

Higher serum TSH levels correlate with a higher incidence of differentiated thyroid cancer and extrathyroidal extension of tumor in elderly patients

Haymart MR, Glinberg SL, Liu J, Sippel RS, Jaume JC, Chen H. Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. Clin Endocrinol (Oxf) 2009;71:434-9.

SUMMARY

BACKGROUND Previous studies by Haymart and associates have shown that a higher than usual serum thyrotropin (TSH) level is associated with a greater than usual risk of differentiated thyroid cancer in patients with a thyroid nodule, and of advanced tumor stage at the time of diagnosis. It is also known that age over 45 years is also associated with more advanced disease at the time of diagnosis. The aim of this study was to determine the relationship between higher serum TSH levels in patients with advanced age and tumor stage.

METHODS This is a retrospective study of 1361 patients who had thyroid surgery at the University of Wisconsin, Madison, from May 1994 through December 2007, among whom demographic and pathological data were available in 980 patients with preoperative TSH measurements. Of this group, 26 were excluded from the study, 8 without initial surgical records and 18 with thyroid malignancy other than differentiated thyroid cancer (DTC), leaving 954 patients, 249 with DTC (26%) and 705 with benign thyroid disease (74%). The latter had symptomatic goiters, follicular adenomas, and large benign nodules, and a few had Graves' disease. Of the 954 patients, 772 were women (81%) and 182 were men (19%). Here and elsewhere, percentages are rounded to an integer.

Age was evaluated as a continuous variable within age ranges of <45 versus ≥45 years and <20 years, and categorically in ranges of 20 to 44, 45 to 59, and ≥60 years. Age 45 was used as a cutoff, as DTC of similar extent has a worse prognosis in

older patients than in younger patients; also measured were categories of age ranges <20 and ≥60 years, as the likelihood of cancer recurrence is greatest in patients younger than 20 and in those 60 years or older.

High-risk cancer such as a primary tumor >4 cm, distant metastases, and extrathyroidal extension were also analyzed in relation to TSH; however, lymph-node metastases were not included as a high-risk feature, mainly because central compartment lymph-node dissection was not routinely performed, and such an analysis would likely exclude patients with undetected lymph-node metastases. All analyses were repeated without the 118 patients taking levothyroxine (L-T₄) preoperatively to avoid an artificially determined TSH value.

RESULTS The incidence of DTC was 31% (118 of 383) in patients younger than 45 and 23% (131 of 571) in those 45 years or older (P = 0.04) (Figure 1). Men comprised 14% of the younger group (53 of 383) and 22% (129 of 571) of the older group. The thyroid nodule size resulting in surgery was 2.37±0.01 cm in the younger group, versus 2.74±0.01 cm in older patients (P = 0.007). Multiple thyroid nodules were detected in 46% (173 of 383) of the younger patients, versus 53% (302 of 571) of the older group (P = 0.012). The mean TSH was 2.24±0.24 μIU/ml in the younger patients, versus 1.52 ± 0.11 μIU/ml in the older patients (P = 0.108). The only demographic or pathological variable that did not differ significantly between groups was Hashimoto's thyroiditis.

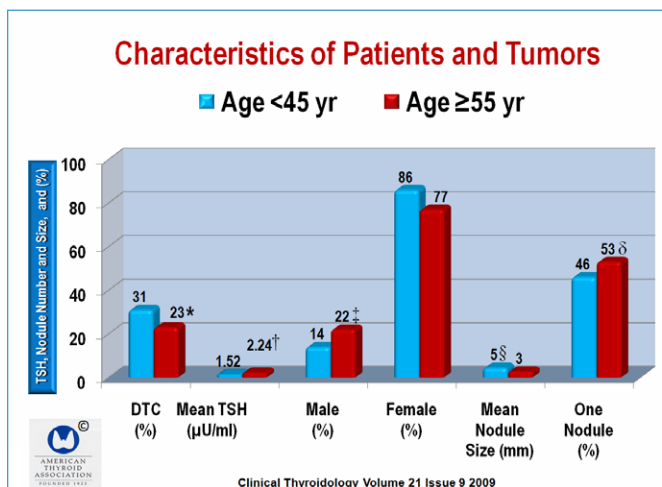


Figure 1. This figure shows the patient and tumor characteristics of the study cohort. Hashimoto's thyroiditis was present in 83 patients (21%) <45 years of age and 19% in patients ≥45 (not shown). *P = 0.004. †P = 0.018. ‡P = 0.001. §P = 0.007. ¶P = 0.012, comparing age <45 with age ≥ 45 years.

