The influence of incidental detection of thyroid nodule on thyroid cancer risk and prognosis—A systematic review

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Abstract
Background: Clinically inapparent thyroid nodules discovered serendipitously on imaging for nonthyroid indications are termed as thyroid incidentalomas. It is unclear whether these incidentalomas have a lower prevalence of malignancy or slower tumour progression compared to symptomatic nodules. The aims of this systematic review were to determine the impact of incidental detection of thyroid nodules on both the risk of malignancy and on prognosis in patients with thyroid cancer.

Method: PubMed and MEDLINE® on Web of Science databases were searched from inception to March 2020 for English language articles reporting on human studies of thyroid cancer risk and/or prognosis in incidental and nonincidental nodules.

Results: Eighteen observational studies published between 1998 and 2020 were eligible for analysis; four studies reported on risk, nine on prognosis and five studies reported on both risk and prognosis. When comparing the incidental and nonincidental groups in the risk study, the odds of incidental detection in the cancer and benign groups ranged from 0.16 to 0.5 and 0.06 to 0.38, respectively (odds ratio [OR] = 0.64–2.86) in case-control studies (n = 6); the risk of malignancy for thyroid nodules ranged from 4% to 23.5% in the incidental and 3.8% to 28.7% in the nonincidental groups (relative risk = 0.13–6.27) in the cohort studies (n = 3). A meta-analysis of the eligible case-control studies (n = 3) showed a nonsignificant summated OR of 1.04 (95% confidence interval = 0.63–1.70; p = .88). In the prognosis study, five direct and thirteen indirect markers of prognosis were compared between the incidental and nonincidental groups. A meta-analysis was not possible but incidentally detected thyroid cancer had better progression-free and overall survival.

Conclusion: Current evidence suggests that investigation and management of thyroid nodules should not be influenced by the mode of detection.

Keywords
incidental detection, incidentaloma, prognosis, risk, thyroid cancer, thyroid nodule
INTRODUCTION

Thyroid cancer is the most common endocrine cancer worldwide and its incidence has doubled since the early 1990s. It predominantly affects females and incidence increases with age. Patients may present with a palpable lump or local compressive symptoms (hoarse voice, difficulty swallowing, difficulty breathing). Thyroid cancer could also be discovered during investigation for benign thyroid disease or incidentally detected on imaging for nonthyroid illness.

Thyroid nodules exist more frequently than they are clinically detected. Autopsy studies showed that 50%–60% of individuals with no clinical suspicion of thyroid pathology had thyroid nodules; 13% of which were malignant on histology. Another autopsy study showed that one-third of the individuals without previous thyroid disease had at least one papillary carcinoma detected at autopsy. This suggests that some patients with thyroid cancer have an indolent course that may not become clinically apparent and does not affect life expectancy.

The proportion of patients with thyroid cancer presenting with incidentally detected nodules has increased in recent decades. This increase (particularly of small [≤2 cm] papillary thyroid cancer (PTC)) has been attributed to the widespread use of diagnostic imaging and the increase in sensitivity and resolution of these modalities. Thyroid incidentaloma is defined as a clinically unsuspected, asymptomatic thyroid lesion, that is, detected serendipitously on imaging for indications unrelated to the thyroid gland.

Up to two-thirds of thyroid incidentalomas are detected on ultrasound performed to examine the parathyroid glands (46%), carotid arteries (9%–13%) or lymph nodes. Computed tomography and magnetic resonance imaging performed to evaluate the lungs, ‘non-thyroid’ neck or cervical spine disease also contribute (16%) to the detection of asymptomatic thyroid lesions. Positron emission tomography imaging detected thyroid incidentalomas in 2%–3% of patients; the risk of malignancy in these patients ranges from 33% to 55%.

While these incidentalomas exist in over 50% of individuals over the age of 50, the clinical and oncological implications remain unclear. Ultrasound is widely accepted as an imaging of choice to evaluate thyroid nodules because it is noninvasive, readily available and its sensitivity in identifying carcinomas ranges from 87% to 95%. Thyroid nodules with suspicious characteristics on ultrasound or patients with risk factors should undergo cytological assessment; and if required, surgery for definitive diagnosis and treatment.

