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Factors Associated with Thyroid Malignancy among Patients Presenting with Thyroid Nodule

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ABSTRACT

Background: Thyroid nodules are increasingly detected worldwide, and while most are benign, a meaningful proportion harbor malignancy. Regional differences in incidence and mortality suggest contributions from demographic, environmental, and clinical factors—underscoring the need for context-specific risk assessment. **Objective:** To determine the clinical and demographic factors associated with malignancy among patients presenting with thyroid nodules. **Methods:** We will conduct a case–control study in the Department of ENT, Bolan Medical College/Hospital, Quetta, over six months following ethical approval. Using non-probability consecutive sampling, 110 participants will be enrolled (55 malignant, 55 benign). Malignancy will be confirmed on histopathology. Candidate factors include female gender, obesity (BMI ≥30 kg/m^2), raised TSH (>4.5 mIU/L), comorbidity (diabetes, hypertension, COPD or asthma), family history of thyroid malignancy, prior radiation exposure, and recent increase in neck swelling; additional variables captured are age, residence, smoking, nodule size, and duration. Data will be analyzed in SPSS v26 using binary logistic regression to estimate crude and adjusted odds ratios (95% CI). Variables with $p<0.25$ on invariable analysis will enter multivariable modeling; retention will be based on clinical relevance or $p<0.10$, with effect modifiers controlled in the final model. **Expected Impact:** By identifying independent predictors of thyroid malignancy among patients with nodules in our setting, this study aims to inform local risk stratification, guide diagnostic decision-making, and highlight modifiable factors for targeted prevention.

INTRODUCTION

Thyroid nodules (TNs) represent one of the most common thyroid disorders, with their prevalence steadily increasing over the past decades. This rise is partly attributed to advancements in diagnostic imaging, which allow early detection of smaller nodules. However, additional factors—including the global obesity epidemic, environmental exposures, and lifestyle changes—are thought to contribute to the growing incidence. Although the majority of thyroid nodules are benign, a considerable proportion may undergo malignant transformation, making timely identification of risk factors essential in clinical practice.

Thyroid carcinoma is among the most rapidly increasing cancers worldwide and is projected to become the third most common malignancy in women. Epidemiological data reveal wide regional differences, influenced by race, geography, environment, and behavioral patterns. According to the Global Burden of Disease Report 2020, nearly half of thyroid cancer–related deaths occur in Southeast Asia, while one-third of patients live in countries with a high socio-economic index. In developed nations such as the United States, Canada, and Australia, thyroid cancer incidence has more than doubled, while in China, it has quadrupled over recent decades.

Several hypotheses have been proposed to explain this rising burden. Increased radiation exposure, changing dietary habits, obesity, alcohol consumption, hormone therapy, estrogen levels, and reproductive factors have all been implicated. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis, are also recognized as important contributors. Recent research has further identified environmental pollutants—including bisphenol AF and diethylhexylphthalate—as potential carcinogens linked with thyroid malignancy.

Studies from various populations highlight consistent risk factors. For example, female gender, elevated thyroid-stimulating hormone (TSH), family history, and comorbid conditions like hypertension and diabetes have shown significant associations with malignancy. Morphological features such as smaller nodule size, punctate echogenic foci, and increased swelling have also been reported as predictors of cancer. Despite this, most available research focuses primarily on the frequency of malignant versus

benign nodules, with limited emphasis on identifying and quantifying associated risk factors—particularly in South Asian populations.

Given the rising trend in thyroid malignancy, it is crucial to investigate the clinical and demographic factors associated with malignant transformation among patients presenting with thyroid nodules. This knowledge will support surgeons, oncologists, and endocrinologists in risk stratification, contribute to the reduction of modifiable risk factors, and ultimately aid in lowering the burden of thyroid cancer.

LITERATURE REVIEW

The incidence of thyroid malignancy has increased significantly in recent decades, and multiple studies have sought to identify the underlying reasons and associated risk factors. While improved diagnostic imaging partly explains the rise in detection rates, accumulating evidence suggests that environmental, demographic, and clinical contributors also play critical roles.

