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Permalink
https://escholarship.org/uc/item/8r41673f

Journal
Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 21(9)

ISSN
1530-891X

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Publication Date
2015-09-01

DOI
10.4158/ep15733.or

Peer reviewed

SERUM THYROTROPIN CONCENTRATIONS ARE NOT PREDICTIVE OF AGGRESSIVE BREAST CANCER BIOLOGY IN EUTHYROID INDIVIDUALS

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Abstract

Objective—The potential influence of hypothyroidism on breast cancer remains incompletely understood. The objective of this study was to investigate the relationship between serum thyrotropin [thyroid-stimulating hormone (TSH)] concentration and markers of aggressive breast cancer biology, as defined by receptor expression profile, tumor grade, and American Joint Committee on Cancer (AJCC) stage characteristics.

Methods—This was a retrospective cohort study of patients from 2002–2014. All breast cancer patients who had complete receptor (estrogen receptor, ER; progesterone receptor, PR; and Her2/ neu) and pre-diagnosis serum TSH data (n=437) were included. All patients had one of six receptor profiles: ER+ PR+ Her2/neu −, ER+ PR− Her2/neu−, ER+ PR+ Her2/neu+, ER+ PRHer2/ neu+, ER− PR− Her2/neu+, ER− PR− Her2/neu−. Log-transformed serum TSH concentrations were analyzed using multinomial and logistic regressions for a potential relationship with markers of breast cancer aggressiveness.

Results—Increasing serum TSH concentration was associated with a lower probability of having the receptor expression profile ER+ PR+ Her2/neu+ compared to patients with the ER+ PR+ Her2/neu− profile (OR=0.52, p=0.0045). No significant associations between other receptor expression profiles and serum TSH concentration were found. All time-weighted and unweighted median serum TSH concentrations were within normal limits. No significant associations between serum TSH concentration and tumor grade, overall AJCC stage, or tumor size (T), lymph node positivity (N), or presence of metastasis (M) were observed.

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Disclosure Statement: The authors have nothing to disclose.

Conclusions—Serum TSH was not associated with markers of breast cancer aggressiveness in our cohort.

Key terms

Hypothyroidism; breast cancer; TSH; thyrotropin

Introduction

Breast cancer is the most common malignancy among women with a five-year prevalence of 1.30% in the U.S. (1), while primary hypothyroidism is the most common clinical disorder of thyroid dysfunction, affecting approximately 9.5% of the general U.S. population (2). Although it has been postulated as early as the 1960s that hypothyroidism may be associated with an increased incidence of breast cancer (3), the available limited data on this topic have not shown a definitive relationship (4–8). Various confounding factors contribute to the challenging aspects of establishing an association between hypothyroidism and breast cancer, as the two conditions have increased prevalence specifically among a similar patient population (i.e. adult women). Breast cancer has also been associated specifically with autoimmune thyroid disease (9) and relative iodine deficiency (10–13), conditions which predispose individuals to hypothyroidism.

Prior studies have been inconsistent in demonstrating a definitive association between breast cancer aggressiveness and thyroid disease, particularly thyroid autoimmunity (14–16). One study reported that patients with any type of thyroid disease (including hyperthyroid patients) were more likely to have a greater degree of lymph node involvement, a larger primary tumor, and vascular invasion, but there was no significant correlation with breast cancer stage or ER or PR status (17). Farahati et al found that the presence of thyroid peroxidase antibodies (TPO Ab) were protective against distant metastases at the time of presentation, and were inversely related to the levels of breast tumor markers CA-15-3 and CEA (18). Conversely, Mourouzis et al found an inverse correlation between cell proliferation as measured by Ki-67 and free triiodothyronine (T3) levels within the euthyroid range in patients with Her2/Neu+ tumors (19), demonstrating a harmful effect of thyroid function on breast cancer aggressiveness.

