CANCER RISK IN DIABETES: COMPARATIVE EFFECTS OF GLP-1 RECEPTOR AGONISTS AND SGLT-2 INHIBITORS IN A REAL-WORLD COHORT

By

Vibha Suresh

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APPROVED

Dr. Masoumeh Ghaffari, M.D.

Department of the School of Medicine

Dr. Begoñia Echeverria, Howard H Hays, Jr. Chair

University Honors

ABSTRACT

Obesity and type-2-diabetes mellitus (T2DM) are associated with increased malignancy risk. Glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i) are increasingly used for diabetes management, but their association with cancer-risk is poorly defined. Here we compared all-cause or obesity-associated cancer (OAC) incidence among diabetics treated with first-line therapy (FLT) versus GLP-1RA or SGLT-2i.

Using the TriNetX US Collaborative Network, T2DM adults (ICD-10 E11) were categorized into 3 groups- FLT (dipeptidyl peptidase-4 inhibitor or metformin) excluding GLP-1RA and SGLT-2i, or GLP-1RA or SGLT2i plus FLT- based on first recorded exposure to medication (index event). Insulin usage and cancer diagnosis before the index event was excluded. Primary and secondary outcomes were incident diagnosis of any malignant neoplasm (ICD-10 C00-C96) or OAC, respectively. Cohorts were balanced using propensity score matching and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Kaplan-Meier analyses.

GLP-1RA and SGLT-2i were associated with a reduced risk of all-cancer risk compared to FLT. Compared to the FLT cohort which had an increased risk of 76.1%, the GLP-1RA cohort showed an approximate risk of 70.3% and the SLGT-2i cohort showed a risk of around 66.0%. The GLP-1RA cohort also had a hazard ratio (HR) of 0.934 and a relative risk ratio (RR) of 0.924. The SGLT-2i cohort resulted in a HR value of 0.862 and a RR value of 0.878. Based on the risk (%) as well as HR and RR values, SGLT-2i shows a greater protective effect compared to GLP-1RA. As for the secondary outcome of OAC, there were consistent reductions across several cancers. The risk reductions were substantial and ranged from 25% to 40%. Notably, SLGT-2i showed slightly stronger associations across various cancers.

From this study, it is shown that cancer risk is decreased in cohorts of patients that are being treated with newer anti-diabetic therapies compared to patients that are on FLT exclusively. Both GLP-1RA and SGLT-2i showed a decreased risk but SGLT-2i seemed to have a stronger effect. The longitudinal effects of this study still remains unclear as there were some time-to-event analyses that were less consistent across cancers. Ultimately this study can be used to create more personalized therapeutic treatments, particularly for patients at a higher risk for OAC.

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INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) represent two of the most significant and rapidly growing public health challenges in the US. According to the Center for Disease Control (CDC), more than 40 million Americans have diabetes, with T2DM accounting for 90-95% of those cases. Parallely, the CDC also reports that more than 100 million adults have obesity and more than 22 million adults have severe obesity. Obesity and T2DM are biologically connected, as the accumulation of excess body fat induces a variety of metabolic abnormalities, including T2DM, atherogenic dyslipidemia (high plasma triglyceride and low plasma HDL-cholesterol concentrations), insulin resistance, and nonalcoholic fatty liver disease (NAFLD) (Klein et al., 2022). Additionally, both conditions have been associated with an elevated risk of developing malignancies, as well as other cancer-related outcomes (Scully et al., 2021).

There is substantial epidemiologic evidence that patients with T2DM have an increased risk of several site specific cancers, including but not limited to liver, pancreatic, colorectal, endometrial, breast, and kidney cancers. The CDC recognizes obesity as a major risk factor for at least 13 malignancies otherwise known as obesity associated cancers (OAC). Proposed mechanisms that have been found to link T2DM and obesity to cancer outcomes include increased signaling of insulin-like growth factor-1 (IGF-1), hyperinsulinemia. Hyperinsulinemia may promote tumor formation by activating mitogenic and anti-apoptotic pathways that could act as growth stimulus for neoplastic cells. Additionally, adipose tissue-derived cytokines can create an environment that may be conducive to cancer-cell proliferation (Giovannucci et al., 2010). Increased IGF-1 signaling leads to increased cell proliferation and enhanced survival of IGF-responsive cells. In addition to an uptake in cell proliferation, the IGF system also inhibits

apoptosis which can help cancer cells evade programmed cell death and contribute to malignancy (Weroha & Haluska, 2012).

Given these risks, the long-term oncologic implications of diabetes therapies have become an area of increasing interest. Traditionally first-line therapy, most commonly metformin, has been studied and in some studies has been associated with potential protective effects against certain cancers. When metformin is introduced into the cell, it blocks complex I of the electron transfer chain activity, reduces oxygen consumption and production of adenosine triphosphate (ATP) and puts the cell under stress conditions. With this inhibition, the level of adenosine monophosphate (AMP) increases and activates adenosine monophosphate-activated kinase (AMPK). AMPK can play a significant role in regulating the amount of energy in the cell. AMPK increases glucose uptake in muscle cells in diabetic patients and thus leads to a decrease in glucose and insulin levels. Another anticancer effect reported is the activation of ataxia telangiectasia mutated (ATM) and liver kinase B1 (LKB1). LKB1 and ATM are both tumor suppressors and the activity of LKB1 regulates AMPK activity. ATM reacts to metformin by phosphorylating LKB1 and thereby activating AMPK. Metformin is also thought to have an anti-tumor effect by lowering insulin levels and disabling the mammalian target of rapamycin (mTOR) in the cell. With mTOR activation, cell growth, and proliferation increase. Therefore, metformin may reduce the growth and proliferation of cancer cells by inhibiting mTOR activity (Saraei et al., 2019). Di-peptidyl peptidase-4 inhibitors (DPP-4i), another first line treatment also has potential to have protective effects against certain cancers like hepatocellular carcinomas (Busek et al., 2022), although less studied compared to metformin. DPP-4 in the body acts on enzymes like glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) and degrades them immediately due to their short half-life. DPP-4i's on the other hand inhibit DPP-4 and

thereby increase levels of GLP-1 and GIP which in turn increase beta-cell insulin secretion in the pancreas which helps in controlling blood sugar (Kasina & Baradhi, 2026). Additionally, it is important to note that sulfonylureas (SUs) were previously used as first-line therapies along with metformin. However, studies have shown that SUs are seen as less durable compared to other diabetes medications and although they are able to increase insulin production, they are typically unable to correct the underlying issue of beta cell dysfunction (Schroeder, 2000). SUs have also been seen to have weight gain effects on patients as well as increased risk of hypoglycemia and therefore are typically used in the lowest dose possible. Due to these facts, SUs were not included as first-line therapies for this project.

