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Systematic review and meta-analysis of the association between the use of SGLT2 inhibitors and hepatocellular carcinoma

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Abstract

Introduction: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are increasingly recognized for their potential role beyond glycemic control, particularly in the context of hepatocellular carcinoma (HCC). This systematic review and meta-analysis aims to evaluate the association between SGLT2 inhibitor use and the incidence or prognosis of HCC, drawing on emerging evidence that suggests these agents may improve liver function and reduce cancer cell proliferation.

Materials and Methods: This investigation was executed in accordance with the PRISMA guidelines, employing a systematic review and meta-analysis methodology. In this investigation, the databases ProQuest, PubMed, Embase, Web of Science, Cochrane, as well as the Google Scholar search engine, were scrutinized until August 25, 2024. The analysis of the data was conducted utilizing STATA 14 software, with the threshold for statistical significance established at $P<0.05$.

Results: In seven reviewed studies, 422,174 individuals were evaluated, and the results indicated that there was no significant association between the use of SGLT2i and HCC (HR: 0.65; 95% CI: 0.41, 1.01). However, SGLT2i use reduced the risk of HCC by 36% compared to dipeptidyl peptidase-4 inhibitors (DPP4) and by 73% compared to beta blockers. The use of SGLT2i decreased the risk of HCC in women (56%) and men (55%). In Asia, there was no significant relationship between SGLT2i use and HCC (HR: 0.57; 95% CI: 0.27, 1.16), while in Europe and the Americas, it reduced the risk of HCC by 22% and 32%, respectively. Among patients aged 50 to 59 years, there was no significant association between SGLT2i use and HCC (HR: 0.89; 95% CI: 0.63, 1.25), but in those aged 60 to 69 years, SGLT2i use resulted in a 62% reduction in HCC risk. There was no significant association between SGLT2i use and liver cirrhosis (HR: 0.98; 95% CI: 0.76, 1.26).

Conclusion: In conclusion, while the overall analysis reveals no significant association between SGLT2 inhibitor use and HCC, the findings suggest a noteworthy reduction in HCC risk compared to other treatments, particularly in older adults and across different regions. These results highlight the potential benefits of SGLT2 inhibitors in mitigating HCC risk, warranting further investigation to clarify their role in liver cancer prevention.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024593426) and Research Registry (UIN: reviewregistry1888) websites.

Introduction

In the year 2020, hepatocellular carcinoma (HCC) ranked as the sixth most prevalent neoplasm globally and constituted the third principal etiological factor for mortality attributed to neoplastic diseases (1). HCC accounts for approximately 75 to 85 percent of primary liver cancers (2,3), and several antidiabetic drugs have shown promising antitumor effects against HCC (4,5).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) represent a novel category of medications for diabetes management that enhance the elimination of glucose through urine (6). In addition to their hypoglycemic effects, SGLT2 inhibitors have shown

Key point

The findings from the reviewed studies suggest that while there is no significant overall association between SGLT2 inhibitors (SGLT2i) and hepatocellular carcinoma (HCC), their use may confer a protective effect against HCC, particularly when compared to dipeptidyl peptidase-4 inhibitors and beta blockers. Specifically, the administration of SGLT2i was associated with a notable reduction in HCC risk across different demographics, with a 36% decrease compared to DPP4 inhibitors and a 73% decrease compared to beta blockers. Furthermore, the data indicate that this protective effect is consistent across genders and is particularly pronounced in older age groups, with a 62% reduction in risk for those aged 60 to 69 years. However, geographic variations were observed, since the protective association was not significant in Asia, while it showed reductions in Europe and the Americas. Additionally, SGLT2i use did not demonstrate a significant relationship with liver cirrhosis, indicating that while SGLT2i may reduce HCC risk, their impact on liver disease more broadly remains unclear.

beneficial effects on body weight and liver enzymes, leading to a reduction in the progression of metabolic disorder-related liver steatosis (7). The benefits of these inhibitors on liver function have also been demonstrated in type 2 diabetes individuals and non-alcoholic fatty liver disease (8).

