

## Original article

# Association of Preoperative Serum Thyroid-stimulating Hormone Levels with Thyroid Cancer in Patients with Nodular Thyroid Disease

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## Abstract

The aim of the current study was to determine the frequency of carcinoma thyroid among patients presenting with goiter and its association with preoperative serum thyroid-stimulating hormone (TSH) levels. A total of 73 ( $n = 73$ ) adult patients of either gender with solitary solid cold nodule and multinodular goiter with predominant solid cold nodule were analyzed. All surgically resected samples were sent for histopathology. The frequency of thyroid cancer and its subtypes was noted and tested for association with preoperative serum TSH values. Thyroid cancer was diagnosed in 26% ( $n = 19$ ) of the patients. In patients with thyroid cancer ( $n = 19$ ), 73.7% ( $n = 14$ ) were diagnosed with papillary thyroid cancer and 26.3% ( $n = 5$ ) were diagnosed with follicular thyroid cancer. Presence of thyroid cancer was found to be significantly associated with preoperative higher mean TSH values ( $P < 0.05$ ). Higher preoperative serum TSH levels may be useful in predicting thyroid cancer in nodular thyroid disease. Further studies are recommended with different cutoff values of serum TSH and its association with the development and progression of thyroid cancer.

**Keywords:** Goiter, thyroid cancer, thyroid nodules, thyroid-stimulating hormone

## Introduction

Thyroid carcinoma is the most frequent form of cancers of the endocrine glands. It accounts for 1% of all human neoplasias, and globally its annual incidence is estimated to be 0.5–10/100,000 people in the world population.<sup>[1]</sup> The peak incidence is in the third and fourth decades of life.<sup>[2]</sup> Worldwide, incidence rates of thyroid cancers vary widely, with the causes potentially related to inherent racial or ethnic differences, geographical or environmental differences

including iodine excess or deficiency, and possible radiation exposure.<sup>[3]</sup> Majority of the patients with thyroid carcinoma present with nodular goiters with the frequency of malignancy being 3% among multinodular goiters (MNGs) and 4.4% among solitary nodule.<sup>[4]</sup> In Pakistan, the most common thyroid malignancy is papillary carcinoma.<sup>[5]</sup> Patients usually present with swelling in the neck, which may have recently increased in size, small lumps in other areas of neck, hoarseness of voice, and difficulty in breathing and swallowing (in case of larger swelling size). Clinical examination of the gland may also provide clues such as a hard lump, palpable lymph nodes, a positive berry's sign, and

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immobile vocal cords on indirect laryngoscopy for a suspected malignancy.<sup>[6,7]</sup> Serum thyroid-stimulating hormone (TSH) is the first-line investigation in patients presenting with thyroid nodules, and several studies have reported its association with thyroid cancer; however, the increasing cancer risk in patients with TSH within normal and above normal reference range remains unexplained.<sup>[8,9]</sup>

Internationally, there is a growing awareness about the significant consequences of thyroid carcinoma. On national level, we need mass awareness and to foster knowledge about this cancer as the prognosis is excellent after surgery and radioactive iodine treatment. The epidemiological data on thyroid cancer and its associated risk factors were scarce in our settings. The present study was designed to gather the data in our settings which could be helpful in providing insights to the thyroid physicians and surgeons who are primarily dealing with these patients. Our objective was to determine the frequency of carcinoma thyroid among patients presenting with goiter and its association with preoperative serum TSH levels.