There is a lack of clarity in the risk of cancer and progression of thyroid incidentalomas compared to symptomatic nodules; and therefore, uncertainty over whether incidentally detected nodules should be managed differently.

The aims of this systematic review were to determine (i) the risk of malignancy in incidentally detected thyroid nodules and (ii) the impact of incidental detection on the prognosis of patients with thyroid cancer.
direct prognostic markers that were time-dependent (such as disease-free survival, overall survival, residual/recurrence disease); and indirect prognostic markers that were not time-dependent (such as the size of the nodule, histological subtypes, lymph node and distant metastasis, extrathyroidal extension, bilaterality, multifocality/multicentricity, cancer staging, lymphocytic infiltration, distant Metastasis, patient Age, Completeness of resection, local Invasion, tumour Size [MACIS] and age, metastases, extent, size [AMES] scores).

2.4 | Data extraction and analysis

A word-based data extraction form was developed and piloted in five studies and subsequently modified and used by two observers to extract the data from all included manuscripts. Discrepancies were resolved by consensus or addressed by the senior author. The final data set (available upon request) was transferred to an excel spreadsheet. All included studies were assessed for ‘risk of bias’ using the modified Newcastle–Ottawa Scale (NOS) for quality assessment, taking into account the different observational study designs (case-control studies, cohort studies and cross-sectional studies).

Descriptive reporting was done using Excel. Odds ratios and relative risks not reported in individual studies were calculated by the researcher; but testing for statistical significance was not performed.

Two meta-analyses were performed using Review Manager v5.4 (https://tinyurl.com/y7kepe2e) on risk to produce a summated odds ratio. The first meta-analysis included case-control studies with comparable study populations and definitions of incidental detection (n = 4) whereas the second reported on data from good quality case-control studies (NOS score of >50%; n = 3). The three retrospective cohort studies were not subjected to a meta-analysis due to heterogeneity in populations and unit of the study presented (nodules/patients). Two of these studies had NOS scores of less than 50%. Meta-analysis was not carried out for the prognosis studies due to the heterogeneity in the definitions of incidental detection, subtypes of thyroid cancer and the outcomes assessed.

The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement17 guided the planning and conduct of this systematic review and the PRISMA checklist (shown in Tables S1A,B) and flow diagram were used for reporting. This systematic review was registered with the PROSPERO database (Registration number CRD42020172291).

3 | RESULTS

The initial searches yielded 3095 manuscripts. After removing non-English, nonhuman studies and duplications, 2159 manuscripts were assessed for eligibility using the inclusion and exclusion criteria.
A total of 18 studies reporting comparison between the incidental and nonincidental arms were included; four studies evaluated cancer risk; nine reported on prognosis; and five reported on both risk and prognosis. Due to the duplication of the patients included in the 201718 and 202019 studies by Marina et al., only the latter one is included in the analysis. No additional manuscripts were identified on screening the bibliographies of these eighteen studies.

### 3.1 | Case-control studies on thyroid cancer risk

#### 3.1.1 | Characteristics of studies on thyroid cancer risk

Six case-control and three retrospective cohort studies with study periods ranging from 1991 to 2016 were included. The patient eligibility criteria as defined in Table S3. Eight were single centre studies and one study involved two centres. Six studies were carried out in the United States whilst the rest were from the United Kingdom, Australia, and Israel.

#### 3.1.2 | Case-control studies on thyroid cancer risk

A total of 738 malignant thyroid nodules and 2508 benign thyroid nodules were included in the six case-control studies. The odds of incidental detection in the cancer and benign groups ranged from 0.16 to 0.5 and 0.06 to 0.38, respectively (odds ratio 0.44–2.86; statistical significance testing was not performed; shown in Table 1). The results of the individual case-control studies were described in Table S5.

#### 3.1.3 | Cohort studies on thyroid cancer risk

A total of 91 patients in the incidental group and 398 patients in the nonincidental group were included in the three cohort studies. The risk of malignancy for thyroid nodules ranged from 4% to 23.5% in the incidental and 33% to 26.7% in the nonincidental groups.

