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ORIGINAL

Usefulness of serum thyrotropin for risk prediction of differentiated thyroid cancers does not apply to microcarcinomas: results of 1,870 Chinese patients with thyroid nodules

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Abstract. The objectives of this study were to investigate whether preoperative serum thyrotropin (TSH) concentrations can be used for risk prediction of differentiated thyroid cancers (DTC), in particular, microcarcinomas (DTMC), which may be in an early stage of development of DTC. The cohort of this retrospective study consisted of 1,870 patients who underwent surgery on thyroid nodules at a single hospital in an iodine-sufficient region in China. Serum TSH and anti-thyroid antibodies were measured and diagnoses were based on surgical pathology reports. Of 1,870 patients, 14.4% (n=269) had DTC. Eighty-nine DTCs were DTMC. As TSH increased, the prevalence of DTC rose clearly. The odds ratio in favor of having DTC with a serum TSH 1.9-4.8 mIU/L and > 4.8 mIU/L, compared with having a serum TSH 1.0-1.9 mIU/L were 1.57 (95% CI 1.03-2.40, *P*=0.038) and 5.71 (95% CI 2.31-14.14, *P*=0.0002), respectively. A similar pattern was yielded when excluding subjects with high thyroid autoantibodies. Higher TSH was also associated with lymph node metastasis and advanced disease (stage Ⅲ and Ⅳ). However, preoperative TSH was 1.17 mIU/L in patients with DTMC *vs.* 1.08 mIU/L in patients with benign pathology (*P* = 0.80). The pattern of escalating prevalence with higher TSH did not apply to DTMC. In conclusion, serum TSH is not a good risk predictor of DTMCs. Elevated TSH level may be related to advanced stage, that is, progression of thyroid cancer, but not with the development of thyroid cancer, since microcarcinomas do not have any relation with TSH level.

Key words: Thyrotropin, Differentiated thyroid cancer, Microcarcinoma, Risk factor

FOLLICULAR epithelial cell-derived thyroid cancer is the most common endocrine malignancy and its incidence is rapidly rising in many areas of the world, including China [1-6]. The vast majority of thyroid cancer are differentiated thyroid cancer (DTC), consisting of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), which accounts for more than 90% of all thyroid malignancies [2, 3, 7, 8]. Although thyroid cancer-associated mortality is low, the negative psychosocial and economic impact due to this disease can be significant and the quality of life for patients can be compromised. Moreover, following the increased use of screening and diagnostic testing, the diagnosis of DTC is attributing to the increased detection of differentiated thyroid microcarcinomas (DTMC), which were defined as a size of 10 mm or smaller in its greatest dimension [5].

Thyroid nodule is a common manifestation of DTC. Thus, when patients are presented with thyroid nodule(s), it is of importance to evaluate their risk of being malignant. To date, several factors, such as very young and very old age, history of ionizing radiation or head and neck beam radiation in their youth, family history of thyroid cancer, fixed lesion, vocal cord paralysis, and rapid growth, are considered to be risk predictors of malignancy [9, 10]. In recent years, a slightly elevated preoperative serum TSH concentration has been reported to be a potential predictor in several studies [11].

However, so far only six studies of this type have enrolled more than 1,000 patients [12-17]. Among them, most did not have final diagnoses based on sur-

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gical pathology reports. Neither can we find any data from Chinese cases, which involve a distinctly different ethnic population from western populations. In addition, only two studies have analyzed the association of TSH concentration with thyroid microcarcinomas [18, 19] with conflicting conclusions.

Thus, the present study includes two objectives: first, to investigate whether preoperative serum TSH concentrations can predict DTC in Chinese patients with thyroid nodules; and second, to test the hypothesis that TSH can also be used for risk prediction of DTMC, which may be in an early stage of development of DTC. With these objectives in mind, we took the advantage of a large cohort of patients who underwent surgery on thyroid nodule(s) at a single hospital in an iodine-sufficient region in China, to compare TSH concentrations in individuals with benign thyroid nodule(s) and patients with DTC, or patients in whom DTMC was confirmed. We also analyzed the relationship of preoperative serum TSH with the aggressive clinicopathological characteristics and cancer stages.

