

## EXPLORING THE RELATIONSHIP BETWEEN BISPHENOL A, IODINE AND PAPILLARY THYROID CARCINOMA

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### Summary

*Bisphenol A, one of the environmental endocrine disrupting chemicals, was shown to have a weak estrogen activity and could disrupt thyroid function to some degree. Iodine, which is the most essential microelement that is used for the synthesis of thyroid hormones in humans, was proven to give rise to thyroid diseases, such as thyroiditis, thyroid nodular goiter, and so on. There are relatively very few studies that have considered the role that both Iodine and Bisphenol A play in the development of papillary thyroid carcinoma. Therefore, this cross-sectional observational study was carried out to explore the relationship between Iodine, Bisphenol A and Papillary Thyroid Carcinoma. The study included 113 subjects aged from 20 years to 80 years selected from Qilu Hospital of Shandong University from February 2015 to September 2015 and 65 healthy volunteers residing in Jinan, P.R. China. We compared the differences of the concentrations of Urinary Iodine, Urinary Bisphenol A and Serum Bisphenol A among patients of Papillary Thyroid Carcinoma, nodular goiter and normal population. In the PTC and nodular goiter group, urinary BPA and Iodine concentrations were significantly higher than controls stating that the excretion of Iodine and BPA were increased. Meanwhile 23 patients with papillary thyroid carcinoma (43%) had excessive iodine nutrition compared to only 6 volunteers with excessive iodine intake in the control group (9%). These findings suggest that excessive dietary iodine intake is a risk factor for thyroid cancer. Moreover, the significant association between urinary creatinine-adjusted BPA and iodine suggest that they might have a synergistic effect on the thyroid.*

### Key words

Bisphenol A; Iodine; Papillary thyroid carcinoma.

### Introduction

Bisphenol A (BPA) which is one of the most popular organic compounds used for production of polycarbonate plastics and epoxy resins worldwide, is available in our daily life, including the mineral water bottles, feeding bottles, food containers, glasses, medical devices, such as infusion sets, dental fillings, and so on [1]. Every year, 5.5 million tons of BPA are outputted throughout the world, in which 2.7 million tons are demanded in China [1]. Studies show that the exposure to BPA is primarily through dermal exposure, food intake, inhalation of dust and intravenous administration [1, 2]. According to the study performed by National Center for Environmental Health in USA, BPA was detected in 92.6% of the volunteers that participated in the 2003-2004 National Health and Nutrition Examination Survey [3]. In 129 Danish children and adolescents, BPA was detectable in more than 80% of urine samples with the median concentration of 1.37ng/ml [4]. Overall, it was clear to see that BPA exposure was widespread and persistent.

BPA, one of the Endocrine Disrupting Chemicals (EDCs) has been shown to have a slight estrogen activity that can bind to the Estrogen Receptors (ERs) and disrupt the hormonal metabolism [5]. It is reported that BPA could be found in various human fluids and tissues, including serum, urine, breast milk, cord blood, mammary tissue, and so on [6]. Researchers have paid high attention to the BPA-induced health issues. Quite a few studies also suggest that BPA exposure may relate to insulin resistance, diabetes mellitus, and thyroid dysfunction [5,7-8]. For thyroid hormonal metabolism, BPA can competitively bind to thyroid hormone receptors and obstruct the thyroid hormone mediated gene expression [9]. Interestingly, thyroid cancer was 3-4 times more prevalent in females than in men, and the incidence decreased after menopause [10, 11]. Patients with breast cancer are more likely to

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suffer from the papillary thyroid cancer due to the estrogen-associated pathologic change [12]. All these studies indicate estrogen involvement in thyroid cancer. E2 induced the proliferation of different thyroid cancer cell lines (KAT5, NPA89, WRO) mediated by ER  $\alpha$  and ER  $\beta$ . Moreover, in vitro experiments, BPA as an estrogen-like compound can promote the proliferation of MCF-7 human breast cancer cells and up-regulate the expression of ERs [13]. Also, BPA induces the propagation of ovarian cancer cell lines and cell migration [14]. On the basis of this aforementioned data, we assume that BPA may promote thyroid cancer.

