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Original Article

Identification of risk factors for thyroid cancer in Urumqi, China

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Abstract: Aims: Risk factors for thyroid cancer in Urumqi were investigated. Methods: This study enrolled 153 cases of thyroid cancer, 154 cases of benign thyroid nodule and 327 controls between March 2014 and December 2014. Patient demographic information was obtained. Serum total triiodothyronine (TT3), total thyroxine (TT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), serum selenium concentration (Se), and urinary iodine concentration (UIC) were recorded. Results: Significant difference was observed in gender, age, and serum TT3, TT4, TSH, TgAb, TPOAb and Se levels as well as UIC in the thyroid cancer, benign thyroid nodule and control groups ($P<0.05$). Serum TT3 and TT4 levels were significantly lower in the thyroid cancer group than that in the benign thyroid nodule and control groups ($P<0.001$). In addition, the thyroid cancer group showed significant difference in serum TSH and TgAb levels from the group of benign thyroid nodule ($P<0.05$). Significantly a higher serum TPOAb level was noted in the groups of thyroid cancer and benign thyroid nodule than in the control group ($P<0.05$). Between different serum Se level subgroups, difference was noted in the serum TT3, TSH and TPOAb levels with significance ($P<0.001$) instead of TT4 and TgAb. With the rise of serum Se level, the TT3 level increased while TSH and TPOAb levels decreased. Serum TgAb and TPOAb levels were showed to be significantly different between groups of different UIC ($P<0.05$), while serum TT3, TT4 and TSH levels did not differ significantly. Serum TgAb and TPOAb levels increased with the increasing UIC. Multivariate logistic regression analysis revealed that female, low Se level and high UIC were risk factors for thyroid cancer. Conclusions: Female, low Se level and high iodine intake were dependent risk factors for thyroid cancer.

Keywords: Thyroid cancer, risk factor, multivariate analysis, thyroid nodule, thyrotropin

Introduction

In recent years, the incidence of thyroid cancer has been rising and thyroid cancer is the most frequent endocrine malignancy [1]. The cause of thyroid cancer is not yet clear. In most cases, early diagnosis results in a better prognosis [2]. At the current time, ionizing radiation, excessive intake of iodine, female hormone levels and a family history of cancer have been identified to be related to thyroid cancer, however, the mechanism is still not clear. The past years witnessed an increase in the incidence of thyroid cancer in Urumqi, China. Moreover, thyroid cancer attacks more women than men, and the pathological type and age of onset show significant differences in different ethnic groups.

In the current study, patients with thyroid cancer or benign thyroid nodules, and healthy controls in Urumqi were enrolled. Demographic data including age and gender as well as serum total triiodothyronine (TT3), total thyroxine (TT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), serum selenium concentration (Se), and urinary iodine concentration (UIC) were collected and analyzed to study their associations with thyroid cancer. The risk factors for thyroid cancer in Urumqi were further identified.

Materials and methods

Study population

The study population is composed of 153 patients with thyroid cancer, 154 patients with benign thyroid nodule and 327 healthy controls. The diagnosis of thyroid cancer and benign thy-

Table 1. Demographic characteristics of the study subjects

	Age (years)	Gender (Male/Female)
Thyroid cancer (n=153)	43.87±11.79	43/110
Benign thyroid nodule (n=154)	51.02±12.02	45/109
Control (n=327)	40.95±9.68	201/126
F/χ^2	45.698	69.818
P value	P<0.001	P<0.001

roid nodules was confirmed by histopathological analysis. Between March 2014 and December 2014, patients that underwent thyroidectomy for thyroid cancer or benign thyroid nodule in the Department of Thyroid and Vascular Surgery, the First Affiliated Hospital of Xinjiang Medical University, were consecutively recruited. Histological type of the thyroid cancer included in 147 cases of papillary thyroid cancer, 2 cases of follicular thyroid cancer, 2 cases of medullary thyroid cancer, and 2 cases were undifferentiated. In the group of patients with benign thyroid nodule, there were 142 cases of nodular goiter, 6 cases of nodular goiter with adenoma, 5 cases of adenoma and 1 case of nodular goiter with Hashimoto's thyroiditis.