Subjects and Methods

Subjects

This study was conducted at the First Affiliated Hospital of China Medical University, Shenyang, China. Shenyang is an iodine sufficient intake area, where median urinary iodine level in residents was documented to be normal (188 μg/L) [20]. A cohort of 2,500 patients who underwent thyroid surgery due to thyroid nodule(s) at the hospital between Jan. 2005 to Oct. 2009 were retrospectively reviewed. In our hospital, during the period of the present study, diagnostic work-up before surgical procedure included physical examination, thyroid profiles and thyroid ultrasonography, while unfortunately, fine needle aspiration biopsy (FNAB) test was not performed. Indications for surgical procedure were: 1) thyroid nodule(s) confirmed by ultrasound; and 2) no contradictions of surgical procedure; and 3) with the patient's option of being treated by surgery.

In order to minimize the likelihood that medical conditions or prescribed medication might affect the development of DTC and the concentration of thyroid profiles, we excluded 277 patients (11.1% of 2,500 patients) who reported a personal history of thyroid dysfunction no matter whether they were being managed with thyroid hormone or antithyroid drugs, 123 patients (4.9%) who reported a history of thyroid surgery, 1 patient (0.04%) who had been exposed to high levels of radiation, 32 patients (1.3%) were pregnant or lactating or taking estrogen replacement therapy, and 156 patients (6.2%) who were missing serum TSH data. Forty-one patients (1.6%) with presence of undifferentiated thyroid cancer or medullary thyroid cancer on final pathology were not included when final analysis was done, either. The remaining 1,870 individuals (74.8% of 2,500 patients, 421 men and 1,449 women) met the criteria for constituting the study cohort.

Thyroid profiles

Preoperative blood tests were obtained five and one day prior to thyroidectomy between 7:00 and 10:00 a.m. with the patient in a fasting state. Each thyroid profile consisted of a serum TSH, thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb). They were measured using the automated immunochemiluminescent assay (ICMA) (Abbott, Abbott Park, IL, USA) at the same laboratory in our hospital. The sensitivity of TSH assay was 0.01 mIU/L. The reference range, intra-assay and inter-assay coefficients of variation were 0.3-4.8 mIU/L [21], 4.9% and 5.2%, respectively, for TSH. Serum TPOAb exceeding a level of 50 KIU/L and/or TgAb exceeding a level of 40 KIU/L were considered as high serum autoantibody values [22]. The intra-assay and inter-assay coefficients of variations for TPOAb and TgAb were less than 8.5%.

Thyroid ultrasonography

Thyroid ultrasonography was performed by four trained observers using high-resolution equipment (Aplio80, TOSHIBA, Japan) two weeks and one day prior to thyroidectomy. Thyroid nodule number, size and echo pattern were documented. In order to assess the intraobserver and interobserver reliability, we designed a double-blinded test before the start of the study, in which thirty volunteers were involved. Their agreement for abnormal echo pattern and nodules was 96.7%. As for nodule size, the intra- and inter- observer CVs were 8.7% and 9.3%, respectively.

Pathology

Final histological results following resection (after surgery) were available for the entire cohort of the patients. All results were reviewed by an experienced pathologist (Wang Y) to confirm the presence or absence of DTC consists of PTC and FTC. For DTCs, tumor size, status of extrathyroidal invasion, lymph

node metastasis, and distant metastasis were recorded so that tumors were staged as per the staging system of the American Joint Committee on Cancer [9].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or percentages. Student's *t* test and *ANOVA* test were used for numeric variables. Since data for TSH do not adhere to a Gaussian distribution, a log-transformation was made before comparison and descriptive statistics were therefore reported as median and empirical percentiles. The chi-square test (χ^2) or Fisher's exact test was used for categorical variables. Finally, a binary logistic regression analysis was used to evaluate the independent influence of factors. The outcomes were the presence or absence of DTC (or DTMC) on final pathology. The level of significance was set at 5%. Statistical analysis was done using SPSS software (version 13, Chicago, IL, USA).

