

A meta-analysis examining the independent association between thyroid nodule size and malignancy

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Background: Tumor size is recognized as an important predictor of malignancy in many types of cancers. However, there is no clear line of characterization when it comes to the association between thyroid nodule size and malignancy risk prediction; and the current data remains inconsistent across different studies. The aim of our study is to examine the association between nodule size and malignancy using meta-analysis of the current literature.

Methods: Data sources were gathered through systemic search of PubMed, Embase and other scientific databases for articles published between January 1, 1996 and June 1, 2013. A reference group with nodule sizes <3 cm was set as a control group. Two other nodule size categories were established and these included nodules from 3–5.9 cm and nodules ≥6 cm in size. Primary outcome was a histologically proven malignancy per nodule size category. The effect sizes of clinicopathologic parameters, which are the quantitative measures of association strength between two variables, were calculated by the means of odds ratios (OR). The effect sizes were then combined using a random-effects model.

Results: Seven studies met our inclusion criteria with 10,817 thyroid nodules evaluated. Malignancy was identified in 2,206 (20.4%) nodules. After adjusting for patient age and gender, nodules that measured 3–5.9 cm had a 26% greater malignancy risk compared to those measuring <3 cm [OR, 1.26; 95% confidence interval (CI): 1.13–1.39]. However, nodules 6 cm or larger had a 16% lower risk of malignancy compared to those measuring <3 cm (OR, 0.84; 95% CI: 0.73–0.98).

Conclusions: Thyroid nodule size predicts cancer risk. However, a threshold effect of thyroid nodule size 6 cm or greater is significantly associated with a more benign disease.

Keywords: Thyroid nodule; thyroid malignancy; thyroid nodule size; fine-needle aspiration biopsy (FNA biopsy); follicular neoplasm

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Introduction

Thyroid cancer is the most common endocrine malignancy. The incidence is rising quickly in both genders, and it was estimated to represent 3.8% of all the new cancer cases in the United States as estimated by the American Cancers Society (ACS) (1). Predicting the likelihood of malignancy is the main concern when examining any thyroid nodule. The initial evaluation for all thyroid nodules includes both high-resolution ultrasound and fine-needle aspiration (FNA) when indicated.

A combination of clinical factors and ultrasound features helps determine whether a nodule is likely to be cancerous or not. These usually include, but are not limited to, nodule hypoechogenicity, presence of calcifications, ill-defined or infiltrative margins, or increased intra-nodular vascularity (2). Nevertheless, the accuracy of these features in predicting the malignant potential of a nodule is not recognized.

Of these different variables, nodule size is easily measured. However, data examining the relationship between thyroid nodule size and malignancy risk remains inconsistent. Multiple studies have been published on the subject (3-6), but many shortcomings have been identified, including small study population (6), study populations from a single institution (7), retrospective studies (3), inconsistent results across different studies, and nodules that were rendered benign based on FNA results only. We hypothesized that a cutoff of 3 cm might be more precise in determining malignancy risk. Therefore, we conducted a meta-analysis evaluating the available evidence in the literature regarding nodule size and its relationship to malignant behavior of thyroid nodules.

Materials and methods

Search strategy

A preliminary search was conducted for articles related to nodule size and its associated risk of malignancy to evaluate the volume of the relevant bibliography and choose keywords for the main search. Two reviewers (Hammad M. Masoodi, Yasin Ibrahim) conducted an independent systematic review of articles published in electronic databases (PubMed, Embase, Medline, and Web of Science) from January 1, 1996 through June 1, 2013. Articles were identified using the following keywords: (I) thyroid nodule; (II) thyroid carcinoma; (III) thyroid malignancy; (IV) follicular neoplasm; and (V) thyroid FNA

biopsy. These terms were identified in the title, abstract, or medical subject heading (MeSH). The studies were further restricted to articles written in English, and those involving adult human populations.

Data were abstracted using a standardized form. For each of the included studies, two reviewers extracted the following data: the country where the study was conducted, primary author of the study, number of patients and patient demographics, nodule size and characteristics, FNA results, and final histopathology results. Patients were divided into three major categories. Our reference category included those with nodule sizes <3 cm. The other categories were nodules sized 3–5.9 cm and those with nodules \geq 6 cm. In our spreadsheet used for data collection, we recorded the incidence of malignancy for each category, P values, and study conclusion. The primary outcome was histologically proven malignancy per nodule size category.

