# The association between electrolyte and malignant tendency of thyroid nodules: a case-control study

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**Abstract：** Background and aims: Thyroid nodules are common, aberrant electrolyte homeostasis can produce carcinogenic synergies. This study aimed to assess the association between electrolyte and malignant tendency of thyroid nodules.

Methods: This study aimed to investigate the association between malignant tendency of thyroid nodules and electrolyte. A total of 509 patients with malignant thyroid nodules (MTNs) and 454 patients with benign thyroid nodules (BTNs) were included in our study according to histopathological biopsy, and the electrolyte and thyroid function indexes were detected by the automatic biochemical analyzer and the fully automated microparticle chemiluminescence instrument.

Results: We found that the concentrations of magnesium (Mg), chlorine (CL), and sodium (Na) in blood of patients with MTNs were significantly lower than those in patients with BTNs ($P < 0.05$). Logistic regression analysis showed that low Mg, CL, and Na concentrations were consistent risk factors for thyroid nodule malignancy. Further more, partial correlation analysis and multiple linear regression analysis showed that the Na was positively correlated with free triiodothyronine (FT3) in female.

Conclusion: Our study suggests that electrolyte (Mg, CL, Na) is negatively associated with an increased risk of thyroid cancer (TC), and have a protective effect on TC. Low level of Na increase the malignant tendency of thyroid nodules in female, which may be associated with disturbing the balance of FT3.

**Keywords:** benign thyroid nodules； malignant thyroid nodules；electrolyte

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## 1 Introduction

The prevalence of thyroid nodules in the general population is high, up to 60%, as documented by high-resolution ultrasonography, and approximately 5% of these lesions eventually become malignant.1 At present, a large number of studies focus on exploring the etiology of thyroid nodules, such as obesity, metabolic syndrome, and insulin resistance may be the most important factors causing the increased incidence of thyroid nodules.2 However, few studies have described the factors affecting the malignant tendency of thyroid nodules on the basis of existing benign thyroid nodules (BTNs). Early identification of the risk factors that affect malignant tendency of thyroid nodules is extremely important for the prevention and treatment of TC.

Electrolyte is the basis to ensure the stability of osmotic pressure in the body, maintain the function of human organs and normal metabolism. The cumulative effects of aberrant electrolyte homeostasis on different metabolic pathways and a variety of related systems, organs, tissues and cells can produce carcinogenic synergies.3 Chlorine (CL), magnesium (Mg), potassium (K), sodium (Na), calcium (Ca), phosphorus (P) are the most common electrolyte in human blood, and are the most commonly tested and referred by doctors. Hyponatremia, hypokalemia, hypomagnesemia and hypocalcemia are very common comorbidities in cancer patients. Such dysregulated electrolyte homeostasis can contribute to multiple stages of tumor development by influencing the tumor microenvironment. Furthermore, ingestion of water with low concentrations of Na, K, Mg and Ca can affect the tonicity and osmolality of body fluids and hence the effective cell volume and blood pressure -- thereby creating osmotic stress.3 Studies on several mammalian cell lines suggest that osmotic stress, regardless of its origin, can cause DNA damage leading to chromosome aberrations; genome malfunction occasioned often is a prerequisite for the development of cancer.3 Therefore, it is of great research value to explore the association between electrolyte and thyroid cancer.

In this study, we investigated the background status of selected and whether there are differences in electrolyte (Mg, CL, Na, K, Ca, P) in BTNs and MTNs. In order to explore the association between electrolyte and benign or malignant thyroid nodules.

## 2 Materials and methods

### 2.1 Study population

Participants in this study were from People's Hospital of Deyang City in Sichuan Province, China. The samples were collected from June 2018 to June 2025. Patients with BTNs (n=454) and MTNs (n=509) were enrolled in this study. All underwent surgery and were tested using histopathological biopsy, according to the National Comprehensive Cancer Network (NCCN) guidelines for TC. The inclusion criterion was a history of TC or thyroid nodular goiter, diagnosed through both B-ultrasound and thyroid function test , particularly with regard to histopathological diagnoses. The exclusion criterion were participants with advanced thyroid malignancies or who have undergone chemotherapy and radiation; participants with a history of thyroid surgery, abnormal thyroid function, pregnant women, taking iodine or thyroid hormone medications, and recent use of contraceptives or estrogen that affect the thyroid; participants with other types of malignancies or chronic diseases, such as liver or kidney related diseases. All human studies were approved by the People's Hospital of Deyang City (Ethical code: 2022-04-019-K01).