However, as diabetes management has evolved, newer classes of medications, specifically, glucagon-like peptide-1 analogues (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i), have been adopted not only for glycemic control but also for their various cardiological and weight-reducing benefits (American Diabetes Association Professional Practice Committee for Diabetes*, 2025). GLP-1 is a peptide produced by the cleavage of proglucagon and mainly synthesized in the pancreatic islet α- cells. GLP-1RA's mimic the action of endogenous GLP-1 and activate glucagon-like peptide-1 receptors (GLP-1R). Thus enhancing insulin secretion, inhibiting glucagon release, and reducing food intake through appetite suppression. These mechanisms make GLP-1RA's a powerful tool for controlling blood glucose and improving various metabolic syndromes, which includes T2DM. GLP-1RA's are a result of intricate structural modifications to GLP-1 which enables them to not only replicate the functions of GLP-1 while also impeding the hydrolysis by DPP-4 which extends the half-life of the drug (Zheng et al., 2024). SGLT-2 cotransporters are part of a large family of symporters. SGLT-2 cotransporters are mostly found in renal tissue and are responsible for the reabsorption of

90-97% of filtered glucose (Fonseca-Correa & Correa-Rotter, 2021). SGLT-2i works by inhibiting glucose reabsorption within the proximal renal tubules, which results in glucosuria (presence of excess glucose in urine), weight loss, and blood pressure reduction. This drug reduces glucose absorption by 30%-60% and thus leads to an average hemoglobin A1c (HbA1c) reduction of 0.5%-1.0% in patients with T2DM (Padda et al., 2025).

However, clinical evidence remains mixed and causal relationships have not been established. As these medications are increasingly prescribed to broader patient populations, it is important to clarify their long-term safety profile. Real-world data sources offer an opportunity to evaluate cancer incidence across large and diverse patient populations beyond randomized clinical trials. Comparative analyses of these newer antidiabetic agents versus standard first-line therapies could provide valuable insights into whether these medications modify overall malignancy risk of site-specific obesity-related cancer risk.

The objective of this study was to compare the risk of incident malignancy among adults with T2DM treated with first-line diabetes therapy versus those treated with GLP-1RA or SGLT-2i. Additionally, the risk of developing specific obesity related cancers in these cohorts was also evaluated. This study aims to contribute to the growing body of evidence regarding the long-term oncologic implications of diabetes therapeutics.

METHODOLOGY

This retrospective cohort study was conducted using the TriNetX research network, a cloud-based platform that collects de-identified electronic health record data from various healthcare organizations. The database includes patient-level data on demographics, diagnoses, procedures, medications, laboratory values, and mortality. All data is de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA), and IRB approval was

not required. This research, conducted entirely on the TriNetX platform, has been determined by the UC Riverside Office of Research Integrity to be non-human subjects research under Protocol #30442.

Patients with T2DM were identified using International Classification of Disease, Tenth Revision (ICD-10) code, E11 or by a hemoglobin A1c (HbA1c) level of over 6.5%. Patients were required to have a T2DM diagnosis prior to the initiation of medications. The patients were then sorted into three cohorts with the index event being the first recorded prescription of SGLT-2i or FLT or GLP-1RA based on the cohort. The SGLT-2i cohort was defined as the first recorded prescription of medications classified under Anatomical Therapeutic Chemical (ATC) code A10BK. In this cohort a temporal relationship was defined so that the first instance of SGLT-2i came after a diagnosis of T2DM as well as a prescription of metformin or DPP-4i because patients are prescribed metformin or DPP-4i before they are prescribed with SGLT-2i or GLP-1RA. The GLP-1RA cohort was defined as the first recorded prescription of medications (ATC code A10BJ). The temporal relationship was defined so that the first instance of GLP-1RA's came after a diagnosis of T2DM as well as after a prescription of metformin or DPP-4i. The first-line therapy cohort consisted of patients initiated on first-line therapies, defined as the first recorded prescription of metformin (RxNorm 6809) or DPP-4i (ATC code A10BH) and the temporal relationship was defined by including patients that were prescribed these medications after they had been diagnosed with T2DM.

To ensure mutually exclusive exposure groups and minimize misclassification, patients were excluded if they had any prior exposure to SGLT-2i (ATC code A10BK), GLP-1RA (ATC code A10BJ), and exogenous insulin (ATC code A10A) before the index date. Additionally, to ensure the validity of incident outcomes, patients with a prior history of malignancy (ICD-10 codes

C00-C97) before the index date were excluded as well. Patients were followed from the index date until outcome occurrence, death, or the end of an available follow-up data.

The primary outcome for this study was all-cancer incidence, defined as a patient diagnosis of malignant neoplasm (ICD-10 C00-C97) during follow-up. Secondary outcomes included the incidence of 13 obesity-related cancers, identified by the CDC. These included pancreatic (C25), esophageal (C15), breast (C50), colorectal (C18-C20), uterus (C55), gallbladder (C23), stomach (cardia) (C16), kidney (C64), liver (C22), ovary (C56), thyroid (C73), meningioma (D32), and multiple myeloma (C90). In total, 14 outcomes were evaluated.

To reduce confounding, 1:1 propensity score matching using nearest-neighbor matching without replacement was performed to balance baseline characteristics between cohorts. Covariates included demographic variables (age, sex, race), clinical comorbidities including obesity (ICD-10 E65-E68), BMI as categorized by the various classes of obesity by the CDC (TNX curated 9083) the categories were as follows, 25-29.9 kg/m^2, 30-34.9kg/m^2, 35-39.9 kg/m^2, and $\geq$40 kg/m^2. Additionally, baseline glycemic control as measured by HbA1c was included as a covariate.

Following matching, outcomes were analyzed using comparative risk estimates. Risk ratios (RRs) and odds ratios (ORs) with corresponding 95% confidence intervals as well as time-to-event analyses were calculated to assess the association between treatment exposure and outcomes. Given the evaluation of 14 outcomes, a bonferroni correction was applied to adjust for multiple comparisons, with a corrected threshold for statistical significance defined as $p<0.0036$ (0.05/14). All statistical analyses were performed within the TriNetX platform.

RESULTS

A total of 539,861 patients in the GLP-1RA cohort and 495,585 in the SGLT-2i cohort were identified prior to matching, compared to 2,579,902 patients receiving first-line therapy (metformin or DPP-4i). After 1:1 propensity score matching, 529,552 patients remained in each group for the GLP-1RA comparison and 490,582 patients per group for the SGLT-2i comparison, with balanced baseline characteristics across cohorts.

Primary Outcome: All-Cancer Risk

Both GLP-1RA and SGLT-2i were associated with significantly lower risk of all-cancer outcomes compared to first-line therapy, with all findings remaining significant after Bonferroni correction ($p<0.0036$).

In the GLP-1RA cohort, the cumulative risk of cancer was 70.312%, compared to 76.074% in the FLT group, corresponding to an absolute risk difference (ARD) of 5.762% ($p<0.0001$). The RR was 0.924 (95% CI: 0.906-0.942) and the OR was 0.745 (95% CI: 0.693-0.8). The log rank test was significant ($p=0.0004$) and the HR was 0.934 (95% CI: 0.9-0.97), indicating a 6.6% decreased hazard in the GLP-1RA cohort compared to the FLT cohort.

In the SGLT-2 cohort, the cumulative risk of cancer was 66.038% compared to 75.234% in the FLT group, corresponding to an ARD of 9.196% ($p<0.0001$). The RR was 0.878 (95% CI: 0.859-0.897) and the OR was 0.64 (95% CI: 0.596-0.687). The log rank test was significant ($p<0.0001$) and the HR was 0.862 (95% CI: 0.829-0.897), indicating a 13.8% decreased hazard in the SGLT-2i cohort compared to the FLT cohort.

