**Triggers of Thyroid Cancer Diagnosis: A Systematic Review and Meta-analysis.**

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**Abstract**

**Background:**  Understanding the method of thyroid cancer detection has potential implications on interpreting incidence rates, the diagnosis and management of thyroid cancer. We conducted a systematic review of studies reporting methods of thyroid cancer detection to estimate the frequency of incidentally found cancers and classify triggers of incidental thyroid cancer diagnosis.

**Methods:** We searched multiple bibliographic databases from inception to September 2018. A pair of reviewers, working independently and in duplicate selected studies for inclusion, extracted data, and evaluated each trial’s risk of bias. Incidental thyroid cancer was defined as cases found during the use of imaging test requested for reasons unrelated to a thyroid nodular disorder, or found incidentally in the histological examination of the thyroid gland removed for a benign condition, while non-incidental thyroid cancer included cases when a thyroid nodule harboring thyroid cancer was found because a clinician or patient noted an abnormality on physical examination possibly related to the thyroid mass, patient presented with neck compression symptoms including dysphagia, dysphonia, and neck-pain.

**Results:** 16 cohorts and 1 cross-sectional study, conducted between 1991 and 2015, with a total of 4,470 patients with thyroid cancer were included: 89% had papillary thyroid cancer and 26% had micropapillary thyroid cancer. The proportion of patients with non-incidental and incidental thyroid cancer was the same: 50% [95% confidence interval (CI): 41-59%]. Subgroup analysis showed that most patients with incidental thyroid cancers had tumor size <10 mm (76%; 95% CI: 56-92%), age >45 (61%; 95% CI: 56-67%), and were detected through imaging (36%; 95% CI: 26-47%), of which ultrasound was the most common modality (31%; 95% CI: 17-48%). The heterogeneity for all the effect sizes was large and significant.

**Conclusions:** About half of thyroid cancers were found incidentally through the use of imaging studies, in particular neck ultrasound. These incidentally found cancers were mostly small papillary thyroid cancer. These results highlight opportunities for interventions aimed at reducing drivers of over-diagnosis.

**Introduction**

The incidence of thyroid cancer has increased worldwide(1, 2)*.* In the United States, for instance, it increased from a 4.9 to 14.2 per 100,000 person-years over the last two decades(3), 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. Outside South Korea, some studies have suggested that the rise of thyroid cancer incidence is driven by the incidental detection of small and asymptomatic thyroid cancer lesions(1, 4–6) by increased use of imaging technologies(7), or detection of thyroid cancer lesions found in the course of histologic review of thyroid glands removed for apparently benign conditions(8, 9). Others have shown that the increased in incidence is also caused by larger, likely palpable and symptomatic, advanced stage thyroid cancer(10).

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.

**Methods**

A protocol was developed to perform this study and is available online(11). Additionally, preliminary results of this study were presented previously as abstract in the 89th Annual Meeting of the American Thyroid Association(12). Overall, this manuscript is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines(13).

**Eligibility criteria and study selection**

We included original studies with patients older than 18 years with thyroid cancer confirmed by histology and reporting non-incidental thyroid cancer and at least one incidental pathways of thyroid cancer detection. Only manuscripts written in English, Spanish, or Portuguese were included. We excluded studies in which the aim was only to assess the impact of thyroid cancer screening (e.g. thyroid cancer screening programs in South Korea).

**Data sources and searches**

We applied a searched strategy developed in collaboration with an experienced librarian to find potentially eligible studies in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, and Scopus from each database’s inception until September, 2018. Controlled vocabulary supplemented with keywords was used to search for studies of triggers of diagnosis in patients with thyroid cancer. Conference abstracts, literature reviews, case reports and editorials were excluded. Reference lists of selected studies were searched to identify additional publications.

**Study selection**

Search results were uploaded into a systematic review software program (DistillerSR, Ottawa, ON, Canada)(14). Reviewers (E.L-N., P.S-P.; O.J.P., T.L.; B.A., T.R.), working independently and in duplicate, screened abstracts and titles and full-text screening for eligibility using standardized instructions. Before initiating the abstract screening phase, a pilot was performed with 20 articles to assess the clarity of the eligibility criteria among reviewers. It helped us to improve our abstract screening instructions. For abstract screening, articles included by at least one reviewer were considered for full-text screening. Similarly, a pilot was performed with 10 articles before starting the full-text screening to harmonize the research question. At this stage, only articles included by both reviewers were deemed eligible for this systematic review and in case of disagreements, these were resolved by consensus between the 6 reviewers previously mentioned. Full text screening agreement using Cohen’s kappa was substantial (k=0.76).

