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Impact of Incretin Mimetics on Thyroid Cancer Among Patients with Type 2 Diabetes: A Retrospective Cohort Time-to-Event Analysis

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Abstract: Background: Incretin mimetics, including glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonist) and dipeptidyl peptidase-4 (DPP-4) inhibitors, have been increasingly utilized for glycemic control in patients with type 2 diabetes (T2D). Studies have demonstrated additional improvements in weight loss, cardiovascular health, and renal outcomes. Animal studies have shown an association between GLP-1 receptor agonists and C-cell proliferation and elevated calcitonin, resulting in an FDA black box. Insulin resistance in patients with T2D, along with the use of other glucose control medications, confounds the relationship between incretin mimetics and thyroid cancers. The true effect of incretin mimetics on thyroid cancer remains uncertain and speculative due to this confounding. **Methods**: This retrospective cohort study compared patients with T2D, who were new users of incretin mimetics, to new users of metformin. Study patients used no other anti-diabetes medications beyond the study medications. The risks of incident thyroid cancer and subsequent thyroidectomy were quantified using Cox proportional hazards regression models fitted with adjustments for demographic and medical covariates over a three-year study period. Medullary thyroid cancer (MTC) and multiple endocrine neoplasia type II (MEN2) cases were quantified. **Results**: Of the 91,394 patients, 28 incretin mimetic users had a diagnosis of thyroid cancer, and nine of these patients underwent a subsequent thyroidectomy procedure. No incretin mimetic user was diagnosed with MTC or MEN2. There was no statistically significant effect on the overall incretin mimetic category (1.28 aHR, 0.83–1.96), the incretin mimetic subcategories of GLP-1 receptor agonists (1.35 aHR, 0.80–2.29), or DPP-4 inhibitor (0.62 aHR, 0.33–1.17) users in developing thyroid cancer within three years of drug initiation. Similarly, no association was found between the overall incretin mimetic category (1.02 aHR, 0.49–2.10), the subcategories of GLP-1 receptor agonists (1.26 aHR, 0.54–2.96), or DPP-4 inhibitors (0.32 aHR, 0.08–1.37) and a subsequent thyroidectomy. **Conclusions**: In this real-world cohort study, exposure to incretin mimetics overall or through the incretin mimetic subcategories of GLP-1 receptor agonists and DPP-4 inhibitors was not associated with risks of thyroid cancer or thyroidectomy compared to metformin users.

Keywords: incretin mimetics; thyroid cancer; survival analysis; time-to-event; retrospective cohort

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1. Introduction

Exponential growth in utilization rates of the glucagon-like peptide-1 (GLP-1) receptor agonists and glucose-dependent insulinotropic polypeptides (GIPs) has been demonstrated in recent literature [1], with monthly growth rates in the first year since the launch of 84% for subcutaneous semaglutide and 254% for GLP-1 RA/GIP dual-agonist tirzepatide with indications for diabetes. The incretin mimetics with FDA approval for weight management have also experienced spectacular growth, with a 119.2% monthly growth rate for FDA-approved subcutaneous semaglutide for weight management. This high use rate has led to a forecasted global market growth from $22.4 billion in 2022 to $55.8 billion in 2032 [2]. While these medications have demonstrated meaningful health outcomes for patients, such as reducing A1c, body mass, and cholesterol and improving kidney outcomes [3–6], their relative recency in massive-scale use has left gaps in the understanding of long-term usage effects. Thyroid cancer has emerged as one potential risk associated with incretin mimetic use [7–9]. Given the expected continual growth in use of these drugs due to their potential benefits in improving glycemic control [5], chronic weight management [3], and a rapidly growing list of cardiovascular [3,6] and renal benefits [4,6], it is imperative to study their potential deleterious side effects, including thyroid cancer.

Thyroid cancer rates are increasing, and multiple investigators have postulated a potential link between insulin resistance and diabetes in general as an explanation for this trend [10–15]. Thus far, findings linking thyroid cancer to diabetes have been inconclusive [13]. Many hypotheses have been posited towards a multi-factorial relationship involving glucose metabolism, triglyceride levels, body mass index (BMI), and chronic exposure to some hypoglycemic agents [11]. A review of the influence of multiple antidiabetic agents has highlighted possible associations between sulfonylureas, insulin, and glitinides on thyroid cancer while showing mixed or limited associations for thiazolidinediones, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [14]. Evidence exists suggesting metformin may also have a growth-inhibiting effect on thyroid cancer stem cells, which adds complexity to evaluating the relationship between incretin mimetics and thyroid cancer as many antidiabetic agents are used as second-line treatments to metformin [16,17]. Understanding mechanisms of excess thyroid cancer risk among patients with diabetes demands more focused studies of isolated antidiabetic agent medication use in real-world populations.

