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ORIGINAL ARTICLE

Retrospective Analysis of Thyroid Nodules: Thyroid Cancer Risk Factors in Suzhou, China

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SUMMARY

Background: **Thyroid nodules are common, frequently discovered in clinical practice and the incidence has increased in recent decades. They are clinically important primarily due to their malignant potential, because 2 to 5% are malignant. Correct identification of the malignancy in thyroid nodules is a diagnostic challenge, leading to potentially unnecessary surgery in patients for whom final histology is benign. Because there is no accurate preoperative detection, it is very important to predict the risk of malignancy in patients with nodular thyroid disease.**
Methods: **The medical records of 405 patients who underwent surgery for nodular thyroid disease were retrospectively reviewed. Then clinical parameters and preoperative serum markers were compared between benign thyroid nodular disease and thyroid cancer groups.**
Results: **Younger than 40 years (OR 2.14, 95% CI 1.02 - 4.47, p = 0.044), preoperative TSH levels equal to or higher than 1.79 mIU/L (OR 1.76, 95% CI 1.05 - 2.95, p = 0.033), TgAb positivity (OR 2.59 95% CI 1.25 - 5.37, p = 0.01) and nodules less than or equal to 1 cm (OR 5.51, 95% CI 2.61 - 11.66, p < 0.001) were associated with increased risk of thyroid cancer in patients with thyroid nodules.**
Conclusions: **The retrospective analysis suggests that younger patients with nodular thyroid disease cannot ignore the small size nodules, especially those with higher TSH levels and TgAb positivity.**
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KEY WORDS

thyroid cancer, thyroid stimulating hormone, thyroglobulin antibody, age, nodule size

INTRODUCTION

In recent years, thyroid nodules have been considered as clinical common diseases, and the incidence increased year by year. Epidemiological studies have shown that the detection rate of thyroid nodules through palpation in iodine-rich areas is about 5% for women and about 1% for men. In the general population, thyroid nodules are found in 19% to 68% through high-resolution ultrasound and are frequently detected in women and the elderly [1]. Although most thyroid nodules do not require any specific intervention or can be managed conservatively, it makes patients feel panic when finding nodules inadvertently or during physical examination as 2 to 5%

are malignant. At present, there is no accurate preoperative detection for distinction between benign and malignant thyroid nodules. Many patients, even without any symptoms, may finally choose surgery to prevent life-threatening malignant nodules. Therefore, it is very important to assess the risk factors of thyroid cancer in patients with nodular thyroid disease. It could prevent over-treatment for low-risk patients, avoid many risks induced by thyroid gland surgery and improve the detection rate of high-risk patients for timely treatment. In this study, we analyzed the risk factors associated with thyroid cancer by assessing clinical data and thyroid function in local Suzhou patients with nodular thyroid disease.

MATERIALS AND METHODS

We retrospectively reviewed the medical records (January 2014 to December 2016) of 405 patients aged 17 - 88 years old who underwent surgery for nodular thyroid disease (NTD). The final diagnosis of thyroid nodules was dependent on postoperative pathological diagnosis. The study included 307 patients with benign thyroid nodular disease (BTND) and 98 patients with thyroid cancer (TC). The inclusion criteria were as follows: (1) born and long-term residence in Suzhou; (2) thyroid nodules were found inadvertently or during physical examination, without obvious symptoms; (3) no exposure history to hazardous chemicals and radiation; (4) no other disease in discharge diagnosis. Thyroid nodules were found from 1 day ago to 30 years ago. A faction (about 5.93%) of the patients had a TSH level that exceeded the reference range. Patients who felt nodules enlarged were in 9.88% of all patients. Patients with a history of hypertension accounted for 21.98% and with a history of diabetes accounted for 2.72%. Five female patients had undergone surgery for breast cancer. In all 405 cases, most of them have the information of preoperative serum free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), thyroid stimulating hormone (TSH), thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (TPOAb) levels. However, the results of TgAb and TPOAb are missing in 30 and 44 cases respectively.

The measurements of preoperative serum thyroid function and autoantibodies were performed with the Chemiluminesent Microparticle Immuno Assay (Abbott Architect i2000SR, Abbott Laboratory, USA). The reference range for FT3, FT4, TT3, TT4, TSH, TgAb, and TPOAb was 2.63 - 5.70 pmol/L, 9.01 - 19.05 pmol/L, 0.89 - 2.44 nmol/L, 62.68 - 150.84 nmol/L, 0.35 - 4.94 mIU/L, 0.00 - 34.00 IU/mL and 0.00 - 12.00 IU/mL, respectively.