**Homogenization of incidental and non-incidental definitions**

Given the variations in the definitions of thyroid cancer diagnosis triggers in some articles, two extractors (E. L-N., P. S-P.) homogenized and discussed the debatable cases to achieve consensus with the definition we proposed. Thus, some patients of the “non-incidental” group were grouped as “incidental imaging”. For instance, patients with thyroid nodules detected by neck ultrasound because of the presence of altered laboratory test results, categorized previously in the non-incidental group, were categorized as incidental imaging. It was based on a published framework(9)and recommendations for the use of ultrasound in guidelines(15). These changes were made in 6 articles (Appendix Table A3).

**Data collection and management**

For all included articles, one reviewer (E.L-N) extracted studies data into a spreadsheet form and second reviewer (P.S-P) checked randomly 30% of data extracted for accuracy and completeness. Variables extracted were: general characteristics of the studies (author, date of publication, country, study design, data collection period), setting (single center, multicenter and population based-study), participant characteristics (age, sex, mean tumor size, thyroid cancer histological types), and pathway of thyroid cancer diagnosis into two categories: incidental and non-incidental diagnosis. Incidental pathway including: i) cases when a thyroid nodule harboring thyroid cancer was found during the use of imaging test requested for reasons unrelated to a thyroid nodular disorder or symptoms, or ii) when thyroid cancer was found incidentally in the histological examination of the thyroid gland removed for a benign condition (e.g., goiter, Graves’ disease). Non-incidental triggers included cases when a thyroid nodule harboring thyroid cancer was found because a clinician or patient noted an abnormality on physical examination possibly related to the thyroid mass, or patient presented with neck compression symptoms including dysphagia, dysphonia, and neck-pain. Additionally, we extracted the type of imaging modality driving the detection of incidental thyroid cancer (Figure 2).

**Risk of bias in individual studies**

Study quality was assessed by two independent reviewers based on the nine-star Newcastle Ottawa Scale (NOS) for cohort-studies(16),(17) and an adapted form of the NOS for cross-sectional studies(18), using three predefined domains, namely: selection of participants (population representativeness), comparability (adjustment for confounders) and ascertainment of outcomes of interests. For both tools, studies that received a score of nine to eight were judged to be at low risk of bias; studies that scored five or seven were considered at moderate risk, and those that scored four or less were considered at high risk of bias. (Table A2).

**Statistical analyses**

By using the number of people with an incidental diagnosis and the total number of people in each study, we determined the overall proportion estimates and their confidence intervals (95% CI). Every confidence interval was calculated by using the exact method for binomial proportions(19),(20) and the overall proportion was estimated with the Freeman-Turkey double arcsine transformation to stabilize the variances(21). We chose the Freeman-Turkey double arcsine as the main analyses method over others, because it depicts the weights for individual studies and it seems to perform similar to other methods when the proportions are not consistently close to 0 or 1(22). The random-effects model was performed with the Dersimonian and Laird method (23). Since we estimated that we could encounter studies with proportions close to 0 or 1, a sensitivity analysis was conducted by using generalized linear mixed models (22). In such scenarios, this meta-analysis model seems to perform better than other (e.g. less biased estimates)(22).

Heterogeneity across studies was assessed with the I2 statistic and visually(24). We considered that I2 < 25% reflected low inconsistency and I2 > 75% reflected high inconsistency. In terms of subgroups analyses, predefined comparisons based on age, sex, and tumor size were planned: > 45 years vs. ≤ 45 years, female vs. male, and tumor size > 10mm vs. tumor size ≤ 10mm. Other post-hoc subgroup analyses were additionally executed and they include studies performed in the United States vs. studies performed outside the United States and population-based studies vs. non-population-based studies. The statistical program R Studio was employed to perform all types of analyses and forest plots. Coding scripts, excel files with the extracted data, and figures are available online(11).