The controls were selected from healthy volunteers who visited the Second Affiliated Hospital of Xinjiang Medical University for medical examination during the same period, and ultrasonography was performed for screening.

The patients and controls were local residents of Urumqi and had been living in Urumqi for at least 10 years at enrollment.

Exclusion criteria were history of thyroid disease, intake of Se- or iodine-containing drugs and iodinated contrast media in half a year prior to the enrollment, liver and kidney dysfunction, and pregnancy.

The study was approved by the institutional review board of the Xinjiang Medical University, and informed consent was obtained from each participant.

Data collection and laboratory test

Patient demographic data including age and gender as well as pathological results were obtained. Serum TT3, TT4, TSH, TgAb, and TPOAb levels as well as Se and UIC were tested and recorded. The normal ranges of TT3, TT4, TSH, TgAb and TPOAb were 0.80~2 ng/mL, 51~141 ng/mL, 0.27~0.42 μIU/ml, 0~115 IU/mL and 0~34 IU/mL, respectively.

Preoperative serum TT3, TT4, TSH, TgAb, and TPOAb were tested using chemiluminescence detection kits following the manufacturer's instructions. Se level in serum was detected with graphite furnace atomic absorption spectrometry (GFAAS). UIC was measured by As-Ce catalytic spectrophotometry.

Statistical analysis

The statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). The normality test was carried out on quantitative data and normally distributed data were presented as mean ± standard deviation. The student's t-test was performed for pairwise comparison while ANOVA was used for comparison between different groups. The non-normally distributed data were showed as median and interquartile range (IQR) and the rank sum test was performed for comparisons. The quantitative data were expressed as absolute number of cases and percentage. The χ^2 test was performed for pairwise comparison and comparison between groups. Multivariate logistic regression to estimate odds ratios (OR) with 95% confidence interval (CI) was conducted for the risk of thyroid cancer. A *P* level of <0.05 was regarded as statistically significant.

Results

Demographic characteristics of the study subjects

Totally, 634 subjects including 153 thyroid cancers, 154 patients with benign thyroid nodule and 327 controls were enrolled in this study. There were 289 males and 345 females. As shown in **Table 1**, the age was significantly different in the thyroid cancer group compared to the benign thyroid nodule and control groups. Moreover, significant difference was also noted in the age between the benign thyroid nodule and thyroid cancer groups (*P*<0.001). With regard to the gender, significant differences were observed between the thyroid cancer and

Table 2. Thyroid hormone and autoantibody levels in different groups

	TT3 (ng/ml)	TT4 (ng/ml)	TSH (μIU/mL)	TgAb (IU/mL)	TPOAb (IU/mL)
Thyroid cancer (n=153)	1.10 (1.00~1.26)*	88.67 (76.59~96.48)*,#	2.81 (1.82~3.73)*,#	19.66 (13.75~67.99)#	14.63 (8.09~27.18)*
Benign thyroid nodule (n=154)	1.11 (1.01~1.25)*	89.90 (86.74~98.52)*	1.85 (1.12~3.43)*	16.98 (12.65~26.26)	13.18 (6.23~19.63)*
Control (n=327)	1.78 (1.560~1.98)	96.77 (87.27~106.85)	2.14 (1.56~3.14)	19.47 (14.03~56.06)	7.81 (5.00~14.99)
H value	328.133	48.012	22.404	7.593	54.355
P value	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.05	*P*<0.001

Note: *$P<0.05$ versus the control group; #$P<0.05$ versus the benign thyroid nodule group.

Table 3. Distribution of thyroid cancers, benign thyroid nodule and controls in different serum selenium concentration (Se)

		Se ug/L		
	Total	<100	100~149	>150
Thyroid cancer (n, %)	153	102 (66.66)	35 (22.88)	16 (10.46)
Benign thyroid nodule (n, %)	154	85 (55.19)	45 (29.22)	24 (15.59)
Control (n, %)	327	63 (19.26)	140 (42.81)	124 (37.93)

control groups, and between the benign thyroid nodule and control groups.

