Check for updates

Received: 15 March 2023 | Revised: 23 January 2024 | Accepted: 22 February 2024

DOI: 10.1002/dmrr.3797

RESEARCH ARTICLE

WILEY

SGLT2 inhibition and three urological cancers: Up-to-date results

Lede Lin[1] | Kang Ning[2,3] | Liyuan Xiang[4] | Liao Peng[1] | Xiang Li[1]

[1]Department of Urology and Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

[2]Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

[3]State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

[4]Department of Clinical Research Management, West China Hospital, Chengdu, Sichuan, China

Correspondence

Xiang Li and Liao Peng, Department of Urology and Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
Email: xiangli872021@163.com and pengliao@wchscu.cn

Abstract

Objective: To identify the causal role of sodium-glucose cotransporter 2 (SGLT2) inhibition on three urological cancers.

Methods: Six single nucleotide polymorphisms associated with the expression level of SLC5A2, a proxy for SGLT2 inhibition, from a recent publication were extracted. Three common urological cancers, including bladder cancer, prostate cancer and kidney cancer, were analysed. The main cohort of bladder cancer was derived from UK Biobank (1279 cases and 372,016 controls). The prostate cancer cohort was from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium (79,148 cases and 61,106 controls). The kidney cancer phenotype was from the UK Biobank cohort of 463,010 individuals (1114 cases and 461,896 controls). Primary and sensitivity analysis were performed to validate the results. In vitro analysis was also incorporated to validate the Mendelian randomisation results.

Results: In primary analysis, SGLT2 inhibition was associated with reduced risk of bladder cancer (OR: 0.98, 95% CI: 0.97–0.99) per unit lowering of HbA1c level. A protective association was also observed for prostate cancer with odds ratio = 0.31 (95% CI = 0.21–0.47). However, we did not discover a causal relationship between SGLT2 inhibition and kidney cancer (OR: 1.00, 95% CI: 0.99–1.00). Sensitivity analysis and in vitro validation did not support the causal role of SGLT2 inhibition in increasing cancer risk.

Conclusions: We did not find any evidence that SGLT2 inhibition could increase the risk of the three cancers. Even in some analysis, SGLT2 inhibition tended to show protective effects on the three urological cancers.

KEYWORDS

bladder cancer, kidney cancer, prostate cancer, SGLT2 inhibition

1 | INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, the newest drug treatment for type II diabetes including canagliflozin, dapagliflozin and empagliflozin, are recommended to reduce glycaemic level and blood pressure, improve body mass index and lower atherosclerotic cardiovascular disease, chronic kidney disease, heart failure and all-cause mortality.[1–5] Moreover, SGLT2 inhibition has also been reported to yield protective effects on non-cardiovascular mortality and cancer patients.[6–9] However, the

Lede Lin, Kang Ning and Liyuan Xiang have contributed equally to this work.

 © 2024 John Wiley & Sons Ltd.

debate on the utilisation of SGLT2 inhibitors and cancer risk is still ongoing.[10–12]

To our urologists, the most concerns relate to the use of SGLT2 inhibitors and the risk of common urological cancer. Recently, an international multi-canter cohort study with a large sample size reported that the utility of SGLT2 inhibitors did not increase the risk of bladder cancer.[13] However, their causal relationships are still unclear. Thus, we aim to identify the causal role of SGLT2 inhibition on three urological cancers, including bladder cancer occurrence, based on genome-wide analysis and in vitro data.

2 | MATERIALS AND METHODS

The study utilised Mendelian randomisation (MR) analysis to detect the causal effect of SGLT2 inhibition on three urological cancers (Figure 1). MR analysis was a powerful tool to determine the causal role of the exposure phenotype in the outcome phenotype. We provided a detailed workflow of the MR study in Figure S1. Data were from recent genome wide association studies (GWAS) with a large sample size and a publication indicating six variants associated with SGLT2 inhibition through multiple selection and validation (Table S1).

2.1 | Variants associated with SGLT2 inhibition

To imitate the effect of SGLT2 inhibition, we retrieved six single nucleotide polymorphisms (SNPs) associated with the expression level of SLC5A2, a proxy for SGLT2 inhibition, from a recent publication,[14] which had validated their effects of lowering HbA1c level (Table S2). Generally, genetic variants linked to the mRNA expression levels of the SLC5A2 gene were first identified through expression quantitative trait locus data from the Genotype-Tissue Expression and eQTLGen Consortium.[15,16] Then, the causal association between each variant and the HbA1c level was calculated by MR analysis. The data of HbA1c were from UK Biobank with 344,182 unrelated participants (Figure 1 and Table S1). Only those variants passing the MR test could be forwarded for further colocalisation analysis. After colocalisation analysis, those with probability >0.7 were considered as colocalised variants and included in our study (Table S2A). Finally, a loose clumping threshold (r^2 < 0.8) was utilised to remove variants with very high correlation as those SNPs were adjacent in the gene position.[14] F-statistic (β^2/se^2) was calculated to quantify the statistic power of each SLC5A2-related variant as previously reported.[17] A total of six SNPs were included for further analysis (Table S2B).