The present study investigated the potential relationship between hypothyroidism and breast tumor aggressiveness at a large academic medical center in the U.S., a region which is considered generally iodine-sufficient (20). We hypothesized that breast cancer patients with higher serum thyrotropin [thyroid stimulating hormone (TSH)] levels were more likely to express markers of more aggressive breast cancer biology. The markers included receptor (estrogen receptor [ER], progesterone receptor [PR], and Her2/neu) expression profile, tumor grade, and American Joint Committee on Cancer (AJCC) stage and characteristics.

Patients and Methods

We included all breast cancer patients with known profiles of ER, PR, and Her2/neu receptor status and at least one serum TSH concentration obtained before the diagnosis of breast cancer who received care at our institution between 2002–2014. Labs were obtained

at UCLA Health clinical laboratories. Only serum TSH values obtained prior to the diagnosis of breast cancer were used to avoid including any cases of hypothyroidism that developed in the setting of active breast cancer. Breast cancer aggressiveness data (receptor status, grade, and staging) was extracted from the UCLA Cancer Registry, and serum TSH concentrations and demographic information were extracted from the UCLA Integrated Clinical and Research Data Repository. Study approval was obtained from the UCLA Institutional Review Board. The reference range for TSH is 0.3–4.7.

Serum TSH values were log-transformed due to the linear-logarithmic relationship between serum TSH and thyroid hormone concentrations (21) and, for patients with multiple TSH values, weighted to reflect the duration of time between each laboratory assessment. Any data regarding receptor status, height, weight, or family history that was recorded alongside a later diagnosis was updated if missing in the earliest available record.

Weighted log-transformed serum TSH concentrations were evaluated both as a continuous variable and as a categorical variable after the creation of quintiles. The outcome variables were composite receptor expression phenotype (ER, PR, Her2/neu); AJCC stage grouping; and the individual staging elements of tumor size (T), extent of lymph node involvement (N), and extent of metastasis (M). Multinomial regression was performed to evaluate TSH as a predictor of tumor grade, AJCC stage grouping, tumor size (T), and extent of lymph node involvement (N). Logistic regression was performed to evaluate TSH as a predictor of receptor status and the presence of metastasis (M). Because of small sample size, patients with tumor grades 3 and 4 were pooled, as were patients with T0 and T1 tumors, and patients with AJCC stage groupings 0 and 1. Analyses controlled for race/ethnicity as defined by the United States Office of Management and Budget, age at diagnosis, family history of breast cancer (first- and second-degree) and marker of breast cancer aggressiveness (either staging or receptors). Race/ethnicity was grouped into Asian, African-American, Caucasian, and other because several categories had a very small sample size. The group labeled "other" includes American Indian or Alaska Native, multiracial, Native Hawaiian or other Pacific Islander, other, and unknown, representing 7.8% of the sample. Receptor expression profiles represented in the cohort were: ER+ PR+ Her2/neu−, ER+ PR− Her2/neu−, ER+ PR+ Her2/neu+, ER+ PR− Her2/neu+, ER− PRHer2/ neu+, ER− PR− Her2/neu−.

Results

A total of 437 patients were included in the study (Table 1), of which 422 (97%) had complete AJCC staging data and 420 (96%) had complete tumor grade data. 95.7% of the patients were euthyroid based on the weighted TSH (0.3–4.7). When TSH concentration was evaluated as a continuous variable, increasing TSH was associated with a lower likelihood of ER+ PR+ Her2/neu+ disease in comparison to ER+ PR+ Her2/neu− disease (OR=0.52, p=0.0045). No other significant associations between TSH as a continuous variable and receptor profile were found (Figure 1). There were no significant associations between serum TSH concentration as a continuous variable and tumor grade, AJCC stage grouping, and individual staging elements (T, N, M). Time-weighted and unweighted median TSH concentrations by tumor grade and AJCC stage are shown in Figures 2 and 3, respectively.

When TSH concentration was evaluated as a categorical variable, there were no significant associations between serum TSH concentration and any markers of breast cancer aggressiveness (data not shown). Increasing age at diagnosis was significantly associated with a higher likelihood of T4 breast cancer (OR=1.07, p=0.0053), M1 breast cancer (OR = 1.04, p=0.028), and a lower likelihood of N1 breast cancer (OR=0.98, p=0.0069).

