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Associations between essential microelements exposure and the aggressive clinicopathologic characteristics of papillary thyroid cancer

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Abstract Aim of this study was to evaluate the association between multiple essential microelements exposure and the aggressive clinicopathologic characteristics of papillary thyroid carcinoma (PTC). The concentrations of 10 essential microelements in urine [cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), strontium (Sr), zinc (Zn), and iodine (I)] were measured in 608 patients newly diagnosed with PTC, including 154 males and 454 females. Chi square test and Wilcoxon rank sum test were used to compare general characteristics among males and females. Multivariate logistic regression was used to evaluate the associations between essential microelements and PTC clinicopathologic characteristics in single- and multi-microelement models. In this study, we only observed that the frequency of lymph node metastasis in males was higher than in females, and males had higher levels of zinc than females, but males had lower levels of iodine than females. It was found that high levels of Fe were associated with decreased risk of PTC tumor size > 1 cm, capsular invasion, and advanced T stage (T3/4a/4b). High levels of Co and Mo were associated with decreased risk of capsular invasion and lymph node metastasis, respectively. However, high levels of Mn and Sr were associated with increased risk of capsular invasion and multifocality respectively, and both were associated with increased risk of advanced T stage (T3/4a/4b). These findings indicated that certain essential microelements might have potential effects on PTC progression and aggressiveness. Further studies are required to confirm these findings.

Keywords Essential microelements · Papillary thyroid cancer · Aggressiveness · Clinicopathologic characteristics · Risk factor

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Introduction

Thyroid cancer is the most common endocrine malignancy and the dramatic increases in incidence worldwide appear to be well known over the past few years (La Vecchia et al. 2015; Siegel et al. 2020). According to histopathological classification, this increase was mainly caused by papillary thyroid cancer (PTC), taking up 80% of all types of thyroid cancers (Lim et al. 2017). Although improved medical accessibility and advanced ultrasonography may have played a certain role in this increase, accumulating evidence proved there is a substantial increase in large tumor sizes and advanced-stage PTC simultaneously (Park et al. 2016; Sanabria et al. 2018). This means that other unclear factors may be implicated in this increase.

Currently, the prognosis of PTC is considered to be inert so that more conservative approach towards treatment and management of PTC is gradually mentioned. However, with more PTC being detected, there are a certain proportion of PTC patients with persistent or recurrent disease, poor prognosis and even death (Tam et al. 2018). Because there is a 10%–30% risk of PTC recurrence depends on its initial stage (Niemann et al. 2017). For those patients with poor prognosis of thyroid cancer, their average life expectancy is between 3 and 5 years (Fugazzola et al. 2019). It is necessary to recognize the factors related to active treatment and prognostic management of patients at the earliest stage of PTC. Identification of these factors will help to facilitate the clinical treatment, including restricting surgical excision, reducing tumor aggressiveness, and improving patients' survival. Previous studies have suggested that age, male gender, large diameter tumor, extrathyroidal extension, and lymph node metastasis were associated with high recurrence and death risk of thyroid cancer (Lango et al. 2013; Niemann et al. 2017). Therefore, with the exception of unchangeable factors such as age and gender, it is urgent to investigate relevant controllable factors for managing the aggressiveness and prognosis of thyroid cancer.

Some risk factor for thyroid cancer have been presumed but require further investigate, such as medical radiation exposure, obesity, insulin resistance, female reproductive factors, nutrient and environmental pollutants (Hu et al. 2020; Liu et al. 2021; Mannathazhathu et al. 2019). Essential microelements like iodine, zinc, iron, and selenium are directly involved in the synthesis of thyroid hormone and in maintaining normal thyroid function (O'Kane et al. 2018). However, several studies also reported the association of iodine, zinc, and selenium with the risk of thyroid cancer, but the findings were controversial (Chung et al. 2016; Jonklaas et al. 2013; Zhang et al. 2018). It is worth noting whether the abnormal levels of these microelements can affect the occurrence and development of thyroid cancer remains unclear. For example, Zhao et al. (Zhao et al. 2018) found high urinary iodine levels were positively associated with aggressive clinicopathologic characteristics of PTC, including multifocality and larger tumor size. Jonklaas and colleagues reported a potential association between decreased serum selenium levels and the higher thyroid cancer stage (Jonklaas et al. 2013). In addition, Baltaci et al. examined the changes in the serum levels of trace elements before and after the operation in thyroid cancer patients and indicated that zinc and selenium might be involved in the pathogenesis of thyroid cancer (Baltaci et al., 2017). Given the potential role of trace elements in the pathogenesis, more attention is paid to the assessment of trace elements (Rahman et al. 2019). Even essential microelements also have an adverse effect after excessive uptake or exposure (Stojsavljevic et al. 2019). Therefore, it is necessary to further investigate the association of PTC aggressiveness with co-exposure to multiple essential microelements.