2.2 | Phenotypes of three urological cancer

We included three common urological cancers in our MR analysis (bladder cancer, prostate cancer and kidney cancer). The main cohort of bladder cancer was derived from UK Biobank (1279 cases and 372,016 controls). The prostate cancer cohort was from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium (79,148 cases and 61,106 controls). The kidney cancer phenotype was from the UK Biobank cohort of 463,010 individuals (1114 cases and 461,896 controls) curated by the MRC Integrative Epidemiology Unit (MRC-IEU) consortium. The above three cohorts were included in our primary analysis. We also enroled other cohorts of the three urological cancers with less sample size or inferior quality in sensitivity analysis. Further details are described in Table S1.

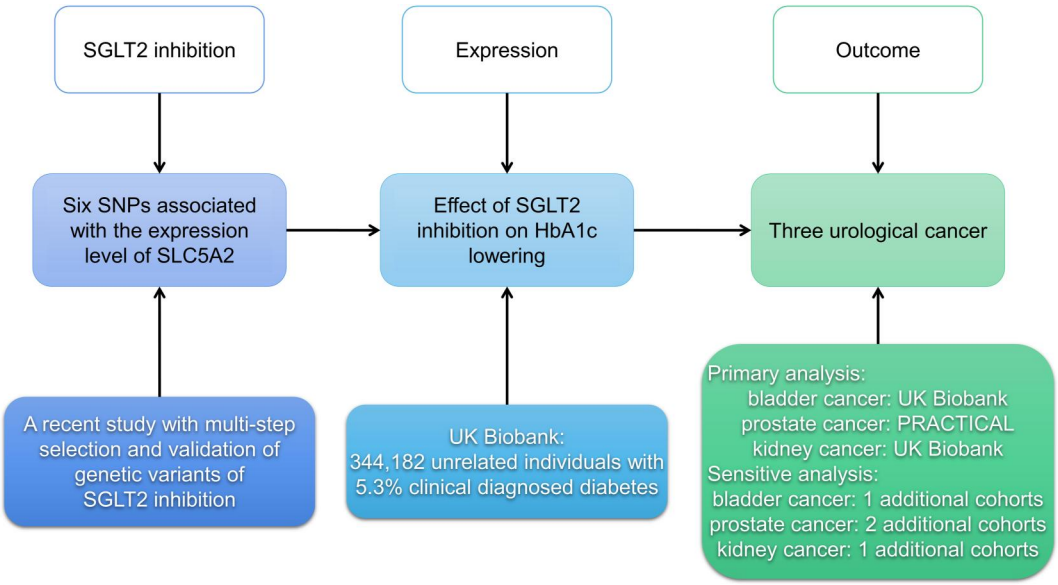

FIGURE 1 Study design and flowchart. PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; SGLT2: sodium-glucose cotransporter 2; SNPs: single nucleotide polymorphisms.

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2.3 | RNA-sequencing data from in vitro cell lines

To validate the MR results, we performed RNA-sequencing (RNA-seq) analysis from available datasets in the Gene Expression Omnibus repository. Through a thorough review, we discovered two datasets (GSE118337 and GSE239688),[18,19] involved with SGLT2 inhibition in human proximal tubular cells (HK2 and RPTEC/TERT1 cell lines) and prostate cancer cell lines (PC3 and 22rv1). The GEO2R tool was utilised to implement RNA-seq analysis to discover differentially expressed genes between groups. More details about GEO2R could be accessed at https://www.ncbi.nlm.nih.gov/geo/info/geo2r.html.

Briefly, we explored the effect of SGLT2 inhibition on cancer risk based on numerous cancer markers. For kidney cancer, we considered the following as malignant markers: KRT7, CA9, MME, KIT, VIM, AMACR, TFE3, TFEB, CTSK, PMEL and MLANA. For prostate cancer, the following cancer markers were enroled: ABCG2, BMI1, KIT, PROM1, A4GALT, CD44, ITGA2, ITGA6, CSF2RA, HES1, JAG1, NANOG, NES, POU5F1, SMO, SOX2, ITGB1, WWTR1, TP63, CTNNB1, CDH1, AMACR, KRT5, KRT19, CASP3, KLK3 and FOLH1. We compared the transcript per kilobase per million mapped reads (TPM) normalised expression of corresponding genes in groups to identify differentially expressed genes. As most genes did not show significant adjusted p value, we used p value instead of adjusted p value to include differentially expressed genes maximally. We considered genes with p value < 0.05 and log2 fold change > 2 as differentially expressed genes to enrol an appropriate number of genes.

2.4 | Statistical analysis

2.4.1 | Primary analysis

We utilised two-sample MR analysis to examine the effect of SGLT2 inhibition (six associated SNPs) on the three urological cancer cohorts. Combined methods included inverse variance weighted (IVW), IVW (multiplicative random effects), MR Egger, MR Egger (bootstrap), weighted median and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO). The IVW method with multiplicative random effects was considered as the primary outcome to boost the analysis power as a result of lack of heterogeneity and pleiotropy. Results are shown as odds ratio (OR, risk reduced) with 95% confidence interval (95% CI).

2.4.2 | Sensitivity analysis

In addition to the MR-PRESSO method mentioned above, we obtained replication cohort data to validate the causal role of SGLT2 inhibition on the three urological cancers. There were 1, 2 and 1 additional cohorts for bladder, prostate and kidney cancers, respectively (Figure 1 and Table S1). Heterogeneity and pleiotropy tests were also conducted to validate the results. As we included three outcome phenotypes, a p value threshold with the Bonferroni corrected method was applied (0.05/3 = 0.017).

