Triggers of thyroid cancer diagnosis: a systematic review and meta-analysis

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Abstract

Purpose 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 June 2020. A pair of reviewers, working independently and in duplicate selected studies for inclusion, extracted data, and evaluated each trial's risk of bias. Studies enrolling patients older than 18 years with thyroid cancer confirmed histologically were included.

Results In total, 17 cohorts and 1 cross-sectional study, conducted between 1991 and 2018, enrolling 4668 patients with thyroid cancer were included: 88% had papillary thyroid cancer and 23% had papillary thyroid microcarcinoma. The proportion of patients with non-incidental and incidental thyroid cancer was similar: 49% [95% confidence interval (CI): 40–58%]. 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 (35%; 95% CI: 26–45%), of which ultrasound was the most common modality (27%; 95% CI: 14–43%). 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 overdiagnosis.

Keywords Thyroid cancer · Mechanism of detection · Incidental diagnosis · Systematic review · Meta-analysis

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 sevenfold, from 6.3 per 100,000 person year in 1999 to 47.5 per 100,000 population in 2009.

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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 incidence is explained 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 internationally.

Methods

A protocol was developed to perform this study and is available in Online Resource [11]. Overall, this manuscript is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Fig. 1) [12].

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 detected thyroid cancer and at least one incidental pathway of thyroid cancer detection (Fig. 2). 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 search 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 June, 2020. Controlled vocabulary supplemented with keywords was used to search for studies of triggers of

diagnosis in patients with thyroid cancer. The actual strategy is in the Appendix. 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) [13]. Reviewers (E.L-N., P.S-P., O.J.P., T.L., B.A-M., T.R.), working independently and in duplicate, screened abstracts and titles and full-text 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 and modifications were done to refine our instructions accordingly. For abstract screening, articles included by at least one reviewer were considered for full-text screening. Similarly, a pilot was performed with ten articles before starting the full-text screening and no modifications were done. At this stage, only articles included by each pair of reviewers were deemed eligible for this systematic review and in case of disagreements, these were resolved by consensus between the six aforementioned reviewers. Full-text screening agreement was calculated using Cohen's kappa, and it was substantial ($k = 0.76$).

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. No changes were made. 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 pathways of thyroid cancer diagnosis (incidental and non-incidental diagnosis). Incidental pathway included: (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.

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the studies selection process

Additionally, we extracted the type of imaging modality and indications driving the detection of incidental thyroid cancer. Due to variations in the definitions of triggers of thyroid cancer diagnosis, two extractors (E.L-N., P.S-P.) homogenized and discussed the debatable definitions to

achieve consensus with the one we proposed. For instance, patients categorized as “non-incidental diagnosis” having thyroid nodules detected by neck ultrasound because of the presence of altered laboratory test results, were categorized to “incidental imaging” [14]

Fig. 2 Definition and frequency of triggers of thyroid cancer diagnosis

(Appendix Table 1). This approach is based on a published framework [9] and recommendations for the use of ultrasound in guidelines [15].

Risk of bias in individual studies

Study quality was assessed by two independent reviewers (E.L-N. and P.S-P.) 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: a 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.

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 I^2 statistic and visually [24]. We considered that $I^2 < 25\%$ reflected low inconsistency and $I^2 > 75\%$ 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 >10 mm vs. tumor size ≤ 10 mm. 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 [25] was employed to perform all types of analyses and forest plots.

Online resource

To support reproducible research, we have made all of our files freely available in an online GitHub platform. Protocol, documents used in the screening phases (references screened in abstract screening and full-text screening), extra

Fig. 3 Overall incidental diagnosis in patients with thyroid cancer by population group

information (tables, figures) and as well as analysis phase (analysis codes or script, raw data) are available in this site (<https://github.com/poncescarj/Overdiagnosis/blob/master/Overdiagnosis.md>) [11].

