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In the Name of God

Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes

JAMA. 2024;7(7):e2421305.

presenter: Taiebeh Khajehali

1403/08/15

JAMA Network Open

Original Investigation | Oncology

Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes

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Thirteen human malignant neoplasms have been identified as obesity-associated cancers (**OAC**), the presence of excess body fat is associated with increased risk of developing cancer and worse prognosis.

Obesity also contributes to insulin resistance and type 2 diabetes (**T2D**), which may further increase the risk and worsen the prognosis of the OACs.

The glucagon-like peptide 1 receptor agonist (GLP-1RA) class of pharmaceuticals are highly effective agents for the **treatment of T2D** and for achieving **weight loss**. GLP-1RAs have further been shown to reduce the risk of adverse **cardiovascular** outcomes in patients with obesity and to contribute to the resolution of **nonalcoholic steatohepatitis**.

Because of their efficacy in controlling T2D, obesity, and related comorbidities, we hypothesized that these agents might reduce the risk of the OACs.

Here we conducted a nationwide multicenter **retrospective cohort** study in patients with T2D who were prescribed GLP-1RAs vs insulins or metformin to determine whether GLP-1RAs were associated with changes in the risk of each of 13 OACs, **including** esophageal, breast, colorectal, endometrial, gallbladder, stomach, kidney, ovarian, pancreatic, and thyroid cancer as well as hepatocellular carcinoma, meningioma, and multiple myeloma.

Methods:

Database

We used the TriNetX platform to access de-identified electronic health records (EHRs) of **113 million** patients from 64 health care organizations across 50 states, covering diverse age, racial and ethnic, income, and insurance groups and clinical settings.

The platform has been used for retrospective cohort studies. Similar to this study, we have examined the association of GLP-1RAs with colorectal cancer incidence in patients with T2D12 and the associations of GLP-1RA (semaglutide) with suicidal ideations and with cannabis use in patients with obesity and those with T2D.

The MetroHealth System institutional review board determined that the research as described in this study was not human participant research and informed **consent were not required**.

Available data elements of EHRs include extensive information on demographics, diagnoses, medications, procedures, laboratory tests, genomics, visits, and socioeconomic and lifestyle information.

The data on the analytic platform have been expanded to include oncology-specific data from cancer registry data from North American Association of Central Cancer Registries (NAACCR) records and other data resources.

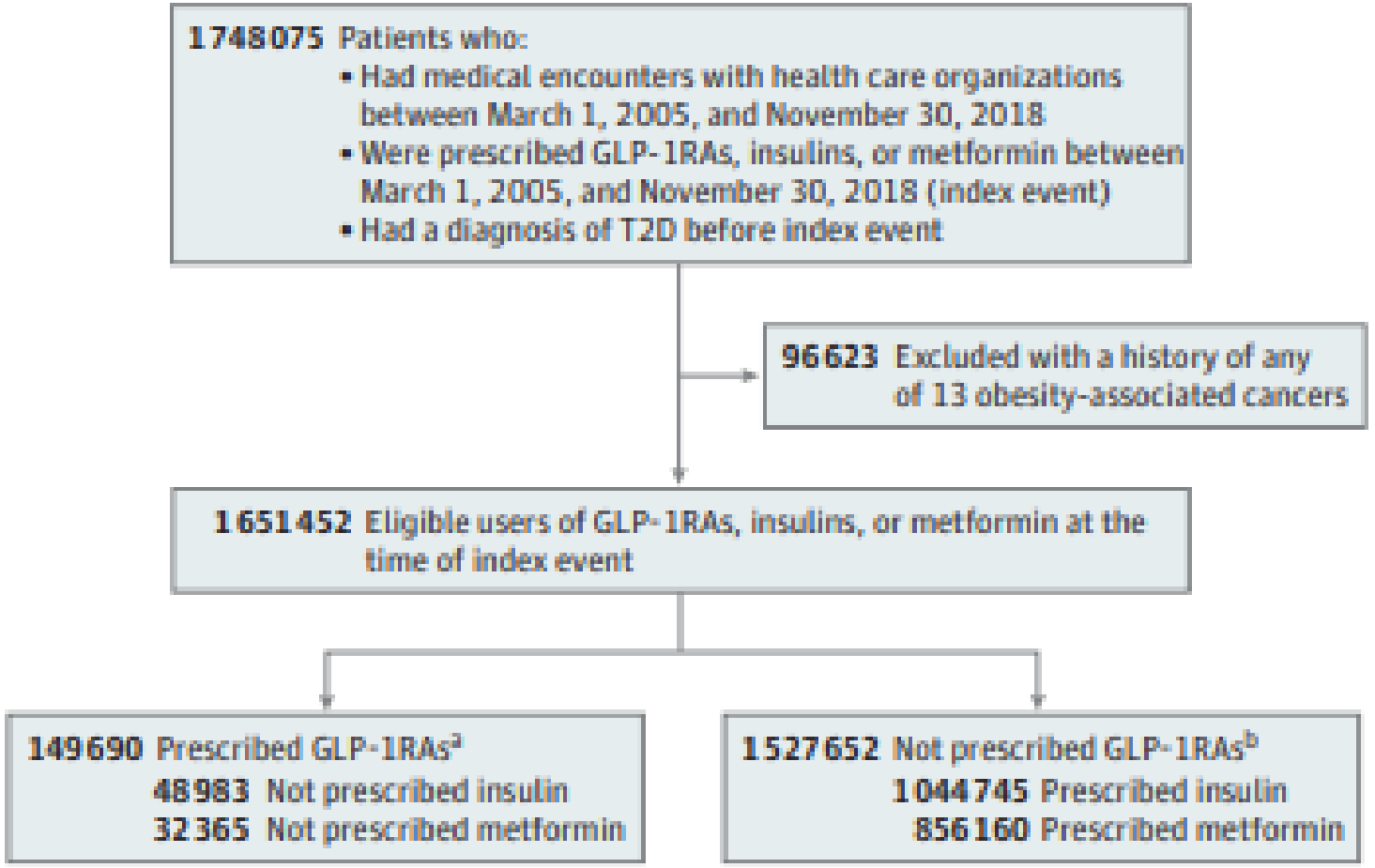
Self-reported sex, race, and ethnicity data from contributing health care systems are mapped by according to Office of Management and Budget standards into (1) race, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and unknown race; and (2) ethnicity, Hispanic or Latin, not Hispanic or Latin, or unknown ethnicity.

Age is guaranteed to exist. Missing sex values are represented using "unknown sex." The missing data for race and ethnicity are presented as "unknown race" or "unknown ethnicity." For other variables, including medical conditions, procedures, laboratory tests, and socioeconomic determinants of health, the value is either present or absent so missing is not pertinent.

