Urinary iodine is increased in papillary thyroid carcinoma but is not altered by regional population iodine intake status: a meta-analysis and implications

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Abstract. Excessive iodine intake has been associated with increased risk of thyroid cancer (TC) in many studies, but the results have not been consistent. Since it was common knowledge that urinary iodine (UI) is considered a sensitive marker of current iodine intake, we conducted a meta-analysis to clarify the association between high UI and TC. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, and the Cochrane Collaboration. Between-group meta-analyses were performed to compare UI between TC patients and the healthy/euthyroid subjects in local residents and benign thyroid nodules (BTN) patients. Then, between-group meta-analyses to compare the incidence rate of iodine excess were also conducted. The 22 case-control studies included in the meta-analyses represented 15,476 participants. It is the first time to clarify that UI was increased in PTC patients, but was not altered by regional population iodine intake status. Compared with BTN patients, PTC patients exhibited both higher UIC and higher odds ratio of iodine excess only in adequate iodine intake status subgroup; UIC, not the odds ratio of iodine excess, was higher in patients with PTC than those with BTN in above requirements iodine intake subgroup. A novel insight is offered that high UI in PTC patients was less influenced by regional population iodine intake status. It is indicted that high iodine intake is not a risk factor for PTC and high urinary iodine is just a specific characteristic of the disease.

Key words: Thyroid cancer, Papillary thyroid carcinoma, Excessive iodine intake, Urinary iodine, A meta-analysis

IODINE is an essential element for life and is the heaviest element commonly needed by living organisms [1]. Deficiency of this element leads to a range of disorders commonly referred to as iodine deficiency disorders (IDD). To prevent IDD, universal salt iodization has been recommended as the most cost-effective, safe and sustainable strategy for iodine supplementation [2]. However, balancing iodine intake and the risk of health problems is delicate. Extremely high levels of iodine intake have adverse health consequences, so do low levels of iodine intake. It has been confirmed that iodine excess-induced thyroid dysfunction may lead to benign thyroid disease, such as autoimmune thyroiditis, benign thyroid nodules (BTN), hypothyroidism and hyperthyroidism [3]. But, it remains considerable controversy about the relationship between high iodine intake and thyroid cancers (TC) risk [4-13].

TC is a disease in which cells grow abnormally in the thyroid gland and have the potential to spread to other parts of the body. There are four main types-papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC). PTC is the most common thyroid cancer, representing 75 percent to 85 percent of all thyroid cancer cases. Over the past few decades, TC incidence has rapidly increased, PTC predominated in the histological types of TC after universal salt iodization (USI) [4-6, 14]. It is considered that increasing iodine intake has contributed to the increase in
PTC incidence, whereas it is debatable [4-13].

Much attention has been paid to the study of the association of high iodine intake with TC, especially PTC. Iodine is an essential nutrition of thyroid hormones. Ingested iodine can be bound to serum proteins and mediated by thyroid follicular cells from plasma. The rest of ingested iodine, which remains unlinked and free in bloodstream, is removed from the body through urine. Within 24 h, 100% of iodine is excreted from urine in the form of a prototype. As such, urinary iodine is considered a sensitive marker of current iodine intake and can reflect recent changes in iodine status [15]. Several studies have explored the association of high urinary iodine with TC; however, the results are inconsistent: some studies reported a strong association between high urinary iodine and TC [7, 16-25], whereas other studies reported no association [26-28].

To explore the association of high iodine intake with TC, many studies were also involved in the association of the distribution of iodine nutrition status and TC. The median urinary iodine concentration (UIC) in different cut-off value and interval is used as epidemiologic criteria for assessing iodine nutrition status. Applies to adults, it is proposed by the WHO criteria [15] that the cut-off value of median UIC for insufficient iodine intake is lowered than 100 μg/L; the range of median UIC for adequate iodine intake is between 100 μg/L and 199 μg/L; the interval of median UIC for above requirements iodine intake is between 200 μg/L and 299 μg/L; and the cut-off value of median UIC for excessive iodine intake is above 300 μg/L. The findings among the studies about the association between the incidence rate of thyroid cancer and TC are inconsistent. Some studies provided evidences that the incidence rate of iodine excess in TC was higher than that in the healthy subjects or BTN patients [17-19, 20-23, 29]; while other studies reported no association [9, 27, 28, 30].

Inconsistent findings among the studies might be caused by heterogeneous patient populations, variations in methodology or small sample sizes lacking statistical power. Meta-analysis helps to combine the results from independent studies to increase statistical power and determine whether the variation in effects among studies is merely due to the expected random statistical fluctuation or instead due to sample variations or trait assessment.

