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Nutrition

High iodine intake and central lymph node metastasis risk of papillary thyroid cancer

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ABSTRACT

The relationship between iodine intake and clinicopathologic characteristics of papillary thyroid cancer (PTC) is unclear. We aim to investigate the relationship between iodine intake and central lymph node metastasis (CLNM) of PTC. A total of 4040 consecutive patients with PTC receiving thyroidectomy and central lymph node dissection were enrolled from 2013 to 2018. Pathological features of tumors and urinary iodine concentration (UIC) were recorded. Multivariate analysis was performed to investigate the association between iodine intake and CLNM of PTC. More than adequate (UIC: 200.0-299.9 μg/L) and excessive iodine intake (UIC ≥ 300.0 μg/L) were present in 1741 cases (43.09%). Iodine deficiency (UIC ≤ 99.9 μg/L) was inversely associated with female PTC risk only with OR (95% CI): 0.48 (0.29–0.80) relative to adequate iodine intake (UIC: 100.0–199.9 μg/L). However, more than adequate and excessive iodine intake was not associated with PTC risk among the general population and patients with thyroid nodules. In addition, high iodine intake was not associated CLNM risk of PTC. After defining CLNM as metastatic lymph nodes ≥ 2, excessive iodine intake was marginally associated with CLNM among female PTC patients with OR (95% CI): 1.25 (0.99–1.57) by multivariate analysis. Additionally, excessive iodine intake was marginally associated with larger tumor size and capsular invasion. Furthermore, we found that female PTC patients were more closely linked with iodine intake than male ones. In conclusion, high iodine intake appears not to be an initiator, but may be a weak promoter for female PTC progression, which needs further validation.

1. Introduction

Iodine is an essential microelement for synthesis of thyroxine which plays a vital role in organic health such as body growth, organ development, and metabolism [1]. Iodine intake is through diet (80%–90%), water (10%–20%), and air (0–5%). More than 90% of iodine consumed is excreted in the urine, making urine iodine concentration (UIC) a good biomarker of recent iodine intake. The median UIC (MUI) is an excellent indicator for iodine status of a population [2].

China was a severe iodine-deficient country, with high prevalence of iodine deficiency disorders (IDDs) [3]. The universal salt iodization (USI) program has been carried out throughout China since 1995, and IDDs were generally eliminated in 2005 nationwide. Data from Chinese Center for Disease Control and Prevention reported that the MUI of 8-10-year-old children was 246.3, 238.6, and 197.9 μg/L in 2005, 2011 and 2014, respectively [4]. With the transition of iodine status, recent years has witnessed an abrupt increased in the incidence of thyroid cancer with an annual percentage change from 4.9 (2000–2003) to 20.1 (2003–2011) in China [5]. Meanwhile, there is a lot of discussion about the overdiagnosis and overtreatment of thyroid diseases [6,7]. The incidence of papillary thyroid cancer (PTC) especially for papillary thyroid microcarcinoma (PTMC) has been appreciably increasing in the last few decades, whereas the mortality has steadily declined in most parts of the world [8,9].

The relationship between iodine intake and PTC risk was still obscure. Previous animal studies indicated that both long-term iodine deficiency and excess were insufficient to stimulate thyroid carcinogenesis [10]. In addition, the incidence of thyroid cancer was not associated with high water iodine intake [11]. Additionally, a higher dietary iodine intake was associated with a decreased risk of thyroid

Abbreviations: CLNM, central lymph node metastasis; LT, lymphocytic thyroiditis; MUI, median urinary iodine concentration; NG, nodular goiter; OR, odds ratio; CI, confidence interval; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; UIC, urinary iodine concentration; USI, universal salt iodization

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cancer [12]. However, Wang et al found that high urinary iodine was a risk factor for thyroid cancer [13]. We previously found that more than adequate iodine intake was associated with larger tumor size compared with adequate iodine intake, suggesting that high iodine intake might be associated with the growth of PTC [14]. We thus expected that high iodine intake might be associated with the progression of PTC: central lymph nodes metastasis (CLNM). As far as we known, studies focusing on this topic were limited. We aimed to investigate the association of iodine intake with PTC risk and CLNM of PTC.

