OHDSI: Evaluating of Iodine-131 exposure effect on the occurrence of secondary cancer in survivors of thyroid cancer.

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# **List** **of abbreviations**

|  |  |
| --- | --- |
| OHDSI | Observational Health Data Sciences and Informatics |
| I-131 | Iodine-131 |
| PS | Propensity Score |

# **Abstract**

In this study, the relative risk of I-131 therapy associated with the incidence of 2nd cancer will be estimated by conducting population-level-estimate study. We will compare the hazards of the outcome during several time-at-risk periods by applying a Cox proportional hazards model after PS adjustment.

# **Rationale and Background**

There have been studies about the correlation between medical radiation and the incidence of secondary cancer, but it is still not reported clearly. We are interested in I-131 therapy which is one of the treatments for removal of remnant thyroid using medical radiation exposure. (1) From the previous study, which conducted meta-analysis with results from systematic review of literature using two multi center studies(each from Europe and North America), the relative risk of second cancer in thyroid cancer survivors treated with radioactive Iodine treatment has been slightly increased than non-treatment survivors. The incidence of leukemia was significantly increased, but the other cancers which related to prior radioactive Iodine treatment were not observed. There have been methodological limitations such as a lack of important factors from the patient, a limited extension of study, and statistical heterogeneity of pooled analyses. The real-world evidence of cancer risk in relation with I-131 therapy could be insufficient for these limitations, and it can be resolved using observational health data.

In this study, we will conduct population-level-estimate to generate real-word evidence about the effect of I-131 therapy with the incidence of secondary cancer using observational healthcare databases. Furthermore, we hope to collaborate with OHDSI research network to investigate the effects of “real world” factors on observational studies’ findings.

# **Study Objectives**

# **Primary Objectives**

* To validate the effect medical radiation exposure from I-131 therapy in thyroid cancer patients on the incidence of secondary cancer

# **Research methods**

# **Study Design**

This study will be a retrospective, observational cohort study. We define ‘retrospective’ to mean the study will use data already collected prior to the start of the study. We define ‘observational’ to mean there is no intervention process in this study. We define ‘cohort study’ to mean that compare of two cohorts, a treatment and comparator cohort, and assess for the occurrence of the outcomes of interest from each cohort.

# **Study population**

# **Target cohort(s)**

Initial Event cohort) People having any of the following:

* a procedure of I-131 therapy
  + - * with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to **latest event per person**

Inclusion Rules) Inclusion Criteria #1: Diagnosed thyroid cancer at least once

* + - * at least 1 of occurrences of a condition occurrence of thyroid cancer where event start between all days Before and 0 days After index start date

Inclusion Rules) Inclusion Criteria #2: Had thyroidectomy at least once

* + - * at least 1 of occurrences of a procedure of thyroidectomy where event start between 1095 days Before and 0 days After index start date

Inclusion Rules) Inclusion Criteria #3: No other cancer diagnosis

* + - * exactly 0 of occurrences of a procedure of Any Condition  
          🢭 Condition Source Concept is Overall cancer without Thyroid cancer   
        where event start between All days Before and 0 days Before index start date

Limit qualifying cohort to **earliest event per person**

# **Comparator cohort(s)**

Initial Event cohort) People having any of the following:

* + - * a procedure of thyroidectomy
      * with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to **earliest** **event per person**

Inclusion Rules) Inclusion Criteria #1: Diagnosed thyroid cancer at least once

* + - * at least 1 of occurrences of a condition occurrence of thyroid cancer where event start between all days Before and 30 days After index start date

Inclusion Rules) Inclusion Criteria #2: Excepted for I-131 therapy

* + - * exactly 0 of occurrences of a procedure of I-131 therapy where event start between 0 days Before and All days After index start date

Inclusion Rules) Inclusion Criteria #3: No prior other cancer diagnosis

* + - * exactly 0 of occurrences of a procedure of Any Condition  
         🢭 Condition Source Concept is Overall cancer without Thyroid cancer where event start between All days Before and 30 days After index start date

Limit qualifying cohort to **earliest event per person**

Finally, we removed the subject from both cohorts and subjects that had the outcome prior to the risk window start.