Since it is well known that urinary iodine is considered a sensitive marker of current iodine intake, urinary iodine concentration is a surrogate for the level of iodine intake in the studies about the association of iodine intake with TC. To date, no meta-analysis has examined the association between high urinary iodine and TC. Therefore, the aims of this study were to perform between-group meta-analyses to compare urinary iodine concentration and the incidence rate of iodine excess between TC patients, the healthy subjects and BTN patients. We verified firstly, if UIC and the incidence rate of iodine excess in TC indeed were higher than those in the healthy subjects or BTN patients; secondly, if different regional population iodine intake status had divergent impact on UIC and the incidence rate of iodine excess; thirdly, if UIC and the incidence rate of iodine excess were changed by one specific type of TC-papillary thyroid carcinoma; lastly, the further subgroup analyses were conducted to ascertain whether the results of our analyses were the same as those comparing PTC patients with the healthy subjects or BTN patients according to population iodine status in a region. This will help to clarify that urinary iodine concentration is increased in patients with PTC, but is not altered by regional population iodine intake status; ultimately clarifying that high urinary iodine may be a specific characteristic of PTC.

**Methods**

The primary meta-analysis measured the association between high urinary iodine and TC. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA), and the Cochrane Collaboration.

**Search strategy**

We conducted a systematic search in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase (Ovid), Wangfang, CNKI, CQVIP databases and MEDLINE (Ovid). The Boolean search term used for the electronic database search was ((urine iodine) OR (urinary iodine) OR iodine in urine)) and ((thyroid cancer) OR (thyroid tumor) OR (thyroid carcinoma) OR (papillary thyroid carcinoma) OR (papillary thyroid cancer)) in the titles, abstracts and keywords. Studies were not limited to those published in English to avoid language publication bias. No limits on year of publication were set. The last search was performed on Apr 30th 2018. We then manually checked the reference lists of relevant reviews and individual studies to identify additional studies that may have been missed. Study selection eligibility and exclusion criteria were pre-specified.

**Study selection**

Inclusion criteria in the study were the following: (1) types of studies: case-control study; (2) case patients: adult subjects with TC (PTC predominantly) or PTC (diagnosed by the histopathological reports of post-thyroidectomy or ultrasonography) without iodine ther-
apy or radioiodine exposure or restricted iodine diet; control subjects: the healthy/euthyroid subjects in local residents or the patients with BTN or thyroid adenoma (TA) or nodular goiters (NG); and all participants were not pregnant and lactating women; (3) comparison: case patients with TC and control subjects; the patients with TC (PTC predominantly) or PTC were as TC patients; the healthy/normal subjects in local residents were as the normal control; the patients with BTN or thyroid adenoma or NG were as BTN control; and (4) primary outcomes: urinary iodine concentration (UIC), the incidence rate of iodine excess (iodine excess cases in a population of each group, such as case and control groups; the WHO criteria do define cut-off value of 300 μg/L in urinary iodine as “excess”). Urine samples were collected before thyroidectomy or radioactive iodine (RAI). Exclusion criteria were as follows: (1) no data reported; or (2) multiple reports of the same study. The article selection process was carried out independently by two authors. The decision of whether include studies in the meta-analyses was made based on the above criteria, and disagreement was resolved by consensus or discussion with the third author.

Data extraction

The following data were extracted: authors, year of publication, details of the trial, diagnostic status, UIC, the proportion of subjects with iodine excess. The demographic characteristics of study participants were also extracted: sex and age. When the same trials were reported, we retained only the more detailed report for the meta-analytic calculations to avoid duplication of information. Discrepancies in data entry were double-checked by the reviewers with the originally published data and consensus was reached. When the necessary data were not available from the published paper, we contacted the authors of the original articles and requested the necessary information. Where means and standard deviations (SDs) were not reported in the publication (median and range, quartile or inter-quartile range (IQR) were instead presented instead). Median for conversion was used to calculate means and range, quartile or IQR for conversion was used to calculate SD according to Hozo’s recommendation [31].

Quality assessment and publication bias

All case-control studies were assessed with the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [32], which includes the following six domains: 1) the selection of participants; 2) confounding variables; 3) measurement of exposure; 4) the blinding of outcome assessments; 5) incomplete outcome data; and 6) the selective outcome domains.

Studies with negative results are less likely to be published than studies with positive results. To evaluate publication bias, we analyzed a funnel plot graph and Egger’s linear regression to determine its asymmetry when we had more than ten studies. While the Egger’s ρ value of <0.1 indicates publication bias [33]. Asymmetry of funnel plot predicts publication bias.

Statistical analysis

Review-Manager 5 software (Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration) was employed in all analytic processes. Studies were weighted such that the studies with the most precise parameters. Odds ratios (OR) with 95% confidence intervals (95%CI) were shown for dichotomous data and standardized mean differences (SMD) with 95%CI were demonstrated for continuous data. We performed the overall analysis for all meta-analytic processes.

We explored heterogeneity by using the chi-square test, where with a p-value of <0.10 a significant heterogeneity is considered. Inconsistency across studies was then quantified with the F statistic test, where the F value between 50% and 75% indicates a moderate heterogeneity, while the value of >75% indicates a high heterogeneity. Fixed effects were carried out with low levels of clinical or statistical heterogeneity, and random effects were used when the heterogeneity was high.