Apart from the EDCs, the dietary factor was paid high attention to, as well. As we all know, iodine which is obtained through food mainly is an essential microelement used to take part in the biosynthesis of thyroid hormone. Epidemiologic studies reported that iodine was closely associated with different kinds of thyroid diseases, for instance, autoimmune thyroiditis with an increase of antibodies, hypothyroidism, hyperthyroidism, nodular goiter and thyroid cancer [15]. In recent years, the prevalence of thyroid cancer which is a common endocrine carcinoma has increased incredibly all over the world, in particular to the papillary histotype [16]. H. Ruben Harach et al reported that a high intake of dietary iodine may be associated with PTC (Papillary Thyroid Carcinoma) [17].

The objective of this study therefore was to explore whether serum and urinary BPA and iodine concentrations in patients with papillary thyroid carcinoma are different from the controls and benign thyroid disease (Nodular goiter) and seek the association among BPA, iodine and papillary thyroid carcinoma.

## Materials and methods

### Study Population

We performed an investigation in a population selected from Qilu Hospital of Shandong University, Jinan, Shandong Province, China. 66 paired blood and urine samples from patients with papillary thyroid carcinoma and 71 pairs with nodular goiter were respectively selected from February 2015 to September 2015. For the controls, 148 volunteers from the population of healthy examination in Jinan were recruited under the screening examination focusing on thyroid

function and thyroid ultrasonography. All participants were classified into three groups (PTC group, nodular goiter group and control group) according to the pathological results conducted post-operatively. We excluded those who met the following criteria:

- i) abnormal thyroid function (n=3) having nodular goiter or thyroid cyst (n=80) in the controls.
- ii) history of hyperthyroidism or hypothyroidism, or had taken antithyroid drugs or thyroid hormone previously (n=13 in the papillary thyroid carcinoma group, n= 9 in the nodular goiter group).
- iii) abnormal renal function and hepatic function (n=2 in the nodular group).

Thus, a total of 178 participants were included in the analysis of the relationships among BPA exposure, iodine intake and papillary thyroid carcinoma.

The paired blood and spot urine samples were collected in the morning before surgery (Fasting time>8h). The serum samples were obtained from the collected whole blood samples by centrifuge within 2 hours and was removed to the 5ml glass tubes immediately, then stored at -80 C for the measurement of iodine and bisphenol A. The urine samples were collected in the 5ml glass tubes and stored at -20°C until detection.

Thyroid measurements (FT3, free thyroxine, TSH) were detected with the autoanalyzer (ADVIA centaur Automated Chemiluminescence System, Siemens AG, Germany) in Qilu Hospital. The measurement of urinary creatine was performed with an autoanalyzer (Roche C8000 Chemistry system, Roche, Switzerland). The mean age (Range) in the papillary thyroid carcinoma group, nodular goiter group and control group were 46.26 (20-81), 51.05 (21-70), 32.54 (22-83) years respectively. The committee on Human Research at Qilu Hospital of Shandong University approved the study protocol, and all participants in the study provided written informed consent.

BPA, KI,  $\beta$ -glucuronidase and sulfatase from Helixpomatia were purchased from Aldrich-Sigma, St.Louis, MO, USA. Bisphenol A D16 was purchased from Dr. Ehrenstorfer GmbH, Augsburg, Germany. The urinary C18 column (2.8 $\mu$ m, 100A, 2.1 $\times$ 100mm) was purchased from

ACCHROM, China. The C18 Solid-phase extractor was purchased from Agela Technologies Inc., Delaware, USA and the TSQ vantage HPLC-MS-MS was purchased from Thermo Electron Corporation, America.

#### **Quantification of BPA**

Total (Free and conjugated) urinary and serum BPA were detected with a sensitive and selective HPLC-MS/MS method after zymohydrolysis by isotope-dilution in Solid-phase extraction at Shandong Province Analysis and Test Center, Shandong Academy of Sciences.