2. Patients and methods

2.1. Study population

Patients with thyroid disease were retrospectively reviewed in Union hospital, Wuhan, China from November 2013 to February 2018. Individuals who met the following criteria were enrolled. Patients received the first thyroid surgery, and underwent total thyroidectomy or lobectomy combined with bilateral/unilateral central lymph node dissection. Patients with radiation exposure in the head and neck, family history of thyroid cancer, recent use of iodine-containing contrast-enhanced imaging, renal failure, pregnancy, or iodine-containing drug therapies were excluded. A total of 4040 consecutive patients with PTC were finally enrolled. This study was approved by the Ethics Committee of Union hospital (2019-S023). Informed consent requirement was waived because personal identifying information was not accessed.

2.2. Surgery

Thyroid surgery was carried out by experienced surgeons (5–20 years). Intraoperative frozen section was performed on all patients receiving thyroid surgery to determine the nodule malignancy. Bilateral or unilateral central lymph node dissection was performed based on tumor characteristics, preoperative imaging results, and intraoperative exploration. Informed consent forms were obtained from all patients preoperatively.

2.3. Pathological diagnosis

Routine pathological diagnosis was performed on postoperative specimen of the thyroid and fat-like tissues with 2–3 μm sections. Hematoxylin & eosin staining with or without immunohistochemistry was performed to determine the pathological types. The final pathological diagnosis was PTC. Papillary thyroid microcarcinoma (PTMC) was defined as tumors ≤ 1 cm in its largest diameter. Solitary focus means only one tumor in the thyroid, while multiple foci mean two or more tumor foci limited to the thyroid. Bilaterality is defined as the presence of tumor foci in the right and left lobes of the thyroid. Capsular invasion means that one tumor invades the thyroid capsular but not penetrates it; while one tumor penetrates the capsular into the strap muscle or perithyroidal fibrofatty tissues, which will be defined as extracapsular extension. Intrathyroidal dissemination means that the primary tumor spreads to the other parts of the thyroid.

CLNM was defined as metastatic lymph nodes ≥ 1 unless otherwise indicated. Clinical and pathological variables of interest such as age, sex, tumor size, tumor number, capsular invasion, extracapsular extension, intrathyroidal dissemination, bilaterality of tumor foci, and CLNM were recorded.

2.4. Urinary iodine determination

Quantitative test kit type AR for urinary iodine (Wuhan Zhongsheng Biochemical Technique Co, LTD, Wuhan, China) was used to determine UIC. UIC > 400.0 μg/L was assayed by dilution. The coefficient of variation of intra-assay and inter-assay was less than 10%. The limit of detection of the assay kit was less than 10 μg/L. More details can be found in our previous description [15].

Iodine nutrition was divided into four categories: iodine deficiency, adequate iodine intake, more than adequate iodine intake, and excessive iodine intake with UIC < 100.0, 100.0–199.9, 200.0–299.9, and ≥ 300.0 μg/L, respectively [2].

2.5. Statistical analysis

Statistical analyses were performed using SPSS Statics 22.0 (Chicago, IL, USA). UIC was expressed as median (upper and lower quartile) for its skewed distribution and analyzed with Mann-Whitney *U* test. Multivariate analysis was performed to investigate the association of urinary iodine with PTC risk and CLNM of PTC. Statistical differences were set at a two-sided *P* value < 0.05.

3. Results

3.1. Iodine status of the study population

Among the 4040 PTC patients, a total of 684 subjects (16.93%) were deficient in iodine intake (UIC < 100.0 μg/L). Iodine deficiency was more common among female than male PTC patients (18.60% vs 11.28%). Adequate iodine intake accounted for 39.98% of the total population. More than adequate and excessive iodine intake was present in 1741 out of 4040 cases (43.09%) (Fig. 1).

