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Original Research

Preoperative thyroid-stimulating hormone associated risk of differentiated thyroid cancer in patients with thyroid nodules

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Abstract: In an assessment of risk for differentiated thyroid cancer (DTC) in individuals with human papillary thyroid cancer (PTC) and thyroid nodules a cohort prospective study was undertaken to establish the significance of preoperative thyroid-stimulating hormone (TSH) levels. Confirmed histologically PTC cases in one tertiary care center, and matched healthy individuals were tested for TSH, T3, T4 and T4 free total. The ORs and 95% confidence intervals have been calculated using conditional logistic regression models (CI). The blood TSH levels were related to the higher risk of PTC for men (OR,0,09; 95% Ci, 04–0,21, 95% CI and women) compared with the middle tertile of the TSH levels in the normal range (OR,0,07; 95 percent CI, 0,04–0,1). Over the normal range of TSH levels, an elevated PTC risks were connected amongst women (OR 0,09; 95% CI, 0,04–0,21) but not amongst men (OR,0,07; 95% CI, 0,04–0,1). With an increase in TSH level in the normal range between men and women, the risk for PTC reduced (Ptrend=0.041 and 0.0001). The risk of PTC related to TSH levels has been dramatically elevated above the normal range for men and TSH values below the normal range for women.

Key words: Papillary thyroid cancer (PTC); Thyroid stimuli (TSH); Differentiated thyroid cancer (DTC).

Introduction

Thyroid cancer is one of the most common endocrine system malignancies, accounting for around 1% of all neoplasms in China, with an annual incidence of up to 20 per 100,000 people. Thyroid cancer is more common in high-income areas than in middle- or low-income areas, and the incidence is much higher in high-income areas than in middle- or low-income areas (1). Thyroid cancer is the most common of all endocrine cancers, and its incidence is rising faster than any other cancer in both men and women 1. Thyroid cancer is the tenth most prevalent cancer in the United States, accounting for 3.8% of all cancers and 0.3% of all cancer fatalities (2). Papillary thyroid (PTC), which represents over 80% of all thyroid carcinoma, is the most frequent histological type of thyroid cancer (3). There is little understanding of the causative mechanisms driving thyroid cancer. Increased age, gender, ionizing radiation exposure, history of benign thyroid disease, and family history of thyroid cancer are the most well-documented risk factors for thyroid cancer (4). Higher body weight and height have recently been established as risk factors for thyroid cancer (5).

Overall, the prevalence of thyroid cancer is increasing in both sexes, and this increase can mostly be attributed to the increasing occurrence of small indolent papillary thyroid carcinomas (PTCs) (6). In China, the incidence rates of thyroid cancer in women are rising, partly because of the increasingly westernized changes in Chinese lifestyles 1. The overall burden of the disease is predicted to increase dramatically in the next years, in accordance with the increasing number of instances of thyroid cancer diagnosed (7). Typically, thyroid cancer is nodular and is identified as malignant with around 3.0% of multinodular and 4.5% of solitary nodules (8). Due to the higher occurrence of solitary nodules, it is crucial for better prognostics to early diagnosis of thyroid nodules. Thyrotropin is a recognized factor in thyroid stimuli (TSH), although the association between TSH and differentiated thyroid cancer (DTC) is contentious. Thyrotropin is a recognized factor of development (9). Several studies have shown an increased risk of thyroid cancer in people with nodular thyroid disease and the connection between high preoperative TSHs (10). Moreover, a recent meta-analysis indicated the increased risk of PTC in relation to a greater level of serum TSH (11). For numerous reasons a confirmatory analysis is, therefore, necessary to combine the preoperative TSH and the risk of DTC in thyroid nodular patients: First, there is still limited data on risk factors for thyroid cancer and early diagnosis strategies (12); second, serum TSH is the first laboratory test and is often still studied in thyroid nodule patients (13); Third, a number of major studies have indicated that TSH in the normal and supernormal reference ranges is related with thyroid cancer; and fourth, the higher cancer risk for patients with TSH remains unexplained. Preoperative TSH screening is expected to help identify the elevated risk of thyroid cancer for a population of patients with substantial medical and economic consequences.