Secondary Outcomes: Obesity-Associated Cancers

Across 14 evaluated outcomes, both GLP-1RA and SGLT-2i were associated with reductions in multiple obesity related cancers compared to the FLT cohort.

Pancreatic Cancer (ICD-10: C25)

In the GLP-1RA cohort, the risk for pancreatic cancer was 0.252%, compared to 0.376% in the FLT group, corresponding to an ARD of 0.124% ($p<0.0001$). The RR was 0.669 (95% CI: 0.625-0.717) and the OR was also 0.669 (95% CI: 0.624-0.717). The log rank test was not significant ($p=0.0156$), but the HR was 0.917 (95% CI: 0.854-0.984), indicating a 8.3% decreased hazard in the SGLT-2i cohort compared to the FLT cohort.

In the SGLT-2i cohort, the risk for pancreatic cancer was 0.306%, compared to 0.455% in the FLT group, corresponding to an ARD of 0.15% ($p<0.0001$). The RR was 0.671 (95% CI: 0.628-0.717) and the OR was 0.67 (95% CI: 0.628-0.716). The log rank test was not significant ($p=0.3849$), and the HR value was 0.971 (95% CI: 0.907-1.038), however because the 95% CI crosses 1, the HR value is not significant and shows no significant difference between the two groups in this time-to-event analysis.

Adenocarcinoma Esophagus (ICD-10: C15)

In the GLP-1RA cohort, the risk for esophageal cancer was 0.067%, compared to 0.114% in the FLT group, corresponding to an ARD of 0.046% ($p<0.0001$). The RR and OR were both 0.593 (95% CI: 0.52-0.676). The log rank test was not significant ($p=0.0230$), but the HR value was 0.857 (95% CI: 0.75-0.979), indicating a 14.3% decreased hazard in the GLP-1RA cohort compared to the FLT cohort.

In the SGLT-2i cohort, the risk for esophageal cancer was 0.074%, compared to 0.133% in the FLT group, corresponding to an ARD of 0.059% ($p<0.0001$). The RR was 0.557 (95% CI:

0.48-0.633) and the OR was 0.57 (95% CI: 0.49-0.633). The log rank test was not significant (p=0.0292), but the HR value was 0.884 (95% CI: 0.758-0.985), indicating a 11.6% decreased hazard in the SGLT-2i cohort compared to the FLT cohort.

Breast Cancer (ICD-10: C50)

In the GLP-1RA cohort, the risk for breast cancer was 0.824%, compared to 1.152% in the FLT group, corresponding to an ARD of 0.328% (p<0.0001). The RR is 0.715 (95% CI: 0.688-0.744) and the OR is 0.713 (95% CI: 0.686-0.742). The log rank test was not significant (p=0.3468), and the HR value is 0.981 (95% CI: 0.943-1.021), however because the 95% CI crossed 1, the HR value is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk for breast cancer is 0.662%, compared to 1.064% in the FLT group, corresponding to an ARD of 0.402% (p<0.0001). The RR was 0.622 (95% CI: 0.596-0.65) and the OR was 0.62 (95% CI: 0.593-0.647). The log rank test was significant p<0.0001 and the HR value was 0.905 (95% CI: 0.866-0.947), indicating a 9.5% decreased hazard in the SGLT-2i cohort compared to the FLT cohort.

Colon Cancer (ICD-10: C18)

In the GLP-1RA cohort, the risk of colon cancer was 0.362%, compared to 0.552% in the FLT cohort, corresponding to an ARD of 0.196% (p<0.0001). The RR was 0.648 (95% CI: 0.612-0.686) and the OR was 0.647 (95% CI: 0.611-0.685). The log rank test was significant (p=0.0004) and the HR value is 0.9 (95% CI: 0.849-0.954), indicating a 10% decreased hazard in the GLP-1RA cohort compared to the FLT cohort.

In the SGLT-2i cohort, the risk of colon cancer was 0.385%, compared to 0.621% in the FLT group, corresponding to an ARD 0f 0.236% (p<0.0001). The RR was 0.62 (95% CI:

0.586-0.657) and the OR was 0.619 (95% CI: 0.584-0.656) The log rank test was significant (p=0.0019) and the HR value was 0.911 (95% CI: 0.859-0.966), indicating a 8.9% decreased hazard in the SGLT-2i cohort compared to the FLT cohort.

Rectal Cancer (ICD-10: C20)

In the GLP-1RA cohort, the risk of rectal cancer was 0.096%, compared to 0.154% in the FLT group, corresponding to an ARD of 0.058% (p<0.0001). The RR and OR were both 0.622 (95% CI: 0.557-0.695). The log rank test was not significant (p=0.0100), but the HR value was 0.862 (95% CI: 0.77-9.965), indicating a 13.8% decreased hazard in the GLP-1RA cohort compared to the FLT cohort.

In the SGLT-2i cohort, the risk of rectal cancer was 0.113%, compared to 0.169% in the FLT group, corresponding to an ARD of 0.056% (p<0.0001). The RR and OR were both 0.668 (95% CI: 0.6-0.744). The log rank test was not significant (p=0.9981) and the HR value was 1 (95% CI: 0.896-1.117), however because the HR value is 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Uterine Cancer (ICD-10: C55)

In the GLP-1RA cohort, the risk of uterine cancer was 0.101%, compared to 0.152% in the FLT cohort, corresponding to an ARD of 0.051% (p<0.0001). The RR and OR were both 0.667 (95% CI: 0.598-0.744). The log rank test was not significant (p=0.2229) and the HR value was 0.933 (95% CI: 0.835-1.043), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of uterine cancer was 0.086%, compared to 0.125% in the FLT cohort, corresponding to an ARD of 0.039% ($p<0.0001$). The RR was 0.686 (95% CI: 0.606-0.776) and the OR was 0.685 (95% CI: 0.605-0.776). The log rank test was not significant ($p=0.8697$) and the HR value was 1.011 (95% CI: 0.835-1.043), however because the HR value was greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Gallbladder Cancer (ICD-10: C23)

In the GLP-1RA cohort, the risk of gallbladder cancer was 0.016%, compared to 0.027% in the FLT cohort, corresponding to an ARD of 0.011% ($p<0.0001$). The RR and OR were both 0.589 (95% CI: 0.449-0.772). The log rank test was not significant ($p=0.2303$) and the HR value was 0.845 (95% CI: 0.641-1.113), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of gallbladder cancer was 0.02%, compared to 0.03% in the FLT cohort, corresponding to an ARD of 0.01% ($p=0.0016$). The RR and OR were both 0.662 (95% CI: 0.512-0.857). The log rank test was not significant ($p=0.8978$) and the HR value was 0.983 (95% CI: 0.755-1.28), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Stomach Cancer (Cardia) (ICD-10: C16)