The effect of incretin mimetics on cancer rates, including thyroid cancers, has yet to be firmly established. While there is evidence that these drugs protect against some cancers [18], the United States Food and Drug Administration (FDA) placed a black boxed warning on all recently approved GLP-1 receptor agonists. This warning was issued due to the increased risk of C-cell tumors, specifically medullary thyroid cancer (MTC) observations in rodent studies. Per the FDA, its use is contraindicated for patients with a history of MTC or multiple endocrine neoplasia type II (MEN2). However, no link between GLP-1 receptor agonists and thyroid cancer has been established in human studies [19–23]. Studies have been hampered by low case counts, partly because of the infrequency of MTC and MEN2. The rare nature of MTC [24] and MEN2 [25], coupled with the recency of the most popular incretin mimetics such as semaglutide, jointly create challenges attributable to small sample sizes. This is further exacerbated by the limited prevalence of patients taking incretin mimetics exclusively; GLP-1 receptor agonists and DDP-4 inhibitors are infrequently used as first-line medications for patients with type 2 diabetes [26]. Therefore, longer-term studies examining single-agent use in large, population-level databases are needed.

Several randomized controlled trials were conducted over the last decade to examine the relationship between specific GLP-1 receptor agonists and thyroid cancer. However,

the findings were generally non-significant. A 2024 systematic review examined the results of five randomized controlled trial meta-analyses among people with diabetes or obese individuals and described a non-significant increased risk in the form of elevated odds ratios of 1.54, 1.49, 2.04, 1.19 and a risk ratio of 1.30 for the GLP-1 receptor agonist groups, with only one study having a significant fixed-effect of 1.52 [CI 1.01–2.29] [19]. However, the authors suggested these results are imprecise due to the limited counts of thyroid cancer outcomes and short follow-up periods. This same review also examined six case-control or cohort observational studies performed in claims and research databases, two of which found statistically significant increased risks of thyroid cancer (hazard ratio of 1.46 for 1–3 years of cumulative GLP-1 receptor agonist use and a risk ratio of 1.66 for liraglutide compared to other antidiabetic agents) [19]. The authors commented on moderate-to-high levels of bias and high degrees of variability in terms of follow-up, lag time, exposure, and lack of important covariates and indicators. While these studies benefited from higher sample sizes in general, their results were hindered by a lack of uniformity and validity in the outcome definition. Specifically, it was difficult to isolate MTC from a broader thyroid cancer diagnosis. Instead, other indicators were relied on to define MTC cases, such as treatment with vandetanib, thyroid surgery, diagnostic tests, the presence of nodules or goiters, or elevated calcitonin levels. However, no combination of these indicators provides sufficient evidence of MTC, even when paired with a positive cancer diagnosis [19].

An issue little reconciled in other studies, randomized or observational, is that patients with diabetes rarely take GLP-1 receptor agonists on their own, and, as second-line treatments, GLP-1 receptor agonists are frequently paired with other antidiabetic agents. Since diabetes and obesity have a well-established connection to many cancers, including thyroid cancers [12,27], the added effect of using other medications on such outcomes is particularly difficult to establish. Metformin is the most frequently used antidiabetic agent, and there is evidence that it lowers the growth rate of benign and cancerous thyroid cells [15,17,28]. Therefore, for this study, we included patients exclusively taking incretin mimetics and compared them to patients exclusively taking metformin, ensuring drug nativity between the groups as well as to any other antidiabetic agent.

2. Methods

2.1. Data Source

This study utilized the University of California Health Data Warehouse (UCHDW) for all analyses. The UCHDW captures health data including but not limited to visits, procedures, diagnoses, drug and prescription dispensing, and lab measures from all six UC Health systems (Davis, Irvine, Los Angeles, Riverside, San Diego, San Francisco). Extending back to 2012, this dataset holds records for over 11 million distinct patients and 1.5 billion distinct drug exposures across just under 200 million health center visits. These data are structured according to the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) and are suited to studying cohorts of patients longitudinally.