In brief, urinary samples (1ml) or serum samples (0.5ml) were mixed with 20 $\mu$ l (50ng) D16-BPA and 50 $\mu$ l  $\beta$ -glucuronidase/sulfatase dissolved in the sodium acetate (PH=5.5) then diluted with 1ml water for urine and 2ml water for serum. Then the incubated samples which were hydrolyzed in the water bath at 37 C for 3 hours were passed through the pre-conditioned C18 SPE cartridges (With 4ml methanol and 3ml water) with a rate of 1.0ml/min by vacuum pumping. The retained BPA on the SPE cartridges after being washed with 2ml water and 3ml water/methanol (3:20) was eluted with 4ml methanol into the glass tubes and then the eluate was evaporated to dryness under a steady stream of nitrogen. The samples were reconstituted with 200ml methanol and subjected to HPLC-MS/MS analysis.

Due to lack of appropriate blanks for the analysis of blank controls and calibration standards, the blank human urine or serum was prepared with mixing samples from six healthy individuals. The blank human samples were for the preparation of a calibration curve and quality control. The calibration curve ranged from 0.10 to 100ng/ml for BPA, and the regression coefficient was greater than 0.995. The inter-day RSD, calculated from quality control samples at three levels (1.0, 10.0, 100.0ng/ml), were less than 10.8% and 8.6%, respectively. There was no significant loss of BPA during the SPE procedure. The Limit Of Quantification (LOQ) of BPA was 0.1ng/ml for urine and 0.2ng/ml for serum. The above analytic data showed great sensitivity, reproducibility for detection of BPA concentration in urine and serum.

#### **Quantification of Iodine**

Urinary iodine concentrations were measured in Shandong University by the method recommended by MINISTRY OF HEALTH OF THE PEOPLE'S REPUBLIC OF CHINA in 2006 that was based on the Sandell Kolthoff reaction after the ammonium per sulfate digestion. The limit of detection was 3 $\mu$ g/L when taking 250 $\mu$ l of the samples. The calibration curve of iodine ranged from 0 $\mu$ g/L to 300 $\mu$ g/L and the relative deviation of duplicate measurement was 2.8%~5.5%. The recovery of iodine ranged from 92.6% to 107%. The regression coefficient was greater than 99%.

#### **Statistical Analysis**

The analysis of all data was performed by SPSS (Statistical Package for Social Sciences) version 20.0. The urinary BPA concentrations varied in the biological samples. The values of urinary iodine and creatine, free thyroxine, free triiodothyronine, TSH were transformed in log-10-normal to achieve normal distributions, while the urinary BPA and serum BPA which were not in normality were also log-10-normal transformed. According to the previous study, a value of 0.05ng/ml was substituted for analysis for BPA levels below LOQ. We summarized laboratory characteristics as mean  $\pm$  Standard Deviation (SD) medians, GM, Interquartile Range IQR and percentiles for the continuous variables.

According to the epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentration announced by WHO, UNICEF, we classified iodine concentrations in urine as non-excessive iodine intake and excessive iodine intake.

We compared the differences between groups by one-way analysis of variance when the data conformed to normal distribution, otherwise Mann-Whitney U-test which was one of the non-parametric tests was used. And, Pearson correlation coefficients and Spearman's rank correlation coefficient was used for the analysis of relationships among the variables. Furthermore, we analyzed the risk factor by Chi-square test.

## Results

Data including total creatinine-unadjusted/adjusted urinary iodine, BPA concentrations in urine and serum, Free Triiodothyronine (FT3) Free Thyroxine (FT4) Thyroid Stimulating Hormone (TSH) of patients with papillary thyroid carcinoma and nodular goiter and volunteers (Mean±SD, GM, median, ranges and percentiles) were shown in Table I.