All analysis was conducted on R software (4.1.2) and the package TwoSampleMR was the main package. The GWAS summary statistics were accessed through the OpenGWAS database API.[20,21]

3 | RESULTS

3.1 | The strength of six variants associated with SGLT2 inhibition

As shown in the previous publication,[14] all the six SNPs had sufficient strength to be included in our analysis (all F-statistics >10, Table S2B).

3.2 | The effect of SGLT2 inhibition on three urological cancer

In our primary analysis, we found that SGLT2 inhibition was associated with reduced risk of bladder cancer (OR: 0.98, 95% CI: 0.97–0.99 for IVW method with multiplicative random effects) per unit lowering of HbA1c level (Table 1). A protective association was also observed for prostate cancer with OR = 0.31 (95% CI = 0.21–0.47 for IVW method with multiplicative random effects, Table 1). However, we did not discover a causal relationship between SGLT2 inhibition and kidney cancer (OR: 1.00, 95% CI: 0.99–1.00 for IVW method with multiplicative random effects, Table 1). The causal effect of SGLT2 inhibition on three urological cancers is depicted in Figure 2.

In our sensitivity analysis, we did not always find the same associations as in the primary analysis. All analysis of additional bladder cancer cohorts did not show significant associations with SGLT2 inhibition (Table S3). While for prostate cancer and kidney cancer we could not observe a significant association with SGLT2 inhibition either (Tables S4 and S5).

3.3 | In vitro data revealed no positive associations between SGLT2 inhibition and cancer risk

We further conducted RNA-seq data analysis from two datasets. Generally, HK2 and RPTEC/TERT1 cell lines received either empagliflozine (500 nM) or canagliflozine (500 nM) in one dataset.[19] In another dataset, PC3 and 22rv1 cell lines were treated with canagliflozin at a concentration of 10 uM.[1] We obtained RNA-seq data from all the groups to validate the results from MR analysis.

When treated with either empagliflozine or canagliflozine, HK2 cells showed similar differentially expressed genes (up-regulated genes: DHRS2, down-regulated genes: FLRT3 and SCL17A3,

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 The effect of SGLT2 inhibition on three urological cancers in primary analysis based on two-sample MR.

Exposure	Outcome	Consortium	SNPs	Method	OR (95% CI)	$P_{Heterogeneity}$	$P_{pleiotropy}$
SGLT2 inhibition	Bladder cancer	UK biobank	6	IVW	**0.98 (0.97–0.99)**	0.595	
			6	IVW (multiplicative random effects)	**0.98 (0.97–0.99)**		
			6	MR egger	1.01 (0.97–1.06)	0.743	0.259
			6	MR egger (bootstrap)	1.01 (0.97–1.06)		
			6	Weighted median	0.99 (0.98–1.00)		
			6	MR-PRESSO	**0.98 (0.97–0.99)**	0.660	
SGLT2 inhibition	Prostate cancer	PRACTICAL	6	IVW	**0.31 (0.18–0.55)**	0.774	
			6	IVW (multiplicative random effects)	**0.31 (0.21–0.47)**		
			6	MR egger	0.24 (0.01–4.02)	0.649	0.853
			6	MR egger (bootstrap)	0.81 (0.03–18.82)		
			6	Weighted median	**0.35 (0.17–0.72)**		
			6	MR-PRESSO	**0.31 (0.21–0.47)**	0.830	
SGLT2 inhibition	Kidney cancer	UK biobank	4	IVW	1.00 (0.98–1.01)	0.509	
			4	IVW (multiplicative random effects)	1.00 (0.99–1.00)		
			4	MR egger	1.02 (0.98–1.05)	0.538	0.408
			4	MR egger (bootstrap)	1.02 (0.96–1.07)		
			4	Weighted median	0.99 (0.98–1.00)		
			4	MR-PRESSO	1.00 (0.99–1.00)	0.477	

Abbreviations: 95% CI, 95% confidence interval; IVW, inverse variance weighted; MR, Mendelian randomisation; MR-PRESSO, Mendelian Randomisation Pleiotropy RESidual Sum and Outlier; OR, odds ratio; PRACTICAL, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; SGLT2, sodium-glucose cotransporter 2; SNPs, single nucleotide polymorphisms.

Note: Bold values indicated significant results.

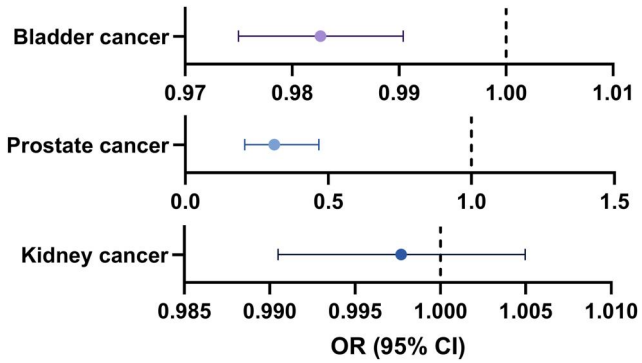

FIGURE 2 The effect of SGLT2 inhibition on three urological cancers in primary analysis using two-sample MR. The results were based on the IVW method with multiplicative random effects. 95% CI: 95% confidence interval; IVW: inverse variance weighted; MR: Mendelian randomisation; OR: odds ratio; SGLT2: sodium-glucose cotransporter 2.

