

Characteristics of Thyroid Nodules: Prevalence, Size, and Associated Complications: A Literature Review

Syarifah Wahidah^a, Nila Kurniasari^{b*}, Hermawan Susanto^c

^a syarifah.wahidah-2020@fk.unair.ac.id

^aFaculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

^bDepartement of Anatomical Pathology, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

^cDepartement of Internal Medicine, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

Abstract

Background: Thyroid nodules are an endocrine neoplasia that is generally benign. The incidence of thyroid nodules increases with age and is more common in women. The unique anatomical location of the thyroid gland, which is superficial, can easily be detected either through physical examination or by using various diagnostic media. The prevalence of thyroid nodules increases with age, exposure to ionizing radiation and iodine deficiency. Functional thyroid nodules can result in hyperthyroidism such as sweating, palpitations, and impaired glucose tolerance. Cystic thyroid nodules can sometimes cause thyroid pain, which may indicate sudden bleeding or hemorrhagic infarction. **Method:** The research design used in this study is to use the Literature review method. This technique is carried out with the aim of expressing various theories that are relevant to the problem being faced or being researched as reference material in the discussion of research results. **Results:** Research results from the review of articles show that increasing the size of thyroid nodules has a nonlinear impact on cancer risk. The threshold was detected at 2 cm, and extension beyond 2 cm did not affect the risk of cancer. However, the risk of follicular carcinoma and other rare thyroid malignancies increases as the nodule enlarges. In malignant thyroid nodules, this technique has a longer surgical duration and does not differ in terms of complications in the form of laryngeal nerve injury, hypoparathyroidism with open thyroidectomy. Endoscopic thyroidectomy can be an option in managing low-risk thyroid carcinoma patients. **Conclusion:** Thyroid nodules are more common in women than men and occur mostly in the age group 41 – 50 years. In this study, there were more cases of malignant thyroid nodules than benign thyroid nodules.

Keywords: Charectiristics, thyroid nodules, prevalence, size, complications of thyroid nodules

1. Introduction

As per the American Thyroid Association (ATA) definition a thyroid nodule is a well-demarcated lesion in the thyroid gland, which is radiologically distinct from the surrounding thyroid parenchyma. Thyroid nodules are the most common endocrine nodules found in the clinic. The prevalence of thyroid nodules ranges from 5-50% depending on the specific population and the sensitivity of the detection technique, the prevalence of thyroid nodules increases with age, exposure to ionising radiation and iodine deficiency. In the United States,

1 in 14 adults have thyroid nodules, of which approximately 5% are malignant nodules, i.e. carcinomas. Carcinoma of the thyroid gland is a common neoplasia worldwide. A survey sponsored by the World Health Organization (WHO) in 2010 reported that approximately 44,670 new cases and 1690 people die from this disease every year. 3 In Indonesia until now there is no data on thyroid nodules, while the prevalence of thyroid malignancy according to data from the Cancer Registration Board of the Indonesian Pathology Specialist Association in 2008, ranks 5th out of ten most common malignancies in Indonesia.

Thyroid nodules are the most common endocrine neoplasia found in the clinic. The prevalence of nodules ranges from 5 - 50% depending on the specific population and the sensitivity of the detection technique, the prevalence of thyroid nodules increases with age, exposure to ionising radiation and iodine deficiency. In the United States the prevalence of solitary thyroid nodules is approximately 4%-7% of the adult population, 3-4 times more common in women than men.¹ Based on the Whickam Survey, thyroid nodules are estimated to be present in 5.3% of the female population and 0.8% of the male population. A study conducted in the Japanese military population from 1990 to 2012 found a significant increase in the prevalence of thyroid nodules in young men when compared to middle-aged men, but not vice versa. A thyroid nodule in some cases can transform into malignancy although the frequency is relatively low at around 5%-10% (Yan et al., 2023a).

Thyroid nodule is an endocrine neoplasia which is generally benign. The incidence of thyroid nodules increases with age and is more common in women. The unique anatomical location of the thyroid gland, which is superficial, can easily be detected either through physical examination or by using various diagnostic media. In a case that occurred in China, nodules were generally found at the age of 21-60 years with a high prevalence rate of malignancy, which was around 18.46%, while in Shanghai there was an increase in the incidence of malignancy from 1 to 3.7 per 1,000,000 cases in men and in women it was even higher, from 2.8 to 10.5 per 1,000,000. Exposure to ionising radiation is a factor that triggers the growth of thyroid nodules and is also a risk factor for turning thyroid nodules into malignancies.^{2,7} In the Hiroshima and Nagasaki atomic bomb blasts, thyroid nodules were found in 12.3% of men and 24.8% of women, while malignant tumours were identified in 2.1% and benign tumours in 5.1%.