### 2.2 Data collection

We surveyed all participants in the form of self-made questionnaire, including general demographic characteristics (sex, age) and behavior of lifestyle (alcohol consumption status, smoking status, iodine intake status, thyroid surgery history, medication history including anti-glycemic drugs and antihypertensive drugs). For anthropometric parameters, height and weight were measured following standardized protocols from the World Health Organization (WHO). Body mass index (BMI, kg/m2) was calculated by as the ratio of the weight in kilograms to the square of height in meters. Smoking was defined as taking more than or equal to one cigarette each day for more than six months, and drinking alcoholic for more than once a week for more than six months was considered as drinking.

### 2.3 Laboratory Assays

Participants' fasting blood was collected by intravenous sampling between 7 and 8 am. The blood was cooled to 4 °C and transported to a center laboratory within 2–4 h. Electrolyte (CL, Ca, P, Na, K, Mg) were measured by the automatic biochemical analyzer (Beckman Coulter AU580). Thyroid function indexes (thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroglobulin (Tg), thyroperoxidase antibodies (TPOAb) and thyroglobulin antibody (TGAb)) were detected by the fully automated microparticle chemiluminescence instrument (Beckman Coulter UniCel DxI 800). Laboratory reference range of electrolyte: CL (99-110 mmol/L), Ca (2.03-2.6 mmol/L), P (0.73-1.65 mmol/L), Na (137-157 mmol/L), K (3.5-5.3 mmol/L), Mg (0.6-1.2 mmol/L); thyroid function indexes: TSH (0.27-4.2 mU/L), FT4 (12-22 pmol/L), FT3 (3.1-6.8 pmol/L), Tg (3.5-77 ng/mL), TPOAb (<34 IU/mL) and TGAb (<115 IU/mL).

### 2.4 Statistical analysis

Data management and analysis were performed using the SPSS 26.0 software (SPSS, Chicago, IL). The Shapiro–Wilk test was used to test the normality of the measurement data; normally distributed data were expressed as the mean ± standard deviation (SD), while non-normally distributed data were expressed as the median (interquartile range). The Kruskal-Wallis rank sum test, Student's t-test, and Chi-square tests were used to analyse the difference between the MTNs and BTNs. Partial correlation analysis was used to analyse the relationship between electrolyte and thyroid function indexes. The association between electrolyte and the malignant tendency of thyroid nodules was evaluated by conditional logistic regression models, the concentrations of electrolyte were processed as categorical variables and classified into four quartiles, and the lowest concentration (first quartile) group was used as a reference.In all analysis, P < 0.05 was considered statistically significant. GraphPad Prism 8.0 (GraphPad Software, San Diego, CA) was used for chart analysis.

## 3 Results

### 3.1 The characteristics of the research subjects

A total of 963 subjects' general demographic and clinical features are summarized in Table 1. Whether in the BTNs and MTNs, the incidence of women is much greater than that of men. Compared to participants with BTNs, the proportion of men, smoking, drinking was significantly higher among those with MTNs (P < 0.05 or 0.01).

Table 1 Demographic characteristics and information of the research subjects (n = 963).

| | MTNs (n = 509) | BTNs (n = 454) | P |
|---|---|---|---|
| Gender | | | 0.000** |
| Male | 152（0.30） | 63（0.14） | |
| Female | 357（0.70） | 391（0.86） | |
| Age (years) | 42.33±11.56 | 50.22±11.96 | 0.186 |
| BMI (kg/m2) | 23.70±3.31 | 23.00±3.21 | 0.295 |
| Smoking | | | 0.006** |
| Yes | 78（0.15） | 43（0.09） | |
| No | 431（0.85） | 411（0.91） | |
| Drinking | | | 0.011* |
| Yes | 115（0.23） | 73（0.16） | |
| No | 394（0.77） | 381（0.84） | |

Age and BMI are shown as mean ± standard deviation (SD) and were compared by using the Students' T test. The Chi-square test was used for the categorical data, which are shown as frequency (rate). * P < 0.05, ** P < 0.01, compared with BTNs. Abbreviations: BMI, body mass index; BTNs, benign thyroid nodules; MTNs, malignant thyroid nodules.