### 3.1 | Characteristics of studies on thyroid cancer risk

#### Study

| Number of patients/nodules (n) | Cancer Incidental (%) | Nonincidental (%) | Total |
|-------------------------------|-----------------------|-------------------|-------|
| Iwata et al. (2018)20          | 1794                  | 1388              |       |
| Sinnott et al. (2017)21        | 297                   | 5                 | 15    |
| Farra et al. (2017)22          | 809                   | 65                | 466   |
| Mevawalla et al. (2013)24      | 419                   | 294               | 56    |
| Davies et al. (2010)28         | 295                   | 149               | 51    |
| Carmeci et al. (1998)26        | 497                   | 309               | 22    |
| Note: All units represent the number of patients except for one paper (Iwata et al.20) which used the number of nodules as the unit of study. Odds ratios were calculated as a measurement of risk for these studies. | | | |

### Table 1

| Study | Number of patients/nodules (n) | Cancer Incidental (%) | Nonincidental (%) | Total |
|-------|--------------------------------|-----------------------|-------------------|-------|
| Iwata et al. (2018)20 | 1794 | 32.8% | 67.2% | 128 |
| Sinnott et al. (2017)21 | N/A | 33.3% | 66.7% | 15 |
| Farra et al. (2017)22 | 809 | 13.9% | 86.1% | 466 |
| Mevawalla et al. (2013)24 | 419 | 19.6% | 80.4% | 56 |
| Davies et al. (2010)28 | 295 | 27.5% | 72.5% | 51 |
| Carmeci et al. (1998)26 | 497 | 13.6% | 86.4% | 22 |
| Measurement of risk (value) | Odds ratio (0.86) | Odds ratio (1.64) | Odds ratio (1.52) | Odds ratio (0.64) | Odds ratio (0.99) | Odds ratio (2.86) |
Table S5. The results of the individual cohort studies were described in comparable study populations and definition of incidental detection prognosis.

### 3.2.1 Characteristics of studies on thyroid cancer

Studies 19,20,22,23,27,28,31 were the case-control and cohort studies with the range of 22.2%–66.7% and 44.4%–66.7%, respectively (Figure S1A,B). Major issues affecting study quality were lack of adjustment for confounding factors, exclusion of patients due to incomplete medical records, inadequate outcome assessment (cancers were diagnosed on cytology instead of histopathology) and inadequate or unclear follow up.

#### 3.1.4 Quality of studies on thyroid cancer risk

The scores of study quality assessed using the modified NOS ranged from low to moderately high in the case-control studies \( n = 6 \) and cohort studies \( n = 3 \) with the range of 22.2%–66.7% and 44.4%–66.7%, respectively (Figure S1A,B). Major issues affecting study quality were lack of adjustment for confounding factors, exclusion of patients due to incomplete medical records, inadequate outcome assessment (cancers were diagnosed on cytology instead of histopathology) and inadequate or unclear follow up.

#### 3.1.5 Meta-analysis of thyroid cancer risk studies

Meta-analysis was carried out for the case-control studies with comparable study populations and definition of incidental detection \( n = 4 \) (shown in Figure 2A). The summated odds ratio was 1.11 (95% confidence interval [CI] = 0.74–1.68) and \( I^2 \) of 28%. Previous studies have suggested that studies scoring 5 out of 9 on NOS were considered of high risk of bias. A second meta-analysis looking at good quality case-control studies (NOS > 50%; \( n = 3 \) showed a summated odds ratio of 1.04 (95% CI = 0.63–1.70; \( p = .88 \)) and \( I^2 \) of 46% (shown in Figure 2B). Publication bias was not assessed due to the low number of studies in the meta-analysis.