**Results**

Figure 1 describes the results of our search. We included 17 studies, conducted between 1991 and 2015, enrolling 4470 patients with thyroid cancer. Their age ranged from 18 to 89 years old, and most were female (76%) with papillary thyroid cancer (89%). Around 24% of all patients with thyroid cancer had papillary microcarcinoma. Of 17 studies, 1 was cross-sectional(25) and 16 were cohort studies(8–10, 26–38), mostly performed in the United States (8, 9, 26, 27, 36–38) and Italy(28–32) (Table A1). Overall, in cohort studies, risk of bias seems to be low (11) to moderate (5), and low in the cross-sectional study (Table A2).

The overall proportion of people whose thyroid cancer was found incidentally is 50% [95% confidence interval (CI): 41-59%, heterogeneity (I2): 97%] (Figure 4). When the total incidental diagnosis data was further analyzed by country, the lowest proportion of incidental thyroid cancer was seen in Canada with 17% (95% CI: 11-23%) and the highest in Argentina, Spain and Italy [66% (95% CI: 58-73%), 65% (95% CI: 59-71%, and 64% (95% CI: 44-82%) respectively] (Figure 3).

**Incidental thyroid cancer diagnosis by imaging techniques and histological examination**

The proportion of people whose diagnosis of thyroid cancer was triggered by imaging methods was 36% (95% CI: 26-47%, I2: 98%) and that of triggered by histological examination was 23% (95% CI: 15-32%, I2: 97%). The specific imaging modalities for triggers of incidental thyroid cancer was 31% (95% CI: 17-48%, I2: 99%) for ultrasound, 6% (95% CI: 4-9%, I2: 83%) for computed tomography (CT), 3% (95% CI: 1-4%, I2: 72%) for positron emission tomography (PET), and 2% (95% CI: 1-4%, I2: 77%) for magnetic resonance imaging (MRI) (Figure 4).

**Incidental thyroid cancer diagnosis by subgroups**

Overall, incidental thyroid cancer subgroup analysis by tumor size showed that tumor ≤ 10mm was incidentally found in 76% (95% CI: 56-92%, I2: 97%), while tumors > 10mm were 31% (95% CI: 15-50%, I2: 98%), with a *p* value for interaction test of <0.01. Furthermore, the frequency of incidental thyroid cancer was similar in women and men, 52% (95% CI: 39-64%, I2: 96%) vs. 55% (95% CI: 43-66%, I2: 84%), respectively, with a *p* value for subgroup interaction of 0.74, and different in age ≤ 45 years 41% (95% CI: 34-48%) vs. > 45 years 61% (95% CI: 56-67%), *p* value for interaction test of <0.01. Similar findings were found when comparing studies performed in the United States (42%; 95%CI: 32-53%, I2: 96%) vs. studies performed outside the United States (56%; 95%CI: 42-69%, I2: 98%) with a p value for subgroup interaction of 0.12, and population-based studies 53% (95% CI: 38-68%, I2: 94%) vs. non-population-based studies (50%; 95%CI: 39-60%, I2: 97%) with a *p* value of 0.72 for interaction (Figure 4 )

**Incidental imaging by subgroups**

Incidental imaging subgroup analysis by tumor size showed that tumor ≤ 10mm was incidentally found in 50% (95% CI: 35-65%, I2: 93%), while tumors > 10mm were 29% (95% CI: 10-52%, I2: 98%), with a *p* value for interaction test of 0.14. Furthermore, the frequency of incidental imaging was slightly higher in men than women, 34% (95% CI: 13-59%, I2: 93%) vs. 21% (95% CI: 02-52%, I2: 99%), respectively, with a *p* value for subgroup interaction of 0.47. Similar findings were found when comparing studies performed in the United States (35%; 95%CI: 27-43%, I2: 93%) vs. studies performed outside the United States (38%; 95%CI: 19-0.60%, I2: 99%) with a p value for subgroup interaction of 0.76, and population-based studies 36% (95% CI: 10-68%, I2: 99%) vs. non-population-based studies (37%; 95%CI: 26-47%, I2: 97%) with a *p* value of 0.95 for interaction (Figure 5).