We analyzed heterogeneity with subgroup meta-analysis. We compared TC group with the healthy control group or BTN group in the different characteristics, including regional population iodine intake status and the types of TC. (1) The median UIC in the healthy residents was defined as regional population iodine intake status. Population iodine intake status was determined by the WHO criteria [15]. Three subgroups were classified: insufficient iodine intake group with the median UIC below 99 μg/L; adequate iodine intake group with the median UIC range between 100 and 199 μg/L; above requirements iodine intake group with the median UIC range from 200 to 299 μg/L. 7 studies were excluded from the subgroup meta-analyses due to missing the data of median UIC. (2) Only one TC type-PTC was analyzed with subgroup comparison. When PTC group was assessed, the healthy control group or BTN group was as the control group.

Results

The literature search was performed up to April 30th 2018. A total of 1,092 records were identified from the initial search. The study inclusion and exclusion processes are showed in the flow diagram (Fig. 1). Finally, 22 unique studies were included in the meta-analysis.
Overall, pooled data of 22 studies comprised 15,476 participants, distributing in 14 cities and 1 province in China, and 1 city in Korea. The sample size of the included studies ranged from 43 to 5,890. 6 studies were published in English and 16 studies in Chinese. 71 trials were included in the included studies, of which there were 12 trials for the between-group meta-analysis of TC versus the normal control and 15 trials for the between-group meta-analysis of TC versus BTN in the incidence rate of iodine excess, 18 trials and 26 trials for the between-group meta-analysis of TC versus the normal control and TC versus BTN in UIC, respectively. Key characteristics are displayed in Table 1. We reviewed the included 22 studies by using RoBANS. The key elements of trial quality for each study are presented in Fig. 2. 22 studies presented the adequate selection of participants, the adequate measurement of exposure, the adequate blinding of outcome assessments, complete outcome data and unselective reporting of outcomes, but only 36.4% of studies completed the confirmation and consideration of confounding variables. Overall risk of bias was moderate. The normal control group was matched by age (SMD = 0.75, 95%CI 0.55 to 1.02, \( p = 0.06 \), 11 between-group comparisons, \( n = 3,360 \)) and sex (OR = 0.18, 95%CI –0.19 to 0.55, \( p = 0.33 \), 15 between-group comparisons, \( n = 11,543 \)) to the TC group (Table 2). Symmetrical funnel plots did not suggest publication bias. And the Egger’s test was non-significant except the between-analyses of TC versus BTN in the incidence rate of iodine excess (Fig. 3).

**UIC and the incidence rate of iodine excess in patients with TC vs. the normal subject**

Based on our primary analyses and summary of findings, TC patients had a higher UIC (SMD = 1.48, 95%CI 0.89 to 2.07, \( p < 0.00001, n = 5,763 \)) (Fig. 4A), and a higher incidence rate of iodine excess (OR = 3.77, 95%CI 1.70 to 8.36, \( p = 0.001, n = 3,797 \)) compared to the normal subjects (Fig. 4B). Because of the high heterogeneity in the pooled studies, the strength of evidence was classified as moderate. Subgroup meta-analyses were conducted to assess UIC and the incidence rate of iodine excess on the data stratified by regional population iodine intake status and TC categories.