### BPA Concentrations in Serum and Urine

All serum samples in the study contained detectable BPA (Free BPA and conjugated BPA) that ranged from 4.03ng/ml to 13.80ng/ml. There were no differences of serum BPA concentrations among patients suffering from papillary thyroid carcinoma or nodular goiter and the controls (Fig 1). Urinary BPA was detected in 83% of participants and the concentration ranged from less than 0.1ng/ml to 30.67ng/ml. BPA in papillary thyroid carcinoma group was detected more frequently (96%) than the control group (69%). Moreover, urinary BPA concentration in papillary thyroid carcinoma group was higher than that in the control group, as was creatinine-adjusted BPA concentration ( $p=0.00$ ) (Fig 1). In patients having nodular goiter, 86.67% of urine samples had BPA (Above LOQ) that was higher than controls, as well, and the urinary BPA concentration was statistically higher than controls ( $p=0.00$ ). Nevertheless, the detection rate, unadjusted/creatinine-adjusted urinary BPA concentrations showed no statistical differences between patients with papillary thyroid carcinoma and nodular goiter.

### Urinary Iodine Concentrations

Urinary iodine concentrations in papillary thyroid carcinoma or nodular goiter group were statistically higher than the control group ( $p=0.00$ ) as was the creatinine-adjusted iodine concentration ( $p<0.04$ ) (Fig 2). Furthermore, iodine concentrations measured in papillary thyroid carcinoma patients were significantly higher than those measured in nodular goiter patients ( $p=0.021$ ). But in the creatinine-adjusted iodine concentrations, there was no difference between them.

On the basis of iodine nutrition assessment declared by WHO, all participants had no iodine deficiency in the study. 23 patients with papillary thyroid carcinoma (43%) had excessive iodine

nutrition that was obviously more than controls and only 6 urine samples (9%) that were measured were more than 300ug/L (Fig 3). Similarly, 37% of nodular goiter patients took excessive iodine that was similarly higher than controls. However, it showed no distinction between papillary thyroid carcinoma and nodular goiter groups in excessive iodine intake. Analyzed by Chi-squared test, excessive iodine intake was a risk factor for papillary thyroid carcinoma ( $p<0.00$ ).

### Thyroid Function

Compared with controls, FT3 and free thyroxine in patients with papillary thyroid carcinoma and nodular goiter were significantly lower, while of serum TSH concentration no obvious difference was found. Furthermore, patients with papillary thyroid carcinoma had higher TSH concentration than nodular goiter ( $p=0.037$ ).

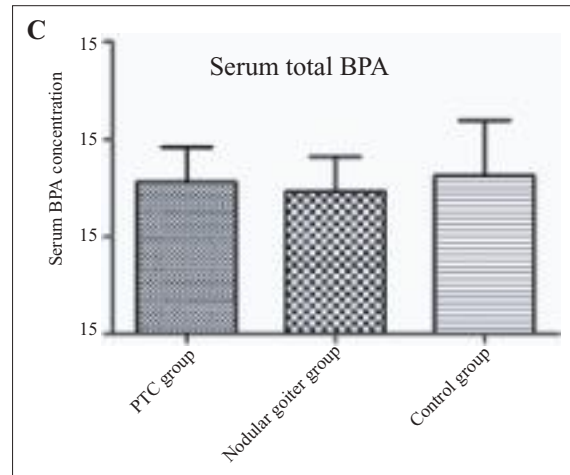
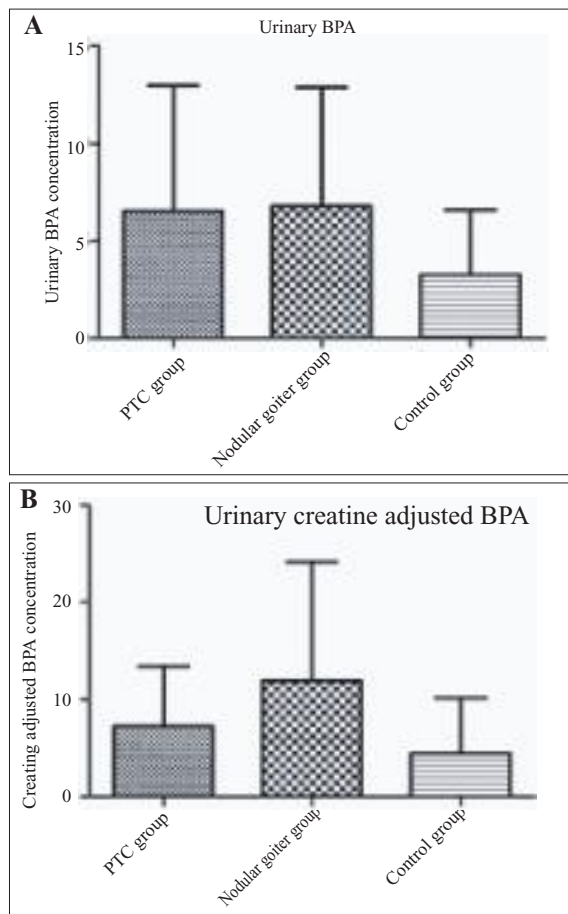
### Correlation Analysis

