Effect of Incretin Analogues and Dipeptidyl-peptidase-IV inhibitors on the risk of thyroid cancer

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Background

Incretin based therapies (glucagon-like peptide 1 receptor agonists [GLP-1RA] and dipeptidyl-peptidase-IV [DPP-IV] inhibitors) are commonly used as second-line antihyperglycemic drugs in the treatment of type 2 diabetes mellitus (T2DM). GLP-1RA promote glucose dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety. DPP-IV inhibitors potentiate the action of incretin hormones by blocking DPP-IV – the enzyme responsible for the degradation of incretin hormones.[1]

The GLP-1 receptor is expressed in normal, premalignant, or malignant thyroid tissues.[2] Activation of the GLP-1 receptor has been shown to cause thyroid C-cell hyperplasia and C-cell tumors in carcinogenicity studies in preclinical studies using rodents.[3,4] Informed by this finding, the U.S. Food and Drug Administration (FDA) issued a warning regarding medullary thyroid cancer for long-acting GLP-1RA. Still, the relevance of these findings in humans has since been questioned, as there is a discrepancy in the level of expression and biology of GLP-1 receptors in the thyroid between rodents and primates.[5]

Currently, there remains uncertainty about the risk of thyroid cancer associated with the use of incretin (GLP-1)-based therapies with data from clinical and observational studies showing conflicting results.[6–14] Some studies have reported no increased risk of thyroid cancer with the use of GLP-1RA relative to placebo or other antihyperglycemic drugs[7–14], while a recent study by Bezin et al. found an increased risk of all thyroid cancer and medullary thyroid cancer, particularly after 1-3 years of treatment.[6]

Most of the existing studies suffer from methodological issues, including short durations of follow-up, limited lag period, uncertainty about valid ascertainment of outcomes, diagnostic suspicion, insufficient confounding control, incomplete covariate ascertainment and inadequate power. Additionally, apart from Bezin et al., studies so far have only focused on the effect of exenatide and liraglutide on thyroid cancer. The study by Bezin et al, however, highlighted only statistically significant results, estimated relative effect measures due to the inherent case-control design, and did not rule out detection bias/diagnostic suspicion.[15]

This work, therefore, aims to address these issues, expand the current literature, and contribute critical evidence to inform clinical decision-making by exploring the effect of GLP-1RA and DPP-IV inhibitors on thyroid cancer incidence in older people in a U.S. setting.

Objective

To estimate the comparative effect of GLP-1RA and DPP-IV inhibitors versus sodium-glucose cotransporter-2 (SGLT-2) inhibitors on the incidence of thyroid cancer.

Study Design
We will implement an active-comparator, new user (ACNU) cohort study design to identify new users of GLP-1RA and new users of SGLT-2 inhibitors as well as new users of DPP-IV inhibitors and new users of SGLT-2 inhibitors after a washout period of 12 months without any dispensed prescriptions for the two drug classes compared. (Note that the SGLT-2 inhibitor comparison cohort will therefore be different in cohort I and cohort II). New users of GLP-1RA will also be compared with new users of DPP-IV inhibitors (cohort III). By enrolling only new users and following subjects from the start of treatment, time-varying hazards, including lag times, can be assessed, and described, while preserving the temporality of covariate assessment. The rationale behind choosing an active comparator (a guideline treatment alternative for GLP-1 agonists or DPP-IV inhibitors) is to minimize the impact of confounding by indication and other unmeasured patient characteristics (such as healthy initiator bias or frailty). [16]

Cohort	Index Drug	Comparator Drug
I	GLP-1 receptor agonists	SGLT-2 inhibitors
II	DPP-IV inhibitors	SGLT-2 inhibitors
III	GLP-1 receptor agonists	DPP-IV inhibitors

Data Source
Medicare Fee-for-Service (FFS) Database (Parts A, B, and D) 2007-2019 (or additional years of data if available). This US federal database contains deidentified individual-level, longitudinal information on demographics, diagnoses, and procedures, and outpatient prescription dispensations recorded during billing of all health care encounters.
The Medicare data available at UNC comprises a randomly selected 20% sample of Medicare FFS beneficiaries aged 65 years and older who were continuously enrolled in Medicare Part A (inpatient services), B (physician and outpatient services), and D (prescription drugs) plans for a minimum of one calendar month from 2007 to 2019. Once selected into the sample, all future claims become part of the database.

Study population
The base population for the analysis will consist of all fee-for-service Medicare beneficiaries aged 66 years or older with at least one prescription dispensing claim for GLP-1RA, DPP-IV inhibitors or SGLT-2 inhibitors between January 1, 2008, and December 31, 2018.