According to the data stratified by regional population iodine intake status, we verified that TC patients had a higher UIC than the normal subjects in all the three strata, including above requirements iodine intake subgroup (SMD = 1.69, 95%CI 0.77 to 2.61, \( p = 0.003, n = 7,924 \)) and an adequate iodine intake subgroup (SMD = 1.20, 95%CI 0.26 to 2.15, \( p = 0.01 \), 9 subgroup comparisons, \( n = 2,537 \)), and insufficient iodine intake sub group (SMD = 1.42, 95%CI 1.02 to 1.81, \( p < 0.00001, 1 \) subgroup comparison, \( n = 184 \)).
| No. | First author, publication year | Study design | Sample size (n) | Study period (year/month) | Location (City/Province, Country) | Comparisons | The median UIC (the normal controls in Local residents, μg/L) | The proportion of excessive iodine status cases (Thyroid cancer) | Presentation of results | UIC (Thyroid cancer) |
|-----|--------------------------------|--------------|----------------|--------------------------|--------------------------------|-------------|---------------------------------------------------|-------------------------------------------------|----------------------|-------------------|
| 1   | Kim, 2000                      | Case-control study | 254            | From 1997/06 to 1998/07  | Seoul, Korea                    | 11 cases PTC  | (1) 207 euthyroid subjects; (2) 36 BTN patients     | 211.9±5.2                                      | ND                   | ND                | Higher             | Higher             |
| 2   | Liu L, 2011                    | Case-control study | 942            | From 2009/08 to 2010/02  | Tianjin, China                  | 240 cases TC (including 228 cases PTC, 8 cases MTC, 4 cases ATC) | (1) 400 euthyroid inhabitants from Tianjin; (2) 302 cases BTN | 201.0±5.2                                      | Higher              | NC                | Higher             | NS                |
| 3   | Shen YHL, 2011                 | Case-control study | 208            | From 2010/01 to 2010/07  | Shanghai, China                 | 91 cases PTC   | (1) 40 euthyroid controls; (2) 77 cases BTN         | 187.5±5.2                                      | Higher              | Higher            | Higher             | Higher             |
| 4   | Li Q, 2012                     | Case-control study | 497            | From 2009/12 to 2010/05  | Rizhao, China                   | 51 cases TC    | (1) 162 euthyroid subjects; (2) 203 cases NG; (3) 81 cases TA | 175.4±5.2                                      | NC                  | Lower             | NC                 | Lower             |
| 5   | Li SF, 2013                    | Case-control study | 561            | From 2010/01 to 2012/10  | Huaye, China                    | 145 cases TC (including 141 cases PTC, 3 cases MTC, 1 case ATC) | (1) 200 euthyroid subjects; (2) 216 cases BTN (including NG, and TA) | 244.0±5.2                                      | Higher              | Higher            | Higher             | Higher             |
| 6   | Wei LN, 2013                   | Case-control study | 5,845          | From 1991/01 to 2006/12  | Guangxi, China                  | 493 cases PTC  | (1) 1,000 euthyroid regional inhabitants; (2) 3,916 cases NG; (3) 599 cases TA | ND                                               | ND                  | ND                | Higher             | NC                |
| 7   | Wang F, 2014                   | Case-control study | 460            | From 2000/06 to 2011/06  | Qingdao, China                  | 103 cases PTC  | (1) 306 inhabitants who had normal thyroid functions and had no thyroid nodules on thyroid ultrasonography; (2) 51 BTN patients | 174.3±5.2                                      | Higher              | NC                | Higher             | Higher             |
| 8   | Hu CX, 2015                    | Case-control study | 359            | From 2011/08 to 2012/03  | Tianjin, China                  | 159 cases PTC  | 200 euthyroid inhabitants                            | 196.0±5.2                                      | Higher              | ND                | Higher             | ND                |
| 9   | Huang TJ, 2015                 | Case-control study | 375            | From 2013/02 to 2014/12  | Shenzhen, China                 | 123 patients with TC | (1) 102 normal subjects selected randomly from four different region of Shenzhen; (2) 150 patients with NG | 124.5±5.4                                      | NC                  | NC                | NS                 | NS                |
| 10  | Zhong H, 2015                  | Case-control study | 400            | From 2012/02 to 2012/12  | Urumqi, China                   | 106 cases TC (including 91 cases PTC, 3 cases FCT, 5 cases MTC, 1 case ATC) | 300 local residents with normal thyroid functions and thyroid gland on ultrasonography | 161.4±5.2                                      | Higher              | ND                | Higher             | ND                |
| 11  | Zhang Y, 2015                  | Case-control study | 100            | From 2011/01 to 2012/08  | Liaocheng, China                | 44 cases PTC   | 56 cases benign thyroid disease (including 45 cases NG, 11 cases follicular adenoma) | ND±4                                            | ND                  | ND                | ND                 | Higher             |
| 12  | Liu WH, 2016                   | Case-control study | 423            | From 2012/06 to 2014/01  | Ningbo, China                   | 31 cases TC (including 26 cases PTC, 4 cases FCT, 1 case MTC) | (1) 325 normal individuals from Beilun region; (2) 67 cases benign thyroid tumor (including 51 cases NG, 16 cases TA) | 135.2±5.2                                      | NS                  | NS                | NS                 | NS                |
| No. | First author, Publication year | Study design | Sample size (n) | Study period (year/month) | Location (City/Province, Country) | Comparisons | The median UIIC (the normal controls in local residents, μg/L) | The proportion of excessive iodine status cases (Thyroid cancer) | Presentation of results |
|-----|-------------------------------|--------------|----------------|--------------------------|----------------------------------|-------------|-------------------------------------------------------------|-------------------------------------------------------------|------------------------|
| 13  | Zhang RX, 2016               | Case-control study | 615            | From 2014/03 to 2014/12 | Urumqi, China                   | 156 cases TC (including 151 cases FTC, 2 cases FTC, 1 case MTC, 2 cases ATC) (1) 301 subjects with normal thyroid gland on ultrasonography; (2) 158 cases BTN (including 147 cases NG, 5 cases TA, 6 cases thyroid nodules with adenoma) | 257.6±2.5 | NC | NC | Higher | Higher |
| 14  | Chen LX, 2017               | Case-control study | 120            | From 2016/01 to 2016/05 | Qingdao, China                  | 60 cases TC (including 47 cases FTC, 4 cases FTC, 3 cases MTC, 6 cases ATC) | ND±2.5 | ND | ND | ND | ND |
| 15  | Kim, 2017                    | Case-control study | 1,770          | From 2010/11 to 2013/05 | Seoul, Korea                    | 206 cases TC (including 201 cases FTC, 5 cases FTC) | ND±3.5 | ND | ND | NS | ND |
| 16  | Lee, 2017                    | Case-control study | 300            | From 2015/03 to 2015/12 | Seoul, Korea                    | 210 cases FTC | 964 cases BTN | ND±4.5 | ND | ND | Higher | ND |
| 17  | Li B, 2017                   | Case-control study | 183            | From 2014/04 to 2016/08 | Jinting, China                  | 110 cases FTC | 110 healthy individuals from the Ganghwa community cohort | ND±3.3 | ND | ND | Higher | ND |
| 18  | Li HL, 2017                  | Case-control study | 171            | From 2016/03 to 2016/08 | Tangshan, China                | 14 cases TC | (1) 130 healthy adults; (2) 27 cases BTN | ND±3.7 | ND | ND | Higher | ND |
| 19  | Ni J, 2017                   | Case-control study | 234            | From 2012/08 to 2016/05 | Wuhan, China                    | 78 cases FTC | 156 cases BTN | ND±3.2 | ND | ND | ND | Higher |
| 20  | Zhao HQ, 2017                | Case-control study | 2,041          | From 2013/11 to 2015/03 | Wuhan, China, Deficiency        | 1,120 cases FTC | 921 cases BTN | ND±3.7 | NC | NC | NC | NS |
| 21  | Zheng WL, 2017               | Case-control study | 43             | From 2013/10 to 2014/04 | Shiyuan, China                  | 13 cases TC (including 12 cases FTC) | 13 cases FTC | ND±3.7 | ND | ND | ND | NC |
| 22  | Zhou ZZ, 2017                | Case-control study | 178            | From 2013/02 to 2013/09 | Jinan, China                    | 60 patients with FTC | (1) 65 healthy participants who had normal thyroid functions and gland on ultrasonography; (2) 53 patients with NG | 230.2±3.5 | Higher | NS | Higher | NS |