The anticancer effect of SGLT2 inhibitors, after diabetes, cardiology, and nephrology, is an area where these drugs can be utilized (9). A study involving 2000 participants showed that the use of SGLT2i was linked to a 46% decrease in the risk of HCC among patients with type 2 diabetes and chronic hepatitis B (10). The positive impacts of these inhibitors on HCC may involve hindering glucose absorption by cancer cells, promoting weight loss, lowering inflammation, or reducing oxidative stress (9,11-13). However, in a cohort study conducted in Korea, researchers demonstrated that SGLT2 inhibitors are a risk factor for HCC (14). The correlation between SGLT2i and HCC has attracted great attention in recent years, particularly due to the inconsistent findings reported in various studies. While some research suggests that SGLT2 inhibitors may confer protective effects against HCC, other studies indicate a potential increased risk. This variability in results necessitates a comprehensive evaluation to clarify the true impact of SGLT2 inhibitors on HCC risk

Objectives

The objective of this systematic review and meta-analysis is to evaluate and clarify the association between the use of SGLT2i and the risk of developing HCC. The analysis will focus on identifying patterns in data across various populations and study designs, thereby providing a comprehensive assessment that can inform clinical practice and guide future research directions in the context of diabetes management and liver health.

Materials and Methods

Study design

To design this systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (15) was utilized, and the study protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) and Research Registry websites.

PICO components

- Population: Studies that addressed the association between the use of SGLT2 inhibitors and HCC.
- Exposure/Intervention: Use of SGLT2 inhibitors.
- Comparison: Individuals who did not use SGLT2 inhibitors.
- Outcomes: Risk of HCC.

Search strategy

Using the keywords Sodium-Glucose Transporter 2 Inhibitors, SGLT-2 Inhibitor, Gliflozins, Liver Neoplasms, Hepatocellular Cancer, Hepatic Neoplasm, along with their MeSH equivalents, the ProQuest, PubMed, Embase, Web of Science, Cochrane, and the Google Scholar databases were searched up to August 25, 2024. The search process was conducted without any time or location restrictions. For advanced searching, the keywords were combined using logical operators (AND, OR), and for manual searching, the reference lists of selected studies were reviewed. The search strategy in the PubMed database is outlined as follows:

(Sodium-Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitor OR Gliflozins) AND (Liver Neoplasms OR Hepatocellular Cancer OR Hepatic Neoplasm)

Inclusion and exclusion criteria

Studies that examined the association between SGLT2 inhibitors and HCC use were included in the study. However, studies with incomplete data, duplicate studies, case reports, posters, and reviews, as well as low-quality studies, studies for which the full text was not available, and studies that investigated the combined effect of SGLT2 inhibitors and another ant diabetic medication on HCC were excluded from the review process.

Qualitative assessment

Two authors evaluated the cohort studies using the Newcastle Ottawa Scale (NOS) checklist. In this checklist, each question was awarded a maximum of one star, and only the question related to comparison could receive two stars. Therefore, the minimum score was zero (indicating the weakest quality) and the maximum score was ten (indicating the highest quality) (16). The Strengthening the Reporting of Observational Studies in Epidemiology using the Mendelian Randomization (STROBE-MR) checklist was used to assess the Mendelian randomization study. This checklist contained 20 questions that covered various aspects of a research study (17).

Data extraction

Two authors conducted this phase. The following

information was extracted from each study: author name, study design, age, continent, country, sample size, study duration, kind of disease, comparison group, the relationship between SGLT2 inhibitor use and HCC (including its upper and lower limits), study duration, and the association between SGLT2 inhibitor use and liver cirrhosis.

Statistical analysis

For the analysis of the collected data, the logarithm of the hazard ratio (HR) was used, and ultimately the studies were combined. The heterogeneity of the studies was assessed using the Cochrane Q test and the I^2 index. Due to significant heterogeneity in this study (I^2=90.1%), a random-effects model was employed. Subgroup analysis was conducted to examine the relationship between SGLT2 inhibitor use and HCC based on variables such as age, continent, comparison group, and study type. Additionally, meta-regression and publication bias analyses were performed. Data analysis was conducted using STATA 14 software, and a significance level of $P < 0.05$ was considered for the tests.

Results

Study selection

After searching the databases, 418 studies were found. Of these, 223 studies were duplicates and were removed. Subsequently, 195 studies proceeded to the next stage, and by reviewing the information in the abstracts, 36 studies were eliminated due to incomplete abstract information and the unavailability of their full texts. The full texts of 159 studies were reviewed, and 48 studies that did not report essential data for data analysis were excluded. From the remaining 111 articles, 104 studies were removed based on other exclusion criteria, leaving 7 studies (Figure 1).