Results

We included 18 studies, conducted between 1991 and 2018, enrolling 4668 patients with thyroid cancer. Figure 2 describes the results of our search. Participants' age ranged from 18 to 89 years old, and most were female (76%) with papillary thyroid cancer (88%) follicular thyroid cancer (6%), and others (6%). Around 23% of all patients with thyroid cancer had papillary thyroid microcarcinoma. Of 18 studies, 1 was cross-sectional [26] and 17 were cohort studies [8–10, 14, 27–39], mostly conducted in the United States [8, 9, 31–35, 39] and Italy [14, 27, 36–38] (Appendix Table 2). Overall, in cohort studies, risk of bias seems to be low (12) to moderate (5), and low in the cross-sectional study (Appendix Table 3).

The overall proportion of people whose thyroid cancer was found incidentally is 49% [95% confidence interval (CI): 40–58%, heterogeneity (I^2): 97%] (Fig. 3).

Overall incidental thyroid cancer diagnosis by triggers of diagnosis

The proportion of people whose diagnosis of thyroid cancer was triggered by imaging methods was 35% (95% CI: 26–45%, I^2 : 98%) and that of triggered by histological

examination was 24% (95% CI: 16–33%, I^2 : 97%). The specific imaging modalities for triggers of incidental thyroid cancer was 27% (95% CI: 14–43%, I^2 : 98%) for ultrasound, 7% (95% CI: 6–9%, I^2 : 36%) for computed tomography, 3% (95% CI: 2–5%, I^2 : 64%) for positron emission tomography, and 3% (95% CI: 1–5%, I^2 : 71%) for magnetic resonance imaging (Fig. 3).

Overall incidental thyroid cancer diagnosis by subgroups

Overall incidental thyroid cancer were analyzed by subgroup. Subgroup analysis by tumor size showed that tumor ≤ 10 mm was incidentally found in 76% (95% CI: 56–92%, I^2 : 97%), while tumors > 10 mm were 31% (95% CI: 15–50%, I^2 : 98%), with a p value for interaction test of < 0.001 . Furthermore, the frequency of incidental thyroid cancer was similar in women and men, 43% (95% CI: 30–56%, I^2 : 96%) vs. 46% (95% CI: 33–60%, I^2 : 89%), respectively, with a p value for subgroup interaction of 0.722, 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 < 0.001 . Similar findings were found when comparing studies performed in the United States (41%; 95% CI: 31–51%, I^2 : 95%) vs. studies performed outside the United States (56%; 95% CI: 42–70%, I^2 : 98%) with a p value for subgroup interaction of 0.087, and population-based studies (53%; 95% CI: 38–68%, I^2 : 94%) vs. non-population-based studies (49%; 95% CI: 38–59%, I^2 : 98%) with a p value of 0.643 for interaction (Fig. 3).

Fig. 4 Imaging and histological incidental diagnosis in patients with thyroid cancer by population group

Incidental imaging by subgroups

Incidental imaging subgroup analysis by tumor size showed that tumors ≤ 10 mm were incidentally found in 50% (95% CI: 35–65%, I^2 : 93%), while tumors > 10 mm were 29% (95% CI: 10–52%, I^2 : 98%), with a p value for interaction test of 0.141. The frequency of incidental imaging was slightly higher in men than women, 34% (95% CI: 13–59%, I^2 : 93%) vs. 21% (95% CI: 02–52%, I^2 : 99%), respectively, with a p value for subgroup interaction of 0.471. These frequencies were similar when comparing studies performed in the United States (34%; 95% CI: 27–42%, I^2 : 92%) vs. studies performed outside the United States (37%; 95% CI: 19–57%, I^2 : 99%) with a p value for subgroup interaction of 0.807, and population-based studies (36%; 95% CI: 10–68%, I^2 : 99%) vs. non-population-based studies (35%; 95% CI: 26–45%, I^2 : 97%) with a p value of 0.994 for interaction (Fig. 4).