## Patients and Methods

It was a cross-sectional study and was carried out at the Department of Surgery, Pakistan Institute of Medical Sciences (PIMS), a tertiary care hospital in Islamabad, Pakistan, from January 2014 to June 2015. The study was approved by the Hospital's Ethical Committee. All the patients who presented for thyroid surgery during this period were assessed with adequate history, thorough clinical examination, and necessary investigations, where needed (thyroid function tests [TFTs], thyroid scintigraphy, ultrasound neck, and fine-needle aspiration biopsy [FNAC]). Patients who presented with diffuse toxic goiter, pure cystic nodules, and autonomously hyper-functioning thyroid nodule were excluded from the study. Patients who already underwent any thyroid surgery were also excluded. Patients who had solitary solid cold nodule and MNG with predominant solid cold nodule were selected for further analysis. A fully informed, understood, and voluntarily written consent was taken from all the patients. The operative procedures were undertaken under general anesthesia. The procedure was tailored according to the presumptive preoperative diagnosis. The entire resected surgical specimen was subjected to histopathology examination to establish the final diagnosis of the thyroid disorder. The frequency and percentage of thyroid cancer and its subtypes were noted and tested for association with serum TSH levels by employing independent *t*-test. *P* < 0.05 was considered statistically significant.

## Results

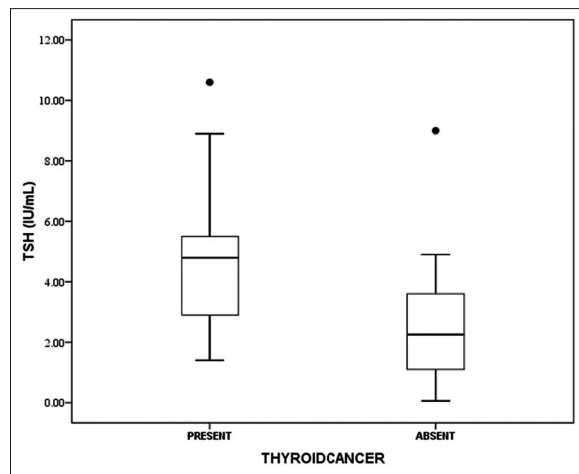
A total of 181 patients irrespective of gender with goiter presented to the Surgery Department during the study period. One hundred and eight patients were excluded from the study. Out of those, 53 patients presented with diffuse toxic goiter (confirmed on TFTs and thyroid scintigraphy), 26 patients presented with pure cystic nodules (confirmed on ultrasound neck), 18 patients presented with autonomously hyper-functioning thyroid nodule (confirmed on TFTs and thyroid scintigraphy), and 11 patients had a history of previous thyroid surgery and presented with regenerated nodules (confirmed on history and clinical examination). Seventy-three patients fulfilled the recruitment criteria and were further analyzed. Demographic characteristics of the study population are shown in Table 1. Thyroid cancer was diagnosed in 26% (*n* = 19/73) of the patients. In patients with thyroid cancer (*n* = 19), 73.7% (*n* = 14/19) were diagnosed as papillary thyroid cancer and 26.3% (*n* = 5/19) were diagnosed as follicular thyroid cancer. No other subtypes noted in our results. In patients with thyroid cancer, mean TSH level was 4.76 IU/mL ± 2.43 standard deviation (SD), while it was 2.48 IU/mL ± 1.65 SD in patients with benign disease (*P* = 0.001). Results are shown in Figure 1.

## Discussion

In our overall study sample after exclusion criteria had been observed, thyroid cancer was found in 26% (*n* = 19/73) of the patients. In patients with thyroid cancer, 73.7% (*n* = 14/19) were diagnosed with papillary thyroid cancer and 26.3% (*n* = 5/9) were diagnosed with follicular thyroid cancer. No other subtypes noted in our results. In one of the largest, most recent and single-center studies conducted at the Department of Pathology, Holy Family Hospital, Rawalpindi, Pakistan, Qureshi *et al.* found the percentage of neoplastic lesions as 18% (26.3% in our study).<sup>[10]</sup> The difference may be attributed to different inclusion criteria. In another recent study conducted at the Department of Pathology, Taibah University, Madinah, Saudi Arabia, Albasri *et al.* found that 27.7% cases were neoplastic.<sup>[11]</sup> Two other reports based on large population-based studies probably provide a best accurate estimate of the true frequency of thyroid cancer among patients with thyroid nodules.

