients with diabetes: a systematic review and meta-analysis

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Abstract

Aims This systematic review and meta-analysis aimed to compare the overall and site-specific cancer risk associated with SGLT2i versus DPP4i in patients with type 2 diabetes mellitus.

Methods We systematically searched PubMed, Scopus, and Web of Science for cohort studies comparing cancer incidence in adult type 2 diabetes patients treated with SGLT2i versus DPP4i. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model due to significant heterogeneity (I^2). Subgroup analyses by cancer type and publication bias assessment were performed.

Results Seventeen cohort studies met the inclusion criteria. Overall, SGLT2i use was associated with a significantly lower risk of incident cancer compared to DPP4i use (Pooled RR = 0.77, 95%CI:0.70–0.84; I^2=81.6%). Subgroup analyses revealed significantly lower risks for liver (RR = 0.76), lung (RR = 0.87), and prostate (RR = 0.75) cancers with SGLT2i. Trends towards lower risk were observed for colorectal (RR = 0.80) and stomach (RR = 0.69) cancers. No significant differences were found for bladder, breast, or pancreatic cancer risk.

Conclusion This meta-analysis suggests that SGLT2 inhibitors are associated with a reduced overall risk of cancer compared to DPP-4 inhibitors in patients with type 2 diabetes mellitus, particularly for liver, lung, and prostate cancers. However, these findings are based on observational data with significant heterogeneity and varying follow-up times, requiring additional long-term research to confirm.

Keywords Sodium-Glucose transporter 2 inhibitors, Dipeptidyl-Peptidase IV inhibitors, Diabetes mellitus, type 2, Neoplasms

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Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, also known as gliflozins, are a class of oral antidiabetic drugs used to treat type 2 diabetes mellitus (T2DM) [1]. The most widely used agents from this category are Empagliflozin, Canagliflozin, and Dapagliflozin [2]. SGLT-2 inhibitors received approval from the Food and Drug Administration (FDA) back in 2013 [3]. Beyond their glucose-lowering effects, SGLT2 inhibitors offer additional benefits, including weight loss, blood pressure management, and cardiovascular and renal protection even in non-diabetic patients [4, 5].

Dipeptidyl-peptidase-4 (DPP-4) inhibitors, known as gliptins, constitute a new class of oral antidiabetic agents. Such medications include Sitagliptin, Saxagliptin, and Linagliptin. DPP-4 inhibitors work by blocking DPP-4, preventing degradation of incretins, allowing for increased levels of active incretins in response to a meal and therefore enhanced insulin secretion and decreased glucagon secretion [6]. This glucose-dependent mechanism lowers blood sugar with a low risk of hypoglycemia [7]. They also show cardiovascular safety, though their renal benefits are not as strong as those observed with SGLT2 inhibitors [8]. DPP-4 inhibitors, which were approved by the FDA in the mid-2000s, are now an important addition to the options available to manage type 2 diabetes, especially in patients who may not tolerate other therapies well [9].

While both SGLT-2 inhibitors and DPP-4 inhibitors are effective in managing blood glucose levels, their long-term safety profiles, particularly concerning cancer risk, have received significant attention. Preclinical and mechanistic studies suggest that SGLT-2 inhibitors may exert protective effects against cancer by reducing hyperglycemia, lowering insulin levels, and improving metabolic parameters, which could theoretically mitigate cancer risk [10]. In contrast, DPP-4 inhibitors, which modulate incretin hormones and immune responses, have raised concerns due to their potential to promote tumor growth and angiogenesis, particularly in preclinical models [11]. However, clinical evidence remains inconclusive, with some studies reporting no significant increase in overall cancer risk associated with either drug class, while others suggest potential site-specific risks, such as bladder cancer with SGLT-2 inhibitors or pancreatic cancer with DPP-4 inhibitors [12, 13]. These discrepancies highlight the need for a comprehensive synthesis of existing data to clarify the comparative cancer risks associated with these medications.

Given the rising global prevalence of T2DM and the chronic nature of treatment, clarifying the comparative cancer risk between SGLT2 and DPP-4 inhibitors is a public health priority. This meta-analysis aims to systematically evaluate and compare the overall and site-specific cancer risks associated with these two drug classes to inform safer, evidence-based therapeutic choices.

Materials and methods

This systematic review and meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study was registered in PROSPERO (id: CRD420250649007). Our investigation was structured using the PICO framework, where the population comprised adult patients with T2DM; the intervention was treatment with SGLT2 inhibitors—including agents such as dapagliflozin, canagliflozin, empagliflozin, tofogliflozin, ertugliflozin, luseogliflozin, and bexagliflozin; the comparator was treatment with DPP-4 inhibitors; and the outcome of interest was the incidence of cancer, both overall and by specific cancer type.

A comprehensive literature search was performed across PubMed, Scopus, and Web of Science. In PubMed, for example, 90 articles were initially identified using a search string that combined both MeSH terms and free-text keywords. The search query incorporated terms for type 2 diabetes (such as "type 2 diabetes mellitus," "T2DM," or "T2D"), for SGLT2 inhibitors (including "Sodium-Glucose Transporter 2 Inhibitors," "SGLT-2i," "Gliflozins," "Sodium-Glucose Cotransporter-2 Inhibitors," among others), for DPP-4 inhibitors (e.g., "Dipeptidyl-Peptidase IV Inhibitors," "DPP-4 Inhibitors," "Gliptins," "DPP4I"), and for cancer-related outcomes (including "Neoplasms," "Cancer," "Malignancy," "Tumor," "Carcinoma," "Oncology"). Similar search strategies were applied in Scopus and Web of Science, yielding 494 and 58 articles, respectively. No restrictions were imposed regarding publication date or language during the initial search to capture all potentially relevant literature. To enhance sensitivity and minimize omission of negative findings, we used a broad vocabulary for malignancies and thoroughly reviewed each article, including supplementary materials. A manual citation screening of the reference lists of all included full-text articles and relevant systematic reviews was performed to identify any additional eligible studies.