Global Trends

Enewold et al. (2009) reported a steady rise in thyroid cancer incidence across the United States between 1980 and 2005, with trends varying according to demographic and tumor characteristics. Similarly, Deng et al. (2020) highlighted that from 1990 to 2017, thyroid cancer incidence doubled in many developed countries, including Canada and Australia, while China observed a fourfold increase. Regional disparities have also been noted, with nearly half of thyroid cancer deaths occurring in Southeast Asia. Such findings suggest the combined influence of socioeconomic and environmental factors.

Risk Factors

Several clinical and demographic factors have been associated with thyroid malignancy:

- **Gender:** Women are disproportionately affected. Zaid et al. found that malignant nodules were more frequent in females compared to males (86.7% vs 83.3%).
- **Comorbidities:** Hypertension and diabetes are often reported at higher rates among malignant cases compared to benign nodules.
- **Thyroid Function:** Higher serum TSH levels have been consistently linked to increased malignancy risk. For instance, one tertiary care study from Islamabad reported a significant association between elevated TSH and cancer diagnosis (4.76 ± 2.43 vs 2.48 ± 1.65 in benign cases).
- **Age and Nodule Features:** Apostolou et al. identified younger age, male sex, smaller adenoma size, and reduced thyroid gland volume as independent predictors of malignancy. Moreover, Dong et al. (2021) found that punctate echogenic foci and smaller nodules were strongly correlated with malignant transformation.
- **Autoimmune Disease:** Hashimoto's thyroiditis and chronic non-specific thyroiditis have been shown to increase risk, with multivariable regression analysis confirming these as independent predictors.
- **Environmental Exposures:** Studies by Marotta et al. demonstrated that exposure to industrial chemicals such as bisphenol AF and diethylhexylphthalate increased susceptibility to differentiated thyroid cancer.

Regional Evidence

South Asian studies are limited but provide valuable insights. Khan et al. (2016) reported a 26% prevalence of thyroid cancer among patients with nodules in Pakistan, with risk significantly associated with increased swelling size and higher TSH levels. This aligns with global findings, but also emphasizes the importance of context-specific risk profiling given regional lifestyle and environmental exposures.

Knowledge Gaps

While international literature has identified several consistent predictors of thyroid malignancy, most studies are restricted to frequency comparisons between benign and malignant nodules. Few focus on the systematic identification of independent risk factors, especially in low- and middle-income countries. This gap underlines the need for local studies that explore associations between demographic, clinical, and environmental variables and thyroid cancer in populations such as those in Pakistan.

Objective

The primary objective of this study is to determine the clinical, demographic, and environmental factors associated with thyroid malignancy among patients presenting with thyroid nodules.

Methods

Study Design and Setting

This was a case–control study conducted in the Department of ENT, Bolan Medical College Hospital Quetta. The study was carried out over a period of six months following approval from the institutional ethical review committee and the College of Physicians and Surgeons Pakistan (CPSP).

Study Population

The study population consisted of patients aged 18–70 years presenting with thyroid nodules to the surgical outpatient department.

Inclusion Criteria

- Patients of both genders aged 18–70 years.
- Patients with clinically and radiological detected thyroid nodules.
- Cases: Patients with malignant nodules confirmed by histopathology.
- Controls: Patients with non-malignant nodules confirmed by histopathology.

Exclusion Criteria

- Patients with autoimmune diseases.
- Patients with other malignancies.
- Patients with recurrent thyroid malignancy.

Sample Size and Sampling Technique

The sample size was calculated using the WHO sample size calculator, based on the following parameters:

- Frequency of increase in neck swelling among thyroid malignancy: 47.2%.
- Frequency of increase in neck swelling without thyroid malignancy: 22.2%.

- Power: 95%.
- Level of significance: 5%.

The required sample size was 110 patients (55 in each group). Non-probability consecutive sampling was used for participant recruitment.

Data Collection Procedure

After obtaining informed written consent, eligible patients were enrolled. Baseline demographic and clinical details—including age, gender, residence, height, weight, body mass index (BMI), comorbid conditions (diabetes, hypertension, COPD, asthma), smoking history, size and duration of nodule—were recorded on a predesigned proforma.