Among all participants, no gender-related differences were found in serum BPA, urinary BPA, urinary creatinine-adjusted BPA. Considering the influence of age in the study, we explored the relationship among the other detected objects by Spearman correlation coefficients. And, a non-significant positive association was found between age and urinary BPA ( $R=0.166$ ,  $p=0.026$ ). Furthermore, a non-significant positive association between age and urinary creatinine-adjusted BPA was also observed ( $R=0.291$ ,  $p=0.00$ ). Nevertheless, we found no association between age and serum BPA, urinary iodine, and urinary creatinine-adjusted iodine.

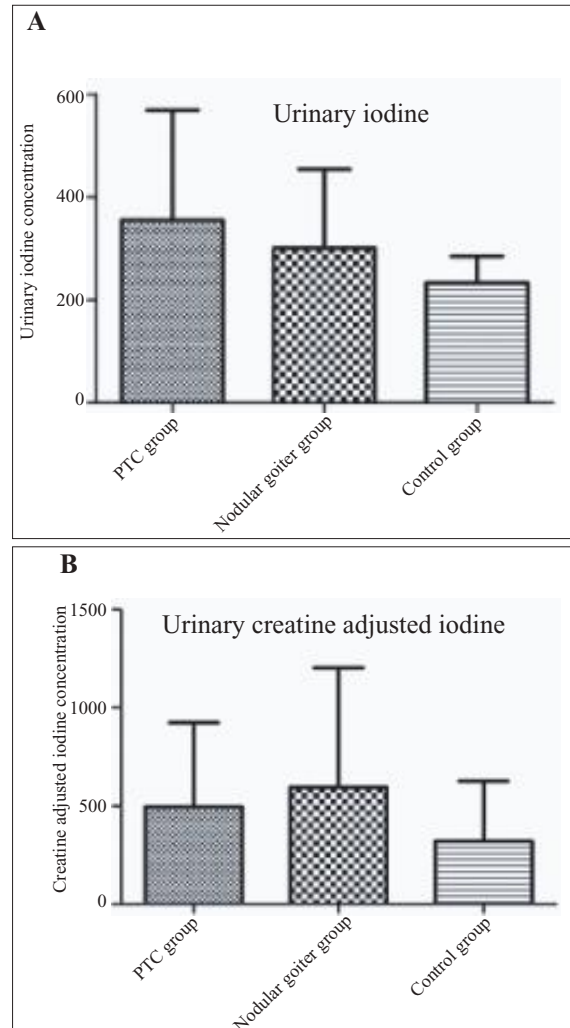
The associations between serum thyroid function and urinary BPA concentration were analyzed. Free triiodothyronine had a slightly negative association with urinary creatinine-adjusted BPA concentration ( $R=-0.327$ ,  $p=0.00$ ), but no associations came out in free thyroxine and TSH. In addition, there was no apparent association of total BPA concentration ( $R=0.002$ ,  $p=0.910$ ) between paired serum and urine samples across all samples collected, even adjusted ( $R=-0.047$ ,  $p=0.534$ ). However, the positive association between iodine concentrations and BPA concentrations in urine samples was more significant by adjusting creatine ( $R=0.537$ ,  $p=0.00$ ).

