Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

Serum TSH Levels in the Upper Normal Range Suggest That a Thyroid Nodule Is Malignant

McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab 2012;97(8):2682-92. Epub May 23, 2012.

SUMMARY

Background

Since Boelaert et al. in the United Kingdom first reported that serum TSH was a dose-related risk factor for thyroid carcinoma in thyroid nodules (1), there have been a large number of additional studies to evaluate this association. In the current study, the authors performed a systematic review of clinical studies that examined the relationship between serum TSH and the diagnosis of thyroid cancer.

Methods

The authors used MEDLINE and EMBASE to find appropriate articles. They required that each paper contain evidence of pathologically confirmed thyroid cancer as well as serum TSH concentrations and to have nested case controls in prospective, retrospective, or cross-sectional studies. Studies that consisted of only patients with thyroid cancer and no controls were excluded. To derive odds ratios (OR), they used the "aggregate generalized least squares for trend" method.

Results

Of the 6833 abstracts of articles obtained in the literature search, only 97 passed the screening phase and were read in full text. Of these, 28 studies were selected for systematic review; 22 of them included data that could be combined for meta-analyses. These 22 studies included 40,929 subjects and 5605 cases of thyroid cancer. Using a linear dose-response model, the pooled OR for higher serum TSH was 1.23 (95% CI, 1.11 to 1.37) per milliunit of TSH per liter. At a TSH of 3 mU/L, this model predicts an OR for thyroid cancer of 1.87 (95% CI, 1.36 to 2.55), and at 5 mU/L an OR of 2.83 (95% CI, 1.67 to 4.77). Because of considerable heterogeneity in the linear model, a spline model was constructed using data from 17 studies. The slope of OR vs. TSH was slightly steeper at a TSH of 0 to 1 mU/L, leading to the OR of a TSH <1.0 of 1.72 (95% CI ,1.42 to 2.07) per milliunit per liter; above a TSH of 1.0, the OR was lower, at 1.16 (95% CI, 1.12 to 1.21) per milliunit of TSH per liter in a spline analysis.

Interestingly, studies adjusting for autoimmune thyroiditis reported lower TSH-related OR for thyroid cancer; for TSH <2.5 mU/L , OR was 1.23 (95% CI, 1.02 to -1.47) per milliunit per liter and somewhat surprisingly, for TSH >2.5 mU/L, the OR was 0.98 (95% CI, 0.89 to 1.09) per milliunit per liter.

Conclusions

Higher serum TSH concentrations are generally associated with an increased risk of thyroid cancer.

ANALYSIS AND COMMENTARY

Presumably the data and conclusions apply to patients with thyroid nodules who are being evaluated for the possibility of thyroid cancer, but this assumption tended to get lost in the presentation of data. Nevertheless, the paper is a very useful and timely summary of the literature on this topic. In my analysis of their table summarizing the studies, I note that 15 of 25 studies show a TSH-related increase in the OR of cancer, frequently extending to supranormal serum TSH, but the lower confidence limit of the OR was often less than 1.0. As occurs with the additional power of meta-analysis, combining studies will often show significance that may be "lost" with smaller numbers of subjects. I like the linear analysis because it implies that the higher the TSH, the higher the chance of cancer in a nodule. The spline analysis showing that the OR per milliunit of TSH is higher with a TSH <1.0

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mU/L makes no clinical sense because in all but one of the various studies there is no increase in OR with TSH <1.0 mU/L; in fact, in most studies the authors set TSH <1.0 as the control OR of 1.0.

The authors carefully avoided recommending TSH suppression of nodules as a means of reducing the risk of thyroid cancer. However, one large study of 27,914 patients included in the analysis reported that patients with thyroid nodules treated with levothyroxine had a lower TSH and a lower frequency of papillary thyroid cancer than those not so treated (2). The authors also recommend that future studies should investigate the validity of using serum TSH for diagnostic nomograms in the evaluation of nodules. I think that the large body of data summarized by the authors already provides a basis for considering that a relatively low serum TSH suggests that a nodule is more likely to be benign and that a relatively high serum TSH, even if in the normal range or slightly above it, makes the nodule more worrisome, unless the patient has overt Hashimoto's disease. I also think the autoimmunity issue is fascinating and could well impact on the shape of the relationship between TSH and thyroid cancer. But, the fact that the TSH effect was attenuated after adjusting for thyroid autoimmunity suggests that thyroid autoimmunity, via hypothyroidism, may be driving the "TSH effect,", so it doesn't make Hashimoto's "less worrisome"; it just makes it an explanation for the TSH effect.

— Jerome M. Hershman, MD

References

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2. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, Di Coscio G, Miccoli P, Grasso L, Pinchera A, Vitti P. L-thyroxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27,914 patients. Endocr Relat Cancer 2010;17:231-9.