In current study, we aimed to determine the association between the aggressive clinicopathologic characteristics of PTC and preoperative concentrations of 10 essential microelements in urine, since urine samples are a convenient non-invasive biomonitoring media for body's metabolites and are considered a reliable indicator of exposure in epidemiological studies with a large sample size (Malandrino et al. 2016). A multi-microelement model was used to analyze the simultaneous effects of co-exposure to multiple essential microelements on PTC aggressiveness, which can represent the real scenarios of multiple essential microelements exposure in human body.

Materials and methods

Study population

We recruited those patients who were planning to undergo a thyroidectomy and actively cooperating with this study at Anhui Provincial Cancer Hospital, First Affiliated Hospital of Anhui Medical University, and Second Affiliated Hospital of Anhui Medical University from May 2017 to March 2019. Once the study participants were enrolled, a fasting urine samples were collected in the next morning (between 6:00 a.m. and 8:00 a.m.) to avoid the impacts of potential clinical factors on study indicators. Overall, all specimens were collected from one to two weeks prior to thyroid surgery.

Among all participants, only those newly diagnosed with PTC, based on definite histopathological diagnosis, were included in the final analysis. In addition, the subjects with a combination of history of severe diseases in liver, kidney and gastrointestinal system or other carcinomas, and the autoimmune diseases, including Graves' disease and Hashimoto's thyroiditis, were excluded from current study. Finally, 608 patients with first incident PTC were included in current analyses, of whom 154 were male and 454 were female. All participants were from Chinese Han population. This study was approved by the Ethics Committee of Anhui Medical University. All participants gave their informed consent.

Data collection

Based on previous study reports, we investigated potential covariates that might affect the onset of PTC. These covariates about demographic characteristics, lifestyle and behavioral habits (including smoking status, tea drinking, physical activity), personal disease history (including thyroid gland, gastrointestinal tract, and other malignancies), and medical radiation exposure such as X-ray and CT scans were collected via face-to-face interview upon enrollment. The height and weight of participants was measured by a trained nurse and who was asked to report the weight of each participant to one decimal place.

The information on clinicopathologic diagnosis and characteristics of all participants was collected by carefully retrospective chart review, including histologic type, primary tumor size, lymph node metastasis, and so on. According to postoperative biopsy outcomes, the largest diameter of the cancer was considered as tumor size. Multifocality was defined as two or more tumor foci in thyroid gland. All PTC patients were classified according to the tumor/node/metastasis (TNM) staging criteria recommended by American Joint Committee on cancer (AJCC) staging system (8th edition) (Amin et al. 2017). The tumor size was classified into ≤ 1 cm versus (*vs.*) > 1 cm (*i.e.*, microcarcinoma *vs.* non-microcarcinoma). The capsular invasion was classified into negative *vs.* positive. The multifocality was classified into negative *vs.* positive. The T stage (tumor) was classified into T1/2 *vs.* T3/4a/4b. The N stage (lymph node) was classified into N0 *vs.* N1.

Urine sample collection and analysis

First morning urine specimens were collected between 6:00 a.m. and 8:00 a.m. from each participant by using a clean polyethylene centrifuge tube (approximately 50 mL). All urine specimens were stored at − 80 °C within 2 h of collection until analysis.

In this study, we measured the concentrations of 10 essential microelements in urine [*i.e.*, cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), strontium (Sr), zinc (Zn), and iodine (I)]. The levels of 9 essential microelements (*i.e.*, Co, Cr, Cu, Fe, Mn, Mo, Se, Sr, and Zn) were measured using an inductively coupled plasma optical emission spectrometry (ICP-OES; PerkinElmer Optima 7000DV, USA) at the Central Laboratory of Public Health and Preventive Medicine, Anhui Medical University. The measurements of 9 microelements were based on accordingly 9 sets of calibration standards in nitric acid (HNO_3) with internal standards. For the chemical analysis of the urine samples, 5 mL of urine from each participant was diluted with 5 mL of 1% (*v*/*v*) HNO_3 (guarantee reagent, GR). Following mixing, the resulting solution was microwave-digested at 90 °C for 1 h. After digestion, the resulting solution was centrifuged at 1724 g for 8 min and the liquid supernatant was extracted for further analysis. As the part of test, one standard reference material was used for every 10 test samples analyzed to ensure the instrument performance. Meanwhile, spike recovery test for nine metals showed the recovery rate ranged from 92 to 105%. For those specimens with concentration below the limit of

detection (LOD), their values were replaced with the half of LOD (Wu et al. 2018).

The urinary iodine levels were determined at Micro Iodine Analysis Laboratory, Anhui Provincial Center for Disease Control and Prevention with commercial kit (Wuhan Zhongsheng Biochemical Technique Co., Ltd, Wuhan, China), using a $As^{3+} - Ce^{4+}$ catalytic spectrophotometry. Iodine catalyzes the arsenic-cerium oxidationreduction reaction, where yellow Ce^{4+} is reduced to colorless Ce^{3+}. Then, iodine concentration in the reaction system is determined based on the residual Ce^{4+} absorbance value (Wang et al. 2014). Urinary creatinine levels were measured using alkaline picric acid spectrophotometric for standardizing urinary iodine and other microelements. The detection kit was using a commercial kit (Jiancheng 135 Bioengineering Ltd. Nanjing, China).