Following the initial search, articles underwent a rigorous screening process. Two researchers independently reviewed titles and abstracts, excluding articles not directly relevant to the research question. if they were not directly related to our research question. Full-text screening was then performed, and studies were excluded if they were reviews, non-English publications, animal studies, case reports, or case series, or if they did not provide sufficient data on malignancy outcomes. In cases where multiple reports on the same study population were identified, the most complete or most recent report was retained. Ultimately, 17 articles met the

inclusion criteria and were selected for data extraction. The included cohort studies used both prospective and retrospective designs, and they followed distinct groups of patients with and without SGLT2i or DPP4i exposure over time to assess cancer incidence.

Data extraction was carried out independently by two reviewers using a pre-designed extraction form, and discrepancies were resolved by discussion or consultation with a third reviewer. From each included study, we extracted detailed bibliographic information (author, year of publication, study type, and country), participant characteristics (age, gender, and total number of patients), and intervention details (number of patients treated with SGLT2 inhibitors, specific drug names, and dosages). Comparator details, including the number of patients receiving DPP-4 inhibitors and their specific drug names, were also recorded. Key outcome data were extracted, including follow-up duration, primary outcome, cancer type, the number of cancer events in each treatment group, and reported effect estimates (odds ratios with corresponding lower and upper 95% confidence intervals).

Given that all included studies were cohort studies, the methodological quality of each study was assessed using the Newcastle-Ottawa Scale (NOS). No specific NOS score cut-off was used for study exclusion. Instead, the quality assessment results were used to assess the risk of bias and inform the interpretation of findings, with a focus on studies with a high risk. This evaluation focused on three domains: the selection of study cohorts (including representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and confirmation that the outcome of interest was absent at baseline), the comparability of cohorts (in terms of controlling for confounding factors), and the assessment of outcomes (considering the method of outcome assessment, follow-up duration, and completeness of follow-up). Any discrepancies between reviewers were resolved by consensus.

Meta-analysis was performed using STATA 17. The primary effect measure was the risk ratio (RR) with corresponding 95% confidence intervals, comparing the incidence of cancer between the SGLT2 inhibitor and DPP-4 inhibitor groups. Heterogeneity among studies was assessed using the I^2 statistic; an I^2 value below 50% was considered indicative of low heterogeneity. Due to high heterogeneity between studies, random-effects model was used. A two-tailed p-value of <0.05 was deemed statistically significant, with p-values <0.10 interpreted as suggestive of potential influence. Pre-specified subgroup analyses were conducted based on cancer type. Publication bias was evaluated through visual inspection of funnel plots as well as with Egger's test. Finally, the trim-and-fill method was used to adjust the observed asymmetry.

Results

The study selection process identified a total of 17 studies for inclusion in this systematic review and meta-analysis (Fig. 1). After screening titles and abstracts, full-text articles were assessed for eligibility, and all 17 studies met the inclusion criteria. These studies, published between 2021 and 2024, evaluated the comparative risk of cancer associated with SGLT inhibitors and DPP-4 inhibitors in patients with diabetes. The characteristics of the included studies varied in terms of sample size, population, and geographic location, with sample sizes ranging from small cohorts to larger populations. The included studies originated from the following countries: seven from China, three from the USA, two from Japan, two from Hungary, and one study each from Taiwan, Canada, and South Korea. The geographic locations of the included studies are as follows: 7 studies from China, 3 from the USA, 2 from Japan, 2 from Hungary, and 1 study each from Taiwan, Canada, and South Korea. Most of the included studies were cohort studies and the sample size ranged from 8408 to 873,320 participants (Table 1).

Risk of bias assessment indicated that the majority of studies had a low to moderate risk of bias, with common concerns related to potential confounding and incomplete outcome data. The results suggested that the risk of bias was high in 5 of the included studies [19, 21, 24, 25, 28]. The meta-analysis was conducted using a random-effects model due to significant heterogeneity among the studies (I^2 = 81.6%, $p=0.000$). The overall pooled effect size for the comparative risk of cancer was 0.77 (95% CI: 0.70–0.84), suggesting a lower risk associated with SGLT inhibitors compared to DPP-4 inhibitors. Effect sizes in individual studies ranged from 0.22 (95% CI: 0.04–0.38) to 1.01 (95% CI: 0.79–1.31. The forest plot visually summarized these findings, highlighting the consistency of the direction of effect across most studies despite the observed heterogeneity (Fig. 2).

Analysis based on the type of cancer

The subgroup analysis of the comparative risk of bladder cancer between SGLT inhibitors and DPP-4 inhibitors included five studies published between 2022 and 2024. The overall pooled effect size was 0.79 (95% CI: 0.51–1.04, I^2 = 79.4%, $p=0.001$), indicating no statistically significant difference in the risk of bladder cancer between the two groups (Fig. 3).

The subgroup analysis for the comparative risk of breast cancer included five studies, further exploring heterogeneity. The overall pooled effect size was 0.85 (95% CI: 0.71–1.01, I^2 = 68.8%, $p=0.012$), indicating no

