

Prevalence of Thyroid Nodules and Predictive Factors for their Malignancy: Is there any Correlation between Level of TSH and Type of Malignancy?: A Cross Sectional Study

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Abstract

Background: Thyroid nodule is a common finding of the endocrine system. Despite thyroid nodules in most cases being symptom-free and mostly benign, there are always malignancy risks. This study aimed to evaluate the frequency of types of thyroid nodules according to histopathology characteristics in Ahvaz hospitals.

Materials and Methods: This retrospective cross-sectional study was performed on patients with thyroid nodules with histopathological diagnosis referred to the educational hospitals of Ahvaz Jundishapur University of Medical Sciences and private endocrine clinics in Ahvaz from 2018 to 2021. Demographic characteristics, clinical history, histopathological results, ultrasonographic findings, and the presence of lymphadenopathy were collected from the patient's medical records.

Results: A total of 380 patients with thyroid nodules with a mean age of 41.2 ± 12.28 years, 79.37% of whom were female were included in the study. A total of 267 (70/3%) cases were benign. Malignancy was found in 113 (29.7%) patients in which papillary thyroid cancer was the commonest histological diagnosis ($n = 99$; 87.61%). Age between 30 and 45 years ($P = 0.001$), bilateral involvement ($P = 0.028$), nodules size ($P = 0.004$), and lymph node involvement ($P < 0.0001$) were significantly associated with malignancy of thyroid nodules. However, there was no significant relationship between malignancy with gender ($P = 0.450$), BMI ($P = 0.258$), and history of head and neck radiotherapy ($P = 0.200$). There was no significant relationship between high thyroid stimulating hormone (TSH) and the type of malignancy ($P = 0.059$).

Conclusion: Malignant thyroid nodules were associated with factors including age between 30 and 40 years, bilateral nodules, and lymphadenopathy. Therefore, it is important to consider these risk factors in the management and risk assessment of thyroid nodules.

Keywords: Histopathology of thyroid nodules, risk factor, thyroid cancer, thyroid nodules

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Submitted: 12-May-2023; **Revised:** 19-Oct-2023; **Accepted:** 21-Oct-2023; **Published:** 29-Jul-2024

INTRODUCTION

Thyroid nodules are one of the most common endocrine disorders that are seen in 60% of the general population and their prevalence is increasing worldwide.^[1,2] Although some of them may cause some local symptoms and be diagnosed

through clinical examination, currently most thyroid nodules are reported as incidental findings during unrelated imaging^[3] and only 3.7% to 7% of thyroid nodules in the general population are diagnosed through examination and palpation.^[4]

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How to cite this article: Moradi L, Hani Tabaei Zavareh M, Zaman F, Shareghi Bruojeni A, Taravati SAM, Naderi Boldaji H, *et al.* Prevalence of thyroid nodules and predictive factors for their malignancy: Is there any correlation between level of TSH and type of malignancy?: A cross sectional study. *Adv Biomed Res* 2024;13:48.

Access this article online

Quick Response Code:



Website:
www.advbiores.net

DOI:
10.4103/abr.abr_158_23

Most thyroid nodules are benign and the risk of malignancy is observed in about 5% of them.^[5,6] Some known factors that increase the risk of malignancy are radiation exposure, especially in childhood, the rapid growth of the nodule, hoarseness, and a family history of thyroid cancer or other syndromes (multiple endocrine neoplasia type II, familial adenomatous polyposis).^[5,7,8]

Fine needle aspiration (FNA) is a valuable tool for evaluating the benign or malignant type of thyroid nodules and has reduced the need for unnecessary thyroidectomy.^[5] The decision to perform FNA depends on the ultrasound characteristics (microcalcification and irregular margin, hypoechogenicity, and vascularity) and the size of the nodule (larger than 1 cm).^[9,10]

Evaluation of thyroid nodules is very important to distinguish malignant types and to avoid unnecessary surgery and related problems.^[11] Although most thyroid nodules are benign, there is always a risk of malignancy of nodules. In addition, the incidence of thyroid cancer has been increasing worldwide in the past few decades, and today it is the third most common cancer in women,^[12] whereas it was ranked 14th about 20 years ago.^[13] Therefore, it is very important to know the factors influencing the occurrence of thyroid nodules and their malignancy to adopt preventive strategies for thyroid cancer. Different studies have reported different statistics about the individual and clinical characteristics of people with thyroid nodules as well as the characteristics related to thyroid nodules.^[14-16]

This study aims to determine the histopathological characteristics of thyroid nodules and their relationship with some malignant risk factors including age, sex, family history of thyroid disease, and ultrasound findings. Also because of the high prevalence of thyroid nodules and concern about malignancy of these nodules, we have assessed the risk of these nodules malignancy according to pathological, laboratory, and clinical assessment to ensure the patients and early diagnose of disease.