2.2. Study Cohort

This retrospective cohort included patients with type 2 diabetes (T2D) who were new drug users initiating a prescription regimen of either (1) oral metformin or (2) an incretin mimetic, which was either a DPP-4 inhibitor, GLP-1 receptor agonist, or GLP-1RA/GIP agent, between 1 January 2012 and 1 March 2025. Patients were required to have at least one refill per month or a proportion of days covered of at least 0.8 during a three-month "lag period" defined as the first 90 days since their initial prescription fill. Patients were excluded if they had any prescription fills of antidiabetic agents other than metformin or the first incretin mimetic used before or during the follow-up period. The excluded

antidiabetic agents were sodium-glucose cotransporter-2 inhibitors, sulfonylureas, amylin analogs, thiazolidinediones, alpha-glucosidase inhibitors, insulin glargine, glitinides, or any drugs that are combinations of blood glucose-lowering medications. Additionally, incretin mimetic users must have used no more than one type of incretin mimetic (DPP-4 inhibitor, GLP-1 receptor agonist, or GLP-1 RA/GIP) before or during the follow-up period. Patients were required to have evidence of a healthcare interaction in the form of either a visit to any UC Health care facility, a record of exposure to a drug or device, any record of a lab or physical measurement or observation, any record of a procedure, or any new health condition at least two months prior to their first prescription to ensure patients were drug-naive. Patients diagnosed with thyroid cancer or those who had a thyroidectomy at any point prior to the end of the lag period were excluded to account for the time required for cancer development.

Patients were eligible for cohort entry if they were determined to have T2D at the UCHDW. Given the potential for the absence of diagnosis for T2D in some patients with diabetes, plasma glucose and A1c levels were also used to identify patients with T2D, consistent with other observational studies [29,30] and the American Diabetes Association (ADA) 2023 standards of care [31]. The following approaches were applied:

- Type 2 diabetes mellitus diagnosis: Patients were included if they had a condition having SNOMED codes 201826 or 443732 for either "Type 2 diabetes mellitus" or "Disorder due to type 2 diabetes mellitus", respectively. Any electronic health record codes derived from these codes were also considered indicative of a T2D diagnosis;
- Hemoglobin A1c (HbA1c): Consistent with the American Diabetes Association (ADA) 2023 standards of care, patients with an A1c measure of 6.5% (48 mmol/mol) or greater were considered to have T2D [31]. Therefore, we considered a patient having at least two HbA1c measurements at or above 6.5% to have T2D;
- Plasma glucose: The ADA 2023 standard of care criteria permits a T2D diagnosis given an 8-h fasting plasma glucose of 126 mg/dL (7.0 mmol/L) or greater or a plasma glucose measure of 200 mg/dL (11.1 mmol/L) or greater using an anhydrous glucose load equivalent to 75 g [31]. In our study, patients who had two of either measurement beyond this threshold were considered to have T2D;
- Hyperglycemia: In line with the ADA 2023 standards, patients with a diagnosis of hyperglycemia or a symptom (excessive thirst, frequent urination, or blurred vision) and a random plasma glucose of at least 200 mg/dL (11.1 mmol/L) were included;
- Patients lacking a hyperglycemia diagnosis were required to have at least two elevated A1c or (fasting) plasma glucose test results.

2.3. Exposure Definition

We defined an incretin mimetic exposure group to include patients meeting the cohort criteria and who filled a prescription for any one of the incretin mimetics, including DPP-4 inhibitors, GLP-1 receptor agonists, or GLP-1 receptor agonist/GIPs. Specifically, a GLP-1 receptor agonist or DPP-4 inhibitor user is one whose first agent had a respective drug concept id of any coding ancestor of the Anatomical Therapeutic Chemical (ATC) 4th or 5th code of 1123618 or 21600783. GLP-1 receptor agonist/GIP users were identified using the same ancestry approach with the RxNorm code 779705. The latter exception is required as there was no corresponding ATC code for GLP-1 receptor agonist/GIP tirzepatide drugs at the time of this study.