The thyroid gland can form a variety of neoplasms, ranging from benign well-demarcated adenomas to highly aggressive anaplastic carcinomas. Malignant nodules are more common in young age and male gender. The incidence of thyroid nodule malignancy ranges from 5 - 10%. The prevalence of malignancy in multinodular is not significantly different. The prevalence of single nodules is 4.1% and multiple nodules is 4.7%. When viewed from the type of carcinoma, $\pm$ 90% of papillary 2 and follicular carcinoma types, 5 - 9% of medullary carcinoma types, 1 - 2% of anaplastic carcinoma types, and 1 - 3% of other types (Masjhur, 2014).

Some studies suggest a prevalence of 6% of thyroid nodules diagnosed by palpation, 19-35% by ultrasound and 8-65% in autopsy data (Dean, 2008). Thyroid nodules are found more frequently in women than in men, but the ratio between the sexes is smaller than what is observed for clinically detectable goiters.

Thyroid nodules are a disease in the form of lumps that can be benign or malignant which can be caused by several risk factors such as a low iodine diet, genetic factors, a history of radiation exposure, and depending on the age and gender of a person where the disease must be eliminated because it is in accordance with the Islamic view that the obligation to avoid a misfortune or the obligation to make preventive efforts (prevention) so that no misfortune occurs with all efforts that can be done (Sugianto, 2014). Thyroid nodules generally do not cause symptoms, but when thyroid nodules produce symptoms, the most common symptom is a lump in the neck followed by a feeling of a mass when swallowing. Swallowing difficulties will be felt when the thyroid nodule is large enough to be located in a certain place, thus blocking the passage of food through the oesophagus (Clayman, 2018).

Based on the above background, researchers are interested in knowing the characteristics of thyroid nodules related to prevalence, size, and their relationship with the incidence of complications.

2. Material and Method

The research design used in this study is to use the Literature review method. In this study, the authors chose quantitative research articles with a cross sectional or case control design. The author uses a database that is used as a search source related to the research, namely Google Scholar. In searching the source of the article, the author used Indonesian keywords, namely: characteristics, thyroid nodules, prevalence, size, complications of thyroid nodules. After searching through a predetermined database, the findings were selected using inclusion and exclusion criteria. The inclusion and exclusion criteria are presented.

A. Inclusion Criteria

- Research results in the form of articles with primary research data.
- Articles are full-text articles that are free and accessible.
- Articles using cross sectional or case control design.
- Articles using English language.

B. Exclusion criteria

- Research articles in the form of theses and theses not in the form of published articles.
- The article used a cross-sectional or case control design.
- Research articles do not use research designs other than cross sectional or case control.

3. Results

Table. 1 Literature Review Search Results

Title	Author	Method	Research Results
Prevalence of Thyroid Nodules and Associated Clinical Characteristics: Findings from a Large Sample of People Undergoing Health Checkups at a University Hospital in Vietnam	(Tran et al., 2023)	A retrospective and cross-sectional descriptive study was conducted, based on the electronic medical records of people who underwent health examination at the Department of Health Examination, University Medical Centre in Ho Chi Minh City.	A total of 16,784 participants (mean age: 40.4 ± 12.7 years, 45.1% female) were included in this study. The overall prevalence of thyroid nodules was 48.4%. The mean nodule diameter was 7.2 ± 5.8 mm. The prevalence of malignant nodules was characterised by 36.9%. Women had a significantly higher prevalence of thyroid nodules than men (55.2% vs 42.9%, $p < 0.001$). Advanced age, hypertension, and hyperglycaemia were significantly associated with thyroid nodules in both genders. In men, significant factors also included increased body mass index. In women, these included elevated total and LDL cholesterol, hypertriglyceridemia, and hyperuricemia.
Thyroid NPrevalence of thyroid nodules and characteristics of thyroid ultrasound in children with goiter: a single center experience	(Al Juraibah et al., 2022)	A retrospective review of children and adolescents under 18 years of age (2015-2020) referred for neck ultrasound due to goitre in clinical examination.	A total of 262 patients were included with a mean age of 13.77 ± 3.7 years. Thyroid antibodies were positive in 119/262 (45.4%) patients. Thyroid US was reported as abnormal in 210/262 (80%) patients. Thyroid nodules were found in 33.6% ($n=88/262$) of patients with goiter and in 41.9% ($n=88/210$) of patients with abnormal thyroid results. Patients with positive antibodies had more glandular heterogeneity and hypervascularity on thyroid US ($P < 0.001$). On the other hand, thyroid nodules were more likely to appear in patients with antibody negative thyroid ($P=0.025$).