High TSH, TgAb and TPOAb, and, low TT3 and TT4 levels in thyroid cancer

The thyroid hormone and autoantibody levels in different groups were analyzed. As shown in **Table 2**, there was significant difference in the levels of TT3, TT4, TSH, TgAb and TPOAb among different groups (P<0.05). The levels of TT3 and TT4 in the groups of thyroid cancer and benign thyroid nodule were significantly lower than that in the control group (*P*<0.001). Compared with the group of benign thyroid nodule, the levels of serum TSH and TgAb were higher in thyroid cancer with significant difference (*P*<0.05). The groups of thyroid cancer and benign thyroid nodule presented with significantly higher level of TPOAb than the control group (*P*<0.05).

Low Se in thyroid cancer

The mean Se of 634 subjects was 118.55 ug/L (range: 76.26~150.93 ug/L). It was 71.32 ug/L (range: 26.79~103.56 ug/L) in the group of thyroid cancer, 88.34 ug/L (range: 49.95~129.87 ug/L) in the group of benign thyroid nodule and 133.00 ug/L (range: 94.07~169.00 ug/L) in the control group. The Se was significantly lower in thyroid cancer than that in the groups of benign thyroid nodule and controls (P<0.05).

According to the different Se levels, subjects were assigned to three subgroups of <100 ug/L, 100~149 ug/L and >150 ug/L (**Table 3**). In the subgroup of Se <100 μg/L, the ratio of thyroid cancer cases was higher than that of other subgroups with significant difference (*P*< 0.001, **Table 3**). Moreover, significant difference was noted in the levels of TT3, TSH and TPOAb in subgroups of different Se (P<0.001), while there was no significant difference in the levels of TT4 and TgAb. TT3 increased while TSH and TPOAb decreased as Se increased (**Table 4**).

High UIC in thyroid cancer

The median UIC was 9.53 μg/L in all 634 subjects with a range of 180.40~394.97 μg/L. It was 328.10 μg/L (range: 209.20~571.20 μg/L), 257.20 μg/L (range: 168.85~390.15 μg/L) and 245.55 μg/L (range: 163.83~367.13 μg/L) in the groups of thyroid cancer, benign thyroid nodule and controls, respectively. The UIC was higher in the group of thyroid cancer than that in the groups of benign thyroid nodule and controls with significant difference (P<0.05).

All subjects were assigned into subgroups according to the criteria on iodine nutrition status released by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) in 2007. A median UIC<100 μg/L is indicative of insufficient iodine intake (iodine deficiency), 100~199 μg/L of adequate intake, 200~299 μg/L of intakes above requirements, and ≥300 μg/L of excessive intake [3]. Subjects were assigned into subgroups according to the above-mentioned assessment standard criteria.

The proportions of patients with thyroid cancer or benign thyroid nodule in subgroups of diff-

Table 4. Thyroid hormone and autoantibody levels in different serum selenium concentration (Se) groups (median, IQR)

Se ug/L	TT3 (ng/ml)	TT4 (ng/ml)	TSH (μIU/mL)	TgAb (IU/mL)	TPOAb (IU/mL)
<100	1.34 (1.28~1.40)	109.99 (90.51~129.48)	3.79 (2.07~5.51)	75.10 (31.16~119.05)	38.14 (26.52~49.78)
100~149	1.58 (1.51~1.66)	118.48 (87.54~149.41)	3.49 (2.04~4.94)	96.26 (40.97~151.55)	31.34 (18.73~43.94)
>150	1.64 (1.56~1.72)	115.75 (75.35~156.15)	2.79 (2.48~3.10)	78.33 (39.68~116.99)	27.43 (16.20~38.56)
H value	-7.013	-1.922	-2.343	-0.458	-3.590
P value	P<0.001	0.065	P<0.001	0.255	P<0.001

Table 5. Distribution of thyroid cancers, benign thyroid nodules and controls in different urinary iodine concentration (UIC)

		UIC μg/L			
	Total	<100	100~200	200~300	≥300
Thyroid cancer (n, %)	153	6 (3.9)	34 (22.2)	33 (21.6)	80 (52.3)
Benign thyroid nodule (n, %)	154	8 (5.2)	51 (33.1)	40 (26.0)	55 (35.7)
Control (n, %)	327	23 (7.1)	94 (28.8)	93 (28.4)	117 (35.7)

erent UIC were significantly different ($P<0.05$). A significantly higher proportion of patients with thyroid cancer was noted in the subgroup of excessive iodine intake than other groups ($P<0.05$, **Table 5**). Further, the levels of serum TgAb and TPOAb were significantly different in groups of different UIC (P<0.05), while no significant difference was observed in TT3, TT4 or TSH. The TgAb and TPOAb levels increased as the UIC became higher (**Table 6**).