Most early studies revealed increased thyroid cancer risk associated with high levels of TSH (14), no significant association was identified in a few studies

(15), and one reported a lower risk (16). The cross-sectional (14) or case-control studies have shown a positive relationship between HSR and thyroid cancer. The potential, TSH levels were evaluated. Only three future cohort studies are available. The risk of thyroid cancer associated with high TSH levels has been considerably lowered (16). In thyroid cancer cases, two smaller studies show lower but not substantial TSH than in controls (17). There were also no conclusive connections between thyroid hormones and thyroid cancer risk (14, 16). Two investigations found that decreased levels of thyroid hormones were related to a significant risk of thyroid cancer (14). Therefore, this study was done to establish the significance of preoperative thyroid-stimulating hormone (TSH) levels in differentiated thyroid cancer (DTC) in individuals with human papillary thyroid cancer (PTC) and thyroid nodules.

Materials and Methods

We retrospectively reviewed a prospectively collected data of the patients who underwent total thyroidectomy and pathology postoperatively shows thyroid carcinoma. These cases were done by a single surgeon faculty in the period January 2016 to December 2020 at one tertiary care hospital in Riyadh, Saudi Arabia. Adult patients above age 18 years were required to be enrolled in studies included in this cohort prospective study, and the following patient criteria were used to select which studies would be retrieved before being included in the analysis: Patients had thyroid nodules, the FNA biopsy/cytology and operation/surgery was performed in patients, if necessary and the DTC was performed in patients (papillary and follicular subtypes were both included; these were analyzed both separately and together). In patient studies under one of the following circumstances, studies were excluded: Developing toxic goiter; pure cystic nodules; autonomous thyroid nodules; prior thyroid operations; anaplastic thyroid cancer; or pregnancy.

To determine the studies to be taken into consideration in a meta-analysis, the following criteria were used: Clinical studies (controlled and uncontrolled); cohort, observational, and epidemiologic studies (retrospective and prospective); studies where serum TSH level was studied as the prognostic variable (defined as studies with a minimum follow-up from preoperative TSH in order to consider DTC as a binary classification [present/absent] rather than as a time-to-event with censoring); studies where serum TSH level was studied as the prognostic variable (defined as studies with a minimum follow-up). TSH and thyroid hormones measurement Using manufacturer reagents and calibrators, a calibrated Roche Cobas E601 Analyzer was utilized to quantify serum TSH levels and thyroid hormones. TSH was bound between 2 monoclonal antibodies that were specific to human TSH sterically interfering epitopes (one biotinylated and the other tagged with ruthenium complexes). TT3 and TT4 were dissociated from 8-Anilino-1-naphthalene (ANS) binding proteins and were competitive with the ruthenium labeled exogenous biotinylated T3 or T4 binding antibodies.

FT4 has directly competed for binding to a T4-specific antibody with a ruthenium complex, the exogenous biotinylated T4. All antibodies were captured by streptavidin-coated magnetic microparticles, then captured by an electrode magnet and by the application of ruthenium complex voltage-induced emissions of photons. The luminescence intensity was inversely proportional to TSH and thyroid hormone serum concentrations. The normal ranges were 0.3 to 4.2 mU/ml, 79 to 149ng/dl, 5.0– 10.6 mg/dL and 0.80-1.80 ng/dL for serum concentrations of TSH, TT3, TT4 and FT4.

TSH, TT3, TT4 and the FT4 serum concentration were separated into three classes according to the standard range (below, within, and above the normal range). Based on serum concentration variations across controls, the normal range group was further classified into tertiles. Therefore, for every hormone 5 categories existed: below the normal range, below the normal range, below the medium level and the normal range. The middle tertiles were employed as a reference for all analyzes within the normal range. The body mass index (BMI; <18.5, 18.5–24.9, 24–29,9, and _30kg/m2) has been used for all the conditional logistic regression models. TT3, TT4, and FT4 models have also been adapted for TSH serum levels. Additional adjustments of TT3, TT4 and FT4 serum levels in TSH models have not, however, resulted in any substantial change in the relationships identified, and so have not been incorporated in final models. Practitioners, estimated by the treatment of serum concentrations of TSH and thyroid hormones as continuous variables, were also investigating the dose-response relationship. Gender, histological subtype, tumor size (10 and >10 mm), and years from blood samples taken with PTC diagnostics (<3, 3–6, and >6 years, according to sample size) were stratified. Women and men were also tested for sensitivity up to 85 years.