MATERIALS AND METHODS

The current research is a descriptive and analytical study that is cross-sectional using the medical records of patients with thyroid nodules with histopathological diagnoses referring to educational hospitals and endocrinology clinics in Ahvaz City and using the information of the 4 years of patients from 2017 to 2018. This study was conducted after obtaining permission from the research council and approval from the ethics committee of Ahvaz University of Medical Sciences (code of ethics: IR.AJUMS.HGOLESTAN.REC.1400.106). Also, in all stages of this research, the provisions of the Helsinki Research ethics statement and the principles of confidentiality of patient information were respected.

Sampling was done by census method and the studied sample size was calculated based on $P=0.5$ sensitivity, 95% confidence,

and $d=5\%$ accuracy, using the sample size calculation formula to estimate the proportion equal to 380 people.

Hospital Information System (HIS) was used to collect information. People with incomplete information in the file and a lack of cytology or histopathology reports were excluded from the study.

At the beginning of the study, information about each patient including demographic characteristics (age, gender, and body mass index), history of previous head radiotherapy, family history of thyroid disease, ultrasound findings (size of the nodule, involved lobe), presence of lymphadenopathy (involvement of glands, lymphatic), and serum TSH (thyroid stimulating hormone) levels were collected by carefully examining the patient's medical records. The result of the biopsy and histopathology (whether the nodule is benign or malignant) and the type of malignancy were also recorded.

In this study, hypoechoic nodules ≥ 1 cm with a high or median suspicious pattern, hyperechoic nodules with a diameter ≥ 1.5 cm and low suspicious pattern, and spongiform nodules with size ≥ 2 cm and very low suspicion of malignant patterns in ultrasound, and nodules of 5 to 10 mm that had characteristics in favor of malignancy in ultrasound were biopsied by FNA.^[17] All ultrasounds were performed by an experienced thyroid radiologist, and all FNA evaluations were performed in the same laboratory.

The size of nodules was divided into four groups: < 2 cm, 2 to 3 cm, 3 to 4 cm, and ≥ 4 cm. According to body mass index (BMI), patients were divided into four groups: thin (BMI < 18.5), normal (BMI: 18.5–24.9), overweight (BMI: 25–29.5), and obese (BMI > 30). TSH was divided into three groups: normal TSH (normal levels in the range of 0.4–4.0 mIU/L), high TSH (higher than normal levels), and low TSH (lower than normal levels).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL, U.S.A.) version 22 was used for statistical analysis. To describe the data, mean, standard deviation, frequency, and percentage were used. The Chi-square test (or Fisher's exact test) was used to measure the correlation of variables. The significance level in the tests was considered 0.05.

RESULTS

In this study, 380 people with thyroid nodules, including 227 women (79.37%), 72 men (20.63%), and an average age of 41.2 ± 12.28 years (range, 15–73 years) were investigated. The basic characteristics of patients with thyroid nodules are presented in Table 1. Most patients were in the age group of 30–45 years (47.1%) and the least frequency of patients was in the age of over 60 years (13.2%).

Thyroid nodules of 2–3 cm were the most frequent among the investigated cases regarding nodule size (38.4%) and most patients had involvement in both lobes (45.3%) and only 6.8% had lymph nodes involved.