2.4. Outcome Definition

The primary outcome of interest was a thyroid cancer event during the follow-up period of three years from the first prescription date that did not precede the end of the three-

month lag period. A thyroid cancer diagnosis was identified in a patient having a recorded condition occurrence with a concept id coordinated with International Classification of Diseases 10th revision (ICD-10) code C73 for 'Malignant neoplasm of thyroid gland'. In the source database, the only condition concept id to satisfy this was the SNOMED 'Primary malignant neoplasm of thyroid gland' concept with id 133424. The secondary outcome of a subsequent thyroidectomy or lobectomy, total or subtotal, within the three-year study interval, was identified in patients having a procedure with the SNOMED code 4030107 or any descendant concept ID. Patients having an MTC or MEN2 diagnosis during the study period were identified in the same manner as thyroid cancer using the International Classification of Diseases for Oncology 3rd revision (ICD-O-3) code C73.9 and the ICD-10 codes E31.22 and E31.32, respectively.

2.5. Statistical Analysis

A Cox proportional hazard multiple regression model (CPH) [32] was used to model the instantaneous risk of the primary outcome of thyroid cancer attributed to the exposure category as the explanatory variable of interest. This model yielded adjusted hazard ratios (aHRs) comparing incretin mimetics to the reference medication metformin. Time-to-event was measured in weeks from the conclusion of the lag period until the standard binary outcome of either event occurrence or censoring in the data. Patient censoring manifested itself by either reaching the end of the study period without an event or loss to follow-up during the study period. For the secondary outcome of subsequent thyroidectomy procedures, a separate Cox proportional hazard multiple regression model was used for the subsequent thyroidectomy outcome. For the secondary thyroidectomy outcome, time was measured in weeks from drug initiation until the first thyroidectomy procedure for patients who had already experienced a thyroid cancer outcome. The proportionality assumption was assessed in both Cox models [33].

Both Cox proportional hazard multiple regression models were fit with stabilized weights estimated from an inverse probability of treatment weighing matching procedure [34]. Probability of exposure to an incretin, by type, was calculated using a multinomial logistic regression with adjustments made for baseline demographics and comorbidities as well as the starting year, number of outpatient visits in the first three months since drug initiation, nearest A1c measurement, and the change in weight observed over the study interval.

2.6. Covariates

To adjust for potential influential factors, the multiple-regression Cox model included prespecified independent confounding variables including gender [35], race [36,37], ethnicity [36], obesity [27,38], diabetes [12], age [39], a prior diagnosis of non-thyroid cancer, a family history of cancer, goiter, or other thyroid issues. Baseline A1c (%), defined as the nearest available measurement within six months preceding the first drug usage, was also included to adjust for patients of different glycemic status. Change in weight over the study interval, defined as the nearest measurement in pounds within the six months preceding drug initiation minus the furthest measurement in pounds within three years following drug initiation, was also added. Other cancers or neoplasms were determined using a diagnosis with a concept mapped from any ICD-10 code in the C00-C96 category for "malignant neoplasms", excluding C73, E31.22, and E31.23. The "other thyroid issues" variable was a composite of thyroid disorders, including SNOMED codes for acquired hypothyroidism, disorder of the thyroid gland, autoimmune thyroiditis, hyperparathyroidism, and Hashimoto's and Grave's disease. The year of drug initiation and the number

of outpatient visits during the lag period were also included to adjust for detection bias. Mean imputation was employed for patients lacking A1c or weight measurements.

3. Results

From 1 January 2012 to 1 March 2025, a total of 91,394 patients met the criteria to be considered as having T2D and were new users of either metformin exclusively or an incretin mimetic, with no other antidiabetic agents taken previously or during the three-year study interval (Table 1). Of these 91,394, a total of 82,964 were metformin users, 4912 were GLP-1 receptor agonist users, and 3518 were DPP-4 inhibitor users having at least three prescriptions or a 0.8 PDC since their first prescription during the first three months of use. There were significant demographic and baseline health characteristic differences between metformin, DPP-4 inhibitor, and GLP-1 receptor agonist users. GLP-1 receptor agonist users were more often White and female than metformin and DPP-4 inhibitor users (54.2% vs. 45.8% and 42.9% White and 61.2% vs. 51.0% and 49.0% female). Adverse health conditions were more prevalent among GLP-1 receptor agonist patients. Of GLP-1 receptor agonist users, 26.6% had a BMI greater than 30 during the year preceding drug initiation compared to 8.1% for metformin and 4.9% for DPP-4 inhibitor users. GLP-1 receptor agonist and DPP-4 inhibitor users were more likely to have had any type of cancer before their first drug usage at 12.0% and 11.0%, respectively, as opposed to 9.9% for metformin users. Similarly, GLP-1 receptor agonist users, compared to metformin and DPP-4 inhibitor users, had higher rates of prior goiter (4.4% vs. 2.8% and 2.1%), other thyroid issues (18.2% vs. 10.0% and 13.3%), and a record of a family history of cancer (13.5% vs. 11.6% and 8.6%).

