



# Risk factors associated with malignancy in thyroid nodules: A single-center observational study.

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## Abstract

**Introduction:** Approximately 60% of adults have one or more thyroid nodules. The primary concern is the potential for cancer, though only about 5% of cases are malignant. This study aimed to determine the clinical characteristics of patients with thyroid nodules diagnosed at a public Social Security referral center in Riobamba, Ecuador.

**Methods:** This observational and analytical study was conducted from January 2010 to July 2011. Records of patients with thyroid nodules who underwent a histopathological study were included. Two study groups were analyzed: the first with benign nodule histological results and the second with malignant nodules. Sociodemographic criteria, clinical and ultrasound characteristics, and laboratory results were evaluated. The sample was probabilistic. Proportions were compared using a chi-square test, and risk factors were presented with odds ratios.

**Results:** Of the 580 patients, 454 did not require a biopsy. A total of 126 patients were included, of whom 54 had malignant nodules (9.31% CI 7.07–11.97%). There were no differences in sex, origin, or age between the groups. Risk factors associated with the occurrence of a malignant thyroid nodule included pain (OR 155.9), a hard consistency of the nodule (OR=21.7), and a solid ultrasound image of the nodule (OR=16.2).

**Conclusions:** While many patients with thyroid nodules do not require a biopsy, the malignancy rate among those who do was significantly higher than anticipated. The presence of certain factors, such as age, geographical origin, and histological characteristics of the nodules, was associated with an increased risk of malignancy.

## Keywords:

Thyroid nodule, nodule biopsy, risk factors.

## Abbreviations

OR: odds ratio.

## Additional information

No supplementary materials were declared.

## Acknowledgments

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## Authors' contributions

**Byron Alexander Toapanta García:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, writing - original draft, writing - original draft, writing - review and editing.

## Financing

The author funded the expenses of this research.

## Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

## Introduction

Approximately 60% of adults have one or more thyroid nodules. The possibility of cancer is the primary concern, but only approximately 5% of cases are malignant [1].

The prevalence of thyroid nodules increases with age. Although thyroid nodules in older adults have a lower risk of malignancy, the cancers identified are more likely to be of high-risk histology. The goals of thyroid nodule evaluation and the tools used for diagnosis are similar for older and younger patients with thyroid nodules [2].

Over the past 30 years, there has been a substantial increase in the detection of thyroid nodules. Largely asymptomatic, thyroid nodules are often incidental findings that pose minimal risk. This implies either unnecessary or excessive care. To address this issue, the past decade has witnessed an increasingly conservative approach to nodule management, seeking to individualize care and provide the most focused intervention, leading to favorable outcomes [3]. Benign nodules can be safely monitored with minimal or long-interval follow-up imaging. Molecular testing should be considered for cytologically indeterminate nodules because of their ability to improve preoperative cancer risk determination and reduce unnecessary surgery. The management of biopsy-proven malignant nodules has become increasingly nuanced as recommendations for near-total thyroidectomy are no longer routine [4]. Hemithyroidectomy is now commonly considered when surgical intervention is preferred. Some patients with isolated small-volume cancerous nodules are safely managed nonsurgically with active monitoring. Modern management strategies for thyroid nodular disease seek to incorporate increasing diagnostic and prognostic data, including demographic, radiologic, pathologic, and molecular findings. Once obtained, an individualized management plan can be effectively formulated [4].

This study aimed to determine the clinical characteristics of patients with thyroid nodules diagnosed in the outpatient clinic of a public Social Security referral center in Riobamba, Ecuador.

## Materials and methods

### Study design

This cross-sectional observational study is descriptive. The source is retrospective.

### Scenery

The study was conducted at the Ecuadorian Social Security Institute Hospital in Riobamba, Ecuador, from January 1, 2010, to July 31, 2011.

### Participants

Records of patients diagnosed with thyroid nodules and histopathological examinations were included. Two study groups were analyzed: the first with a histological result of a benign nodule and the second with a malignant nodule.

### Variables

The variables included age, sex, place of origin, social level, clinical characteristics of the nodule, laboratory results (leukocytes, hemoglobin, triglycerides, cholesterol, TSH, FT4, and FT3), histology, and cyst ultrasound.

### Data sources/measurements

The source was indirect; an electronic form was filled out using the institutional AS400 clinical history data.

### Biases

The application of the participant selection criteria avoided observation and selection bias. The principal investigator kept the data using a guide and records approved in the research protocol to prevent interviewer, information, and memory biases. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

### Study size

The study universe is determined by all patients who are registered as such in the MIS system of the IESS Riobamba hospital and who make an appointment for the outpatient service in the internal medicine area; the study population size is determined by calculating the established formulas in which a security level of 99% has been formed, an estimated precision within 5%, and the estimated proportion of the sample is assumed to be 50%, with the following formula:  $n = Z_{\alpha/2} * p * q / d^2 = 126$ .