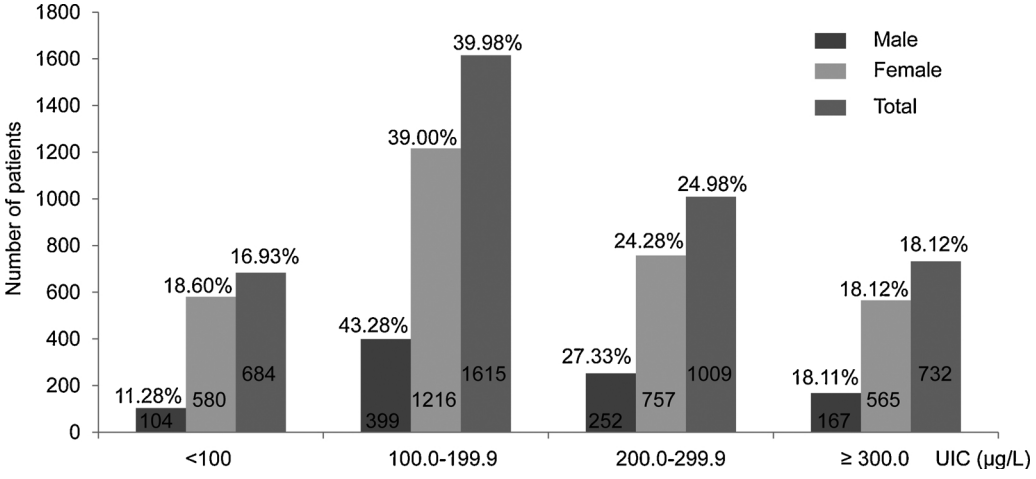

Fig. 1. Iodine status of the study population.
Iodine nutrition was classified into four categories: iodine deficiency (UIC < 100.0 μg/L), adequate iodine intake (UIC: 100.0–199.9 μg/L), more than adequate iodine intake (UIC: 200.0–299.9), and excessive iodine intake (UIC ≥ 300.0 μg/L). Data were expressed as the number of patients (%). UIC, urinary iodine concentration.

Table 1
Association between iodine intake and PTC risk relative to healthy control subjects (n = 415 vs 272) [15].

Category	Univariate		Multivariate [a]	
	OR (95% CI)	P value	OR (95% CI)	P value
Total (n = 687)				
≤99.9	0.49 (0.31-0.77)	**0.002**	0.48 (0.30-0.74)	**0.001**
100.0–199.9	Reference		Reference	
200.0–299.9	0.86 (0.57-1.29)	0.464	0.84 (0.56-1.26)	0.393
≥300.0	1.15 (0.70-1.89)	0.588	1.13 (0.69-1.86)	0.631
Male (n = 228)				
≤99.9	0.66 (0.26-1.66)	0.467	0.67 (0.26-1.69)	0.392
100.0–199.9	Reference		Reference	
200.0–299.9	0.64 (0.34-1.21)	0.166	0.63 (0.33-1.19)	0.157
≥300.0	0.80 (0.38-1.66)	0.547	0.78 (0.38-1.63)	0.513
Female (n = 459)				
≤99.9	0.45 (0.27-0.75)	**0.002**	0.48 (0.29-0.80)	**0.005**
100.0–199.9	Reference		Reference	
200.0–299.9	1.01 (0.60-1.70)	0.977	1.05 (0.62-1.78)	0.869
≥300.0	1.68 (0.83-3.41)	0.151	1.57 (0.76-3.32)	0.221

Iodine nutrition was divided into four categories: ≤ 99.9, 100.0–199.9, 200.0–299.9, and ≥ 300.0 μg/L.
PTC, papillary thyroid cancer; OR (95% CI), odds ratio (95% confidence interval).
These data were obtained but not reported in our previous study.
[a] Adjusted for age (≥ 55 vs < 55 years), sex (for total) in the multivariate model.