Study selection

Articles were included in our study if they met the following criteria: (I) prospective clinical studies, retrospective or cohort analyses discussing the association between nodule size and malignancy; (II) studies where the final histopathology result for the nodules was included; (III) articles including nodules labeled indeterminate by FNA (includes follicular neoplasm and Hürthle cell neoplasm) were also included in our study analysis.

Articles excluded from our study were: (I) abstracts, posters and literature reviews; (II) articles that are not examining the association between nodule size and malignancy development; and (III) studies using non-categorical data. After obtaining a full list of studies, the same reviewers independently assessed each study for eligibility for inclusion in the meta-analysis, and data was extracted according to the study criteria into a spreadsheet. Differences between reviewers were resolved by discussion, and agreement on the final dataset was reached by consensus.

Statistical analysis

We analyzed the correlation between nodule size and incidence of cancer in each of our three groups. Nodule sizes were divided and categorized into three major groups: <3, 3–5.9 and \geq 6 cm nodules. Adjustments were made for age and gender, and the effect size of clinicopathologic parameters, defined as the quantitative measure of the

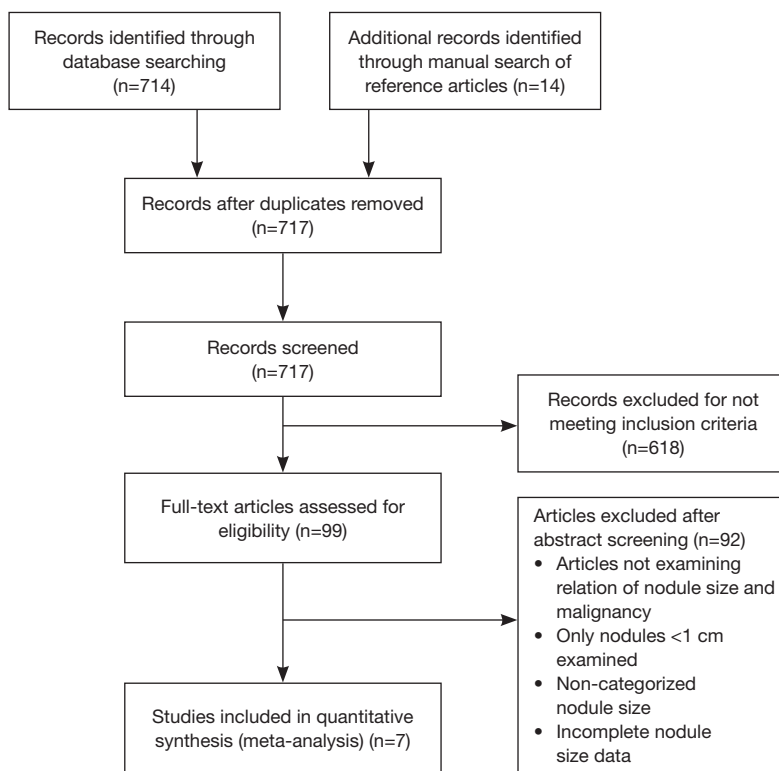


Figure 1 PRISMA flowchart demonstrating the selection process of included studies.

association strength between two variables, was calculated by the means of odds ratio (OR) for malignancy in each group. A DerSimonian and Laird random effects model was used to estimate and pool data for heterogeneity testing. The presence of heterogeneity was assessed by the Q test, and the extent of heterogeneity was quantified by the Chi-squared index. P value was estimated using Fisher's exact test and a P value less than 0.05 was considered significant. A funnel plot was constructed to assess the publication bias, where each group was compared to the reference group. The Begg's rank correlation test was used to examine the funnel plot asymmetry, and the Egger's weighted linear regression test was used to examine the association between the mean effect and its variance. Single studies were removed one at a time and data analysis was run to validate the heterogeneity of the data. Sensitivity analysis was performed to test the robustness of the results. The two studies originating from outside the United States were excluded, and the consistency of the results was examined. Forest plots were constructed to compare different OR between different studies and get the overall 95% confidence interval (CI). Age- and gender-adjusted OR

was done as previous studies have shown that the incidence of malignancy increases in young, male patients (8). An adjusted OR for these variables was used to ensure the elimination of any bias. All analyses were conducted using SATA analytical software.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to reach a total of seven articles that met our inclusion criteria (*Figure 1*). All articles underwent a full-text review and were included in the final meta-analysis (3,9-14).