Incidental histological by subgroups

Incidental histological subgroup analysis by tumor size showed that tumors ≤ 10 mm were incidentally found in 55% (95% CI: 28–81%, I^2 : 98%), while tumors > 10 mm

were 6% (95% CI: 0–27%, I^2 : 98%), with a p value for interaction test of 0.141. Furthermore, the frequency of incidental thyroid cancer was similar in men and women, 35% (95% CI: 14–59%, I^2 : 95%) vs. 39% (95% CI: 18–63%, I^2 : 98%), respectively, with a p value for subgroup interaction of 0.800, and was different in studies performed in the United States (13%; 95% CI: 11–16%, I^2 : 38%) vs. studies performed outside the United States (30%; 95% CI: 19–43%, I^2 : 97%) with a p value for subgroup interaction of < 0.003 . Similar findings were found when comparing population-based studies (15%; 95% CI: 04–31%, I^2 : 97%) vs. non-population-based studies (27%; 95% CI: 17–39%, I^2 : 98%) with a p value of 0.178 for interaction (Fig. 4).

Indications for incidental diagnosis by ultrasound

Only three studies reported indications for ultrasound imaging [9, 14, 32]. There were 255 cases that reported indications: family history of thyroid disease and/or presence of altered laboratory test results, such as TSH, FT4, TPO antibodies (62%), palpated nodule or symptoms not associated with nodule harboring thyroid cancer (15%), nonspecific neck symptoms (4%), nonspecific constitutional symptoms (2%), hyperparathyroidism/

hypercalcemia (2%) gynecological exam (1%), history of radiation exposure (1%), goiter (1%), routine sonogram (1%), self-sonography (1%), previous thyroid surgery (no malignancy) (1%), and unknown (8%). Although these studies reported the indications, none identified which were ordered appropriately or not (Appendix Table 3).

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 ≤ 10 mm the proportion was 76% (95% CI: 56–92%, I^2 : 97%), while for tumors >10 mm it was 31% (95% CI: 15–50%, I^2 : 98%). In contrast, by using the generalized linear mixed model, the estimate for the ≤ 10 mm group was 83% (95% CI: 52–95%, I^2 : 98%), whereas for the >10 mm the proportion was 26% (95% CI: 11–50%, I^2 : 98%). (Online Resource).

Discussion

Summary of evidence

We found that a significant proportion of thyroid cancer (49%) was discovered incidentally in asymptomatic people through histological examination and the use of imaging studies, in particular neck ultrasound (27%). These incidentally found cancers were mostly small papillary thyroid cancer (76%). 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 [40]. Furthermore, we found among the studies that reported indication for ultrasound use, that 62% were triggered by abnormal thyroid tests.

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 [41]. This increased sensitivity coupled with improved reimbursement and access to US has led to increase in use by endocrinologists close to 80% [42]. The increased use of thyroid ultrasound raises question about whether or not

its use is appropriate. Thyroid ultrasound is 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 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. Our analysis shows, in the studies that reported reason for thyroid ultrasound use, that approximately two-third of the thyroid ultrasounds were ordered due to thyroid hormone values abnormalities. The Endocrine Society along with the Choosing Wisely Campaign recommend against the use thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland [43]. This misuse of thyroid ultrasound, coupled with easy access, increased sensitivity, and the noninvasiveness nature of the test, make thyroid ultrasound an important driver of thyroid cancer diagnosis [41, 42, 44].

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 [45]. Thyroid surgeries are now more likely to involve the removal of the whole gland, rather than a part of the thyroid [46]. Several autopsy studies have demonstrated that about 11% of thyroid glands harbor small incidental thyroid cancers and interestingly, there is no significant increase in the prevalence of these lesions since 1949 [47]; thus, the higher rates of thyroid surgery, in particular with removal of the whole gland, will uncover this large reservoir of disease. As shown in this study, most of thyroid cancers detected histologically are smaller than 10 mm. 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.

Implications for research and practice

Although efforts to reduce over treatment of these small thyroid cancer lesions with strategies such as active surveillance are being implemented [48], approaches that

address avenues promoting thyroid cancer overdiagnosis are needed. Firstly, guidelines should provide recommendations on low-yield diagnostic tests such as unnecessary ultrasound with focus on high-value meaningful use. 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 [49]. Although, ultrasound is an incredibly useful diagnostic tool, its routine use needs to be re-examined in the context of thyroid cancer overdiagnosis.