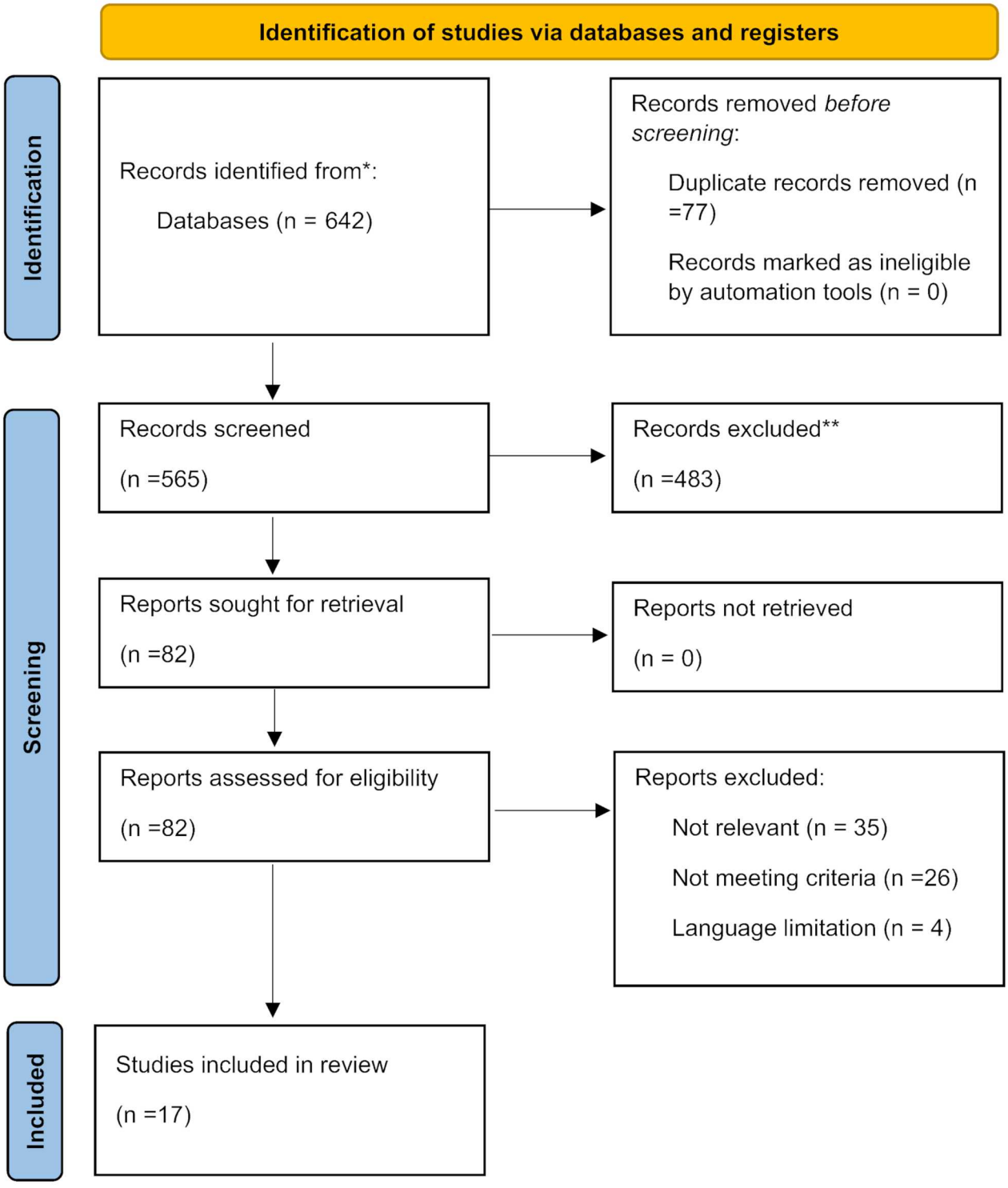

Fig. 1 Prisma flowchart illustrating the process of screening

significant difference in breast cancer risk between SGLT inhibitors and DPP-4 inhibitors (Fig. 3).

The subgroup analysis for the comparative risk of colorectal cancer included four studies, with an overall pooled effect size of 0.80 (95% CI: 0.56–0.98, I^2 = 49.1%, p = 0.117), suggesting a trend toward a lower risk with SGLT-2 inhibitors compared to DPP-4 inhibitors (Fig. 3).

Similar to the previous subgroup, the subgroup analysis for the risk of liver cancer included five studies, with an overall pooled effect size of 0.76 (95% CI: 0.62–0.95,

Table 1 Studies evaluating cancer risk in patients treated with SGLT2 inhibitors (SGLT2i) vs. DPP-4 inhibitors (DPP4i)

Author	year	type of study	country	Age	male	Number (total)	Number (SGLT2)	Number (DPP4)	cancer type	SGLT drug	DPP4 drug	Follow-up duration	Ref
Jie Zheng	2024	cohort	China	SGLT-2: 63 (55–69) DPP-4: 62 (55–69)	48,310 (all male)	48,310	24,155	24,155	prostate cancer	dapagliflozin canagliflozin Licogliflozin ertugliflozin empagliflozin	NR	1.33 years	[14]
Fengge Wang	2024	retrospective cohort	USA	SGLT-2: 62.76 (12.27) DPP-4: 64.23 (13.02)	0 (all female)	101,464	50,732	50,732	Breast Cancer	anagliflozin dapagliflozin empagliflozin ertugliflozin	sitagliptin saxagliptin linagliptin alogliptin vildagliptin	2.2 years	[15]
Yuta Suzuki	2024	retrospective cohort	Japan	SGLT-2: 66 (54–71) DPP-4: 65 (53–71)	17,442	26,823	8,941	17,882	all types of cancer	Dapagliflozin Empagliflozin Canagliflozin Tofogliflozin Ipragliflozin Luseogliflozin	NR	2.0 ± 1.6 years	[16]
Hui-Lin Sung	2024	retrospective cohort	Taiwan	SGLT-2: 56.94 ± 11.72 DPP-4: 58.76 ± 12.67	212,820	384,088	150,061	234,027	all types of cancer		Dapagliflozin Canagliflozin Empagliflozin	NR	[17]
Samantha B. Shapiro	2024	cohort	authors: Canada origin of data: UK	NR	NR	221,170	69,675	151,495	lung cancer	canagliflozin empagliflozin dapagliflozin ertugliflozin	alogliptin linagliptin saxagliptin sitagliptin vildagliptin	mean SGLT-2 inhibitor F/U: 2.4 years mean DPP-4 inhibitor F/U: 3.7 years	[18]
Takumi Kawaguchi	2024	retrospective cohort	Japan	SGLT-2: 62 ± 14 DPP-4: 62 ± 14	5164	8408	4,204	4,204	all types of cancer	NR	NR	12 months	[19]
Gábor Sütő	2021	retrospective cohort	Hungary	SGLT2i arm: 59.6 ± 10.0 DPP-4i arm: 59.8 ± 11.6	19,332	37,166 (both 18583)	18,383	18,316	any type of cancer	NR	NR	mean SGLT-2 inhibitor F/U: 639 days mean DPP-4 inhibitor F/U: 696 days	[20]
Phyo T. Htoo	2024	Comparative safety and effectiveness trial	USA	Empagliflozin: 62.5 ± 8.6 DPP-4i: 62.5 ± 8.7	103,390	230,232	115,116	115,116	all types of cancer	Empagliflozin	sitagliptin saxagliptin linagliptin alogliptin	median follow-up: 5 months (interquartile range: 3–10 months)	[21]
György Rokszin	2021	cohort (post-hoc analysis)	Hungary	SGLT2i arm: 59.6 ± 10.0 DPP-4i arm: 59.8 ± 11.6	19,332	37,166 (both 18583)	17,993	17,843	all types of cancer	NR	NR	mean SGLT-2 inhibitor F/U: 639 days mean DPP-4 inhibitor F/U: 696 days	[22]