Malignancy was identified in 2,206 nodules (20.4%). Four articles evaluated the risk of malignancy in nodules 3-5.9 cm as compared to the control group, while four articles examined the risk in those with nodules ≥ 6 cm. After adjusting for age and sex among groups, an age- and gender-adjusted OR was plotted (*Figure 2*). When compared to the reference group, those with nodule size 3-5.9 cm were found to have a 25% higher malignancy risk (pooled OR, 1.26; 95% CI: 1.13-1.39). Q-testing for heterogeneity

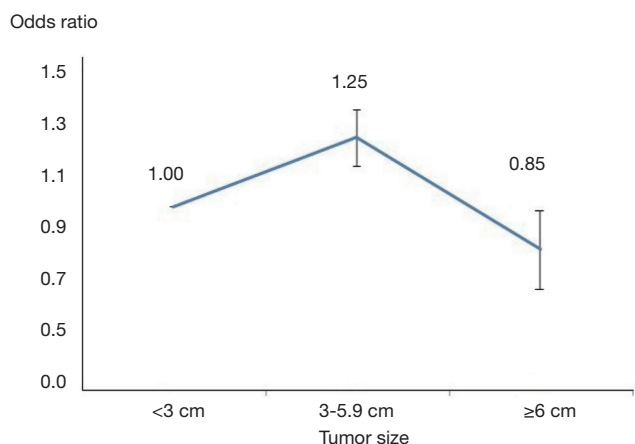


Figure 2 Age and gender adjusted odds ratio (OR) of malignancy across nodule size.

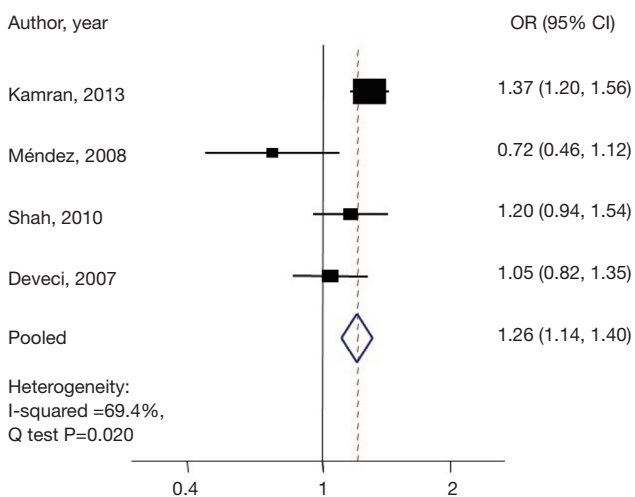


Figure 3 Forest plot showing results of unadjusted association of risk of malignancy comparing nodules <3 vs. 3–5.9 cm. The pooled odds ratio (OR) is 1.26, (95% CI: 1.136–1.397). The heterogeneity test showed significant heterogeneity, P value for Q test =0.02, I-square =69.4%.

was statistically significant (P=0.02) with a Chi-squared of 69.4% (Figure 3), demonstrating a significant association between nodules 3–5.9 cm in diameter and thyroid cancer.

Interestingly when comparing those in the group with a nodule size ≥6 cm to the reference group, a 15% lower risk of malignancy was found (pooled OR, 0.84; 95% CI: 0.73–0.98), with a statistically significant heterogeneity Q test, (P<0.001), and a Chi-square =90.7% (Figure 4).

All of the included studies were conducted in the USA

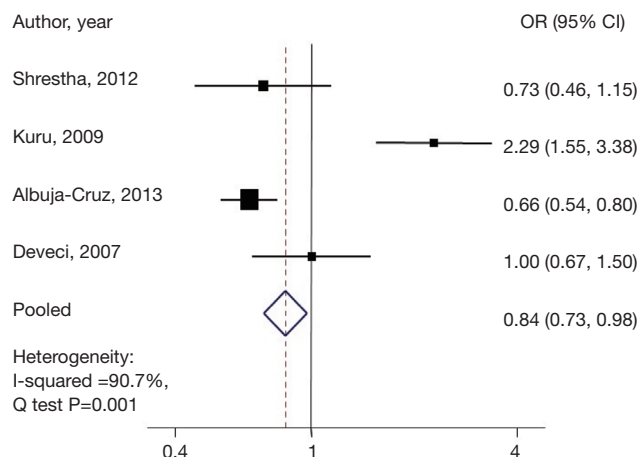


Figure 4 Forest plot showing results of unadjusted association of risk of malignancy comparing nodules <3 vs. ≥6 cm nodule size group. The pooled OR is 0.84, (95% CI: 0.73–0.98). The heterogeneity test showed significant heterogeneity, P value for Q test <0.001, I-square =90.7%.