Ethical aspects

Research protocols were approved by the Medical Ethics Committee of China Medical University. The protocols were carefully explained to all participants, and an informed consent for voluntary participation was obtained from them.

Results

Characteristics of the study cohort

The final study cohort of 1,870 patients consisted of 1,449 (77.5%) females and 421 (22.5%) males. The mean age of the patients was 47.5 ± 12.1 (range 12-78) years and 50.2 ± 11.7 (range 15- 80) years in females and males, respectively. Of them, 85.6% (n = 1,601) were diagnosed with benign and the remaining 14.4% (n = 269) had DTC (Table 1). PTC accounted for the vast majority of the DTC diagnoses (95.5%, n = 257). Eighty-nine (33.1%) of 269 patients had DTMC, with a mean size of 6.7 ± 2.3 mm. Forty-seven (17.5%) of 269 DTC patients were performed total or near-total thyroidectomy. The rate of prophylactic and therapeutic lymphadenectomies for DTC was 45.7% (n=123).

Mean ages of the patients with and without malignancy were 43.4 ± 12.7 and 48.6 ± 11.6 yr, respectively (P = 0.0001). Prevalence of overall DTC, but not micro-DTC, in relation to patients' age in years demonstrated an evident increase in the youngest patient group (≤ 30 yr) (Fig. 1). Female patients had signifi-

Table 1 Patient and tumor characteristics

	DTC	Benign	*P* value
N	269	1,601	
Gender			0.032
Male (n = 421)	47	374	
Female (n = 1,449)	222	1,227	
Mean age (yr)	43.4 ± 12.7	48.6 ± 11.6	0.0001
Mean nodule size (cm)	2.6 ± 1.5	3.2 ± 1.3	0.001
Percentage of co-existence with histopathological evidence of thyroiditis(%)	6.32	3.94	0.074
Nodule type			0.0001
Solitary (n = 650)	169	481	
Multiple (n = 1,220)	100	1,120	
Median TSH (mIU/L) [a]			
Overall	1.57(0.91-2.39)	1.08(0.62-1.77)	0.0001
Excluding patients with high autoantibodies	1.46(0.84-2.24)[b]	1.06(0.64-1.71)[c]	0.016

a, TSH levels are presented as median (25^{th}-75^{th} empirical percentiles); b, n = 171; c, n = 1,272; DTC, differentiated thyroid cancer

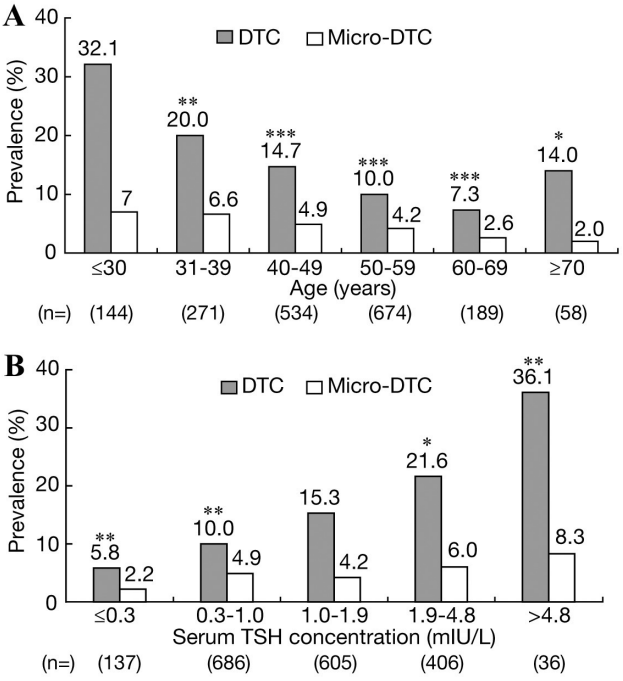

Fig. 1 Prevalence of differentiated thyroid cancer (DTC) and micro-DTC according to patients' age and serum TSH concentration. A, Prevalence of DTC in relation to patients' age demonstrated significant increased prevalence in patients at the youngest age group (*, P < 0.05; **, P < 0.01; ***, P < 0.001, compared with age group ≤ 30), while prevalence of micro-DTC were similar in each group. B, Prevalence of DTC according to patients' TSH concentration indicated a clear TSH-related increase (*, P < 0.05; **, P < 0.01, compared with TSH 1.0-1.9 mIU/L). However, TSH concentration did not relate to prevalence of micro-DTC. The number of patients (n) in each group is given beneath the graph.

cantly higher rates of malignancy when compared with male patients (15.3% *vs*. 11.2%, $P = 0.032$) (Table 1).