**Table I :** Thyroid function, iodine and BPA concentration in all participants

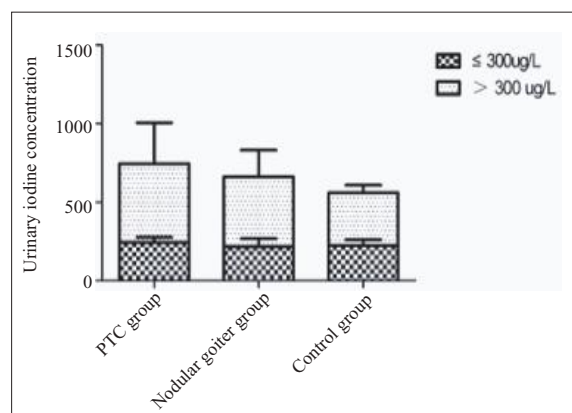
variables	Mean±SD	GM	Range	P25	P50	P75
Age (year)	42.87±15.03	40.13	20~83	26	43	56
Free triiodothyronine (pmol/l)	3.71±0.92	3.60	2.15~5.68	2.90	3.42	4.61
Free thyroxine (pmol/l)	15.37±2.02	15.24	10.82~22.34	13.85	15.24	16.56
TSH (uIU/ml)	1.90±0.96	1.66	0.26~4.73	1.15	1.72	2.49
Serum BPA (ng/ml)	7.75±2.24	7.42	4.03~13.82	6.61	7.50	8.77
Creatine (g/l)	0.99±0.63	0.80	0.10~3.24	0.53	0.85	1.35
Transformed urinary iodine (ug/l)	2.43±0.17	2.42	2.16~3.15	2.33	2.40	2.51
Urinary BPA (ng/ml)	5.43±5.60	2.26	<0.1~34.46	1.74	4.18	7.01
Transformed creatine-adjusted urinary iodine (ug/g)	2.53±0.34	2.50	1.85~3.48	2.29	2.50	2.74
Creatine-adjusted urinary BPA (ug/g)	7.83±9.06	2.82	0.03~50.78	2.18	5.46	9.52



**Figure 1 :** Urinary BPA (A), Urinary Creatine-adjusted BPA (B) and Serumtotal BPA (C) concentrations in the PTC, Nodular goiter and Control groups



**Figure 2 :** Urinary Iodine (A) and Urinary Creatine-adjusted iodine (B) concentrations in the PTC, Nodular goiter and Control groups



**Figure 3 :** Iodine nutrition assessment in the PTC, Nodular goiter and Control groups

### Discussion

BPA is a well-known endocrine disruptor that is a hot research topic worldwide. It has been found to influence the hormone biosynthesis and metabolism, or interfere with the reproduction, because of its similarity with estrogen [18]. Due to its trace level in human fluid or in environment, researchers adopted different detecting methods, such as High-Performance Liquid Chromatography (HPLC) ELISA, Gas Chromatography– Mass Spectrometry (GC–MS) HPLC-MS, and so on [6]. In this study, we detected the concentrations of total BPA in the paired serum and urine samples by HPLC-MS/MS with D16-BPA diluted. Considering the SPE pretreatment was handy and more suitable for the analysis of BPA concentrations in urine, we used the SPE method to handle the urine and serum samples [19].

In human population, BPA is widely exposed through dietary and non-food ingestion pathways [20]. The absorbed BPA was metabolized in the liver by conjugating with glucuronide rapidly and excreted through urine within 24h as reported in pharmacokinetic studies [21]. The BPA in urine was expelled from the body in the form of free BPA (32%), BPA disulfate (7%), BPA glucuronide (57%) and BPA chlorides (4%) showed by Chunyang Liao and Kurunthachalam Kannan [19]. Urinary BPA concentrations varied between day to day and within person to person, regardless of the type of urine (First-morning, spot, 24-hr collection) [22]. 24-hr urine could reflect the daily exposure accurately, but failed to present the variability of daily exposure for a long time [23].

Moreover, Tina Harmer Lassen et al suggested the collection of 24-hr urine would not improve the assessment of BPA exposure in human populations [24]. The single spot urine samples may reflect the BPA exposure appropriately when the study samples were enough [23]. And, in earlier studies, urinary total BPA levels measured in the single spot samples were applied to the evaluation of daily BPA exposure [2, 23, 25]. In our study, we collected the spot urine in the morning and made comparisons in different groups.