Statistical analysis

The study population characteristics were summarized and compared by using descriptive statistics, such as Mean ± SD (standard deviation), Median (IQR, interquartile range), and parametric or nonparametric test. Spearman rank-order correlation coefficient was used to estimate the correlations between 10 microelements.

According to the results of Kolmogorov–Smirnov test, natural logarithm transformation was carried out on all microelements. Odds ratio (OR) and 95% confidence interval (CI) calculated by logistic regression model were used to estimated the associations of urinary microelements with PTC clinicopathologic characteristics. Tests for trend were performed by assigning the quartiles of elements as an ordinal score variable. In order to assess the simultaneously impacts of co-exposure to multiple microelements on the PTC clinicopathologic characteristics, a multi-microelement model was performed by including all urinary microelements and potential covariates in logistic regression. Backward elimination method with alpha at 0.1 set for variable selection was used in this model (Wu et al. 2018). For those covariates that were not initially retained in final model, we would reconsider them based on "change-in-estimate" method. If one covariate can lead to > 10% changes of the effect estimates individually, then it is retained in the final model (Greenland 1989). All analyses were conducted using R software (version 3.3.1). All p values were tested in two-sided, $p < 0.05$ was considered statistically significant.

Results

General characteristics of study population

The selected characteristics of study population were presented in Table 1. Among all participants, women account for the vast majority (74.7%). The means of age and BMI were 43.6 ± 12.5 years and 24.0 ± 3.6 kg/m^2, respectively. The number of non-smokers was 520 (85.5%) and alcohol drinker was 119 (19.6%). The patients had a history of X-ray exposure that accounted for 63.8% (n = 388) of all subjects, and

Table 1 Description of general characteristics for study population

Variables	PTC (n = 608)
Age, years, mean ± SD	43.6 ± 12.5
Gender	
Male, n (%)	154 (25.3)
Female, n (%)	454 (74.7)
Body mass index, kg/m^2, mean ± SD	24.0 ± 3.6
Average annual household income, RMB, n (%)	
≤ 30,000	62 (10.2)
30,001–60,000	237 (39.0)
≥ 60,001	309 (50.8)
Sleeping time, hours/day, n (%)	
≤ 4	7 (1.2)
4.1–6	86 (14.1)
6.1–8	355 (58.4)
≥ 8.1	160 (26.3)
Smoking status, n (%)	
Never	520 (85.5)
Ever	88 (14.5)
Current drinking, n (%)	119 (19.6)
Physical activity, n (%)	
Inactive	366 (60.2)
Active	242 (39.8)
History of X-ray, n (%)	388 (63.8)
History of CT scans, n (%)	280 (46.1)

PTC papillary thyroid cancer, *SD* standard deviation

those with a history of CT scans exposure accounted for 46.1% (n = 280) of all subjects,

Clinicopathologic characteristics of PTC

According to the AJCC staging system (8th edition), all PTC patients were divided into those < 55 years (n = 404, 66.4%) and those ≥ 55 years (n = 204, 33.6%). In current study, the number of PTC patients with tumor size ≤ 1 cm was 325, accounting for 53.5% of all PTC (Table 2). For T (tumor) stage, the most common was T1 (n = 452, 74.3%). For N (lymph node) stage, about half of subjects had lymph node metastasis (n = 302, 49.7%). But only a few patients exhibited distant metastasis (n = 14, 2.3%). In addition, the frequency of lymph node metastasis in men was higher than in women.

Concentrations of urinary essential microelements

The concentrations of urinary 10 essential microelements in PTC patients were shown in Table 3. In Spearman rank-order correlation analysis, we observed that most of 10 microelements were significantly but slightly correlated with each other (Fig. 1). The Spearman rank-order correlation coefficients ranged from − 0.001 to 0.651. Moreover, the content of urinary 10 microelements according to selected clinicopathological characteristics of PTC was summarized in Supplementary Table 1. Except for Zn and I, there were no statistically significant difference in the concentration of other microelements between men and women (Supplementary Table 2).