#### 3.2 Prognosis of thyroid cancers in thyroid incidentalomas

##### 3.2.1 Characteristics of studies on thyroid cancer prognosis

Of the 14 studies included, 12 were retrospective cohort studies \( 19,20,22,23,27,28,31–36 \) and 2 \( 27,28 \) were cross-sectional studies; the study periods ranged from 1998 to 2020. The inclusion and exclusion criteria for the individual studies are described in Table S6. Eight studies were carried out in the United States and the rest were from Italy, Israel, Korea, Canada, Ecuador and Australia. One study \( 23 \) only included individuals under the age of 18 while the others were in the adult population. Most retrospective cohort studies are single centred studies except for the study by Davies et al. which was carried out in two centres. Among these cohort studies, five studies \( 20,22,23,27,28 \) also evaluated the risk of thyroid cancer.

For prognosis, incidental detection refers to cancer detected in a thyroid incidentaloma. The definitions of incidental and nonincidental detection for individual studies are shown in Table S7. Nonincidental detection includes cancer detected in a palpable or symptomatic thyroid nodule or nodule discovered through an abnormal thyroid function test. ‘Unsuspected nodules found on surgery for benign thyroid disease’ were considered as nonincidental nodules in this analysis regardless of how it was classified in the reported studies. However, there were a few exceptions: The study by Shakil et al. where patients with thyroid cancer were discovered histologically after thyroidectomy for benign thyroid disease, the study by Marina et al. where nodules were detected on the investigation of thyroid disease or during pathological examination for a benign lesion and the study by Hagag et al. where patients with thyroid cancer detected on ultrasound for nonnodular thyroid disease could not be excluded from the incidental detection group.

A total of 5164 patients (2424 in the incidental group and 2740 in the nonincidental group) were identified from the 14 studies (shown in Table S8). The type of thyroid cancer was not mentioned in the studies by Iwata et al. and Gupta et al.; possibly because not all nodules underwent histological assessment. Two studies focussed exclusively on PTC whilst two studies focussed on differentiated thyroid cancer (DTC) which included papillary, follicular and Hurte cell carcinomas. The rest of the studies included patients with DTC, medullary and anaplastic carcinomas. Three direct and thirteen indirect prognostic markers were discussed in respective studies (shown in Table S8). Only 3 of the 13 studies provided information on patients’ follow up; the median follow-up period ranged from 26.5 to 114 months.

### Table 2 The number of patients/nodules included in the retrospective cohort studies and the risk of thyroid cancer

| Study                     | Number of patients/nodules (n) | Incidental detection | Nonincidental detection | Measurement of risk (value) |
|---------------------------|--------------------------------|----------------------|-------------------------|-----------------------------|
|                           | All patients/nodules eligible for analysis | Cancer (%) | Benign (%) | Total | Cancer (%) | Benign (%) | Total | |
| Gupta et al. (2014)\(^{19}\) | 179 | 141 | 1 (4%) | 25 (96%) | 26 | 33 (28.7%) | 82 (71.3%) | 115 | Relative risk (0.13) |
| Liebeskind et al. (2005)\(^{25}\) | 281 | 97 | 4 (23.5%) | 13 (76.5%) | 17 | 3 (3.8%) | 77 (96.2%) | 80 | Relative risk (6.27) |
| Hagag et al. (1998)\(^{27}\) | 259 | 251 | 4 (8.3%) | 44 (91.7%) | 48 | 20 (10%) | 183 (90%) | 203 | Relative risk (0.85) |

Note: All units represent the number of patients except for one paper (Liebeskind et al.\(^{25}\)) which used the number of nodules as the unit of study. Relative risk was calculated as a measurement of risk for these studies.
3.2.2 | Quality of studies on thyroid cancer prognosis

The risks of bias for the thirteen cohort studies assessed on the modified NOS ranged from moderately low to very low (66.7%–100%) while one study32 scored 100% (shown in Figure S1C). Some criteria were not applicable to some cohort studies; 20, 22, 23, 27, 28, 33–36 an example is where the main prognostic marker reported in the study is not a time-dependent marker (i.e., an indirect marker of prognosis). For the cross-sectional studies, Solis et al.37 scored 77.8% whilst the study by Kahn et al.38 scored the highest score of 100% indicating a low risk of bias (shown in Figure S1D). Despite the high NOS score, a meta-analysis was not done for the prognostic markers due to the heterogeneity in definitions of incidental detection, age of the population studied, subtypes of cancer included, differences in the prognostic outcomes reported and the assessment used for these prognostic markers.