**Incidental histological by subgroups**

Incidental histological subgroup analysis by tumor size showed that tumor ≤ 10mm was incidentally found in 55% (95% CI: 28-81%, I2: 98%), while tumors > 10mm were 6% (95% CI: 0-27%, I2: 98%), with a *p* value for interaction test of 0.14. Furthermore, the frequency of incidental thyroid cancer was similar in men and women, 35% (95% CI: 14-59%, I2: 95%) vs. 39% (95% CI: 18-63%, I2: 98%), respectively, with a *p* value for subgroup interaction of 0.80, and different in studies performed in the United States (13%; 95%CI: 11-16%, I2: 38%) vs. studies performed outside the United States (29%; 95%CI: 16-43%, I2: 98%) with a p value for subgroup interaction of 0.01. Similar findings were found when comparing and population-based studies 15% (95% CI: 04-31%, I2: 97%) vs. non-population-based studies (26%; 95%CI: 16-38%, I2: 98%) with a *p* value of 0.22 for interaction (Figure 5).

**Indications for incidental diagnosis by ultrasound**

Only 4 studies reported indications for ultrasound imaging. The indications (n=384) were: **family history of thyroid disease and/or presence of altered laboratory test results (n=103), p**alpated nodule or symptoms not associated with nodule harboring thyroid cancer **(n=38), neck ultrasound for salivary glands or lymph node studies (n=32), screening (n=25), carotid power duplex (n=25), Hashimoto’s thyroiditis (n=17), hypothyroidism (n=14), family history of thyroid cancer (n=11), hyperthyroidism (n=11), non-specific neck symptoms (n=10), gynecological exam (n=10), cardiologic exam (n=7), non-specific constitutional symptoms (n=6), history of radiation exposure (n=4), hyperparathyroidism (n=4), goiter (n=3), previous thyroid surgery (no malignancy) (n=2), hypercalcemia (n=2), self-sonography (n=2), other lab abnormalities (n=2), and unknown (n=20) (Table A3).**

**Sensitivity analyses**

The overall estimates of studies with proportions different from 0% or 100%, including those close to these numbers (e.g. 1-2%), were similar in both methods: generalized linear mixed model and Freeman-Turkey double arcsine. Nonetheless, in estimates where one of the studies had a proportion of 0% or 100%, the results were divergent. The Freeman-Turkey double arcsine method in the incidental thyroid cancer subgroup analysis by tumor size showed that for tumor ≤ 10mm the proportion was 76% (95% CI: 56-92%, I2: 97%), while for tumors > 10mm it was 31% (95% CI: 15-50%, I2: 97%). In contrast, by using the generalized linear mixed model, the estimate for the ≤ 10mm group was 83% (95% CI: 52-95%, I2: 98%), whereas for the > 10mm the proportion was 26% (95% CI: 11-50%, I2: 98%) (Appendix).

**Discussion**

**Summary of evidence**

We found that a significant proportion of thyroid cancer (50%) was found incidentally in asymptomatic people. Of this, 36% were found through the use of imaging studies, in particular neck ultrasound. These incidentally found cancers were mostly small papillary thyroid cancer. This finding is consistent with a recent study demonstrating that the use of thyroid ultrasound has increased at a rate of 20% per year from 2002 through 2013 among Medicare patients in the United States, associating this with more thyroid cancer diagnosis(39).

Prior to the advent of neck sonography in the 1980s, thyroid cancer nodules had to reach a large size prior to detection; however current neck ultrasonography technology has revolutionized diagnosis and management of thyroid cancer detecting lesions as small as 2 mm(40). This increased sensitivity coupled with improved reimbursement and access to US has led to increase in use by endocrinologists close to 80%(41). Although this increased use of thyroid ultrasound raises questions about whether or not its use is appropriate, few studies have aimed this issue. This differentiation is important, as strategies to decrease the ultrasound overuse from images inappropriately indicated (e.g. ordering ultrasound for hyperthyroidism), pursue a different objective. In the light of this fact, thyroid ultrasound is only indicated when there is a palpable thyroid nodule or in thyroid cancer screening of a high risk population (e.g., head and neck radiation)(15). It is unlikely that the increased use of neck ultrasound reflects a surge of new thyroid nodules found by palpation as more than half of patients with thyroid cancer are asymptomatic(9). In fact, a study included in this meta-analysis showed that many of the thyroid cancers found by ultrasound were detected when clinicians erroneously believed that they felt a nodule and consequently ordered an ultrasound. Interestingly this often revealed no nodule in the palpated area but a small suspicious nodule in the contralateral lobe(9). Besides ordering thyroid ultrasound due to thyroid nodule misdiagnosis, many thyroid ultrasounds are ordered for the wrong indication. An audit of patients referred to an endocrine practice found that 93% of ultrasounds were ordered without appropriate indication but rather for other reasons such as thyroid dysfunction(42). This misuse of thyroid ultrasound, coupled with easy access, increased sensitivity and the non-invasiveness nature of the test, make thyroid ultrasound an important driver of thyroid cancer diagnosis(43),(40),(41).