Table 2 Description of the clinicopathologic characteristics of papillary thyroid cancer in current study [n (%)]

	Total (n = 608)	Male (n = 154)	Female (n = 454)	*p* value[a]
Tumor size				
≤ 1 cm	325 (53.5)	72 (46.8)	253 (55.7)	0.054
> 1 cm	283 (46.5)	82 (53.2)	201 (44.3)	
Capsular invasion				
Negative	351 (57.7)	80 (51.9)	271 (59.7)	0.093
Positive	257 (42.3)	74 (48.1)	183 (40.3)	
Multifocality				
Negative	410 (67.4)	100 (64.9)	310 (68.3)	0.444
Positive	198 (32.6)	54 (35.1)	144 (31.7)	
T stage (tumor)				
T1	452 (74.3)	109 (70.8)	343 (75.6)	0.358
T2	50 (8.2)	11 (7.1)	39 (8.6)	
T3	26 (4.3)	8 (5.2)	18 (4.0)	
T4a/4b	80 (13.2)	26 (16.9)	54 (11.9)	
N stage (lymph node)				
N0	306 (50.3)	51 (33.1)	255 (56.2)	< 0.001
N1	302 (49.7)	103 (66.9)	199 (43.8)	
M stage (metastasis)				
M0	594 (97.7)	151 (98.1)	443 (97.6)	0.977
M1	14 (2.3)	3 (1.9)	11 (2.4)	
TNM stage (AJCC)				
I	550 (90.5)	135 (87.7)	415 (91.4)	0.078[b]
II	32 (5.3)	14 (9.1)	18 (4.0)	
III	16 (2.6)	4 (2.6)	12 (2.6)	
IV	10 (1.6)	1 (0.6)	9 (2.0)	

AJCC American Joint Committee on cancer

[a]*p* values (two-sided) were based on Chi square test

[b]*p* values (two-sided) were calculated by using Fisher's exact test

Table 3 Content of urinary 10 essential microelements among study population

Microelements[a]	Geometric mean (95% CI)	Percentiles (P)						
		P5	P10	P25	P50	P75	P90	P95
Co	1.58 (1.18 − 2.13)	0.07	0.09	0.17	0.82	19.25	52.56	194.84
Cr	33.70 (30.20 − 37.60)	5.02	10.58	21.61	43.23	57.58	82.06	106.66
Cu	5.22 (4.50 − 6.05)	0.26	0.71	3.07	7.88	10.50	15.02	27.84
Fe	22.61 (17.42 − 29.34)	0.07	0.70	10.95	38.41	90.02	166.49	295.19
Mn	1.02 (0.81 − 1.28)	0.04	0.06	0.21	1.15	5.20	10.92	23.22
Mo	36.87 (31.97 − 42.53)	3.17	9.04	22.26	48.25	72.64	125.01	168.45
Se	112.22 (98.00 − 128.51)	12.22	25.40	64.47	118.55	236.94	396.29	760.86
Sr	119.28 (106.66 − 133.41)	21.39	29.95	65.43	144.01	219.03	355.98	404.84
Zn	246.78 (198.18 − 307.26)	0.78	72.56	220.55	385.24	556.40	912.12	1375.23
I	399.49 (352.17 − 453.23)	82.41	117.92	191.61	365.03	764.27	2145.53	2648.12

[a]Concentrations of microelements were presented as ug/g creatinine

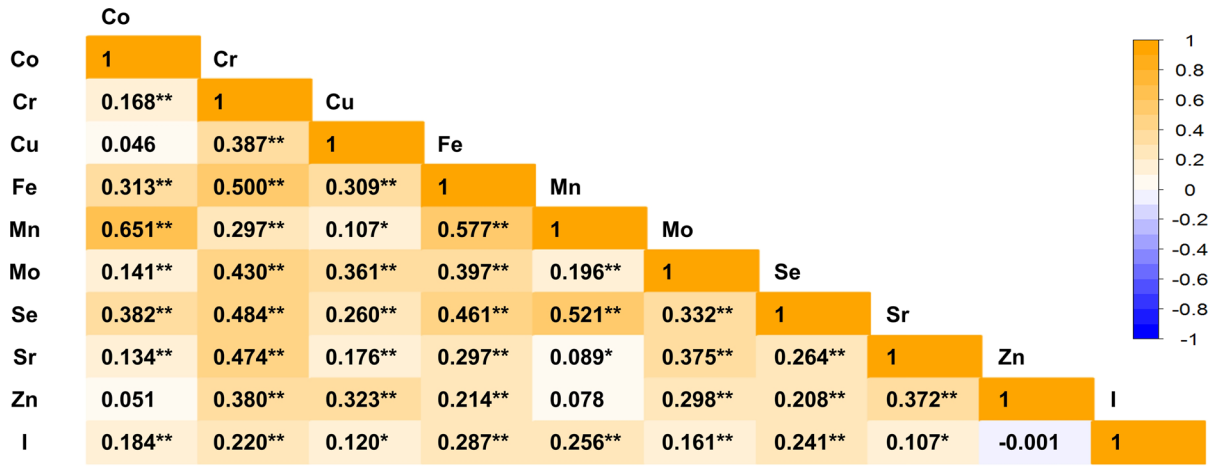

Fig. 1 Spearman rank-order correlation between urinary 10 essential microelements. *$p < 0.05$; **$p < 0.001$