Table 1: Histopathological diagnosis according to demographic characteristics and nodule characteristics

Variables	Categories	Histopathological diagnosis		Total number (%)	P***
		Malignant no (%)	Benign (%) unbern		
Age (years)	15–30	22 (50)	22 (50)	44 (100)	0.001*
	30–45	56 (31.3)	123 (67.7)	179 (100)	
	45–60	29 (27.1)	78 (72.9)	107 (100)	
	>60	6 (12)	44 (88)	50 (100)	
Sex	Female	76 (27.4)	201 (72.6)	277 (100)	0.450*
	Male	23 (31.9)	49 (68.1)	72 (100)	
BMI	Normal	38 (34.9)	71 (65.1)	109 (100)	0.258*
	Overweight	50 (29.6)	119 (70.4)	169 (100)	
	Fat	25 (24.5)	77 (75.5)	102 (100)	
Nodule Size (cm)	2>	47 (42.7)	63 (57.3)	110 (100)	0.004*
	2–3	35 (24)	111 (76)	146 (100)	
	3–4	12 (12.1)	45 (78.9)	57 (100)	
	4≤	19 (28.4)	48 (71.6)	67 (100)	
Involved lobe	Left	28 (33.7)	55 (66.3)	83 (100)	0.028*
	Right	26 (20.8)	99 (79.2)	125 (100)	
	Both	59 (34.3)	113 (56.7)	172 (100)	
Involvement of lymph nodes	Has it	29 (72.5)	11 (27.5)	40 (100)	<0.0001*
	Does not have	84 (24.7)	256 (75.3)	34 (100)	
History of radiotherapy	Has it	4 (57.1)	3 (42.9)	7 (100)	0.200 **
	Does not have	109 (29.2)	264 (70.8)	373 (100)	
Family history thyroid disease	Has it	2 (7.7)	24 (92.3)	26 (100)	0.011*
	Does not have	111 (31.4)	243 (68.6)	354 (100)	

*Chi-square test. **Fisher's test. ***This calculated *P* value is specific to a group of patients and is discussed in the text please find it in the text

Also, a total of 113 patients (29.7%) had malignant thyroid nodules, and the most common type of malignancy (87.61%) was papillary thyroid carcinoma (PTC).

The results of examining the frequency of histopathological diagnosis (malignant or benign nodule) according to demographic characteristics and nodule characteristics are presented in Table 1. As can be seen, there was a significant relationship between age groups and the type of nodule ($P = 0.001$) while the number of people with thyroid nodules was higher in the age group of 30–45, but the percentage of malignancy in the age group under 30 years was higher than over 30 years. There was a significant relationship between the size of the nodules and the benign or malignant nature of the nodules ($P = 0.004$); The percentage of malignancy in nodules below 2 cm was higher than in the size of nodules above 2 cm. There was a significant relationship between the presence of lymph node involvement and the incidence of malignancy ($P < 0.0001$).

The results related to examining the relationship between the type of thyroid nodule malignancy and different variables are presented in Table 2 (in some variables, due to the low frequency of some subgroups, we had to merge some subgroups to perform a statistical test). As can be seen, there was no significant relationship between the variables of age, BMI, node size, involved lobe, lymph node involvement, history of head and neck radiotherapy, and family history of thyroid disease with the malignant type ($P < 0.05$).

The results related to investigating the relationship between TSH and the type of malignancy of thyroid nodules are presented in Table 3. There was a significant relationship between the type of malignancy and low TSH ($P = 0.08$), but there was no significant relationship between high TSH and the type of malignancy ($P = 0.059$). Also, 6.3% of noneuthyroid patients and 20% of patients with normal TSH were diagnosed with a malignant type of MTC and Hertel cell carcinoma, which is almost three times more than nonaffected patients ($P = 0.029$).

DISCUSSION

The results of the present study showed that most patients with thyroid nodules (47.1%) were in the age group of 30–45 years, and the lowest frequency of patients was in the age range of over 60 years. In other studies, the occurrence of thyroid nodules was most common between the ages of 30 and 45, and the average age of people at the time of diagnosis of thyroid nodules was in this range.^[18–20]

Other results of the present study showed that most people with thyroid nodules were female (79.37%). In other studies, more prevalence of thyroid nodules in women than in men has been reported including the prevalence of 75% in women in the study by Yazidi *et al.*^[21] and the study by Varma and his colleagues in the UAE,^[18] and the prevalence of 87.7% in women in the study by Yazdani and his colleagues^[16] and

Table 2: Examining the relationship between the type of malignancy and different variables