Another significant driver of thyroid cancer diagnosis in our study was the histological examination of thyroid glands, particularly when removed in the setting of a benign condition. Parallel to the increased incidence of thyroid cancer, there has been a surge in the diagnosis of thyroid nodules, which in turn has led to higher rates of thyroid surgery(44). Thyroid surgeries are now more likely to involve the removal of the whole gland, rather than a part of the thyroid(45). Several studies have demonstrated that about 10% of thyroid glands harbor small incidental thyroid cancers(46); thus, the higher rates of thyroid surgery, in particular with removal of the whole gland, will uncover this large reservoir of disease. Although factors driving the increase in thyroid surgery for benign conditions remain unclear, it is possible that collective awareness of the high incidence of thyroid cancer could play a factor. For example, as many patients with benign autoimmune thyroid diseases are imaged, incidental thyroid nodules are discovered, to which there may be a decision towards surgery due to reasons such as provider or patient anxiety about the potential malignant nature of the nodule(s). This approach has led to increased, unnecessary thyroid surgery (39% increase in recent years) and its downstream associated risk- increasing rates of postoperative hypoparathyroidism(47). This is best seen in South Korea following a rise in thyroid surgery driven by routine thyroid ultrasound screening, now with reports of increasing postoperative hypoparathyroidism(48).

**Implications for research and practice**

Maybe for some of the lesions is impossible to prevent the incidental detection by either imaging or histology, however, even though this is not possible, we could change the way we response to them. Some strategies to handle these small non-threatening lesions are: changing the communication around diagnosis(49), developing decision aides that provide individualized approaches for suspicious thyroid nodules to avoid unnecessary biopsies(50). offering other treatment modalities, such as active surveillance (51), ect. Approaches that address avenues promoting thyroid cancer overdiagnosis are needed. Firstly, guidelines should provide recommendations on low-yield diagnostic tests such as un-necessary ultrasound with focus on high value meaningful use. And, secondly as ultrasound use becomes adopted into training programs, education on the indications and applicability is crucial. In one study, despite the recent uptake in ultrasound use, 38% of practicing endocrine surgeons who perform it regularly reported no formal training on its use or applicability(52). Although, ultrasound is an incredibly useful diagnostic tool, its routine use needs to be re-examined in the context of thyroid cancer overdiagnosis.

In the face of uncovering subclinical disease through histology, maybe pathological nomenclature of small incidental lesions needs to be re-examined. Referring to these lesions as “thyroid cancer” may influence a more aggressive downstream course of otherwise non-threatening subclinical lesions and despite that a recent survey reported that clinicians are not ready to change the terminology(53),evidence suggests that changing nomenclature used in describing small TC to terms such as “papillary lesion” reduced patient anxiety and influenced management decision making towards a more conservative approach(54). Future studies can support this approachas it has been done in cervical or breast cancers which may mitigate overtreatment(55).

**Limitations and strenghts**

Our study has some limitations, such that some observations should be interpreted with caution. One of the limitation of this systematic reviewis that only generate an overview of what is happening with the incidental diagnosis, as we could not describe in detail whether or not the neck ultrasound indications were appropriate (unclear reported information by only four studies). A better way to understand this issue is through a prospective cohort studies that controls the factors affecting indications, such as: country of origin, hospital where the study is conducted, practice patterns, the age and the sex of the patients, etc. Other important limitation lies in the retrospective nature of extraction of the initial primary data. Significant heterogeneity among studies may exist in defining incidental and non-incidental cancers. Consequently, patients could have been misclassified into wrong categories. Likewise the variations in definitions, made some comparison between studies difficult. Moreover, there is a risk of publication bias given the lack of inclusion of conference abstracts or unpublished literature.