Multivariate results

As shown in **Table 7**, multivariate logistic regression analysis revealed that female (OR=1.874; 95% CI=1.012~3.472), low Se level (OR=0.08; 95% CI=0.078~0.435) and high UIC (OR=0.004; 95% CI=1.548~6.026) were risk factors for thyroid cancer.

Discussion

Thyroid cancer can occur at any age and the papillary type occurs more often in young women than in men at a ratio of three to one [4]. In the present study, the proportion of papillary thyroid cancer was 97.08% in the thyroid cancers and the male/female ratio was 1; 2.56 in the group of patients with thyroid cancer. In the thyroid cancer group, patients had a younger age than that in the group of benign thyroid nodule with significant difference. Female was demonstrated to be a dependent risk factor for thyroid cancer based on multivariate results. It has been confirmed by animal and cell studies that estrogen and its metabolites can promote the proliferation and growth of thyroid cancer cells [5]. Estrogen acts on the thyroid gland through enhancing the peroxidase activity, the iodine intake and serum T3 [6]. It can promote the division of thyroid cancer cells by stimulating mitogen-activated protein kinase (MAPK).

The present study revealed lower TT3, TT4 level and Se, and a higher TSH level in the group of thyroid cancer than control. With the rise of Se, TT3 increased, while TSH and TPOAb decreased. Multivariate results suggested that low Se status is an independent risk factor for thyroid cancer. As a modulator of oncogene expression, Se-containing compound can suppress the division, promote the differentiation and induce programmed death of the cancer cells [7].

The conversion of T4 to T3, catalyzed by selenoproteins, accounts for the major source of T3 in vivo and plays a key role in maintaining the normal thyroid functioning. Se glutathione peroxidase can function as oxide reductase and protect thyroid cells from oxidative stress [8]. When Se-deficient status is present, the decrease of selenoproteins can cause abnormal thyroid hormone metabolism and reduced serum T3 [9, 10]. Meanwhile, the feedback from Se deficiency can stimulate the increased secretion of TSH which promotes the synthesis of cAMP, activates the cAMP-dependent protein kinase signal transduction system, enhances epidermal growth factor-mediated cell proliferation, stimulates the thyroid follicular cell growth, and functions as a mediator and amplifies the signal in tumor invasion [11, 12].

Table 6. Thyroid hormone and autoantibody levels in different UIC groups (median, IQR)

UIC ug/L	TT3 (ng/ml)	TT4 (ng/ml)	TSH (μIU/mL)	TgAb (IU/mL)	TPOAb (IU/mL)
<100	1.42 (1.28~1.57)	122.13 (41.23~203.04)	2.52 (1.90~3.15)	44.03 (28.06~60.00)	28.14 (13.85~38.33)
100~200	1.60 (1.52~1.69)	107.23 (75.66~138.81)	4.02 (1.68~6.36)	83.10 (24.85~141.36)	32.22 (23.19~40.73)
200~300	1.58 (1.48~1.66)	121.32 (89.65~153.00)	2.98 (1.96~4.00)	94.49 (47.76~141.22)	36.31 (20.24~52.11)
≥300	1.38 (1.32~1.43)	156.67 (63.01~250.32)	3.40 (2.50~4.30)	127.29 (22.69~231.88)	50.04 (11.82~94.07)
H value	8.555	5.322	3.383	11.627	24.772
P value	0.887	0.647	0.139	P<0.001	P<0.001

Table 7. Odds ratios (OR) and 95% confidence interval (CI) of thyroid cancer associated with anthropometric factors, thyroid hormone, autoantibody, serum selenium concentration (Se) and urinary iodine concentration (UIC)