3.2. Association between iodine intake and PTC risk

These data were originated but not reported in our previous studies [14,15]. There were 415 PTC patients including 101 males and 314 females. A total of 324 patients (78.07%) were less than 55 years old. Patients with tumors ≤ 1 cm in diameter account for 45.30%. A sum of 272 out of 415 patients present with multiple tumors.

First, we investigated the association between iodine intake and PTC risk via comparison of urinary iodine among 415 PTC patients and 272 healthy control subjects [15]. We found that iodine deficiency was inversely associated with PTC risk in the total population (OR = 0.48, P = 0.001) and in females (OR = 0.48, P = 0.005) after adjustment. However, more than adequate and excessive iodine intake was not associated with PTC risk (Table 1).

We further evaluated whether iodine intake was associated with nodule malignancy among patients with thyroid nodules via comparison of urinary iodine among 1120 PTC patients and 921 patients with NG [14]. We did not observe any association between iodine intake and PTC risk among patients with thyroid nodules in univariate and multivariate analyses (Table 2). However, we found that high iodine intake was associated with the size of malignant and benign thyroid nodules [14]. We therefore supposed that high iodine intake might be associated with the progression of PTC, and investigated the association between urinary iodine and the clinicopathologic features of PTC.

3.3. Urinary iodine status of PTC patients with different clinicopathologic characteristics

Male PTC patients had significantly higher MUI than females (P = 0.001). In addition, PTC patients < 55 years showed higher MUI than those ≥ 55 years (P = 0.036). Consistent with our previous findings, PTC patients with tumors > 1 cm presented higher MUI than those ≤ 1 cm in tumor diameter (P = 0.004). Additionally, patients with tumors presenting capsular invasion and extracapsular extension had significantly higher levels of MUI (P = 0.009 and 0.036, respectively) (Table 3).

Of note, PTC patients with CLNM had higher MUI than those without CLNM (186.5 μg/L vs 176.8 μg/L), however, the difference was not statistically significant (P = 0.188). When we defined the metastatic central lymph nodes ≥ 2 as CLNM, and those with metastatic central lymph nodes < 2 as negative for CLNM, results showed that

Table 2
Association between iodine intake and PTC risk relative to patients with NG (n = 1120 vs 921) [14].

Category	Univariate		Multivariate [a]	
	OR (95% CI)	P value	OR (95% CI)	P value
Total (n = 2041)				
≤99.9	1.14 (0.88-1.47)	0.318	1.08 (0.82-1.43)	0.588
100.0–199.9	Reference		Reference	
200.0–299.9	1.02 (0.82-1.28)	0.843	1.09 (0.85-1.38)	0.506
≥300.0	0.92 (0.72-1.18)	0.511	1.01 (0.77-1.32)	0.956
Male (n = 469)				
≤99.9	0.93 (0.48-1.80)	0.825	0.84 (0.41-1.69)	0.618
100.0–199.9	Reference		Reference	
200.0–299.9	0.77 (0.49-1.19)	0.237	0.87 (0.54-1.42)	0.584
≥300.0	0.84 (0.51-1.40)	0.502	0.81 (0.47-1.42)	0.462
Female (n = 1572)				
≤99.9	1.23 (0.93-1.62)	0.144	1.16 (0.85-1.57)	0.351
100.0–199.9	Reference		Reference	
200.0–299.9	1.12 (0.86-1.45)	0.401	1.17 (0.88-1.56)	0.274
≥300.0	0.95 (0.71-1.25)	0.691	1.07 (0.79-1.46)	0.647

Iodine nutrition was divided into four categories: ≤ 99.9, 100.0–199.9, 200.0–299.9, and ≥ 300.0 μg/L.
OR (95% CI), odds ratio (95% confidence interval); PTC, papillary thyroid cancer; NG, nodular goiter.
These data were obtained but not reported in our previous study.
[a] Adjusted for age (≥ 55 vs < 55 years), sex (for total), tumor size (> 1 cm vs ≤ 1 cm), tumor number (multifocal vs unifocal) in the multivariate model.