			Heterogeneity in the thyroid positive group was significantly correlated with elevated TPOAb ($P<0.001$) and TSH levels ($P<0.028$). Heterogeneity in AS had a positive predictive value ($P=0.041$), whereas hypervascularity had a low predictive value for thyroid nodules ($P=0.022$). Age, gender, family history of thyroid disease, antibody status and echogenicity in AS showed no significant association with thyroid nodules. Papillary thyroid carcinoma was diagnosed in six patients and one of these patients was thyroid antibody positive.
Thyroid Nodule Size and Prediction of Cancer	(Hoang, 2010))	Conducted a retrospective cohort analysis at an academic hospital with 4955 consecutive patients evaluated between 1995 and 2009.	Increasing thyroid nodule size impacts cancer risk in a nonlinear manner. The threshold is detected at 2.0 cm, beyond which the cancer risk does not change. However, the risk of follicular carcinoma and other rare thyroid malignancies increases with the size of the nodule.
The Prevalence of Thyroid Nodules and its Factors Among Chinese Adult Women	(Dong et al., 2022)	Conducted a retrospective cross-sectional study at a tertiary hospital from 2017 to 2019. Included participants underwent thyroid colour Doppler ultrasonography, lipid screening, and dietary evaluation.	A total of 2,784 participants were included, and 933 participants were found to have thyroid nodules on B ultrasound. The prevalence of thyroid nodules was 33.3%. Women aged 50-59 years (OR: 1.746, 95% CI [1.356-2.249]), older than 60 years (2.147 [1.540-2.993]) and predominantly manual occupation (1.780 [1.367-2.317]) were risk factors for thyroid nodules, while moderate dietary diversity (0.624 [0.476-0.817]) and normal triglyceride levels (0.739 [0.604-0.905]) were protective factors.
Risk factors associated with the prevalence of thyroid nodules in adults in Northeast China: a cross-sectional population-based study	(Yan et al., 2023b))	We used a cross-sectional approach involving a questionnaire survey, which focused on the participants' living habits, and a physical examination that included anthropometry and ultrasound imaging.	The prevalence of thyroid nodules was significantly associated with female gender (OR 2.569, 95%CI 1.937 to 3.405, $p<0.001$) and increasing age (OR 1.054, 95%CI 1.041 to 1.066, $p<0.001$). This association was more pronounced in patients with multiple thyroid nodules. For men under 60 years, not smoking was inversely correlated with the prevalence of multiple thyroid nodules (OR 0.321, 95%CI 0.149 to 0.69, $p<0.05$). In women under 60 years, diastolic blood pressure (DBP) was significantly associated with the prevalence of thyroid nodules (OR 0.978, 95%CI 2.614 to 2.705, $p<0.05$).
Prevalence of thyroid nodules and their associated clinical parameters: a large-scale, multicenter-based health checkup study	(Moon et al., 2018)	A total of 72,319 subjects who underwent thyroid US at three medical examination centres in Korea from January 2004 to December 2010 were included in this study. Correlations between the presence of thyroid nodules and other clinical parameters were analysed	The high prevalence of thyroid nodules in people undergoing US thyroid at health screening suggests that increased detection of thyroid nodules results in increased prevalence in the general population. However, metabolic disorders may also contribute to the increased thyroid nodule prevalence in Korea.

Prevalence and predictors of thyroid cancer among thyroid nodules: a retrospective cohort study of 1,000 patients	(Elbalka et al., 2021))	In this study, retrospectively enrolled all patients with nodular goitre admitted to our tertiary hospital and analysed their data with the aim of detecting cancer rates among different types of nodular goitre.	The predilection for solitary thyroid nodules (STN) is found in younger women, with STN tending to be larger than MNG in the same age group. However, both types of nodules have the same risk of becoming malignant. The Thyroid Imaging Data and Reporting System (TI-RADS) and the Bethesda score are the only dependent predictors of malignancy in thyroid nodules.
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4. Discussion

Most cases of thyroid nodules occurring in women are in the age range of 36 - 40 years, and 46 - 50 years of age in men. The data shows that thyroid nodules typically occur in the third to fifth decade regardless of gender. The incidence of thyroid nodules increases with age but tends to decrease again above the age of 50 years. The youngest age in the study showed 14 years and the oldest 73 years.

Cases of thyroid nodules occur mostly in the age range of young adults and old adults, but are very rare in children and the elderly. This data is supported in a study conducted in a case that occurred in China where thyroid nodules were generally found in the second decade to the sixth decade. Cases of thyroid nodules that occur in children and the elderly are cases that should be suspected as a malignancy of the thyroid gland. Patients with thyroid nodules are greater in women, namely 89 cases (91.8%) than men who are only 8 cases (8.2%) with a ratio of 11:1. In the United States, the prevalence of solitary thyroid nodules is about 4-7% of the adult population, 3-4 times more common in women than men. In a previous epidemiological survey, it was stated that the prevalence of thyroid nodules was four times greater in women than in men (Indriani et al., 2021).