Mean nodule size was 2.6 ± 1.5 cm in those patients with DTC, compared with 3.2 ± 1.3 cm in those without malignancy ($P = 0.001$). One hundred and sixty-nine of 269 DTC patients had solitary nodules, and more solitary nodules turned out to be DTC than multiple nodules (26.0% *vs*. 8.2%, $P = 0.0001$), predicting a higher risk of a solitary nodule to be a DTC (Table 1).

TSH and likelihood of malignancy

Preoperative TSH was significantly higher in patients with DTC *vs.* benign pathology. Median TSH in the 269 patients with DTC was 1.57 mIU/L *vs*. 1.08 mIU/L in those 1,601 patients with benign diagnoses ($P = 0.0001$). If all 427 patients with high thyroid autoantibodies were removed from the analysis, the median TSH concentration were still significantly higher in the group of patients with DTC than in the group of patients with benign diseases (1.46 mIU/L *vs.* 1.06 mIU/L, $P = 0.016$) (Table 1).

Serum TSH values were broken down into subgroups as follows: ≤0.3 mIU/L, 0.3-1.0 mIU/L, 1.0-1.9 mIU/L, 1.9-4.8 mIU/L and >4.8 mIU/L, based on cutoff values predetermined in a previous population study (21), in which we have set up reference range (0.3-4.8 mIU/L) and optimal interval (1.0-1.9 mIU/L) for serum TSH in terms of the development of thyroid dysfunction in 5 years. Similar to the population at large, the distribution of patients loosely followed a bell-shaped curve. The majority of patients (n = 1 697) were euthyroid based on TSH alone. The prevalence of DTC (n = 8, 5.8%) was lowest in subjects with serum TSH below the normal range (≤ 0.3 mIU/L). As TSH increased, the prevalence of DTC on final pathology rose. Even within the normal range of TSH (0.3-4.8 mIU/L), the pattern of escalating DTC prevalence with higher TSH persisted. This confirmed the results of previous studies in other races. The prevalence of DTC in subgroups was compared to that in patients with serum TSH 1.0-1.9 mIU/L, the optimal interval of TSH established previously, indicating significant differences as shown in Fig. 1.

Binary logistic regression analysis including gender, age, nodule type, nodule size, ultrasonographic characteristics and serum TSH was performed to determine which factor(s) are independent risk predictors for DTC. Independent risk predictors were listed in Table 2, and the odd ratios (95% CI) in favor of having DTC were calculated as well. Both as a continuous variable and base on divided ranges, higher TSH was independently associated with DTC on the analysis. The regression analysis was also repeated, excluding subjects with high antithyroid antibodies. The higher TSH concentration as well as nodule type, microcalcification and hypoechogenicity on ultrasonography were again identified as independent factors for the diagnosis of DTC, whereas gender and age were not (Table 2).

Table 2 Independent risk predictors of thyroid malignancy defined by binary logistic regression analysis

	P value	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Overall cohort				
Female	0.038	1.595	1.026	2.480
Solitary nodule	0.000	4.691	3.221	6.832
Microcalcification	0.000	39.207	23.356	65.815
Hypoechogenicity	0.000	2.552	1.788	3.643
Age 50-59 yr [a]	0.038	0.542	0.303	0.968
TSH	0.000	1.259	1.141	1.389
TSH 1.9-4.8 [b]	0.038	1.568	1.026	2.398
TSH > 4.8 [b]	0.000	5.712	2.308	14.138
Cohort excluding patients with high autoantibodies				
Solitary nodule	0.000	5.359	3.367	8.531
Microcalcification	0.000	36.788	19.686	68.745
Hypoechogenicity	0.000	1.119	1.052	1.190
TSH	0.001	1.246	1.098	1.414
TSH > 4.8 [b]	0.008	4.965	1.507	16.363