TC, thyroid cancer; FTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; ATC, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma; BTN, benign thyroid nodules; NG, nodular goiter; TA, thyroid adenoma; UIIC, urinary iodine concentration; NS, no significant difference; NC, no comparison; ND, no data.

The method of urine samples collection: 1. single fasting urine specimens were collected in morning; 2. morning fasting urine specimens were collected on two consecutive days; and they were mixed before measurement; 3. single urine specimens were collected in any time; 4. single fasting urine specimens were collected in midnight.

The method of urine iodine measurement: 1. an isotope selective electrode; 2. ammonium persulfate digestion before Sandell-Kolthoff reaction; 3. anion-exchange chromatography with pulsed amperometric detection; 4. 3,3',5,5'-tetramethylbenzidine oxidation by peracetic acid/H2O2; 5. inductively coupled plasma mass spectrometry (ICP-MS).
Fig. 2  Risk of bias graph

Table 2  Baseline characteristics of included studies

| Between-group | No. of pairwise | No. of subjects | Meta-analysis | Heterogeneity |
|---------------|-----------------|-----------------|---------------|---------------|
|               | case | control | analysis | SMD (or OR) | 95% CI | p | Z value | Tau2 | I2 | Chi2 | p |
| Age           | 9    | 1,318   | 1,569   | Random      | 0.18   | −0.19 | 0.55 | 0.33 | 0.97 | 0.30 | 95 | 167.00 | <0.0001 |
| Sex (Male)    | 15   | 8,154   | 3,389   | Random      | 0.75   | 0.55 | 1.02 | 0.06 | 1.86 | 0.29 | 85 | 92.02 | <0.0001 |

Fig. 3  Funnel plot: (A) 18 trials for the between-group meta-analysis of UIC in TC patients versus the normal control; (B) 12 trials for the between-group meta-analysis of the incidence rate of iodine excess in TC patients versus the normal control; (C) 26 trials for the between-group meta-analysis of UIC in TC patients versus BTN patients; (D) 15 trials for the between-analysis of the incidence rate of iodine excess in TC patients versus BTN patients.
When analyzing the incidence rate of iodine excess, the incidence rate of iodine excess was significantly higher in TC patients than the normal subjects in the requirements iodine intake subgroup, \( \text{OR} = 10.98 \), 95%CI 1.94 to 62.08, \( p = 0.007 \), 4 subgroup comparisons, \( n = 1,560 \) and moderately increased in the adequate iodine intake subgroup, \( \text{OR} = 2.20 \), 95%CI 0.97 to 4.98, \( p = 0.06 \), 8 subgroup comparisons, \( n = 504 \)

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### A  
**Supplemental Fig. S1**. When analyzing the incidence rate of iodine excess, the incidence rate of iodine excess was significantly higher in TC patients than the normal subjects in the requirements iodine intake subgroup, \( \text{OR} = 10.98 \), 95%CI 1.94 to 62.08, \( p = 0.007 \), 4 subgroup comparisons, \( n = 1,560 \) and moderately increased in the adequate iodine intake subgroup, \( \text{OR} = 2.20 \), 95%CI 0.97 to 4.98, \( p = 0.06 \), 8 subgroup comparisons, \( n = 504 \)

### B
**Supplemental Fig. S1**. When analyzing the incidence rate of iodine excess, the incidence rate of iodine excess was significantly higher in TC patients than the normal subjects in the requirements iodine intake subgroup, \( \text{OR} = 10.98 \), 95%CI 1.94 to 62.08, \( p = 0.007 \), 4 subgroup comparisons, \( n = 1,560 \) and moderately increased in the adequate iodine intake subgroup, \( \text{OR} = 2.20 \), 95%CI 0.97 to 4.98, \( p = 0.06 \), 8 subgroup comparisons, \( n = 504 \)
With stratification by TC categories, the significant results in TC were confirmed in PTC. The extent of the UIC increase in either TC or PTC patients was higher than that of BTN patients in other two strata: adequate iodine intake subgroup (SMD = 0.10, 95% CI –0.02 to 0.23, p = 0.10, 7 subgroup comparisons, n = 1,120) and insufficient iodine intake subgroup (SMD = 1.74, 95% CI –0.35 to 3.84, p = 0.10, 2 subgroup comparisons, n = 788), or in the incidence rate of iodine excess in stratum of adequate iodine intake (OR = 1.34, 95% CI 0.95 to 1.90, p = 0.09, 7 subgroup comparisons, n = 1,120) (Supplemental Figs. S5 and S6).