Discussion

Although known risk factors for breast cancer include age, family history of breast cancer, occupational exposure, and reproductive and hormonal influences (1), this malignancy is generally relatively slow-growing, with a lag in clinical detection estimated at 5–10 years (22). Although coexisting conditions may confer additional risks, we demonstrate in our cohort that serum TSH concentrations are not associated with more aggressive breast cancer biology at presentation, as defined by tumor grade or AJCC stage characteristics at initial diagnosis. In addition, the ER+ PR+ Her2/neu− subtype, which is typically associated with more indolent disease biology, was associated with higher serum TSH compared to the more biologically aggressive ER+ PR+ Her2/neu+ subtype (22, 24). There was no significant difference in TSH concentrations between the ER+ PR+ Her2/neu− subtype and the triple negative breast cancer subtype, which is often associated with more aggressive disease biology (25). Furthermore, both the time-weighted and unweighted median serum TSH concentrations were within normal limits for all profiles. The evaluation of serum TSH as a categorical variable also did not yield an association with any markers of breast cancer aggressiveness. As there was no consistent significant trend between the various receptor expression profiles and serum TSH concentrations, we conclude that serum TSH concentration is not predictive of breast cancer aggressiveness as defined by receptor expression profile in this cohort.

Existing literature on the relationship between breast cancer prevalence (rather than aggressiveness) and hypothyroidism are also limited by a potential selection bias, in which women with a chronic illness, such as hypothyroidism, may be more likely to undergo more frequent medical care, thereby potentially resulting in a greater incidence of disease detection. One study reported that hypothyroid women were more likely to have breast cancer diagnosed at an earlier stage compared to euthyroid controls (6). The present study is unique due to the assessment of the relationship between serum TSH concentration and breast cancer aggressiveness, rather than breast cancer prevalence. In addition, we evaluated serum TSH concentrations as a weighted measure by duration of all values available prior to the diagnosis of breast cancer, rather than the TSH result closest to the time of diagnosis.

One limitation of our study is the use of elevated serum TSH concentrations to define hypothyroidism, which excludes patients with isolated hypothyroxinemia, and thereby does not address the potential association of hypothyroidism as a specific disease category and breast cancer aggressiveness. Other studies assessing these relationships have also assessed positive thyroperoxidase autoantibody (TPO Ab) titers as indicators of thyroid disease (4–5, 7, 9, 15, 26–30), which we did not evaluate in our cohort. Additionally, our sample may be predisposed to abnormal serum TSH concentrations, as this screening test for thyroid

dysfunction is not routinely obtained unless there is a clinical suspicion or positive family history; however, the median serum TSH of the study population was in the euthyroid range.

Further research may be useful in assessing whether particular thyroid disorders, including thyroid autoimmunity and/or altered dietary iodine nutrition, may be predisposing factors to more aggressive breast cancer or higher breast cancer incidence and/or prevalence. Finally, as only a small proportion of the sample in this study had aggressive tumor biology markers, a larger prospective study would be helpful in defining whether thyroid disease is associated with breast cancer biology.

Conclusion

Serum TSH was not associated with breast cancer receptor expression profile, tumor grade, or AJCC stage characteristics, suggesting that serum TSH is not a conclusive predictor of breast cancer aggressiveness in this sample.