In the GLP-1RA cohort, the risk of stomach cancer (specifically focused in the upper stomach, cardia) was 0.038%, compared to 0.057% in the FLT cohort, corresponding to an ARD of 0.019% ($p<0.0001$). The RR and OR were both 0.674 (95% CI: 0.564-0.806). The log rank

test was not significant (p=0.9779) and the HR value was 0.997 (95% CI: 0.832-1.196), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of stomach cancer (specifically focused in the upper stomach, cardia) was 0.042%, compared to 0.065% in the FLT cohort, corresponding to an ARD of 0.024% (p<0.0001). The RR and OR were both 0.637 (95% CI: 0.535-0.76). The log rank test was not significant (p=0.8411) and the HR value was 1.019 (95% CI: 0.85-1.221), however because the HR value is greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Kidney Cancer (ICD-10: C64)

In the GLP-1RA cohort, the risk of kidney cancer was 0.356%, compared to 0.476% in the FLT cohort, corresponding to an ARD of 0.12% (p<0.0001). The RR and OR were both 0.748 (95% CI: 0.705-0.794). The log rank test was not significant (p=0.0969) and the HR value was 1.035 (95% CI: 0.991-1.119), however because HR value is greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of kidney cancer was 0.343%, compared to 0.508% in the FLT cohort, corresponding to an ARD of 0.165% (p<0.0001). The RR was 0.675 (95% CI: 0.635-0.718) and the OR was 0.674 (95% CI: 0.634-0.717). The log rank test was not significant (p=0.6994) and the HR value was 1.013 (95% CI: 0.95-1.079), however because HR value is greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Liver Cancer (ICD-10: C22)

In the GLP-1RA cohort, the risk of liver cancer was 0.29%, compared to 0.44% in the FLT cohort, corresponding to an ARD of 0.15% ($p<0.0001$). The RR was 0.659 (95% CI: 0.618-0.703) and the OR was 0.658 (95% CI: 0.617-0.702). The log rank test was not significant ($p=0.1568$) and the HR value was 0.954 (95% CI: 0.893-1.018), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of liver cancer was 0.328%, compared to 0.507% in the FLT cohort, corresponding to an ARD of 0.179% ($p<0.0001$). The RR was 0.648 (95% CI: 0.608-0.69) and the OR was 0.647 (95% CI: 0.607-0.689). The log rank test was not significant ($p=0.9549$) and the HR value was 0.998 (95% CI: 0.936-1.065), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Ovarian Cancer (ICD-10: C56)

In the GLP-1RA cohort, the risk of ovarian cancer was 0.105%, compared to 0.158% in the FLT cohort, corresponding to an ARD of 0.052% ($p<0.0001$). The RR and OR were both 0.668 (95% CI: 0.6-0.743). The log rank test was not significant ($p=0.2832$) and the HR value was 0.942 (95% CI: 0.845-1.051), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of ovarian cancer was 0.087%, compared to 0.133% in the FLT cohort, corresponding to an ARD of 0.046% ($p<0.0001$). The RR and OR were both 0.656 (95% CI: 0.581-0.741). The log rank test was not significant ($p=0.7697$) and the HR value was

0.942 (95% CI: 0.866-1.112), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Thyroid Cancer (ICD-10: C73)

In the GLP-1RA cohort, the risk of thyroid cancer was 0.189%, compared to 0.243% in the FLT cohort, corresponding to an ARD of 0.054% ($p<0.0001$). The RR and OR were both 0.779 (95% CI: 0.717-0.846). The log rank test was not significant ($p=0.8587$) and the HR value was 1.008 (95% CI: 0.927-1.096), however because HR value is greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of thyroid cancer was 0.175%, compared to 0.22% in the FLT cohort, corresponding to an ARD of 0.045% ($p<0.0001$). The RR and OR were both 0.797 (95% CI: 0.728-0.872). The log rank test was not significant ($p=0.0391$) and the HR value was 1.101 (95% CI: 1.005-1.207), however because HR value is greater than 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Meningioma (ICD-10: D32)

In the GLP-1RA cohort, the risk of developing a meningioma was 0.255%, compared to 0.357% in the FLT cohort, corresponding to an ARD of 0.101% ($p<0.0001$). The RR was 0.716 (95% CI: 0.668-0.768) and the OR was 0.715 (95% CI: 0.667-0.767). The log rank test was not significant ($p=0.3402$) and the HR value was 1.035 (95% CI: 0.964-1.112), however because HR value is 1 and the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of developing a meningioma was 0.231%, compared to 0.37% in the FLT cohort, corresponding to an ARD of 0.139% ($p<0.0001$). The RR was 0.624 (95% CI: 0.579-0.672) and the OR was 0.623 (95% CI: 0.578-0.671). The log rank test was not significant ($p=0.3032$) and the HR value was 0.961 (95% CI: 0.89-1.037), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Multiple Myeloma (ICD-10: C90)

In the GLP-1RA cohort, the risk of multiple myeloma was 0.158%, compared to 0.237% in the FLT cohort, corresponding to an ARD of 0.08% ($p<0.0001$). The RR and OR were both 0.664 (95% CI: 0.608-0.725). The log rank test was not significant ($p=0.3368$) and the HR value was 0.957 (95% CI: 0.875-1.047), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

In the SGLT-2i cohort, the risk of multiple myeloma was 0.171%, compared to 0.273% in the FLT cohort, corresponding to an ARD of 0.102% ($p<0.0001$). The RR and OR were both 0.626 (95% CI: 0.575-0.683). The log rank test was not significant ($p=0.5170$) and the HR value was 0.971 (95% CI: 0.888-1.061), however because the 95% CI crosses 1, the HR is not significant and therefore there is no significant difference between the two groups in this time-to-event analysis.

Summary of Outcomes

Looking at all-cancer risk, SGLT-2i and GLP-1RA therapies showed a considerably lower risk, with SGLT-2i showing slightly stronger protective effects. Across the evaluated obesity-associated malignancies, both GLP-1RA and SGLT-2i cohorts demonstrated a consistent

pattern of lower incidence compared with FLT, although the magnitude and strength of the associations varied by cancer subtype and method of analysis. The most robust reductions were observed for gastrointestinal malignancies, particularly pancreatic, colorectal, and esophageal cancers. The additional OAC cancers that were analyzed showed significantly lower cumulative incidence in one or both exposure cohorts, based on RR and OR, generally ranging from 22%-41% RR reduction. Many of these outcomes however did not demonstrate statistically significant hazard reductions on survival analysis, as 95% CI's crossed 1 and log rank testing was nonsignificant. Across the observed outcomes, SGLT-2i therapy appeared to demonstrate numerically larger reductions in cancer incidence across many of the OAC's, whereas GLP-1RA therapy showed comparatively stronger HR associations for pancreatic and esophageal cancers.