Despite these limitations, the strengths of this study remain notable. Firstly, this is the first global perspective meta-analysis showing rates of incidental thyroid cancer across multiple cohorts allowing for comparison and a summative perspective. Secondly, as we excluded cohorts that were identified through screening programs, we offer a unique perspective into the avenues leading to incidental thyroid cancer diagnosis other than screening. Finally, sensitivity analyses comparing two analyses methods showed that results are consistent in almost all estimates, except in the tumor size subgroup analysis (≤ 10mm vs >10mm) as studies had proportions of 0% or 100%.

**Conclusion**

Our study shows that frequency of incidental thyroid cancer is high across numerous global geographic regions. Half of the thyroid cancers, and almost all micropapillary thyroid cancers detected are found incidentally, illustrating that incidental thyroid cancer continues to be a large driver of increasing overall thyroid cancer incidence. Subgroup analysis showed that incidental thyroid cancer tends to represent small cancers likely with indolent course and are primarily diagnosed by ultrasound, prompting a debate surrounding ultrasound indications and its misuse and opportunities for interventions aimed at reducing this source of over-diagnosis.

**Disclosure Statement**

The authors declare have no disclosure statement.

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**References**

1. Davies L, Welch HG 2014 Current thyroid cancer trends in the United States. JAMA Otolaryngol - Head Neck Surg **140**:317–322.

2. Kilfoy BA, Zheng T, Holford TR, Han X, Mary H, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y, Haven N 2009 International patterns and trends in thyroid cancer incidence, 1973–2002. Cancer Causes Control **20**:525–531.

3. National Cancer Institute SEER Explorer. Available at https://seer.cancer.gov/explorer/application.php?site=650&data\_type=1&graph\_type=2&compareBy=sex&chk\_sex\_3=3&chk\_sex\_2=2&chk\_race\_1=1&chk\_age\_range\_1=1&hdn\_data\_type=&advopt\_precision=1&advopt\_display=2&showDataFor=race\_1\_and\_age\_range\_1. Accessed December 12, 2019.

4. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A 2010 An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg **34**:28–35.

5. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM 2011 The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid **21**:231–236.

6. Davies L, Morris LGT, Haymart M, Chen AY, Goldenberg D, Morris J, Ogilvie JB, Terris DJ, Netterville J, Wong RJ, Randolph G 2015 American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: the Increasing Incidence of Thyroid Cancer. Endocr Pract **21**:686–696.

7. Brito JP, Morris JC, Montori VM 2013 Thyroid cancer: Zealous imaging has increased detection and treatment of low risk tumours. BMJ **347**:1–6.

8. Bahl M, Sosa JA, Nelson RC, Esclamado RM, Choudhury KR, Hoang JK 2014 Trends in incidentally identified thyroid cancers over a decade: A retrospective analysis of 2,090 surgical patients. World J Surg **38**:1312–1317.

9. Brito JP, Al Nofal A, Montori VM, Hay ID, Morris JC 2015 The Impact of Subclinical Disease and Mechanism of Detection on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Olmsted County, Minnesota During 1935 Through 2012. Thyroid **25**:999–1007.

10. Russo Picasso MF, Vicens J, Giuliani C, Jaén ADV, Cabezón C, Figari M, Gómez Saldaño AM, Figar S 2018 Role of the Mechanisms of Detection in the Increased Risk of Thyroid Cancer: A Retrospective Cohort Study in an HMO in Buenos Aires. J Cancer Epidemiol **2018**.

11. Oscar J Ponce, Eddy Lincango-Naranjo Overdiagnosis. Available at https://github.com/ponceoscarj/Overdiagnosis/blob/master/Overdiagnosis.md. Accessed May 28, 2020.

12. Thyroid 89th Annual Meeting of the American Thyroid Associationahead of print.

13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D 2009 The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med **6**:50931.

14. DistillerSR | Systematic Review and Literature Review Software by Evidence Partners. Available at https://www.evidencepartners.com/products/distillersr-systematic-review-software/. Accessed November 10, 2019.

15. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L 2016 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid **26**:1–133.

16. Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P Ottawa Hospital Research Institute. Newcastle-Ottawa Scale Assess Qual nonrandomised Stud meta-analyses. Available at http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp. Accessed August 9, 2019.

17. Luchini C, Stubbs B, Solmi M, Veronese N 2017 Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Analysis **5**:80–84.