Acknowledgments

Abbreviations

AJCC	American Joint Committee on Cancer
ER	estrogen receptor
L	lymph node positivity
M	metastasis
PR	progesterone receptor
T	tumor size
TPO Ab	thyroid peroxidase antibody
TSH	thyroid stimulating hormone
UCLA	University of California Los Angeles

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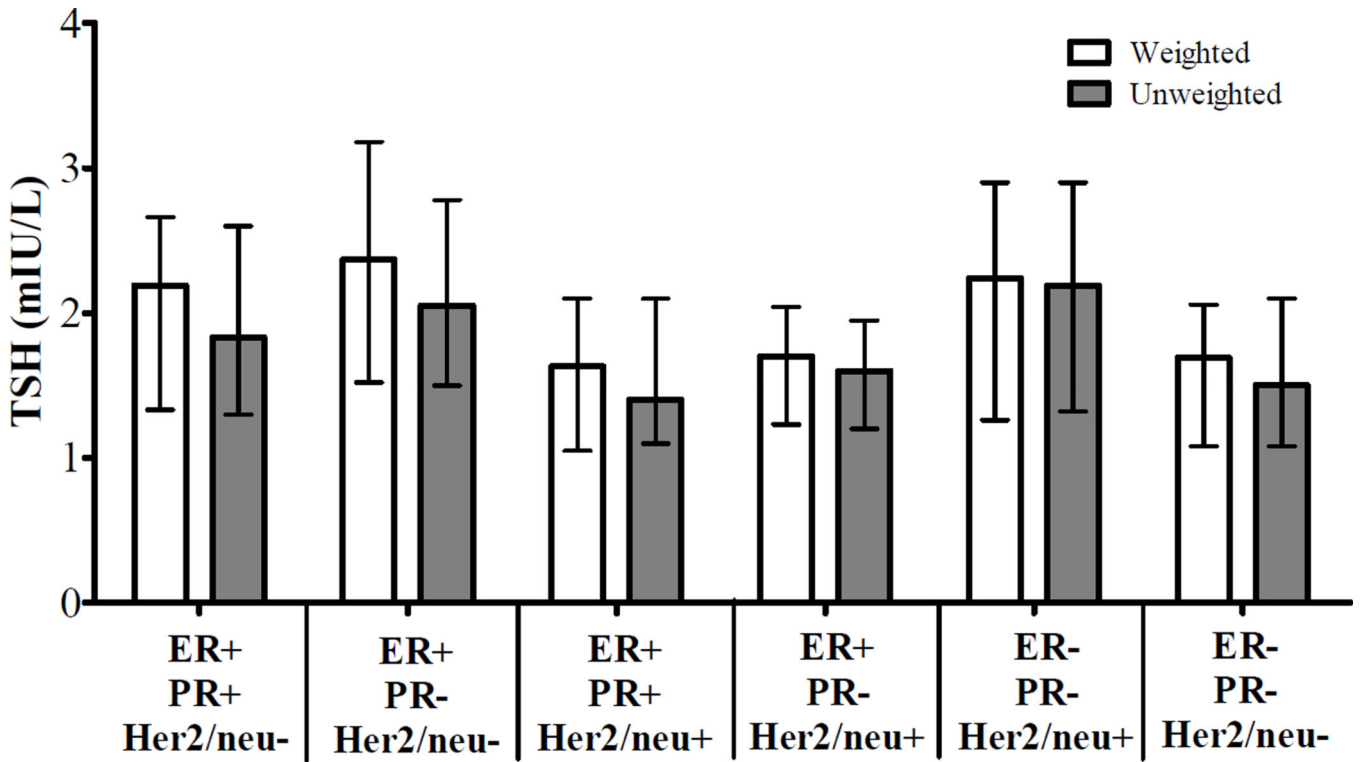
Figure 1.
Median Serum TSH Concentration per Receptor Expression Profile
*Serum thyroid stimulating hormone (TSH) (presented with associated IQR) was evaluated
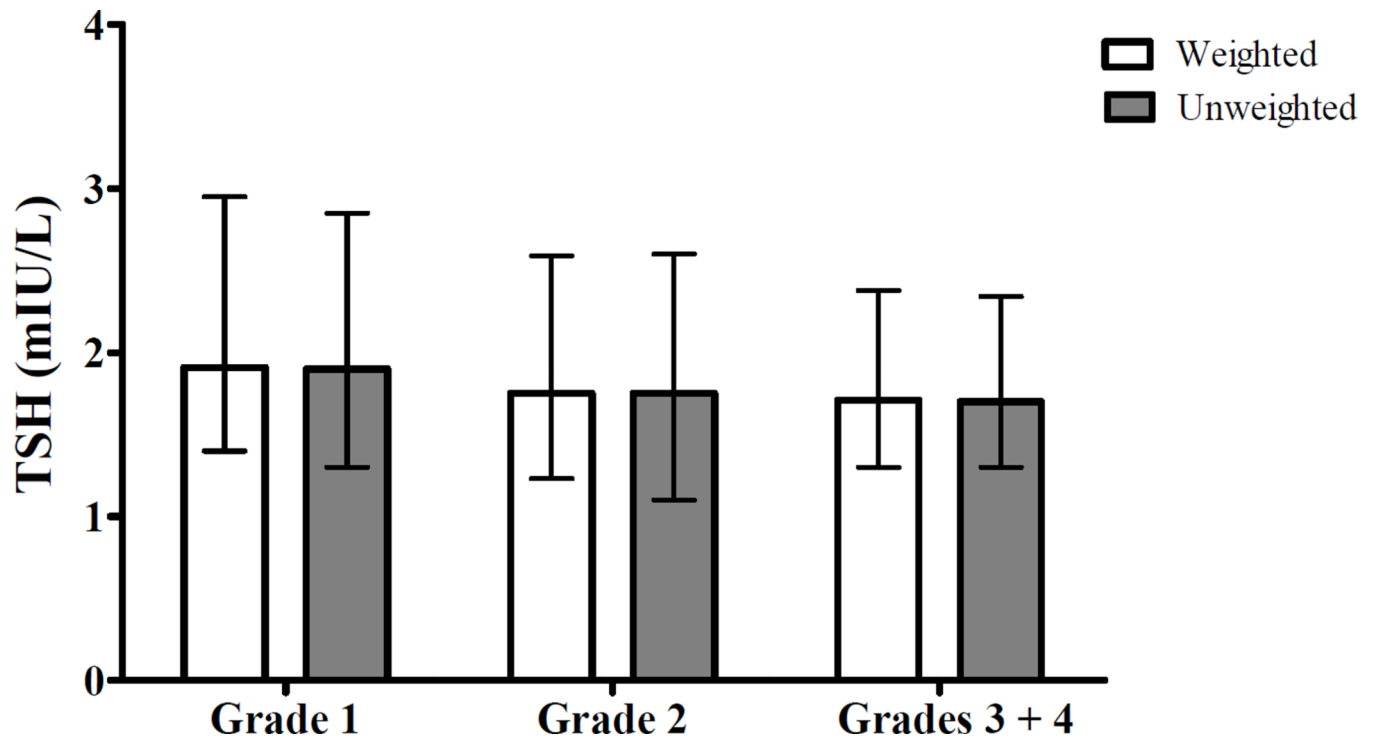as a continuous variable in this analysis. ER: estrogen receptor. PR: progesterone receptor.