Statistical analysis

TSH and thyroid hormones measurements have failed with one serum sample and the final study involved a combination of 384 PTC pairs of patients and matched controls. The distribution via c2 tests between cases and controls has been compared. Using Pearson correlation coefficients, the correlations between TSH, TT3, TT4 and FT4 were estimated. To compute ORs and 95% confidence intervals (95 percent CI) for the connection between TSH, thyroid, and PTC, the individual case-control design was compared. All trials had 0.05 on two sides. SAS software version 9.3 has been used for statistical studies (SAS Institute, Inc.).

Results

In Table 1, the BMI of the cases was slightly higher than that of the controls, but the difference was not statistically significant. The distributions of these variables were similar between cases and controls because the cases and controls were individually matched based on age and gender (Table 1). There were statistically significant strong positive associations between TT3, TT4, and FT4 ($P<0.01$ for FT3 and FT4 respectively), as expected (Table 2). TSH was found to have a weak but statistically significant relationship with TT3, TT4, and FT4 ($P<0.0001$ for TSH and $P<0.01$ for FT3 and FT4, respectively). Male cases had higher mean TSH levels than their matched controls, while female cases had

Table 1. PTC cases and matched controls' distributions of selected characteristics.

	Cases (N= 384) n (%)	Controls (N=384) n (%)	P
(a) Age at diagnosis, y			
<20	5 (1.30)	4 (1.04)	
20-30	10 (2.66)	9 (2.34)	
30-40	73 (19)	15 (3.90)	
40-50	100 (26)	10 (2.60)	
50-60	66 (17)	9 (2.34)	
60-70	28 (7.3)	3 (0.78)	
70-80	8 (2.08)	1 (0.26)	
80-90	1 (0.3)	42(10.9)	**0.90**
	Cases (N= 384) n (%)	**Controls (N=384) n (%)**	**P**
(b) Gender:			
Female	311 (80.9)	311 (80.9)	
Male	73 (19)	73 (19)	**1.00**

(c) BMI kg/m2

	<25		**25-29.9**		**≥30**		**Missing**
	Cases n (%)	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**	
15-20	3 (60)	3 (60)	1 (20)	4 (80)	1(20)	4 (80)	-
20-30	0	0	4(40)	6 (54.5)	6 (54.5)	4 (36.3)	1 (9)
30-40	14 (50)	4 (14.2)	1 (3.5)	13 (46.4)	0	0	-
40-50	0	0	24 (24)	76 (76)	76 (76)	24 (24)	-
50-60	1 (1.5)	1 (1.5)	14 (20.8)	53 (79.1)	52 (77.6)	1 (1.5)	-
60-70	2 (6.4)	2 (6.4)	12 (38.7)	19 (61.3)	17 (54.8)	14 (45.1)	-
70-80	0	0	3 (33.3)	6 (66.6)	6 (66.6)	3 (33.3)	-
80-90	0	0	1	0	0	0	-
P	**0.35**						

Table 2. Cross-validation of the model.

TSH	Case	Control	OR	Lower 95% CI	Upper 95% CI
<0.30	19	365	0.09	0.05	0.12
0.30-1.93	142	242	3.66	2.56	4.79
1.94-4.20	53	331	3.94	2.59	5.79
>4.20	15	369	0.78	0.39	1.35

P trend **(within the normal range): 0.0001
P trend (Overall): 0.80**

Factor	Case	Control	OR	Lower 95% CI	Upper 95% CI
		Free T3*(ng/dL)**			
2.3-4.1	28	356	0.07	0.04	0.1
>4.1	70	314	0.22	0.17	0.29
P trend **(within the normal range):		**0.01**			
P trend (Overall): 0.22**					
		Free T4*(ng/dL)**			
0.80-1.80	0	0	-	-	-
>1.80	159	225	0.7	0.6	0.81

CI, confidence interval; OR, odds ratio (values relative to a 1 mU/L increase in TSH).

lower mean TSH levels. There was no statistical significance in any of these differences. Thyroid hormone levels were likewise not significantly higher in female cases compared to female controls, whereas thyroid hormone levels in men were compared between cases and controls (Table 3).

