

# No Increased Risk for Thyroid Cancer in Diabetic Patients Prescribed GLP-1 Medications Compared to Those Prescribed Insulin

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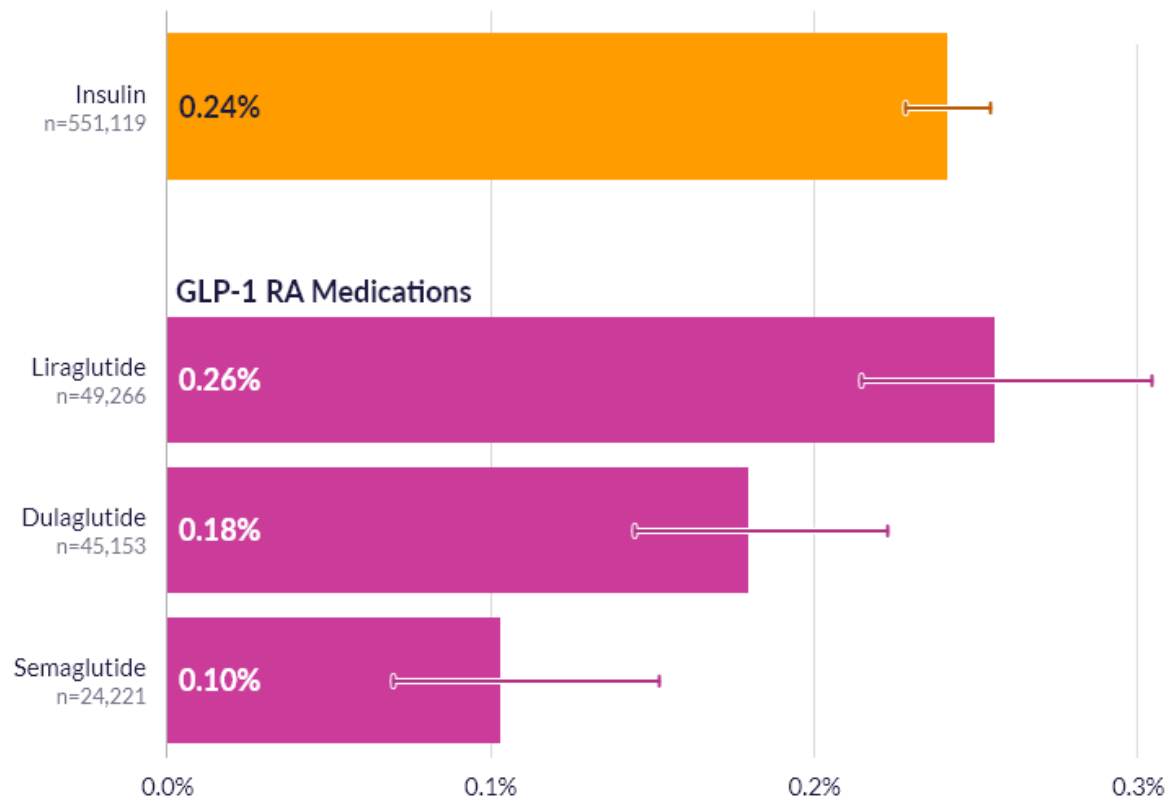
## Key Findings:

- The rate of thyroid cancer for type 2 diabetic patients prescribed semaglutide or dulaglutide is lower than the rate for patients prescribed insulin. This differs from previous studies where the potential for an increased risk of thyroid cancer was noted for GLP-1 receptor agonist (GLP-1 RA) medications.
- The rate of thyroid cancer for type 2 diabetics prescribed liraglutide is similar to the rate for patients prescribed insulin.

In 2022 and 2023, prescriptions for glucagon-like peptide 1 receptor agonist (GLP-1 RA or GLP-1) medications increased significantly, even resulting in shortages of the medications.<sup>1</sup> GLP-1 medications, like semaglutide, liraglutide, and dulaglutide, have been approved in the U.S. as a treatment for type 2 diabetes for several years, but they only recently made their way into national media headlines, largely due to their recent approval and use for weight loss. Initial animal studies and studies of other GLP-1 medications have shown an increased risk of thyroid cancer, which has prompted a warning of the potential side effect to patients prescribed GLP-1 medications.<sup>2,3</sup> We sought to understand whether patients prescribed these medications were at an increased risk of thyroid cancer in the five years after their initial diabetes diagnosis compared to patients prescribed insulin, another frequently prescribed medication for the treatment of type 2 diabetes.