Age and serum TSH concentration were analyzed as categorical variables. a, Compared with the age group ≤ 30 yr; b, Compared with the TSH group 1.0-1.9 mIU/L. DTC, differentiated thyroid cancer

TSH and clinicopathological characteristics of DTC

Median serum TSH concentrations in DTC patients with and without lymph node metastasis were 1.75 mIU/L and 1.46 mIU/L, respectively (P = 0.0001). Median serum TSH in DTC patients with extrathyroidal invasion was higher than that in patients without, but had no statistical significance (1.84 mIU/L *vs.* 1.50 mIU/L, P = 0.13). The patients with advanced disease (cancer stages Ⅲ and Ⅳ) had a median TSH of 1.73 mIU/L, which was slightly higher relative to those with stages I and Ⅱ diseases (1.52 mIU/L, P = 0.66).

Fig. 2 shows the association of serum TSH concentration and clinicopathological characteristics in differentiated thyroid cancer based on divided ranges. Prevalence of lymph node metastasis and extrathyroidal invasion raised in the higher TSH groups, while prevalence of advanced cancer stages were similar among groups.

Serum TSH concentration cannot predict DTMC

As shown above, we noticed a clear association between serum TSH and likelihood of malignancy of thyroid nodules. However, the risk prediction role of serum TSH was not yielded when only DTMC was included in the analysis. Preoperative TSH was 1.17 mIU/L in patients with DTMC *vs.* 1.08 mIU/L in patients with benign pathology (P = 0.80). The pattern of escalating prevalence with higher TSH did not apply to DTMC, either (Fig. 1). No relationship was found between serum TSH concentration and clinicopathological characteristics of DTMC.

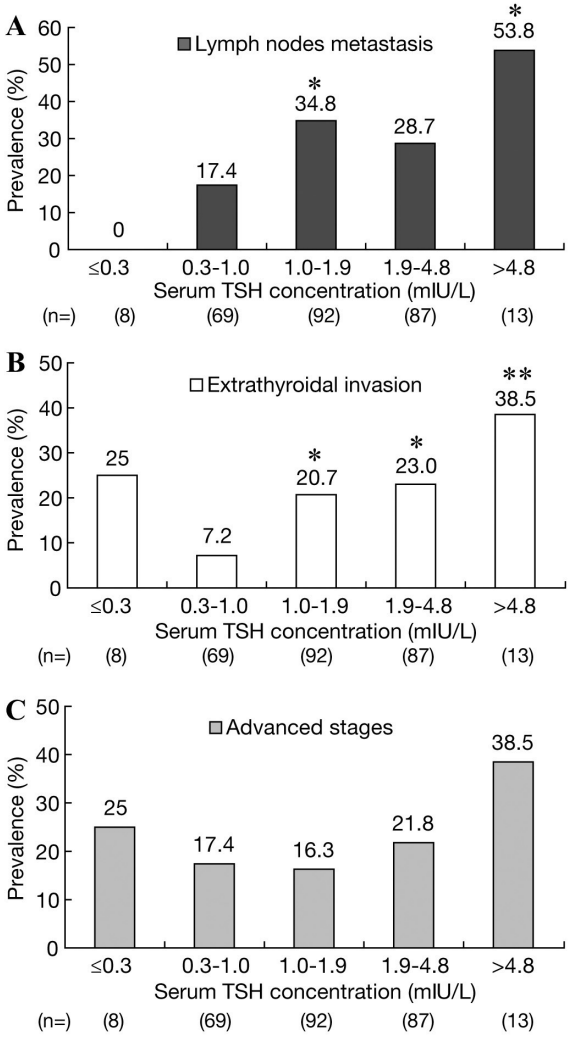

Fig. 2 Association of serum TSH concentration and clinicopathological characteristics in differentiated thyroid cancer. A, Prevalence of lymph nodes metastasis increased in the higher TSH groups. B, Prevalence of extrathyroidal invasion increased in the higher TSH groups. C, Prevalence of advanced cancer stages (stage Ⅲ and Ⅳ) were similar in groups. *, $P < 0.05$; **, $P < 0.01$, compared with TSH group 0.3-1.0 mIU/L. The number of patients (n) in each group is given beneath the graph.