Table 1: Risk and Hazard Ratios for GLP-1RA cohort (All Outcomes)

Outcome	GLP-1RA Risk (%)	FLT Risk (%)	ARD (%)	RR	95% CI (RR)	OR	95% CI (OR)	HR	95% CI (HR)
All cancer	70.312	76.074	5.762	0.924	0.906 - 0.942	0.745	0.693 - 0.8	0.934	0.9 - 0.97
Pancreatic	0.252	0.376	0.124	0.669	0.625 - 0.717	0.669	0.624 - 0.717	0.917	0.854 - 0.984
Esophageal adenocarcinoma	0.067	0.114	0.046	0.593	0.52 - 0.676	0.593	0.52 - 0.676	0.857	0.75 - 0.979
Breast	0.824	1.152	0.328	0.715	0.688 - 0.744	0.713	0.686 - 0.742	0.981	0.943 - 1.021
Colon	0.362	0.552	0.196	0.648	0.612 - 0.686	0.647	0.611 - 0.685	0.900	0.849 - 0.954
Rectum	0.096	0.154	0.058	0.622	0.557 - 0.695	0.622	0.556 - 0.695	0.862	0.77 - 0.965
Uterus	0.101	0.152	0.051	0.667	0.598 - 0.744	0.667	0.598 - 0.744	0.933	0.835 - 1.043
Gallbladder	0.016	0.027	0.011	0.589	0.449 - 0.772	0.589	0.449 - 0.772	0.845	0.641 - 1.113
Cardia	0.038	0.057	0.019	0.674	0.564 - 0.806	0.674	0.564 - 0.806	0.997	0.832 - 1.196
Kidney	0.356	0.476	0.120	0.748	0.705 - 0.794	0.747	0.704 - 0.793	1.053	0.991 - 1.119
Liver	0.290	0.440	0.150	0.659	0.618 - 0.703	0.658	0.617 - 0.702	0.954	0.893 - 1.018
Ovary	0.105	0.158	0.052	0.668	0.6 - 0.743	0.668	0.6 - 0.743	0.942	0.845 - 1.051
Thyroid	0.189	0.243	0.054	0.779	0.717 - 0.846	0.779	0.717 - 0.846	1.008	0.927 - 1.096

Meningioma	0.255	0.357	0.101	0.716	0.668 - 0.768	0.715	0.667 - 0.767	1.036	0.964 - 1.112
Multiple myeloma	0.158	0.237	0.080	0.665	0.609 - 0.725	0.664	0.608 - 0.725	0.957	0.875 - 1.047

Table 2: Risk and Hazard Ratios for SGLT-2i cohort (All Outcomes)

Outcome	SGLT-2i Risk (%)	FLT Risk (%)	ARD (%)	RR	95% CI (RR)	OR	95% CI (OR)	HR	95% CI (HR)
All cancer	66.038	75.234	9.196	0.878	0.859 - 0.897	0.64	0.596 - 0.687	0.862	0.829 - 0.897
Pancreatic	0.306	0.455	0.150	0.671	0.629 - 0.717	0.67	0.628 - 0.716	0.971	0.907 - 1.038
Esophageal adenocarcinoma	0.074	0.133	0.059	0.557	0.49 - 0.633	0.57	0.49 - 0.633	0.884	0.758 - 0.985
Breast	0.662	1.064	0.402	0.622	0.596 - 0.65	0.62	0.593 - 0.647	0.905	0.866 - 0.947
Colon	0.385	0.621	0.236	0.62	0.586 - 0.657	0.619	0.584 - 0.656	0.911	0.859 - 0.966
Rectum	0.113	0.169	0.056	0.668	0.6 - 0.744	0.668	0.6 - 0.744	1	0.896 - 1.117
Uterus	0.086	0.125	0.039	0.686	0.606 - 0.776	0.685	0.605 - 0.776	1.011	0.89 - 1.148
Gallbladder	0.020	0.030	0.010	0.662	0.512 - 0.857	0.662	0.511 - 0.857	0.983	0.755 - 1.28
Cardia	0.042	0.065	0.024	0.638	0.535 - 0.76	0.637	0.535 - 0.76	1.019	0.85 - 1.221
Kidney	0.343	0.508	0.165	0.675	0.635 - 0.718	0.674	0.634 - 0.717	1.013	0.95 - 1.079

Liver	0.328	0.507	0.179	0.648	0.608 - 0.69	0.647	0.607 - 0.689	0.998	0.936 - 1.065
Ovary	0.087	0.133	0.046	0.656	0.581 - 0.741	0.656	0.58 - 0.741	0.982	0.866 - 1.112
Thyroid	0.175	0.220	0.045	0.797	0.729 - 0.872	0.797	0.728 - 0.871	1.101	1.005 - 1.207
Meningioma	0.231	0.370	0.139	0.624	0.579 - 0.672	0.623	0.578 - 0.671	0.961	0.89 - 1.037
Multiple myeloma	0.171	0.273	0.102	0.626	0.575 - 0.683	0.626	0.574 - 0.682	0.971	0.888 - 1.061

Figure 1: Forest Plot of Hazard Ratio for GLP-1RA cohort (All Outcomes)