In this study, 7 studies were systematically reviewed, comprising 6 cohort studies and one Mendelian randomization study, to evaluate the association between SGLT2i use and HCC. The primary index analyzed across all studies was the HR, which quantifies the risk of developing HCC associated with SGLT2 inhibitors. The study included a substantial sample size, with 173 099 individuals using SGLT2 inhibitors compared to 249 075 individuals in the comparison group (Table 1).

Main outcome

In Figure 2, the relationship between SGLT2i usage and HCC was assessed, revealing that there was no statistically significant correlation between the use of SGLT2 inhibitors and the risk of developing HCC (HR: 0.65; 95% CI: 0.41, 1.01).

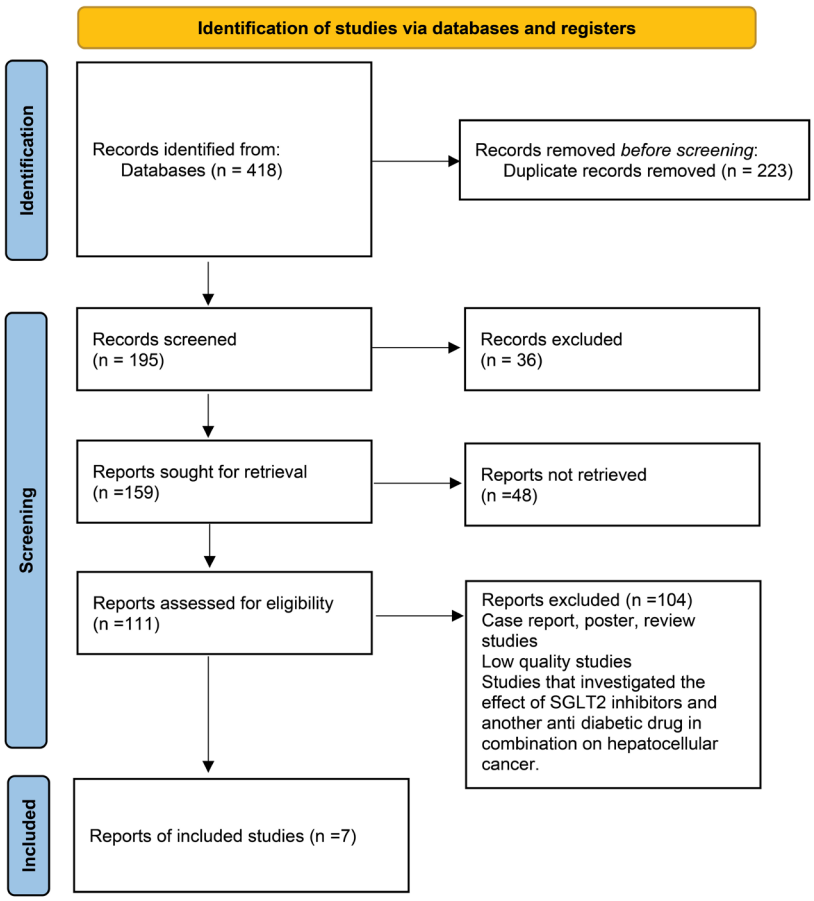

Figure 1. PRISMA Flowchart of the study.

Table 1. A summary of the information of the reviewed articles

Author, year	Continent	Country	Design	Sample size in SGLT2 group	Mean age in SGLT2 group (year)	Sample size in compare group	Mean age in compare group (year)	Duration of study	Patients	Compared with
Shen TH, 2024 (18)	America	USA	Cohort	22100	53.2	22551	53.2	Jan 1, 2014 to 31 Dec 2022	T2D and MASLD	DPP4
Mao X, 2024 (19)	America	USA	Cohort	53628	53.5	53628	54.2	Apr 2013 and Dec 2021	T2D and MASLD	NR
Chou OH, 2024 (20)	Asia	China	Cohort	22154	62.8	40545	62.8	between Jan 1, 2015, and Dec 31, 2020	T2D	DPP4
Cho HJ, 2024 (14)	Asia	South Korea	Cohort	53986	50.37	53986	50.61	between Jan 1, 2014, and Dec 31, 2021	Fatty liver disease and diabetes	NR
Chung SW, 2024 (21)	Europe	UK Biobank	Mendelian randomization	13208	55.3	70342	56.4	2006 to 2010	Diabetes	DPP4
Hu WS, 2023 (22)	Asia	Taiwan	Cohort	7023	60.21	7023	60.39	between 2016 and 2018	Hepatitis B or C virus infection and diabetes mellitus	Beta-blocker
Lee CH, 2023 (10)	Asia	China	Cohort	1000	60.7	1000	61	between 2015 and 2020	T2D and hepatitis B infection	NR

NR: Not reported; T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; SGLT2: Sodium-glucose transporter 2; DPP4: Dipeptidyl peptidase-4.