Table 1 (continued)

Author	year	type of study	country	Age	male	Number (total)	Number (SGLT2)	Number (DPP4)	cancer type	SGLT drug	DPP4 drug	Follow-up duration	Ref
Sungho Bea	2023	cohort	south korea	SGLT-2i:53.9 DPP4i:61	506,874	873,320	74,830	798,490	liver	Dapagliflozin Empagliflozin Ipragliflozin	NR	mean SGLT-2:2.5 years: (1.6–3.7) Mean DPP-4: 3.6 years (2.2–4.9)	[23]
Ngai chiu Chan	2023	retrospective cohort	China	SGLT2i = 60.5 DPP4i = 61.2	SGLT2i = 7111 DPP4i = 6898	25,318	12,659	12,659	Colorectal	NR	NR	SGLT-2i = 1810 DPP4i = 1770	[24]
Hou In Chou	2023	retrospective cohort	China	62.2 (sd:12.8)	35,160	62,858	23,442	39,416	stomach	NR	NR	257,947.7 person year	[25]
Hou In Chou-1	2024	retrospective cohort	China	57 (SD = 10.7)	34,240	42,129	17,120	17,120	Prostate cancer	Empagliflozin Ertugliflozin Dapagliflozin Canagliflozin	Alogliptin Linagliptin Sitagliptin Linagliptin Saxagliptin Vildagliptin	DPP4i = 5.6 years (5.31–5.83) SGLT-2i = 5.62 years (5.35–5.83)	[26]
Hou In Chou-2	2024	retrospective cohort	China	58.6	40,333	44,308	22,154	22,154	liver	NR	NR	DPP4i = 5.52 years (IQR:5.19–5.78) SGLT-2i = 5.64 years (IQR:5.37–5.83)	[27]
Hou In Chou-3	2024	retrospective cohort	China	61.9 (SD:11.2)	7605	12,958	6479	6479	Pancreatic Cancer	NR	NR	1.42 years (IQR:0.73–2.8)	[28]
D. Abrahami	2022	cohort	UK-USA	sglt = 61.1 dpp4 = 65.7	sglt = 53.2 dpp4 = 49.3	1,200,245	347,059	853,186	Bladder	Canagliflozin dapagliflozin empagliflozin	NR	1.6–2.6 years	[29]
Cheuk To Chung	2023	retrospective cohort	China	58.2 (SD:11)	22,288	36,334	18,167	18,167	Any type of cancer	Canagliflozin dapagliflozin empagliflozin ertugliflozin	NR	NR	[30]

SGLT2i, sodium-glucose cotransporter-2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; NR, not reported