We compared 24,221 type 2 diabetic patients prescribed semaglutide, 49,266 patients prescribed liraglutide, and 45,153 patients prescribed dulaglutide to 551,119 type 2 diabetic patients prescribed insulin to determine whether there were differences in the risk of thyroid cancer in each group. We found that the rate of thyroid cancer in the five years after diabetes diagnosis was lower for patients prescribed dulaglutide or semaglutide than patients prescribed insulin, as shown in Figure 1. The observed rate of thyroid cancer in patients prescribed liraglutide is similar to that of patients prescribed insulin. A sensitivity analysis adjusted for timing of treatment and HbA1c showed that there was no increased risk of thyroid cancer for any of the three GLP-1 medications studied as compared to insulin.

## Thyroid Cancer Rates for Patients Prescribed Diabetic Medications



"Thyroid Cancer Rates for Patients Prescribed Diabetic Medications," 2023. EpicResearch.org

Figure 1. Rate of thyroid cancer in type 2 diabetic patients prescribed insulin, liraglutide, dulaglutide, or semaglutide.

Previous studies have shown people with a BMI  $\geq 40$ , also known as class 3 obesity, and women have an increased risk of thyroid cancer.<sup>4,5</sup> We stratified the rates of thyroid cancer by patient BMI to understand how BMI might interplay with the diabetic medication prescribed. For this analysis, we compared patients prescribed insulin to patients prescribed any GLP-1 medication. We found that the rate of thyroid cancer was lower in the patients prescribed GLP-1 medications, but the decrease was only statistically significant in the patients with a BMI between 30 and 35, or class 1 obesity, as shown in Figure 2.