Urinary essential microelements and PTC clinicopathological characteristics

In a single-microelement regression model adjusted for age, gender, and BMI, the association between PTC clinicopathological characteristics and microelements was shown in Supplementary Fig. 1. After further adjustment for average annual household income, smoking status, physical activity, history of X-ray and history of CT scan, a decreased risk of tumor size > 1 cm in PTC was still significantly associated with higher levels of Fe [Quartile 4 (Q4) *vs.* Quartile 1 (Q1), OR = 0.56, 95% CI 0.35–0.90, *p*-trend = 0.026] (see Fig. 2). The decreased risk of capsular invasion was significantly associated with higher levels of Co [Q4 *vs.* Q1, OR = 0.66, 95% CI 0.41–1.05, *p*-trend = 0.042] and Fe [Q4 *vs.* Q1, OR = 0.64, 95% CI 0.40–1.04, *p*-trend = 0.037], respectively. However, the positive associations of Cr quartile [Q4 *vs.* Q1, OR = 1.68, 95% CI 1.02–2.77, *p*-trend = 0.031] and Sr quartile [Q4 *vs.* Q1, OR = 1.92, 95% CI 1.15–3.20, *p*-trend = 0.036] with risk of multifocality were significant (Fig. 2).

In multi-microelements model, we further assessed the simultaneously effects of co-exposure to multiple microelements on the PTC aggressiveness (Table 4).

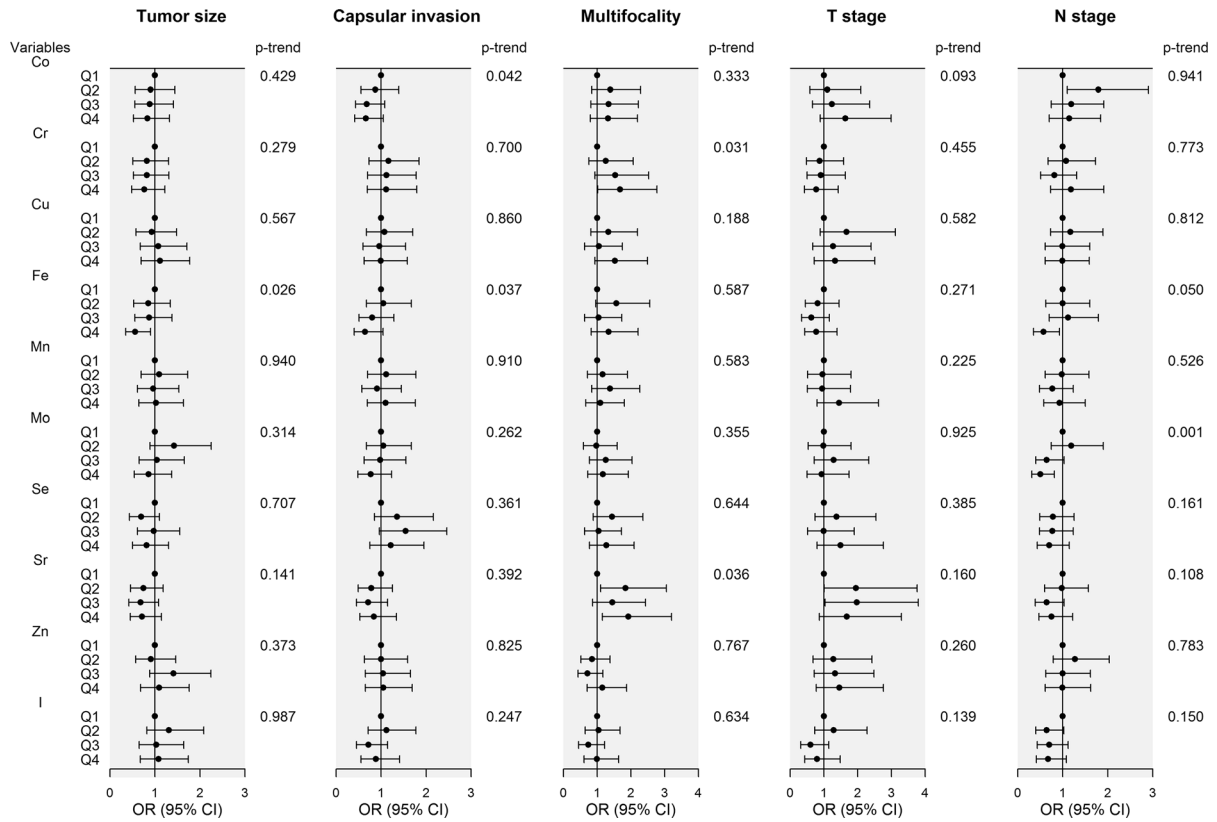

Fig. 2 Odds ratios (95% CI) of clinicopathological characteristics of PTC according to each microelement in the single-microelement model, adjusted for age, gender, body mass index, average annual household income, smoking status, physical activity, history of X-ray and history of CT scan: tumor size ($>$ 1 cm *vs.* $\leq$ 1 cm), capsular invasion (positive *vs.* negative), multifocality (positive *vs.* negative), T stage (T3/4a/4b *vs.* T1/2), and N stage (N1 *vs.* N0). Natural logarithm transformation had been carried out on all microelements. *Q* quartile