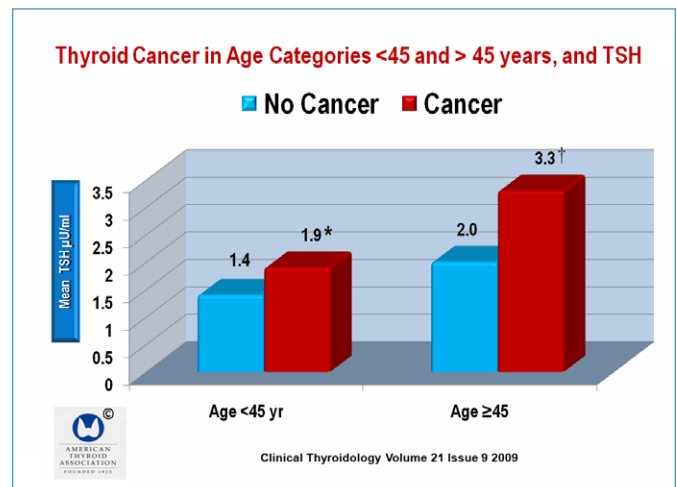
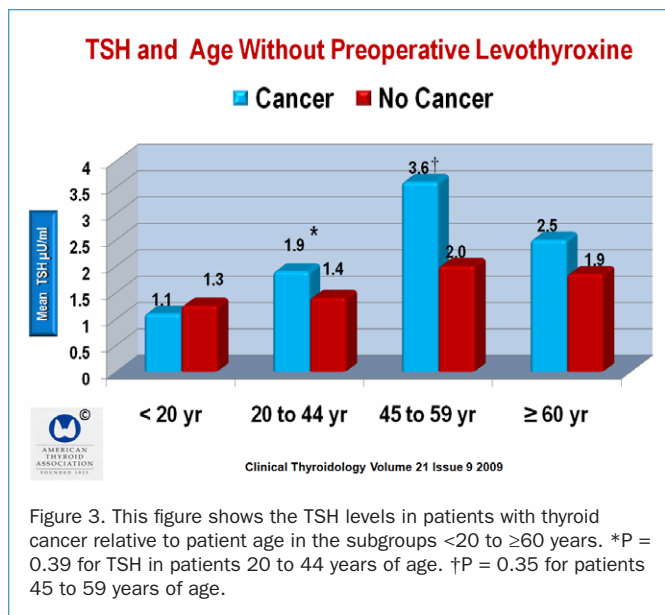


Figure 2. This figure shows the mean serum TSH and the presence or absence of thyroid cancer in patients <45 and ≥45 years. *P = 0.046 and †P = 0.027, comparing patients <45 versus ≥45 years.



Among the two age groups younger than 45 years and 45 or older, the mean TSH in patients not taking L-T₄ was significantly higher in patients with thyroid cancer as compared with patients without cancer, both in patients younger than age 45 (P = 0.46) and those 45 years or older (P = 0.027) (Figure 2). When the patients were further subdivided by age categories <20, 20 to 44, 45 to 59, and 60 years or older, there was a nonsignificant trend toward a rise in mean TSH with age in the patients with benign tumors and a parallel but more rapid increase in TSH in the patients with thyroid cancer in the age categories of 20 to 44 years and 45 to 59 years (P <0.05). The difference between cancer and no cancer within each subgroup was statistically significant in those 20 to 44 (P = 0.39) and 45 to 59 (P = 0.35) years of age (Figure 3). When the 118 patients on preoperative L-T₄ were excluded, the same pattern of higher mean TSH levels

in patients with thyroid cancer versus those without cancer persisted in the age categories of 20 to 44 (P = 0.019) and 45 to 59 years (P = 0.027). Although the serum TSH was higher in the groups with thyroid cancer, it consistently remained in the normal range.

Statistical significance was established in the age groups with the largest number of patients: thyroid cancer was found in 14 of 48 patients (29%) in the age group <20 years; 104 of 335 (31%) in the group 20 to 44 years; 82 of 334 (25%) in the group 45 to 59 years; and 49 of 237 (21%) in the group 60 years or older.

On multivariate analysis, there was a significant association of higher TSH with the incidence of thyroid cancer. There was a trend for an association between higher TSH and advanced age when only age and cancer were compared (P = 0.01 for cancer and P = 0.124 for age). However, when patients who were taking L-T₄ were excluded and the analysis included sex, nodule size, nodule number, and Hashimoto's thyroiditis, only Hashimoto's thyroiditis (P = 0.001) and thyroid cancer (P = 0.39) were independently associated with higher TSH. Patients ≥45 years had a nonsignificant trend for higher mean TSH in patients with stages III and IV disease versus those with stages I and II disease (P = 0.125). When the high-risk features of age, extrathyroidal tumor extension, tumor >4 cm, and distant metastases were analyzed in relation to the mean TSH in patients with thyroid cancer, only extrathyroidal extension was associated with higher mean TSH on univariate (P = 0.04) and multivariate analysis (P = 0.002). When only patients ≥45 years were evaluated, extrathyroidal extension was the only high-risk feature associated with higher TSH (P = 0.008)

CONCLUSION Higher serum TSH levels correlate with a higher incidence of thyroid cancer and extrathyroidal extension of tumor.