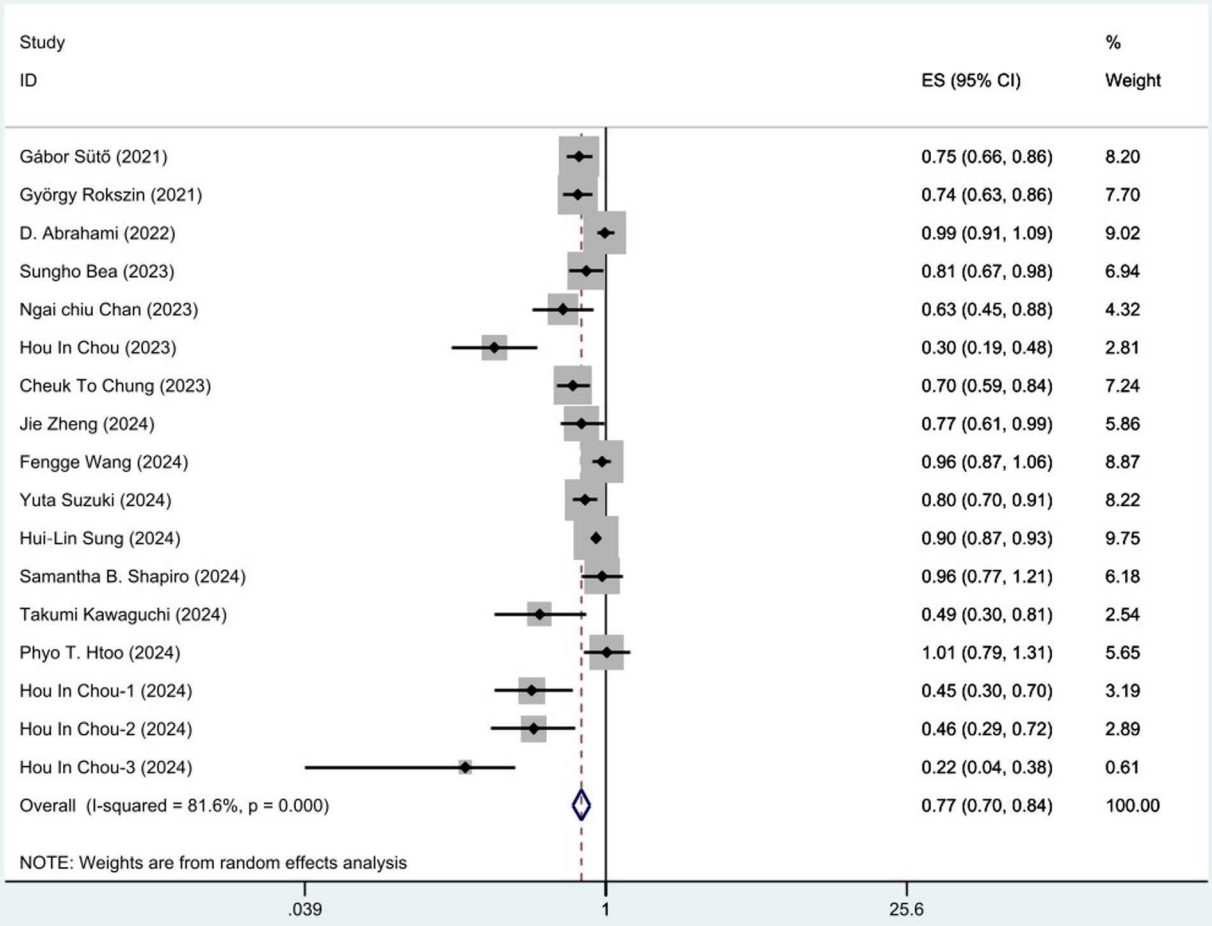

Fig. 2 Forest plot depicting the results of the meta-analysis assessing the overall cancer risk in patients using SGLT2 inhibitors compared to DPP-4 inhibitors. The plot presents individual study effect sizes with corresponding confidence intervals and weights. The diamond at the bottom represents the pooled effect size, summarizing the overall association between SGLT2 inhibitor use and cancer risk

I^2 = 59.6%, $p = 0.042$), indicating a statistically significant reduction in liver cancer risk with SGLT-2 inhibitors compared to DPP-4 inhibitors (Fig. 3).

The subgroup analyses for lungs, pancreas, prostate, and stomach cancers further explore the comparative risk between SGLT inhibitors and DPP-4 inhibitors (Fig. 4). For lung cancer, the overall pooled effect size was 0.87 (95% CI: 0.81–0.94, I^2 = 0.0%, $p = 0.814$), indicating a significant reduction in risk with SGLT inhibitors. For pancreatic cancer, the ES was 0.85 (95% CI: 0.63–1.14, I^2 = 55.2%, $p = 0.082$), suggesting no significant difference. For prostate cancer, the ES was 0.75 (95% CI: 0.58–0.97, I^2 = 75.4%, $p = 0.003$), showing a significant reduction in risk. For stomach cancer, the ES was 0.69 (95% CI: 0.22–1.08, I^2 = 62.2%, $p = 0.001$), indicating a trend toward reduced risk. These findings suggest varying protective effects of SGLT inhibitors across different cancer types, with the most consistent benefit observed in lung and prostate cancers.

Publication bias

The publication bias assessment for the study was conducted using a funnel plot and Egger's test (Fig. 5). The initial funnel plot showed slight asymmetry, suggesting potential publication bias, as smaller studies with null or negative results appeared to be missing. Egger's test confirmed this asymmetry with a statistically significant result ($p = 0.001$), indicating the presence of publication bias. To address this potential bias, we applied the trim-and-fill method, which imputed one study to adjust for the observed asymmetry (Fig. 5). After adjustment, the overall effect size changed slightly from 0.727 (95% CI: 0.631–0.837) to 0.737 (95% CI: 0.639–0.850). While the trim-and-fill analysis suggests that publication bias may have influenced the results, the robustness of the overall