We observed that increased Fe levels were inversely associated with risk of PTC tumor size $>$ 1 cm (p-trend = 0.023), capsular invasion (p-trend = 0.003), and advanced T stage (T3/4a/4b) (p-trend = 0.011). PTC patients with high urinary levels of Co (p-trend = 0.006) and Mo (p-trend $<$ 0.001) also had a significantly decreased risk of capsular invasion and lymph node metastasis, respectively. However, increased Mn levels were positively associated with risk of capsular invasion (p-trend = 0.033) and advanced T stage (T3/4a/4b) (p-trend = 0.013). Increased Sr levels were positively associated with risk of multifocality (p-trend = 0.044) and advanced T stage (T3/4a/4b) (p-trend = 0.032).

Discussion

In current study, we measured urinary concentrations of 10 essential microelements in patients newly diagnosed with PTC and investigated the associations between PTC clinicopathologic characteristics and multiple essential microelements. Taken together, PTC patients with increased urinary levels of Mn and Sr, and decreased urinary levels of Fe, Co and Mo seemed to have aggressive clinicopathologic characteristics. To the best of our knowledge, this study is the first to evaluate the simultaneous effects of the co-exposure to multiple essential microelements on PTC aggressiveness. Our findings are important to those diagnose patients at the earliest possible stage of PTC and are providing more risk stratification evidence to estimate the probability of PTC progression and aggressiveness.

Table 4 Odds ratios (95% CI) of clinicopathological characteristics of PTC according to all microelements and potential covariates in the multi-microelement model

Characteristics	Quartile 1	Quartile 2	Quartile 3	Quartile 4	$p-$ trend
Tumor size (> 1 cm *vs.* ≤ 1 cm)[a]					
Fe	1.0 (Ref)	0.83 (0.53 − 1.32)	0.84 (0.53 − 1.33)	0.56 (0.35 − 0.89)	0.023
Capsular invasion (positive *vs.* negative)[b]					
Co	1.0 (Ref)	0.91 (0.56 − 1.48)	0.62 (0.38 − 1.02)	0.44 (0.23 − 0.84)	0.006
Fe	1.0 (Ref)	0.81 (0.48 − 1.34)	0.61 (0.35 − 1.08)	0.41 (0.22 − 0.76)	0.003
Mn	1.0 (Ref)	1.10 (0.68 − 1.77)	1.24 (0.68 − 2.24)	2.51 (1.22 − 5.18)	0.033
Multifocality (positive *vs.* negative)[c]					
Sr	1.0 (Ref)	1.90 (1.15 − 3.14)	1.42 (0.85 − 2.38)	1.90 (1.14 − 3.15)	0.044
T stage (T3/4a/4b *vs.* T1/2)[d]					
Fe	1.0 (Ref)	0.57 (0.29 − 1.09)	0.39 (0.18 − 0.81)	0.41 (0.19 − 0.91)	0.011
Mn	1.0 (Ref)	1.06 (0.56 − 2.01)	1.41 (0.65 − 3.04)	2.32 (1.12 − 4.80)	0.013
Sr	1.0 (Ref)	1.97 (1.02 − 3.83)	2.22 (1.14 − 4.32)	2.07 (1.04 − 4.14)	0.032
N stage (N1 *vs.* N0)[e]					
Mo	1.0 (Ref)	1.07 (0.65 − 1.76)	0.61 (0.37 − 1.02)	0.41 (0.24 − 0.70)	< 0.001

Natural logarithm transformation had been carried out on all microelements

[a]Retained covariates including age, gender and history of CT scan

[b]Retained covariates including average annual household income, body mass index, smoking status and history of X-ray

[c]Retained covariates including age, gender, body mass index, history of X-ray

[d]Retained covariates including gender, body mass index, history of X-ray and history of CT scan

[e]Retained covariates including age, gender, body mass index and smoking status

Current many aspects of thyroid cancer management are still controversial and unclearly defined, whose the treatment methods are diversified and more risk-adapted, such as the customizable extent of surgery, radioactive iodine therapy, and thyroid-stimulating hormone (TSH) suppressive therapy (Tuttle 2018). More accurate and specific preoperative diagnostic techniques and indicators need to be developed for thyroid cancer patients. These diagnostic techniques and indicators are designed to reduce diagnostic errors and spare patients from thyroid surgery. If some preoperative indicators can be determined as more accurate prognostic indicators for thyroid cancer, more active therapeutic strategies and prognosis management also can be performed to extend patients' survival and ensure cost savings. In this study, 325 patients were newly diagnosed with papillary thyroid microcarcinoma, accounting for 53.5% of total study population. This proportion is relatively moderate. However, almost half of PTC patients had lymph node metastasis and 42.3% of PTC patients had capsular invasion. When all PTC patients were divided into those < 55 years (n = 404) and those ≥ 55 years (n = 204) according to the AJCC staging system (8th edition), since the general prognosis is worse in latter PTC group (Amin et al. 2017), there nearly one-third of PTC patients were at higher risk of poor prognosis. These data suggested that current PTC patients still need to pay more attention to their prognosis, because large tumor size, extrathyroidal extension, lymph node metastasis, and older age were all associated with high recurrence and death risk of thyroid cancer (Lango et al. 2013; Niemann et al. 2017).