Study Population

The study population comprised 1 651 452 patients with a diagnosis of T2D who had medical encounters with health care organizations and were prescribed GLP-1RAs vs insulin or metformin between March 2005 and November 2018 and had no history of any of the 13 OACs. The study population was divided into exposure and comparison groups. For comparing GLP-1RAs with insulins, the study population was divided into a GLP-1RA/no insulin group (48 983 patients prescribed a GLP-1RA but not insulins) and a insulin/no GLP-1RA group (1 044 745 patients prescribed insulins but not GLP-1RAs). (Figure 1).

Figure 1. Study Group Selection Flow Diagram



Statistical Analysis

Each of the 13 OACs was examined as a separate outcome in groups that were **propensity-score** matched for covariates related to the specific OAC.

For each OAC outcome, the exposure and comparison groups were propensity-score matched (1:1) for baseline covariates related to the specific OAC, including demographic characteristics (age, sex, race, and ethnicity); adverse socioeconomic determinants of health; family and personal history of cancer; genetic susceptibility to cancer; preexisting medical conditions, including obesity and overweight; and medical procedures, including cancer screening, bariatric surgery, and prior prescription of antidiabetes medications.

Each eligible individual was followed up from the **index event** (the first prescription of GLP-1RAs, insulins, or metformin during March 2005 to November 2018) until the occurrence of the outcomes, death, loss to follow-up, or 15 years after the index event, whichever **occurred first**.

Cox proportional hazard analyses were used to compare rates of time to events on a daily basis during the follow-up time after the index event. Hazard ratios (HRs) and 95% CIs were calculated. Cumulative incidences were estimated using the Kaplan-Meier survival analysis.

All models are adjusted for confounders at baseline by propensity-score matching baseline covariates. The data were collected and analyzed on April 26, 2024.

Results

Associations of GLP-1RAs With 13 OACs in Patients With T2D Compared With Insulins

The study population included 1 651 452 patients with T2D (mean [SD] age, 59.8 [15.1] years; 827 873 [50.1%] male and 775 687 [47.0%] female participants; 5780 [0.4%] American Indian or Alaska Native, 65 893 [4.0%] Asian, 281 242 [17.0%] Black, 13 707 [0.8%] Native Hawaiian or Other Pacific Islander, and 1 000 780 [60.6%] White participants).

For comparing GLP-1RAs with insulins in patients with T2D, the study population included 1 093 728 patients with T2D who had no prior diagnosis of any OAC and were prescribed GLP-1RAs or insulins but not both between March 2005 and November 2018.

The **GLP-1RA/no insulin group** (n = 48 983) compared with the insulin/no GLP-1RA group (n = 1 044 475) was **younger**; included **more women and White** participants; had a higher prevalence of **family history** of cancer, obesity or overweight, medical encounters for cancer screening, and prior prescriptions of other antidiabetic agents, including insulins, metformin, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors.

For each OAC outcome, the GLP-1RA/no insulin and the insulin/no GLP-1RA groups were separately matched for covariates associated with the OAC.

The Table shows the characteristics of the GLP-1RA/no insulin and insulin/no GLP-1RA groups before and after propensity-score matching for covariates related to colorectal cancer. The characteristics of the exposure and comparison groups before and after matching for each of the other 12 OACs are in eTables 2 to 13 in Supplement 1

Table. Characteristics of the GLP-1RA/No Insulin Group and the Insulin/No GLP-1RA Group Before and After Propensity Score Matching for Baseline Covariates Related to Colorectal Cancer

Characteristic[a]	Before propensity-score matching			After propensity-score matching		
	GLP-1RA/no insulin, No. (%) (n = 48 983)	Insulin/no GLP-1RA, No. (%) (n = 1 044 745)	SMD	GLP-1RA/no insulin, No. (%) (n = 48 443)	Insulin/no GLP-1RA, No. (%) (n = 48 443)	SMD
Age at index event, mean (SD), y	55.9 (11.7)	61.5 (15.9)	0.42[b]	55.9 (11.7)	56.2 (13.4)	0.02
Sex						
Female	26 011 (53.1)	476 110 (45.6)	0.15[b]	53.4	54.1	0.02
Male	20 720 (42.3)	541 314 (51.8)	0.19[b]	42.4	41.8	0.01
Unknown	2252 (4.6)	27 321 (2.6)	0.11[b]	4.5	4.1	0.02
Ethnicity						
Hispanic or Latinx	4151 (8.5)	94 136 (9.0)	0.02	8.5	8.3	0.007
Not Hispanic or Latinx	33 188 (67.8)	659 375 (63.1)	0.09	67.8	68.5	0.02
Unknown	11 644 (23.8)	291 234 (27.9)	0.09	23.7	23.2	0.01
Race						
American Indian or Alaska Native	199 (0.4)	3443 (0.3)	0.01	0.4	0.4	0.003
Asian	1204 (2.5)	41 822 (4.0)	0.09	2.5	2.2	0.02
Black or African American	6265 (12.8)	178 267 (17.1)	0.12[b]	12.8	12.2	0.02
Native Hawaiian or Other Pacific Islander	205 (0.4)	10 677 (1.0)	0.07	0.4	0.3	0.03
White	32 592 (66.5)	633 989 (60.7)	0.12[b]	66.6	68.7	0.05
Unknown	7099 (14.5)	142 470 (13.6)	0.03	14.4	13.5	0.03
Adverse socioeconomic	686 (1.4)	12 921 (1.2)	0.02	1.4	1.1	0.02

Table. Characteristics of the GLP-1RA/No Insulin Group and the Insulin/No GLP-1RA Group Before and After Propensity Score Matching for Baseline Covariates Related to Colorectal Cancer

Characteristic[a]	Before propensity-score matching			After propensity-score matching		
	GLP-1RA/no insulin, No. (%) (n = 48 983)	Insulin/no GLP-1RA, No. (%) (n = 1 044 745)	SMD	GLP-1RA/no insulin, No. (%) (n = 48 443)	Insulin/no GLP-1RA, No. (%) (n = 48 443)	SMD
Adverse socioeconomic determinants of health	686 (1.4)	12 021 (1.2)	0.02	1.4	1.1	0.03
Family history of cancer	2042 (4.2)	19 398 (1.9)	0.14[b]	4.1	3.8	0.02
Family history of cancer of digestive organs	784 (1.6)	6889 (0.7)	0.09	1.6	1.4	0.01
Family history of colonic polyps	149 (0.3)	579 (0.1)	0.06	0.3	0.3	0.006
Genetic susceptibility to cancer	24 (0.0)	156 (0.0)	0.02	0.0	0.0	0.003
Personal history of cancer	1239 (2.5)	38 294 (3.7)	0.07	2.5	2.1	0.03
Preexisting medical conditions, procedures, and medications						
Obesity or overweight	18 401 (37.6)	166 445 (15.9)	0.50[b]	37.1	37.1	<.001
Obesity due to excess calories	9157 (18.7)	69 998 (6.7)	0.37[b]	18.4	18.3	0.003
Obesity, unspecified	13 805 (28.2)	118 555 (11.3)	0.43[b]	27.8	28.2	0.009
Morbid (severe) obesity with alveolar hypoventilation	150 (0.3)	3643 (0.3)	0.007	0.3	0.2	0.02
BMI 30.0-39.0, adult	4204 (8.6)	43 128 (4.1)	0.18[b]	8.3	7.5	0.03
BMI ≥40, adult	3886 (7.9)	33 396 (3.2)	0.21[b]	7.8	7.1	0.03
Overweight defined by *ICD-10* code E66.3	1010 (2.1)	6796 (0.7)	0.12[b]	2.0	1.8	0.02
BMI 25.0-25.9, adult	157 (0.3)	3510 (0.3)	<.001	0.3	0.3	0.01
BMI 26.0-26.9, adult	171 (0.3)	3632 (0.3)	<.001	0.4	0.3	0.007
BMI 27.0-27.9, adult	288 (0.6)	4209 (0.4)	0.03	0.6	0.5	0.008
BMI 28.0-28.9, adult	344 (0.7)	4508 (0.4)	0.04	0.7	0.6	0.02
BMI 29.0-29.9, adult	398 (0.8)	4843 (0.5)	0.04	0.8	0.8	0.002