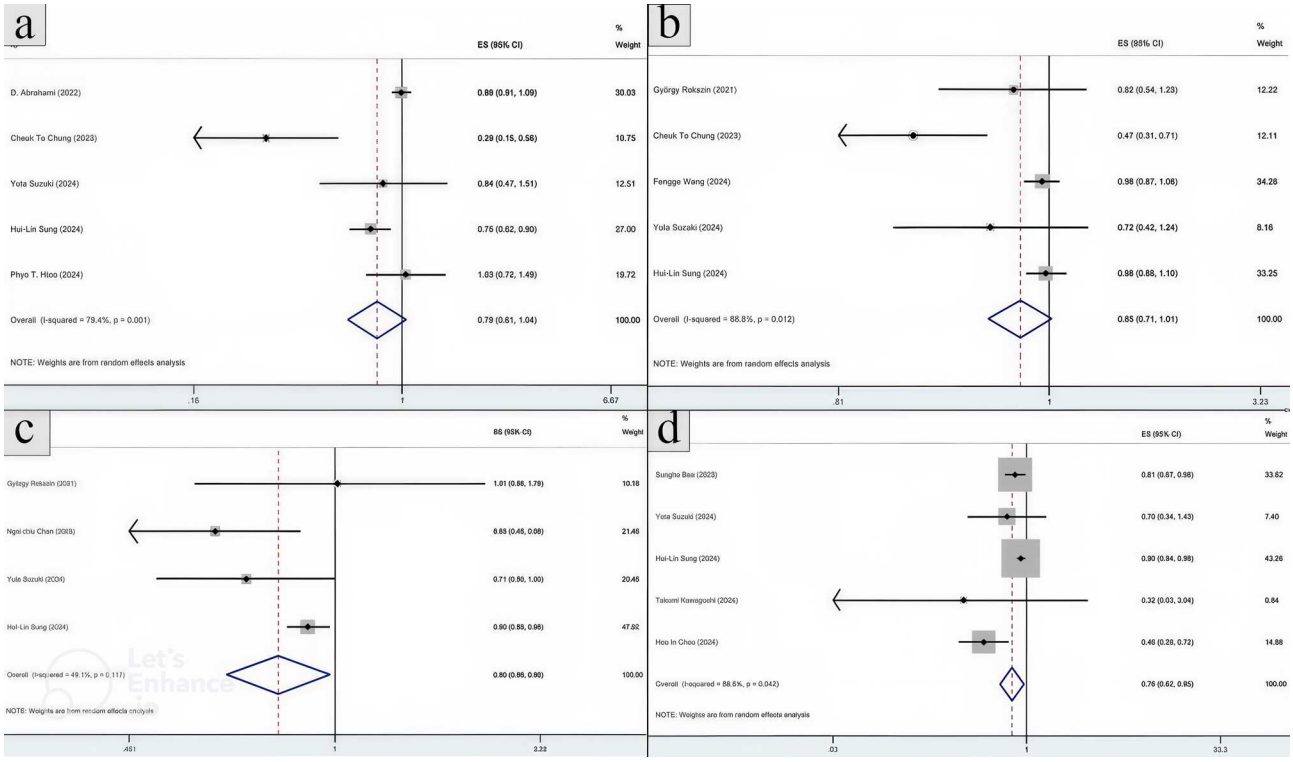

Fig. 3 Forest plots illustrating the results of the meta-analysis assessing the comparative cancer risk between SGLT2 inhibitors and DPP-4 inhibitors for specific cancer types: (**a**) bladder cancer, (**b**) breast cancer, (**c**) colorectal cancer, and (**d**) liver cancer. Each plot displays individual study effect sizes with corresponding confidence intervals and weights. The diamond at the bottom of each plot represents the pooled effect size, summarizing the overall association between SGLT2 inhibitor use and the risk of each cancer type

findings was maintained, as the effect size remained consistent and statistically significant.

Discussion

Overview of T2DM and cancer risk

T2DM is among the most prevalent non-communicable diseases globally, affecting approximately 828 million adults, with its incidence rising annually due to lifestyle changes [31]. It is commonly associated with risk factors such as hypertension, cardiovascular diseases, and metabolic syndrome [32]. Effective therapeutic management is crucial to preventing disease onset, progression, and associated complications. Given the substantial global burden, timely and safe interventions that provide the greatest benefits for this patient population can significantly mitigate its impact on public health.

T2DM is inherently associated with an increase of cancer risk. Cancers of the liver, pancreas, endometrium, colon, breast, and bladder have been shown to occur more frequently in individuals with T2DM, whereas prostate cancer appears to have a lower incidence in this population [33]. The increased cancer risk in diabetic patients is influenced by multiple factors, including hyperinsulinemia, hyperglycemia, obesity, and oxidative stress, all of which contribute to tumor initiation and progression [33]. Insulin, a key metabolic regulator, also exerts mitogenic effects, promoting malignant cell proliferation through both receptor and post-receptor mechanisms [33]. Additionally, variations in metabolic control, diabetes duration, and the pharmacologic agents used for treatment may further modify cancer risk [33]. While metformin appears to reduce cancer incidence, other glucose-lowering agents have a negligible or uncertain impact [33].

Mechanistic insights into SGLT2 and DPP-4 inhibitors

In this study, we have found that SGLT2 inhibitors are associated with a lower cancer incidence compared to DPP-4 inhibitors, a finding that may be explained through several mechanistic pathways. First, SGLT2 inhibitors appear to exert a protective effect by lowering circulating insulin levels; since obesity-related hyperinsulinemia acts as a potent mitogen, its reduction can diminish the stimulus for cellular proliferation and carcinogenesis [34]. In addition, the improved glycemic control achieved with SGLT2 inhibitors mitigates hyperglycemia, a factor that has been linked to cancer progression in various malignancies, thereby potentially reducing tumor-promoting metabolic stress [35]. Furthermore, these agents contribute to the improvement of metabolic syndrome, a

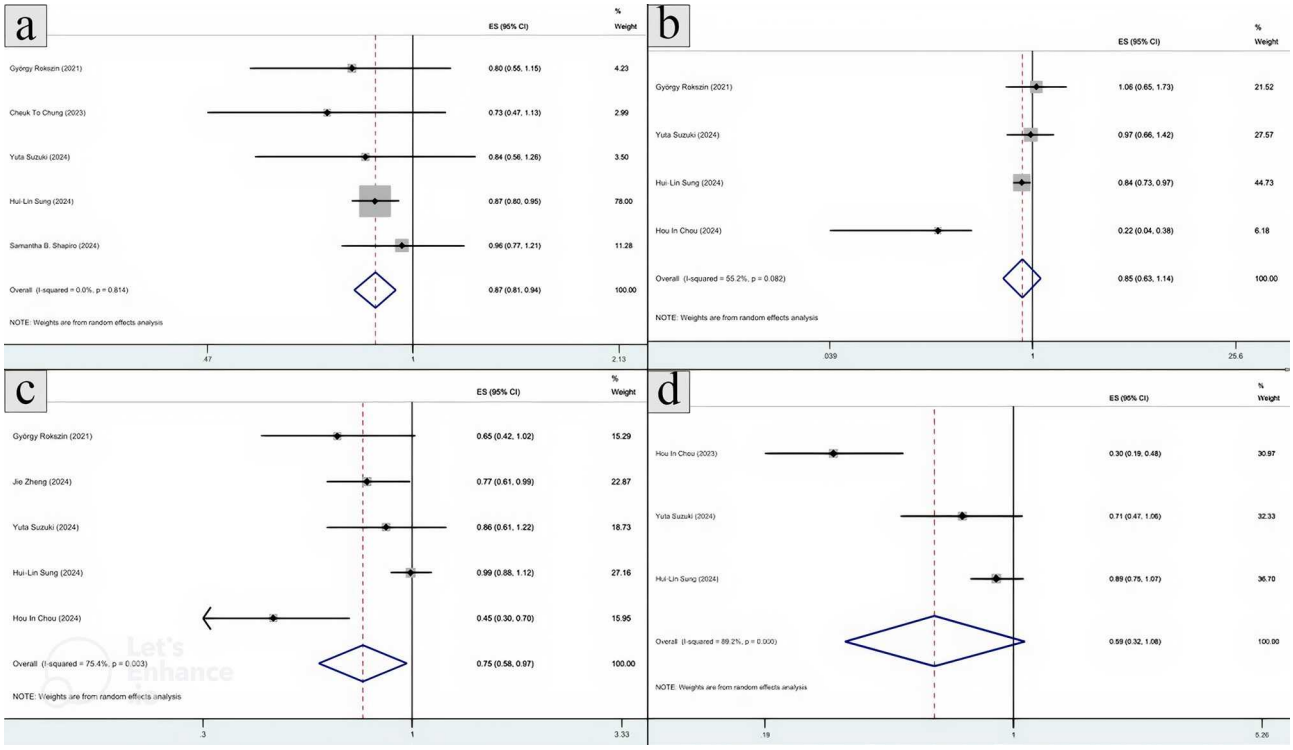

Fig. 4 Forest plots presenting the meta-analysis results comparing the cancer risk between SGLT2 inhibitors and DPP-4 inhibitors for (**a**) lung cancer, (**b**) pancreatic cancer, (**c**) prostate cancer, and (**d**) stomach cancer. Each plot includes individual study effect sizes with corresponding confidence intervals and study weights. The diamond at the bottom of each plot represents the overall pooled effect size, summarizing the association between SGLT2 inhibitor use and the risk of each cancer type