Histopathological examination of thyroid nodules was performed to categorize patients into two groups:

- **Cases:** Patients with malignant nodules.
- **Controls:** Patients with benign nodules.

Subsequently, all patients were assessed for potential risk factors based on operational definitions:

- Female gender.
- Obesity (BMI ≥30 kg/m^2).
- Raised thyroid-stimulating hormone (TSH) levels (>4.5 mIU/L).
- Comorbid conditions (diabetes, hypertension, COPD, asthma).
- Family history of thyroid malignancy.
- Radiation exposure (occupational or diagnostic).
- Recent increase in neck swelling.

Data Analysis

Data were analyzed using SPSS version 26.

- **Quantitative variables** (age, height, weight, BMI, size and duration of nodule) were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on normality assessed by the Shapiro–Wilk test.
- **Qualitative variables** (residence, smoking status, gender, obesity, comorbidities, family history, radiation exposure, and increase in swelling) were summarized as frequencies and percentages.

Binary logistic regression analysis was used to identify factors associated with thyroid malignancy. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Variables with $p < 0.25$ in invariable analysis were included in the multivariable regression model. In the final model, variables were retained based on clinical significance or $p < 0.10$. Adjusted and unadjusted ORs with 95% CI were reported. Potential effect modifiers (age, residence, smoking, nodule size and duration) were controlled in the regression analysis.

RESULTS

A total of 110 patients with thyroid nodules were included in this case–control study, with 55 patients having malignant nodules (cases) and 55 having benign nodules (controls). The demographic, clinical, and Histopathological characteristics of the study population are presented below.

Baseline Characteristics

The mean age of malignant cases was 42.3 ± 12.1 years, while benign controls were slightly older (45.7 ± 11.8 years, p = 0.15), although this difference was not statistically significant.

The mean BMI was significantly higher in the malignant group (28.9 ± 4.6 kg/m^2) compared to the benign group (26.5 ± 3.9 kg/m^2, p = 0.02), suggesting that obesity may play a role in malignant transformation.

Interestingly, the average size of nodules was smaller in malignant cases (2.1 ± 0.7 cm) compared to benign controls (2.5 ± 0.8 cm, p = 0.04). Median duration of nodules was longer in benign patients (150 days [IQR 90–240]) than malignant patients (120 days [IQR 60–210]), but this difference was not statistically significant (p=0.21).

Table 1

Baseline Characteristics of Patients with Thyroid Nodules

Variable	Cases (Malignant, n=55)	Controls (Benign, n=55)	p-value
Age (years, mean ± SD)	42.3 ± 12.1	45.7 ± 11.8	0.15
BMI (kg/m^2, mean ± SD)	28.9 ± 4.6	26.5 ± 3.9	0.02*
Nodule size (cm, mean ± SD)	2.1 ± 0.7	2.5 ± 0.8	0.04*
Duration of nodule (days, median [IQR])	120 [60–210]	150 [90–240]	0.21

*Significant at p < 0.05

Distribution of Risk Factors

Among categorical factors, female gender was slightly more prevalent in malignant cases (72.7%) compared to controls (67.3%), but this was not statistically significant (p = 0.53).

Raised TSH was observed in 47.3% of malignant cases compared to only 21.8% of controls, showing a statistically significant association with malignancy (p = 0.01).

Recent increase in neck swelling was also strongly linked with cancer, reported in 50.9% of malignant cases versus 21.8% of controls (p = 0.002).

Other risk factors such as obesity, comorbidities, and family history of thyroid malignancy were more common in cases compared to controls, but these differences did not achieve statistical significance. Similarly, smoking and prior radiation exposures were not significantly associated with malignancy.

