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New evidence on the association between pre-diagnostic thyroid stimulating hormone levels and thyroid cancer risk

Cari M. Kitahara[1]

[1]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, 9609 Medical Center Drive, Bethesda, MD 20892

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Thyroid stimulating hormone (TSH) has long been hypothesized to play a role in thyroid cancer development in humans, including as a mediator of the observed associations for ionizing radiation, obesity, smoking, and iodine intake, among other known and suspected risk (and protective) factors, due to its demonstrated ability to stimulate follicular thyroid cell growth and follicular-cell derived thyroid cancer development in experimental studies.[1-5] Elevated TSH levels are also used as a clinical predictor of thyroid malignancy among thyroid nodule patients.[6] However, few studies have prospectively evaluated TSH in relation to subsequent thyroid cancer risk, and fewer have evaluated this association within the normal (euthyroid) range of thyroid function.

In this issue of *Cancer Epidemiology, Biomarkers and Prevention*,[7] Huang and colleagues published findings from a nested case-control study measuring pre-diagnostic serum concentrations of TSH and thyroid hormones in 741 U.S. military personnel diagnosed with papillary thyroid cancer (PTC, the most common histologic type) and 741 age-, sex-, and race/ethnicity-matched controls. After adjusting for body mass index and branch of military service, the authors found that higher TSH within the normal range was inversely associated with PTC risk in men and women. The association was stronger for tumors >10 mm, which are more likely to progress and require treatment, than those ≤10 mm.

Outside the normal range, there was a sex difference in the association between TSH and PTC risk. TSH below the normal range (consistent with overt hyperthyroidism) was associated with elevated PTC risk in women but not men, while TSH above the normal range (consistent with overt hypothyroidism) was associated with higher PTC risk in men but not women. The association between overt thyroid dysfunction and thyroid cancer risk is not well-understood, and results of the few epidemiologic studies on the topic have been conflicting.[8-11] Residual confounding by exposures not collected in this and other studies on the topic, including treatment for overt thyroid disease or other medical conditions that

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influence thyroid function (e.g., thyroid autoimmunity[8,12]) might account for some of these inconsistencies.

The inverse association between pre-diagnostic TSH and thyroid cancer risk is surprising considering the hypothesized role of TSH in thyroid cancer development.[1] However, it is consistent with findings from a genome-wide association study showing a positive association between variants associated with low TSH levels and thyroid cancer risk,[13] as well as another recent nested case-control study of 357 cases and matched controls, most of whom had TSH levels within the normal range, which similarly showed an inverse association between pre-diagnostic TSH and differentiated thyroid cancer risk.[14]

These findings highlight a critical gap in our understanding of the etiology of thyroid cancer, a malignancy which has been rapidly increasing in incidence over the past 30 years but for which few modifiable risk factors have yet been established.[15] There remains a need for additional large prospective studies examining pre-diagnostic measures of thyroid function and thyroid cancer risk that can account for potential confounding factors, including thyroid hormone treatment, medical conditions, and other factors that influence concentrations of these hormones.

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