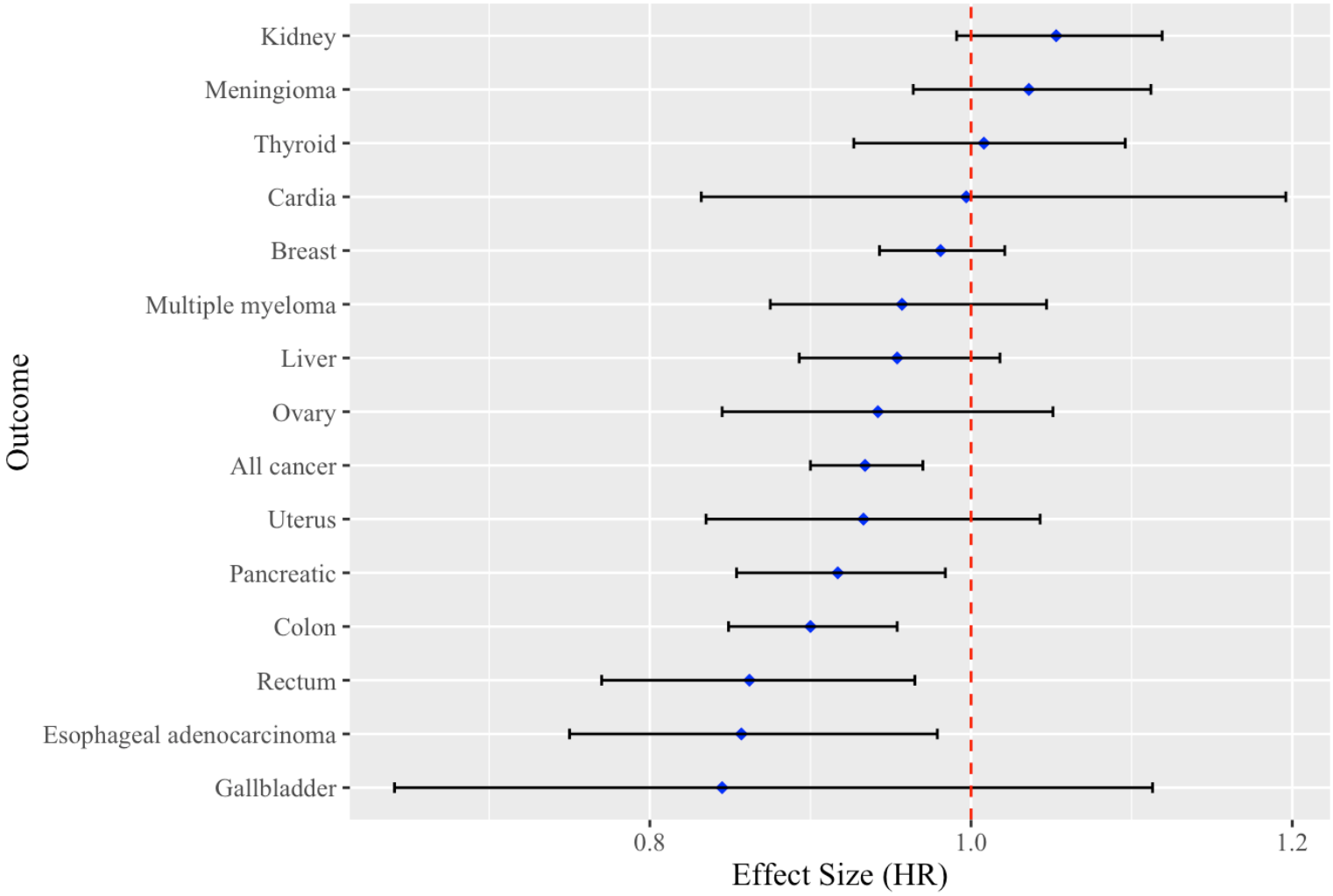


Figure 2: Forest Plot of Risk Ratio for GLP-1RA cohort (All Outcomes)

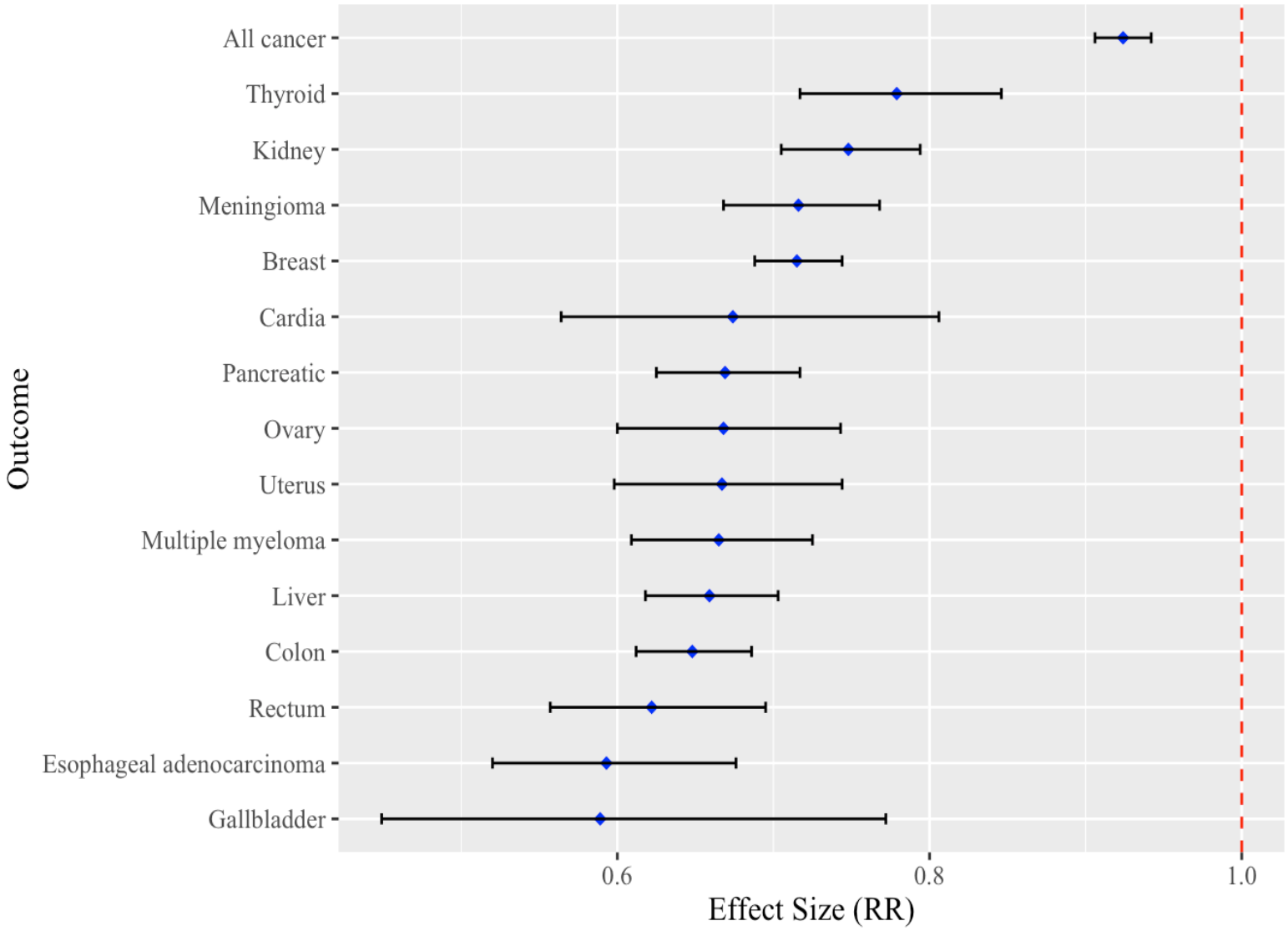


Figure 3: Forest Plot of Hazard Ratio for SGLT-2i cohort (All Outcomes)