Limitations and strengths

Our study has some limitations, such that some observations should be interpreted with caution. The main limitation of this review is that it can 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 ordered appropriately in each cohort. Studies are needed to explore this gap; the entry-point into the entire thyroid nodule diagnostic pathway. Another related limitation is 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 and selection bias given the lack of inclusion of conference abstracts or unpublished literature and inclusion of studies written only in English, Spanish, and Portuguese.

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

(≤ 10 vs. >10 mm) 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 papillary thyroid microcarcinomas 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 misuse. Interventions aimed at reducing this source of overdiagnosis and prospective cohort studies assessing the appropriateness of neck ultrasound indications are needed.

Data availability

Everything is available in <https://github.com/ponceoscarj/Overdiagnosis/blob/master/Overdiagnosis.md>.

Code availability

Everything is available in <https://github.com/ponceoscarj/Overdiagnosis/blob/master/Overdiagnosis.md>.

Author contributions All authors whose names appear on the submission. (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Table 1 Definition of the triggers of thyroid cancer diagnosis in each study

Reference	Definition of the triggers of thyroid cancer diagnosis in each study	Reasons for imaging use
Marina et al. [36]	Incidental imaging: •Incidental during carotid power-duplex. •Incidental during neck imaging other than carotid power-duplex. •Incidental during imaging work up of thyroid disease, including goiter. Incidental histology: Pathological examination of an expected benign lesion. Non-incidental: Patients in whom a nodule harboring thyroid cancer was discovered because of a self-report of a visual finding or a self-palpation of a neck lump or a complain of compressive symptoms.	Not reported
Rothberger et al. [39]	Incidental imaging: •Cases detected on any imaging modality that included the neck but was performed for non-thyroid indications. •Cases detected on an ultrasound examination specifically performed of the thyroid without clinical suspicion or knowledge of a thyroid nodule. Common reasons for these ultrasound examinations include evaluation of abnormal thyroid function tests, unrelated symptoms such as fatigue or weight gain, or as part of a screening program offered at the workplace. Non-incidental: Nodules that were found clinically were nodules palpated by the patient or a physician.	Not reported
Russo et al. [10]	Incidental imaging: Unexpected finding of thyroid cancer in an asymptomatic patient during a routine examination, imaging study, or surgical procedure, or a pathological examination of a surgical specimen in a patient with no thyroid mass, no benign thyroid disease, and no family history of thyroid cancer including ultrasounds performed during a multiphase check-up module. Non-incidental: •Detection of thyroid cancer by the patient or people outside the healthcare system. This category includes patients with and without symptoms related to the nodule that harbored thyroid cancer. •Clinical evaluation with a presumptive diagnosis of thyroid cancer including a physical exam or diagnostic workup of a cervical mass or lymph node detected by a physician belonging to the healthcare system. This category also included findings by a diagnostic cascade for benign thyroid disease ^a .	Not reported
Iwata et al. [34]	Incidental imaging: Nodules within the thyroid gland that are discovered during diagnostic imaging, which is performed for reasons unrelated to the thyroid gland. Non-incidental: Palpable nodule.	Not reported
Seifert et al. [30]	Incidental histological: The patients underwent thyroid surgery with an indication of benign thyroid disease, not for suspicion of differentiate thyroid cancer. Non-incidental: •Preoperative suspicion of malignancy ^a . •Preoperative assessment of unclear dignity ^a .	Not reported
Zagzag et al. [31]	Incidental imaging: Included patients for whom further diagnostic workup was indicated because of a nodule that was initially detected on an imaging study. The indications for these imaging studies were unrelated to the thyroid tumor. Non-incidental: Included those patients in whom further diagnostic studies were initiated because a physician had noted an abnormality on physical examination or because the patient or another nonprofessional had noted a mass in the neck.	Not reported
Shakil et al. [35]	Incidental imaging: histologically proven thyroid cancer initially discovered on imaging not intended for evaluation of the thyroid by computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or ultrasonography (US). Incidental histological: thyroid cancers discovered histologically after thyroidectomy for benign thyroid diseases, such as Graves' disease or multinodular goiter. Non-incidental: cancer that had been first discovered due to clinical signs or symptoms or imaging done specifically to evaluate thyroid anatomy	Not reported
González-Sánchez-Migallón et al. [29]	Incidental histological: Malignant neoplasms of thyroid origin, not detected clinically or by preoperative imaging tests, and that are evidenced in the pathological study of the surgical piece removed by an a priori benign process (goiter or hyperthyroidism). Non-incidental: When the diagnosis of thyroid cancer was established based on clinical, ultrasound, and fine needle aspiration cytology.	Not reported
Provenzale et al. [37]	Incidental histological: identified postoperatively at histological examination of thyroid in patients submitted to surgery for large multinodular goiter with compressive symptoms and/or incidentally detected in the extra-nodular parenchyma of thyroid gland of patients submitted to surgery for nodules with an 'indeterminate' cytological diagnosis and with a final histological diagnosis of benign nodules. Non-incidental: •Diagnosed before surgery as small thyroid nodule incidentally detected at thyroid ultrasound and submitted to FNAC because of the presence of suspicious signs at ultrasound ^a . •Papillary thyroid cancer larger than 1 cm.	Not reported
Brito et al. [9]	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. This category, however, also includes patients who had an imaging test for possible palpable or symptomatic nodule but the nodule harboring thyroid cancer is not related to any of	Incidental imaging by ultrasound (n = 54): •Palpated nodule or symptoms not associated with nodule harboring

