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A case-control study of urinary levels of iodine, perchlorate and thiocyanate and risk of papillary thyroid cancer

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ABSTRACT

Background: The incidence of thyroid cancer has recently increased worldwide. With the exception of radiation exposure, the effects of potential risk factors on thyroid cancer incidence remain controversial.
Objectives: The association between exposure to iodine, perchlorate, and thiocyanate and papillary thyroid cancer (PTC) incidence was evaluated and risk factors were predicted.
Methods: A pair-matching case-control study was performed including 116 age- and sex-matched PTC cases and 116 non-PTC controls. Iodine, perchlorate, and thiocyanate concentrations in urine specimens were determined by inductively coupled plasma mass spectrometry and ultra-performance liquid chromatography–tandem mass spectrometry. The association between iodine, perchlorate, and thiocyanate urinary concentrations and PTC was evaluated using univariable conditional regression logistic analysis followed by multivariable conditional logistic regression analyses with backward stepwise selection to predict risk factors for PTC.
Results: After adjusting for confounders and creatinine standardization, urinary concentrations of iodine [odds ratio (OR) = 11.01, 95% confidence interval (CI): 1.97–30.52] and perchlorate (OR = 2.27, 95% CI: 1.03–5.03) were associated with the risk of PTC, whereas urinary thiocyanate concentration showed a negative association (OR = 0.24, 95% CI: 0.09–0.65).
Conclusions: Increased exposure to iodine and perchlorate may affect PTC development, whereas high thiocyanate exposure may have a beneficial effect.

1. Introduction

Thyroid cancer is a common endocrine malignancy, accounting for < 2% of all cancers (Ron and Schneider, 2006). The incidence of thyroid cancer has increased worldwide in the last decades (Kilfoy et al., 2009; Mitro et al., 2016). This trend is attributed to an increased incidence of papillary thyroid cancer (PTC), a major histotype of well-differentiated thyroid cancer (Mitro et al., 2016; Veiga et al., 2013). Although the etiology and underlying mechanisms remain unclear, this pronounced increase is unlikely to be entirely due to improved diagnostic procedures and medical accessibility, and may represent a true increase in the occurrence of thyroid cancer (Leux and Guénel, 2010; Vigneri et al., 2015). Despite the clear association between radiation exposure and thyroid cancer, this risk factor cannot be applied to the general population (Brenner et al., 2011; Ron and Schneider, 2006). Therefore, studies have focused on investigating potential contributors to PTC, including iodine (Kim et al., 2017; Wang et al., 2014), obesity (Peterson et al., 2012; Xu et al., 2014), and dietary habits (Cho and Kim, 2015; Peterson et al., 2012).

Iodine is used by the thyroid gland for the synthesis of thyroid hormones, and plays a crucial role in the regulation of thyroid hormone metabolism. Iodine deficiency can act as a carcinogen and tumor promoter, and is associated with follicular thyroid cancers, whereas iodine excess is associated with PTC in laboratory animals (Ron and Schneider, 2006). However, the role of iodine in the development of thyroid cancer in humans remains controversial. Despite the fact that PTC incidence increased after the implementation of universal iodine supplementation in some countries (Dal Maso et al., 2009; Mitro et al., 2016; Veiga et al.,

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2013), the rates of incidence of PTC began to increase since 1978 before the Denmark national salt iodination in 2000 (Blomberg et al., 2012). In addition, the occurrence of PTC increased between 1991 and 2005 in Italy, which has no national iodination policy (Ceresini et al., 2012). The relationship between dietary intake of iodine and thyroid cancer prevalence remains unclear, which may be attributed to the use of semiquantitative methods for measuring dietary iodine (Cléro et al., 2012; Truong et al., 2010). Analysis of urinary iodine is ideal for assessing iodine status. Studies show a positive association between high urinary iodine concentrations and thyroid cancer risk (Kim et al., 2017; Wang et al., 2014). However, the lack of data on iodine competitors, including perchlorate and thiocyanate, could decrease the power of these associations.

Perchlorate is an anthropogenic and naturally occurring chemical substance distributed ubiquitously in the environment (Kumarathilaka et al., 2016). The widespread human exposure to perchlorate occurs mainly through ingestion of contaminated water and food (Charnley, 2008). Thiocyanate exposure in humans occurs predominantly through dietary intake of specific vegetables, including cruciferous vegetables, as well as cigarette smoking (Willemin and Lumen, 2017). Experimental studies show that perchlorate and thiocyanate are stronger inhibitors of the sodium iodide symporter (NIS) than iodine, and are clear goitrogens with marked antithyroid activity (Tonacchera et al., 2004). However, the association between simultaneous exposure to iodine, perchlorate, and thiocyanate and the risk of PTC risk remains to be evaluated. In the present study, we performed a cross-sectional study to determine whether urinary levels of iodine, perchlorate, and thiocyanate are associated with the prevalence of PTC.