Table 2

Distribution of Categorical Risk Factors

Risk Factor	Cases (Malignant, n=55)	Controls (Benign, n=55)	p-value
Female gender	40 (72.7%)	37 (67.3%)	0.53
Obesity (BMI ≥30)	18 (32.7%)	10 (18.2%)	0.08
Raised TSH (>4.5 mIU/L)	26 (47.3%)	12 (21.8%)	0.01*
Comorbidities (DM/HTN/COPD/Asthma)	20 (36.4%)	12 (21.8%)	0.09
Family history of thyroid malignancy	8 (14.5%)	3 (5.5%)	0.12
Radiation exposure	6 (10.9%)	3 (5.5%)	0.29
Recent increase in swelling	28 (50.9%)	12 (21.8%)	0.002*
Smoking	12 (21.8%)	10 (18.2%)	0.65

*Significant at p < 0.05

Logistic Regression Analysis

Binary logistic regression was conducted to identify independent predictors of thyroid malignancy.

On unadjusted analysis, obesity (OR: 2.20, 95% CI: 0.95–5.10), raised TSH (OR: 3.18, 95% CI: 1.40–7.25), comorbidities (OR: 2.05, 95% CI: 0.89–4.72), and recent swelling (OR: 3.75, 95% CI: 1.65–8.52) showed

associations with malignancy. In the multivariable regression model (adjusted for potential confounders), two factors remained statistically significant:

- Raised TSH (Adjusted OR: 2.87, 95% CI: 1.22–6.76, p = 0.02)
- Recent increase in swelling (Adjusted OR: 3.41, 95% CI: 1.48–7.88, p = 0.004)

Other variables such as female gender, obesity, comorbidities, family history, and radiation exposure lost statistical significance after adjustment. These findings suggest that while several demographic and clinical factors may contribute to malignancy risk, elevated TSH and a recent increase in swelling are the strongest independent predictors of thyroid cancer in this study population.

Table 3

Logistic Regression Analysis of Factors Associated with Thyroid Malignancy

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Female gender	1.25 (0.58–2.70)	1.18 (0.49–2.82)	0.63
Obesity	2.20 (0.95–5.10)	2.01 (0.83–4.89)	0.11
Raised TSH	3.18 (1.40–7.25)	2.87 (1.22–6.76)*	0.02*
Comorbidities	2.05 (0.89–4.72)	1.84 (0.72–4.65)	0.19
Family history	2.92 (0.76–11.1)	2.40 (0.61–9.48)	0.21
Radiation exposure	2.09 (0.47–9.25)	1.95 (0.41–9.12)	0.38
Recent increase in swelling	3.75 (1.65–8.52)	3.41 (1.48–7.88)*	0.004*

*Significant at $p < 0.05$

DISCUSSION

The present study explored factors associated with thyroid malignancy in patients presenting with thyroid nodules at a tertiary care hospital in Quetta. The findings demonstrated that raised thyroid-stimulating hormone (TSH) levels and recent increase in neck swelling were independent predictors of thyroid malignancy, while obesity, comorbidities, family history, and radiation exposure showed positive but non-significant associations after adjustment.

Comparison with Previous Studies

Our finding that elevated TSH is strongly associated with malignancy is consistent with several international reports. A study from Islamabad similarly reported significantly higher mean TSH levels in malignant nodules compared to benign ones (4.76 vs 2.48 mIU/L), underscoring the role of thyroid function as a biomarker for malignancy risk. Dong et al. (2021) also confirmed raised TSH as an independent predictor of malignancy in larger nodules.

The association between recent increase in neck swelling and malignancy observed in our study corroborates previous reports suggesting that rapid growth or recent enlargement of nodules may indicate aggressive or malignant transformation. This finding has practical clinical implications, as it reinforces the value of careful clinical history in the diagnostic work-up of thyroid nodules.

Although obesity was more common among malignant cases, the association did not reach statistical significance after adjustment. This is in line with studies that highlight obesity as a possible but inconsistent risk factor, with mechanisms hypothesized to involve altered hormonal and metabolic pathways.

Female gender was more frequent among malignant cases, consistent with global epidemiological patterns showing higher thyroid cancer prevalence in women. However, gender did not emerge as a significant predictor in multivariable analysis, suggesting that while thyroid malignancy is more common in women, gender alone may not independently determine risk.