### Quantitative variables

Descriptive statistics were used. The results are expressed as frequencies and percentages. The categorical variables were not converted into quantitative variables.

### Statistical analysis

Qualitative variables are presented as frequencies and percentages. A 95% confidence interval is given for a proportion of the relevant prevalences. Proportions are compared with the chi-square test. The odds ratio is provided with the 95% confidence interval when the association is appropriate. The statistical package used was IBM Corp.,

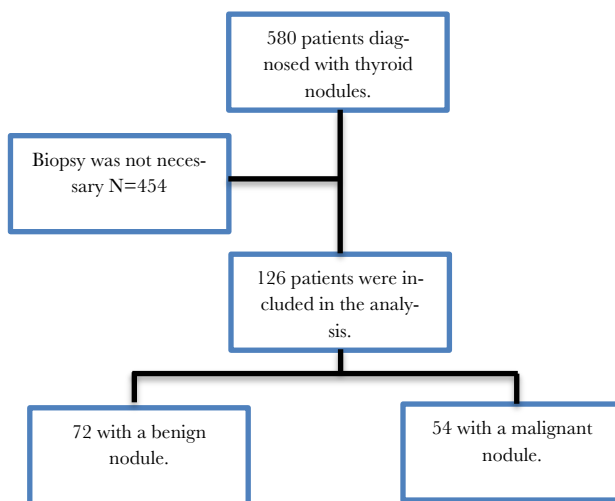
released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

## Results

### Participants

Among the 580 patients, 454 did not require a biopsy based on the clinical and ultrasound criteria. A total of 126 records of patients with thyroid nodules with histological results who needed a biopsy were included (Figure 1). This represents 21.72%, with a 95% confidence interval of 18.43% to 25.31%. Among the 126 cases, 54 were malignant. Compared with the general sample, this figure was 9.31% (95% CI 7.07-11.97%).

**Figure 1.** Study participants.



### Main characteristics of the study group

There were 116 women (92.06%) and ten men (7.93%). The most prevalent age of the group was over 35 years in 88.88% of the cases (Table 1).

In 38 cases (30.0%), the patients were from urban areas (Riobamba), in 26 cases (21%), from rural areas (Cantones de Chimborazo), and in 47 cases (37%) from other cities in the mountains of Ecuador (Table 1).

Concerning social status assessment, most patients had a low social status (70.6%).

### Histological report

Most patients had benign nodules (n=72, 57%), and 54 had malignant nodules (43%). The most benign nodules were follicular adenomas (23 patients, 18.25%), multinodular goiters (19 patients, 15.07%), and thyroiditis. There were 12 cases (9.52%) of malignant nodules: 68 cases of Papillary carcinoma

(53.96%), 3 cases of follicular carcinoma (2.38%), and 1 case of medullary carcinoma (0.79%).

**Table 1.** Demographic and clinical characteristics of the study group.

	N=126	Standard deviation/Percentage
<b>Age</b>		
18-23 years	0	0%
24-29 years	3	2.38%
30-35 years	11	8.73%
> 35 years	112	88.88%
<b>Origin of the patient</b>		
Central region	47	37.0%
Riobamba	38	30.0%
Cantons of Chimborazo	26	21.0%
Coast	8	6.0%
Amazonia	7	6.0%
<b>Social State</b>		
Low	88	70.6%
Average	26	21.0%
High	12	9.0%

**Table 2.** Social characteristics of the study group by malignancy.

	Benign n=72	Malignant n=54	P
Women	65 (90.28%)	51 (94.44%)	0.392
<b>Age</b>			
24-29 years	1 (1.4%)	2 (3.7%)	0.483
30-35 years	5 (6.9%)	6 (11.1%)	
> 35 years	66 (91.7%)	46 (85.2%)	
<b>Origin</b>			
Riobamba (Urban area)	20 (27.8%)	18 (33.3%)	0.12
Chimborazo (rural area)	15 (20.8%)	11 (20.4%)	
Central region (Sierra)	24 (33.3%)	23 (42.6%)	
Coast	6 (8.3%)	2 (3.7%)	
Amazonia	7 (9.7%)	0 (0%)	
<b>Socioeconomic level</b>			
Low	42 (58.3%)	46 (85.1%)	0.01
Half	21 (29.2%)	5 (9.3%)	0.06
High	9 (12.5%)	3 (5.6%)	0.189

### Analysis of the benign and malignant nodule groups

There was no difference in sex, age, or origin in classifying benign and malignant nodules (Table 2). Malignant nodules were more prevalent at low socioeconomic levels ( $P < 0.01$ ). There was no association between middle and high socioeconomic levels and benign or malignant nodules (Table 2).

