GLP-1 receptor agonists and breast cancer risk in type 2 diabetes.

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Background: Type 2 diabetes mellitus (T2DM) is associated with an increased risk of breast cancer. Glucagon-like peptide 1 receptor agonists (GLP-1RAs), which improve glucose metabolism and promote weight loss, are widely used to treat T2DM. However, the trophic activity of GLP-1RAs is concerning. In diabetic patients, GLP-1 receptors are highly expressed in breast cancer tissues and their activation can lead to breast cancer cell proliferation. Combining GLP-1RAs and dipeptidyl-peptidase IV inhibitors (DPP4i), which also enhance GLP-1 pathway, was associated with more cases of breast cancer in the FDA Adverse Event Reporting system. We investigated the relationship of GLP-1RAs with breast cancer in T2DM patients using Epic Cosmos, a HIPPA law-compliant dataset with longitudinal records of 289 million de-identified patients. **Methods:** A retrospective cohort study was performed on patients with T2DM but without breast cancer. Patients treated with GLP1-1RAs between 1/1/2010 and 12/31/2020 were compared to those treated with metformin, sodium-glucose cotransporter-2 inhibitor (SGLT2i), sulfonylurea (SU), DPP4i, thiazolidinediones (TZD) or insulin. The incidence of breast cancer was tracked from 1/1/2021 to 12/12/2024. Subgroup analysis was conducted on White patients, African American patients, and five subgroups with different BMI ranges. Risk ratio (RR) and 95% confidence interval (CI) were calculated via RStudio (version 2024.09.1). **Results:** Patients with T2DM and treated with GLP-1RAs had a higher incidence of breast cancer compared to patients treated with each of the other antidiabetics (Table). Results of subgroup analysis were consistent with the overall effect; except that in the obese subgroups, GLP-1RA exposure was not associated with breast cancer compared with DPP4i. Weight and age were not significantly different between each pair of cohorts. **Conclusions:** GLP-1RAs was associated with an increased incidence of breast cancer compared to other antidiabetic regimens in patients with T2DM in a long-term observation. Acting on identical pathway, GLP-1RAs may show a blunt effect versus DPP4i in obese patients. The study is empowered by an enormous sample size in Epic Cosmos. Future improvements include stratifying exposure levels and stringently matching confounders. Research Sponsor: None.

GLP-1RAs cohorts	Non-GLP-1RAs cohorts	GLP-1RAs cohorts cancer cases (%)	Non-GLP-1RAs cohorts cancer cases (%)	RR (95% CI)
(-) Metformin (N=209090)	(+) Metformin (N=4989038)	1406 (0.67%)	25037 (0.50%)	1.34 (1.27-1.41)
(-) SGLT2i (N=639303)	(+) SGLT2i (N=826786)	4014 (0.63%)	4380 (0.53%)	1.19 (1.14-1.24)
(-)SU (N=497603)	(+) SU (N=2465377)	3109 (0.63%)	11271 (0.46%)	1.37 (1.31-1.42)
(-)DPP4i (N=716984)	(+) DPP4i (N=1123264)	4220 (0.59%)	5966 (0.53%)	1.11 (1.07-1.15)
(-)TZD (N=838249)	(+) TZD (N=464680)	5212 (0.62%)	2141 (0.46%)	1.35 (1.28-1.42)
(-) Insulin (N=467130)	(+) Insulin (N=2757742)	2921 (0.63%)	9895 (0.36%)	1.74 (1.67-1.82)