COMMENTARY

Haymart et al. published an important article (1) showing that higher serum TSH levels in patients with thyroid nodules is associated with a greater risk of differentiated thyroid cancer and advanced tumor stage at the time of diagnosis. On both univariate and multivariate analyses, the risk of malignancy was found to correlate with higher TSH levels. The likelihood of malignancy was 16% when the serum TSH was <0.06 µIU/ml, versus 52% when the TSH was ≥5.0 µIU/ml (P = 0.001). When the serum TSH was 0.40 to 1.39 µIU/ml, the likelihood of malignancy was 25%, versus 35% when the TSH ranged between 1.40 and 4.99 µIU/ml. Moreover, mean (±SD) TSH was 2.1±0.2 µIU/ml in patients with stage I or II as compared with 4.9±1.5 µIU/ml in patients with stage III or IV disease (P = 0.002). The main conclusion of the study was that the likelihood of thyroid cancer increases with higher serum TSH concentration; even when TSH was within the normal range. A TSH level above the population mean was found to be associated with a significantly greater likelihood of thyroid cancer than a TSH below the mean, showing that a higher TSH level is associated with advanced DTC stage.

This study is an extension of the idea that higher serum TSH levels are significantly associated with extrathyroidal extension of tumor. However, the major thrust of the current study is that high serum TSH is the harbinger of advanced disease, whereas age, per se, is not the cause of advanced disease. This is a giant leap from our current understanding of the pathophysiology of DTC and the high risk for poor outcomes in patients 45 years or older. The younger patients in the Haymart study were more likely to have DTC, along with a smaller nodule size and a solitary nodule. Surgical patients under age 45 had a 31% incidence (118 of 383) of DTC, versus those ≥45 years, who had a 23% likelihood of DTC. Further supporting the hypothesis that there is an independent relationship between serum TSH and the incidence of thyroid cancer, multivariate analysis found that thyroid cancer was associated with the higher serum TSH concentrations, not age.

There are, however, several limitations to the current study. The authors acknowledge that all the patients had undergone thyroidectomy, and this population may not be representative of the broad population. Also, not all of the patients had

preoperative TSH levels measured. A more significant limitation is that the serum TSH was not related to patient race and ethnicity. During the past 15 years, the reported upper limit of TSH has been considered to be approximately 4.1 μ U/ml when TSH is measured by immunochemiluminometric assay (2). Moreover, recent studies have shown that the reference limits for TSH differ between races and with age and that the use of race- and age-specific reference limits decreases misclassification of patients with lowered or raised TSH in an urban practice (3). In addition, the TSH shifts to higher concentrations with age,

which appears to be a continuum that extends even to people with exceptional longevity (4). TSH was found to be distributed at higher concentrations, without skew, in whites as compared with blacks (median, 1.54 μ U/ml vs. 1.18 μ U/ml; $P < 0.001$) and in old (>80 years) as compared with young (20 to 29 years) persons. These observations raise some question that TSH, per se, is responsible for the increase in thyroid cancer in thyroid nodules, regardless of patient age.

Ernest L. Mazzaferri, MD, MACP

References


1. Haymart MR, Repplinger DJ, Levenson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* 2008;93:809-14.

2. Hamilton TE, Davis S, Onstad L, et al. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2008;93:1224-30.


3. Boucai L, Surks MI. Reference limits of serum TSH and free T₄ are significantly influenced by race and age in an urban outpatient medical practice. *Clin Endocrinol (Oxf)* 2009;70:788-93.

4. Atzmon G, Barzilai N, Hollowell JG, et al. extreme longevity is associated with increased serum thyrotropin. *J Clin Endocrinol Metab* 2009;94:1251-4.


DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, PUBLIC SERVICE, EDUCATION, AND COLLABORATION.




AMERICAN THYROID ASSOCIATION
FOUNDED 1923



ATA Publications



Public & Patients



Physicians & Professionals

ABOUT THE ATA

GIVE ONLINE

JOIN THE ATA

FELLOWS' CORNER

MEMBERS ONLY

JOIN THE AMERICAN THYROID ASSOCIATION

Are you intrigued by the study of the thyroid? **You belong in the ATA!**

ATA members are leaders in thyroidology who promote excellence and innovation in clinical care, research, education, and public policy.

Join us as we advance our understanding of the causes and improve the clinical management of thyroid diseases in this era of rapid pace biomedical discovery.

A close-knit, collegial group of physicians and scientists, the ATA is dedicated to the research and treatment of thyroid diseases. ATA's rich history dates back to 1923 and its members are respected worldwide as leaders in thyroidology.

The ATA encourages you to apply for membership. We want you to experience the wealth of knowledge and enjoy the benefits of being active in this highly specialized and regarded society. The ATA looks forward to having you as a member!

<http://www.thyroid.org/professionals/join/index.html>