Table 1. Baseline patient characteristics with a chi-square test for independence *p*-values comparing metformin to incretin mimetic counts and an ANOVA for age, baseline A1c, and lag-period outpatient visit count comparisons.

	Metformin	**Incretin Mimetic**		***p***
		GLP-1 Receptor Agonist	**DPP-4 Inhibitor**	
N	82,964	4912	3518	
Age (avg, sd)				
At first prescription	62.5 (13.8)	58.0 (13.9)	69.3 (12.5)	<0.01
Gender (%)				
Female	42,289 (51.0)	3008 (61.2)	1723 (49.0)	<0.01
Race (%)				
Asian	13,970 (16.8)	341 (6.9)	688 (19.6)	<0.01
Black	4970 (6.0)	406 (8.3)	210 (6.0)	<0.01
White	37,999 (45.8)	2661 (54.2)	1510 (42.9)	<0.01
Ethnicity (%)				
Hispanic or Latino	16,414 (19.8)	1091 (22.2)	739 (21.0)	<0.01
Comorbidities (%)				
Obesity	6743 (8.1)	1304 (26.6)	172 (4.9)	<0.01
Thyroid issues	8313 (10.0)	895 (18.2)	466 (13.3)	<0.01
Goiter	2286 (2.8)	217 (4.4)	73 (2.1)	<0.01
Prior cancer	8210 (9.9)	589 (12.0)	388 (11.0)	<0.01
Family history of cancer	9653 (11.6)	664 (13.5)	302 (8.6)	0.63
Measurements (avg, sd)				
A1c	7.2 (2.0)	6.7 (4.4)	6.4 (1.3)	<0.01
Outpatient visits	1.0 (3.0)	1.0 (2.6)	2.6 (7.3)	<0.01

A total of 317 patients developed thyroid cancer during the study interval. There were 289 thyroid cancer incidences among metformin users, 17 among GLP-1 receptor agonist users, and 11 among DPP-4 inhibitor users. Of these patients with thyroid cancer,

135 had a subsequent thyroidectomy during the study interval: 126 of them were metformin users, seven were GLP-1 receptor agonist users, and two were DPP-4 inhibitor users. Only three patients had the specific diagnostic code for either MTC or MEN2, with all three being from the metformin group and having MEN2 (Table 2). By drug type, the highest prevalence of thyroid cancer was among patients taking tirzepatide (3 of 453, 0.66%) and alogliptin (1 of 62, 1.61%) for the GLP-1 receptor agonist and DPP-4 inhibitor patients, respectively (Table 3). Patients in the metformin group had a median follow-up time of 156 weeks, and patients in the incretin group had a median follow-up time of 152 weeks.

Table 2. Three-year study period outcomes.

	Metformin	**Incretin Mimetic**		***p***
		GLP-1 Receptor Agonist	**DPP-4 Inhibitor**	
Outcome (%)				
Thyroid cancer	289 (0.35)	17 (0.35)	11 (0.31)	0.81
Thyroidectomy	126 (0.15)	7 (0.14)	2 (0.06)	0.30
MTC or MEN2	3 (0.00)	0 (0)	0 (0)	NA

Table 3. Three-year study period outcomes by drug type.

	Thyroid Cancer	**Thyroidectomy**
Metformin (%)		
Metformin	289 (0.35)	126 (0.15)
DPP-4 inhibitor (%)		
Alogliptin	1 (1.61)	0 (0)
Linagliptin	3 (0.27)	0 (0)
Saxagliptin	1 (1.09)	1 (1.09)
Sitagliptin	6 (0.27)	1 (0.04)
GLP-1 receptor agonist (%)		
Dulaglutide	2 (0.22)	1 (0.11)
Liraglutide	1 (0.18)	1 (0.18)
Semaglutide	11 (0.38)	4 (0.14)
Tirzepatide	3 (0.66)	1 (0.22)

The adjusted Cox model results demonstrated no significant difference in the risk of thyroid cancer between the overall incretin mimetic group (1.28 aHR, 0.83–1.96) and the metformin group. Comparing the different incretin mimetic subgroups, the adjusted model showed a non-significant increase in risk for GLP-1 receptor agonist users (1.35 aHR, 0.80–2.29) and a non-significant decrease among DPP-4 inhibitor users (0.62 aHR, 0.33–1.17) for thyroid cancer compared to metformin users (Figure 1). The proportionality assumption was satisfied with this model.