Subgroup analysis

In the analysis of data using continent-based subgrouping, the results found no correlation between SGLT2 inhibitor use and HCC in Asia (HR: 0.57; 95% CI: 0.27, 1.16). However, in Europe (HR: 0.78; 95% CI: 0.64, 0.94) and America (HR: 0.68; 95% CI: 0.48, 0.96), the use of SGLT2 inhibitors was associated with a reduction in HCC risk (Figure 3).

In Figure 4, the analysis of data using age-based subgrouping found no significant correlation between SGLT2 inhibitor use and the risk of HCC in patients aged 50 to 59 years (HR: 0.89; 95% CI: 0.63, 1.25). However, in individuals aged 60 to 69 years, the use of SGLT2 inhibitors resulted in a reduction in HCC risk (HR: 0.38; 95% CI: 0.24, 0.59).

In Figure 5, the analysis of data according to the study design showed that there was no statistically significant relationship between SGLT2i use and HCC risk in cohort studies (HR: 0.65; 95% CI: 0.38, 1.11). However, in the Mendelian randomization study, the use of SGLT2i resulted in a reduction in HCC risk (HR: 0.68; 95% CI: 0.48, 0.96).

The analysis of data by gender demonstrated that the SGLT2i use decreased the HCC risk in both women (HR:

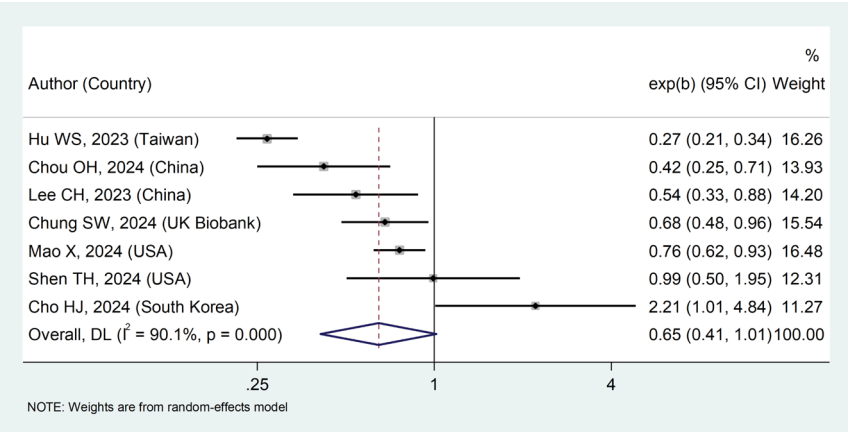

Figure 2. Forest of the correlation between the use of SGLT2i and HCC.

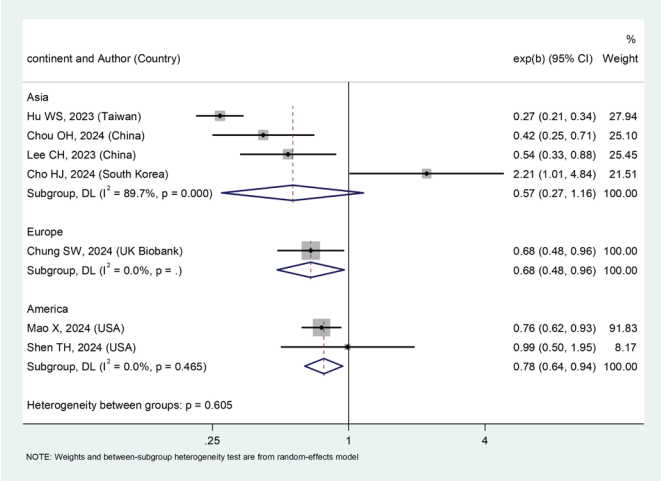

Figure 3. Forest of the relationship between the use of SGLT2i and HCC by continent.