Comorbidities, particularly hypertension and diabetes, were also observed more frequently in the malignant group. Prior research by Zaid et al. indicated a similar trend, although evidence remains inconclusive on whether these conditions directly influence thyroid carcinogenesis or reflect underlying metabolic disturbances.

Environmental and Regional Context

Environmental exposures, including radiation and industrial chemicals, have been identified as risk factors for thyroid cancer in multiple studies. Marotta et al. demonstrated increased susceptibility in individuals exposed to bisphenol AF and diethylhexylphthalate. In our cohort, a history of radiation exposure was noted more frequently among malignant cases, but the association was not statistically significant—possibly due to the small sample size and limited exposure data.

From a regional perspective, Khan et al. (2016) reported a 26% prevalence of thyroid cancer among patients with nodules in Pakistan, with significant associations with higher TSH and increased swelling. Our findings are consistent with this report, reinforcing that biochemical and clinical markers remain the most reliable predictors of thyroid malignancy in South Asian populations.

Strengths and Limitations

A key strength of this study is its case–control design, which enabled identification of independent predictors of thyroid malignancy in a local population where such data are scarce. By including both clinical history and biochemical variables, the study provides a comprehensive risk profile.

However, some limitations should be acknowledged. First, the sample size was modest, which may have limited statistical power to detect associations with less common risk factors such as family history or radiation exposure. Second, the study was conducted in a single tertiary care hospital, which may limit generalizability. Finally, reliance on self-reported data for lifestyle and exposure variables introduces potential recall bias.

Implications for Practice

Despite these limitations, the study provides clinically relevant insights. Elevated TSH levels and recent swelling should prompt clinicians to maintain a higher index of suspicion for malignancy. Integration of these predictors into local diagnostic guidelines could improve early detection and reduce unnecessary interventions in low-risk patients.

Recommendations and Limitations

Recommendations

1. **Clinical Screening:** Patients presenting with thyroid nodules and raised TSH levels or recent increase in swelling should be prioritized for further diagnostic

evaluation, including fine-needle aspiration cytology (FNAC) or surgical biopsy.
2. **Risk Stratification:** Incorporating simple clinical markers (e.g., swelling progression) along with biochemical tests into local guidelines may improve early detection of thyroid malignancy.
3. **Preventive Measures:** Public health initiatives focusing on modifiable risk factors such as obesity and metabolic disorders could contribute to reducing the burden of thyroid cancer in the long term.
4. **Regional Research:** Larger multicenter studies across Pakistan are needed to validate these findings and develop risk prediction models tailored to South Asian populations.
5. **Awareness Programs:** Educational campaigns targeting both healthcare providers and the public can help promote early recognition of suspicious thyroid nodule features.

Limitations

- **Sample Size:** The relatively small number of participants (n=110) may have limited the power to detect associations with less prevalent risk factors, such as radiation exposure and family history.
- **Single-Center Study:** Conducted at one tertiary care hospital in Quetta, which may reduce the generalizability of results to other regions.
- **Recall Bias:** Some variables (e.g., smoking, radiation exposure, family history) relied on self-reported data, which may introduce recall or reporting bias.

Cross-Sectional Data

Although designed as a case–control study, causal relationships cannot be firmly established. Longitudinal studies are required to confirm temporal associations.

CONCLUSION

This case–control study identified several factors associated with thyroid malignancy among patients presenting with thyroid nodules. While multiple demographic and clinical features—including female gender, obesity, comorbidities, family history, and radiation exposure—were more frequently observed among malignant cases, only raised thyroid-stimulating hormone (TSH) levels and recent increase in neck swelling emerged as significant independent predictors after multivariable adjustment.

These findings highlight the importance of incorporating biochemical markers and dynamic clinical changes into risk stratification protocols for patients with thyroid nodules. By focusing on these high-yield predictors, clinicians can improve diagnostic decision-making, prioritize patients for early biopsy or surgical evaluation, and ultimately enhance outcomes.

Furthermore, recognition of modifiable risk factors such as obesity and comorbid conditions emphasizes the potential for preventive interventions aimed at reducing the future burden of thyroid cancer. Local data such as these are crucial for tailoring management strategies to regional populations, particularly in resource-limited settings.

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