Table. Characteristics of the GLP-1RA/No Insulin Group and the Insulin/No GLP-1RA Group Before and After Propensity Score Matching for Baseline Covariates Related to Colorectal Cancer

Characteristic[a]	Before propensity-score matching			After propensity-score matching		
	GLP-1RA/no insulin, No. (%) (n = 48 983)	Insulin/no GLP-1RA, No. (%) (n = 1 044 745)	SMD	GLP-1RA/no insulin, No. (%) (n = 48 443)	Insulin/no GLP-1RA, No. (%) (n = 48 443)	SMD
Alcohol use disorder	563 (1.1)	28 538 (2.7)	0.12[b]	1.2	0.8	0.03
Nicotine dependence	3593 (7.3)	96 860 (9.3)	0.07	7.4	6.4	0.04
Crohn disease	130 (0.3)	3290 (0.3)	0.009	0.3	0.2	0.009
Ulcerative colitis	165 (0.3)	3393 (0.3)	0.002	0.3	0.3	0.004
Cystic fibrosis	<10 (<0.1)	1411 (0.1)	0.04	0.0	0.0	0.004
Colon polyps	2634 (5.4)	31 528 (3.0)	0.12[b]	5.3	4.8	0.02
Benign neoplasm of colon and rectum	3124 (6.4)	37 914 (3.6)	0.13[b]	6.3	5.6	0.03
Encounter for cancer screening	12 272 (25.1)	105 217 (10.1)	0.40[b]	24.6	23.8	0.02
Colonoscopy	3806 (7.8)	38 112 (3.6)	0.18[b]	7.7	6.9	0.03
Bariatric surgery	632 (1.3)	5136 (0.5)	0.09	1.3	1.2	0.003

Table. Characteristics of the GLP-1RA/No Insulin Group and the Insulin/No GLP-1RA Group Before and After Propensity Score Matching for Baseline Covariates Related to Colorectal Cancer (continued)

Characteristic[a]	Before propensity-score matching			After propensity-score matching		
	GLP-1RA/no insulin, No. (%) (n = 48 983)	Insulin/no GLP-1RA, No. (%) (n = 1 044 745)	SMD	GLP-1RA/no insulin, No. (%) (n = 48 443)	Insulin/no GLP-1RA, No. (%) (n = 48 443)	SMD
Metformin	27 075 (55.3)	199 802 (19.1)	0.81[b]	54.8	55.5	0.01
Dipeptidyl peptidase 4 inhibitors	9485 (19.4)	44 595 (4.3)	0.48[b]	18.7	18.9	0.005
Sodium-glucose cotransporter 2 inhibitors	4808 (9.8)	6447 (0.6)	0.42[b]	8.9	7.8	0.04
Sulfonylureas	14 077 (28.7)	125 703 (12.0)	0.42[b]	28.4	29.3	0.02
Thiazolidinediones	4107 (8.4)	35 435 (3.4)	0.21[b]	8.3	8.8	0.02
α-Glucosidase inhibitors	229 (0.5)	1718 (0.2)	0.05	0.5	0.5	0.002
Other blood glucose lowering drugs	614 (1.3)	7048 (0.7)	0.06	1.2	1.2	0.009

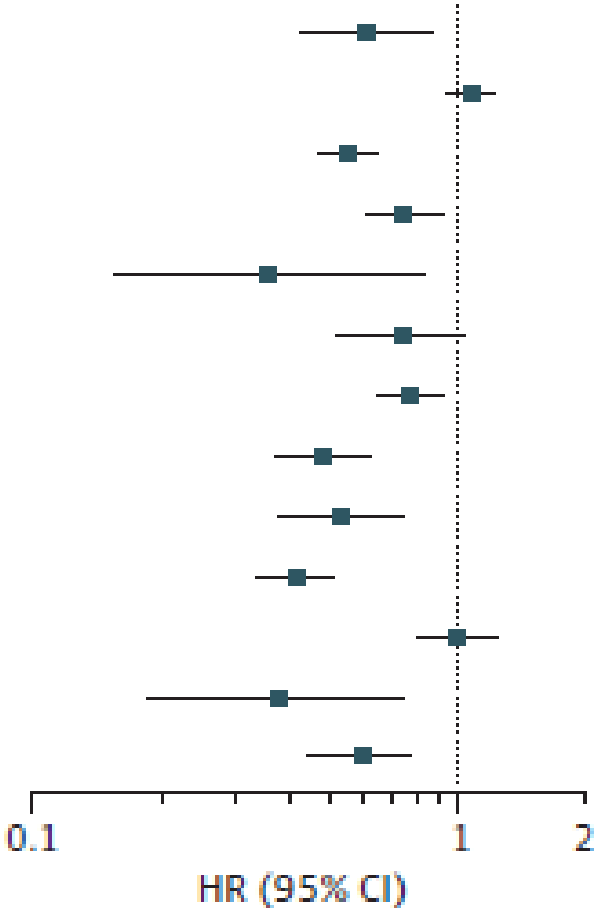
Compared with insulins, GLP-1RAs were associated with a significantly lower risk of **10** of the 13 OACs, including **gallbladder cancer** (HR, 0.35; 95% CI, 0.15-0.83), **meningioma** (HR, 0.37; 95% CI, 0.18-0.74), **pancreatic cancer** (HR, 0.41; 95% CI, 0.33-0.50), **hepatocellular carcinoma** (HR, 0.47; 95% CI, 0.36-0.61), **ovarian cancer** (HR, 0.52; 95% CI, 0.03-0.74), **colorectal cancer** (HR, 0.54; 95% CI, 0.46-0.64), **multiple myeloma** (HR, 0.59; 95% CI, 0.44-0.77), **esophageal cancer** (HR, 0.60; 95% CI, 0.42-0.86), **endometrial cancer** (HR, 0.74; 95% CI, 0.60-0.91), and **kidney cancer** (HR, 0.76; 95% CI, 0.64-0.91).