When compared to the normal range, serum TSH levels below the normal range were associated with a significantly higher risk of PTC (OR,0.09; 95% CI, 0.05–0.12; Fig. 1). Surprisingly, TSH levels beyond the normal range were related with a borderline significant elevated risk of PTC (OR,0.22; 95% CI, 0.17–0.29). TT3, TT4, and FT4 serum concentrations that were below or beyond the normal range were not linked to an increased risk of PTC. PTC risk decreased with increasing TSH levels within normal ranges (Ptrend = 0.0001), but no dose-response correlations were found for TT3, TT4, or FT4 (Table 4). When compared to the normal range, TSH levels below the normal range were linked with an elevated risk of PTC in Men (OR,0.09; 95%

Table 3. Cross-validation of the model (Gender- Female).

TSH	Case	Control	OR	Lower 95% CI	Upper 95% CI
<0.30	20	291	0.07	0.045	0.11
0.30-1.93	184	127	1.45	1.16	1.81
1.94-4.20	65	246	0.26	0.20	0.34
>4.20	30	281	0.10	0.07	0.15

P trend **(within the normal range): 0.0001
P trend (Overall): 0.15**

Factor	Case	Control	OR	Lower 95% CI	Upper 95% CI
			Free T3*(ng/dL)**		
2.3-4.1	16	47	0.34	0.30	0.64
>4.1	47	16	2.94	1.67	5.19

P trend **(within the normal range): 0.01
P trend (Overall): 0.35**

			Free T4*(ng/dL)**			
0.80-1.80	0	0	-	-	-	-
>1.80	96	215	0.45	0.36	0.58	

CI, confidence interval; OR, odds ratio (values relative to a 1 mU/L increase in TSH).

Table 4. Cross-validation of the model (Gender- Male).

TSH	Case	Control	OR	Lower 95% CI	Upper 95% CI
<0.30	6	67	0.09	0.04	0.21
0.30-1.93	48	25	1.92	1.83	3.11
1.94-4.20	12	61	0.20	0.11	0.37
>4.20	4	69	0.06	0.02	0.16

P trend **(within the normal range): 0.041
P trend (Overall): 0.27**

Factor	Case	Control	OR	Lower 95% CI	Upper 95% CI	P value
				Free T3***(ng/dL)		
<2.3	2	71	0.03	0.01	0.12	
2.3-4.1	4	69	0.06	0.02	0.16	
>4.1	20	53	0.38	0.23	0.64	
	P trend **(within the normal range):			0.008		
	P trend** (Overall): 0.18					
				Free T4***(ng/dL)		
0.80-1.80	1	72	0.01	0.001	0.07	-
>1.80	72	1	1.00	0.14	7.17	

P trend **(within the normal range): 0.001
P trend (Overall): 0.01**

CI, confidence interval; OR, odds ratio (values relative to a 1 mU/L.

CI, 0.04–0.21) but not in women ((OR,0.07; 95% CI, 0.04–0.1); Fig. 2) Furthermore, only men (OR,0.38; 95% CI, 0.23-0.64) but not women (OR,0.10; 95% CI, 0.07–0.15) had an increased risk of PTC in association to TSH levels beyond the normal range. Increased TSH levels within the normal range reduced the incidence of PTC in both men and women (Ptrend= 0.041 and 0.0001, respectively).

Lower TSH levels within the normal range, on the other hand, were associated with a higher risk of PTC in Men (OR, 1.92; 95% CI, 1.83–3.11) than in Women (OR, 1.45; 95% CI, 1.16–1.81). Higher TSH levels within the normal range, on the other hand, were associated with a lower risk of PTC in men (OR,0.20; 95% CI, 0.11–0.37). Only among men was there an inverse relationship between TT3 levels above the normal range and the risk of PTC (OR, 0.38; 95% CI, 0.23–0.64; Fig. 2), but the risk of PTC rose with rising TT3 serum concentrations among women (OR, 0.38; 95% CI, 0.23–0.64).

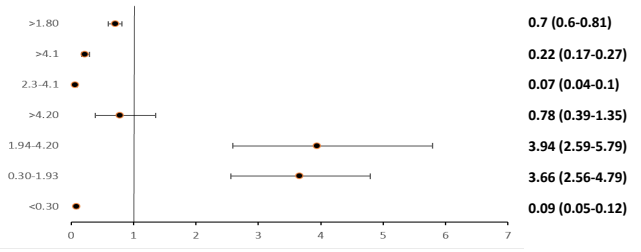

Figure 1. Risk of PTC associated with serum concentrations of TSH and thyroid hormones. *, Conditional logistic regression, adjusted for BMI. **, Estimated by continuous variables. ***, Additionally, adjusted for serum concentration of TSH. CI, confidence interval; OR, odds ratio (values relative to a 1 mU/L increase in TSH).