Inclusion criteria
We will include three active comparator new user cohorts where (I) GLP-1 agonists are compared with SGLT-2 inhibitors, (II) DPP-IV inhibitors with SGLT-2 inhibitors, and (III) GLP-1 agonists with DPP-IV inhibitors. New users are defined as individuals who initiate the drugs of interest or their active comparator after a preceding washout period of at least 12 months without a prescription for the drug classes compared. Participants are allowed to have other anti-hyperglycemic drugs during the washout period except the drugs being compared. Study subjects are required to have at least 12 months of continuous part A, B, and D coverage before the first prescription date. Earliest pharmacy data (part D claims) available is January 1, 2007, so earliest possible first prescription date will be January 1, 2008. Since SGLT2 inhibitors were approved in March 2013, the earliest possible first prescription date for cohorts I and II will be January 1, 2013.

Follow-up will begin after a six-month lag period following the second prescription date to allow for induction and latent periods.

Exclusion criteria

We will exclude all patients who do not refill the same drug class within the days supply and a grace period of 30 days after the first prescription. Requiring two prescriptions increases the probability that patients actually started therapy. We will describe the patients who do not meet the refill criterion to assess the potential selection imposed by requiring a refill. Patients with any cancer diagnosis (except non-melanoma skin cancer) or cancer related procedures identified by International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT) codes (Table 1.) within the 12 months prior to the first prescription or between the first and 2nd prescription will be excluded from the study.

Table 1. Codes Used to Identify Prevalent Cancer at Baseline

ICD-9-CM diagnosis codes*: 140.0–208.92 (except 173.X), 209.00–209.36, 209.70-209.79, 230.X, 231.X, 233.X, 234.X, 235.X, 236.X, 237.0-237.1, 237.3, 237.5-237.6, 237.7, 237.9, 238.4, 238.6, 238.7 (all but 238.78), 239.6, 239.7, 273.2, 273.3, 277.89, 288.4, 795.06, 795.16, 796.76, V10.X, V87.41, V66.1, V66.2, V67.1, V67.2, V71.1
ICD-10-CM diagnosis codes†: C00–D49 (except C44)
HCPCS codes‡: G8371, G8372, G8377, J9999, G0355, G0356, G8376, G8377, G8380, G8381, G8464, G8465, G8518, G8519, G8520, G9050-G9054, G9063-G9067, G9069-G9117, G9131-G9133, G9118-G9130, G9134-G9139, G9714-G9715, G9726, G0256, G0261
CPT§: 49220, 3271F, 3272F, 3273F, 3274F, 3300F – 3318F, 3321F, 3370F, 3372F, 3374F, 3376F, 3378F, 3380F, 3382F, 3384F, 3386F, 3388F, 3390F, 4163F, 4164F, 4180F, 4201F

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification
†ICD-10-CM International Classification of Disease, Tenth Revision, Clinical Modification
‡HCPCS Healthcare Common Procedure Coding System
§CPT Current Procedural Terminology

Exposure

Exposure will be defined by at least two same drug class prescription dispensing claims of either GLP-1 agonists, DPP-IV inhibitors or the active comparator between January 1, 2008 and December 31, 2018, identified using Anatomical Therapeutic Chemical (ATC) classification codes and National Drug Codes (NDCs). We will identify three active comparator cohorts where (I) GLP-1 agonists are compared with SGLT-2 inhibitors, (II) DPP-IV inhibitors with SGLT-2 inhibitors, and (III) GLP-1 agonists with DPP-IV inhibitors.

Table 2. Anatomical Therapeutic Chemical (ATC) classification codes used to identify exposure

Drug class	ATC code
GLP-1 agonists	
Exenatide	A10BJ01
Exenatide Extended Release	A10BJ01
Liraglutide	A10BJ02
Insulin degludec and Liraglutide	A10AE56
Lixisenatide	A10BJ03
Insulin glargine and Lixisenatide	A10AE54
Albiglutide	A10BJ04
Dulaglutide	A10BJ05
Semaglutide	A10BJ06
DPP-IV inhibitors	
Sitagliptin	A10BH01
Vildagliptin	A10BH02
Saxagliptin	A10BH03
Alogliptin	A10BH04
Linagliptin	A10BH05
SGLT-2 inhibitors	
Dapagliflozin	A10BK01
Canagliflozin	A10BK02
Empagliflozin	A10BK03
Ertugliflozin	A10BK04