The HR for stomach cancer among patients taking GLP-1RAs vs those taking insulin was less than 1, but it was not statistically significant (HR, 0.73; 95% CI, 0.51-1.03).

GLP-1RAs were not associated with risk of postmenopausal breast cancer or thyroid cancer (Figure 2).

Figure 2. Risk of 13 Obesity-Associated Cancers Among Patients Receiving Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RAs) vs Those Receiving Insulins

Outcome (N = 1 651 452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48 983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1 044 745)	HR (95% CI)
Esophageal cancer (n = 48 437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13 768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48 443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25 750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48 587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48 449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48 322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48 397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25 739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48 490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48 527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48 518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48 527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



Associations of GLP-1RAsWith 13 OACs in Patients With T2D Compared With Metformin

For comparing GLP-1RAs with metformin in patients with T2D, the study population included 888 525 patients with T2D who had no prior diagnosis of any OAC and were prescribed GLP-1RAs or metformin but not both between March 2005 and November 2018. For each OAC outcome, the GLP-1RA/no metformin group (n = 32 365) and the metformin/no GLP-1RA group (n = 856 160) were separately matched for covariates related to the OAC.

Compared with metformin, GLP-1RAs were **not associated** with a lower risk of **colorectal cancer, gallbladder cancer, and meningioma** but were associated with an **increased risk of kidney cancer** (Figure 4).

Figure 4. Risk of 13 Obesity-Associated Cancers Among Patients Receiving Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RAs) vs Those Receiving Metformin

Outcome (N = 1651452)	Group prescribed GLP-1RAs but not metformin, No (%) (n = 32 365)	Group prescribed metformin but not GLP-1RAs, No (%) (n = 856 160)	HR (95% CI)
Esophageal cancer (n = 32 263)	37 (0.12)	42 (0.13)	0.94 (0.60-1.47)
Breast cancer (n = 10 419)	295 (2.8)	320 (3.1)	1.02 (0.87-1.20)
Colorectal cancer (n = 32 275)	228 (0.71)	279 (0.86)	0.88 (0.73-1.04)
Endometrial cancer (n = 17 168)	122 (0.71)	119 (0.69)	1.11 (0.86-1.43)
Gallbladder cancer (n = 32 261)	<10 (<0.03)	14 (0.04)	0.37 (0.13-1.02)
Stomach cancer (n = 32 267)	52 (0.16)	60 (0.19)	0.90 (0.62-1.30)
Kidney cancer (n = 32 162)	252 (0.78)	178 (0.55)	1.54 (1.27-1.87)
Hepatocellular carcinoma (n = 32 267)	125 (0.39)	142 (0.44)	0.97 (0.76-1.23)
Ovarian cancer (n = 17 197)	54 (0.31)	59 (0.34)	0.99 (0.68-1.44)
Pancreatic cancer (n = 32 271)	142 (0.44)	166 (0.51)	0.93 (0.74-1.16)
Thyroid cancer (n = 32 259)	127 (0.39)	121 (0.38)	1.10 (0.86-1.41)
Meningioma (n = 32 263)	<10 (<0.03)	20 (0.06)	0.54 (0.25-1.17)
Multiple myeloma (n = 32 256)	104 (0.32)	95 (0.30)	1.18 (0.89-1.56)

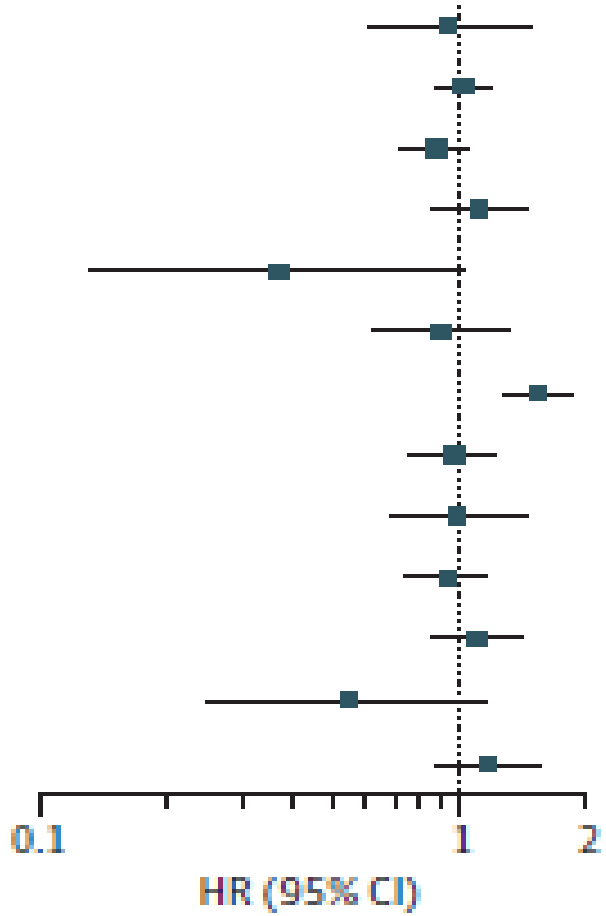
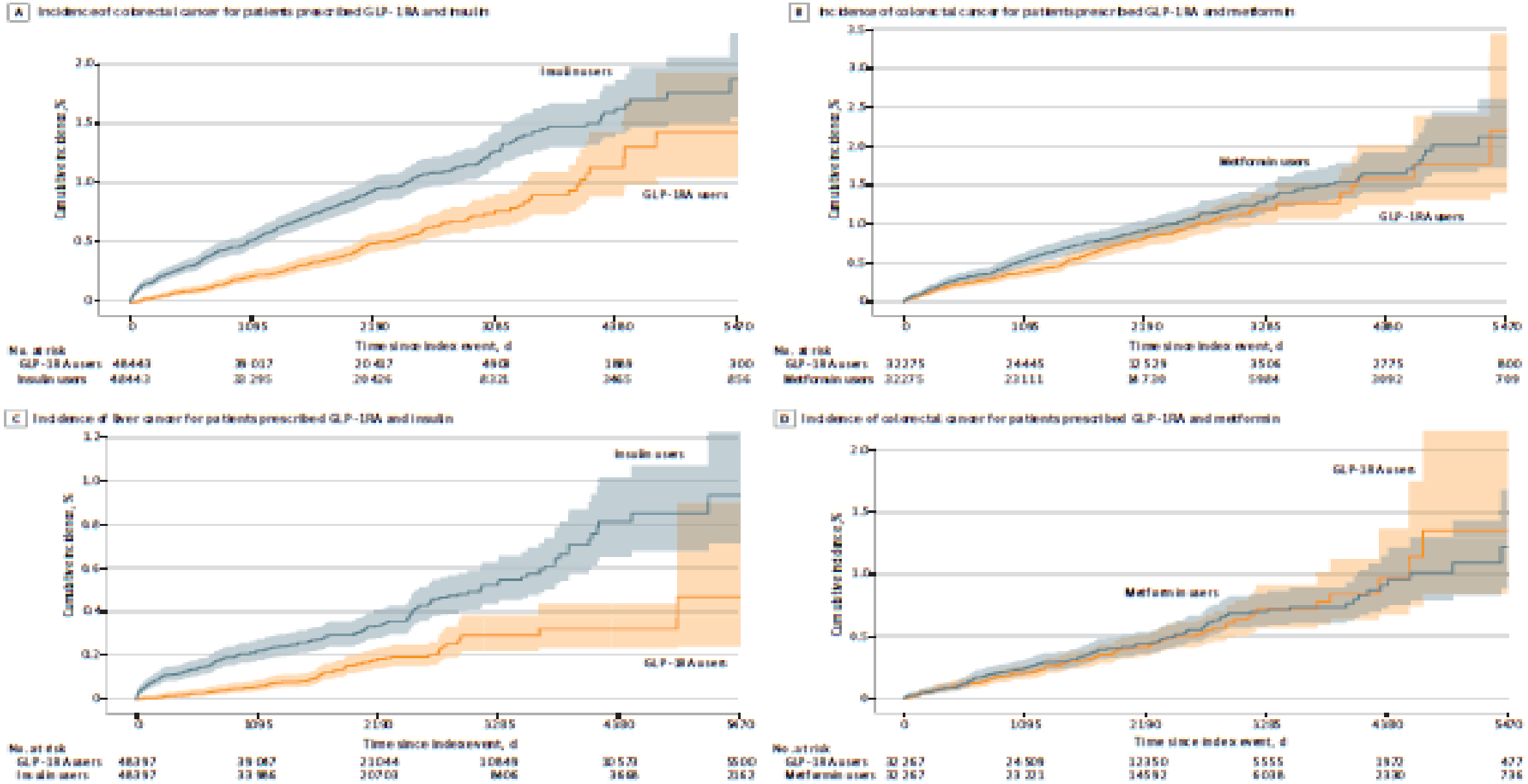