Table 1 (continued)

Reference	Definition of the triggers of thyroid cancer diagnosis in each study	Reasons for imaging use
	<p>these symptoms.</p> <ul style="list-style-type: none"> •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). •When a thyroid nodule harboring thyroid cancer is found during a physical exam (thyroid palpation) of an asymptomatic patient. <p>Incidental histological: Thyroid cancer is found incidentally in the histological examination of the thyroid gland removed for a benign condition (e.g., Graves' disease).</p> <p>Non-incidental:</p> <ul style="list-style-type: none"> •When a thyroid nodule harboring thyroid cancer is found during a physical exam (thyroid palpation) or imaging study in a symptomatic patient. 	<p>thyroid cancer ($n = 37$).</p> <ul style="list-style-type: none"> •Hypothyroidism ($n = 5$). •Unknown ($n = 12$).
Choi et al. [28]	<p>Incidental imaging: The detection of thyroid nodule by imaging performed for indications unrelated to the thyroid mass.</p> <p>Non-incidental:</p> <ul style="list-style-type: none"> •The patient presents with complaints possibly related to the thyroid mass such as dysphagia, dysphonia, neck pain, self-detection of a neck mass, or self-requested screening for thyroid cancer. •The thyroid nodule detected by a clinician during an evaluation for complaints not related to a thyroid mass. 	Not reported
Bahl et al. [8]	<p>Incidental imaging: Incidental cancers were detected on imaging studies performed for other reasons in patients without any clinical symptoms, examination findings, or suspicion for thyroid cancer.</p> <p>Incidental histological: An incidental cancer on pathology was found on the surgical specimen when surgery was performed for benign disease or resection of another nodule that was subsequently found to be benign.</p> <p>Non-incidental:</p> <ul style="list-style-type: none"> •A clinical cancer was defined as a palpable nodule. •A clinical cancer was defined as a nodule discovered in the workup of abnormal thyroid function test or in the context of suspicion for thyroid cancer^a. 	Not reported
Malone et al. [32]	<p>Incidental imaging: patients in whom the indication for surgery was a suspicious or malignant cytological finding on fine needle aspiration biopsy (FNAB) of a tumor that was initially detected on an imaging study.</p> <p>Incidental histological: patients in whom incidental cancers were found on pathological study of the surgical specimen that were not related to the indication for thyroidectomy, the indications for surgery included nodules with suspicious cytology that proved to be benign, symptomatic or enlarging nodules with benign cytology, multinodular goiters, and thyrotoxicosis.</p> <p>Non-incidental: patients in whom the indication for surgery was a suspicious or malignant cytological finding on FNAB and in whom the patient stated that further diagnostic studies were initiated because a physician had noted an abnormality on physical examination or because the patient or another nonprofessional had noted a mass in the neck</p>	<p>Incidental imaging by ultrasound ($n = 98$):</p> <ul style="list-style-type: none"> •Hashimoto's thyroiditis ($n = 17$). •Family history of thyroid cancer ($n = 11$). •Hyperthyroidism ($n = 11$). •Nonspecific neck symptoms ($n = 10$). •Hypothyroidism ($n = 9$). •Nonspecific constitutional symptoms ($n = 6$). •Hyperparathyroidism/hypercalcemia ($n = 6$). •Gynecological exam ($n = 4$). •History of radiation exposure ($n = 4$). •Goiter ($n = 3$). •Previous thyroid surgery (no malignancy) ($n = 2$). •"Routine" sonogram ($n = 2$). •Self-sonography ($n = 2$). •Other lab abnormalities ($n = 2$). •Surveillance of another thyroid nodule ($n = 1$). •Unknown ($n = 8$).
Minuto et al. [38]	<p>Incidental histological: Patients who underwent surgery for presumed benign disease and demonstrated at least 1 focus of thyroid cancer on final histology.</p> <p>Non-incidental: Patients with clinically evident thyroid cancer.</p>	Not reported
Kahn et al. [26]	<p>Incidental imaging: Tumor incidentally found during diagnostic imaging for another health problem.</p> <p>Incidental histological: Cancer diagnosed after surgery for a benign thyroid disorder.</p> <p>Non-incidental:</p> <ul style="list-style-type: none"> •Initially presented due to patient's concern about a mass in their neck or obstructive symptom. •A doctor noticed a lump in the patient's neck of which they were unaware. 	Not reported
Davies et al. [33]	<p>Incidental imaging:</p> <ul style="list-style-type: none"> •The patient specifically requested a thyroid test or evaluation. •When the identification of a thyroid finding was through a radiologic test done for an indication unrelated to the thyroid gland, such as a computed tomography scan of the 	Not reported