Variables	Categories	Type of malignancy		Total number (%)	P*** (The calculated P is discussed in the text)
		Other no (%)	PTC (%) umbern		
Age	45 ≥	11 (14.1)	67 (85.9)	78 (100)	0.54*
	>45	3 (8.6)	32 (91.4)	35 (100)	
BMI	Normal	6 (15.8)	32 (84.2)	38 (100)	0.16*
	Overweight	3 (6)	47 (94)	5 (100)	
	Fat	5 (20)	20 (80)	25 (100)	
Nodule size (cm)	≤3	8 (9.8)	74 (90.2)	82 (100)	0.20*
	>3	6 (19.4)	25 (80.6)	31 (100)	
Involved lobe	Left	4 (14.3)	24 (85.7)	28 (100)	>0.05**
	Right	8 (30.8)	18 (69.2)	26 (100)	
	Both	2 (3.4)	57 (96.6)	59 (100)	
Involvement of lymph nodes	Had	2 (6.9)	27 (93.1)	29 (100)	0.51*
	Has not	12 (14.3)	72 (85.7)	84 (100)	
History of radiotherapy	Had	0 (0)	4 (100)	4 (100)	0.99*
	Has not	14 (12.8)	95 (87.2)	109 (100)	
Family history of thyroid disease	Had	1 (50)	1 (50)	2 (100)	0.23*
	Has not	13 (11.7)	98 (88.3)	111 (100)	

*Fisher's exact test. **Chi-square test. ***This calculated P value is specific to a group of patients and is discussed in the text please find it in the text

Table 3: Investigating the relationship between TSH and the type of malignancy of thyroid nodules

Variable	Category	PTC	MTC	Hertel cell carcinoma	PTC	Other	Total	P
Decreased level of TSH (low)	No	46 (82.2)	4 (7.1)	6 (10.7)	46 (82.1)	10 (17.9)	56 (100)	0.08*
	Yes	53 (93)	0 (0)	4 (7)	53 (93)	4 (7)	57 (100)	
TSH (normal)	No	59 (93.7)	0 (0)	4 (6.3)	59 (93.7)	4 (6.3)	63 (100)	0.029*
	Yes	40 (80)	4 (8)	6 (12)	40 (80)	10 (20)	50 (100)	
Increased level of TSH (high)	No	91 (86.7)	4 (3.8)	10 (9.5)	91 (86.7)	14 (13.2)	105 (100)	0.59**
	Yes	8 (100)	0 (0)	0 (0)	8 (100)	0 (0)	8 (100)	

*Chi-square test. **Fisher's test

the prevalence of 87% in the study by Joseph-Auguste and colleagues in France^[22] and a prevalence of 83% in women was reported in the study by Uyar and colleagues in Turkey.^[15]

Although thyroid cancer has been increasing worldwide in the past few decades and is the third most common cancer in women today,^[12] the etiology of the increase in thyroid cancer is currently unclear, although environmental and hormonal factors play a role in this.^[22] Also, the increase in the prevalence of thyroid nodules can be due to the progress in radiographic equipment, especially ultrasound imaging, which provides the possibility of early diagnosis of thyroid nodules.^[20]

Other factors, including the obesity pandemic, also seem to play a role in increasing the incidence of thyroid nodules and thyroid carcinoma.^[20,23,24] As in the present study, 44.5% of people with thyroid nodules were overweight and 26.8% were obese.

In the present study, most thyroid nodules (38.4%) were in the size range of 2–3 cm, a significant percentage of patients had involvement in both lobes (45.3%), and only 6.8% of cases involved lymph nodes. In other studies, it has been reported that about half of thyroid nodules (between 45% and 55% of cases) are seen bilaterally (in both thyroid lobes).^[18,19,25]

In the present study, out of a total of 380 patients with thyroid nodules, 113 patients (29.7%) had malignant thyroid nodules, and papillary thyroid carcinoma was the most common malignancy with 87.6%. In other studies, papillary carcinoma has been reported as the most common type of thyroid nodule malignancy.^[26,27] Thyroid papillary nodules are common in the study by Yazidi and his colleagues with a prevalence of 89%,^[21] in the study by Joseph-Auguste and his colleagues in France with a prevalence of 80%,^[22] and in the study by Uyar and his colleagues in Turkey^[15] with a prevalence of 94.2%. They had the most histological type of thyroid nodules.

The results of the present study showed that there was a significant relationship between age groups and the type of thyroid nodule, so the highest frequency of malignancy was in the age group of 30–45 years (49.6%) and after that, the frequency of malignant nodules decreased with increasing age.