## Thyroid Cancer Rates by BMI Classification

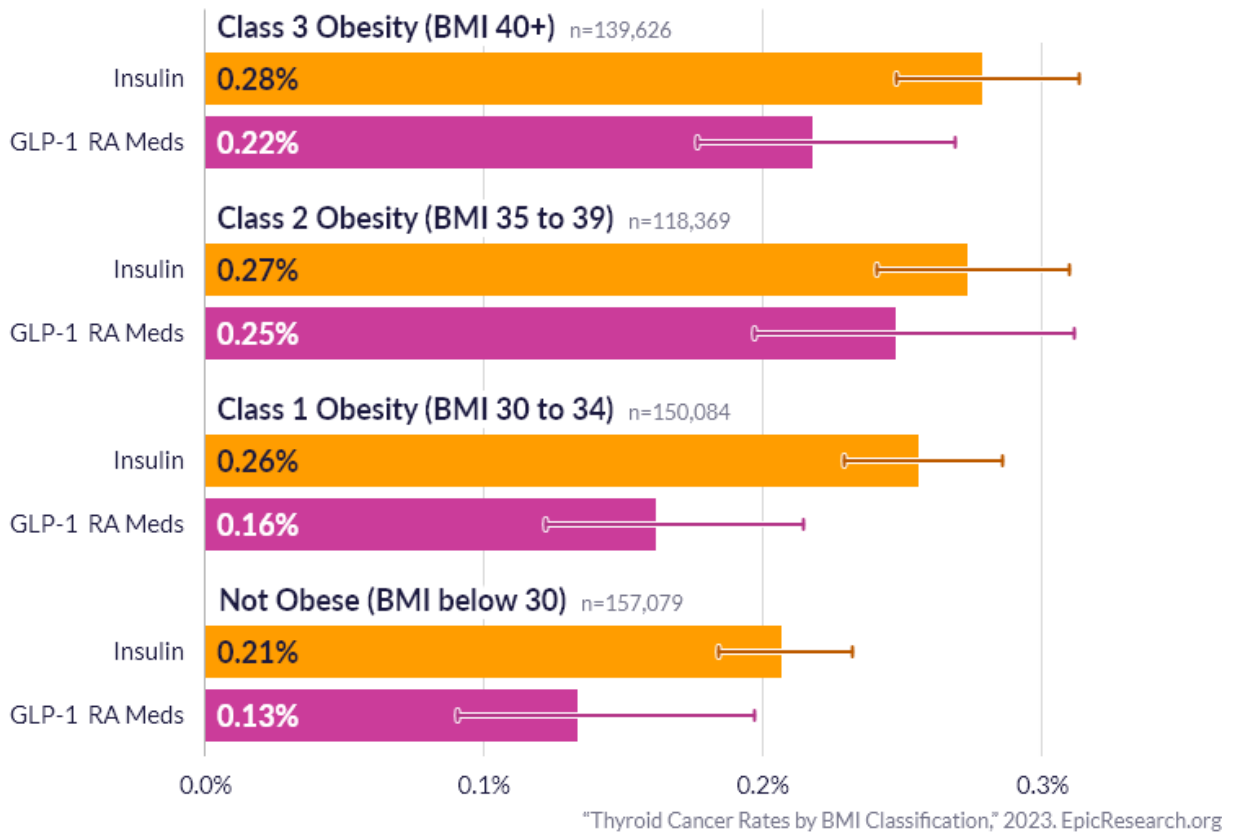


Figure 2. Rate of thyroid cancer in type 2 diabetic patients prescribed GLP-1 medications or insulin stratified by BMI classification at diabetes diagnosis. A BMI below 30 is not obese, a BMI between 30 and 35 is class 1, a BMI between 35 and 40 is class 2, and a BMI of 40 or greater is class 3.

Our results aligned with previous studies showing rates of thyroid cancer for females are around double the rates for males for both insulin and GLP-1 RA patients, as shown in Figure 3.

## Thyroid Cancer Rates by Sex

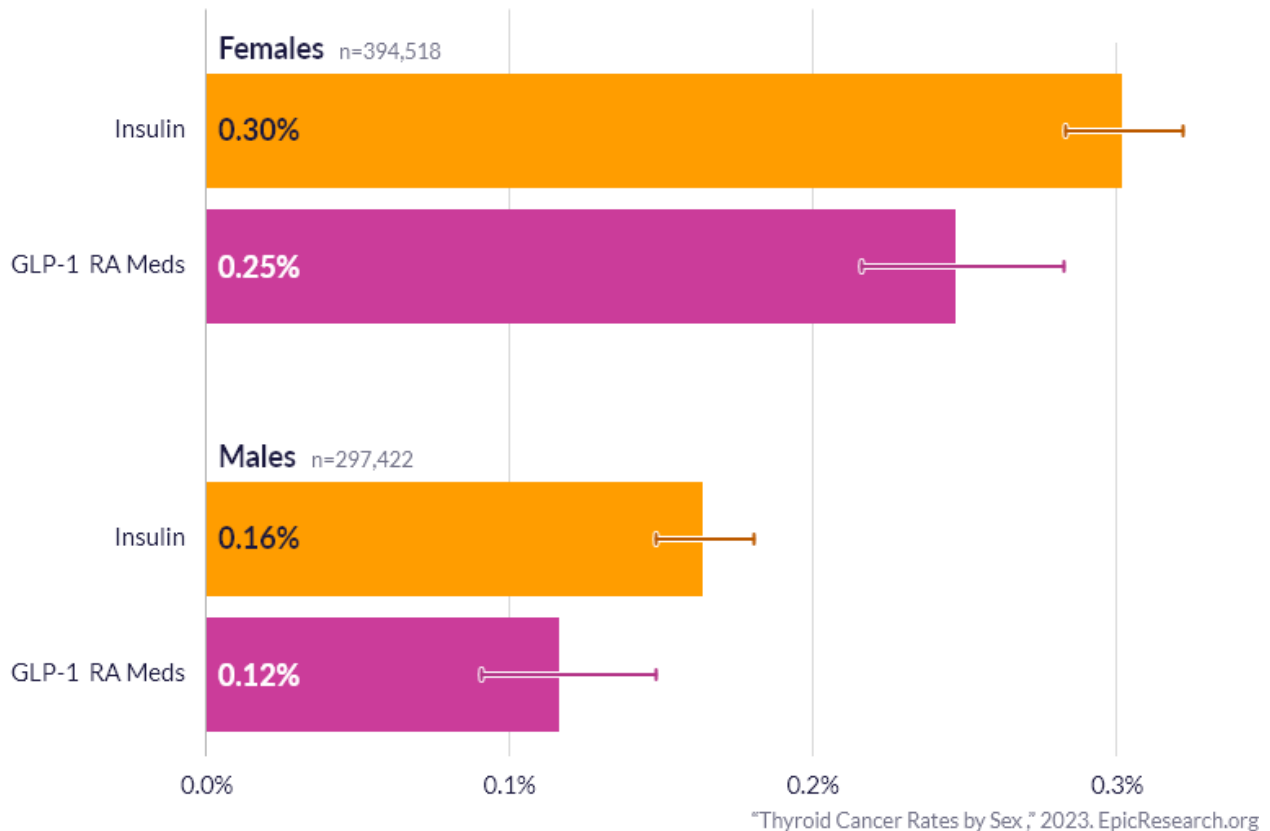


Figure 3. Rate of thyroid cancer in type 2 diabetic patients prescribed GLP-1s or insulin by patient sex.

