Editorial

Cancer Epidemiology, Biomarkers & Prevention

New Evidence on the Association between Prediagnostic Thyroid-Stimulating Hormone Levels and Thyroid Cancer Risk

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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 & Prevention* (7), Huang and colleagues published findings from a nested case–control study measuring prediagnostic 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 $\leq$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, whereas 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 influence thyroid function (e.g., thyroid autoimmunity; refs. 8, 12), might account for some of these inconsistencies.

The inverse association between prediagnostic 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 prediagnostic TSH and differentiated thyroid cancer risk (14).

These findings highlight a critical gap in our understanding of the etiology of thyroid cancer, a malignancy that 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 prediagnostic 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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References

1. Ron E, Schneider AB. Chapter 50: thyroid cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention, 3rd edition. New York, NY: Oxford University Press; 2006. pp. 975–94.
2. Williams ED. Mechanisms and pathogenesis of thyroid cancer in animals and man. Mutat Res 1995;333:123–9.
3. Hard GC. Recent developments in the investigation of thyroid regulation and thyroid carcinogenesis. Environ Health Perspect 1998;106:427–36.
4. Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. Am J Epidemiol 2010;171:242–52.
5. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control 2009;20:75–86.
6. 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;97:2682–92.
7. Huang H, Rusiecki J, Zhao N, Chen Y, Ma S, Yu H, et al. Thyroid-stimulating hormone, thyroid hormones and risk of papillary thyroid cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2017;28:1209–18.

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8. Balasubramaniam S, Ron E, Gridley G, Schneider AB, Brenner AV. Association between benign thyroid and endocrine disorders and subsequent risk of thyroid cancer among 4.5 million U.S. male veterans. J Clin Endocrinol Metab 2012;97:2661–9.
9. Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer Causes Control 1999;10:583–95.
10. Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. Am J Epidemiol 2010;171:242–52.
11. Iribarren C, Haselkorn T, Tekawa IS, Friedman GD. Cohort study of thyroid cancer in a San Francisco Bay area population. Int J Cancer 2001;93:745–50.
12. Feldt-Rasmussen U, Rasmussen AK. Autoimmunity in differentiated thyroid cancer: significance and related clinical problems. Hormones 2010;9:109–17.
13. Gudmundsson J, Sulem P, Gudbjartsson DF, Jonasson JG, Masson G, He H, et al. Discovery of common variants associated with low TSH levels and thyroid cancer risk. Nat Genet 2012;44:319–22.
14. Rinaldi S, Plummer M, Biessy C, Tsilidis KK, Østergaard JN, Overvad K, et al. Thyroid-stimulating hormone, thyroglobulin, and thyroid hormones and risk of differentiated thyroid carcinoma: the EPIC study. J Natl Cancer Inst 2014;106:dju097.
15. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016;12:646–53.

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