Statistical analysis

All data were tested for normal distribution by the D'Agostino normality test and for equal variances by Bartlett's test. Differences for continuous variables were assessed by independent-samples *t*-tests and category data used the chi square tests or Fisher's exact tests for percentages. To establish the cutoff value that provided the best sensitivity and specificity for the relationship between serum TSH and cancer risk, we performed ROC (receiver operating curve) analysis. Binary logistic regression analysis was used to identify the independent risk factors associated with thyroid cancer. Data were analyzed with SPSS 17.0 statistics software (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Comparisons of general characteristics

The final diagnosis depended on postoperative pathological data which showed that malignant lesions were present in 98 patients (24.20%) including 95 papillary thyroid carcinomas, 2 follicular thyroid carcinomas, and 1 medullary carcinoma. The remaining 307 patients (75.80%) were diagnosed as BTND including 298 benign nodular goiters and 9 thyroid adenomas. The mean age of patients with TC was 47.23 ± 13.82 years which was significantly younger than the patients with BTND, 52.40 ± 12.13 years ($p < 0.001$) (Table 1). Of these 405 patients, 317 patients were female and 88 patients were male. Women had a higher prevalence of NTD than men (by a ratio of about 3.6 to 1). However, there was no significant difference in males between BTND (22.48%) and TC (19.39%) (Table 1). The nodules of BTND or TC groups were classified as three groups: less than or equal to 1 cm, less than or equal to 2 cm, and larger than 2 cm in maximal diameter. The chi-square test showed that there was significant difference among these groups ($p < 0.001$) (Table 1). No significant difference was found in the past history between the two groups (Table 1).

Comparisons of preoperative thyroid function and autoantibody levels in serum

The preoperative TSH concentration was significantly higher in patients with TC versus BTND (2.51 ± 1.57 mIU/L versus 2.03 ± 1.37 mIU/L, $p = 0.003$) (Table 2). The proportion of TgAb-positive patients in the TC group was significantly higher than that in the BTND group (18.89% versus 8.07%, $p = 0.0037$). There was no significant difference in the positive rate of TPOAb between the two groups ($p = 0.3970$) (Table 3).

ROC curve analysis of optimal TSH concentration for TC prediction

ROC curve analysis was performed to determine the optimal TSH concentration for thyroid cancer prediction. It showed an area under the curve (AUC) of 0.60 (95% CI 0.53 - 0.67, $p = 0.003$). By calculating Youden's index, the optimal TSH concentration was 1.79 mIU/L. At this cutoff value, the sensitivity was 65.31% and speci-

Table 1. Comparisons of general characteristics.

	BTND (%)	TC (%)	p-value
Mean age (years) [a]	52.40 ± 12.13	47.23 ± 13.82	< 0.001
Male/female [b]	69/238 (22.48)	19/79 (19.39)	0.5187
Maximal diameter (cm) [b]			< 0.001
≤ 1	22	27	
≤ 2	129	36	
> 2	156	35	
History of hypertension [b]	69 (22.48)	20 (20.41)	0.667
History of diabetes [b]	7 (2.28)	4 (4.08)	0.5496
History of breast cancer surgery [b]	3 (0.98)	2 (2.04)	0.5985

BTND - benign thyroid nodular disease, TC - thyroid cancer, [a] - described as mean ± SD, [b] - showed the number of patients, and the numbers between parentheses showed the percentages. Statistical significance was set at p < 0.05.

Table 2. Comparisons of preoperative serum thyroid function.

	BTND	TC	p-value
FT3 (pmol/L)	4.42 ± 0.50	4.34 ± 0.51	0.1713
FT4 (pmol/L)	13.75 ± 1.52	13.61 ± 1.66	0.4291
T3 (nmol/L)	1.61 ± 0.23	1.58 ± 0.22	0.2438
T4 (nmol/L)	86.91 ± 16.25	83.64 ± 14.16	0.1511
TSH (mIU/L)	2.03 ± 1.37	2.51 ± 1.57	0.003

BTND - benign thyroid nodular disease, TC - thyroid cancer, FT3 - free triiodothyronine, FT4 - free thyroxine, TT3 - total triiodothyronine, TT4 - total thyroxine, TSH - thyroid stimulating hormone. Data in BTND and TC columns correspond to the mean ± SD. Statistical significance was set at p < 0.05.

Table 3. Comparisons of preoperative serum autoantibodies levels.