Unadjusted/adjusted urinary BPA concentrations in papillary thyroid carcinoma group and nodular goiter group were significantly higher than the control group by Mann-Whitney test ( $p=0.00$ ). However, the papillary thyroid carcinoma group did not differ from the nodular goiter group in unadjusted/adjusted urinary BPA concentrations. Few studies surveyed the urinary BPA concentration in patients with papillary thyroid carcinoma. Our results suggested BPA could have something to do with thyroid cancer. In ovarian cancer, BPA could induce cell migration by up-regulating the expression of MMP-2, MMP-9 and N-cadherin called migration-related factors [15]. Consequently the effect was blocked by inhibitors of the Mitogen-Activated Protein Kinase (MAPK) and phosphatidylinositol 3-kinase pathways (PI3K) [15]. Researches about BPA and papillary thyroid cancer in vivo and vitro were demanded. Moreover, the relationship between BPA and nodular goiter should be followed.

In the three groups, no differences of total serum BPA concentrations which was made up of free BPA (20%) BPA disulfate (34%) and BPA glucuronide (46%) were found which suggested BPA in serum continuously exists in the human population, in spite of fasting more than eight hours [19]. Richard W. Stahlhut et al investigated the association between urinary BPA levels and fasting time, the results demonstrated BPA concentrations didn't decrease rapidly with increasing fasting time ( 8.5h) [20]. It also reflected indirectly that BPA exposure is continuous in blood. Our study was limited to measure and compare the free BPA concentrations in serum.

To our knowledge, this was the first case-control study to report the matched serum and urinary BPA concentrations in thyroid cancer. In our study, we found no gender-related differences in serum BPA concentrations. Our finding was consistent with the results showed in children, adults and pregnant women from China [2]. Nevertheless, we found no differences in urinary BPA concentrations or creatine-adjusted concentrations in males and females [26]. However, among the participants in NHANES, urinary BPA concentrations in females were higher than males [3]. Another study in China found a significant gender difference in creatine-adjusted BPA concentrations [2]. The difference of urinary BPA concentration between females and males in human population is still controversial. The pharmacokinetics of BPA has been reported previously [21]. No association between serum and urinary BPA concentrations were found in our study.

Previous studies showed that dietary exposure of BPA in rats led to thyroid dysfunction in pups as the total thyroxine increased [26]. Our result manifested urinary BPA concentration had a slightly negative association with free triiodothyronine, but no relationship with free thyroxine and TSH. The inconsistent results could be explained by the different metabolic pathways considering that human do not have an enterohepatic circulation as rodents [21]. Furthermore, an epidemiology study including 3394 subjects with or without thyroid dysfunction in China showed that high urinary BPA level was associated with increased free triiodothyronine and decreased TSH concentrations [6]. BPA could disrupt the internal hormone environment. It act as the antagonist binding to the thyroid hormone receptor and recruiting the nuclear corepressor which reduces the triiodothyronine-mediated gene expression [10]. John D. Meeker et al observed an inverse relationship between urinary BPA and total thyroxine and TSH, analyzing data from NHANES 2007-2008 that 1,346 adults and 329 adolescents took part in [27]. In the previous study, an inverse association between urinary BPA and serum TSH were found in 167 men [28]. Even though, a few epidemiologic and animal studies showed that BPA disturbed the levels of thyroid hormone, the relationship between them were still conflicting.