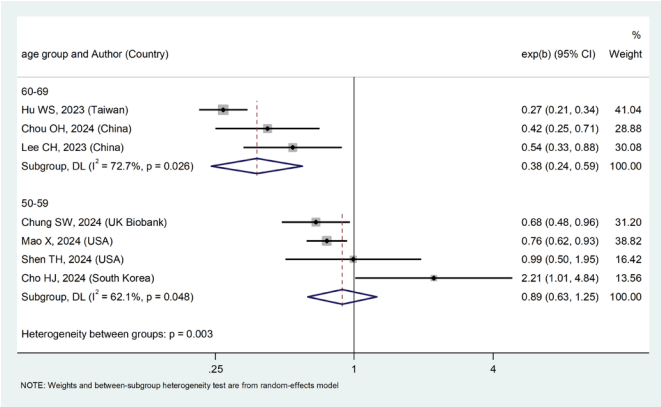

Figure 4. Forest of the relationship between the use of SGLT2i and HCC by age.

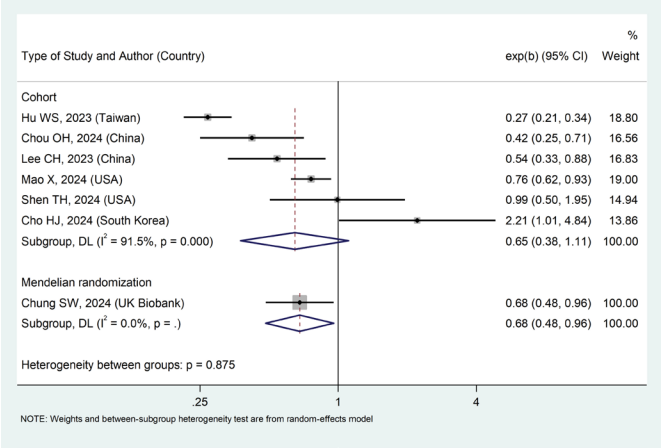

Figure 5. Forest of the relationship between the use of SGLT2i and HCC by study design.

0.44; 95% CI: 0.31, 0.63) and men (HR: 0.45; 95% CI: 0.21, 0.97) (Figures 6 and 7).

The use of SGLT2 inhibitors reduced the risk of HCC compared to both DPP4 inhibitors (HR: 0.64; 95% CI: 0.42, 0.97) and beta blockers (HR: 0.27; 95% CI: 0.21, 0.34) (Figure 8).

In Figure 9, the relationship between SGLT2 inhibitor use and the risk of liver cirrhosis was examined, and the results indicated that there was no statistically significant association between them (HR: 0.98; 95% CI: 0.76, 1.26).

The meta-regression analysis demonstrated that there was no significant association between the "impact of

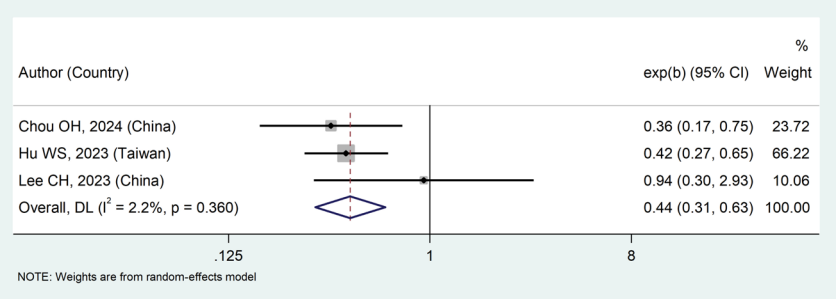

Figure 6. Forest plot of correlation between use of SGLT2i and HCC in females.

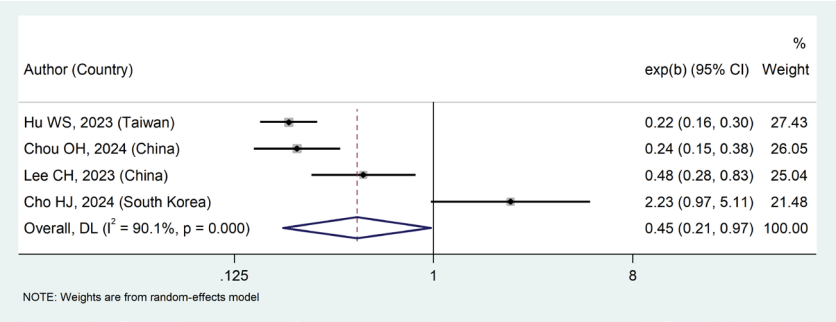

Figure 7. Forest plot of correlation between use of SGLT2i and HCC in males.