UIC and the incidence rate of iodine excess in patients with PTC vs. the normal subjects

Based on the data stratified by TC categories, PTC patients had significantly increased UIC (SMD = 0.95, 95% CI 0.64 to 1.26, p < 0.00001, 9 subgroup comparisons, n = 2,862) and incidence rate of iodine excess (OR = 6.87, 95% CI 5.03 to 9.36, p < 0.00001, 4 subgroup comparisons, n = 1,017), compared to the normal control (Fig. 4C and 4D). With stratification by TC categories, the low heterogeneity across the studies of the incidence rate of iodine excess was observed, while the heterogeneity across UIC studies was high.

With the data further stratified by regional population iodine intake status, similar to what observed in TC patients, we verified that PTC patients had a higher UIC than the normal control in all the three strata, including above requirements iodine intake subgroup (SMD = 1.15, 95% CI 0.49 to 1.82, p = 0.0007, 4 subgroup comparisons, n = 1,482), adequate iodine intake subgroup (SMD = 0.73, 95% CI 0.39 to 1.07, p < 0.00001, 4 subgroup comparisons, n = 1,199) and insufficient iodine intake subgroup (SMD = 1.42, 95% CI 1.02 to 1.81, p < 0.00001, 1 subgroup comparison, n = 184) (Supplemental Fig. S3), and it has been seen in two strata that PTC patients had a significantly increased incidence rate of iodine excess, which were above requirements iodine intake sub-group (OR = 7.54, 95% CI 2.77 to 20.50, p < 0.00001, 1 subgroup comparison, n = 118) and adequate iodine intake subgroup (OR = 6.79, 95% CI 4.90 to 9.41, p < 0.00001, 3 sub-group comparisons, n = 899). But it was also lack of data in insufficient iodine intake subgroup (Supplemental Fig. S4).

UIC and the incidence rate of iodine excess in TC patients vs. BTN patients

When compared to BTN patients, TC patients had a higher UIC (SMD = 0.55, 95% CI 0.30 to 0.79, p < 0.00001, n = 11,317), but there was no difference in the incidence rate of iodine excess between TC patients and BTN patients (OR = 1.09, 95% CI 0.95 to 1.25, p = 0.22, n = 5,954), (Fig. 5A and 5B).

With further stratification by regional population iodine intake status, it was only seen in above requirements iodine intake stratum that TC patients had higher UIC (SMD = 0.77, 95% CI 0.39 to 1.15, p < 0.00001, 9 sub-group comparisons, n = 5,764) and incidence rate of iodine excess (OR = 1.56, 95% CI 1.17 to 2.09, p = 0.003, 4 sub-group comparisons, n = 1,330) than BTN patients, while there was no significant difference between TC patients and BTN patients either in UIC in other two strata: adequate iodine intake subgroup (SMD = 0.10, 95% CI –0.02 to 0.23, p = 0.10, 7 subgroup comparisons, n = 1,120) and insufficient iodine intake subgroup (SMD = 1.74, 95% CI –0.35 to 3.84, p = 0.10, 2 subgroup comparisons, n = 788), or in the incidence rate of iodine excess between TC patients and BTN patients (OR = 1.11, 95% CI 0.92 to 1.33, p = 0.27, n = 2,769) (Fig. 6A and 6B), which was consistent with the result from the comparison between TC patients and BTN patients.

With further stratification by regional population iodine intake status, it was found that PTC patients had a significantly increased UIC only in two strata (Supplementary Figs. S7 and S8): above requirements iodine intake subgroup (SMD = 0.84, 95% CI 0.52 to 1.17, p < 0.00001, 6 subgroup comparisons, n = 4,547), and adequate iodine intake subgroup (SMD = 0.43, 95% CI 0.20 to 0.66, p = 0.0002, 2 subgroup comparisons, n = 322), but not in the stratum of insufficient iodine intake (SMD = 1.74, 95% CI –0.35 to 3.84, p = 0.10, 2 subgroup comparisons, n = 788). Likewise, PTC patients had a higher incidence rate of iodine excess than BTN patients only in adequate iodine intake subgroup (OR = 1.73, 95% CI 1.09 to 2.74, p = 0.02, 2 subgroup comparisons, n = 322). The heterogeneity after stratification was low.