For thyroid cancer patients, the adjusted model showed no significant difference in the risk of having a thyroidectomy between the incretin mimetic group (1.02 aHR, 0.49–2.10) and the metformin group. There was a non-significant increase in risk for GLP-1 receptor agonist users (1.26 aHR, 0.54–2.96) and a non-significant decrease among DPP-4 inhibitor users (0.32 aHR, 0.08–1.37) for a thyroidectomy compared to metformin users (Figure 1). This model also satisfied the proportionality assumption.

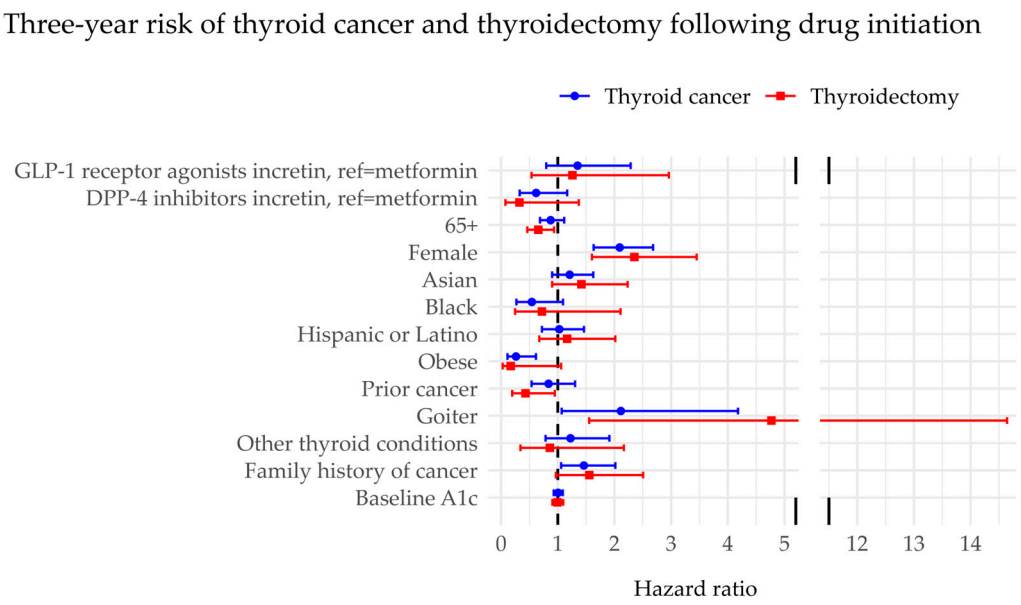


Figure 1. Adjusted hazard ratios fitted with an inverse probability of treatment weights for the risk of developing thyroid cancer and of a subsequent thyroidectomy during the first three years following drug initiation.

4. Discussion

These analyses compared the risks for new incretin mimetic users against new metformin users in developing thyroid cancer and experiencing a subsequent thyroidectomy. These groups had no overlapping drug usage or any other antidiabetic agents use before or during the study period. Care was taken to control potential demographic and health factors believed to influence thyroid cancer rates. After making these adjustments, we did not observe any statistically significant differences in the risk of thyroid cancer or a subsequent thyroidectomy following a period of new incretin mimetic drug usage, overall or at the drug level, compared to metformin users.

Insulin resistance has been discussed as a possible explanation for the rising incidence of thyroid cancer. However, the specific mechanism behind this association remains uncertain [12,13,40,41]. In addition to the potential increased cancer risk from factors such as obesity and hyperglycemia, patients with type 2 diabetes often require extensive treatment regimens involving one or more anti-diabetes medications. The individual or joint relationships to thyroid cancer are not well understood and vary from agent to agent within drug classes. For example, in patients with type 2 diabetes, the thiazolidinedione rosiglitazone has potential protective effects against thyroid cancer [42], while another thiazolidinedione, pioglitazone, was observed to have no impact [43]. Therefore, it is prudent to assess these medications in isolation.