Outcome

The primary outcome is thyroid cancer (TC). We will identify outcomes using a prior published algorithm that has been shown to have high reported positive predictive value (PPV) of 0.91 (95% confidence interval [CI] 0.81–0.96).[17] Thyroid cancer will be defined if there are both a thyroidectomy and at least 2 separate diagnoses for malignant neoplasm of thyroid gland (ICD-9 193 or ICD-10 codes C73, D09.3 or D44.0) within 90 days after the thyroidectomy. Date of diagnosis will be assigned at the first TC claim associated with thyroidectomy (we realize that this introduces some immortal time but see the surgery date as a better-defined date than the diagnosis dates). Because this algorithm has not been validated in Medicare claims data, we will implement three other algorithms for defining thyroid cancer: 1) Claims for any non-surgical thyroid cancer treatment (chemotherapy, radio-iodine, radiation)[17] 2) Two or more diagnoses of thyroid cancer within 2 months[18] 3) Claims for any non-surgical thyroid cancer treatment (chemotherapy, radio-iodine, radiation) or both a thyroidectomy and at least 2 separate diagnoses for malignant neoplasm of thyroid gland.

We will implement all these algorithms in cohort III to assess changes in incidence across calendar years of study and compare the observed incidence rates with age-standardized expected US incidence rates (from SEER) without stratifying the cohorts by treatment. We will thus make our decision of which algorithm to use for our primary analyses (and which ones for secondary/sensitivity analyses) before stratification by treatment (i.e., blinded to treatment status).

Definitions of thyroid cancer and incidences

Algorithm definition	Thyroid cancer Incidence
1. Claims for any non-surgical thyroid cancer treatment (chemo, radioiodine, radiation)	XXX
2. Thyroid surgery and ≥2 ICD-9 193 codes ≤ 90 days after surgery	XXX
3. ≥2 ICD-9 193 codes within 60 days[18]	XXX
4. 1 OR 2	XXX

Table 3. Codes used to identify thyroid cancer outcome

Code Type	**Code**	**Outcome**
ICD-9-CM Diagnosis code	193.0	Malignant neoplasm of thyroid gland
ICD-10-CM Diagnosis codes	C73, D09.3, D44.0	Malignant neoplasm of thyroid gland, Carcinoma in situ of thyroid and other endocrine glands, Neoplasm of uncertain behavior of thyroid gland
ICD-9 Procedure codes	06, 06.2 ,06.3x, 06.4, 06.5x, 06.6	Operations on thyroid and parathyroid glands, Unilateral thyroid lobectomy, Other partial thyroidectomy, Complete thyroidectomy, Substernal thyroidectomy, Excision of lingual thyroid
ICD-10 Procedure codes	Equivalent ICD-10 procedure code lists will be created using a combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services General Equivalence Mapping (GEMs)[19] and clinical input.	Operations on thyroid and parathyroid glands, Unilateral thyroid lobectomy, Other partial thyroidectomy, Complete thyroidectomy, Substernal thyroidectomy, Excision of lingual thyroid
CPT-4	60200, 60210, 60212, 60220, 60225, 60240, 60245, 60246, 60252, 60254, 60260, 60270, 60271	Remove thyroid lesion, Partial thyroid excision, Partial removal of thyroid, Removal of thyroid,

		Thyroidectomy subtotl/part, Extensive thyroid surgery, Repeat thyroid surgery
CPT-4	96400, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96500, 96501, 96504, 96505, 96508, 96509, 96510, 96511, 96512, 96524, 96526, 96535, 96538, 96540, 96542, 96545, 96549	Chemotherapy
HCPCS	C8953, G9021, G9025, S5020, S9329	
HCPCS	A9517, A9525, A9530, A9545, Q0105, Q0106, Q0107, Q9945, Q9946, Q9948, Q9951, Q9958, Q9959, Q9960, Q9961, Q9962, Q9963, Q9964	Radio-iodine therapy
HCPCS	X7945, G0173, G0174, G0178, G0179, S8049	Radiation therapy
CPT-4	76950, 76965, 77261, 77262, 77263, 77280, 77285, 77290, 77295, 77299, 77300, 77301, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331, 77332, 77333, 77334, 77336, 77338, 77370, 77371, 77372, 77373, 77380, 77381, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417, 77418, 77419, 77420, 77421, 77422, 77423, 77425, 77427, 77430, 77431, 77432, 77435, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77785, 77786, 77787, 77789, 77790, 77799, 79000, 79001, 79005, 79020, 79030, 79035, 79100, 79101, 79200, 79300, 79400, 79403, 79420, 79440, 79445, 79999	

ICD-9 Procedure codes	92.2, 92.20, 92.21, 92.22, 92.23, 92.24, 92.25, 92.26, 92.27, 92.28, 92.29, 92.3, 92.30, 92.31, 92.32, 92.33, 92.39, 92.4, 92.41	
ICD-10 Procedure codes	Equivalent ICD-10 procedure code lists will be created using a combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services General Equivalence Mapping (GEMs)[19] and clinical input.	