Figure 3A,B). MIR205HG was down-regulated in canagliflozine-treated HK2 (log2FC: −2.04, *p* value: 7.18e-04, Figure 3A and Table S6A). Malignant markers were all insignificant (Figure 3A,B, Table S6A,B).

For RPTEC/TERT1 cells receiving empagliflozine or canagliflozine, two genes (TM4SF4 and PADI1) were both down-regulated (log2FC of TM4SF4: −2.58 for canagliflozine-treated group and −2.73 for empagliflozine-treated group, *p* value of TM4SF4: 3.15e-06 for canagliflozine-treated group and 3.66e-06 for empagliflozine-treated group; log2FC of PADI1: −2.01 for canagliflozine-treated group and −2.18 for empagliflozine-treated group, *p* value of PADI1: 5.79e-05 for canagliflozine-treated group and 1.49e-05 for empagliflozine-treated group; Figure 3C,D, Table S6C,D).

As for prostate cancer cells treated with canagliflozine, all genes yielded insignificant results (Figure 4A,B). Table S6E,F provide more details about relative gene expression.

To go a step further, we focused on the expression of malignant markers mentioned in the method section (Figure S2–S36). PMEL tended to decrease in empagliflozine-treated RPTEC/TERT1 group (log2FC: −0.357, *p* value: 0.04, Figure 5A and Table S6D). Also, JAG1 and NES demonstrated similar tendency (log2FC: −0.362 for JAG1 in canagliflozine-treated PC3 group and −0.318 for NES in canagliflozine-treated PC3 group; *p* value: 2.26e-03 for JAG1 in canagliflozine-treated PC3 group and 1.43e-03 for NES in canagliflozine-treated PC3 group; Figure 5B,C, and Table S6E). Generally, SGLT2 inhibition did not result in up-regulated genes with *p* value < 0.05 (Figure S2-S36).