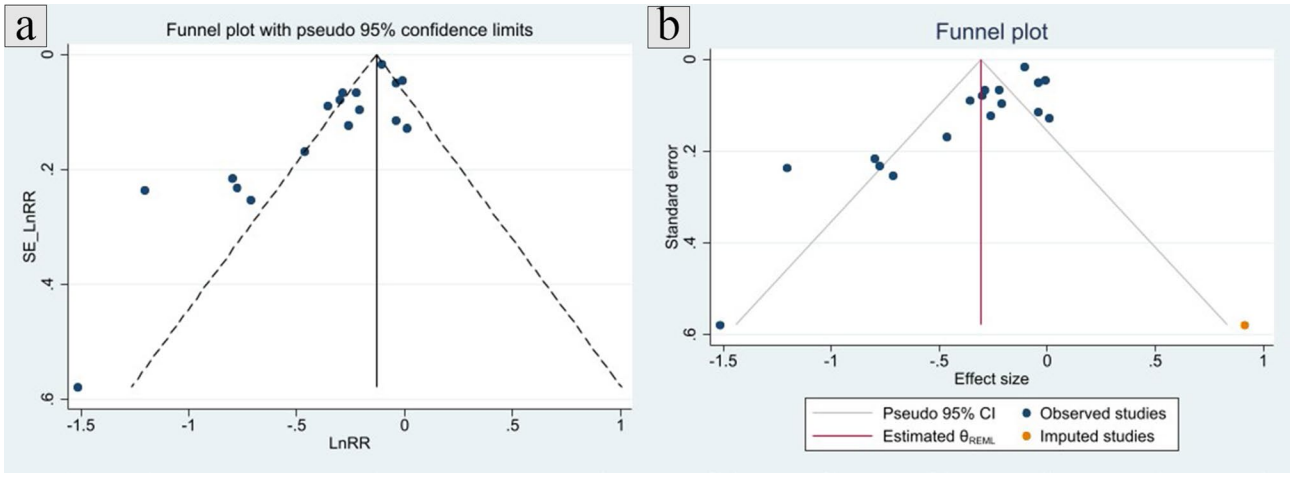

Fig. 5 (**a**) Funnel plot indicating a possible publication bias in the included studies. (**b**) The forest plot indicating the imputed study after performing Trim and fill analysis

cluster of conditions characterized by chronic inflammation, dyslipidemia, and insulin resistance, all of which are recognized as contributors to cancer development [36]. Another potential mechanism is the reduction of oxidative stress induced by hyperglycemia in T2DM, which plays a critical role in DNA damage, mutation accumulation, and cancer progression [37, 38]. SGLT2 inhibitors have also been reported to decrease oxidative stress by lowering glucose toxicity and improving mitochondrial function, which may further contribute to their protective effects against cancer [38].

In contrast, DPP-4 inhibitors, while effective at modulating incretin hormones to improve glycemic control, have shown complex and context-dependent effects on cancer risk. Some preclinical studies indicate that DPP-4 inhibition may influence tumor progression by altering

the tumor microenvironment, immune modulation, and inflammatory pathways. For instance, CD-26, the target of DPP-4 inhibitors, plays a role in T-cell activation and cytokine signaling, potentially affecting immune surveillance of tumors [39]. While certain studies suggest that DPP-4 inhibition may be associated with increased metastatic potential in some cancers, such as breast cancer, others indicate a protective effect in colorectal and lung cancer [39]. To date, meta-analyses on clinical studies have not established a significant association between DPP-4 inhibitor use and increased cancer risk, including pancreatic and thyroid cancer [39, 40], but a significant link has been found between these medications and other pancreatic events [40]. However, given the heterogeneity of findings and potential dose-dependent effects observed in some studies, further research is needed to clarify the long-term impact of DPP-4 inhibitors on carcinogenesis.

Certain other treatments used in T2DM have previously been associated with an increased risk of various cancers. Pioglitazone, a thiazolidinedione used to enhance insulin sensitivity, has been linked to a potential increase in bladder cancer risk [41]. Additionally, some evidence suggests that sulfonylureas may elevate the risk of pancreatic and colorectal cancer due to their affinity to induce hyperinsulinemia [42, 43]. Furthermore, GLP-1 receptor agonists have been associated with an increased risk of medullary thyroid carcinoma in rodent models [44]. Although earlier reports suggested a potential link between GLP-1 receptor agonists and an increased risk of pancreatic cancer, recent evidence has not supported this association [45–47].

Regarding renal cancer, preclinical evidence demonstrates high SGLT2 expression in clear-cell renal cell carcinoma and dapagliflozin's antiproliferative effects in vitro and in xenograft models [48, 49]. However, no clinical or large-scale observational study has systematically assessed renal malignancies in SGLT2 inhibitor users, likely due to the relatively low incidence of renal cancer within diabetic cohorts, the comparatively short exposure and follow-up periods in randomized trials and real-world databases, and the difficulty of capturing site-specific cancer outcomes in broad pharmacoepidemiologic analyses.

