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LETTER TO THE JOURNAL

Risk of colorectal cancer and cancer-related mortality in type 2 diabetes patients treated with metformin, SGLT-2 inhibitors, or their combination

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths worldwide [1]. A considerable proportion of CRC is attributed to metabolic risk factors including type 2 diabetes (T2D), with the relative risk reported to be 1.4 [2]. It is therefore imperative to develop effective preventive strategies to reduce CRC incidence in individuals with T2D.

Among individuals with T2D, growing evidence supports the role of diabetes medications for CRC prevention. The current guidelines of the American Gastroenterological Association have recommended metformin as a potential chemopreventive medication against colonic neoplasia in patients with T2D [3]. However, the use of metformin may be limited by various side effects including gastrointestinal disturbances, and is contraindicated in moderate-to-severe renal impairment. Furthermore, a clinical trial found diabetic patients on metformin, as compared to rosiglitazone and glyburide, had similar CRC risk [4]. Emerging evidence suggests that the use of sodium-glucose cotransporter-2 inhibitors (SGLT-2is) may prevent colorectal tumorigenesis by reducing body weight chronic inflammation, hyperglycemia, and insulin-resistance [5]. Prior observational studies have been limited by lacking detailed information about key determinants of colorectal-related outcomes, such as body mass index (BMI) and glycemic status [5, 6]. To address these knowledge gaps, by utilizing a population-wide electronic registry, we aimed to evaluate the comparative effectiveness of metformin, SGLT-2i, and SGLT-2i/metformin combination therapy on the risk of CRC and CRC-related mortality in patients with T2D.

Among 396,641 T2D individuals who received metformin within the past year before the index date, 349,522 (88.1%) continued metformin, 4,758 (1.2%) switched to SGLT-2i, and 42,361 (10.7%) had SGLT-2i as an add-on therapy to metformin. The baseline characteristics of the three treatment groups before and after overlap weighting adjustment are presented in Supplementary Tables S1-S2. All standardized mean differences were less than 0.1, indicating a good balance among the treatment groups after weighting. The primary combined antidiabetic medications were sulfonylureas and insulin. Detailed methods are described in the Supplementary Materials and Methods (Supplementary Figure S1).

During a mean duration of 5.5 (±2.5) years of follow-up, 4,456 (1.1%) incident CRC cases and 1,042 (0.3%) CRC-related deaths were recorded. Compared with metformin, SGLT-2i (2.2 per 1,000 person-years vs. 1.4 per 1,000 person-years; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.35-0.90) and SGLT-2i/metformin groups (2.2 per 1,000 person-years vs. 1.5 per 1,000 person-years; HR, 0.61; 95% CI, 0.49-0.77) had a significantly lower incidence rate of CRC (Figure 1). There was no difference in the risk of CRC between the SGLT-2i and SGLT-2i/metformin groups (HR, 1.10; 95% CI, 0.67-1.80).

SGLT-2i use was associated with a lower risk of left-sided CRC regardless of concomitant metformin use (SGLT-2i vs. metformin: HR, 0.35; 95% CI, 0.14-0.85; SGLT-2i/metformin vs. metformin: HR, 0.57; 95% CI, 0.41-0.80). For right-sided CRC, the association was of borderline significance with respect to SGLT-2i/metformin (HR, 0.63; 95% CI, 0.40-1.01) while SGLT-2i had no beneficial effect (HR, 0.34; 95% CI, 0.10-1.13). Similar findings were noted for rectal cancer (SGLT-2i/metformin: HR, 0.71; 95% CI, 0.47-1.06; SGLT-2i: HR, 0.97; 95% CI, 0.55-2.21).

SGLT-2i/metformin, when compared with metformin, was associated with a significantly lower incidence rate and risk of CRC-related mortality (0.2 per 1000 person-years vs. 0.5 per 1000 person-years; HR, 0.40; 95% CI, 0.23-0.70). No significant difference in the risk of CRC-related mortality was found when SGLT-2i was compared

List of abbreviations: BMI, body mass index; cDDD, cumulative daily defined dose; CI, confidence interval; CRC, colorectal cancer; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