These data come from Cosmos, a HIPAA-defined Limited Data Set of more than 214 million patients from 218 Epic organizations including 1,235 hospitals and more than 26,800 clinics, serving patients in all 50 states and Lebanon. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

## References

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2. National Library of Medicine. Semaglutide Injection. *MedlinePlus*. [Semaglutide Injection: MedlinePlus Drug Information](#). Accessed July 25, 2023.
3. Benzin J, Gouverneur A, Mathieu C, et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. *Diabetes Care*. 1 February 2023; 46 (2): 384–390. <https://doi.org/10.2337/dc22-1148>
4. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794–798. doi:10.1056/NEJMs1606602.
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## Data Definitions

| Term   | Definition  |
|--|---|
| <b>Diabetes (index event)</b>                | <p>The first encounter or billing diagnosis associated with the following codes:<br/>           SNOMED: 44054006<br/>           ICD-10-CM: E11*</p> <p>The patient must also not have a history of <b>thyroid cancer</b> or onset within the first 90 days. Additionally, the index date must start after 1/1/2003 and be preceded by at least one encounter in the last two years.</p> <p>The index event will end on the fifth year following their first diabetes diagnosis or the date of their last encounter, whichever comes first.</p> <p>Patients must contribute data for at least two years of the study and have three or more encounters during their follow-up period.</p>                      |
| <b>Thyroid cancer</b>                        | <p>The first diagnosis within the first five years following the <b>diabetes index event</b> associated with the following codes:<br/>           SNOMED: 363478007 or 92767001<br/>           ICD-10-CM: C73* or D09.3</p>  |
| <b>Initial BMI</b>                           | <p>The most recent BMI measurement within the 12 months prior to or 1 month following index event</p> <ul style="list-style-type: none"> <li>• Not Obese: BMI &lt;30</li> <li>• Class 1 Obesity: BMI [30,35]</li> <li>• Class 2 Obesity: BMI [35,40]</li> <li>• Class 3 Obesity: BMI &gt; 40</li> </ul>   |
| <b>Initial HbA1C</b>                         | <p>HbA1C was taken from the numeric lab results of labs related to the following LOINC codes: 17855-8, 17856-6, 41995-2, 4548-4, 4549-2, or 55454-3</p> <p>Those numeric values were then partitioned into the following groups:</p> <ul style="list-style-type: none"> <li>• &lt;5.7</li> <li>• [5.7, 6.4)</li> <li>• [6.4, 8.5)</li> <li>• 8.5+</li> </ul>  |
| <b>GLP-1 RAs</b>                             | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLY,INCRETIN MIMETIC(GLP-1 RECEPT.AGONIST)</li> <li>• ANTIHYPERGLY,INSULIN,LONG ACT-GLP-1 RECEPT.AGONIST</li> </ul>  |
| <b>Liraglutides</b>                          | <p>A <b>GLP-1 RA</b> drug with a simple generic name like “liraglutide” or “insulin degludec/liraglutide”</p>   |
| <b>Semaglutides</b>                          | <p>A <b>GLP-1 RA drug</b> with a simple generic name like “semaglutide”</p>   |
| <b>Dulaglutides</b>                          | <p>A <b>GLP-1 RA drug</b> with a simple generic name like “dulaglutide”</p>   |
| <b>Insulins</b>                              | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• INSULINS (Must have a route of intravenous, injection, or subcutaneous)</li> <li>• ANTIHYPERGLY,INSULIN,LONG ACT-GLP-1 RECEPT.AGONIST</li> </ul>  |
| <b>Cox proportional hazards model events</b> | <p>This model was constructed with the following entry criteria:</p> <ul style="list-style-type: none"> <li>• First diagnosis of type 2 diabetes diagnosis</li> <li>• At least two face-to-face visits in the three years prior</li> <li>• No history of <b>thyroid cancer</b></li> </ul> <p>Censorship was acknowledged at the first of either:</p> <ul style="list-style-type: none"> <li>• Five years following type 2 diabetes diagnosis</li> <li>• Date of last known face-to-face visit</li> </ul> <p>The following covariates were considered:</p> <ul style="list-style-type: none"> <li>• History or onset of <b>hypothyroidism</b></li> <li>• History or onset of <b>hyperthyroidism</b></li> </ul> |