CPT-4 Current Procedural Terminology, 4th Edition, ICD-9, International Classification of Diseases, 9th Revision, ICD-10, International Classification of Diseases, 10th Revision, HCPCS, Healthcare Common Procedure Coding System (HCPCS)

Follow-up

The primary analysis of this study will employ an "as-treated" approach. Follow-up will begin six months after the second prescription date, allowing for an induction and latent period of cancer, and will continue until the occurrence of the outcome of interest or any censoring event. Censoring events include treatment discontinuation, switching to comparator, or augmentation with comparator, death from any cause (with the exception of an analysis treating death as a competing event, see below), termination of enrollment in Medicare Part A, B, and D claims data, or December 31, 2019, whichever comes first. We will add a six month latent period after discontinuation, switching, or augmentation before censoring, i.e., we will count both person-time and events up to six months after these events. Patients who develop thyroid cancer during the initial six-month induction and latent period will be described and excluded from the study. In addition, patients will be censored if they develop any non-thyroid cancer (excluding non-melanoma skin cancer) within the six-month period following the second prescription or during the follow-up period. This censoring decision is based on the rationale that diagnostic investigations or treatment modalities for other cancers may influence the outcome of thyroid cancer.

Treatment discontinuation will be defined as the absence of a prescription of the cohort drug class within the days of supply plus a 30-day grace period following the last prescription. The same definition will be applied to switching. Augmenting with comparator will be defined as first dispensed prescription of the comparator. We will vary the length of the grace period and the lag-periods (both initial and after stopping, switching, or augmenting) in sensitivity analyses in both directions (longer and shorter) separately to assess the robustness of the primary analysis results to the length of these periods.

Covariates
Potential confounders and indicators of screening bias will be assessed during the 1 year before the first prescription date. We will examine the following baseline covariates:

Potential Confounders
Demographics:

- Age, Sex, Race/ethnicity, Year of Cohort Entry, Available measures of socioeconomic status

Codes for Comorbidities:

- Diabetes mellitus, Hypertension, Hyperlipidemia, Chronic obstructive pulmonary disease, Congestive heart failure, Myocardial infarction, Chronic kidney disease, Depression, Thyroid disorders (Hypothyroidism, Hyperthyroidism, Goiter), Pancreatic disorders (Pancreatic disease, Acute Pancreatitis, Chronic Pancreatitis), Diabetic complications (neuropathy, nephropathy, cataract, retinopathy), Obesity

Codes for Health Behaviors:

- Tobacco use, Alcohol use

Comedications:

- Insulin (long and short acting separately), Metformin, thiazolidinediones, Sulfonylureas, GLP-1RA, DPP4-I, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Statins, Loop diuretics, Other diuretics, Beta blockers, Calcium channel blockers, NSAIDs, Hormone therapy

Healthcare utilization:

- Number of hospital admissions, Duration of hospital admissions, number of outpatient visits, number of Emergency department visits, Number of surgical procedures, Number of HbA1c tests, Lipid panel, Flu vaccination, Endocrinology visit

Potential Indicators of Screening

Thyroid diagnostic procedures and imaging:

- Thyroid hormone tests (calcitonin, Thyroid stimulating hormone (TSH), T3, T4)
- Thyroid antibody tests (antithyroglobulin, antimicrosomal)
- Thyroid ultrasound
- CT of neck
- Thyroid biopsy
- MRI of neck

