**Triggers of Thyroid Cancer Diagnosis: a Systematic Review and Meta-Analysis Protocol**

**Research question**

The proportion of incidental thyroid cancer diagnosis is high and the majority are found through the use of imaging studies.

**Searches**

Based on our research question, an experienced librarian will design and conduct a search strategy in the following databases: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, and Scopus. Databases will be searched from inception to September, 2018. The language will be restricted to English, Spanish and Portuguese. This search strategy will be discussed with evidence-based medicine experts for thoroughness. Discussions and modifications will continue until agreement is reached among the librarian, experts and authors.

**Types of study to be included**

We will include observational studies, including case-control, cohorts, and cross-sectional. We will exclude letters, editorials, consensus statements, guidelines and review articles.

**Condition or domain being studied**

The incidence of thyroid cancer has increased worldwide*.* In the United States, it increased from a 4.9 to 14.2 per 100,000 person-years over the last two decades, while in South Korea, thyroid cancer increased by more than seven fold, from 6.3 per 100,000 person year in 1999 to 47.5 per 100,000 population in 2009. This difference in thyroid cancer trends reflects underlying different mechanisms of thyroid cancer detection. In South Korea, 90% of the new thyroid cancers were detected by screening with neck ultrasound. In other countries, however, the mechanism of detection of thyroid cancer is unclear. Understanding the method of thyroid cancer detection has potential implications on interpreting incidence rates, the diagnosis and management of thyroid cancer. The aim of this study is to summarize the available evidence to assess the frequency of incidental thyroid cancer and examine the triggers that lead to diagnosis with comparison across multiple cohorts.

**Participants/population:**

Inclusion criteria:

* Any patient confirmed with thyroid cancer by histology.

Exclusion:

* Patients enrolled in screening program.
* Patients expose to radiation like Chernobyl.

**Intervention**:

Inclusion:

* Studies reporting palpable nodule or ganglion and at least one incidental pathways of thyroid cancer detection (incidental diagnosis by imaging, and incidental histological findings).

Symptomatic or palpable nodule: When a thyroid nodule harboring thyroid cancer is found during a physical exam (thyroid palpation) or imaging study in a symptomatic patient.

Incidental imaging: When a thyroid nodule harboring thyroid cancer is found during an imaging test requested for reasons unrelated to a thyroid disorder or symptom (Ultrasound, TC, PET)

Unrelated tests: When a thyroid nodule harboring thyroid cancer is found during the work up of non-nodular thyroid disease (e.g., patient with hyperthyroidism who has a thyroid ultrasound positive for a nodule).

Incidental histological:When thyroid cancer was found incidentally in the histological examination of the thyroid gland removed for a benign condition (e.g., goiter, Graves’ disease).

**Comparator**: Not applicable.

**Outcomes:**

* Frequency of thyroid cancer cases attributed to each trigger of diagnosis.

**Data extraction**

Reviewers, working independently and in duplicate, will assess each study title and abstract for eligibility. At commencement, we will calibrate our abstract screening eligibility criteria with 20 articles until agreement and understanding among reviewers is reached. These articles will be selected by the principal investigators. If necessary, inclusion criteria will be modified for clarity. Further, reviewers working independently, and in duplicate will consider all available full text reports for eligibility. We will pilot our full-text screening phase with 10 articles until understanding and agreement is reached. Subsequently, disagreements will be harmonized by a third investigator. Agreement for full-text screening will be measured using kappa test. For this phase, studies need to meet the full eligibility criteria to be included.

**Risk of bias**

Study quality will be assessed by two independent reviewers based on the nine-star Newcastle Ottawa Scale (NOS) for cohorts and cross-sectional studies.

**Strategy for data synthesis**

We will calculate standardized mean difference (SMD) or relative risk (RR) for each outcome of interest and pool results using random-effect models. All statistical analyses will be performed using Stata v15.0 (StataCorp, College Station, TX). For continuous outcomes reported in different trials with different scales but reflecting the same construct (e.g., quality of life), we calculated their SMD. We also pooled scales, domains, or results that were reported in more than one trial (e.g., physical function quality of life from the SF-36 questionnaire). In general, SMDs of 0.2, 0.5, and 0.8 are considered small, medium, and large treatment effects, respectively. Inconsistency for each outcome, not attributable to chance, was assessed visually using forest plots and estimated using the percentage of variance in a meta-analysis that is attributable to study heterogeneity (I2) statistic. I2 < 25% reflects low inconsistency; I2 > 75% reflects high inconsistency.

**Analysis of subgroups**

Overall incidental, incidental imaging, and incidental histological by sex, tumor size, and age.