Table 1 (continued)

Reference	Definition of the triggers of thyroid cancer diagnosis in each study	Reasons for imaging use
Roti et al. [14]	<p>chest done for a trauma workup or a chest x-ray done during a preoperative visit.</p> <ul style="list-style-type: none"> •When the diagnostic cascade stated when a thyroid finding was revealed during a laboratory or other non-radiologic workup for a patient complaint but the thyroid finding did not plausibly explain the patient's presenting complaint. <p>Non-incidental:</p> <ul style="list-style-type: none"> •When a thyroid nodule or other finding had been known about for some time but had been managed expectantly. •When the person had no complaints referable to the neck or thyroid function and was identified as having a thyroid finding during a routine physical exam performed by a primary care practitioner in a primary care setting. •A patient was said to be "symptomatic" if the patient's presenting complaint was clearly referable to the region of the thyroid gland or the soft tissues of the neck. <p>Incidental histological: Thyroid cancer diagnosed incidentally during thyroid surgery for benign thyroid disorders such as Graves' disease and nodular goiter.</p> <p>Non-incidental: were thyroid nodules detected by neck ultrasonography conducted for other reasons, because of a family history of thyroid disease and/or presence of altered laboratory test results (TSH, FT4, and thyroid peroxidase antibodies).^a</p>	<p>Incidental imaging by ultrasound ($n = 103$):</p> <ul style="list-style-type: none"> •Family history of thyroid disease and/or presence of altered laboratory test results (TSH, FT4, and thyroid peroxidase antibodies) ($n = 103$).
Ruggieri et al. [27]	<p>Incidental histological: Patients in whom the histological diagnosis of cancer was incidental after an operation performed for benign disease.</p> <p>Non-incidental:</p> <ul style="list-style-type: none"> •Patients with a clinically suspicious neoplastic lesion diagnosed before surgical treatment. •Patients in whom a neck lymph node metastases were clinically found before diagnosis of an occult papillary carcinoma in thyroid gland. 	Not reported

