Sodium–Glucose Cotransporter 2 Inhibitors and the Short-term Risk of Breast Cancer Among Women With Type 2 Diabetes

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are second- to third-line anti-diabetes drugs that have been shown to have cardiovascular benefits. However, in premarketing trials of the SGLT2 inhibitor dapagliflozin, there were numerical imbalances in breast cancer events compared with placebo; all occurred within 1 year of randomization (rate ratio 2.47, 95% CI 0.64–14.10) (1). In contrast, no imbalances were observed in subsequent large cardiovascular outcome trials of dapagliflozin and other SGLT2 inhibitors (2–4).

While the discrepant findings between the pre- and postmarketing trials could be due to chance, one hypothesis is that the early breast cancer imbalances are the result of an accelerated tumor-promoting effect of SGLT2 inhibitors. However, this is unlikely, given that sodium–glucose cotransporter proteins are not expressed in mammary tissue, and animal studies have failed to demonstrate that SGLT2 inhibitors have any neoplastic activity (5). Another hypothesis relates to the weight-lowering effects of SGLT2 inhibitors, which could facilitate the detection of existing breast lumps, thus leading to a transient overdetection of breast cancer. To date, this possible association has not been investigated in the real-world setting.

We conducted a population-based cohort study using the U.K. Clinical Practice Research Datalink (CPRD) (protocol: 19_272). We identified all female patients newly treated with either an SGLT2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or a dipeptidyl peptidase 4 (DPP-4) inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin) between 1 January 2013 (the year the first SGLT2 inhibitor, dapagliflozin, entered the U.K. market) and 30 June 2018. Cohort entry was the date of the first prescription of either drug class during the study period. To be included in the cohort, patients were required to be at least 40 years of age and have at least 1 year of medical history in the CPRD before cohort entry. This 1-year period served as a washout window to identify new users and was used as a baseline covariate assessment period. We excluded patients previously diagnosed with end-stage renal disease or undergoing dialysis (contraindications to receiving SGLT2 inhibitors), as well as those previously diagnosed with breast cancer at any time before cohort entry. Patients were followed using an intention-to-treat approach until an incident diagnosis of breast cancer (identified using Read codes with a positive predictive value of 90%, compared with U.K. National Cancer Data Repository [6]), death from any cause, or end of study period (31 December 2018)—whichever occurred first.

We used propensity score fine stratification weighting to control for confounding. The propensity score model considered >40 covariates (Table 1), including age, BMI, smoking status, proxies of diabetes severity, prescription drugs, and breast cancer risk factors. Cox proportional hazards models were used to estimate weighted hazard ratios (HRs) of breast cancer, and corresponding 95% CIs, in comparison of new users of SGLT2 inhibitors with new users of DPP-4 inhibitors. We also assessed whether there was a duration-response relation in terms of cumulative duration of use and time since treatment initiation and investigated whether the association varied according to type of SGLT2 inhibitor. Finally, in sensitivity analyses, we imposed lag periods, accounted for death as a competing risk using inverse probability of censoring weighting, and repeated the analysis by matching on propensity score.
The study included 9,938 new users of SGLT2 inhibitors and 36,631 new users of DPP-4 inhibitors. After a median follow-up of 2.6 years, these exposure groups generated 67 and 382 breast cancer events, yielding crude incidence rates of 2.8 (95% CI 2.2–3.6) and 3.7 (95% CI 3.3–4.1) per 1,000 person-years, respectively. Overall, compared with DPP-4 inhibitor use, SGLT2 inhibitor use was not associated with an overall increased risk of breast cancer compared with DPP-4 inhibitors. While these findings provide some reassurance on the short-term effects of SGLT2 inhibitors on breast cancer incidence among female patients with type 2 diabetes, future studies will be needed to investigate their long-term effects on this malignancy.

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The study was repeated by matching of SGLT2 inhibitor users to DPP-4 inhibitor users on propensity score, in a 1:1 ratio, using nearest neighborhood matching within a caliper of 0.01.
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References