Table 3
Comparison of urinary iodine according to clinicopathologic features among PTC patients (n = 4040).

Variables	n	MUI (μg/L)	P value
Sex			
Male	922	190.4 (134.8-259.7)	**0.001**
Female	3118	177.1 (116.5-263.8)	
Age			
< 55	3367	183.2 (122.1-265.4)	**0.036**
≥ 55	673	172.7 (113.1-251.6)	
Tumor size			
≤ 1 cm	2811	177.0 (118.2-261.0)	**0004**
> 1 cm	1229	190.1 (127.2-266.9)	
Tumor number			
Single	2255	181.6 (119.4-259.6)	0.621
Multiple	1785	179.8 (121.4-266.6)	
Bilaterality			
Yes	1324	176.9 (119.2-265.0)	0.694
No	2716	183.1 (121.3-261.9)	
Capsular invasion			
Yes	2469	186.9 (125.4-264.5)	**0.009**
No	1571	175.2 (113.9-260.8)	
Extracapsular extension			
Yes	472	192.3 (130.4-275.5)	**0.036**
No	3568	179.4 (119.5-261.9)	
Intrathyroidal spread			
Yes	196	205.8 (132.3-274.8)	0.062
No	3844	179.9 (119.5-262.2)	
CLNM [a]			
Yes	2089	186.5 (122.2-262.1)	0.188
No	1951	176.8 (118.6-263.4)	
CLNM [b]			
Yes	1518	191.7 (126.7-270.1)	**0.003**
No	2522	176.2 (118.3-259.8)	

PTC, papillary thyroid cancer; CLNM, central lymph node metastasis; MUI, median urinary iodine concentration.
[a] CLNM was defined as metastatic central lymph nodes ≥ 1.
[b] CLNM was defined as metastatic central lymph nodes ≥ 2.

Table 4
Comparison of MUI among PTC patients with different clinicopathologic features by gender (n = 4040).

Variables	Male			Female		
	n	MUI (μg/L)	P value	n	MUI(μg/L)	P value
Age						
< 55	787	189.5 (137.2-259.3)	0.676	2580	183.6 (117.8-266.7)	0.057
≥ 55	135	193.9 (119.1-267.3)		538	167.2 (111.9-247.4)	
Tumor size						
≤ 1 cm	545	187.8 (131.8-258.6)	0.187	2266	174.4 (114.4-262.1)	**0.033**
> 1 cm	377	193.7 (142.4-263.1)		852	187.7 (119.3-270.7)	
Tumor number						
Solitary	543	188.8 (135.6-255.0)	0.703	1712	177.9 (115.1-262.9)	0.621
Multiple	379	192.3 (133.9-273.1)		1406	176.2 (118.4-265.5)	
Bilaterality						
Yes	286	191.1 (134.1-268.0)	0.838	1038	173.2 (113.3-264.3)	0.629
No	636	189.8 (134.9-259.1)		2080	179.4 (117.8-263.6)	
Capsular invasion						
Yes	591	190.3 (137.4-257.8)	0.948	1878	184.4 (119.3-266.0)	**0.007**
No	331	193.1 (129.8-262.0)		1240	169.1 (109.1-260.4)	
Extracapsular extension						
Yes	132	192.8 (132.9-274.7)	0.852	340	192.3 (128.9-275.5)	**0.033**
No	790	189.8 (135.6-259.5)		2778	175.6 (115.5-262.7)	
Intrathyroidal spread						
Yes	66	193.8 (142.6-289.9)	0.458	130	210.4 (128.2-271.9)	0.144
No	856	190.2 (134.2-259.2)		2988	176.3 (115.9-263.6)	
CLNM [a]						
Yes	603	188.3 (132.4-257.3)	0.110	1486	183.9 (118.1-266.1)	0.097
No	319	195.2 (144.1-278.2)		1632	172.8 (114.6-262.4)	
CLNM [b]						
Yes	478	192.4 (134.9-264.4)	0.621	1040	192.3 (120.9-275.3)	**0.012**
No	444	188.8 (133.8-257.0)		2078	173.1 (114.7-260.8)	

MUI, median urinary iodine concentration; PTC, papillary thyroid cancer; CLNM, central lymph node metastasis.
[a] CLNM was defined as metastatic central lymph nodes ≥ 1.
[b] CLNM was defined as metastatic central lymph nodes ≥ 2.