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

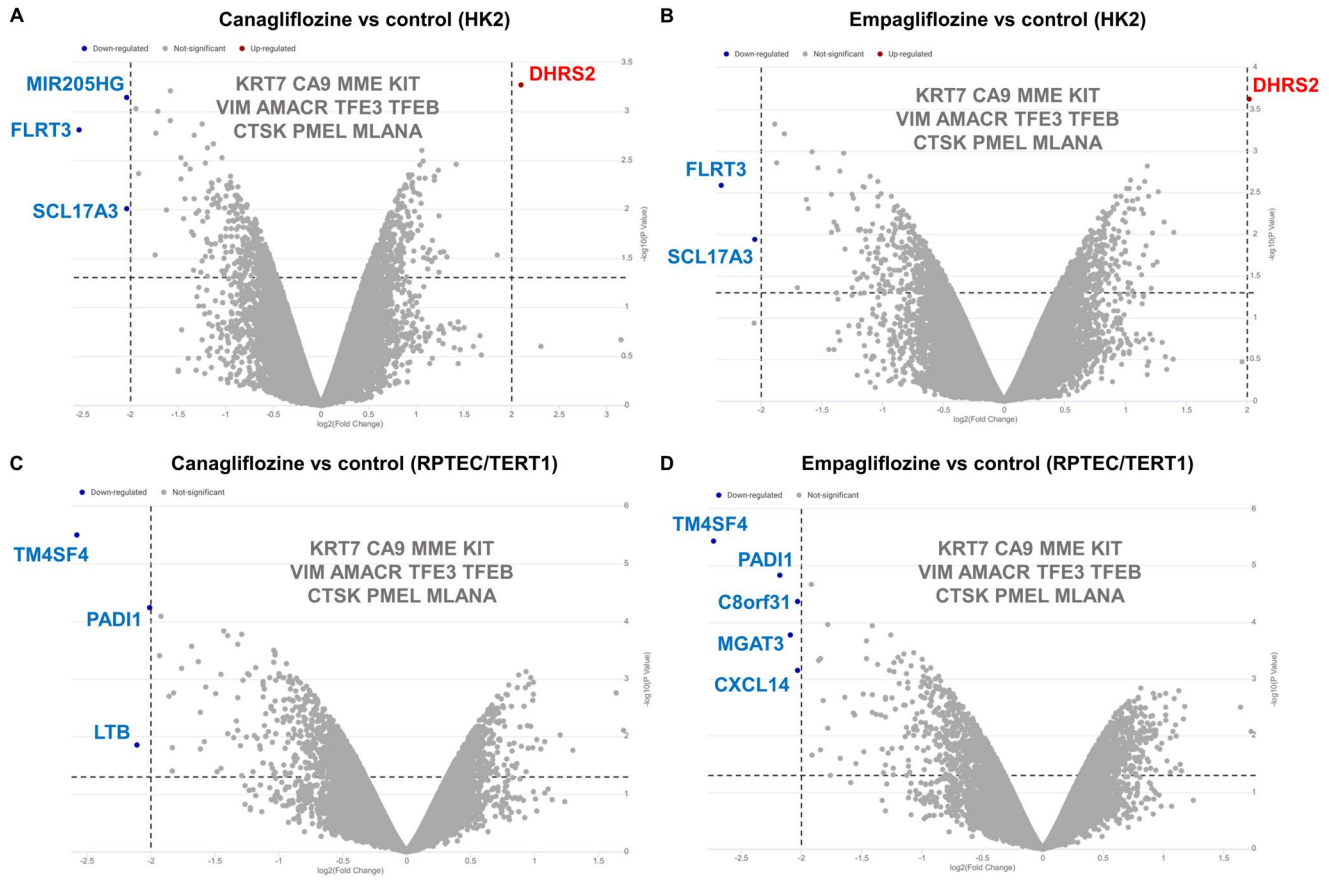

FIGURE 3 The volcano plots of differentially expressed genes in the corresponding groups. (A) The volcano plots of differentially expressed genes between canagliflozine-treated HK2 and control HK2 groups. (B) The volcano plots of differentially expressed genes between empagliflozine-treated HK2 and control HK2 groups. (C) The volcano plots of differentially expressed genes between canagliflozine-treated RPTEC/TERT1 and control RPTEC/TERT1 groups. (D) The volcano plots of differentially expressed genes between empagliflozine-treated RPTEC/TERT1 and control RPTEC/TERT1 groups. Blue dots indicated down-regulated genes; grey dots indicated insignificant genes; red dots indicated up-regulated genes.

4 | DISCUSSION

In this study, we tested the causal associations between SGLT2 inhibition and three urological cancers, including bladder, prostate, and kidney cancers. We did not find any evidence that SGLT2 inhibition could increase the risk of the three cancers. Even in some analysis, SGLT2 inhibition tended to show protective effects on the three urological cancers (Figure 6).

SGLT2 inhibitors, including dapagliflozin, empagliflozin and canagliflozin to date, have been considered as a new class of antidiabetic and anti-cardiovascular drugs.[4,22–24] However, numerous studies have reported the incidence of cancer, especially bladder cancer, after treatment initiation.[13,25–27] Those studies generated confusing results and we could not confirm the causal association between SGLT2 inhibition and cancer incidence. Recently, three original studies explored the same topic.[13,25,26] One extracted data from European pharmacovigilance database[26] and concluded that SGLT2 inhibitors could increase the risk of bladder cancer in sensitive analysis (OR: 6.84, 95%CI: 5.41–8.65). While the other two did not report the risk of bladder cancer incidence compared with placebo or positive controls,[13,25] the follow-up year was relatively short (<3 years). MR analysis was able to overcome the shortcomings of conventional cohort studies and establish a causal relationship from the genetic level. We discovered that the variants involved in SGLT2 inhibition did not increase the risk of a certain urological cancer. And even in some cohorts, SGLT2 inhibition yielded protective effects from cancer incidence (OR: 0.98, 95% CI: 0.97–0.99 for bladder cancer; OR = 0.31, 95% CI: 0.21–0.47 for prostate cancer). In vitro RNA-seq analysis also conformed the MR results, which indicated that SGLT2 inhibition did not induce up-regulated malignant markers with p value < 0.05.

SGLT2 is mainly located in the renal proximal convoluted tubule and reabsorbed glucose from the glomerular filtrate.[28] The biological mechanism between SGLT2 inhibitors and cancer risk might be through directly influencing tumour energy metabolism or indirectly affecting cancer risk factors (lowering blood glucose, weight, fat mass and endogenous insulin secretion) indirectly.[29] All these mechanisms pose negative effects on cancer development and SGLT2 inhibitors were reported to inhibit the growth of numerous cancer cell lines.[29] Nevertheless, we still could not