Previous studies of trace metal exposure and thyroid cancer have mainly focused on cadmium, lead and mercury, because they can behave as endocrine disruptors and disrupt the hormonal system (Petrosino et al. 2018; Rezaei et al. 2019). However, evidence on the effects of co-exposure to essential microelements on the occurrence and development of thyroid cancer is sparse and undetermined. Several studies have

observed that high iodine level is associated with the development and aggressiveness of PTC, but this association has not been confirmed (Yan et al. 2019; Zhao et al. 2018, 2019). It was reported that high urinary iodine level was just a specific feature of PTC rather than a risk factor for it (Yan et al., 2019). BRAF(V600E) mutation is common in PTC. However, BRAF(V600E) mutation in PTC could inhibit the expression of several genes that are involved in iodine metabolism, especially the sodium/iodide symporter (NIS) gene (Lee et al., 2018). As a result, the function of NIS to transport active iodine from outside the thyroid follicle cell into the cell might be impaired. In contrast, people are currently more likely to recognize that low levels of iodine can elevate the risk of thyroid cancer and favor the development of more aggressive histotypes (Barrea et al. 2021). Because iodine deficiency can mediated up-regulation of the vascular endothelial growth factor expression to fuel vessel growth, thereby acting as a tumor promoter (Zhang et al. 2018). In current study, we did not observe that increased levels of urinary iodine were associated with the selected aggressive clinicopathologic characteristics of PTC. Actually, most of our study population had higher levels of urinary iodine, with a geometric mean of 399.49 ug/g creatinine, but this mean level was still within the reference intervals of urinary iodine levels (22–450 μg/g creatinine) of the Chinese normal population (Yu et al., 2020). For this phenomenon, one possible reason is the implementation of salt iodization policy in China (Chen et al. 2013). Therefore, the associations of high urinary iodine levels with PTC progression and aggressiveness need to be further investigated.

In this study, we observed that PTC patients with high urinary levels of Fe had a significantly decreased risk of large tumor size (> 1 cm), capsular invasion, and advanced T stage (T3/4a/4b). This means that Fe deficiency might be a strongly correlated risk factor for PTC aggressiveness. Compared with normal levels of iron and iodine, combined low levels of iron and low iodine was related with decreased levels of free triiodothyronine (FT3) and increased levels of TSH (Luo et al. 2017). In animal experiment, the hyperthyroid rats model had lower concentration of Fe compared to control groups (Baltaci et al., 2013a). In contrast, the concentration of Fe in hypothyroid rats model was higher than in control groups (Baltaci et al., 2013b). These results suggested that Fe levels were closely related to thyroid metabolism. It is worth noting that there is an interaction between dietary Zn and Fe. Specifically, the excessive intake of Zn can inhibit the absorption of Fe (McDonald and Keen, 1988). However, Fe deficiency could inhibit the activity of heme-dependent thyroid peroxidase and have a direct effect on the conversion of thyroxine (T4) to triiodothyronine (T3) (O'Kane et al. 2018). It is well known that the decrease in circulating T3 and T4 will stimulate the secretion of TSH through a positive feedback mechanism of hypothalamus–pituitary–thyroid axis. However, TSH can facilitate the thyroid cell growth, and long-term high TSH levels are the stimulating factor of thyroid nodule, which may induce and promote the occurrence and development of thyroid cancer (Huang et al. 2017; Hu et al. 2019). Given that Zn also is an essential element for the metabolism and synthesis of thyroid hormones, it is important to maintain the balance of Zn and Fe levels in the human body.

Mn is a component of several enzymes and cofactors, which plays an important role in life activities. For example, manganese superoxide dismutase has strong antioxidant properties and can neutralize the toxic effects of reactive oxygen species (Soldin and Aschner 2007). However, human exposure to high levels of Mn can cause manganism. In the process of manganism, there is a change in an important neurotransmitter, namely dopamine, which damages the basal ganglia nucleus. For dopamine, it also can act as inhibitory modulator of TSH secretion (Soldin and Aschner 2007). Hanif et al. suggested mean concentrations of serum Mn were significantly increased in hyperthyroid patient compared with the controls (Hanif et al. 2018). But another case–control study found out that the PTC patients had a lower level of Mn compared to the normal subjects (Zhang et al. 2019). In current study, the PTC patients with high urinary levels of Mn had a significantly increased risk of capsular invasion and advanced T stage (T3/4a/4b). One potential mechanism is that the damaging effects of high levels of Mn to dopaminergic neurons may cause the loss of dopaminergic control of TSH secretion and the disruption of thyroid homeostasis (Soldin and Aschner 2007).