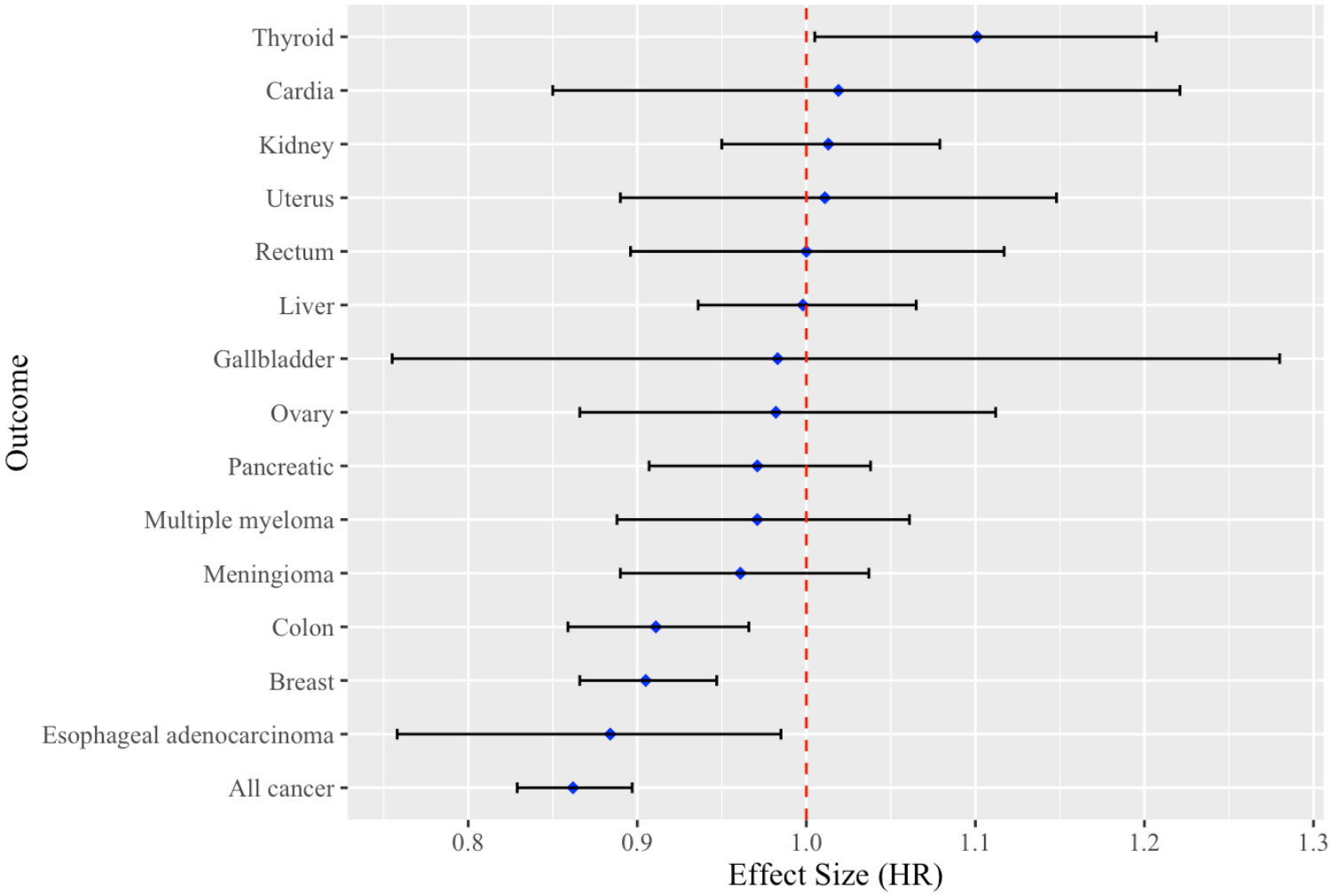
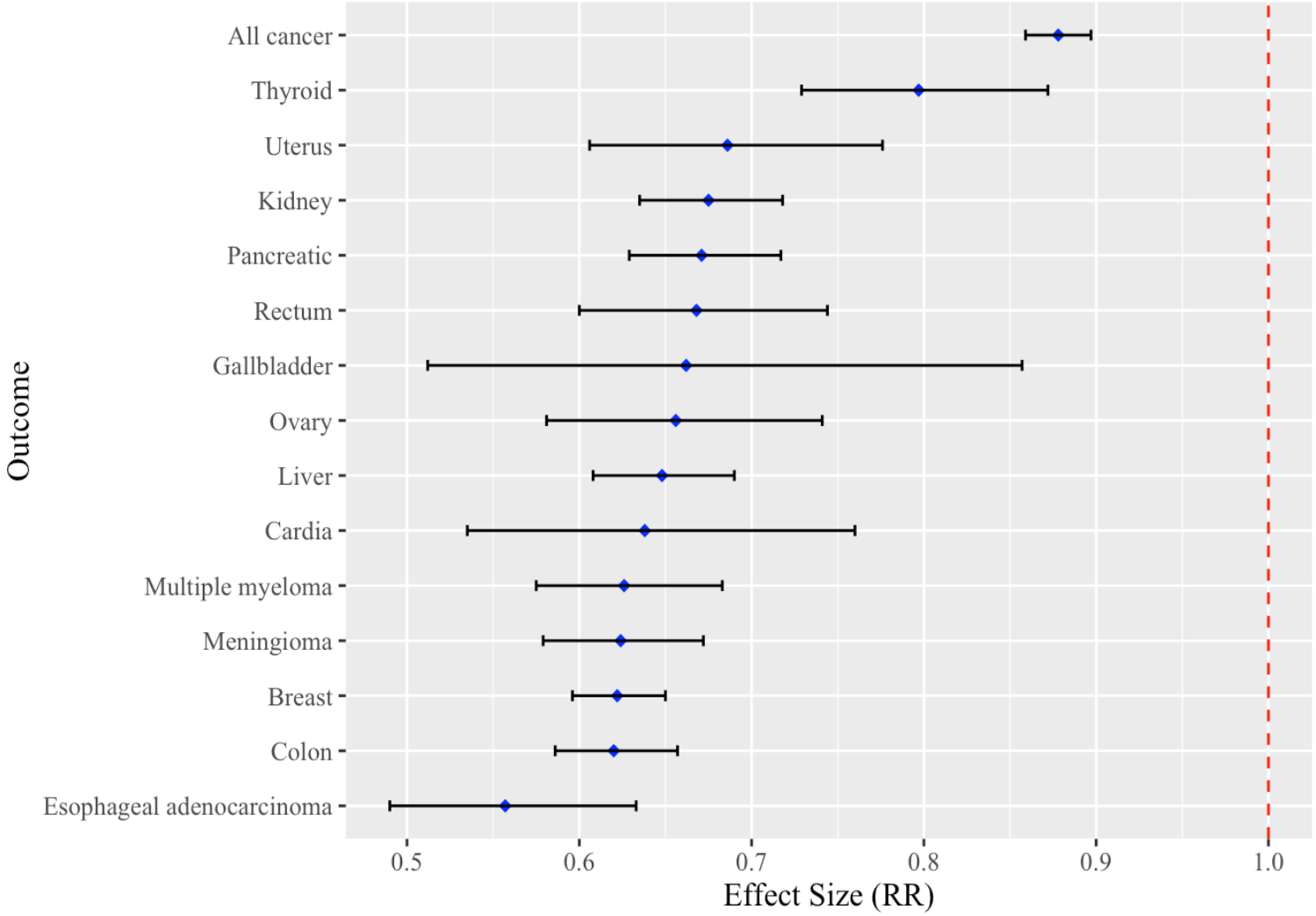


Figure 4: Forest Plot of Risk Ratio for SGLT-2i cohort (All Outcomes)



DISCUSSION

In this large retrospective cohort study of adults with T2DM, treatment with GLP-1RA's and SGLT-2i's were associated with a significantly lower risk of incident malignancy compared with FLT (metformin or DPP-4i) after propensity score matching. Both newer therapeutic classes demonstrated reductions in overall cancer incidence, with SGLT-2i showing a stronger association than GLP-1RA. These findings suggest that beyond glycemic control and cardiovascular benefits, newer antidiabetic therapies may also be associated with potentially favorable long-term oncologic outcomes.

The observed reduction in all cancer risk is biologically plausible. Both GLP-1RA and SGLT-2i improve insulin resistance, lower circulating insulin levels, reduce adipose tissue, and improve systemic inflammation, all of which are mechanistically linked to malignancy. Chronic hyperinsulinemia may stimulate insulin and IGF-1 signaling pathways that promote cell proliferation and inhibit apoptosis. Additionally, obesity-related inflammation contributes to a pro-tumorigenic environment through increased cytokine signalling. By improving metabolic dysfunction and facilitating weight loss, these therapies may reduce several pathways that are a part of cancer development.

Among OAC's, the most consistent reductions were observed in gastrointestinal malignancies, particularly pancreatic, colorectal, and esophageal cancers. This pattern is particularly notable because these malignancies are strongly associated with obesity, insulin resistance, and inflammation. For pancreatic cancer, both GLP-1RA and SGLT-2i cohorts showed approximately ⅓ lower cumulative risk compared to FLT. Similar reductions were also seen for colorectal cancer, with RR generally ranging from 33% to 38%. Esophageal adenocarcinoma also demonstrated reductions in both the exposure cohorts. These findings raise

the possibility that therapies targeting weight loss and metabolic improvement may be relevant for malignancies that are found in obesity-related tissues.