except for two, one conducted in Turkey (13), and the other in Canada (14). Following the sensitivity analysis, the results were still significant, where those with nodules between 3–5.9 cm were significantly associated with malignancy (OR, 1.28; 95% CI: 1.14–1.43). Similarly, those with nodule size ≥6 cm were still associated with lower risk of malignancy (OR, 0.71; 95% CI: 0.60–0.83) (Table 1).

Discussion

In this meta-analysis, we scrutinized published articles examining the effect of thyroid nodule size as the sole predictor of malignancy risk. We included 10,817 thyroid nodules, making this one of the largest analyses of thyroid nodule size and cancer risk to date. The results of this meta-analysis suggest that nodule size may predict cancer risk. A recently published article by Shin *et al.* group suggests that surgery represents a reasonable option for nodules 3 to 4 cm (15). In our study, patients in the nodule group of size 3–5.9 cm have a 26% higher malignancy risk compared to those <3 cm in size. On the other hand, the risk of malignancy was found to drop by 16% when nodule size is 6 cm or more. These data elucidate previously conflicting reports as to whether nodule size affects thyroid cancer risk, and could alter clinical decision making (2,16,17).

Two major concerns for many surgeons are nodules shown to be follicular neoplasms and/or Hürthle cell on

Table 1 Association between nodule size and malignancy risk

Subgroups	0–2.9 cm	3–5.9 cm	≥6 cm
All	1	1.26 (95% CI: 1.13–1.39)	0.84 (95% CI: 0.73–0.98)
Excluding the two studies from outside the USA	1	1.28 (95% CI: 1.14–1.43)	0.71 (95% CI: 0.60–0.83)

CI, confidence interval.

FNA cytology. Follicular neoplasms represent a challenge as FNA cytology cannot differentiate between follicular carcinoma and follicular adenoma, requiring a thorough pathological examination. A nodule suspicious for follicular neoplasm may carry a risk of malignancy of 20–30% (18). Hürthle cell neoplasms have often been considered a more aggressive variant of follicular carcinoma due to their early metastasis and aggressive lymphovascular invasion (19). The 2009 American Thyroid Association guidelines recommend thyroid lobectomy for suspicious solid lesions of follicular neoplasms or Hürthle cell carcinomas without accompanying risk factors, and total thyroidectomy for tumor size >4 cm or displaying signs of atypia. Large nodules size are associated with false negative results (16), and are typically difficult to sample entirely. The 2009 guidelines did not differentiate between nodules ≥6 cm and those measuring 4–6 cm. Our study confirms the previous guidelines showing an increased risk of cancer in patients with nodules 3–5 cm, while pointing out the lower risk of malignancy seen in patients with nodules ≥6 cm.

This study is not without shortcomings. First, one of the included studies contributed with over 50% of the examined nodules (3). Although the risk of bias in each study was examined and our results were adjusted according to the age, sex, clinicopathologic diameters, yet, the effect of this study on the overall results remains to be considered. Additionally, another study excluded patients with nodules <1 cm from the <3 cm group (3). The effect of this exclusion might affect the overall results reported by this group as subcentimeter malignancies exist and can affect the total number of malignancies reported in the <3 cm category.

Based on our results, we propose an additional cutoff point of 6 cm. This is where the incidence of carcinoma decreases with larger size thyroid nodules. Therefore, if the patients in this group choose to undergo surgery for compressive symptoms or other reasons, a less invasive surgical procedure such as thyroid lobectomy may be offered, avoiding the certain life-long hormonal replacement needed after total thyroidectomy.

Conclusions

The size of thyroid nodules can be used as predictor for malignancy risk. Those with a nodule size between 3–5.9 cm have an increased risk of 26% when compared to those <3 cm in largest diameter. However, nodules ≥6 cm carry a lower risk for malignancy (16%, as compared to the reference group). Thoughtful consideration of the appropriate surgical intervention should be given to patients with nodules 3–5 cm in size due to their higher malignancy risk, especially if other clinical and/or ultrasonographic features suggestive of malignancy are present. While further validations are needed, our data provides important information to counsel patients and guide personalized clinical decisions.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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