As incretin use continues to rapidly expand [1], population exposure to either DPP-4 inhibitors or GLP-1 receptor agonist-containing products will increase exponentially. Because earlier studies have suggested potentially higher risks of thyroid cancer associated with either DPP-4 inhibitors [44] or GLP-1 receptor agonists [7], the need for robust pharmacovigilance studies further examining this risk will continue to grow. Recent FDA-funded initiatives have emphasized the importance of amplifying the use of real-world studies, including electronic health record (EHR) database studies, to support more robust population-level inference [45]. Efforts to leverage large EHR databases and/or payer claims databases will become both increasingly necessary and feasible as these agents gain broader insurance coverage, including Medicare for obesity indications [46,47]. These efforts will support and bolster future analyses for long-term risk analyses.

Limitations

The limited case counts for MTC or MEN2 in this cohort are to be expected since MTC comprises only about 3–5% of all thyroid malignancies [24], and MEN2 has an estimated prevalence of only 1 in 35,000 [25]. Therefore, this study leaves the relationship between incretin mimetics and MTC and MEN2 an open question for future research. While these findings align with the larger body of evidence suggesting no association between incretin mimetics and thyroid cancer, there is likely a need for studies directly addressing the potential link between GLP-1 receptor agonists and MTC and MEN2. With many GLP-1 receptor agonists now approved to treat obesity, it will be increasingly possible to study this relationship in obese, non-diabetic populations and reduce possible confounding attributed to ADA and T2D. A prospective cohort of longer duration in a large obese population using GLP-1 receptor agonists for weight loss would potentially address this gap.

For the purpose of this analysis, metformin or incretin use was only measured during the first three months after new use initiation. Any use thereafter is possible. Future studies will be needed to ascertain the effects of the duration of incretin exposure on thyroid cancer risk.

Due to the observational nature of this study, a causal relationship cannot be determined. Potential influential factors such as socioeconomic status, health interventions, and observations from outside of the UC Health system are not present within the UCHDW. Therefore, this potentially useful information is absent from our study. Due to these black boxed warnings, there is also potential for detection bias in GLP-1 receptor agonist patient cases, translating into a differential increase in the identification of thyroid issues for GLP-1 receptor agonist users compared to DPP-4 inhibitor users. It is possible that the large, albeit insignificant, increase in risk observed for GLP-1 receptor agonist users compared to DPP-4 inhibitor users may be explained by this bias. Additionally, without an explicit ICD-O-3 diagnosis code, it was not possible to delineate medullary thyroid cancer from generalized thyroid cancer in this dataset. Indicators including vandetanib usage or a lab measure indicating an elevated calcitonin level were also absent from our thyroid cancer cases.

Attributable to recent growth in GLP-1 receptor agonist use, most incretin mimetic use has occurred in recent years [1]. Given advances in thyroid cancer detection [48,49], there is a possibility of increased thyroid cancer detection in the incretin mimetic group and, consequently, elevated measures of excess risk tied to the incretins. To address this potential secular effect in risk measurement, we included the year of the first prescription of study medication. It is important to note that any residual confounding would likely result in an overestimate of the risk associated with incretin exposure. This observation is encouraging, given our study findings of the estimated null effect of incretins on cancer.

5. Conclusions

This real-world study found no association between exposure to incretin mimetics and the risk of thyroid cancer or a subsequent thyroidectomy in patients compared to patients taking metformin. Within incretin mimetic subgroups, GLP-1 receptor agonist users had a higher but non-significant risk of 1.35 compared to DPP-4 inhibitor users at 0.62 of developing thyroid cancer within three years of drug initiation. Our results agree with similar studies showing no association between incretin mimetics—GLP-1 receptor agonists or DPP-4 inhibitors—and thyroid cancer, but with the added confidence that these findings are not confounded by the use of other antidiabetic agents. Future studies with extended follow-up will be necessary to determine any additional long-term risk.

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Institutional Review Board Statement: The University of California Health Data Warehouse (UCHDW) was constructed as a timely, retrospective, de-identified dataset for research purposes. It is a Health Insurance Portability and Accountability Act (HIPAA) Limited Data Set and was operationalized by UC Health as 'non-human subjects research'. Analyses are considered institutional review board exempt.

Informed Consent Statement: Patient consent was waived in accordance with specifications per above as a retrospective, de-identified dataset HIPAA compliant Limited Data Set. Use of the UCHDW is considered non-human subjects research.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author(s).

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