Figure 2.
Median Serum TSH Concentration per Tumor Grade
*Serum thyroid stimulating hormone (TSH) (presented with associated IQR) was evaluated as a continuous variable in this analysis.
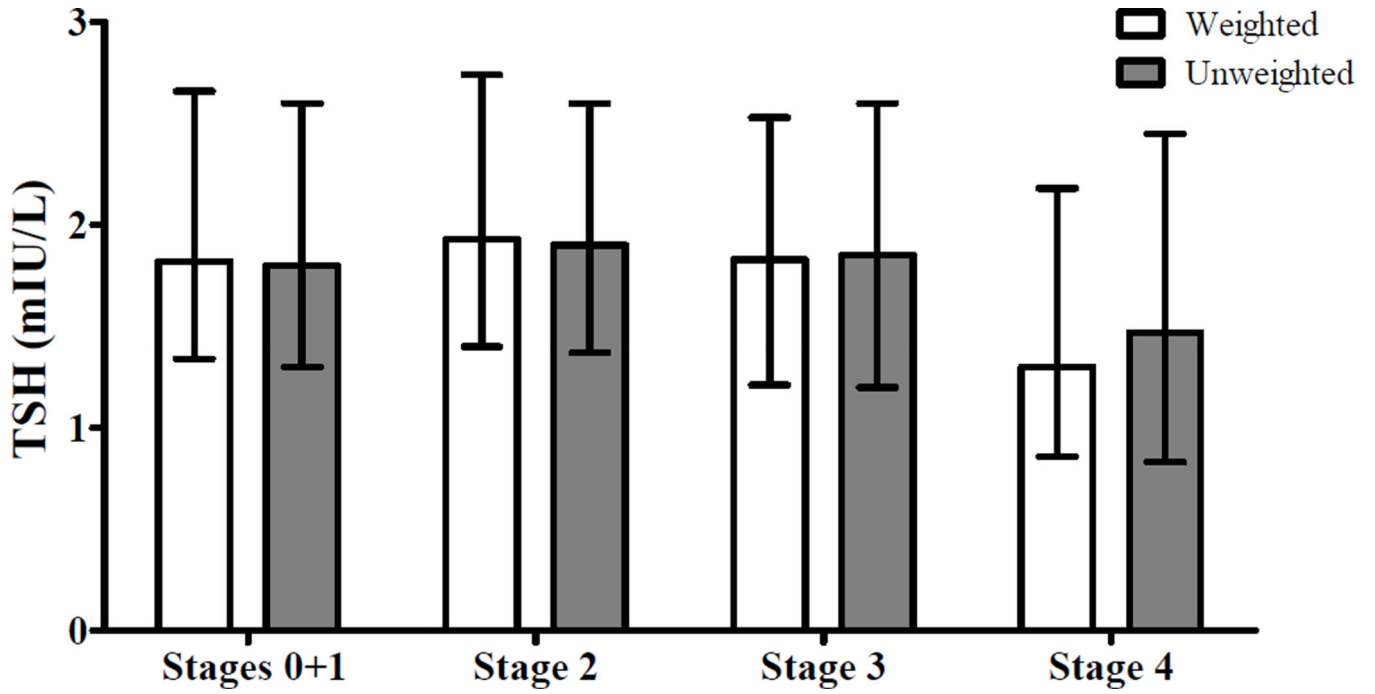
Figure 3.
Median Serum TSH Concentration per AJCC Cancer Staging Characteristics
*Stage 0 and Stage I were combined because the incidence of Stage 0 was low. Serum thyroid stimulating hormone (TSH) (presented with associated IQR) was evaluated as a continuous variable.