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

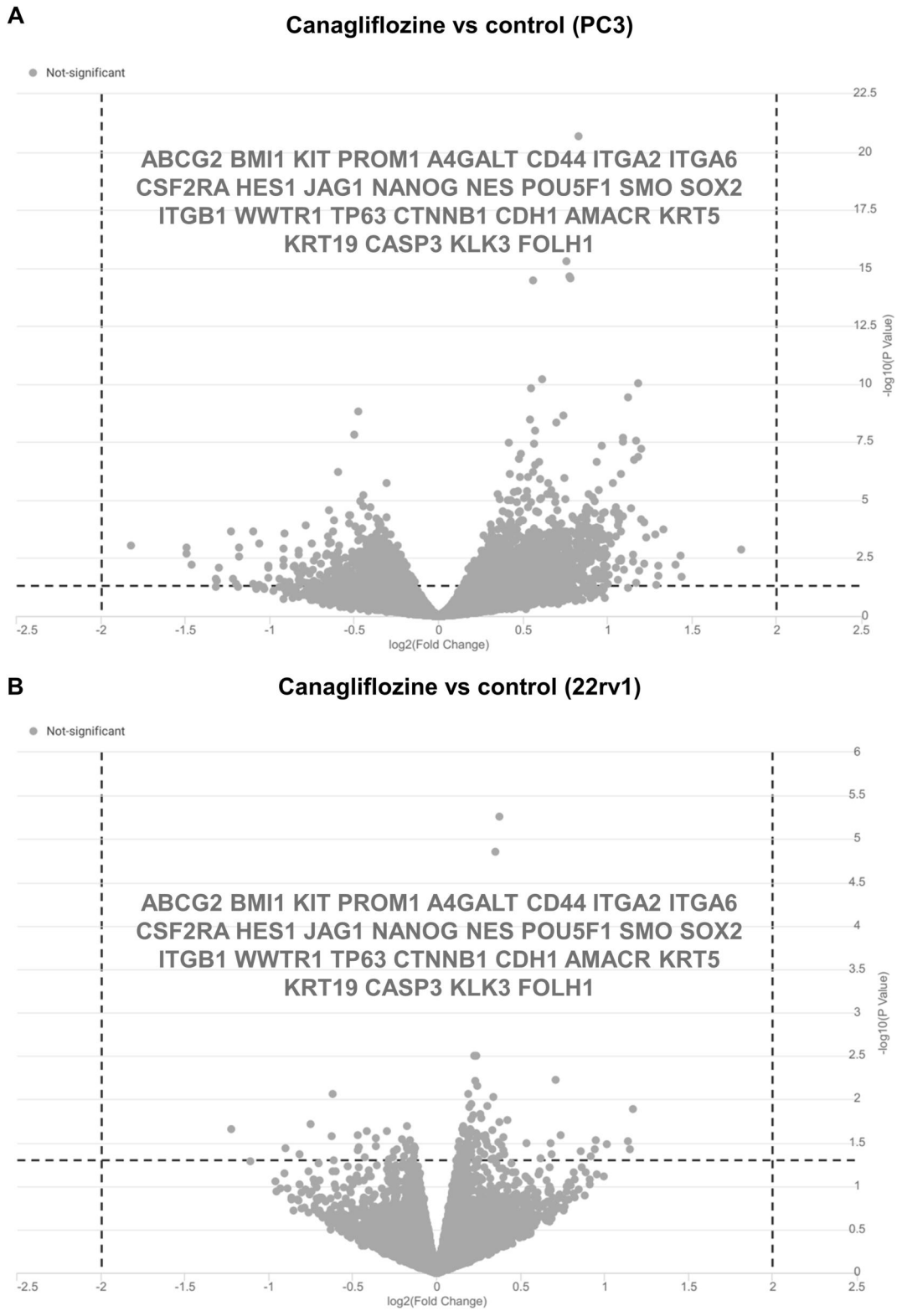

FIGURE 4 The volcano plots of differentially expressed genes in the corresponding groups. (A) The volcano plots of differentially expressed genes between canagliflozine-treated PC3 and control PC3 groups. (B) The volcano plots of differentially expressed genes between canagliflozine-treated 22rv1 and control 22rv1 groups. Grey dots indicate insignificant genes. TPM, transcript per kilobase per million mapped reads.

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

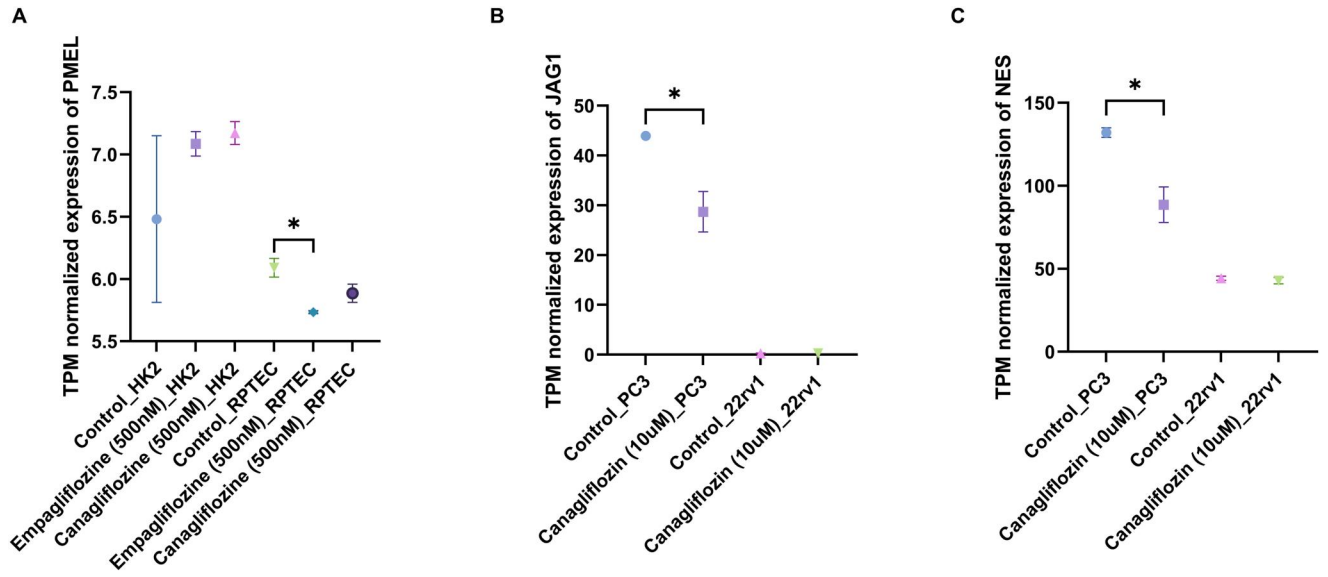

FIGURE 5 The TPM normalised expression values of significant malignant markers for kidney cancer and prostate cancer. (A) The TPM normalised expression values of PMEL among empagliflozine and canagliflozine-treated HK2 and RPTEC/TERT1 groups. (B) The TPM normalised expression values of JAG1 among canagliflozine-treated PC3 and 22rv1 groups. (C) The TPM normalised expression values of NES among canagliflozine-treated PC3 and 22rv1 groups. *p value < 0.05.