Figure 3 shows the cumulative incidences of colorectal cancer and liver cancer comparing GLP-1RAs with insulins. The mean (SD) follow-up time for the outcome of colorectal cancer was 2074.7 (435.3) days for the GLP-1RA/no insulin group and 1981.8 (471.1) days for the insulin/no GLP-1RA group.

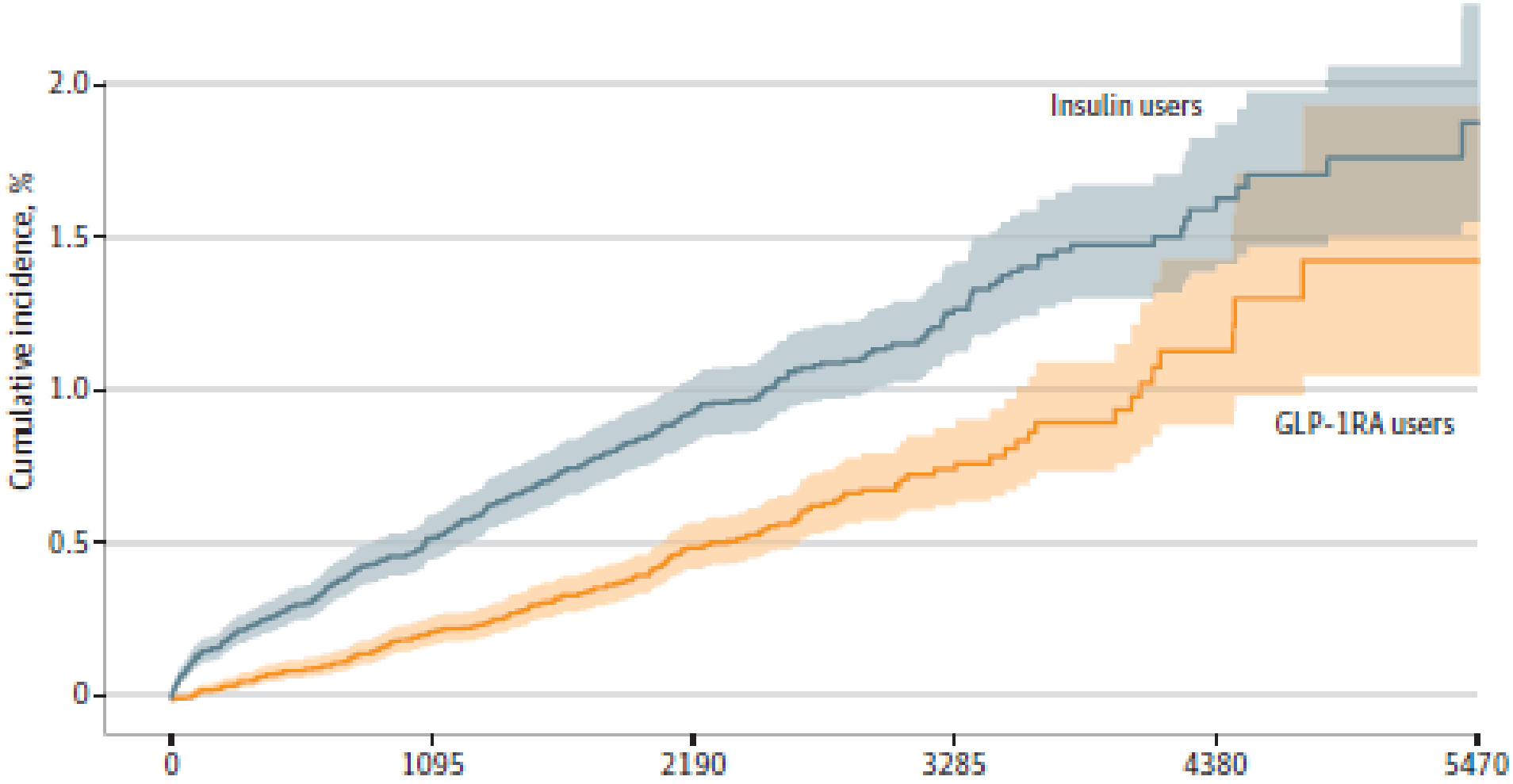
The mean (SD) follow-up time for the outcome of liver cancer was 2023.1 (1112.6) days for the GLP-1RA/no insulin group and 2037.9 (766.4) days for the insulin/no GLP-1RA group.