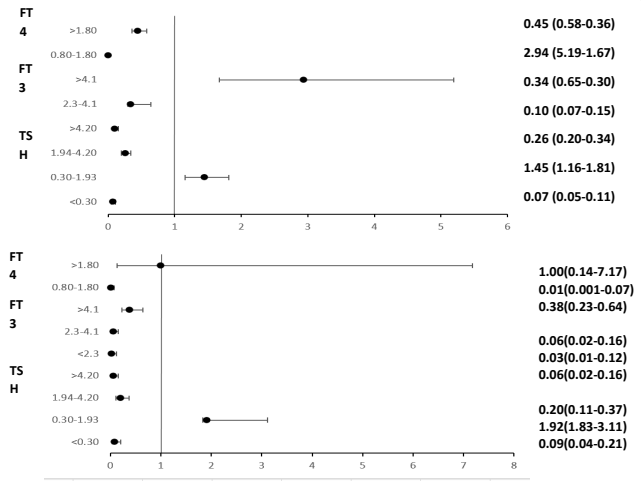

Figure 2. Risk of PTC associated with serum concentrations of TSH and thyroid hormones. *, Conditional logistic regression, adjusted for BMI. **, Estimated by continuous variables. ***, Additionally, adjusted for serum concentration of TSH. (CI, confidence interval; OR, odds ratio (values relative to a 1 mU/L increase in TSH).

Discussion

We found that serum TSH levels below the normal range were related to a high PTC risk for males but not females in this large-scale case-control study using prediagnostic serum measurements and having adequate gender strength to stratify. Only an elevated risk of PTC in women was associated with TSH levels above the normal range. The PTC and TSH levels were inverse within the normal range of both men and women. The found associations vary somewhat in size (10 vs > 10 mm) between men and women, by histologic subtypes (classic versus follicular variants PTCs). Only in classical PTC cases was the gender effect on the TSH-PTC connection observed. TSH levels have shown a greater tumor relationship with PTC. An inverse suggestive correlation was seen among men between increased TT3 levels and PTC risk. Contrary tendencies in a large population-based prospective cohort in Europe between TSH levels and PTC risk found in the present investigation are consistent with the results of a nested case-control study (16). The cohort consisted of almost 520,000 healthy people between the ages of 35 and 69 years who were recruited in 10 European countries between 1992 and 1998. The analysis comprised a total of 357 thyroid incidents (57 male and 300 female) diagnosed from 1992 to 2009 and 767 matched controls. At registration, blood samples were obtained. The reverse dose-reaction association between total TSH and risk of differentiated thyroid carcinoma was found in this EU investigation. Between the European study and our trial, the years between sample collection and thyroid cancer diagnosis were identical. Our people were younger and healthier (18), however, compared to the European study, with participants 15 to 53 years of age collecting blood samples.