Human body requires about 150g daily iodine supplementation. The absorbed iodine is almost completely gathered in thyroid gland where it is used for the production of thyroid hormone and most of the dissociated iodine is excreted through urine. As a result, urinary iodine concentration is a useful indicator that reflects the current iodine intake. We measured the iodine concentration in urine samples and the result showed all urinary iodine concentrations were above 100ug/L which indicated no iodine deficiency in all participants according to WHO and UNICEF. In addition, urinary iodine concentrations in papillary thyroid carcinoma group and nodular goiter group were significantly higher than control group which meant iodine excretion increased in patients, not the healthy controls. However, no difference was found between papillary thyroid carcinoma group and nodular goiter group. Since 1996, Universal Salt Iodization (USI) has been brought into effect throughout China, the increased iodine intake through daily diet has led to the increasing incidence of thyroid disease, such as thyroiditis, hyperthyroidism, goiter, thyroid cancer, especially papillary thyroid cancer and so on [29, 30]. In addition, an increasing incidence of papillary thyroid cancer was found in Germany, Austria and Switzerland after salt prophylaxis [31]. However, animal experiments showed a low-iodine diet reinforced the development of thyroid carcinoma in mice [32]. Besides, a case-control study in Polynesia France where a mild iodine deficiency exists showed a higher iodine intake from diet decreased the risk of thyroid cancer [33]. In Demark, Thomas Sehestedt et al suggested differences in iodine intake had no association with the increasing incidence of thyroid cancer [34]. The relationship between iodine and papillary thyroid cancer was still unclear and debated and few studies exist at present that make certain of the role that iodine acts on thyroid cancer. Some researches indicated the more sensitive diagnostic method and increased diagnostic activity contributed to the increasing incidence of thyroid cancer [35, 36].

Moreover, 43 percent of the patients in papillary thyroid carcinoma group and 37 percentage in nodular goiter group had excessive iodine intake (Urinary iodine concentration >300 ug/L) the percentage was significantly higher than that in

control group (only 9%). It showed excessive iodine intake was a risk factor for thyroid cancer, as well. Guan H et al indicated high iodine intake increased the occurrence of T1799 BRAF mutation (69% vs. 53%) which was a risk factor for papillary thyroid carcinoma [37]. But the research of Cesar Seigi Fuziwara in vitro manifested that high iodine (10 $\mu$ M NaI) abrogated the activation of miR-19 induced by BRAF<sup>V600E</sup> [38]. A further study to explore how iodine promotes the generation of papillary thyroid carcinoma should be carried on.

As we all known, thyroid hormone is necessary for the growth and development, especially for the brain and skeleton, the material metabolism and energy metabolism, and the normal physiology of other systems, such as cardiovascular and reproductive system [18]. As mentioned in the study, there was no dysthyroidism in all participants and that FT3, thyroxine and TSH were in the normal range. We also compared the thyroid function among the three groups and found FT3 and free thyroxine concentrations in the previous two groups were significantly lower than the control group. Jacqueline Jonklaas et al reported that patients with thyroid cancer had a lower total triiodothyronine level than patients with goiter or nodular thyroid disease [39]. In addition, patients with papillary thyroid carcinoma had a higher serum TSH concentration than patients with nodular goiter, and it was consistent with the study which showed preoperative serum TSH level within normal range in patients with thyroid cancer was higher than the benign group [40]. K. Boelaert et al reported the higher serum TSH concentration remained in normal range increased the risk of suffering from thyroid cancer in a prospective cohort study [41]. In other studies, BPA could influence the thyroid hormone metabolism [6, 10]. And urinary BPA was found to have a relationship with FT3, not TSH in our study. However, what was the causal relationship among FT3, BPA and papillary thyroid carcinoma demands a further study.

Of interest, in our study urinary BPA concentrations was associated with urinary iodine concentration in Chinese population and there was a more significant positive relationship ( $R=0.537$ ,  $p=0.00$ ) after creatine-adjustment. But no previous studies mentioned this. Besides we could not

speculate that BPA and iodine have coefficient effect on thyroid gland via the study. Further studies, including vivo and vitro experiments with a large sample size or detailed demographic information focusing to confirm the findings are needed.

### Conclusion

The strengths of our study include the case-control methods and the innovation of analyzing the BPA and iodine concentration in patients with papillary thyroid carcinoma. But there are still several limitations to be considered. First, this is a cross-sectional study, we cannot estimate the causal relationships. Second, urinary BPA and iodine concentrations were measured in single spot urine samples, not the 24hrs urine samples. Third, the sample size should be enlarged and the relative data on diet habits, geographical position or socioeconomic status were not collected.

### Disclosure

All the authors declared no competing interest.

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