Figure 3. Cumulative Incidences of Colorectal Cancer and Liver Cancer Among Patients Receiving Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) vs Those Receiving Insulin or Metformin During a 15-Year Follow-Up



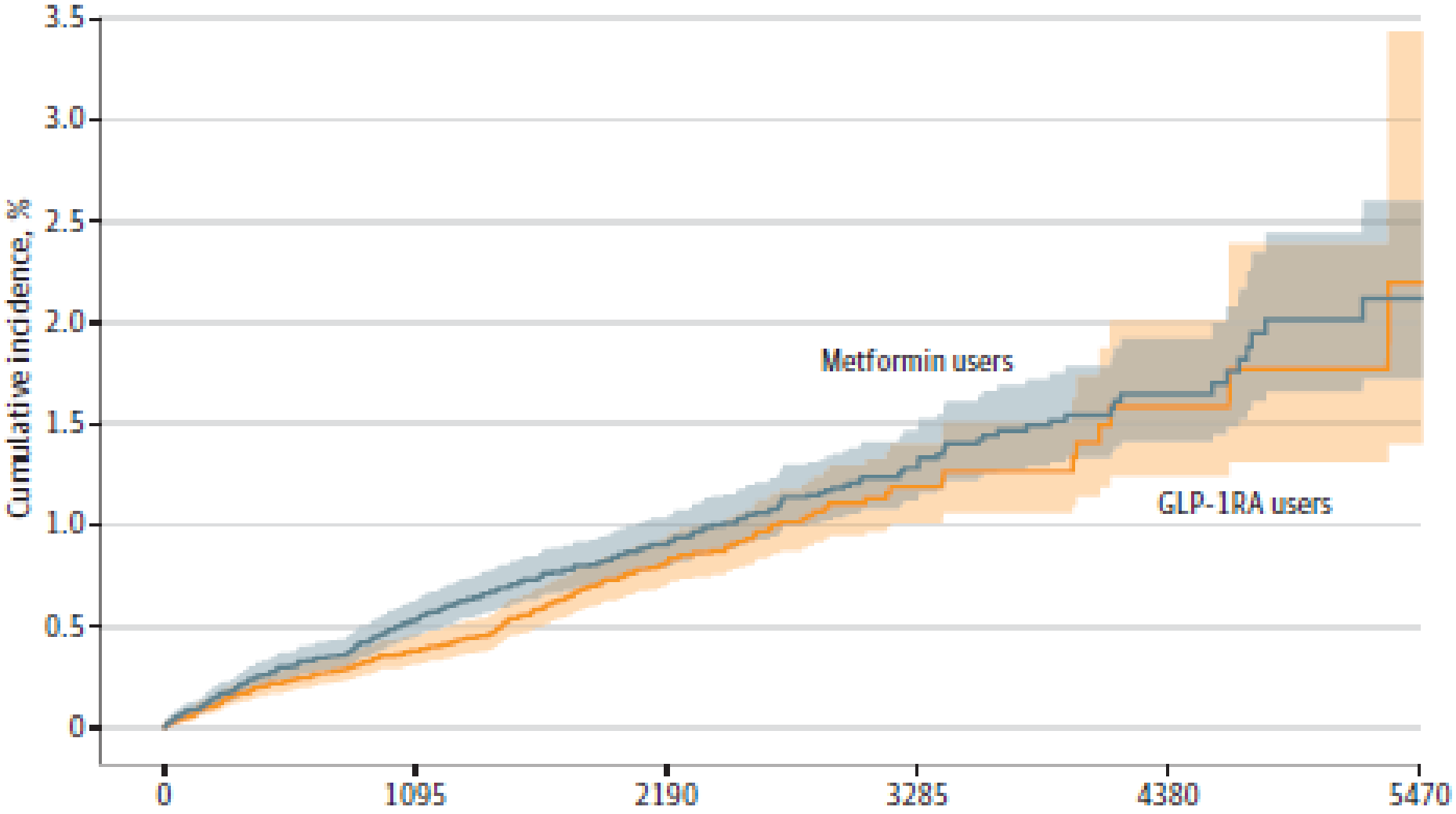
Kaplan-Meier survival analysis was used. Each eligible individual was followed up from the index event until the occurrence of the outcomes, death, loss to follow-up, or 15 years after the index event, whichever occurred first.

A Incidence of colorectal cancer for patients prescribed GLP-1RA and Insulin



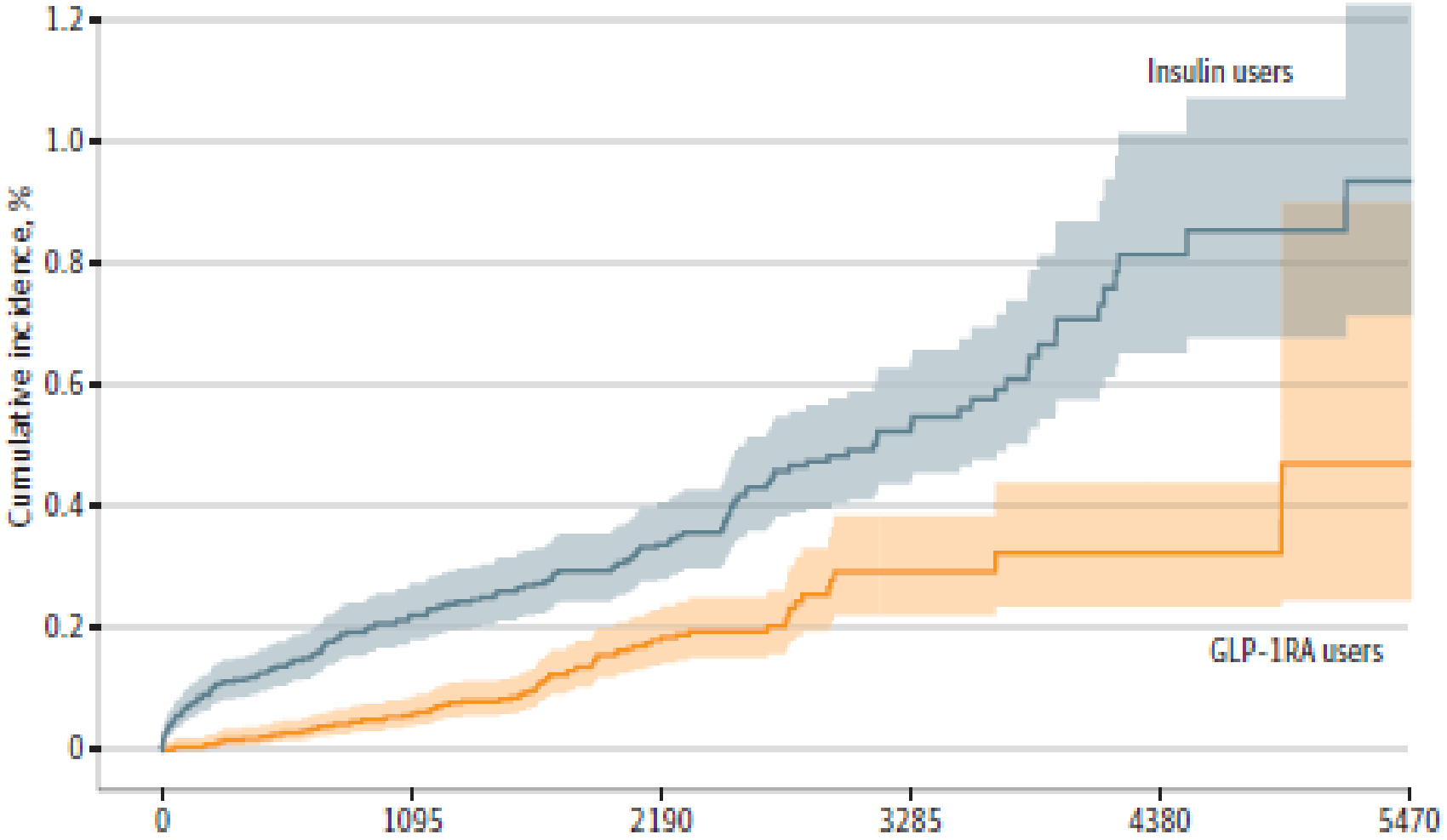
No. at risk						
GLP-1RA users	48443	39017	20417	4903	1889	300
Insulin users	48443	33295	20426	8321	3465	856