|                           |   |
|---------------------------|---|
|                           | <ul style="list-style-type: none"> <li>• <b>Initial BMI</b></li> <li>• <b>Initial HbA1c</b></li> <li>• Patient Sex</li> <li>• Exposure to <b>Insulins</b></li> <li>• Exposure to <b>Biguanides</b></li> <li>• Exposure to <b>SGLT2is</b></li> <li>• Exposure to <b>Semaglutides</b></li> <li>• Exposure to <b>Liraglutides</b></li> <li>• Exposure to <b>Dulaglutides</b></li> <li>• Exposure to other <b>GLP-1 RAs</b></li> <li>• Exposure to <b>Sulfonylureas</b></li> <li>• Exposure to <b>Meglitinides</b></li> <li>• Exposure to <b>DPP-4is</b></li> <li>• Exposure to <b>Thiazolidinedione</b></li> </ul> <p><i>Other demographic factors, such as race, ethnicity, or SVI, were considered but ultimately excluded after separate model iterations showed no significant effect.</i></p> |
| <b>DPP-4is</b>            | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC, DPP-4 INHIBITORS</li> <li>• ANTIHYPERGLYCEMIC, DPP-4 INHIBITOR-BIGUANIDE COMBS.</li> <li>• ANTIHYPERGLY-SGLY-2 INHIB,DPP-4 INHIB,BIGUANIDE CB</li> <li>• ANTIHYPERGLYCEMIC, SGLT-2 AND DPP-4 INHIBITOR COMB</li> </ul>   |
| <b>Biguanides</b>         | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC, BIGUANIDE TYPE</li> <li>• ANTIHYPERGLYCEMIC, BIGUANIDE DIETARY SUPPL. COMB.</li> <li>• ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE AND BIGUANIDE</li> <li>• ANTIHYPERGLYCEMIC, DPP-4 INHIBITOR-BIGUANIDE COMBS.</li> <li>• ANTIHYPERGLY-SGLT-2 INHIB,DPP-4 INHIB,BIGUANIDE CB</li> <li>• ANTIHYPERGLYCEMIC,INSULIN-RELEASE STIM.-BIGUANIDE</li> </ul>   |
| <b>SGLT2is</b>            | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC-SOD/GLUC CONTRANSPORT2(SGLT2) INH</li> <li>• ANTIHYPERGLYCEMIC-SGLT2 INHIBITOR-BIGUANIDE COMBS.</li> <li>• ANTIHYPERGLY-SGLT-2 INHIB,DPP-4 INHIB,BIGUANIDE CB</li> <li>• ANTIHYPERGLYCEMIC, SGLT-2 AND DPP-4 INHIBITOR COMB</li> </ul>  |
| <b>Sulfonylureas</b>      | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE (Not a nateglinide or repaglinide)</li> <li>• ANTIHYPERGLYCEMIC,THIAZILIDINEDIONE-SULFONYLUREA</li> <li>• ANTIHYPERGLYCEMIC,INSULIN-RELEASE STIM.-BIGUANIDE (Not repaglinide/metformin HCl)</li> </ul>  |
| <b>Meglitinides</b>       | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE (Must be a nateglinide or repaglinide)</li> <li>• ANTIHYPERGLYCEMIC,INSULIN-RELEASE STIM.-BIGUANIDE (Must be repaglinide/metformin HCl)</li> </ul>  |
| <b>Thiazolidinediones</b> | <p>A drug with the pharmaceutical class of one of:</p> <ul style="list-style-type: none"> <li>• ANTIHYPERGLYCEMIC,THIAZOLIDINEDIONE(PPARG AGONIST)</li> <li>• ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE AND BIGUANIDE</li> <li>• ANTIHYPERGLYCEMIC,THIAZILIDINEDIONE-SULFONYLUREA</li> </ul>   |

**Table 1: Thyroid Cancer Rates for Patients Prescribed Diabetic Medications**

| Medication  | Count | Pop Size | Rate  | Upper CI | Lower CI |
|-------------|-------|----------|-------|----------|----------|
| Insulin     | 1,328 | 551,119  | 0.24% | 0.01%    | 0.01%    |
| Liraglutide | 126   | 49,266   | 0.26% | 0.05%    | 0.04%    |
| Dulaglutide | 81    | 45,153   | 0.18% | 0.04%    | 0.04%    |
| Semaglutide | 25    | 24,221   | 0.10% | 0.05%    | 0.03%    |