# **Exposures**

# **I-131 therapy Concept Sets**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4036252 | Iodine 131 therapy | Procedure | SNOMED | NO | NO | NO |

# **Thyroidectomy Concept Sets**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4030039 | Total thyroidectomy with cervical lymph node dissection | Procedure | SNOMED | NO | NO | NO |
| 4030107 | Thyroidectomy | Procedure | SNOMED | NO | NO | NO |
| 4073199 | Total thyroidectomy | Procedure | SNOMED | NO | NO | NO |
| 4082277 | Partial  Substernal  thyroidectomy | Procedure | SNOMED | NO | NO | NO |
| 4122303 | Total substernal thyroidectomy | Procedure | SNOMED | NO | NO | NO |
| 4149106 | Subtotal thyroidectomy | Procedure | SNOMED | NO | NO | NO |
| 4200221 | Substernal thyroidectomy | Procedure | SNOMED | NO | NO | NO |

# **Thyroid cancer Concept Sets**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept ID** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 4315809 | Secondary malignant neoplasm of lymph nodes of neck from thyroid | Condition | SNOMED | NO | YES | NO |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | NO | YES | NO |
| 4201622 | Metastasis from malignant tumor of thyroid | Condition | SNOMED | NO | YES | NO |

# **Outcomes**

# **Primary outcome: Second cancers after thyroid cancer**

Initial Event cohort) People having any of the following:

* + - * A condition occurrence of Any Condition
        + Condition Source Concept is Overall Cancer without thyroid cancer

With Continuous observation of at least 0 days prior and 0 days after event index date, and limit initial event to: **all events per person**

Limit qualifying cohort to **all events per person.**

Date Offset Exit Criteria)

* + - * This cohort definition end date will be the index event’s start date plus 1 days

# **Overall cancer without thyroid cancer concept set**

The excel file of this concept sets uploaded in the document folder.

# **Negative Controls**

Negative controls are concepts known to be neither caused by the target nor comparator exposure, so that the true relative risk can be assumed between the two cohorts is 1. The table describes the final list of 68 negative control outcomes which manual review was undergone.

|  |  |
| --- | --- |
| **Concept Id** | **Concept Name** |
| 134438 | Contact dermatitis |
| 374375 | Impacted cerumen |
| 437264 | Tobacco dependence syndrome |
| 373478 | Presbyopia |
| 36713918 | Somatic dysfunction of lumbar region |
| 140641 | Verruca vulgaris |
| 4115367 | Wrist joint pain |
| 194083 | Vaginitis and vulvovaginitis |
| 444132 | Injury of knee |
| 81151 | Sprain of ankle |
| 440329 | Herpes zoster without complication |
| 73560 | Calcaneal spur |
| 433577 | Hammer toe |
| 81378 | Chondromalacia of patella |
| 72748 | Strain of rotator cuff capsule |
| 75911 | Acquired hallux valgus |
| 441788 | Human papilloma virus infection |
| 376707 | Acute conjunctivitis |
| 77965 | Acquired trigger finger |
| 137951 | Acquired keratoderma |
| 73241 | Anal and rectal polyp |
| 4209423 | Nicotine dependence |
| 76786 | Derangement of knee |
| 78619 | Contusion of knee |
| 196168 | Irregular periods |
| 4092896 | Feces contents abnormal |
| 380706 | Regular astigmatism |
| 195873 | Leukorrhea |
| 4344500 | Impingement syndrome of shoulder region |
| 4170770 | Epidermoid cyst |
| 4103703 | Melena |
| 4088290 | Absence of breast |
| 40480893 | Nonspecific tuberculin test reaction |
| 4083487 | Macular drusen |
| 201606 | Crohn's disease |
| 140842 | Changes in skin texture |
| 4201390 | Colostomy present |
| 439790 | Psychalgia |
| 4092879 | Absent kidney |
| 4012570 | High risk sexual behavior |
| 438130 | Opioid abuse |
| 434327 | Cannabis abuse |
| 199192 | Abrasion and/or friction burn of trunk without infection |
| 44783954 | Acid reflux |
| 46269889 | Complication due to Crohn's disease |
| 4166231 | Genetic predisposition |
| 4201717 | Ileostomy present |
| 4091513 | Passing flatus |
| 40481632 | Ganglion cyst |
| 4231770 | Hereditary thrombophilia |
| 259995 | Foreign body in orifice |
| 432303 | Cocaine abuse |
| 46286594 | Problem related to lifestyle |
| 432593 | Kwashiorkor |
| 4202045 | Postviral fatigue syndrome |
| 81634 | Ptotic breast |
| 377572 | Noise effects on inner ear |
| 436409 | Abnormal pupil |
| 4012934 | Homocystinuria |
| 4103640 | Amputated foot |
| 433111 | Effects of hunger |
| 434203 | Late effect of contusion |
| 438329 | Late effect of motor vehicle accident |
| 45757370 | Disproportion of reconstructed breast |
| 133655 | Burn of forearm |
| 443172 | Splinter of face, without major open wound |
| 440193 | Wristdrop |
| 201820 | Diabetes |