	BTND (%)	TC (%)	p-value
TgAb			
Negativity (-)	262 (91.93)	73 (81.11)	0.0037
Positivity (+)	23 (8.07)	17 (18.89)	
TPOAb			
Negativity (-)	252 (91.30)	75 (88.24)	0.3970
Positivity (+)	24 (8.70)	10 (11.76)	

BTND - benign thyroid nodular disease, TC - thyroid cancer, TgAb - thyroglobulin antibody, TPOAb - thyroid peroxidase antibody. Data in BTND and TC columns showed the number of patients, and the numbers between parentheses showed the percentages. Statistical significance was set at p < 0.05.

ficity was 52.12% (Figure 1).

Independent risk factors for TC

The pathological diagnosis (BTND or TC) was the dependent variable, and age, nodule maximal diameter, TSH, and TgAb were the independent variables in the logistic regression analysis. The results showed that patients younger than 40 years had a higher risk of TC compared to patients equal to or older than 60 years (OR 2.14, 95% CI 1.02 - 4.47, p = 0.044) (Table 4). The risk of TC was increased in nodules less than or equal to 1 cm when compared to nodules larger than 2 cm in

Table 4. Independent risk factors for the diagnosis of thyroid cancer by logistic regression analysis.

	OR value	95% CI	p-value
Age (years)			
< 40	**2.14**	**1.02 - 4.47**	**0.044** [a]
< 60	**1.27**	**0.67 - 2.41**	**0.465** [a]
≥ 60			
Maximal diameter (cm)			
≤ 1	**5.51**	**2.61 - 11.66**	**< 0.001** [b]
≤ 2	**1.10**	**0.63 - 1.94**	**0.729** [b]
> 2			
TSH ≥ 1.79 mIU/L	**1.76**	**1.05 - 2.95**	**0.033**
TgAb positivity	**2.59**	**1.25 - 5.37**	**0.01**

TSH - thyroid stimulating hormone, TgAb - thyroglobulin antibody, OR - odds ratio. CI - confidence interval, [a] - comparing with group equal to or older than 60 years, [b] - comparing with nodules larger than 2 cm in maximal diameter. Statistical significance was set at p < 0.05.

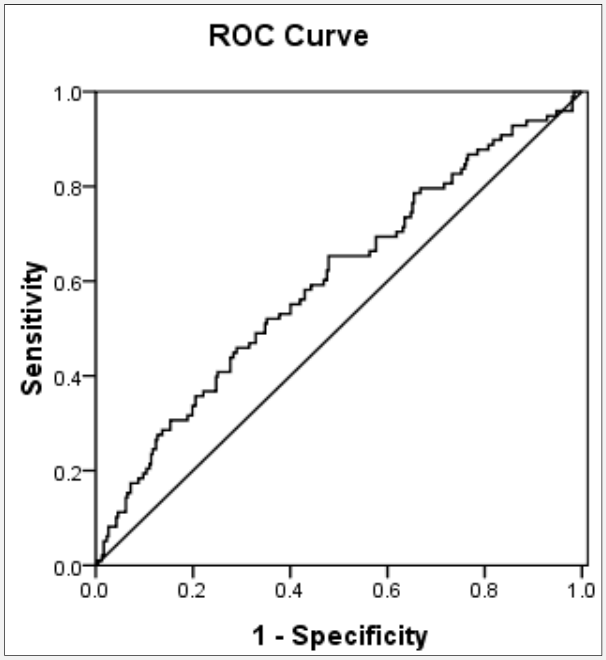

Figure 1. ROC curve analysis of optimal TSH concentration for TC prediction.

maximal diameter (OR 5.51, 95% CI 2.61 - 11.66, p < 0.001) (Table 4). The risk of TC was 1.76-fold higher if the TSH level was equal to or higher than 1.79 mIU/L relative to TSH levels less than 1.79 mIU/L (95% CI 1.05 - 2.95, p = 0.033) (Table 4). The nodules with preoperative positive TgAb showed increased risk (OR 2.59 95% CI 1.25 - 5.37, p = 0.01) (Table 4).