**Table 1: Demographic profile of the study population**

	Number (percentage)	Mean age ± SD (years)
Males	19 (26)	36.95 ± 12.2
Females	54 (74)	39.1 ± 12.3
Total	73 (100)	38.5 ± 12.25



**Figure 1:** Preoperative thyroid-stimulating hormone in patients with and without thyroid cancer

In a community hospital in North Carolina where most patients with nodules were referred for surgery without benefit of biopsy, 6.5% of excised nodules were cancers.<sup>[12]</sup> In Catania, Italy, 2327 patients presenting with nodules were evaluated by FNAC and 391 were selected for surgery.<sup>[13]</sup> Cancers were found in 28% of the surgical specimens, which represented only 5% of all nodules. However, in Boston, among patients referred to a thyroid practice, the rate of malignancy in thyroid nodules was 14%.<sup>[14]</sup> Our exclusion criteria were quite stringent, and we excluded all patients with diffuse toxic goiter, pure cystic nodules, autonomously hyper-functioning thyroid nodule, and regenerated nodules after previous surgery. We only analyzed patients who had solitary solid cold nodules and MNG with predominant solid cold nodule. Moreover, in our settings, usually, surgery is decided on FNAC results for patients showing suspicion for malignancy and malignant category. Patients with benign FNAC results usually do not undergo surgery and are kept on follow-up monitoring with ultrasound. This could be the likely reason of higher frequency of thyroid cancer in our study as compared to North Carolina and Boston study. However, our study results are comparable with the Italian study (28% vs. 26% in our study) as they had the similar selection criteria, and only selected patients underwent surgery who had suspicious FNAC results. Differentiated thyroid cancers (papillary and follicular) accounts for about 90% of all thyroid cancers, usually have a good prognosis.<sup>[15]</sup> All thyroid cancers in our study came out to be papillary and follicular thyroid cancer (100%). Less frequent thyroid cancers (medullary, anaplastic, and lymphoma) did not show up in our study due to relatively smaller sample size.

Preoperative higher TSH values showed a significant association with thyroid cancer in the present study.

Other studies showed similar results, and serum TSH is considered as an independent risk factor for predicting malignancy in a thyroid nodule. In a study of 1500 patients presenting to a thyroid practice, the prevalence of malignancy was 2.8%, 3.7%, 8.3%, 12.3%, and 29.7% for patients with serum TSH concentrations <0.4 mU/L, 0.4–0.9 mU/L, 1.0–1.7 mU/L, 1.8–5.5 mU/L, and >5.5 mU/L, respectively.<sup>[16]</sup> In another study on 108 patients with thyroid tumors who underwent surgical treatment, patients with malignancy had a higher mean value of TSH than that of the patients with benign thyroid disease ( $[1.94 \pm 1.01]$  mIU/L vs.  $[1.16 \pm 0.85]$  mIU/L, respectively,  $P < 0.05$ ).<sup>[17]</sup> In another study, Fiore *et al.* analyzed the relationship between serum TSH and papillary thyroid cancer in 10,178 patients with nodular thyroid disease. They found significantly higher TSH concentrations in patients who were subsequently diagnosed with thyroid cancer compared with those of benign disease.<sup>[18]</sup> Other studies have shown that when cancer was diagnosed, a higher TSH was associated with a more advanced stage of cancer.<sup>[19,20]</sup>

In summary, the evidence that serum TSH concentration is an independent predictor of thyroid malignancy in patients with nodular thyroid disease is rising. Our study showed similar results, and we recommend that patients with higher serum TSH concentrations may need more meticulous investigations and clinical monitoring when compared with those with lower baseline TSH levels. As several studies also reported the association of higher preoperative serum TSH concentrations with more advanced stage tumors, we suggest studies assessing association between elevated TSH levels and clinical stages of thyroid cancer in our settings. We also suggest further studies with different cutoff values of serum TSH using receiver operative curve analysis in a larger sample size.

## Conclusion

Overall percentage of thyroid cancer in our study sample was found to be 26% ( $n = 19$ ; papillary 14, follicular 5), which was significantly higher in patients who had higher preoperative TSH levels.

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## Conflicts of interest

There are no conflicts of interest.

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