The average age of people with malignant thyroid nodules was 41.1 years^[21] and 38.15 years in Yazdani *et al.*'s study.^[16] In the study by Joseph-Auguste and his colleagues, it was also reported that the risk of malignant nodules increases until the age of 50 and decreases after the age of 50.^[22] These results, in line with the findings of the present study, show that malignant

nodules are more common in the forties and after that, the risk of malignancy decreases.

The results of the present study showed that there was a significant relationship between the size of the nodules and the involved lobe with the benignity or malignancy of the nodules; so that most of the malignant nodules were less than 2 cm in size and were involved in both lobes. Also, among the people with lymph node involvement, 72.5% had malignancy. On the other hand, in the present study, benign and malignant nodules had no significant difference in terms of gender distribution of patients, BMI, or history of radiotherapy.

Different risk factors for malignancy have been reported in different studies. For example, in some studies, contrary to the present study, female gender has been reported as a risk factor for thyroid nodule malignancy.^[22,28] Also, contrary to the results of our study, some studies reported a higher risk of malignancy of thyroid nodules in obese patients (high BMI, presence of abdominal, and general obesity).^[16,28,29]

Also, although it has been reported in previous studies that a history of head and neck radiotherapy, especially during childhood, was one of the most important risk factors for thyroid malignancy,^[5,30] the risk of malignant carcinoma in these nodules is reported to be 35%–40%.^[30] However, in the present study, no significant relationship was observed between the occurrence of malignancy and history of radiotherapy. The reason for this can be related to the small volume of the studied sample and the small number of malignant cases. However, in other past studies as in the present study, cervical lymph node involvement has been reported as a risk factor for thyroid nodule malignancy.^[7,31,32]

In the study by Uyar and his colleagues, factors such as lymphadenopathy, microcalcification, and most importantly increased vascularity were reported as risk factors for malignancy of thyroid nodules. However the age and gender of the people as well as the size of the nodules did not differ between benign and malignant nodules.^[15] In the study by Zaid and his colleagues, there is a significant relationship between the age, sex, weight, and BMI of patients with benign and malignant thyroid nodules, and the risk factors of thyroid nodule malignancy included insulin resistance, high HOMA-IR hyperinsulinemia, and visceral obesity (increased waist circumference).^[20] In the study by Yazdani and his colleagues, the most important factors identified in thyroid nodule malignancy in patients with thyroid nodules included severe obesity, bilateral nodules, and high TSH level.^[16] In the study by Joseph-Auguste and his colleagues, there was a difference in terms of age, BMI, nodule location, number of nodules, thyroid function tests, and family history of thyroid cancer between people with nodules. It is neither benign nor malignant. Solid hypoechoic nodules with a size of 2 to 3 cm had a higher risk of malignancy.^[22] Finally, different studies identified different risk factors for thyroid nodule malignancy. This shows that the clinical, histological, and ultrasound characteristics of thyroid nodules are different for assessing the risk of malignancy in different populations, and therefore it is

not possible to introduce a definitive risk factor for malignancy or nonmalignancy of thyroid nodules. Therefore, it is necessary to pay attention to this in the clinical examination and screening of thyroid nodules.

Finally, it should be noted that the present study also faced limitations, such as the fact that in this study, information about the level of education, lifestyle, diet, physical activity and exercise, smoking, economic status, jobs exposed to chemical substances was not available and therefore these factors were not checked. In this study, the level of antithyroid antibodies was not evaluated. Therefore, it is necessary to carry out prospective longitudinal studies for a detailed investigation of the factors affecting the malignancy of thyroid nodules.

It should be done further assessments with a larger sample size and more factors of malignancy in another endocrine system.

CONCLUSION

The results of this study showed that the prevalence of malignant thyroid nodules in histopathology samples was 29.7% and the most common malignant nodule was thyroid papillary carcinoma. Also, some parameters such as age 30–45 years, bilateral thyroid nodule involvement, nodule size less than 2 cm, and lymph node involvement were identified as predisposing factors for thyroid nodule malignancy in the studied population. Therefore, according to these results, it is possible to provide suggested solutions and necessary training to people at risk to predict the occurrence of this disease, to prevent the occurrence of possible risks and problems related to it, and take the necessary measures to manage this disorder.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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