Comparison with previous studies

Prior systematic reviews and meta-analyses have examined cancer risk in patients treated with either SGLT2 inhibitors or DPP-4 inhibitors, but none have provided a direct, head-to-head comparison across multiple cancer types using real-world data. For instance, Li et al. performed a cumulative network meta-analysis of 46 randomized controlled trials up to February 2017 and reported no significant association between SGLT2 inhibitors and overall cancer risk (OR 1.14; 95% CI 0.96–1.36) [50]. Similarly, an extensive meta-analysis of 157 trials assessing DPP-4 inhibitors through September 2019 found no increased overall malignancy risk (MH-OR 0.93; 95% CI 0.86–1.00; $p = 0.07$) and even suggested a possible protective effect for colorectal cancer (MH-OR 0.70; 95% CI 0.53–0.94; $p = 0.02$) [51].

However, these studies were largely confined to placebo- or active-comparator RCTs and did not systematically synthesize observational evidence or focus on direct comparisons between SGLT2 and DPP-4 inhibitor classes. In contrast, our meta-analysis integrates 17 observational cohort studies from diverse geographic regions, specifically comparing cancer incidence in T2DM patients treated with SGLT2 versus DPP-4 inhibitors. We applied a random-effects model to accommodate substantial between-study heterogeneity (I^2 = 81.6%) and conducted trim-and-fill sensitivity analyses to address potential publication bias, thereby enhancing the reliability of our pooled estimates. Furthermore, by reporting cancer-type–specific effect sizes, our work delivers granular insights that previous broad-scope reviews did not, offering clearer guidance for clinicians and informing future updates to treatment guidelines.

Implications for clinical practice

Given these potential risks, careful evaluation of the risk-benefit profile of treatment options is essential. The current approach for T2DM management emphasizes the use of SGLT2 inhibitors alongside GLP-1 receptor agonists to mitigate cardiorenal risk in high-risk individuals [52]. To achieve and sustain optimal glycemic control and weight management, the use of SGLT2 inhibitors, GLP-1 receptor agonists, metformin, sulfonylureas, and thiazolidinediones is commonly recommended [52]. DPP-4 inhibitors are not typically prescribed as first-line treatment. Instead, they are administered as monotherapy in patients with contraindications to metformin or other glucose-lowering agents [53]. Their minimal risk of inducing hypoglycemia makes them a suitable option for individuals at high risk, such as elderly patients and those with chronic kidney disease [53]. However, due to their relatively modest glucose-lowering efficacy and higher cost, DPP-4 inhibitors are generally less preferred in clinical practice [53].

Limitations

Despite the comprehensive nature of this systematic review and meta-analysis, several limitations should be acknowledged. First, as most included studies were observational cohort designs, they are inherently subject to residual confounding and potential bias. Although we made efforts to mitigate this by extracting the most comprehensively adjusted effect estimates from each

study, it is impossible to account for all unmeasured or un-reported confounders. Therefore, the associations reported herein should not be interpreted as causal, such as selection bias and unmeasured confounders, that may influence the reported associations. Second, the heterogeneity among the included studies was substantial (I^2 = 81.6%), reflecting differences in study design, patient populations, follow-up durations, and methods of cancer diagnosis. While we attempted to account for this variability by employing a random-effects model and conducting subgroup analyses, residual heterogeneity may still influence the overall conclusions. We highly suggest that the pooled estimates should be interpreted with caution. Third, the duration of follow-up varied significantly among studies, with some having relatively short follow-up periods that may not capture the long-term effects of SGLT2 or DPP-4 inhibitors on carcinogenesis. Fourth, we were unable to assess the impact of specific drug types or dosages within the SGLT2 and DPP-4 inhibitor classes, limiting our ability to determine whether certain agents within these groups carry a higher or lower risk of cancer. Fourth, a limitation of our study is the potential for variability in cancer diagnosis across the included cohorts. Our analysis combined studies from various periods and regions where diagnostic criteria and technologies have likely evolved. Such differences in diagnostic standards, from imaging sensitivity to histopathological classification, could contribute to the observed statistical heterogeneity and affect the overall results. While we assume diagnoses were consistent with the standards of their time, this lack of uniformity represents a key consideration in the interpretation of our findings. Finally, a further limitation of our analysis is the evidence of publication bias. Visual inspection of the funnel plot revealed asymmetry, which was statistically confirmed by Egger's regression test. This suggests that smaller studies with null or negative findings may have been less likely to be published, potentially leading to an overestimation of the true effect. To quantify this impact, we performed a trim and fill analysis. This adjustment resulted in a more conservative pooled estimate. While our primary findings remain statistically significant, this evidence of publication bias underscores the need for caution and suggests that the true effect may be more modest than observed in our main analysis.

Conclusions

This systematic review and meta-analysis of 17 studies provides evidence that SGLT2 inhibitors are associated with a lower overall risk of cancer compared to DPP-4 inhibitors in patients with T2DM. The pooled effect size (effect size = 0.77, 95% CI: 0.70–0.84) suggests a significant protective effect of SGLT2 inhibitors. Subgroup analyses revealed no significant differences in the risk of bladder, breast, and pancreatic cancers between the two drug classes. However, SGLT2 inhibitors were associated with a significantly reduced risk of liver (effect size = 0.76), lung (effect size = 0.87), and prostate (effect size = 0.75) cancers, with a trend toward reduced risk in stomach (effect size = 0.69) and colorectal cancers (effect size = 0.80). While publication bias was detected, sensitivity analysis using the trim-and-fill method confirmed the robustness of the findings, with minimal changes in effect size. These findings may inform clinical decision-making by highlighting the potential oncologic benefits of SGLT2 inhibitors over DPP-4 inhibitors, particularly in patients with type 2 diabetes at higher baseline risk for certain cancers. As such, they could support updates to treatment guidelines that emphasize long-term safety profiles alongside glycemic control when selecting second-line therapies for T2DM.

Abbreviations

SGLT2	Sodium–Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus
FDA	Food and Drug Administration
DPP	4–Dipeptidyl–Peptidase 4
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta–Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PICO	Population, Intervention, Comparator, Outcome
NOS	Newcastle–Ottawa Scale
RR	Risk Ratio
CI	Confidence Interval
I^2	I–squared (a measure of heterogeneity in meta–analysis)

Supplementary Information

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Supplementary Material 1

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Author contributions
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Declarations

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