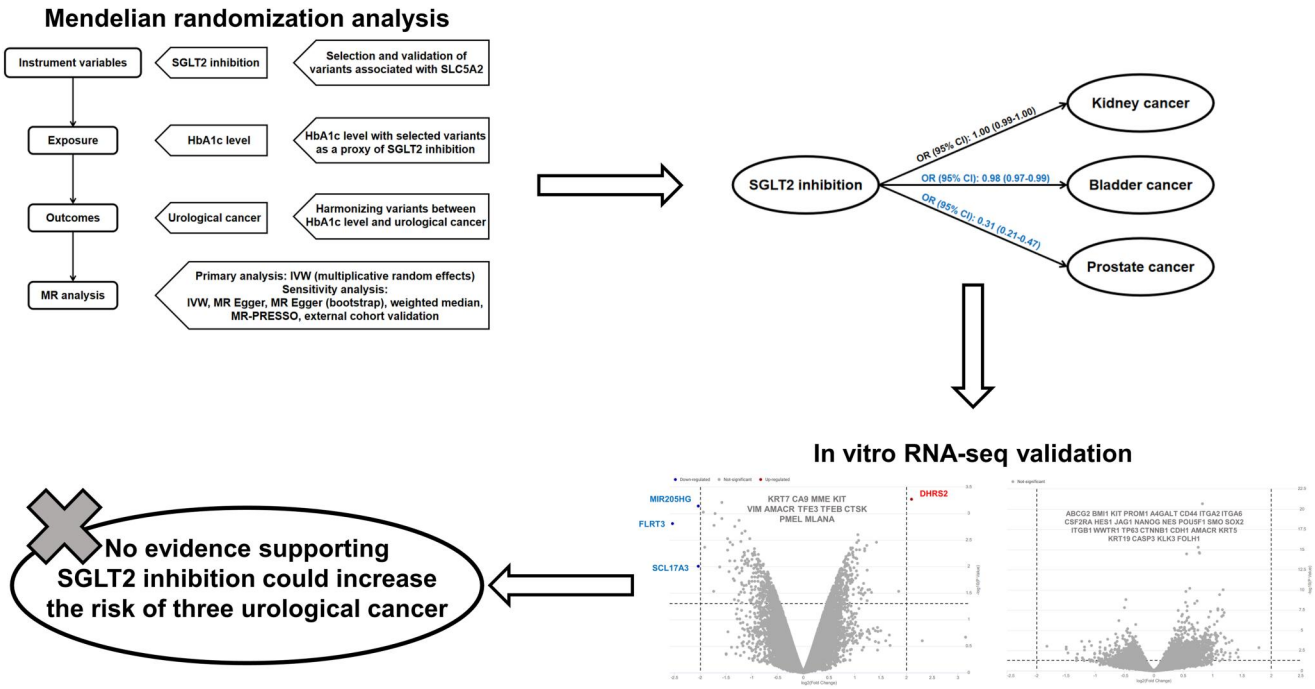

FIGURE 6 Graphical abstracts of study results.

explain the phenomenon that SGLT2 inhibitors might be associated with bladder cancer risk. Maybe there existed several unknown confounders in those studies and over detection of bladder cancer was more easy for individuals who received SGLT2 inhibitors treatment and suffered from urinary tract infection.[13] Our study rejected the hypothesis that SGLT2 inhibitors were associated with the three urological cancers based on the evidence from the genetic level. The results would be conducive to medical decision-making in clinical practice when patients diagnosed with diabetes mellitus and urological cancer intended to receive SGLT2 inhibitors. Patients would be less worried about the side-effects induced by SGLT2 inhibitors.

The study had several strengths. We used the most up-to-date results from a publication of high quality to identify six SNPs

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

associated with SGLT2 inhibition and HbA1c lowering mimicking the effect of SGLT2 inhibitors. To be more specific, we utilised the six SNPs to answer a closely discussed topic of whether SGLT2 inhibitors could lead to any cancer risk. We thought that SGLT2 inhibition could not facilitate the occurrence of three urological cancers. In some analysis, SGLT2 inhibition could even provide protective effects. Additionally, we incorporated MR results with in vitro validation analysis to verify the possible protective effects of SGLT2 inhibitors.

On the other hand, several limitations should be admitted. First, there existed a partial overlap between the exposure and outcome, which led to weak instruments. We calculated the F-statistic for each SNP and all of them exceeded the common threshold of 10, indicating that all those SNPs were of sufficient strength. Moreover, the Bonferroni-corrected p threshold was also applied to avoid type I error when multiple tests were conducted. Second, we could not explain the possible biological mechanism between SGLT2 inhibition and cancer risk. More high-quality GWAS were needed to go a step further. The utilisation of SGLT2 inhibitors in cancer cell lines and preclinical animal models to investigate the role of SGLT2 in carcinogenesis would give us more insights. Additionally, our MR results only included the European population and should be cautiously interpreted when external application was performed.

To summarise, we could not find any evidence that SGLT2 inhibition increased the risk of three urological cancers. Even in some analysis, SGLT2 inhibition showed protective effects on the three urological cancers. These findings provide support for SGLT2 inhibitor utilisation in patients with diabetes mellitus and urological cancer.

AUTHOR CONTRIBUTIONS

Conception and design of study: Lede Lin, Kang Ning and Liyuan Xiang. Acquisition of data: Lede Lin, Kang Ning and Liyuan Xiang. Data analysis and/or interpretation: Lede Lin, Kang Ning and Liyuan Xiang. Drafting of manuscript and/or critical revision: all authors. Approval of final version of manuscript by all authors.