Discussion

Overall, the pooled data of 22 studies demonstrated that UIC and the incidence rate of iodine excess in TC patients were higher than those in the normal subjects in the whole population. The results verified that there was association of TC and high urinary iodine. When performing sub-group analysis according to regional population iodine intake status, UIC and the incidence rate of iodine excess were increased in each regional population iodine intake status subgroup and did not be changed by regional population iodine intake status. After stratification by types of TC, the significant results in TC were verified in PTC. The extent of the UIC increase in either TC or PTC patients was higher than that of BTN patients in unstratified population, while there was no significant
difference in the incidence rate of iodine excess between either PTC patients or TC patients and BTN patients. With the further subgroup analyses, UIC in PTC patients was higher than that in BTN patients only in above requirements iodine intake and adequate iodine intake subgroups, but not in insufficient iodine intake subgroup, but there was no difference in the incidence rate of iodine excess even in above requirements iodine intake subgroup.

High urinary iodine may be a specific characteristic of PTC

The primary meta-analysis results demonstrated that UIC and the incidence rate of iodine excess in TC patients versus BTN patients

![Fig. 5](A) A between-group meta-analysis of UIC in TC patients versus BTN patients; (B) A between-group meta-analysis of the incidence rate of iodine excess in TC patients versus BTN patients.
iodine excess of PTC patients (7.54 and 6.79) in above
requirements iodine intake subgroup and adequate iodine
intake subgroup. By contrast, in the analysis of TC
patients stratified only by regional iodine intake status
but not by TC categories, the odds ratios of iodine excess
of TC patients were 10.98 and 2.22, respectively, in these
two iodine intake subgroups. The present results indicate
that the level of urinary iodine is increased during PTC
and high urinary iodine in PTC patients is less influenced
by regional population iodine intake status.

The present results that the level of urinary iodine was
increased during PTC were consisted with the reports
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PTC and high urinary iodine in PTC patients is less influenced
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PTC and iodine intake was a risk factor for the disease
[7, 16, 22, 24-26]. In fact, there were two issues: one was
the ambiguity of urinary iodine and iodine intake, and
the other was the confusion of cause-effect relationship.
In a word, it is unclear whether high urinary iodine is a
specific characteristic of the disease or increased iodine
intake is a risk factor for the disease. To clarify the issue,
it is necessary to distinguish urinary iodine from iodine
intake; even it is commonly agreed that urinary iodine is
considered as a sensitive marker of current iodine intake,
and the measurement of urinary iodine is useful in deter-
mine the iodine status of populations [15]. Our results
not only found that increased urinary iodine in PTC was
unrelated to regional population iodine intake status.

A novel insight is offered that high iodine intake is not a
risk factor for PTC and high urinary iodine is just a specific
characteristic of the disease. There are several evidences
to support this issue.

Firstly, iodine retention was found in urinary iodine
even with a large single dose iodine administration, e.g.
oral administration or injection of iodinated contrast
(abut 30 g of iodine). Several published studies
addressed that urinary iodine levels were transiently
increased after receiving iodinated contrast, urinary
iodine levels and were soon reverted back to baseline
either in euthyroid subjects or in TC subjects regardless
of thyroidectomy [38, 39], and there was no significant
difference between euthyroid subjects and TC subjects
regardless of thyroidectomy [40].

Secondly, long-term high iodine intake could not induce onset of PTC in animal studies. After a diet containing excess iodine (≈120
mg of iodine per day) for 9 months in rats, there was a
40% increase in thyroid weight, and histological changes
including enlarged follicles with increased colloid lined
by flattened epithelia, but no thyroid tumors were found
[41]. Thirdly, there was no randomized controlled trial
to prove that long-term high iodine intake induced PTC. To
date, it has been observed in several retrospective studies
that there were the highest incidence rates of TC in
Iceland and Hawaii, both of which were known of
long-standing high iodine intake, however exposure to
volcanic activity (natural radiation) has been suggested
as an explanation for the high incidence in these two
areas [42, 43]. Moreover, it was noteworthy that long-

Fig. 6 (A) A subgroup meta-analysis of UIC in PTC patients versus BTN patients; (B) A subgroup meta-analysis of the incidence rate of
iodine excess in PTC patients versus BTN patients

![Fig. 6](A) A subgroup meta-analysis of UIC in PTC patients versus BTN patients; (B) A subgroup meta-analysis of the incidence rate of
iodine excess in PTC patients versus BTN patients
term iodine excess was insufficient to stimulate thyroid carcinogenesis, but promoted thyroid carcinogenesis induced by radiation [44]. Although it was found in the retrospective studies that the prevalence and incidence of TC in iodine-excessive areas were much higher than those in the iodine-deficient or iodine-sufficient areas in China [45, 46], other environmental factors had not been excluded. Other epidemiological studies reported that increased levels of iodine intake caused the increased TC incidence and the proportion of PTC after universal salt iodization (USI). Improved TC diagnosis may be one of the causes of the increased TC incidence [10], and the decreased FTC and UTC incidence may increase significantly the proportion of PTC [4, 5, 11]. Therefore, we support that high iodine intake is not a risk factor of PTC either with a large single dose iodine administration or long-term high iodine intake. Correspondingly, the consistent association of high urinary iodine with PTC in any regional population iodine intake status could be an evidence to prove that high urinary iodine may be a specific characteristic of PTC.