Statistical analysis
Propensity Score (PS) methods will be used to control for measured confounders. Specifically, logistic regression will be utilized to estimate propensity scores - the probability of initiating GLP-1RA or DPP-IV inhibitors compared to SGLT-2 inhibitors (or GLP-1RA vs. DPP-IV inhibitors for cohort III), conditional on baseline covariates. Our primary aim is to estimate the counterfactual scenario of what would have happened to the initiators of GLP-1RA or DPP-IV inhibitors if they had initiated SGLT2 instead. To achieve this goal, we will estimate the

treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)) (Standardized Morbidity Ratio Weighting).[20] The adequacy of covariate balance will be evaluated based on standardized absolute mean differences (SAMD), with a threshold of less than 0.1 indicating satisfactory balance.[21] We will implement Cox models overall and stratified by calendar year of initiation.[22] SMR weighted Kaplan-Meyer survival functions will be compared between our cohorts, adjusted for the same baseline covariates. The main effect measure estimate will be standardized incidence rate differences (IRD) with the assumption that there is no unmeasured confounding. We will also estimate IRD within different times after antihyperglycemic drug initiation to allow for incidence rates to vary over time. Secondary effect measure will be hazard ratios.
When estimating the risk of cancer outcomes in older Medicare patients, censoring those who died before hypothetically experiencing the outcome of interest, as commonly done with survival analyses, could introduce bias in the risk estimation.[23,24] To prevent this potential bias, we will employ Aalen-Johansen (AJ) estimators to estimate risks. First, we will estimate the overall survival function and hazard function for each event type (outcome of interest as well as death), using a population weighted by inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW). Next, we will compute the AJ estimators by multiplying the hazard function of the outcome of interest at each event time by the overall survival at the previous time point. This approach effectively treats death as a competing risk by assigning patients a risk of 0 after experiencing death. Using the AJ estimators, we can accurately estimate the risks of cancer outcomes while accounting for the competing risk of death in the population.[25]

To address the potential for detection bias, we will first describe the incidence of the above listed potential indicators of screening in all cohorts compared. If differences are observed, we will implement a recently proposed method to address differences in screening rates potentially leading to bias. This method uses inverse-probability-of-screening weights to address differential outcome screening, has been shown to work in simulations and has been successfully implemented in a study on the effects of statin persistence on breast cancer risk.[26,27]

Sensitivity analyses
To examine the robustness of our primary results to changes in study population and condition definitions, we plan to perform the following sensitivity analyses:

1. We will repeat the primary analysis using initial treatment analysis (IT) (no censoring for drug discontinuation, switching, or augmentation). Note that for this analysis we do not require part D data during follow-up and will thus only censor for loss of parts A or B coverage.
2. Repeat primary analysis to include individuals with only 1 prescription for a study drug.
3. We will vary the grace period from 30 days to 15, and 60 days.
4. We will vary lag periods (both after initiation and after stopping) separately from 6 months to 0, 12, 24 months, depending on availability of data.
5. We will repeat analyses using the other algorithms for the definition of thyroid cancer incidence.
6. We will perform asymmetric trimming of propensity scores (1%, 2.5%, and 5% cut-points) to assess the significance of any populations treated contrary to expectation (i.e.

populations treated despite low PS, or not treated despite high PS) and the effect they have on the overall weighting and the effect measure estimate [28].

7. Restrict analyses to 1st new use period.
8. Repeat analysis restricting to patients with baseline metformin use. This approach has been shown to improve confounding control and covariate balance by restricting to populations that are using study drugs as second-line therapies following initial metformin use.
9. Repeat analysis excluding exenatide and lixisenatide but not exenatide once-weekly (short-acting GLP-1RA).
10. Repeat analysis excluding patients with prescriptions of levothyroxine for postprocedural hypothyroidism, a history of thyroid nodule or fine needle aspiration of the thyroid at baseline.
11. Compare the cumulative incidence (incidence proportion) of thyroid diagnostic procedures and imaging tests in the 6 months after drug initiation (index date) in the GLP-1RA or DPP-IV inhibitors new-users with the corresponding incidence in SGLT-2 inhibitors new-users.

Table 4. Codes for sensitivity analyses.

Code Type	Code	Condition
ATC code	H03AA01	Levothyroxine
ICD-9-CM Diagnosis code	244.0	Postprocedural hypothyroidism (Postirradiation hypothyroidism, Postsurgical hypothyroidism)
ICD-10-CM Diagnosis code	E89.0	
ICD-9-CM Diagnosis code	226, 237.4, 240.x, 241.x, 242.xx, 246.1, 246.2	Goiters/Nodules[17,29]
ICD-10-CM Diagnosis code	Equivalent ICD-10 diagnosis code lists will be created using a combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services General Equivalence Mapping (GEMs)[19] and clinical input.	
ICD-9-CM Procedure code	06.01, 06.11[30]	Fine Needle Aspiration of thyroid
ICD-10-CM Procedure code	Equivalent ICD-10 procedure code lists will be created using a	

	combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services General Equivalence Mapping (GEMs)[19] and clinical input.	

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