3.2.3 | Direct markers of prognosis

Solis et al.37 showed that the nonincidental group had a higher risk of recurrence (16.5% intermediate and 10% high risks) as defined by the ATA 2009 risk stratification system when compared to the incidental group (6.8% intermediate and 7.6% high risks). However, the prevalence ratios of both risks were not statistically significant among both arms in the multivariate analyses (prevalence ratio [PR] = 0.98, 95% CI = 0.67–1.43; p = .902 and PR = 1.04, 95% CI = 0.82–2.16; p = .239, respectively; shown in Table S9). The study by Marina et al.19 looking at DTC only showed that the disease-free survival was higher in the incidental group when comparing the number of events over 15 years and the time to event (hazard ratio [HR]: not available). One study31 found that the rate of residual disease or recurrence (R/R) was significantly higher in the nonincidental detection group (21%) compared to the incidental detection group (7%) (p = .04); the incidental group also had longer progression-free survival compared to the nonincidental group (log-rank test p = .08). In the univariate analysis, thyroid cancer recurrence was lower (but not significant) in the incidental detection group (HR = 0.36, 95% CI = 0.11–1.26; p = .1). The fourth study32 reported that more patients with nonincidentally detected PTC had a relapse when compared to the incidental group (11% and 3%, respectively; p < .001) regardless of the site of relapse but the time to recurrence was not significant (p = .681). The 5-year recurrence-free survival rates and the overall survival were higher in the incidental detection group (97% and 99%, respectively) when compared to the nonincidental group (91% and 97%, respectively; log-rank test p < .001). In the multivariate analyses, nonincidental detection was found to be an independent predictor of recurrence-free survival (HR = 2.02, 95% CI = 1.02–4.01; p = .043) and overall survival (HR = 5.84, 95% CI = 2.07–16.44; p = .001), respectively.

3.2.4 | Indirect markers of prognosis

Tables S10–S12 show the 13 indirect prognostic markers (size of the nodule, histological subtypes, lymph node and distant metastasis, disease spread at the time of diagnosis, lymphovascular and capsular invasions, extra-thyroidal and extra-nodal extensions, bilaterality, multifocality/multicentricity, cancer staging, lymphocytic infiltration, MACIS and AMES score) that were assessed and compared between the incidental and nonincidental groups. Nonincidentally detected thyroid nodules were significantly more likely to be larger32,34,35,37,38 and have higher rates of extra-thyroidal and extra-nodal extensions,32 multifocality37 and lymph node metastasis.22,31,32 Interestingly,
incidental thyroid nodules were reported to have more advanced disease (Stage III and Stage IV) in one study, this could be explained by the lack of adjustment of age as a confounding factor. Other indirect prognostic markers were not shown to be significantly different between the two groups. The results of the individual studies were described in Table S13.

4  DISCUSSION

The incidence of the incidentally detected thyroid nodule is on the rise, while its clinical significance remains controversial. This systematic review aimed to determine the risk of cancer in these nodules and the impact of incidental detection on prognosis. Apart from two studies published in 1998, other studies included in this review were published in the last 20 years. This could be due to the exponential rise in incidental thyroid nodules detected secondary to the relatively recent widespread use of cross-sectional imaging including ultrasound.

4.1  Risk of thyroid cancer by mode of detection

The number of incidentally detected thyroid nodules was lower than symptomatic nodules in all studies included in this analysis. In the case-control studies (n = 6), 140 (19%) of 738 malignant tumours and 1324 (53%) of 2508 benign tumours were detected incidentally (odds ratio = 0.64–2.86). In the retrospective cohort studies (n = 3), 9 (10%) of 91 patients in the incidental group and 56 (14%) of 398 patients in the nonincidental group had malignant nodules. The risk of malignancy ranged from 4% to 24% in the incidental arm and 4% to 29% in the nonincidental arm (relative risk = 0.13–6.27). These results are consistent with the malignancy rate of 7%–29% in other single-arm studies on incidental thyroid nodules. The wide range is probably due to differing study designs, nature of the population studied and the definitions used for outcomes and exposures.