2. Methods

2.1. Study population

The present study used a cross-sectional case-control design. Patients who visited the Cancer Hospital Chinese Academy of Medical Sciences for the evaluation of newly detected thyroid nodules between June and September 2017 were recruited. Patients with a family history of thyroid cancer, those with a history of radiation exposure during childhood, and those with recent therapeutic exposure to iodine were excluded. Because of potential occupational exposure, patients from coalmine areas were also excluded. Finally, 116 patients with PTC on surgical pathology were included, and there were no patients with follicular thyroid cancer.

The non-PTC controls were unrelated healthy individuals who visited the hospital during the same study period as cases and collected using the same exclusion criteria as those used for cases. Because epidemiological studies identified associations of age and gender with PTC prevalence (Ron and Schneider, 2006), a pair-match design including age and sex was used to eliminate confounding factors. PTC cases and controls were matched by age (differences between birthdays within 1 year) and gender. The stratified control subjects were therefore at risk at the same sex and age.

The study was approved by the Ethics Committee of China National Center for Food Safety Risk Assessment (No. 2015006). All participants were informed of the purpose of the study and provided informed consent.

Multiple covariates and potential confounders were considered in the analysis of the association of urinary iodine, thiocyanate, and perchlorate with PTC. Height and weight were measured at the time of recruitment. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Body fat percentage was estimated using the following formula: body fat percentage $= (1.20 \times BMI) + (0.23 \times age) - (10.8 \times sex) - 5.4$, where age was in years and sex was set to 0 for women and 1 for men (Deurenberg et al., 2007). Body surface area was calculated using the following formula: $body\ surface\ area = 0.007184 \times weight^{0.425} \times height^{0.725}$ (Xu et al., 2014). Cigarette smoking exposure was evaluated using questionnaires for identifying active-smokers and instrumental measurement of nicotine and its metabolites for identifying non-active smokers. Non-active smokers were defined as subjects who were not active smokers despite the detection of biomarkers of cigarettes (nicotine and its metabolites) in the serum.

2.2. Urine sampling and instrumental analysis

A single, fasting, morning urine specimen (approximately 10 mL) and fasting venous blood (approximately 5 mL) were collected from each subject and stored at −40 °C until analysis.

Aliquots (2 mL) of urine specimens were used to measure urinary iodine concentration using an Agilent 7500 inductively coupled plasma mass spectrometer (ICP-MS, Agilent Technologies, Tokyo, Japan) following the reference method for iodine determination in urine (WS/T107.2-2016) released by the China National Health and Family Planning Commission. Thiocyanate and perchlorate in urine specimens were analyzed using an Agilent 1290 Infinity II ultra-performance liquid chromatography (UPLC) (Agilent Technologies, Walbronn, Germany) system equipped with a Primesep B4 column (2.1 mm × 150 mm, 5 μm), and analytes were measured using Agilent 6495 Triple Quad LC-MS (Agilent Technologies, Singapore). Biomarkers of cigarette smoking, including nicotine, cotinine, and trans-3′-hydroxy cotinine, in sera were analyzed using the Waters Acquity UPLC system coupled with a Waters Xevo TQ-S tandem mass spectrometer (Waters, Massachusetts, USA) and a Waters Acquitytm BEH HILIC column (2.1 mm × 100 mm, 1.7 μm). Urinary creatinine levels were measured using the HITACHI 7180 chemistry analyzer for standardizing iodine, perchlorate, and thiocyanate in urine (O'Brien et al., 2016).

The limits of quantification (LOQs) of iodine, perchlorate, and thiocyanate in urine specimens were 2.0 μg/L, 0.2 μg/L, and 5.0 μg/L, respectively. The LOQs of nicotine, cotinine, and trans-3′-hydroxy cotinine in sera were 1.0 μg/L, 2.0 μg/L, and 1.0 μg/L, respectively. Certified reference materials were used to evaluate the accuracy of laboratory measurements, including Iodine in Urine (GBW09109f) purchased from China National Institute of Metrology (Beijing, China) and Mercury, Perchlorate, and Iodide in Frozen Human Urine (Standard Reference Material 3668) and Organic Contaminants in Non-Smokers' Urine (Standard Reference Material 3673) purchased from National Institute of Standards and Technology (Maryland, USA).

2.3. Statistical analysis

Descriptive analyses of the study population characteristics were performed according to study outcomes (PTC, non-PTC). The Mann-Whitney *U* test and Chi-square test were used to analyze differences between groups.

Because of the severely skewed distribution of urinary iodine, perchlorate, and thiocyanate concentrations, natural logarithm transformation was applied to the regression models. Conditional logistic regression analyses were used to evaluate the association of urinary levels of iodine, perchlorate, and thiocyanate with the risk of PTC. Firstly, for each explanatory variable including covariates and potential confounders, a simple univariable logistic regression model was used to calculate the rough odds ratio (OR) and examine statistical significance. Subsequently, variables with $p < 0.15$ were selected for building multiple conditional logistic regression models. Backward stepwise methods were used to select significant variables to fit the final conditional logistic regression models. Due to various approaches for representing the levels of urinary analytes, two types of models were built. In model 1, urinary creatinine was selected as a covariate and the levels of iodine, thiocyanate, and perchlorate measured in microgram per litter urine. In model 2, the urinary concentrations of analytes were dividing by the concentrations of urinary creatinine for standardization.