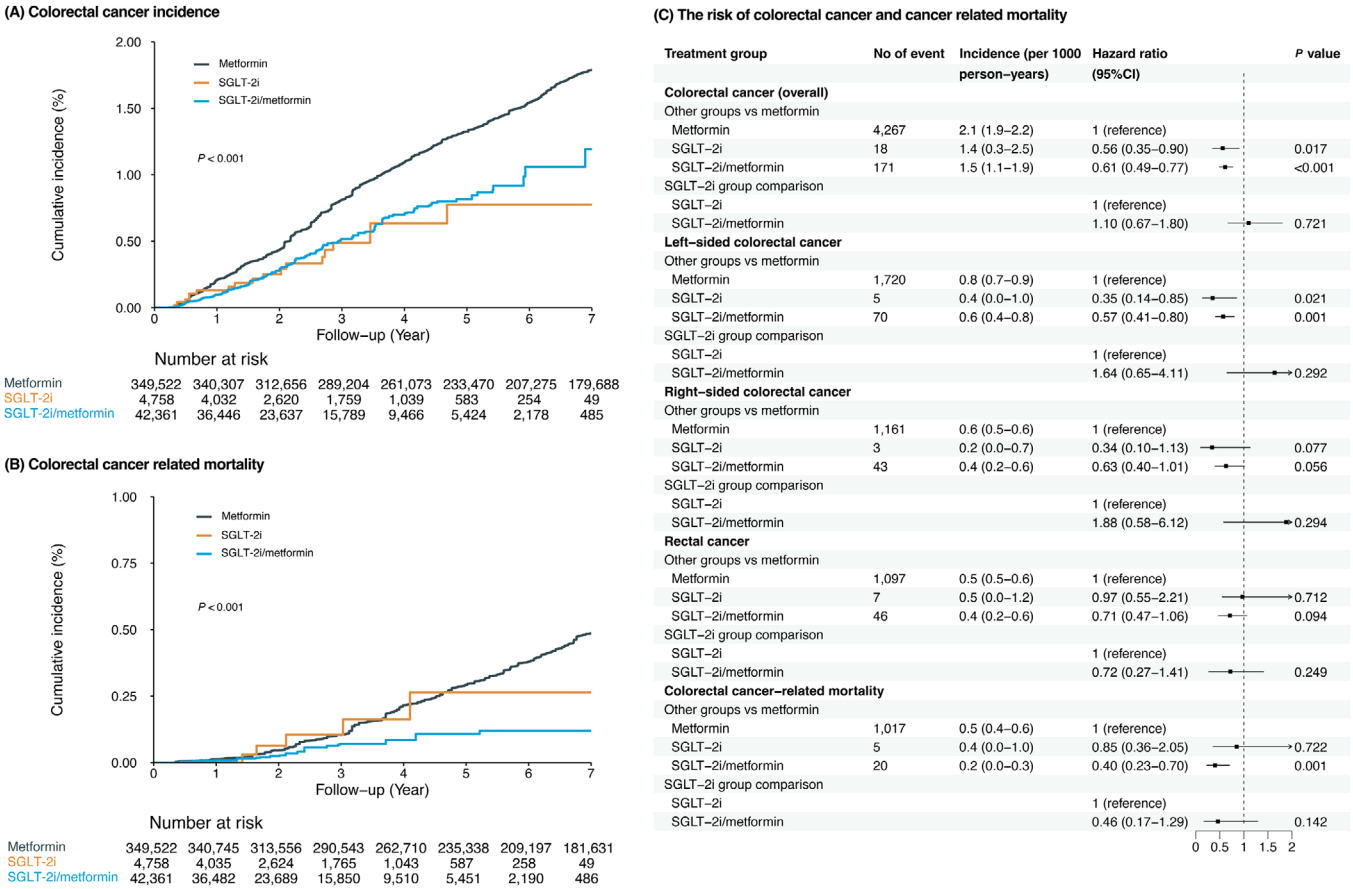

FIGURE 1 Cumulative incidence of (A) colorectal cancer and (B) colorectal cancer related mortality and (C) risk of colorectal cancer and cancer related mortality in individuals with metformin therapy, SGLT-2i therapy, and SGLT-2i/metformin combination therapy. Abbreviations: SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

with metformin (HR, 0.85; 95% CI, 0.36-2.05), or when SGLT-2i/metformin with SGLT-2i groups (HR, 0.46; 95% CI, 0.17-1.29).

We further examined the dose-dependent effects of SGLT-2i. When compared with metformin, a stepwise decreasing risk of CRC was observed in the SGLT-2i group, with HR of 0.77 (95% CI, 0.24-2.44), 0.72 (95% CI, 0.36-1.41), and 0.41 (95% CI, 0.19-0.87) for SGLT-2i 0.1 to 3.0, 3.1 to 6.9, and ≥7.0 cumulative daily defined doses (cDDD) per week, respectively (P_{trend} = 0.030) (Supplementary Table S3). A similar significantly inverse trend was found when comparing SGLT-2i/metformin with metformin, with HR of 0.65 (95% CI, 0.42-1.00), 0.68 (95% CI, 0.53-0.89), and 0.48 (95% CI, 0.37-0.63) for SGLT-2i 0.1 to 3.0, 3.1 to 6.9, and ≥7.0 cDDD per week, respectively (P_{trend} <0.001).

The results were similar within most prespecified subgroups with comparable HRs across demographic, lifestyle, and coexisting clinical and medical characteristics (SGLT-2i vs. metformin, HR, 0.17-0.86; SGLT-2i/metformin vs. metformin, HR, 0.44-0.93) (Supplementary Table S4). Four sensitivity analyses were conducted and consistent results were shown in Supplementary Tables S5-S6.