Table 5
Association between iodine intake and CLNM [a] of PTC.

Category	Univariate		Multivariate [b]	
	OR (95% CI)	P value	OR (95% CI)	P value
Total (n = 4040)				
≤99.9	0.93 (0.77-1.12)	0.429	1.08 (0.88-1.33)	0.461
100.0–199.9	Reference		Reference	
200.0–299.9	1.22 (1.04-1.43)	**0.017**	1.18 (0.99-1.41)	0.072
≥300.0	1.24 (1.04-1.48)	**0.019**	1.19 (0.98-1.45)	0.081
Male (n = 922)				
≤99.9	0.93 (0.60-1.43)	0.738	1.08 (0.67-1.74)	0.750
100.0–199.9	Reference		Reference	
200.0–299.9	1.15 (0.84-1.58)	0.386	1.16 (0.82-1.65)	0.391
≥300.0	1.05 (0.73-1.51)	0.791	1.04 (0.70-1.54)	0.864
Female (n = 3118)				
≤99.9	1.03 (0.83-1.27)	0.817	1.08 (0.86-1.37)	0.485
100.0–199.9	Reference		Reference	
200.0–299.9	1.25 (1.03-1.52)	**0.023**	1.19 (0.97-1.47)	0.102
≥300.0	1.35 (1.09-1.66)	**0.005**	1.25 (0.99-1.57)	0.056

Iodine nutrition was divided into four categories: ≤ 99.9, 100.0–199.9, 200.0–299.9, and ≥ 300.0 μg/L.
CLNM, central lymph node metastasis; PTC, papillary thyroid cancer; OR (95% CI), odds ratio (95% confidence interval).
[a] CLNM was defined as metastatic central lymph nodes ≥ 2.
[b] Adjusted for age (≥ 55 vs < 55 years), sex (for total), tumor size (≥ 1 cm vs ≤ 1 cm), capsular invasion, extracapsular extension and intrathyroidal spread.

patients with CLNM had higher MUI relative to patients without CLNM (P = 0.003) (Table 3).

3.4. Comparison of MUI among PTC patients with different clinicopathologic features by gender

We previously found that males were higher in MUI than females among patients with PTC, nodular goiter, or healthy subjects [14,15]. We thus investigated the differences in MUI among PTC patients with different clinicopathologic characteristics by gender (Table 4). No significant differences in MUI among male PTC patients with different clinicopathologic features were observed. Of females, patients with larger tumor size (> 1 cm) had significantly higher MUI than those < 1 cm in diameter (P = 0.033). Consistent with the results in combined analysis, female patients with capsular invasion and extracapsular extension had higher levels of MUI than patients without capsular invasion and extension (P = 0.007 and 0.033, respectively) (Table 4).

We did not observe any differences in MUI among patients with CLNM or not in either gender (Table 4). After defining CLNM as metastatic central lymph nodes ≥ 2, female patients with CLNM showed higher MUI than those without CLNM (P = 0.012), as opposed to males.

3.5. Association between iodine intake and CLNM of PTC

When CLNM was defined as positive lymph nodes in the central neck ≥ 1, we did not observe any association between iodine intake and CLNM of PTC (data not shown). We therefore investigated the association between iodine intake and CLNM defined as metastatic central lymph nodes ≥ 2.

More than adequate iodine intake and excessive iodine intake were positively associated with CLNM of PTC with OR (95% CI): 1.22 (1.04–1.43) and 1.24 (1.04–1.48) respectively relative to adequate

Table 6
Univariate analysis of the association between iodine intake and tumor size, capsular invasion and extracapsular extension among female PTC patients (n = 3118).

