

Can GLP-1 receptor agonists mitigate cancer progression? A propensity-matched analysis across seven solid tumors.

Mark David Orland, Aashray Mandala, Serhan Unlu, Felipe de Almeida Sartori, Nandini Rajaram Siva, Asfand Yar Cheema, Carmelo Gurnari, Atsushi Marumo, Zachary Brady, Valeria Visconte, Jaroslaw P. Maciejewski; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Cleveland Clinic, Cleveland, OH; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Taussig Cancer Institute - Cleveland Clinic, Cleveland, OH; Cleveland Clinic Lerner Research Institute, Cleveland, OH

Background: GLP-1 receptor agonists (GLP-1RAs) are pleiotropic medications, initially developed for diabetes, yet with beneficial effects on obesity and cardiovascular disease. Given the rapidly expanding therapeutic use of these agents and emerging preclinical data suggesting immunomodulatory effects, we examined whether GLP-1RA exposure following cancer diagnosis was associated with altered risk of progression to metastatic disease. **Methods:** Utilizing the TriNetX Global Health Research Network, we identified 10,225 patients with stage I-III cancer who initiated GLP-1RA therapy after diagnosis. GLP-1RA-exposed patients were propensity-matched 1:1 to DPP-4 inhibitor controls across seven cancers: breast adenocarcinoma, prostate adenocarcinoma, NSCLC, colorectal adenocarcinoma (CRC), hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and pancreatic adenocarcinoma. Matching included demographics, BMI, glycemic factors, smoking, comorbidities, screening frequency, oncologic treatments, and concurrent medications. Primary outcome was progression to stage IV disease. Additionally, we used The Cancer Genome Atlas (TCGA) data to assess whether GLP-1R expression correlated with overall survival. **Results:** GLP-1RA exposure demonstrated reduced metastatic progression across 6/7 malignancies, with statistically significant reductions in four cancer types: NSCLC, breast, CRC, and HCC (Table 1). No significant safety signals or increased adverse events were observed in GLP-1RA-exposed patients compared to controls. Additionally, high tumor GLP-1R expression correlated with improved survival across the seven tumors (HR=0.67, 95% CI 0.54-0.83, $p<0.001$), most notably in breast cancer (HR=0.55, 95% CI 0.35-0.87, $p=0.011$). **Conclusions:** In this large propensity-matched cohort, GLP-1RA initiation after cancer diagnosis was associated with dramatically reduced metastatic progression across multiple solid tumors. Corroborating these clinical findings, elevated GLP-1R expression independently predicted improved overall survival. These findings warrant validation in prospective randomized controlled trials and mechanistic investigation of potential antineoplastic pathways driven by GLP-1RAs. Research Sponsor: None.

Effect of GLP1-1RA exposure compared to DPP-4i exposure on progression of stage I-III cancer to stage IV cancer.

Cancer Type	Matched Pairs (n)	Events GLP-1RA/DPP-4i	Cumulative Incidence (%)	Hazard Ratio (95% CI)	P-value
NSCLC	2,157	215/482	10.0 vs 22.3	0.50 (0.43-0.59)	<0.001
Breast	1,187	121/239	10.2 vs 20.1	0.57 (0.46-0.71)	<0.001
Colorectal	784	105/174	13.4 vs 22.2	0.69 (0.54-0.88)	0.003
HCC	275	52/78	18.9 vs 28.4	0.62 (0.44-0.89)	0.009
Prostate	1,010	83/137	8.2 vs 13.6	0.79 (0.60-1.04)	0.09
RCC	523	75/99	14.3 vs 18.9	0.95 (0.71-1.29)	0.76
Pancreatic	120	28/37	23.3 vs 30.8	0.69 (0.42-1.13)	0.14