Moreover, our study had a greater number of female instances than the European study, which offers significant evidence to evaluate women's connections. In this study, the relationships between TSH and PTC risk among men and women were not consistent, while the European study found similar associations between women and men. The European study reported similar associations. Two further study samples with lower size examined the association of TSH with thyroid cancer risk (17). Although these investigations did not show a statistically inverse association, the TSH levels were less than controls in thyroid cancer cases. An earlier meta-analysis revealed that elevated TSH was associated with an increased risk of thyroid cancer (19). In thyroid cancer patients, low levels of thyroid hormones because the thyroid gland is dysfunctional can cause more TSH to be released by the pituitary gland. Higher TSH levels could further enhance the growth of thyroid cancer that was already established, making it larger and easier to diagnose. Consequently, it could be attributable to the positive relationship shown in cross-sectional studies (20). On the other hand, these trials have consistently been controlled by thyroid nodules and thyroid tumor surgery patients. Certain nodules can create high thyroid hormone levels which decrease TSH levels 16. Many thyroid cancer patients also had extra benign thyroid nodules, and no mutual impact has yet been found between those nodules and TSH levels (21). TSH plays a key role in regulating thyroid function: the increase of thyroid cell count, size and secretion, increased blood flow and increased thyroid hormone production and secretion (19). Classical TSH activities are principally mediated in a method related to the generation of thyroid hormones and the proliferation of thyroid epithelial cells through gasadenyl cyclase protein kinase A-cyclic adenosine monophosphate (cAMP) (22). Somatic mutations in thyroid epithelial cells can however also contribute to the development of an autonomously functioning thyroid adenoma, facilitating cell proliferation and clonal development. The adenoma is capable of independently summing up and secreting thyroid hormones to eliminate TSH secretion (23). Therefore, an increasing carcinogenic potential and a decreasing TSH level can be related to the constitutive activation of the cAMP pathway. The extra nodular tissue would become relaxed due to the loss of TSH stimulation. It can take months to 10 years or more to grow adenoma large enough to produce hyperthyroidism depending on the amount of iodine, growth potential and other factors (24). Two genome-wide association studies showed that 5 common variants of [rs965513[A] on 9q22.23, rs 944289[T] and rs116909374[T] at 14q13.3, rs 966423[C] at 2q35, and rs 2439302[G] at 8p12] were associated with both an increased and low risk of thyroid cancer. The mecha-

nisms underlying the lower TSH increase the PTC risk are not currently clear (25). The five variations could include the genes FOXE1, NKX2-1, DIRC3 and NRG1 according to Gudmundsson and his colleagues. In thyroid-gland development, differentiation, and function, the FOXE1 gene can control the transcription of thyroglobulin and thyroperoxidase genes (26). Although DIRC3's function is uncertain, tumor suppressor activity is supposed to occur (27). The NRG1 gene encoded a transmitting protein that interacted with the cells and plays a crucial function in thyroid gland growth and development. TSH concentrations can be lower for the carriers of these 5 variations. The consequences of reduced TSH can be that the Thyroid Epithelium has less differentiation and that malignant cell transformations are more likely to occur (25). In the current investigation, favorable dose-response correlations between TT3 serum concentrations and PTC risk among men have been reported. The inverse relationship between TSH and PTC risk in males who are not yet 50 years old has been observed. These results indicate that men can be more sensitive than women to the effects of TSH and thyroid hormones. Possible explications such as progesterone impact change and differing exposures by gender to endocrine-disrupting substances need to be explored in future studies. In this study, several relationships of TSH and thyroid hormones on PTC risk by histology and tumor size were observed. Low TSH levels related to the increased risk of follicular PTC and PTC variants > 10 mm, while larger PTC and PTC microcarcinoma risk were associated with reduced risk. These relationships may support the concept that PTC and Papillary microcarcinoma follicular variants are discrete clinical entities with diverse etiological characteristics (28). In this regard, it is necessary to conduct more comprehensive research on the genetics and polymorphism of genes in different societies (29-33)..

A consistent pattern was not found between TSH and PTC risks. It is necessary to study further the crucial temporal frame during which TSH influences thyroid cancer development. There are various strengths to this study. This contained a reasonably significant number of cases for men and provided enough statistical power to examine and evaluate gender-based relationships, which is crucial because men are far more likely to develop thyroid cancer than females. For our study cohort, any selection distortions from differences in access to medical treatment were also eliminated. Serum TSH and thyroid hormone concentrations were evaluated in the future and were not influenced by the illness process or treatment, which offered an opportunity to estimate possible causative relations between TSH, thyroid and thyroid cancer. The study's limitations are that various potential confounding factors such as ionizing expositions to radiation, thyroid illness history, thyroid family history and smoking status have been lacking in information. The number of participants with missing BMI data was high as well, which may have led to a lack of adaptation of BMI. The lack of data on the use of thyroid medicinal products prevents us from doing sensitivity analyzes without taking thyroids. Furthermore, analysis in a subset that had been stratified by the years between sampling and diagnosis, histology, and tumor dimension, due to the small number of subgroups may have generated unstable results. The study concluded that the PTC risk related to TSH levels has been much greater than normal for men and higher than normal for women. These findings could have important therapeutic consequences for doctors who engage in the management of aberrant thyroid and thyroidectomy patients. In future studies, these correlations should be further understood.

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