Category	OR (95% CI)	P value
Tumor size (> 1 cm vs ≤ 1 cm)		
≤99.9	0.89 (0.71-1.12)	0.314
100.0–199.9	Reference	
200.0–299.9	1.01 (0.82-1.24)	0.927
≥300.0	1.24 (1.00-1.54)	0.053
Capsular invasion (yes vs no)		
≤99.9	0.88 (0.72-1.08)	0.213
100.0–199.9	Reference	
200.0–299.9	1.19 (0.98-1.43)	0.074
≥300.0	1.22 (1.00-1.50)	0.056
Extracapsular extension (yes vs no)		
≤99.9	0.91 (0.65-1.28)	0.593
100.0–199.9	Reference	
200.0–299.9	1.26 (0.95-1.68)	0.113
≥ 300.0	1.24 (0.90-1.69)	0.185

Iodine nutrition was divided into four categories: ≤ 99.9, 100.0–199.9, 200.0–299.9, and ≥ 300.0 μg/L.
PTC, papillary thyroid cancer.

iodine status in the total population by univariate analysis. After stratification by gender, more than adequate and excessive iodine intake was associated with CLNM with OR (95% CI): 1.25 (1.03–1.52), and 1.35 (1.09–1.66) respectively among female PTC patients only (Table 5).

After adjustment for potential risk factors for CLNM of PTC such as age, tumor size, capsular invasion, extracapsular extension, and intrathyroidal spread, excessive iodine intake was marginally associated with CLNM among female PTC patients with OR (95% CI): 1.25 (0.99–1.57) (Table 5).

3.6. Association of iodine intake with tumor size, capsular invasion and extracapsular extension of female PTC patients

We further investigated the association of iodine intake and tumor size, capsular invasion, and extracapsular extension among female PTC patients by univariate analysis. Excessive iodine intake were marginally associated with larger tumor size and capsular invasion with OR (95% CI): 1.24 (1.00–1.54) and 1.22 (1.00–1.50), respectively (Table 6).

4. Discussion

In the present study, we investigated the association between iodine intake and PTC risk, as well as the clinicopathologic features of PTC. We found that more than adequate and excessive iodine intake was not associated PTC risk in the general population and patients with thyroid nodules. However, iodine deficiency was inversely associated with female PTC risk. In addition, iodine intake was not associated with CLNM of PTC in either gender. After defining CLNM as metastatic central lymph nodes ≥ 2, excessive iodine intake was marginally associated with CLNM relative to adequate iodine intake after adjustment among female PTC patients. Furthermore, excessive iodine intake was marginally associated with larger tumor size (> 1 cm) and capsular invasion compared with adequate iodine intake among female PTC patients.

Great heterogeneities existed between studies on iodine intake and PTC risk. Zhou et al reported that excessive iodine intake (UIC ≥ 300.0 μg/L) was a risk factor for PTC compared with those of UIC < 300.0 μg/L after adjustment for age and sex with 53 PTC patients and 65 control subjects [16]. However, no participant was deficient in iodine intake. Our results showed that more than adequate and excessive iodine intake was not associated with PTC risk in either gender relative to adequate iodine intake after adjustment of age (< 55 vs ≥ 55 years) and sex, even though iodine deficiency was inversely associated with PTC risk [15]. In addition, Kim et al found that patients with excessive iodine intake (UIC ≥ 2500.0 μg/L) had a greater risk of thyroid cancer than those with UIC of 300–2499 μg/L with OR (95% CI): 1.87 (1.09–3.21) by combining male and female patients with thyroid nodules [17]. However, there are 22 patients in the excessive iodine group only, and the information on nodular size was unclear. We found that more than adequate and excessive iodine intake was not associated with PTC risk in either gender with 1120 PTC patients and 921 patients with NG [14]. The inconsistence between studies might result from iodine nutrition classification, analysis with combined genders, and adjusted confounders (age classification), and sample size.