Discussion

Thyroid cancer accounts for approximately 5-15% of all thyroid nodules [9]. Most patients with thyroid nodules can be managed conservatively after malignancy is ruled out. Identifying the minority of patients with thyroid cancer who therefore need surgical treatment is a great challenge to the clinician, because most thyroid malignancies are clinically indistinguishable from benign loci. Fine needle aspiration biopsy (FNAB) is a good tool for differential diagnosis. However, FNAB has not been well applied in some parts of the world for various reasons. Moreover, when ultrasound guidance or experienced operator is not available, it sometimes may miss very small malignant loci (microcarcinomas) in nodule(s), the detection of which is predominantly increasing in recent years. Thus, researchers have been attempting to find more predictors and markers which can distinguish malignancy from benign nodules.

Measurement of serum TSH, which is a highly sensitive biochemical test for thyroid dysfunction, is recommended in the initial evaluation of patients presenting with thyroid nodules [9, 23]. Encouragingly, several studies discovered an association of serum TSH and thyroid malignancy [12-17, 24-29]. This should not have been surprising, because TSH used to be thought

of as a growth factor of thyrocytes. A recent study has shown that TSH plays a key role in Braf-induced PTC initiation in a mouse model with a thyroid-specific knock-in of oncogenic Braf [30]. However, only two studies have analyzed the association of TSH concentration with thyroid microcarcinomas. In the study of Haymart *et al.*, a separate subset analysis revealed an escalating risk of malignancy with higher TSH concentration [18], while the other indicated that TSH was not involved in the oncogenesis of these small cancers [19]. Therefore, this is still an unresolved question.

The overall rate of DTC in the final pathology outcome in the present study was 14.4%. It is higher compared to studies by Polyzos *et al.* (9.4%) and Boelaert *et al.* (8.0%) which used FNAB results as the final diagnoses [25, 12], but lower compared with that reported by Haymart *et al.* (28.6%) which enrolled a cohort undergoing thyroid surgery instead of a cohort undergoing FNAB [18]. It is true that surgical pathology has higher sensitivity and accuracy for diagnosing DTC. However, this does not explain the data of present study. FNAB test was not performed in our hospital during the period of the present study. Hence, the higher rate of surgical procedures for benign lesions done in our cohort was compared to Haymart *et al.* cohort [18].

Using this large series of patients presented clinically as thyroid nodule(s) who underwent thyroid surgery at a single hospital, we confirmed the pattern of escalating DTC prevalence with higher TSH, even within its normal range. Even excluding patients with high thyroid antibodies, serum TSH concentration is an independent risk factor of DTC, suggesting the increasing risk of DTC in patients with TSH in the upper end of normal or markedly elevated level is unlikely to be solely due to increased antithyroid antibody levels. This demonstrates the real association between TSH and malignancy, given the well known influence of anti-thyroid antibodies on TSH [21, 22]. Moreover, our data show that higher TSH in patients with DTC occurs independent of age, which is also an important influencing factor on serum TSH levels. Also shown in this study, in patients who were diagnosed with DTC, the prevalence of lymph node metastasis and extrathyroidal invasion increased in the higher TSH groups. Together with what Haymart *et al.* and Fiore *et al.* recently reported [13, 14, 18, 24], one may anticipate higher TSH is associated with not only prevalence of DTC but also aggressive characteristics of DTC.