These studies were limited by the lack of adjustment for potential confounding factors (age, ethnicity, nodule size or patients' body mass index [BMI]) and the absence of follow up for nonoperated or benign nodules in many studies.

4.2  Prognosis of thyroid cancer by mode of detection

In this prognosis part of the review, 4293 patients (2129 in incidental group and 2164 in nonincidental group) and 871 patients (295 in incidental group and 576 in nonincidental group) were included in the 12 retrospective cohort studies and two cross-sectional studies, respectively. Nonincidental detection was much more common than incidental detection in all studies except for two studies. Most retrospective cohort studies (n = 9) were limited by lack of adjustment for potential confounding factors (i.e., patient's age, BMI or ethnicity, size of cancer nodules) except for three studies.

Overall, incidentally detected thyroid cancer was significantly less likely to have recurrence/residual disease and had higher 5-year recurrence-free and overall survival rates. When comparing prognosis between these groups, it is important to recognize the potential for 'lead time' bias to impact on these results.

Esserman et al. proposed that asymptomatic, nonpalpable and indolent cancers identified incidentally be redefined as indolent lesions of epithelial origin tumours to mitigate the inevitable anxiety surrounding the diagnosis and the potential for overtreatment and the associated morbidity and cost to society. However, accurate identification of patients with tumours that will express an indolent behaviour is challenging and should therefore be the focus of further research.

4.3  Limitations of the review and future work

The vast majority of studies were either case-control or retrospective cohort; the limitations of which are widely recognized. The number of studies meeting the eligible criteria for this review was limited. Twelve studies were excluded as relevant data on risk or prognosis studies were not available. The quality of the studies included in the review were variable but consistent with the moderate risk of bias demonstrated in two systematic reviews of observational studies in thyroid cancer.

There was significant variation observed in the definitions of incidental and nonincidental detection (shown in Tables S4 and S7), populations studied and outcomes measured. The review protocol defined thyroid incidentaloma as a lesion identified on imaging for reasons unrelated to the thyroid gland; however, in two manuscripts in the risk study, some patients with thyroid incidentaloma detected during imaging for thyroid-related reasons or thyroid cancer screening were unable to be excluded from the incidental detection group during data extraction. Other definitions used by different studies included thyroid nodules found during exploration of the neck or autopsy regardless of any existing benign disease of the thyroid gland. Five studies were excluded at the screening stage of this review because incidental detection was not represented by nodules detected on imaging for nonthyroid indications. There was also variation in eligibility criteria, and in some studies, it was unclear if patients with risk factors were equally represented in both arms. A meta-analysis could not be performed for the prognosis part of the study due to variation in inclusion criteria, assessment of prognosis markers and period of follow up. Reaching a consensus on the definitions of exposures and outcomes will help the standardisation across various studies, improve reporting quality, enable comparisons across populations and reduce heterogeneity in a meta-analysis.

5  CONCLUSION

Data from this review show that incidentally detected thyroid nodules have a similar risk of malignancy as clinically apparent thyroid nodules and should therefore be evaluated in a similar manner to
symptomatic nodules based on the nodule characteristics on ultrasound and existing risk factors. However, the review also found that thyroid cancer diagnosed after incidental presentation tended to have better progression-free survival and overall survival. Further large, well designed prospective cohort studies with long follow-up periods should be carried out to assess the impact of incidental detection on both risk and prognosis of thyroid cancer and confounding factors such as nodule size and stage of disease should be adjusted for.

At the current time, investigation and management of thyroid nodules should not be influenced by the mode of detection. However, incidental detection is likely to impact favourably on prognosis and this study may be used in balancing the risk and benefits of the different management strategies being considered in these patients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JEC led the study and was involved in study design, methodology, data collection, interpretation, analysis, drafting and finalising the manuscript. AR was involved in data collection, interpretation and contributed to the manuscript. SPB conceptualised the study and was involved in study design, methodology, analysis and contributed to the manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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