We found that males had higher UIC than females either in healthy control subjects or patients with NG or PTC [14,15]. However, there was no significant difference in urinary iodine in terms of tumor size, capsular invasion, extracapsular extension, as well as CLNM among male PTC patients, which was different from female subjects. Female PTC patients were more sensitive toward iodine exposure than males. It seems that high iodine intake might not be associated with the initiation and the progression of PTC in males. However, the combined analysis might overestimate the effect of iodine intake on male PTC patients due to the great weight of female PTC patients.

We previously found that more than adequate iodine was associated with larger tumor size (> 1 cm) among female PTC patients [14]. We thus supposed that high iodine intake might be associated with the progression of PTC. However, we did not observe any difference in iodine intake among patients with CLNM or not. After defining CLNM as metastatic lymph nodes ≥ 2, excessive iodine intake was marginally associated with CLNM of PTC compared with adequate iodine intake in females only by multivariate analysis. In addition, excessive iodine intake was marginally associated with larger tumor size and capsular invasion. These results suggested that high iodine intake appeared not to be an initiator, but may be a weak promoter for female PTC development.

The underlying mechanisms for PTC tumorigenicity linked with high iodine intake were not elucidated yet. Guan et al reported that PTC patients with high iodine intake were more likely to present *BRAF* (T1799 A) mutation in areas of iodine-rich water [18]. Unfortunately, they failed to investigate the association between iodine intake and the clinicopathologic features of PTC. In addition, Kim et al reported that relatively low (UIC < 300 μg/L) and more than excessive iodine intake (UIC ≥ 500 μg/L) had a higher OR (95% CI) of 4.76 (1.76–12.85) and 6.24 (2.08–18.73) for the *BRAF* mutation compared with the 300–499 μg/L UIC group among PTC patients [19]. However, Frasca et al found no association between *BRAF* (V600E) and iodine intake [20]. High iodine can abrogate *BRAF* (V600E)-induced upregulation of miR-19 and result in enhanced G1-cell cycle arrest, exerting protective effects in thyroid cells *in vitro* [21].

The recent decades witnessed a sharp increase in the incidence of thyroid cancer [5,7], which coincided with the improvement of iodine nutrition after USI program [4,22]. However, with the popularity of imaging technique and high detection rate of PTMC [6,7,9,14], the high incidence of thyroid cancer was likely due to overdiagnosis and overtreatment [9]. In China, the annual percentage change of thyroid cancer increased from 4.9 (2000–2003) to 20.1 (2003–2011) per 100,000 people [5]. The abrupt increase in the incidence was largely attributable to diagnostic changes, and this tread is likely to grow further in the future [9]. The interpretation of high iodine intake and increased incidence of PTC should be interpreted with caution [10].

Iodine nutrition was not well balanced in population. Although great changes have been made against IDDs [22], iodine deficiency was more commonly found in females than in males (18.60% vs 11.28%); more than adequate and excessive iodine intake accounted for 24.98% and 18.12% of the study population, respectively; and about 40.0% of the population was adequate in iodine intake only, which was similar with our previous reports [15]. Benign thyroid disorders would be incurred even small variations in population iodine intake [23].

Therefore, USI program should be performed in the long run. Importantly, epidemiological investigation and individual examination regarding iodine nutrition are necessary as well. The occurrence and development of thyroid cancer is a long-term process linked with genetic alterations and extrinsic exposure [24]. It's unreasonable to attribute the occurrence of thyroid cancer to a casual urinary iodine determination which can change continuously, especially when the sample size is small. Therefore, identifying a reliable biomarker for measuring iodine nutrition and illumination the mechanisms linked thyroid tumorigenicity with iodine intake seem more urgent in the following studies.

In conclusion, excessive iodine intake was marginally associated with CLNM ($\geq$ 2 metastatic central lymph nodes), larger tumor size and capsular invasion among female PTC patients. However, we did not find that high iodine intake was associated with PTC risk. We thus expected that high iodine intake appears not to be an initiator, but may be a weak promoter for female PTC development.

Declarations of interest

None.

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