DISCUSSION

By analyzing the data, we found that papillary thyroid carcinoma and benign nodular goiter accounted for the vast majority of TC and BTND in Suzhou, respectively. Patients with TC were significantly younger than BTND and the majority were women. Earlier studies

showed that age under 20 and over 70 years was considered to be a risk factor for thyroid cancer [2,3]. Another study found that age was not a risk factor for thyroid cancer [4]. Patients from 17 to 88 years of age were included in our study. However, we found that patients who were younger than 40 years of age had a higher risk of thyroid cancer compared to patients equal to or older than 60 years. This conclusion is consistent with Rago et al's study [5]. Whether gender is a risk factor for TC is still controversial. A large-scale population study in Italy suggested that the male gender is associated with the risk of finding papillary thyroid cancer on fine-needle aspiration cytology in patients with NTD [5]. Our results showed that there was no significant difference when comparing the proportion of men and women between BTND and TC. The male gender could not be a risk factor for TC in patients with NTD which was consistent with the previous studies [4,6,7]. Surprisingly, from the results we found that the maximal diameter of nodules less than or equal to 1 cm had a higher risk than those larger than 2 cm nodules which needs to be further investigated.

Controversy still exists over whether TSH is an independent risk factor for thyroid cancer. A meta-analysis evaluated approximately 3,000 patients with NTD and found no difference in the risk of thyroid cancer associated with TSH levels [8]. Another meta-analysis systematically analyzed 5,786 cases of thyroid cancer and found a positive association between TSH levels and final diagnosis of malignancy [9]. Our findings suggested that a higher level of preoperative TSH was a cancer risk factor consistent with some previous studies [6,7]. It is interesting that NTD patients with positive TgAb but not TPOAb were at higher risk of TC, which was consistent with Kim et al's research [10]. This association still existed after correcting for other variables inconsistent with earlier research [6]. We speculated that there are two reasons: (1) cancer cells with biological characteristics of invasion and migration are inclined to damage the extracellular matrix, which makes it easier for thyroglobulin to leak from follicles; (2) thyroid cancer cells can secrete abnormal thyroglobulin.

In the past, with the rapid improvement of living standards, high incidences of hypertension, and diabetes existed in China. The thyroid gland is an important organ to regulate the body's metabolism. In China, it has been reported that thyroid nodules were associated with metabolic disorders [11]. A study from the United States showed that diabetes could increase the risk of suffering from differentiated thyroid cancer [12]. However, our findings did not show an increased risk of TC in NTD patients with a history of hypertension and diabetes. Investigations on thyroid nodules and metabolic diseases might need to take into account the current state of metabolic diseases. A cross-sectional study of 3,921 women with thyroid disease found that the incidence of breast cancer in patients with thyroid disease was significantly higher than that in the general population (OR = 3.33), especially in younger patients (OR = 15.24). Both benign thyroid disease and thyroid cancer can increase the incidence of breast cancer [13]. Our results did not support that patients with breast cancer are more likely to suffer from thyroid cancer in NTD patients. Further exploration may shine more light on the link between thyroid disease and breast cancer.

There have been some reports of NTD in Chinese population, but since China cover a vast territory, varied natural environment, and diversified ethnic groups, there are many differences among the conclusions from different studies [6,11,14,15]. Suzhou has a slight natural iodine deficiency and salt iodization has been carried out for about 20 years. A sample survey will be organized every two years to ensure that iodine nutrition of residents is at normal levels. At present, iodine deficiency disease has been effectively controlled. However, with the improvement of people's health awareness and the progress of hospital technology, NTD has gradually become a common clinical disease. The significance of detection of thyroid nodules is to exclude the possibility of malignancy, since 2 to 5% of thyroid nodules are malignant. Ultrasonography can assist in distinguishing benign from malignant thyroid nodules, but image interpretation is associated with clinical experience of ultrasound physicians. Thyroid fine needle aspiration biopsy (FNAB) has been found to have a high diagnostic accuracy [16]. However, about 20% of thyroid nodules are categorized as indeterminate nodules and patients usually require thyroid operation for the purpose of definite diagnosis [17]. In addition to the risk of organ damage, some patients might be misdiagnosed due to inappropriate tissue aspirated. The etiology of NTD is complicated and may be caused by genetic, endocrine, autoimmune, radiation, geographical factors and so on. Therefore, it is very important to analyze TC risk factors. Our study has some shortcomings. We did not do any further classification on thyroid nodules, and the factors included were not comprehensive enough. Refined classification and more factors are needed to be taken into account in a future study.

CONCLUSION

Studies on how to distinguish benign from malignant thyroid nodules have been ongoing. There are differences in geographical environment, diet, and human race among different countries or regions. So, there are many inconsistent conclusions. We investigated the clinical data and thyroid function of patients with NTD in Suzhou to determine the risk factors for TC in the area. We hope that this study can provide some reference for the identification of benign and malignant thyroid nodules.

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Declaration of Interest:

None.

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