^aSome non-incidental thyroid cancers where classify as incidental imaging

Table 2 General characteristics of included studies

Reference	Country	Study design	Study period	Setting	Sample size	Female	Papillary thyroid cancer	Follicular thyroid cancer	Papillary thyroid microcarcinoma
Marina et al. [36]	Italy	Retrospective cohort study	January 1998 to October 2018	Single center	440	339	410	30	Not reported
Rothberger et al. [39]	United States	Retrospective cohort study	January 2015 to June 2017	Single center	39	Not reported	33	5	Not reported
Russo et al. [10]	Argentina	Retrospective cohort study	January 2003 to December 2012	Population-based study	176	158	166	10	Not reported
Iwata et al. [34]	United States	Retrospective cohort study	January 2006 to December 2010	Single center	128	Not reported	Not reported	Not reported	Not reported
Seifert et al. [30]	Germany	Retrospective cohort study	October 2009 to September 2015	Single center	103	78	68	35	13
Zagzag et al. [31]	United States	Retrospective cohort study	2004 to 2010	Multicenter in one country	473	352	427	20	100
Shakil et al. [35]	United States	Retrospective cohort study	2005 to 2014	Single center	172	131	160	10	54
González-Sánchez-Migallón et al. [29]	Spain	Retrospective cohort study	2000 to 2014	Single center	259	208	225	34	92
Provenzale et al. [37]	Italy	Prospective cohort study	March 2013 to March 2014	Single center	374	Not reported	374	NA	159
Brito et al. [9]	United States	Retrospective cohort study	2000 to 2012	Population-based study	213	149	199	6	Not reported
Choi et al. [28]	Canada	Retrospective cohort study	January 2000 to January 2013	Single center	168	126	168	Not applicable	Not included
Bahl et al. [8]	United States	Retrospective cohort study	January 2003 to December 2012	Single center	675	499	566	32	206
Malone et al. [32]	United States	Retrospective cohort study	January 2007 to August 2010	Single center	473	345	451	10	156
Minuto et al. [38]	Italy	Retrospective cohort study	February 2002 to November 2003	Single center	188	139	181	7	Not reported
Kahn et al. [26]	Australia	Cross-sectional study	May 2006 to August 2008	Population-based study	419	321	359	60	Not reported
Davies et al. [33]	United States	Retrospective cohort study	2006 to 2007	Multicenter in one country	95	Not reported	86	6	Not reported
Roti et al. [14]	Italy	Retrospective cohort study	1993 to 2002	Single center	243	197	243	Not applicable	243
Ruggieri et al. [27]	Italy	Retrospective cohort study	1991 to 2000	Single center	30	Not reported	28	2	28

Table 3 Risk of bias in individual studies

Reference	Design	Score	Selection/****	Comparability/**	Outcome/***	Total	Overall risk of bias
Newcastle-Ottawa Scale for Cohort Studies							
Marina et al. [36]	Retrospective cohort study	***		**	***	8	Low risk
Rothberger et al. [39]	Retrospective cohort study	***		**	***	8	Low risk
Russo et al. [10]	Retrospective cohort study	***		**	**	7	Moderate risk
Iwata et al. [34]	Retrospective cohort study	***		**	**	7	Moderate risk
Seifert et al. [30]	Retrospective cohort study	***		**	***	8	Low risk
Zagzag et al. [31]	Retrospective cohort study	***		**	***	8	Low risk
Shakil et al. [35]	Retrospective cohort study	***		**	***	8	Low risk
González-Sánchez-Migallón et al. [29]	Retrospective cohort study	***		**	***	8	Low risk
Provenzale et al. [37]	Prospective cohort study	***		**	**	7	Moderate risk
Brito et al. [9]	Retrospective cohort study	***		**	***	8	Low risk
Choi et al. [28]	Retrospective cohort study	***		**	***	8	Low risk
Bahl et al. [8]	Retrospective cohort study	***		**	***	8	Low risk
Malone et al. [32]	Retrospective cohort study	***		**	***	8	Low risk
Minuto et al. [38]	Retrospective cohort study	***		**	**	7	Moderate risk
Davies et al. [33]	Retrospective cohort study	***		**	**	7	Moderate risk
Roti et al. [14]	Retrospective cohort study	***		**	***	8	Low risk
Ruggieri et al. [27]	Retrospective cohort study	***		**	***	8	Low risk
Newcastle-Ottawa Scale adapted for Cross-Sectional Studies							
Kahn et al. [26]	Cross-sectional study	****	Selection/*****	Comparability/**	Outcome/****	Total	Overall risk of bias
				*	**	7	Moderate risk