B Incidence of colorectal cancer for patients prescribed GLP-1RA and metformin



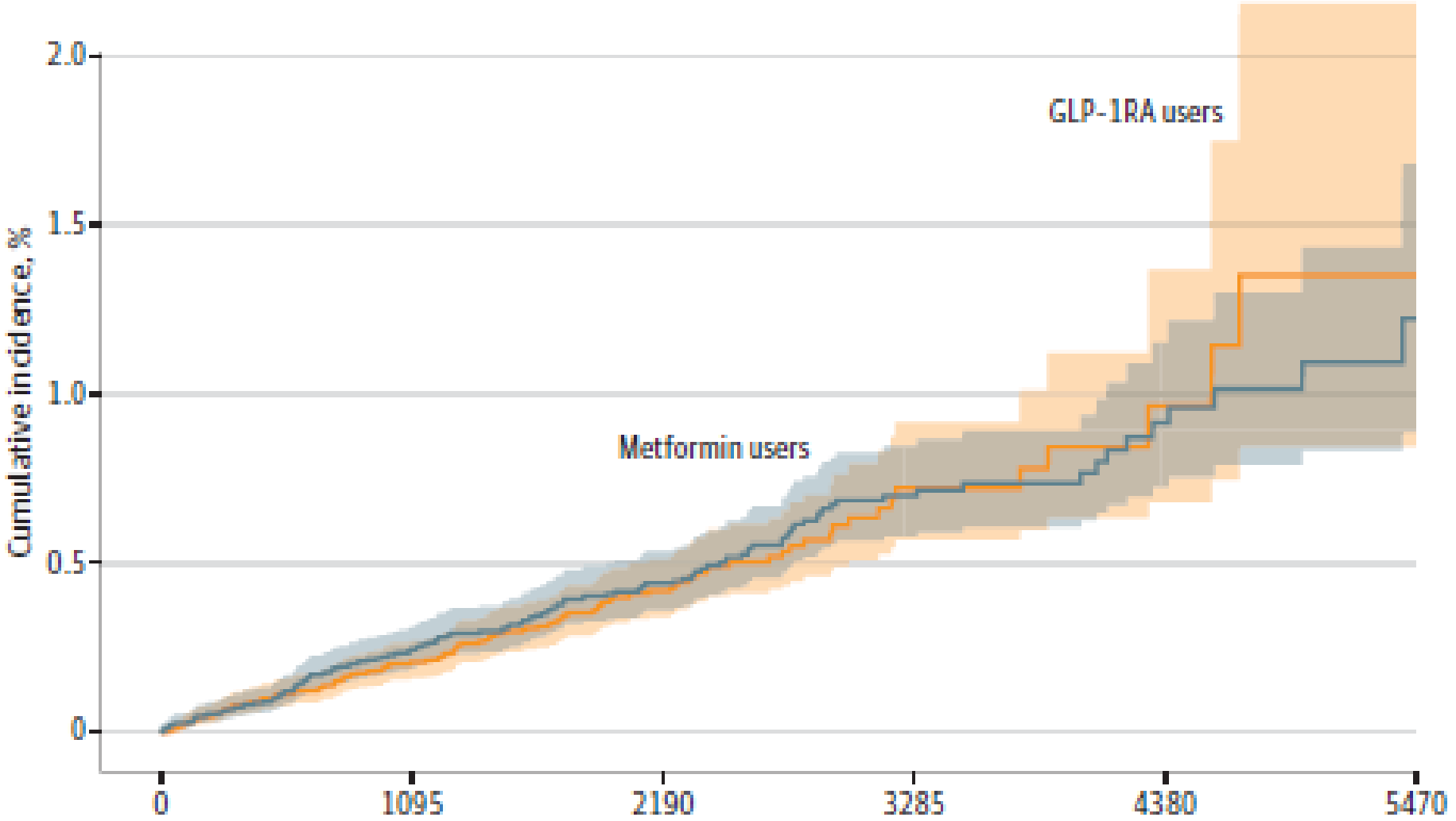
No. at risk						
GLP-1RA users	32 275	24 445	12 529	3506	2775	800
Metformin users	32 275	23 111	14 730	5984	3092	709

C Incidence of liver cancer for patients prescribed GLP-1RA and insulin



No. at risk						
GLP-1RA users	48 397	39 047	21 044	10 849	10 573	5500
Insulin users	48 397	33 986	20 703	8406	3668	2162

D Incidence of colorectal cancer for patients prescribed GLP-1RA and metformin



No. at risk

GLP-1RA users	32 267	24 509	12 350	5555	1972	477
Metformin users	32 267	23 221	14 592	6038	2330	736

Discussion

Using a data platform to analyze more than **15 years** of longitudinal EHRs of a US population-based cohort of more than 100 million individuals, we found that in patients with T2D who had no history of any OAC, GLP-1RAs compared with insulins were associated with a significant risk reduction in **10 of 13 OACs**, including esophageal, colorectal, kidney, pancreatic, gallbladder, ovarian, endometrial, and liver cancers as well as meningioma and multiple myeloma.

Decreased risk reduction that did not reach statistical significance was also noted for stomach cancer.

risk reduction was also noted for GLP-1RAs relative to metformin for colorectal cancer, gallbladder, and meningiomas, although these findings were **not statistically significant**.

Our observations on the reduction in the incidence of OACs in patients with T2D treated with GLP-1RAs compare favorably with the OAC-reducing **effects of intensive lifestyle intervention** (ILI) observed in the Look AHEAD trial (Action for Health in Diabetes) and with the results of metabolic bariatric surgery as recently reported in the SPLENDID (Surgical Procedure and Long-term Effectiveness In Neoplastic Disease Incidence and Death) trial.