Noteworthy, the extent of the UIC increase in PTC patients was higher than that in BTN patients. Generally, it has been demonstrated a significant association of high urinary iodine with BTN [8, 17-19, 27]. In fact, BTN is classified as adenomas, colloid nodules, congenital abnormalities, cysts, infectious nodules, lymphocytic or granulomatous nodules, or hyperplasia. NG the most common type of BTN, was associated with high urinary iodine [9, 21]. Hence, it was considered that no significant difference in UIC was observed between TC patients and BTN patients, especially between patients with PTC and those with NG [8, 21, 35]. The present results rectify the previous view and indicate that urinary iodine level in PTC patients is higher than that in BTN patients. In addition, when stratified by iodine intake status, different from comparison with the normal subjects, the results showed that compared with BTN patients, PTC patients exhibited both higher UIC and higher odds ratio of iodine excess only in adequate iodine intake status subgroup; UIC, not the odds ratio of iodine excess, was higher in patients with PTC than those with BTN in above requirements iodine intake subgroup; and no significant difference in UIC and lack of data in the odds ratio of iodine excess were found in insufficient iodine intake subgroup. It has been well known that the relationship between the thyroid iodine intake level of a population and the occurrence of benign thyroid diseases is U-shaped with an increase in risk from both low and high iodine intake levels [47]. Several types of BTN, e.g. NG, are association with either high iodine intake or chronic iodine deficiency [8, 21, 35]. It was presumed if PTC patients, like BTN patients was increased urinary iodine by iodine intake, it should be that in adequate iodine intake subgroup there is no or little significant difference between PTC patients and either the normal subjects or BTN patients in UIC and the incidence rate of iodine excess. The opposite results that urinary iodine was higher in PTC patients than BTN patients in above requirements iodine intake and adequate iodine intake status, especially in adequate iodine intake status is the further evidence to prove that different from the change by iodine intake in BTN, high urinary iodine may be a specific characteristic of PTC regardless of iodine intake.

Our study has some inherent limitations due to its design and statistical methods employed. Firstly, we evaluated the quality of the studies using the RoBANS and verified that most of the studies included were at least of moderate quality. We believe that by using this approach, the results and conclusions could provide reliable information. Secondly, the between-group meta-analyses of TC versus the normal control and TC versus BTN exhibited the high heterogeneity. Through a series of subgroup analyses, we were able to rule out the possibility that the results were biased due to a unique outlier. However, the heterogeneity was still high in UIC but not in the incidence rate of iodine excess, because the individual urinary iodine concentrations varied greatly and urinary iodine values did not tend to be distributed normally. Thirdly, the median UIC in the healthy adults was defined as regional population iodine intake status, but it would be better to refer to the median UIC in schoolchildren at 8 to 10 years old. Fourth, publication bias was detected from the Egger’s test, which, however, requires the assumption of no or little heterogeneity. It may not be applicable due to the high heterogeneity in the between-group meta-analysis and non-normally-distributed urinary iodine values [48]. Lastly, small number of studies may cause lacking statistical power. For example, in subgroup analysis according to the different iodine intake region, only one study was included in the insufficient group.

**Conclusion**

Our meta-analyses of 22 cross-sectional studies comprising 15,476 participants, distributing in 14 cities and 1 province in China and 1 city in Korea demonstrated that urinary iodine was increased in PTC patients, which was not altered by regional population iodine intake status. The extent of the UIC increase was higher in PTC patients than that in BTN patients, especially in adequate iodine intake status. However, there was no significant difference in the incidence rate of iodine excess between PTC patients and BTN patients. A novel insight is offered that high UI in PTC patients was less influenced
by regional population iodine intake status. It is indicated that high iodine intake is not a risk factor for PTC and high urinary iodine is just a specific characteristic of the disease.

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Disclosure

None of the authors have any potential conflicts of interest associated with the research.

Supplemental Fig. S1 A subgroup meta-analysis of UIC in TC patients versus the normal subjects according to the regional population iodine intake status.

Supplemental Fig. S2 A subgroup meta-analysis of the incidence rate of iodine excess in TC patients versus the normal subjects according to the regional population iodine intake status.
**Supplemental Fig. S3** A further subgroup meta-analysis of UIC in PTC patients versus the normal subjects according to the regional population iodine intake status.

**Supplemental Fig. S4** A further subgroup meta-analysis of the incidence rate of iodine excess in PTC patients versus the normal subjects according to the regional population iodine intake status.
A subgroup meta-analysis of UIC in TC patients versus BTN patients according to the regional population iodine intake status

Supplemental Fig. S5

Supplemental Fig. S6

A subgroup meta-analysis of the incidence rate of iodine excess in TC patients versus BTN patients according to the regional population iodine intake status
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Supplemental Fig. S7 A further subgroup meta-analysis of UIC in PTC patients versus BTN patients according to the regional population iodine intake status

Supplemental Fig. S8 A further subgroup meta-analysis of the incidence rate of iodine excess in PTC patients versus BTN patients according to the regional population iodine intake status

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