The endocrine system and especially the endocrine organs, including the thyroid undergo functional changes with age. The prevalence of thyroid disorders increases with age as well as the morphology and physiology of the thyroid gland which undergoes many changes with age.

In this study there are similarities with previous studies with the incidence of thyroid nodules that occur in women more when compared to the incidence in men. Cases of nodules that occur more in women than men are indicated that there are estrogen receptors in the thyroid gland, while estrogen as is known has carcinogenesis properties, namely properties that stimulate excessive cell growth or what is often referred to as malignancy. Naturally, the hormone estrogen is found more in women than in men because men only get a limited amount of estrogen, which comes from the conversion of testosterone to estrogen. This is what seems to cause the link between gender and the incidence of nodules, but experts have not agreed with this theory given the limited studies so there is no strong evidence of a link between the two.

The influence of hormones in women is one of the factors predisposing to the increase in the number of female patients compared to men. Estrogen can increase thyroid binding globulin (TBG) levels which work as a transport of T4 and T3 in the blood resulting in a decrease in free T4 levels. This stimulates TSH so that glandular hyperplasia occurs as a compensatory mechanism to form more thyroid hormones so that serum T4 and T3 levels can return to normal.

Our study found that the risk of malignancy was highest in nodules <2 cm and there was no increased risk of malignancy in nodules >2 cm. Thyroid nodules with a diameter of 1.0-1.9 cm conferred a baseline risk of cancer in comparison (64.8% cancer risk). The overall cancer prevalence in nodules measuring 2.0-2.9 cm was 17.6%; in nodules measuring 3.0-3.9 cm it was 10.6%; and in nodules measuring 4.0 cm it was 7%, showing a statistically significant difference ($p < 0.001$). However, the main effect of this relationship was the

high malignancy rate in nodules measuring 1.0-1.9 cm. When comparing nodules of 2.0-2.9 cm, 3.0-3.9 cm, or 4.0 cm, no difference in malignancy rate was shown. This suggests a possible threshold effect. Therefore, it is worthwhile to conclude that thyroid nodule size up to 2 cm is associated with an increased risk of thyroid cancer, but growth beyond 2 cm no longer affects cancer risk (IGN Gunawan, 2021).

Thyroid nodules are commonly found in iodine-deficient areas. Exposure to radiation is said to be one of the risk factors, with thyroid nodules occurring about 2% annually after patients undergo radiation therapy.⁸ A retrospective study of patients with childhood Hodgkin's disease found that those who underwent radiation therapy had a 27 times higher risk of developing thyroid nodules compared to their siblings.⁹ Another study of 119 cancer survivors found that those who underwent radiation therapy and chemotherapy had a 2x higher risk of developing thyroid nodules compared to those who underwent only chemotherapy.¹⁰ Most thyroid nodules are asymptomatic and are discovered during a neck palpation examination.

However, sometimes patients may present with a complaint of a lump in the neck that moves with each swallow. The common location of the lump is the border of the isthmus with the lateral lobe. If there is bleeding within the lump, the patient will complain of an enlarged lump and pain. In benign cases, the lump generally has a smooth surface, soft texture with regular borders that can be clearly seen, while malignancy can be predicted if these characteristics change.¹¹ Supportive examinations such as Thyroid Stimulating Hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), ultrasonography, and needle-biopsy examination need to be done to determine whether the thyroid nodule is benign or a malignancy. Management of thyroid nodules is based on the results of the needle-biopsy examination.

In benign and asymptomatic euthyroid nodules, follow-up will be done annually with ultrasound and TSH examination. In some cases of benign thyroid nodules, therapeutic interventions such as levothyroxine, radioiodine, ethanol injection, and surgery can be given, especially in thyroid nodules with large size and obstruction symptoms. In thyroid nodules with suspicion of malignancy, surgery is the recommended therapy.¹² The following is a case report of a single thyroid nodule confirmed by cytological and radiological examination.

5. Conclusion

Based on the results and discussion, it was found that In conclusion, the findings of this study suggest that increasing thyroid nodule size impacts cancer risk in a nonlinear manner. The threshold was detected at 2 cm, and expansion beyond 2 cm did not affect cancer risk. However, the risk of follicular carcinoma and other rare thyroid malignancies increases with nodule size. In malignant thyroid nodules, this technique has a longer surgical duration and has no difference in terms of complications in the form of laryngeal nerve injury, hypoparathyroidism with open thyroidectomy. Endoscopic thyroidectomy may be an option in managing low-risk thyroid carcinoma patients (Pramudita & Kusuma, 2021).

6. Suggestion

Further research is needed in the form of prospective, multicentric, randomised controlled studies in Asian populations, especially Indonesia, or systematic reviews with a higher level of evidence.

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