The Look AHEAD study, a randomized clinical trial in which 4859 patients with T2D and overweight or obesity (age, 45-76 years; median follow-up, 11 years) were randomized to an ILI or diabetes support and education group, found a **16%reduction in risk for OAC** (HR, 0.84; 95%CI, 0.68-1.04).

The SPLENDID trial, a matched cohort study, compared 5053 patients with obesity with 25 265 nonsurgical matched controls, with a median age of 46 years and median follow-up of 6.1 years, showed an **OAC risk reduction of 32%,** (HR, 0.68; 95%CI, 0.53-0.87).

A recent 9-year follow-up population-based cohort study conducted in Israel reported a decrease (although not statistically significant) in incidence of **pancreatic cancer** (HR, 0.50; 95%CI, 0.15-1.71) in patients with T2D treated with GLP-1RAs compared with insulin.

Our US population-based study, with 15 years of follow-up and a larger sample size, now extends these observations, suggesting that treatment of patients with T2D with GLP-1RAs vs insulin is associated with a significantly decreased incidence of pancreatic cancer (HR, 0.41; 95%CI, 0.33-0.50).

In contrast to the risk reduction shown for most of the OACs, **thyroid cancer** showed no statistically different risk in patients treated with GLP-1RAs compared with insulins. Studies in rodents indicate that GLP-1RAs promote thyroid C-cell hyperplasia and medullary thyroid carcinoma (**MTC**) by a GLP-1R mediated increase in calcitonin synthesis.

High levels of fasting serum insulin and insulin resistance are associated with an increased risk of thyroid cancer. Although clinical evidence for an association of thyroid cancer with the use of GLP-1RAs has been reported as **inconclusive**, the findings from our study together with previous reports of insulins promoting cancer growth suggest that GLP-1RAs might be associated with increased risk of thyroid cancer.

Our results are further supported by a recent report by the French National Health Cancer Data System showing that the use of GLP-1RAs for 1 to 3 years was associated with increased risk of all thyroid cancers (adjusted HR, 1.78; 95%CI 1.04-3.05).

These studies support the package warnings included with GLP-1RAs that these agents are **contraindicated** in patients with multiple endocrine neoplasia syndrome type 2 and that patients should be counseled regarding the potential risk of MTC and symptoms of thyroid tumors.

Kidney cancers showed an increased risk with GLP-1RA treatment relative to that with metformin (HR, 1.54; 95%CI 1.27-1.87) but a decrease relative to insulin (HR, 0.76; 95%CI 0.64-0.91). GLP-1RAs have direct effects on kidney function mediated by GLP-1Rs in renal vasculature.
There have been no previous reports of kidney cancers with the use of GLP1-RAs. Nonetheless, they suggest the need for continued monitoring in patients being treated with GLP-1RAs.

Our study, with follow-up over 15 years, found no signs of increase or decrease in risk for **breast cancer** in postmenopausal women with T2D being treated with GLP-1RAs compared with those being treated with insulin or metformin.

GLP-1RAs have been shown to reduce the growth of murine and human breast cancer cell lines in vitro and in vivo murine models. However, a meta-analysis of more than 50 randomized clinical trials, evaluating GLP-1RAs in women aged between 45 to 70 years and followed up from 24 weeks to 7.5 years, showed no differences in benign, premalignant, or malignant breast neoplasms in patients treated with GLP-1RAs compared with other antidiabetic agents or placebos.

A more recent population-based cohort study of 44 984 women 40 years and older treated with GLP-1RAs or other antidiabetic agents for a mean of 3.5 years showed no overall significant difference in the risk for breast cancer occurrence. However, an **increased risk** (HR, 2.66; 95%CI, 1.32-5.38) was noted for those treated **between 2 to 3 years with a return to null after more than 3 years' treatment.**

Interestingly, the SPLENDID trial, which found an overall 32%risk reduction for OACs, showed no significant difference among women for incidence of overall or postmenopausal breast cancer.

The lack of breast cancer risk reduction by GLP-1RAs and the similar lack of protection by bariatric surgery may also suggest the possibility that factors determining the incidence of breast cancer in patients with overweight or obesity may have been **initiated long before intervention** with GLP-1RAs and/or bariatric surgery and therefore require earlier intervention to affect risk reduction.

The concept that early intervention might reduce breast cancer incidence is supported by the observation that both pregnancy and breastfeeding reduce the incidence of breast cancer.

Limitations

First, this is a **retrospective observational study** of patient EHRs, which has inherent limitations including overdiagnosis, underdiagnosis, misdiagnosis; unmeasured or uncontrolled confounders; and biases. Although we controlled for an extensive list of variables, these limitations and biases could not be fully eliminated.

Second, patients in our study represented those who had **medical encounters** with health care systems contributing to the data platform. Although both the exposure and comparison groups were drawn from the same EHR database and from the same time period, which should not significantly affect the HR calculations, results from the platform need to be validated in other HER databases and analytics platforms.

Third, the status of incident cancer was based on the presence of first-ever diagnosis codes of **OACs documented** in patient EHRs, which also included oncology specific data from cancer registry data, such as NAACCR records. However, it is unknown how well cancer diagnoses are captured in patient EHRs. For this study, the main interest was the relative risk (or HR) of cancer diagnosis. Since all patients in the study population were drawn from the same health care organizations in the data platform, cancer under diagnosis, misdiagnosis, or over diagnosis should not have a substantial impact on the relative risk analysis.

Fourth, the built-in functions did not allow us to **control for variables** (eg, weight loss) that occurred after the index event and to identify individual patient data, which precludes our ability to correlate risk reduction with a degree of weight loss, which was demonstrated to be particularly important in the SPLENDID bariatric study. In addition, we could not explicitly control for health care utilization and insurance type although the study population.

Finally, due to the lack of patients' **medication adherence information** in EHRs, we used intention-to treat (medication prescriptions) as a causal contrast of interest regardless of whether the individuals adhered to their medications and the duration of the medication use.

Conclusions

In this study of patients with T2D who were cancer free at baseline, taking GLP-1RAs compared with insulin was associated with a lower risk of 10 of 13 OACs.

The potential cancer-preventative effects of OACs by GLP-1RAs warrant further long-term studies.

Studies are also warranted to evaluate the preventive effects of these agents on non-OACs.

The associations of the GLP-1RA targeted pharmacologic agents with cancer risk should be compared with the use of **ILI** and metabolic-**bariatric surgery** for the control of obesity and diabetes.

As noted previously, it will be important to correlate these associations with the control of T2D and obesity. Moreover, given that T2D and overweight or obesity have negative impacts on patients during cancer therapy, GLP-1RAs should be evaluated for control of these **comorbid** conditions during cancer therapy as well as for secondary prevention to delay cancer recurrence.

THANKS FOR YOUR ATTENTION