18. Herzog R, Álvarez-pasquin MJ, Díaz C, Luis J, Barrio D, Estrada JM, Gil Á 2013 Are healthcare workers ’ intentions to vaccinate related to their knowledge , beliefs and attitudes ? a systematic review. BMC Public Health **13**.

19. Clopper CJ, Pearson ES 1934 The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika **26**:404.

20. Julious SA 2005 Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe,Statistics in Medicine 1998;17:857–872. Stat Med **24**:3383–3384.

21. Freeman MF, Tukey JW 1950 Transformations Related to the Angular and the Square Root. Ann Math Stat **21**:607–611.

22. Trikalinos TA, Trow P, Schmid CH 2013 Simulation-Based Comparison of Methods for Meta-Analysis of Proportions and Rates. Methods Res Rep **13**:1–98.

23. DerSimonian R, Laird N 1986 Meta-analysis in clinical trials. Control Clin Trials **7**:177–188.

24. Higgins JPT, Thompson SG 2002 Quantifying heterogeneity in a meta-analysis. Stat Med **21**:1539–1558.

25. Kahn C, Simonella L, Sywak M, Boyages S, UNG O, O’Connell D 2012 Pathways to the diagnosis of thyroid cancer in New South Wales: a population-based cross- sectional study. Cancer Causes Control **23**:35–44.

26. Iwata AJ, Bhan A, Lahiri S, Williams AM, Taylor AR, Chang SS, Singer MC 2018 Comparison of incidental versus palpable thyroid nodules presenting for fine-needle aspiration biopsy. Head Neck **40**:1508–1514.

27. Shakil J, Ansari MZ, Brady J, Xu J, Robbins RJ 2016 Lower Rates of Residual/Recurrent Disease in Patients With Incidentally Discovered Thyroid Carcinoma. Endocr Pract **23**:163–169.

28. Marina M, Ceda GP, Aldigeri R, Ceresini G 2017 Causes of referral to the first endocrine visit of patients with thyroid carcinoma in a mildly iodine-deficient area. Endocrine **57**:247–255.

29. Provenzale MA, Fiore E, Ugolini C, Torregrossa L, Morganti R, Molinaro E, Miccoli P, Basolo F, Vitti P 2016 “Incidental” and “non-incidental” thyroid papillary microcarcinomas are two different entities. Eur J Endocrinol **174**:813–820.

30. Roti E, Rossi R, Trasforini G, Bertelli F, Ambrosio MR, Busutti L, Pearce EN, Braverman LE, Degli Uberti EC 2006 Clinical and histological characteristics of papillary thyroid microcarcinoma: Results of a retrospective study in 243 patients. J Clin Endocrinol Metab **91**:2171–2178.

31. Minuto MN, Miccoli M, Viola D, Ugolini C, Giannini R, Torregrossa, Liborio Antonangeli L, Aghini-Lombardi F, Elisei R, Basolo F, Miccoli P 2013 Incidental versus clinically evident thyroid cancer: A 5-year follow-up study. Head Neck 408–412.

32. Ruggieri M, Genderini M, Gargiulo P, Del Grammastro A, Mascaro A, Luongo B, Paolini A 2001 Surgical treatment of differentiated microcarcinomas of the thyroid. Eur Rev Med Pharmacol Sci **5**:85–9.

33. Choi H, Kasaian K, Melck A, Ong K, Jones SJM, White A, Wiseman SM 2015 Papillary thyroid carcinoma: Prognostic significance of cancer presentation. Am J Surg **210**:298–301.

34. González-Sánchez-Migallón E, Flores-Pastor B, Pérez-Guarinos CV, Miguel-Perelló J, Chaves-Benito A, Illán-Gómez F, Carrillo-Alcaraz A, Aguayo-Albasini JL 2016 Carcinoma de tiroides incidental versus no incidental: presentación clínica, tratamiento quirúrgico y pronóstico. Endocrinol y Nutr **63**:475–481.

35. Seifert P, Freesmeyer M 2017 Preoperative diagnostics in differentiated thyroid carcinoma. NuklearMedizin **56**:201–210.

36. Zagzag J, Kenigsberg A, Patel KN, Heller KS, Ogilvie JB 2017 Thyroid cancer is more likely to be detected incidentally on imaging in private hospital patients. J Surg Res **215**:239–244.

37. Malone MK, Zagzag J, Ogilvie JB, Patel KN, Heller KS 2013 Thyroid Cancers Detected by Imaging Are Not Necessarily Small or Early Stage. Thyroid **24**:314–318.