Breast cancer risk was also lower in both treatment groups, particularly SGLT-2i users, while several hormonally related cancers like uterine and ovarian cancers demonstrated lower cumulative incidence estimates but were less consistent in time-to-event significance. Because excess adipose tissue contributes to excess estrogen and insulin signaling, it is possible that weight-reducing therapies could increase or decrease risk in these cancers. However, because there were weaker associations among these cancers, this could suggest that longer follow-up periods and adjustment for various reproductive and hormonal factors may be necessary to provide greater context for these relationships.

Additionally, while many secondary outcomes demonstrated lower RR and OR values, very few of them were found as significant in hazard-based analyses. This discrepancy in results likely is a combination of many methodological factors. First, many site-specific cancers were rare events, which limited power in survival models despite the large overall sample size. Second, hazard ratios depend on event timing, not just event frequency; if cancer diagnoses occurred later or at similar time across cohorts, HR differences may be reduced. Third, differential follow-up duration between cohorts may influence cumulative risk estimates, and time-to-event analyses differently. Therefore, the observed reductions in cancer incidence should be interpreted as associations rather than definitive causal evidence of protection against malignancy.

SGLT-2i therapy appeared to demonstrate numerically larger reductions in overall cancer risk than GLP-1RA therapy. This may be because of differences in mechanisms of action between the two treatments. SGLT-2i promotes glucosuria, weight loss, reductions in blood

pressure, and improvements in insulin sensitivity. GLP-1RA, on the other hand, produces significant weight loss and appetite suppression, which may explain why there were stronger hazard associations seen in the gastrointestinal malignancies such as pancreatic and esophageal cancer. These differences could indicate more class-specific anticancer effects that require a more direct head-to-head comparison.

The findings of this study add to an ever-evolving body of literature that examines the benefits of diabetes therapies that are not linked to glycemic benefits. Historically, metformin has been extensively studied for possible anticancer effects through mechanisms like AMPK activation and mTOR inhibition. However, the results from this cohort study suggest that newer therapies may provide equal or greater oncologic benefit in real-world populations. As providers continue to shift their prescribing patterns towards GLP-1RA and SGLT-2i, these potential benefits may become increasingly relevant to decision-making in clinical settings.

LIMITATIONS AND FUTURE RESEARCH

Several limitations should be considered when interpreting the findings of this study. First, this was a retrospective observational study using EHR data, and therefore causality cannot be established. Although propensity score matching was used to balance baseline characteristics between cohorts, there might be residual confounding from unmeasured variables or those that were not properly recorded. Factors such as smoking status, dietary habits, physical activity, family history of cancer, and healthcare access may influence both medication selections and cancer risk but are often not well represented in the EHR database.

Second, confounding by indication is an important consideration in routine clinical settings, the choice to initiate GLP-1RA, SGLT-2i, metformin, or DPP-4i is influenced by many factors like clinician judgement, patient comorbidities, availability of insurance coverage,

severity of obesity, as well as medication tolerance. As a result, patients prescribed newer agents may differ from those receiving FLT therapy in ways that aren't accounted for in the propensity score matching. For example, individuals that are started on GLP-1RA may have had a higher baseline obesity score whereas those receiving SGLT-2i may have had strong cardiovascular issues. The FLT cohort combined metformin and DPP-4i into a single FLT group. These medications have distinct mechanisms of action and may have different independent associations with cancer risks, therefore combining these mechanisms could potentially dilute differences.

Next, medication exposure was determined using prescription records rather than confirmed medication dispensing or adherence to the course of medication. A recorded prescription does not guarantee that the medication was filled or taken consistently. Some patients may have discontinued therapy early, or used medications that were outside the health system. This introduces the potential for exposure misclassification, which could introduce bias in risk estimates.

Additionally, treatment duration, dose, and persistence of therapy may not have been well captured. Cancer risk modification may depend on sustained exposure over time rather than simply receiving an initial prescription. Without detailed longitudinal data, it is difficult to assess the relationship between treatment dose and its respective response or determine if a longer use of medication creates a greater protection.

Finally, patients receiving newer diabetes therapies may engage more frequently with healthcare systems by undergoing more regular lab testing and specialist follow-ups. Increased healthcare contact can lead to an earlier detection of some cancers, while healthier patients engaged in routine care may also receive more preventive services that can lower risk over time. Although the TriNetX network includes a large and diverse patient population, results aren't

generalizable to all healthcare settings or countries. Participating institutions may differ in prescribing patterns, population demographics as well as the way that they are documented.

There are also several important areas for future research that have emerged from these findings. The first area involves evaluating long-term outcomes. Although this study demonstrated consistent reductions in relative risk and cumulative incidence across multiple malignancies, time-to-event analyses were less consistent, with several hazard ratios approaching one and many 95% CI's crossing 1. This suggests that the relationship between these therapies and cancer risk may be time dependent. Future studies should therefore incorporate longer follow-up periods to better assess long-latency cancers and duration response relationships. Another area that is important to discuss is the need to clarify the biological mechanisms underlying these associations, GLP-1RA and SGLT-2i may influence cancer risk through multiple pathways, including reductions in insulin levels, decreased IGF-1 signaling, and improved chronic inflammation. It remains unclear whether the observed associations are driven by direct anti-tumor effects or secondary metabolic consequences. Given the observational nature of this study, prospective validation is critical. Large prospective cohort studies and randomized controlled clinical trials with a long-term follow-up are needed to confirm these findings. Direct head-to-head comparisons between GLP-1RA and SGLt-2i would help determine whether one therapeutic class provides superior oncologic benefit or whether benefits differ by the cancer subtype.

Finally, future research should focus on precision medicine approaches to identify patient subgroups more likely to benefit from these therapies. More analysis based on age, sex, race, BMI, NAFLD status, and family history of malignancy may help define populations at a higher risk for OAC. Such work can help support more personalized therapeutic treatment strategies for

patients with an elevated risk for cancer while considering both metabolic and cancer-prevention outcomes.

CONCLUSION

In this large real-world cohort study of adults with T2DM, treatment with GLP-1 analogues and SGLT-2 inhibitors was associated with a lower incidence of overall malignancy when compared to first-line diabetes therapy consisting of metformin or DPP-4 inhibitors. These associations were found after propensity score matching suggesting that the findings were robust across a broad patient population. Among the two classes of therapeutics, SGLT-2i demonstrated greater reductions in overall cancer risk, while GLP-1RA showed favorable associations for several site-specific malignancies. These findings are highly relevant in modern day management of T2DM. As clinicians increasingly are trending toward selecting therapies that not only look at glycemic control but various other factors like cardiovascular and weight loss benefits. If confirmed in future studies, these medications may offer benefits improving metabolic disease while simultaneously reducing OAC risk. Overall this study adds to the growing body of evidence that contemporary diabetes medications offer extended benefits beyond just lowering glucose levels. Further studies will be necessary to determine the causality of these associations as well as determining patient populations that would be most likely to gain the greatest benefit.

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