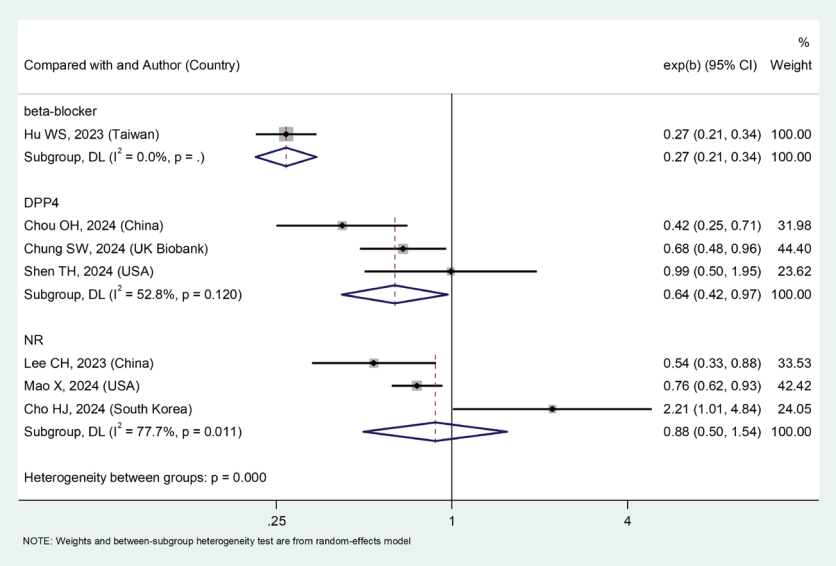

Figure 8. Forest plot showing the association between SGLT2 inhibitor use and HCC compared to other drugs.

SGLT2 inhibitor use on the risk of HCC" and the year of study publication (P = 0.137) or the sample size of the studies (P= 0.103; Figures 10 and 11).

Regarding the publication bias of the included studies, the publication bias chart indicated that there was no publication bias present (P=0.512), and the resource search phase was conducted without bias (Figure 12).

Discussion

The findings of our investigation indicated that there was no statistically significant correlation between the intake of SGLT2 inhibitors and the incidence of HCC. However, the SGLT2i use decreased the risk of HCC compared to DPP4 (36%) and compared to beta blockers (73%). Additionally, the consumption of SGLT2i reduced the risk of HCC in individuals aged 60 to 69 years (62%), women (56%), men (55%), in the United States (32%), and in Europe (22%).

According to the research by Zhang et al, in European populations, the use of SGLT2i was correlated with a significant reduction in thyroid cancer risk (OR: 0.051, 95% CI: 0.006-0.465). In the current study, the use of SGLT2i in the European population also resulted in a 22%

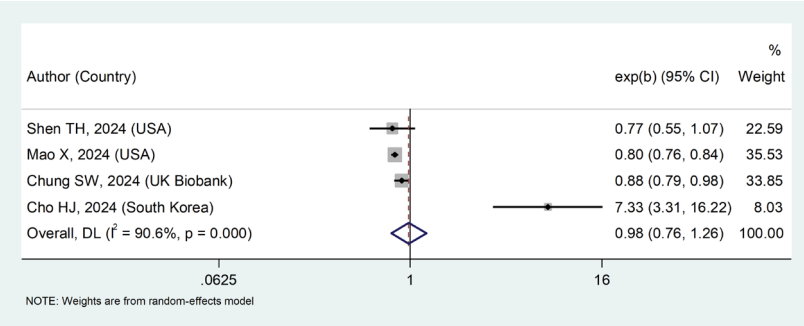

Figure 9. Forest plot of the relationship between use of SGLT2i and liver cirrhosis.

reduction in the HCC risk, which was consistent with Zhang and colleagues' study (23).