** = 2 points, *** = 3 points, **** = 4 points

Appendix

Search strategies

Ovid

Database(s): Embase 1974 to 2020 June 02, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to June 02, 2020 Search Strategy:

#	Searches	Results
1	exp Thyroid Neoplasms/di, dg [Diagnosis, Diagnostic Imaging]	15,940
2	exp thyroid cancer/di [Diagnosis]	24,061
3	(thyroid* adj3 (cancer* or neoplasm* or carcinoma*)),ti,ab,hw,kw.	139,248
4	(diagnos* or detect* or identify* or identified or identification*).ti,ab,hw,kw.	17,002,808
5	1 or 2 or (thyroid* adj3 (cancer* or neoplasm* or carcinoma*) adj3 (diagnos* or detect* or identify* or identified or identification*).ti,ab,hw,kw.	36,818
6	exp incidental findings/	27,510
7	exp Mass Screening/	367,938
8	exp Palpation/	26,410
9	((diagnos* or detect* or event or events or identify* or identified or identification*) adj5 (trigger* or chance)) or incidental or incidentally or palpabl* or palpat* or screen* or serendipit* or subclinical).ti,ab,hw,kw.	2,473,978
10	6 or 7 or 8 or 9	2,484,354
11	5 and 10	4847
12	exp comparative study/	3,262,555
13	exp Cohort Studies/	2,580,088
14	exp longitudinal study/	274,713
15	exp retrospective study/	1,741,673
16	exp prospective study/	1,144,154
17	exp population research/	106,991
18	(cohort* or “longitudinal study” or “longitudinal survey” or “longitudinal analysis” or “longitudinal evaluation” or longitudinal* or ((retrospective or “ex post facto”) adj3 (study or survey or analysis or design)) or retrospectiv* or “prospective study” or “prospective survey” or	14,626,951

Table (continued)

	“prospective analysis” or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or “incidence study” or “incidence survey” or “incidence analysis” or ((“follow-up” or followup) adj (stud* or survey or analysis)) or (compar* and (study or trial))).mp,pt.	
19	or/12-18	14,739,985
20	11 and 19	2002
21	limit 20 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher; records were retained]	8
22	20 not 21	1994
23	remove duplicates from 22	1546

Scopus

1. TITLE-ABS-KEY(thyroid* W/3 (cancer* or neoplasm* or carcinoma*) W/3 (diagnos* or detect* or identify* or identified or identification*)).
2. TITLE-ABS-KEY(((diagnos* or detect* or event or events or identify* or identified or identification*) W/5 (trigger* or chance)) OR incidental OR incidentally OR palpabl* OR palpat* OR screen* OR serendipit* OR subclinical).
3. TITLE-ABS-KEY(cohort* or “longitudinal study” or “longitudinal survey” or “longitudinal analysis” or “longitudinal evaluation” or longitudinal* or ((retrospective or “ex post facto”) W/3 (study or survey or analysis or design)) or retrospectiv* or “prospective study” or “prospective survey” or “prospective analysis” or prospectiv* or (population W/3 (stud* or survey* or analys* or research)) or “incidence study” or “incidence survey” or “incidence analysis” or ((“follow-up” or followup) W/1 (stud* or survey or analysis)) or (compar* and (study or trial))).
4. 1 and 2 and 3.
5. DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh).

6. 4 and not 5.
7. INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*).
8. 6 and not 7.

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