There were no differences between palpation and the location of the nodule in differentiating between malignant and benign nodules.

**Table 3.** Clinical features of malignancy.

	Benign n=72	Malignant	P
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n=54			
<b>Exploration of the nodule</b>			
Palpable vs nonpalpable	50 (69.4%)	43 (79.63%)	0.575
<b>Location</b>			
Left	29 (40.3%)	22 (40.7%)	
Right	17 (23.6%)	12 (22.2%)	0.198
Both	4 (5.6%)	9 (16.7%)	
<b>Pain</b>			
Yes	0 (0%)	28 (51.9%)	<0.001
<b>Consistency</b>			
Hard	11 (15.3%)	43 (79.16%)	<0.001
Soft	39 (54.2%)	0 (0%)	<0.001
Indeterminate	22 (30.6%)	11 (20.4%)	0.198
<b>Ultrasound image</b>			
Solid	10 (13.9%)	39 (72.2%)	<0.001
Cystic	62 (86.1%)	15 (27.8%)	<0.001
<b>Type 2 diabetes mellitus</b>			
Yes	11 (15.3%)	18 (33.3%)	0.017
<b>High blood pressure</b>			
Yes	38 (52.8%)	23 (42.6%)	0.258
<b>Blood count</b>			
Leukocytosis	3 (4.2%)	10 (18.5%)	0.009
Leukopenia	0 (0%)	1 (1.9%)	0.246
Polyglobulia	0 (0%)	2 (3.7%)	0.100
Lymphocytosis	8 (11.1%)	6 (11.1%)	1.00
<b>Lipid profile</b>			
Hypertriglyceridemia	35 (48.1%)	13 (23.8%)	0.005
Hypercholesterolemia	34 (46.8%)	15 (28.6%)	0.027
<b>Clinical condition</b>			
Primary hypothyroidism	54 (75.0%)	50 (92.6%)	0.01
Subclinical hypothyroidism	9 (12.5%)	3 (5.6%)	0.189
Primary hyperthyroidism	1 (1.4%)	0 (0%)	0.385
Subclinical hyperthyroidism	8 (11.1%)	1 (1.9%)	0.046

Pain was more prevalent in the malignant nodule group ( $P = 0.001$ ). Hard nodule consistency was more common in malignant nodules, and soft nodule consistency was more prevalent in benign nodules ( $P < 0.001$ ).

An ultrasound image of a solid nodule was more prevalent in a malignant nodule, whereas a cystic image was more prevalent in a benign nodule ( $P < 0.001$ ).

In terms of comorbidities, type 2 diabetes mellitus was a risk factor for the presence of malignant nodules ( $P = 0.017$ ), and arterial hypertension was similar in both groups.

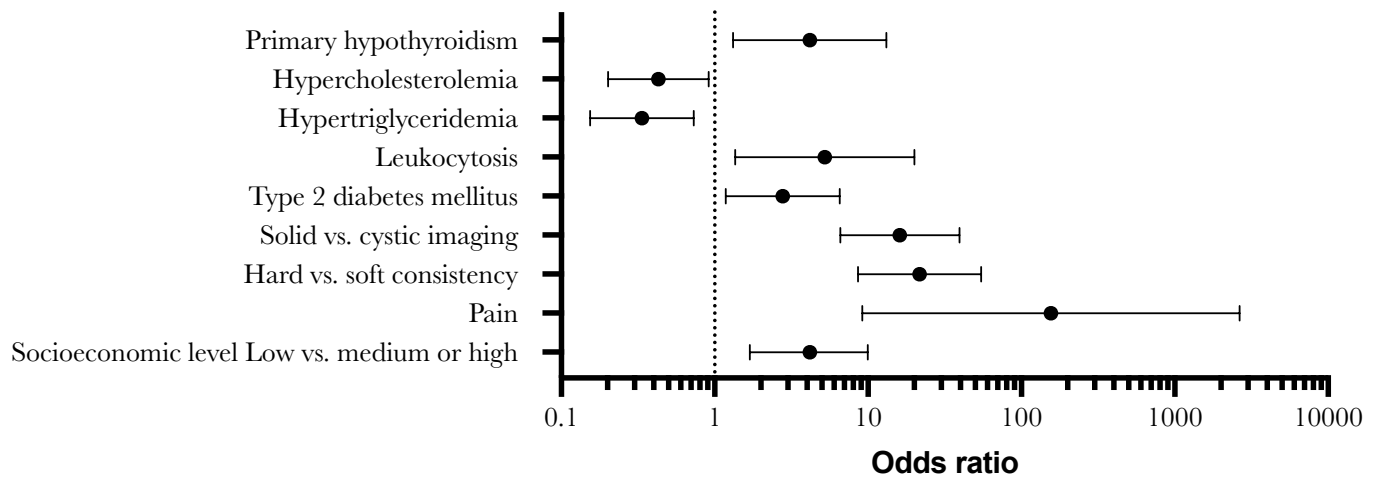
Among the laboratory findings, leukocytosis and primary hypothyroidism were more prevalent in patients with malignant nodules, whereas dyslipidemia was more prevalent in those with benign nodules (Table 3).