In a meta-analysis performed by Xu et al aimed at examining the impact of SGLT2i on cancer, there was no significant relationship between the SGLT2i use and cancer risk compared to placebo (RR: 1.01; 95% CI: 0.94-1.08). Overall, SGLT2 inhibitors did not have a significant effect on the risk of gastrointestinal, thyroid, skin, respiratory, prostate, endometrial, liver, and pancreatic cancers (24). In a meta-analysis by Spiazzi et al, the researchers sought to investigate the connection between SGLT2 inhibitors and cancer outcomes. The findings revealed that SGLT2 inhibitors did not influence the overall risk of cancer (RR: 1.03; 95% CI: 0.96-1.10) or cancer-related mortality (RR: 0.99; 95% CI: 0.85-1.16) (25).

The meta-analysis conducted by Shi et al found that the use of SGLT2 inhibitors did not elevate the risk of cancer in patients with type 2 diabetes when compared to the control group, showing no significant association between SGLT2 inhibitor use and cancer risk (RR: 1.05, 95% CI: 0.97–1.14) (26). Dicembrini et al in a meta-analysis found no significant difference in the risk of developing malignancy between the SGLT2i user group and the comparison group (OR: 0.98, 95% CI: 0.77–1.24) (27).

In the research by Tang et al, SGLT2i did not increase the overall cancer risk compared to comparator drugs (placebo or other active glucose-lowering treatments) (OR: 1.14, 95% CI: 0.96-1.36) (28). The results of these studies were consistent with the overall findings of the current study. Our study aligned with the previous studies in terms of study type and outcome but differed in terms of the type of cancer examined. While previous studies assessed overall cancer risk, our study focused on the risk of HCC. This may explain why our study reported a significant association between SGLT2i and HCC risk in some subgroups.

In the cohort study by Lin et al, no association was found between SGLT2i and kidney cancer (OR: 1.00, 95% CI: 0.99-1.00). The results of this study were consistent with the current study, as no significant association between SGLT2i and HCC was observed in our cohort studies (29).

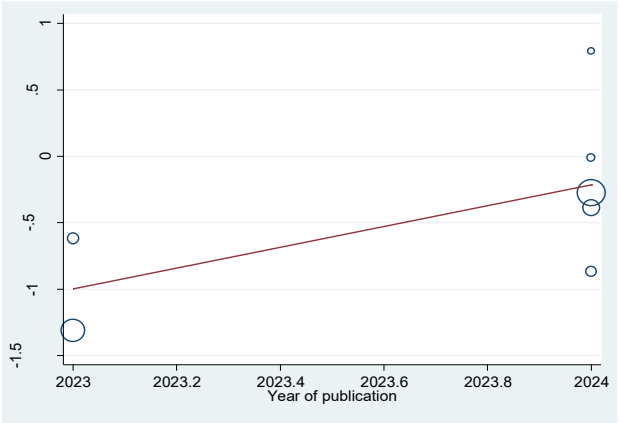

Figure 10. Meta-regression plot of the association between use of SGLT2i and HCC with year of publication.

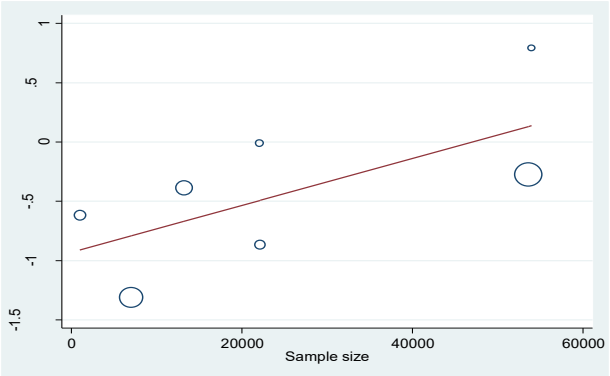

Figure 11. Meta-regression plot of the correlation between use of SGLT2i and HCC with sample size.

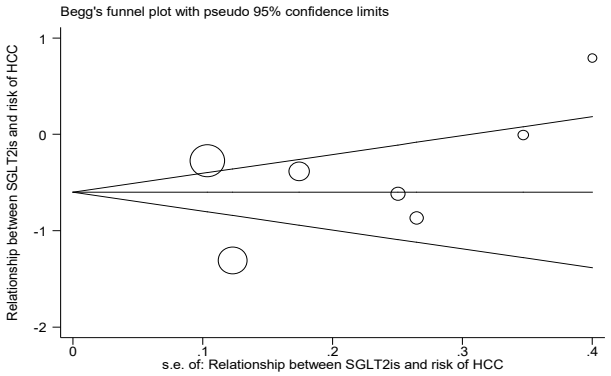

Figure 2. Publication bias.