Table 1

Subject characteristics (n=437)

Age at diagnosis (years), mean ± standard deviation		62.3 ± 15.3
Time-weighted serum thyroid stimulating hormone (TSH) (mIU/L), median (interquartile range)		1.81 (0.05–10.42)
Unweighted serum TSH (mIU/L), median (interquartile range)		1.80 (0.07–9.70)
Median (range) number of serum TSH values per patient		3 (1–39)
		n (%)
Women		431 (98.6%)
Race/ethnicity as defined by the United States Office of Management and Budget		
	Asian	65 (14.9%)
	African-American	40 (9.2%)
	Caucasian	298 (68.2%)
	Other	35 (7.8%)
Receptor expression profile		
	ER+ PR+ Her2/neu−	290 (66.4%)
	ER+ PR− Her2/neu−	32 (7.4%)
	ER+ PR+ Her2/neu+	41 (9.4%)
	ER+ PR− Her2/neu+	9 (2.1%)
	ER− PR− Her2/neu+	23 (5.3%)
	ER− PR− Her2/neu−	42 (9.6%)
AJCC stage (n=422)		
	0	10 (2.4%)
	I	189 (44.8%)
	II	163 (38.6%)
	III	40 (9.5%)
	IV	20 (4.7%)
Grade (n=420)		
	1	107 (25.5%)
	2	191 (45.5%)
	3	121 (28.8%)
	4	1 (0.2%)