Our results demonstrated that SGLT-2i/metformin was associated with a 39% lower risk of CRC than metformin alone, overcoming the limitation of previous observational studies [5, 6], which included a less relevant active comparator (i.e. dipeptidyl peptidase-4 inhibitor), the lack of analysis of key determinants of colorectal outcomes including BMI and prior colonoscopy, as well as the lack of a comprehensive dose-response analysis. Specifically, a lack of information on important confounding factors can constitute imbalanced variables between the study groups, thus mis-estimating the true association. Our present study results found that the SGLT-2i group, when compared with the metformin group, had a lower CRC risk of 47%. To our knowledge, this is the first head-to-head study to evaluate the comparative effectiveness of SGLT-2i and metformin on CRC; further randomized clinical trials are required to confirm current study findings. In addition, consistent dose-dependent effects of SGLT-2i on the risk of CRC in both SGLT-2i and SGLT-2i/metformin groups further support the potentially causative role of SGLT-2i on CRC reduction. We only found a significant inverse association between SGLT-2i (SGLT-2i/metformin) and left-sided CRC but not right-sided CRC and rectal cancer.

The discrepancy may partly be explained by the limited sample size. In addition, this result may be attributed to the more pronounced effect of glycemic control on left-sided CRC [7].

Several lines of evidence suggest SGLT-2i use may protect against CRC development. First, the use of SGLT-2i can ameliorate chronic inflammation and insulin-resistant conditions via reducing blood glucose, serum tumor necrosis factor-alpha (TNF-α), pro-inflammatory mRNA expression, as well as macrophage infiltrations. Second, SGLT-2i inhibits the adhesion of colon cancer cells that express SGLT-2 by increasing A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) activity [8]. Third, metabolic reprogramming not only provides cancer cells with sufficient energy but also promotes the activity of numerous oncoproteins, facilitating tumor onset and progression [9]. SGLT-2i may regulate diabetes- and aging-related metabolic alteration by activating adenosine monophosphate-activated protein kinase-mammalian target of rapamycin (AMPK-mTORC1) signaling [10].

The strengths of this study include its large sample size, relative long duration of follow-up, and longitudinally-updated medication information. Nonetheless, we acknowledge several limitations. First, misclassification of confounder covariates and study outcomes may occur in large datasets. Nonetheless, the Hong Kong-based Clinical Data Analysis Reporting System is a carefully curated and maintained database, which reduces the possibility of potential bias. In addition, misclassification of covariates is likely to be nondifferential among study groups in most situations that underestimates the true association. Second, we did not have detailed information regarding socioeconomic status, diet, and physical activity in the database, although these variables are closely associated with BMI and diabetes severity, which have been incorporated into the multivariable-adjusted model to account for randomization among the study groups. In addition, we lack the information about family history of CRC in the cohort. Third, participants in the database are predominately Asian, living in Hong Kong and this may limit the generalization of our findings to other racial populations or geographic regions.

In this large population of patients with T2D, SGLT-2i was associated with lower risk of CRC and CRC-related mortality, regardless of background metformin use. Future multicenter randomized clinical trials are needed to test the effectiveness of SGLT-2i, with or without concomitant use of metformin, for the chemoprevention of CRC.

AUTHOR CONTRIBUTIONS

Study concept and design: Xianhua Mao, Ka-Shing Cheung, and Wai-Kay Seto. Data acquisition: Xianhua Mao, Ka-Shing Cheung, Rex Wan-Hin Hui, Ho Ming Cheng, and Jing-Tong Tan. Data analysis: Xianhua Mao, Ka-Shing Cheung, and Wai-Kay Seto. Data interpretation: Xianhua Mao, Philip Leung Ho Yu, Wai K Leung, Man-Fung Yuen, and Wai-Kay Seto. Manuscript draft: Xianhua Mao, Ka-Shing Cheung, and Wai-Kay Seto. Data analysis plan and data management: Xianhua Mao. Critical revision of manuscript: Ka-Shing Cheung, Lung-Yi Mak, Chi-Ho Lee, Esther Wai Yin Chan, Wai K Leung, Man-Fung Yuen, and Wai-Kay Seto. Overall study supervision: Ka-Shing Cheung and Wai-Kay Seto. All authors participated in the preparation of the manuscript and have seen and approved the final version.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data

are not publicly available due to identifiers in the dataset and are hence restricted from sharing by the Hospital Authority of Hong Kong.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the board of The University of Hong Kong and Hospital Authority Hong Kong West Cluster (reference No. UW 21-202). Written informed consent was waived due to the study's retrospective nature and adoption of anonymized reference key without true identity of the patients.

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SUPPORTING INFORMATION

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