**Table 2: Thyroid Cancer Rates for Patients Prescribed Diabetic Medications by BMI**

| Group               | Count | Pop Size | Rate  | Upper CI | Lower CI |
|---------------------|-------|----------|-------|----------|----------|
| Ins Class 3 Obesity | 279   | 100,145  | 0.28% | 0.03%    | 0.03%    |
| GLP Class 3 Obesity | 86    | 39,481   | 0.22% | 0.05%    | 0.04%    |
| Ins Class 2 Obesity | 244   | 89,301   | 0.27% | 0.04%    | 0.03%    |
| GLP Class 2 Obesity | 72    | 29,068   | 0.25% | 0.06%    | 0.05%    |
| Ins Class 1 Obesity | 308   | 120,395  | 0.26% | 0.03%    | 0.03%    |
| GLP Class 1 Obesity | 48    | 29,689   | 0.16% | 0.05%    | 0.04%    |
| Ins Not Obese       | 286   | 138,343  | 0.21% | 0.03%    | 0.02%    |
| GLP Not Obese       | 25    | 18,736   | 0.13% | 0.06%    | 0.04%    |

**Table 3: Thyroid Cancer Rates for Patients Prescribed Diabetic Medications by Sex**

| Group      | Count | Pop Size | Rate  | Upper CI | Lower CI |
|------------|-------|----------|-------|----------|----------|
| Ins Female | 930   | 307,971  | 0.30% | 0.02%    | 0.02%    |
| GLP Female | 214   | 86,547   | 0.25% | 0.04%    | 0.03%    |
| Ins Male   | 398   | 243,148  | 0.16% | 0.02%    | 0.02%    |
| GLP Male   | 63    | 54,274   | 0.12% | 0.03%    | 0.03%    |

**Table 4: Sensitivity Analysis of Thyroid Cancer Rates**

|                     | Coefficient | Lower CI  | Upper CI |
|---------------------|-------------|-----------|----------|
| Has Hypothyroidism  | 0.932092    | 0.840879  | 1.023305 |
| Has Hyperthyroidism | 0.75466     | 0.589034  | 0.920285 |
| Is Female           | 0.44925     | 0.347104  | 0.542746 |
| Used Insulin        | 0.410777    | 0.32001   | 0.501544 |
| Used Liraglutide    | 0.317125    | 0.166778  | 0.467473 |
| Used Dulaglutide    | 0.259489    | 0.0868    | 0.432179 |
| Used Semaglutide    | 0.257509    | 0.006877  | 0.508142 |
| Used Sulfonylurea   | 0.211109    | 0.119076  | 0.303143 |
| Used Dpp4i          | 0.201623    | 0.102323  | 0.300924 |
| Used Biguanide      | 0.159125    | 0.057443  | 0.260807 |
| Used Meglitinide    | 0.130337    | -0.215563 | 0.476237 |

|                                 |           |           |           |
|---------------------------------|-----------|-----------|-----------|
| <b>Class 2 Obesity</b>          | 0.118623  | -0.023489 | 0.260735  |
| <b>Class 3 Obesity</b>          | 0.06067   | -0.08075  | 0.202091  |
| <b>Class 1 Obesity</b>          | 0.014665  | -0.12353  | 0.15316   |
| <b>Ages 36-50</b>               | 0.010295  | -0.097178 | -0.117767 |
| <b>Used SGLT2i</b>              | -0.010255 | -0.134633 | 0.114124  |
| <b>Initial HbA1c: 5.7 - 6.5</b> | -0.036476 | -0.355909 | 0.282957  |
| <b>Initial HbA1c: 8.5+</b>      | -0.040702 | -0.35655  | 0.275146  |
| <b>Initial HbA1c: 6.5 - 8.5</b> | -0.086183 | -0.389005 | 0.216638  |
| <b>Ages 66-75</b>               | -0.122923 | -0.237142 | -0.008703 |
| <b>Used Thiazolidinedione</b>   | -0.253257 | -0.426126 | -0.080388 |
| <b>Ages 18-35</b>               | -0.397689 | -0.642814 | -0.152563 |
| <b>Ages 76-85</b>               | -0.706967 | -0.995137 | -0.418796 |