	B value	Wald	*P* value	OR	95% CI
TT3	-0.846	1.535	0.215	0.429	0.112~1.636
TT4	-1.160	5.880	0.319	0.314	0.058~0.494
TSH	-0.351	1.198	0.274	0.704	0.375~1.320
TgAb	-0.604	5.693	0.203	1.396	0.785~1.848
TPOAb	-0.468	1.939	0.164	0.626	0.324~1.210
Se ug/L		0.218	0.008		
100~149	-0.983	4.035	0.000	0.185	0.078~0.435
≥150	-0.409	0.612	0.148	0.664	0.200~1.275
UIC μg/L		5.429	0.045		
<100	0.564	3.363	0.036	2.102	1.342~5.120
100~199	1.116	10.363	0.001	2.276	1.165~4.444
200~299	.822	5.799	0.016	3.054	1.548~6.026
Age at enrollment (yrs)					
≤45	0.090	0.151	0.697	1.094	0.695~1.723
Female	-0.845	12.370	0.000	1.429	1.268~1.688

CI confidence interval.

The TPOAb level in the groups of thyroid cancer and benign thyroid nodule were significantly higher than that in the control group, and significant difference was noted in the TPOAb level in groups with different Se. With the increase of Se, TPOAb decreased. It is indicative that Se deficiency can impair the antioxidant capacity of thyroid selenoproteins, leading to the damage and even apoptosis of thyroid follicular cell structure. As one kind of autoimmune antigen, thyroid peroxidase (TPO) induces the development of TPOAb and immune inflammatory damage. Nitric Monoxide (NO), released from inflammatory cells, is found to be increased in papillary thyroid cancer and induces the production of high-mobility group box 1 (HMGB1), which stimulates the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in thyroid cells and maintains the peritumoral inflammatory response. Low Se status is considered to increase the thyroid cancer risk through mediating immune inflammation.

In this study, the iodine nutritional status was revealed to be suitable in the subjects. UIC in the thyroid cancer group was significantly higher than that in the benign thyroid nodules and control groups. TgAb and TPOAb levels increased as UIC increased, and high UIC was found to be an independent risk factor for thyroid cancer according to the multivariate results. Epidemiological study [13] found that iodine intake was positively associated with the incidence of undifferentiated thyroid cancer, and the ratio of papillary thyroid cancer increased in areas of high iodine intake [14]. The policy of universal salt iodization has improved the iodine nutritional status in the Urumqi city, which belongs to iodine deficiency area, and the iodine nutritional status has been excessive according to the assessment criteria established by WHO [15]. With long-term and excessive iodine intake levels, the transcription and expression of sodium iodide symporter (NIS) were decreased, and the iodine uptake capacity of thyroid tissue is impaired [16, 17]. When thyroid homeostasis cannot be maintained by self-regulation, thyroid function is decreased [18]. The hypothalamic-pituitary-thyroid axis is initiated to increase TSH through feedback, and then the thyroid follicular hyperplasia and nodules are induced [19-21]. Furthermore, the mutations of v-raf murine sarcoma viral oncogene homolog

B1 (BRAF) gene are caused and the transcription and expression of NIS are suppressed, resulting in further impairment of thyroid iodine intake capacity and thyroid cancer [22]. It has been confirmed by animal studies [23] that high iodine intake level can lead to lymphocyte infiltration and follicular cell expansion in thyroid tissues and inflammatory infiltration will be increased with increasing iodine intake. In the present study, high iodine status has been demonstrated to be an independent risk factor for thyroid cancer. Serum TgAb and TPOAb levels increased with the increase of UIC. High iodine status may induce the development of thyroid cancer through immune response.

In conclusion, the present study verified Se deficiency as a risk factor for thyroid cancer. However, further investigations are in need to confirm that whether Se supplement can function in the prevention of thyroid cancer. Urinary iodine test can be used as a routine examination. Population-based studies on the risk factors for thyroid cancer are warranted for a more comprehensive and integrated analysis.

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Disclosure of conflict of interest

None.

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