To date, few studies have investigated the association between Sr levels and thyroid cancer. There was a study directly compared the serum Sr levels between 50 thyroid cancer patients (0.047 ± 0.012 ug/mL) and

50 healthy controls (0.037 ± 0.009 ug/mL) suggested that the Sr levels in cases were significantly higher than the controls (Leung and Li 1996). In our study, we found PTC patients with high urinary levels of Sr had a significantly increased risk of multifocality and advanced T stage (T3/4a/4b). Sr is also a known calcium-sensing receptor (CaSR) agonists. The experiment study suggested that strontium biased CaSR signaling toward extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling and the potency of strontium-stimulated calcitonin secretion was higher than calcium (Thomsen et al. 2012). However, serum calcitonin is a good marker for both initial diagnosis and monitoring of patients with residual or recurrent medullary thyroid cancer (MTC), preoperative calcitonin levels were related to tumor size, number and location of lymph node metastasis (Viola and Elisei 2019). As a result, the issue of whether preoperative urinary Sr level is related to PTC aggressiveness should be further investigated.

In addition, we also observed that PTC patients with high urinary levels of Co and Mo had a significantly decreased risk of capsular invasion and lymph node metastasis, respectively. However, little is known about the association between PTC and the urinary level of Co and Mo. Rezaei et al. pointed out that low level of Co was associated with both hypothyroidism and hyperthyroidism (Rezaei et al. 2019). But a study conducted among American adults in 2007–2008 did not observe that the significant association of thyroid function with Co and Mo (Yorita Christensen 2013). Similarly, a recent epidemiological study suggested that Co and Mo were not associated with thyroid tumor risk (Liu et al. 2021). As we all know, the administration of oral cobalt has been shown to cause reversible reduction in the iodine uptake by thyroid, with subsequent development of goitre and hypothyroidism (Bradberry et al. 2014). For internal exposure to Mo, a recent longitudinal study suggested Mo exposure might elevate risk of the impaired kidney function (Liu et al. 2020). The potential mechanism was that high levels of Mo could reduce glomerular filtration, induce renal cell apoptosis, and produce co-damage effects with cadmium (Liu et al. 2020).

In our current study, multi-microelement model was conducted to investigate the simultaneous effects of the co-exposure to multiple essential microelements on PTC aggressiveness. Given the difference in incidence of thyroid cancer between men and women, we compared the distribution of urinary microelements concentration and clinicopathologic characteristics between two genders and only found there was a significant difference in zinc, iodine and lymph node metastasis. This difference might be related to the small sample size of men in current study. Therefore, to obtain more exact risk estimates, we additionally adjusted some potential confounders in single- and multi-microelement model, such as age, gender, medical radiation exposure (a definite risk factor for thyroid cancer), annual household income (high-income people had more opportunities for health examinations, which might help to detect early cancer) (Vaccarella et al. 2015), and smoking status (on one hand, tobacco smoking could increase the risk of metal exposure, on the other hand, the association between smoking and thyroid cancer was not clear) (Cho et al. 2018).

However, several limitations should be mentioned. First, this study was cross-sectional study with a small sample size, especially for males, it could not represent the causality. Second, the preferred method of urinary element determination is the collection of 24-h urine samples. But we only collected 12-h morning urine, and all specimens were determined only once, single measurements might not precisely reflect the long-term exposure to microelements. Third, the urine sample is not the preferred choice for the measurement of certain metal such as iron and copper, although urinary excessive microelements also can reflect the disruption of homeostasis (Wu et al. 2018). The lack of blood sample exposure assessment was also a limitation. Therefore, the current results need to be further confirmed in other longitudinal and prospective studies.

In conclusion, we observed significant associations of high levels of Mn and Sr as well as low levels of Fe, Co, and Mo in urine with the risk of aggressive clinicopathologic characteristics of PTC, which indicated that certain essential microelements might have potential effects on PTC progression and aggressiveness. These finding might have clinical significance for managing patients with PTC and their prognosis. Given the current higher burden of PTC, further studies are required to clarify the role of essential microelements in the onset and progression of PTC.

Author contributions MJH Conceptualization, Formal analysis, Investigation, Writing—original draft. JLH Formal analysis, Investigation, Writing—review & editing. XRT Investigation, Data curation. WJY: Investigation, Data curation. HHZ Investigation, Data curation. GAL Investigation, Data curation. FH Conceptualization, Funding acquisition, Project administration, Writing—review & editing.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Anhui Medical University Biomedical Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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