ACKNOWLEDGEMENTS

We express our thanks to those people who have contributed to the IEU GWAS database project and the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol. Sincere thanks also go to the many GWAS consortia who have made the GWAS data that they generated publicly available, and many members of the IEU who have contributed to curating these data.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest or financial ties to disclose.

ETHICS STATEMENT

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article and its supplementary information files.

ORCID

Xiang Li https://orcid.org/0000-0002-0730-9989

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3797.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes-2022 abridged for primary care providers. *Clin Diabetes*. 2022;40(1):10-38.
2. Banerjee M, Pal R, Nair K, Mukhopadhyay S. SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: a systematic review and meta-analysis. *Indian Heart J*. 2023;75(2):122-127.
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
5. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139(22):2528-2536.
6. Banerjee M, Pal R, Maisnam I, Mukhopadhyay S. GLP-1 receptor agonists, SGLT2 inhibitors and noncardiovascular mortality in type 2 diabetes: insights from a meta-analysis. *Diabetes Metab Syndr*. 2024;18(1):102943.
7. Perelman MG, Brzezinski RY, Waissengrin B, et al. Sodium-glucose co-transporter-2 inhibitors in patients treated with immune checkpoint inhibitors. *Cardiooncology*. 2024;10(1):2.
8. Huang YM, Chen WM, Jao AT, Chen M, Shia BC, Wu SY. Effects of SGLT2 inhibitors on clinical cancer survival in patients with type 2 diabetes. *Diabetes Metab*. 2023;50(1):101500.
9. Avula V, Sharma G, Kosiborod MN, et al. SGLT2 inhibitor use and risk of clinical events in patients with cancer therapy-related cardiac dysfunction. *JACC Heart Fail*. 2024;12(1):67-78.
10. Wang F, Hendryx M, Liu N, Bidulescu A, Mitra AK, Luo J. SGLT2 inhibitor use and risk of breast cancer among adult women with type 2 diabetes. *Drug Saf*. 2023.
11. Bea S, Son H, Bae JH, Cho SW, Shin JY, Cho YM. Risk of thyroid cancer associated with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: a population-based cohort study. *Diabetes Obes Metab*. 2024;26(1):108-117.
12. Tanaka Y, Yokoyama S, Nakagawa C, Uno T, Hosomi K. Association between sodium-glucose cotransporter 2 inhibitors and pancreatic cancer in the Japanese working-age population. *Int J Clin Pharmacol Ther*. 2023;61(11):492-502.
13. Abrahami D, Tesfaye H, Yin H, et al. Sodium-glucose cotransporter 2 inhibitors and the short-term risk of bladder cancer: an international multisite cohort study. *Diabetes Care*. 2022:dc221174.

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

14. Xu M, Zheng J, Hou T, et al. SGLT2 inhibition, choline metabolites, and cardiometabolic diseases: a mediation Mendelian randomization study. *Diabetes Care*. 2022;45(11):2718-2728.
15. Gtex Consortium. The GTEx consortium atlas of genetic regulatory effects across human tissues. *Science*. 2020;369(6509):1318-1330.
16. Võsa U, Claringbould A, Westra HJ, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat Genet*. 2021;53(9):1300-1310.
17. Lin L, Wang W, Xiao K, Guo X, Zhou L. Genetically elevated bioavailable testosterone level was associated with the occurrence of benign prostatic hyperplasia. *J Endocrinol Invest*. 2023;46(10):2095-2102.
18. Pirklbauer M, Schupart R, Fuchs L, et al. Unraveling reno-protective effects of SGLT2 inhibition in human proximal tubular cells. *Am J Physiol Ren Physiol*. 2019;316(3):F449-F462.
19. Ali A, Mekhaeil B, Biziotis OD, et al. The SGLT2 inhibitor canagliflozin suppresses growth and enhances prostate cancer response to radiotherapy. *Commun Biol*. 2023;6(1):919.
20. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. *Elife*. 2018;7:e34408.
21. Elsworth B, Lyon M, Alexander T, et al. The MRC IEU OpenGWAS data infrastructure. *bioRxiv*. 2020;2020.08.10.244293v1.
22. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134(10):752-772.
23. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
24. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
25. Li YR, Liu CH, Sun WC, et al. The risk of bladder cancer in type 2 diabetes mellitus with combination therapy of SGLT-2 inhibitors and pioglitazone. *J Pers Med*. 2021;11(9):828.
26. García M, Arteche-Martinez U, Lertxundi U, Aguirre C. SGLT2 inhibitors and bladder cancer: analysis of cases reported in the European pharmacovigilance database. *J Clin Pharmacol*. 2021;61(2):187-192.
27. Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM. The association of sodium-glucose cotransporter 2 inhibitors with cancer: an overview of quantitative systematic reviews. *Endocrinol Diabetes Metab*. 2020;3(3):e00145.
28. Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. *J Intern Med*. 2007;261(1):32-43.
29. Dąbrowski M. Diabetes, antidiabetic medications and cancer risk in type 2 diabetes: focus on SGLT-2 inhibitors. *Int J Mol Sci*. 2021;22(4):1680.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lin L, Ning K, Xiang L, Peng L, Li X. SGLT2 inhibition and three urological cancers: up-to-date results. *Diabetes Metab Res Rev*. 2024;e3797. https://doi.org/10.1002/dmrr.3797

15207560, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3797 by <Shibboleth>-member@ox.ac.uk, Wiley Online Library on [01/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License