We had originally hypothesized that serum TSH might be a risk predictor of DTMC as well, but the present study did not provide any supportive data. A subset analysis showed that the median TSH value was comparable between patients with DTMCs and the benign group, and the prevalence of DTMC and any clinicopathological features of DTMCs were not related to different TSH concentrations. This result is consistent with the study of Gerschpacher *et al*. [19], in which the authors demonstrated that TSH was not likely involved in the *de novo* oncogenesis and progression of these small cancers. Although the explanation to this phenomenon remains unclear, it may indicate that DTMC does have some distinct mechanism and features from non-DTMC. TSH may not be essential for oncogenesis [31], but plays an important role in tumor growth. Furthermore, we suspect that this phenomenon might be due to the different extent of damage to thyroxine production caused by tumors between large cancers and microcarcinomas. Unfortunately, only a portion of subjects enrolled in the present study had their serum thyroxine concentration examined, thus we could not test our hypothesis.

Most previous studies have proposed male gender, compared with female gender, as a risk factor of DTC [12, 18, 24, 25]. However, in our series, females had a greater tendency of having DTC rather than males based on binary logistic regression analysis. After removing those patients with high anti-thyroid antibodies from the cohort, gender was no longer a helpful factor in predicting risk of DTC. We have no solid explanation for this inconsistency. Nevertheless, because women tend to have a higher TSH [32], one may anticipate women would be more susceptible to DTC if they are not over-represented in the subgroup undergoing surgery for benign conditions than men.

The limitations of this study are: 1) it included a relatively small sample size of DTMCs (n = 89); 2) it is retrospective; and 3) FNAB was not routinely performed in diagnostic work-up before surgical procedure, which has already been recommended by guidelines and performed in everyday clinical practice in developed countries.

In conclusion, we have confirmed the risk of overall DTC in thyroid nodules increases in parallel with TSH concentration, even within its normal range. This pattern is present regardless of antibody status, race, and iodine nutrition. Higher TSH is also associated with aggressive characteristics of DTC, but serum TSH is not a good risk predictor of DTMCs. Taken together,

elevated TSH level may be related to advanced stage, that is, progression of thyroid cancer, but not with the development of thyroid cancer, since microcarcinomas, which may be in an early stage of development of DTC, do not have any relation with TSH level.

Declaration of interest

All the authors have nothing to declare.

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References

1. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. *CA Cancer J Clin* 62:10-29.
2. Simard EP, Ward EM, Siegel R, Jemal A (2012) Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* 2012 Jan 4. doi: 10.3322/caac.20141. [Epub ahead of print]
3. Chen AY, Jemal A, Ward EM (2009) Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer* 115:3801-3807.
4. Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, Edwards BK (eds) SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007.
5. Cairong Zhu, Tongzhang Zheng, Briseis A. Kilfoy, Xuesong Han, Shuangge Ma, Yue Ba, Yana Bai, Rong Wang, Yong Zhu, Yawei Zhang (2009) A Birth Cohort Analysis of the Incidence of Papillary Thyroid Cancer in the United States, 1973-2004. *Thyroid* 19: 1061-1066.
6. Guan H, Shan Z, Mi X, Wang E, Teng W (2006) Incidence of thyroid carcinoma before and after universal salt iodization: an 11-year retrospective analysis of pathological reports. *J Chin Med Univ* 35: 284-285 (In Chinese).
7. Mazzaferri EL. An overview of the management of thyroid cancer. In: 2006; Mazzaferri EL, Harmer C, Mallick UK, Kendall-Taylor P, eds. Practical Management of Thyroid Cancer: A Multidisciplinary Approach. London, England: Springer-Verlag; 1-28.
8. Hundahl SA, Fleming ID, Fremgen AM, Menck HR (1998) A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer* 83: 2638-2648.
9. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19: 1167-1214.
10. Hegedüs L (2004) Clinical practice. The thyroid nodule. *N Engl J Med* 351:1764-1771.
11. Fiore E, Vitti P (2012) Serum TSH and Risk of Papillary Thyroid Cancer in Nodular Thyroid Disease. *J Clin Endocrinol Metab* 97:1134-1145.
12. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA (2006) Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab* 91:4295-4301.
13. Fiore E, Rago T, Provenzale A, Scutari M, Ugolini C, Basolo F, Di Coscio G, Berti P, Grasso L, Elisei R, Pinchera A, Vitti P (2009) Lower levels of TSH are associated to a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. *Endocr Relat Cancer* 16:1251-1260.
14. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, Di Coscio G, Miccoli P, Grasso L, Pinchera A, Vitti P (2010) L-Thyroxine treated patients with nodular goiter have lower serumTSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27,914 patients. *Endocr Relat Cancer* 17:231–239.
15. Rago T, Fiore E, Scutari M, Santini F, Di Coscio G, Romani R, Piaggi P, Ugolini C, Basolo F, Miccoli P, Pinchera A, Vitti P (2010) Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. *Eur J Endocrinol* 162:763-770.
16. Kim KW, Park YJ, Kim EH, Park SY, Park do J, Ahn SH, Park do J, Jang HC, Cho BY (2011) Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. *Head Neck* 33:691-695.

17. Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A, Scutari M, Basolo F, Di Coscio G, Grasso L, Pinchera A, Vitti P (2011) Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. *Endocr Relat Cancer* 18:429–437.
18. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, Chen H (2008) Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* 93:809-814.
19. Gerschpacher M, Göbl C, Anderwald C, Gessl A, Krebs M (2010) Thyrotropin serum concentrations in patients with papillary thyroid microcancers. *Thyroid* 20:389-392.
20. Guan H, Li C, Li Y, Fan C, Teng Y, Shan Z, Teng W (2005) High iodine intake is a risk factor of post-partum thyroiditis: result of a survey from Shenyang, China. *J Endocrinol Invest* 28: 876-881.
21. Guan H, Shan Z, Teng X, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Chen W, Tong Y, Wang W, Gao T, Li C, Teng W (2008) Influence of iodine on the reference interval of TSH and the optimal interval of TSH: results of a follow-up study in areas with different iodine intakes. *Clin Endocrinol (Oxf)* 69:136-141.
22. Li Y, Teng D, Shan Z, Teng X, Guan H, Yu X, Fan C, Chong W, Yang F, Dai H, Gu X, Yu Y, Mao J, Zhao D, Li J, Chen Y, Yang R, Li C, Teng W (2008) Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. *J Clin Endocrinol Metab* 93:1751-1757.
23. Lim AK, Daykin J, Holder R, Sheppard MC, Franklyn JA (1998) Measurement of serum TSH in the investigation of patients presenting with thyroid enlargement. *QJM* 91:687-689.
24. Haymart MR, Glinberg SL, Liu J, Sippel RS, Jaume JC, Chen H (2009) Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. *Clin Endocrinol (Oxf)* 71:434-439.
25. Polyzos SA, Kita M, Efstathiadou Z, Poulakos P, Slavakis A, Sofianou D, Flaris N, Leontsini M, Kourtis A, Avramidis A (2008) Serum thyrotropin concentration as a biochemical predictor of thyroid malignancy in patients presenting with thyroid nodules. *J Cancer Res Clin Oncol* 134: 953-960.
26. Jonklaas J, Nsouli-Maktabi H, Soldin SJ (2008) Endogenous thyrotropin and triiodothyronine concentrations in individuals with thyroid cancer. *Thyroid* 18:943-952.
27. Jin J, Machekano R, McHenry CR (2010) The utility of preoperative serum thyroid- stimulating hormone level for predicting malignant nodular thyroid disease. *Am J Surg* 199: 294-297.
28. Castro MR, Espiritu RP, Bahn RS, Henry MR, Gharib H, Caraballo PJ, Morris JC (2011) Predictors of malignancy in patients with cytologically suspicious thyroid nodules. *Thyroid* 21: 1191-1198.
29. Kim SS, Lee BJ, Lee JC, Song SH, Kim BH, Son SM, Kim IJ, Kim YK, Kang YH (2011) Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience. *Endocrine* 39:259-265.
30. Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E, Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA (2011) Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. *Proc Natl Acad Sci USA* 108:1615–1620.
31. Derwahl M, Broecker M, Kraiem Z (1999) Clinical review 101: Thyrotropin may not be the dominant growth factor in benign and malignant thyroid tumors. *J Clin Endocrinol Metab* 84: 829-834.
32. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87:489-499.