# **Covariates**

# **Propensity score covariate**

The covariates to fit the propensity score model will be:

* + - * Demographics
* Gender
* Age Groups (5-year bands)
  + - * Condition
* In prior 30 days
* In prior 365 days

Concepts to exclude in baseline covariates in the propensity score model are the concepts used to composed of target/comparator cohorts and its descendant concepts.

# **Data Analysis Plan**

# **Calculation of time-at risk**

* + - * 365 days from Cohort start date ~ 1825days from Cohort start date
      * 365 days from Cohort start date ~ 3650days from Cohort start date
      * 365 days from Cohort start date ~ 99999days from Cohort start date

# **Model Specification**

# **Statistical model**

Propensity Score Adjustment will be:

* + - * 1:1 PS matching (default)
      * The caliper for matching is 0.2 (default)
      * The standardized logit scale is defined on caliper scale (default)

Outcome Model Settings will be:

* + - * Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts

# **Pooling effect estimates across databases**

We will do meta-analysis to calculate summary hazard ratio for pooling effect estimates across databases.

# **Analyses to perform**

The following comparative analysis will be performed:

* + - * One comparison: Thyroidectomy with I-131 therapy cohort (Target) vs Only thyroidectomy cohort (Comparator)
      * One outcome: any cancers excluding thyroid cancer (second cancers after thyroid cancer)
      * Three time-at-risk
      * One model: Cox regression after 1:1 PS matching

# **Output**

|  |  |
| --- | --- |
| Output | Description |
| Propensity score distribution Plot | The propensity score distribution for both cohorts after matching will be provided. |
| Propensity model | The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients. |
| Covariate Balance Scatter Plot | Covariate Balance Scatter Plot will show the absolute standardized difference of mean before and after propensity score matching. |
| Attrition diagram | Attrition diagram will show the counts to meet the various inclusion and exclusion criteria, and loss due to matching. |
| Kaplan-Meier plot | Kaplan-Meier plot will display the survival over time in both cohorts. |
| Population characteristics table | A table which lists some select population characteristics before and after matching will be created. |
| Outcome models | The summarized report will be provided from outcome models. It will report the hazards ration, associated 95% confidence interval, the number of persons, amount of time-at-risk, and number outcome in both cohorts. |

# **Evidence Evaluation**

The following inspection for evaluating the evidence have performed:

* + - * Propensity score distribution
      * Covariate Balance before and after matching
      * Negative control systematic error
      * The true hazard ratio of Negative control outcome is equal to 1, because of the context of negative control outcome.

# **Strengths and Limitations of the Research Methods**

# **Strength**

* + - * Cohort study allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
      * PS matching and outcome model allow balancing on many baseline potential confounders.
      * Use of negative control outcomes allow for evaluating the study design in terms of residual bias.

# **Limitations**

* + - * Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders

# **Protection of Human Subjects**

In this study, we will use only de-identified data from CDM. The results of study will be aggregated and will not identify individual subjects.

# **Plans for Disseminating and Communicating Study Results**

# **References**

1) Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid : official journal of the American Thyroid Association. 2009;19(5):451-7. Epub 2009/03/14.