Based on the results of a study conducted by Wang et al involving 158,483 women with type 2 diabetes, there was no significant association between the use of SGLT2i and breast cancer risk in adults (HR: 0.96; 95% CI: 0.87-1.06) (30). The results of this study were not in agreement with our current study, as the use of SGLT2i in women led to a 56% reduction in HCC risk in our research. However, in the study by Lin and colleagues, SGLT2i use was associated with a reduced risk of prostate cancer (OR: 0.31, 95% CI: 0.21-0.47) (29). In our current study, SGLT2i use in men also resulted in a 55% reduction in HCC risk, aligning with the aforementioned study.

Benedetti et al conducted a meta-analysis on hyperglycemic patients and concluded that SGLT2i reduced the overall cancer risk compared to placebo (RR: 0.35, 95% CI: 0.33-0.37) (31). In a retrospective cohort study conducted by Chan et al involving 13,029 individuals, the use of SGLT2i was associated with a reduced risk of colorectal cancer (HR: 0.52; 95% CI: 0.38-0.72) (32). In the cohort study by Lin et al, the results showed that SGLT2i were associated with a reduced risk of bladder cancer (OR: 0.98, 95% CI: 0.97-0.99) (29). In the current study, SGLT2i also reduced the risk of HCC compared to DPP4 and beta blockers, confirming the findings of the previous studies. The properties of SGLT2i, such as blocking glucose absorption by cancer cells, weight loss, reduced inflammation, and decreased oxidative stress, may explain the reduced cancer risk observed in SGLT2i users.

Conclusion

The findings underscore a complex relationship between SGLT2i and HCC, revealing that while no significant overall association exists, there is compelling evidence suggesting a protective effect against HCC, particularly when juxtaposed with other diabetes medications such as DPP4 inhibitors and beta blockers. The observed 36% reduction in HCC risk compared to DPP4 inhibitors and an impressive 73% reduction compared to beta blockers highlight the potential of SGLT2i as a beneficial therapeutic option for patients with type 2 diabetes, especially considering that this protective effect is consistent across genders and significantly pronounced in older adults, with a remarkable 62% reduction in risk for those aged 60 to 69 years. However, the geographic discrepancies noted in the data where the protective association was not significant in Asia but showed reductions in Europe and the Americas suggest that further research is needed to understand the underlying factors contributing to these variations. Additionally, the lack of a significant relationship between SGLT2i use and liver cirrhosis raises important questions about the broader implications of these medications on liver health, indicating that while SGLT2i may play a role in reducing HCC risk, their effects on liver disease overall remain uncertain. These findings call for a nuanced interpretation of SGLT2i use in clinical practice and highlight the necessity for further investigations to elucidate their mechanisms of action and potential benefits in diverse populations, ultimately aiming to optimize diabetes management strategies while safeguarding against liver-related complications.

Limitations of the study

The reviewed studies presented several limitations that warrant consideration. Firstly, the specific type and dosage of SGLT2i utilized in the studies were not clearly defined, precluding the possibility of conducting a subgroup analysis based on these variables. Furthermore, the distribution of studies across different geographic regions was inconsistent, which may affect the generalizability of the findings. Additionally, some studies failed to specify the type of medication used in the comparison group, introducing variability that could influence outcomes. Lastly, the overall number of studies available for review in this area was limited, which may constrain the robustness of the conclusions drawn from this analysis.

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Authors' contribution

Conceptualization: Ehsan Shabani and Mahin Roozitalab.
Data curation: Mahmoud Dehghani-ghorbi and Ehsan Shabani.
Formal analysis: Shahrzad Ebrahimi and Seyede Mozhgan Heidari.
Investigation: Anna Ghorbani Doshantapeh and Seysed Ali Vatankhah.
Methodology: Seyede Mozhgan Heidari and Afsaneh Mirshekari.
Project management: Mahmoud Dehghani-ghorbi.
Resources: All authors.
Supervision: Ehsan Shabani.
Validation: Hossein Zarei and Anna Ghorbani Doshantapeh.
Visualization: Hossein Zarei and Seysed Ali Vatankhah.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website with (ID: CRD42024593426) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1888). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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