### Risk factors for the presence of malignancy

The following variables were established as risk factors for the presence of thyroid malignancy: low socioeconomic level, the presence of pain in the thyroid area, a hard consistency on palpation of the nodule, the presence of a solid nodular image on ultrasound, the presence of type 2 diabetes mellitus, the presence of leukocytosis in the complete blood count, and the presence of primary hypothyroidism. On the other hand, dyslipidemia is a protective factor associated with metabolic alterations (Table 4). The weights of the risk and protection factors are presented in Figure 2 in the forest graph.

**Table 4.** Clinical characteristics by malignancy.

	Odds ratio	IC 95%	P
<b>Socioeconomic level</b>			
Low vs. Medium vs. High	4.17071	1.6951-9.9516	0.0018
<b>Pain</b>			
Presence vs. Absence	155.9434	9.1912-2645.8239	0.0005
<b>Consistency</b>			
Hard vs. Soft	21.6777	8.6184-54.5254	<0.0001
<b>Ultrasound image</b>			
Solid vs. Cystic	16.12	6.5878-39.4446	<0.0001
<b>Type 2 diabetes mellitus</b>			
Presence vs. Absence	2.7727	1.1783-6.5248	0.0195
<b>Blood count</b>			
Leukocytosis	5.2273	1.3626-20.0532	0.0159
<b>Lipid profile</b>			
Hypertriglyceridemia	0.3352	0.1542-0.7286	0.0058
Hypercholesterolemia	0.4299	0.2022-0.9138	0.0282
<b>Clinical condition</b>			
Primary hypothyroidism	4.1667	1.3197-13.1551	0.0150

**Figure 2.** Forest plot of the predictors of malignant nodule

## Discussion

The results of the present study indicate that, from a group of 580 patients with incidental thyroid nodules, a considerable percentage (21.72%) required a biopsy due to suspicions of malignancy based on clinical and ultrasound criteria. However, it is essential to note that this percentage's confidence interval is moderately wide (18.43% to 25.31%), suggesting some variability in the results. On the other hand, 9.31% of the nodules were malignant, with confidence intervals ranging from 7.1% to 12.0%, which is a broad and relatively high interval compared with other studies [1, 4]. The higher rate of malignancy in thyroid nodules in a regional hospital could be multifactorial and reflect a combination of factors related to the population served, diagnostic protocols, environmental factors, and other biases. Patients seeking care at a regional hospital may have particular characteristics that predispose them to developing thyroid cancer.

These findings reveal a complex relationship between the clinical features and malignancy of thyroid nodules. Notably, patients from lower socioeconomic levels were more likely to develop malignant nodules, suggesting possible environmental or healthcare access factors not explored in this study. The presence of pain, a hard consistency of the nodule, and certain specific ultrasound features, such as solid nodules, were significantly associated with a higher risk of malignancy, corroborating previous findings in the literature [5]. Furthermore, type 2 diabetes mellitus and primary hypothyroidism tended to be associated with a greater likelihood of malignancy.

These results underscore the importance of a thorough clinical evaluation and the use of imaging tools to identify patients at greater risk of thyroid cancer, thus allowing early intervention and improving outcomes for these patients.

In the weighting of variables, the most important factors with an odds ratio greater than 10 for the presence of a malignant thyroid nodule were pain (odds ratio 155.9), hard consistency of the nodule (OR=21.7), and solid image of the nodule on ultrasound (OR=16.2).

Future studies should evaluate these factors and propose a regression equation to predict the presence or absence of malignancy.

## Conclusions

Although a considerable proportion of patients with thyroid nodules do not require biopsy, the malignancy rate in those patients was significantly higher than expected. Certain factors, such as age, geographic origin, and histological characteristics of the nodules, are associated with an increased risk of malignancy. These findings underscore the importance of careful and personalized evaluation of thyroid nodules, especially in specific populations and in the presence of certain risk factors, to optimize the diagnosis and treatment of this pathology.

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## Statements

### Ethics committee approval and consent to participate

The bioethics committee of the Faculty of Public Health, Polytechnic School of Chimborazo, Riobamba, Ecuador, approved the study.

### Consent to publish

This information was unnecessary because the present study did not publish images, radiographs, or specific patient studies.

### Conflicts of interest

The author declares no conflicts of interest.

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