38. Davies L, Ouellette M, Hunter M, Welch HG 2010 The Increasing Incidence of Small Thyroid Cancers : Where Are the Cases Coming From ? 2446–2451.

39. Haymart MR, Banerjee M, Reyes-Gastelum D, Caoili E, Norton EC 2019 Thyroid Ultrasound and the Increase in Diagnosis of Low-risk Thyroid Cancer. J Clin Endocrinol Metab **104**:785–792.

40. Marqusee E, Benson CB, Frates MC, Doubilet PM, Larsen PR, Cibas ES, Mandel SJ 2000 Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med **133**:696–700.

41. Leennhardt L, Bernier MO, Boin-Pineau MH, Conte Devolx B, Maréchaud R, Niccoli-Sire P, Nocaudie M, Orgiazzi J, Schlumberger M, Wëmeau JL, Chérié-Challine L, De Vathaire F 2004 Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol **150**:133–139.

42. Liel Y, Fraenkel N 2005 Use and misuse of thyroid ultrasound in the initial workup of patients with suspected thyroid problems referred by primary care physicians to an endocrine clinic. J Gen Intern Med **20**:766–768.

43. Groen RS, Leow JJ, Sadasivam V, Kushner AL 2011 Review: Indications for ultrasound use in low- and middle-income countries. Trop Med Int Heal **16**:1525–1535.

44. Ospina NS, Maraka S, Espinosa de Ycaza AE, Ahn HS, Castro MR, Morris JC, Montori VM, Brito JP 2016 Physical exam in asymptomatic people drivers the detection of thyroid nodules undergoing ultrasound guided fine needle aspiration biopsy. Endocrine **54**:433–439.

45. Sosa JA, Hanna JW, Robinson KA, Lanman RB 2013 Increases in thyroid nodule fine-needle aspirations, operations, and diagnoses of thyroid cancer in the United States. Surg (United States) **154**:1420–1427.

46. Harach HR, Franssila KO, Wasenius V ‐M 1985 Occult papillary carcinoma of the thyroid. A “normal” finding in finland. A systematic autopsy study. Cancer **56**:531–538.

47. Loyo M, Tufano RP, Gourin CG 2013 National trends in thyroid surgery and the effect of volume on short-term outcomes. Laryngoscope **123**:2056–2063.

48. Ahn S, Lee J-H, Bove-Fenderson E, Park S, Mannstadt M, Lee S 2019 Incidence ofHypoparathyroidism After Thyroid Cancer Surgery in South Korea, 2007-2016. JAMA **322**:2441–2443.

49. Nickel B, Brito JP, Moynihan R, Barratt A, Jordan S, McCaffery K 2018 Patients’ experiences of diagnosis and management of papillary thyroid microcarcinoma: A qualitative study. BMC Cancer **18**:1–10.

50. Genere N, Hurtado MD, Cortes T, Athimulam S, Al Ward R, Callstrom MR, Stan MN, Morris JC, Brito JP 2020 Drivers of the Decision To Biopsy and Follow-Up of Small Suspicious Thyroid Nodules. Endocr Pract.

51. Haymart M, Miller D, Hawley S 2017 Active Surveillance for Low-Risk Cancers — A Viable Solution to Overtreatment? N Engl J Med **377**:203–206.

52. Miller BS, Gauger PG, Broome JT, Burney RE, Doherty GM 2010 An international perspective on ultrasound training and use for thyroid and parathyroid disease. World J Surg **34**:1157–1163.

53. Nickel B, Brito JP, Barratt A, Jordan S, Moynihan R, McCaffery K 2017 Clinicians’ Views on Management and Terminology for Papillary Thyroid Microcarcinoma: A Qualitative Study. Thyroid **27**:661–671.

54. Nickel B, Barratt A, McGeechan K, Brito JP, Moynihan R, Howard K, McCaffery K 2018 Effect of a Change in Papillary Thyroid Cancer Terminology on Anxiety Levels and Treatment Preferences: A Randomized Crossover Trial. JAMA Otolaryngol - Head Neck Surg **144**:867–874.

55. Nickel B, Moynihan R, Barratt A, Brito JP, McCaffery K 2018 Renaming low risk conditions labelled as cancer. BMJ **362**:1–8.