### 3.2 Electrolyte analysis of MTNs and BTNs

In this study, a total of 6 electrolyte (CL, Ca, P, Na, K and Mg) were detected in blood samples (Table 2). In general, the serum concentrations of CL, Na, K, and Mg in the MTNs were lower than those in BTNs (P < 0.05 or 0.01). We then further separated the male and female groups for analysis, and found that compared with the BTNs, women in the MTNs had lower serum concentrations of CL, Ca, Na, K, and Mg, but higher concentration of P (P < 0.05 or 0.01); found that men in the MTNs had lower serum concentrations of CL and Mg, but higher serum concentration of P than those in the BTNs (P < 0.05 or 0.01).

Table 2 Serum essential elements and thyroid function indexes in men and women with BTNs and MTNs

| Characteristic | Men | | | Women | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | MTNs（n = 152） | BTNs（n = 63） | P | MTNs（n = 357） | BTNs（n = 391） | P | MTNs（n = 509） | BTNs（n = 454） | P |
| CL | 104.70（103.00-106.90） | 106.30（104.95-108.00） | 0.000** | 105.40（103.50-107.20） | 106.20（104.60-108.00） | 0.000** | 105.30（103.40-107.00） | 106.25（104.70-108.00） | 0.000** |
| Ca | 2.34（2.25-2.42） | 2.31（2.24-2.37） | 0.133 | 2.30（2.20-2.38） | 2.32（2.24-2.41） | 0.005* | 2.31（2.21-2.40） | 2.32（2.23-2.40） | 0.111 |
| P | 1.08（0.95-1.22） | 0.95（0.90-1.08） | 0.001* | 1.16（1.04-1.32） | 1.14（1.03-1.24） | 0.046* | 1.13（1.01-1.29） | 1.12（1.00-1.23） | 0.071 |
| Na | 141.80（140.60-143.10） | 142.00（140.80-143.85） | 0.253 | 140.90（139.60-142.80） | 141.60（140.40-143.30） | 0.000** | 141.10（139.80-143.00） | 141.70（140.43-143.40） | 0.000** |
| K | 4.06（3.80-4.35） | 4.09（3.84-4.42） | 0.441 | 4.03（3.80-4.29） | 4.09（3.85-4.35） | 0.026* | 4.03（3.80-4.31） | 4.09（3.84-4.36） | 0.030* |
| Mg | 0.86（0.78-0.90） | 0.92（0.86-0.96） | 0.000** | 0.83（0.77-0.89） | 0.88（0.82-0.94） | 0.000** | 0.84（0.77-0.90） | 0.89（0.82-0.95） | 0.000** |
| TSH | 2.15（1.17-3.14） | 2.06（1.32-3.09） | 0.955 | 2.54（1.79-3.46） | 2.05（1.32-3.15） | 0.000** | 2.32（1.62-3.41） | 2.05（1.30-3.15） | 0.000** |
| FT4 | 17.18（15.68-18.91） | 17.62（15.70-19.07） | 0.501 | 16.18（14.65-17.43） | 16.41（14.89-17.93） | 0.052 | 16.45（15.06-18.15） | 16.45（14.85-17.89） | 0.312 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| FT3 | 5.42（4.93-5.73） | 5.38（4.86-5.83） | 0.931 | 4.68（4.32-5.08） | 4.83（4.40-5.31） | 0.003** | 4.86（4.46-5.38） | 4.90（4.43-5.41） | 0.709 |
| Tg | 16.96（8.72-33.98） | 100.10（41.55-379.95） | 0.000** | 19.26（9.42-37.63） | 91.13（27.48-500） | 0.000** | 18.36（9.13-37.14） | 93.36（28.75-500） | 0.000** |
| TPOAb | 10.69（8.33-13.36） | 11.27（7.29-16.15） | 0.608 | 10.90（8.16-14.74） | 11.38（8.35-16.19） | 0.241 | 10.88（8.18-14.27） | 11.38（8.20-16.19） | 0.130 |
| TGAb | 15.43（12.88-18.12） | 14.14（11.11-17.64） | 0.165 | 15.64（12.95-19.55） | 15.09（11.41-19.19） | 0.115 | 15.55（12.88-19.11） | 14.90（11.36-18.99） | 0.082 |

* P < 0.05, ** P < 0.01, compared with the BTNs.

### 3.3 Association between electrolyte and malignant tendency of thyroid nodules

We studied the association between the malignant tendency of thyroid nodules and the concentration of electrolyte by logistic regression analysis (Fig 1A-C). In general, serum Mg, CL, Na concentration showed a negative association with the appearance of thyroid nodules with malignant tendency, while P was positively association. Compared with the lowest quartile, the OR of Mg was gradually decreased from the second quantile to the fourth quantile (P < 0.01); the ORs of CL from the second quantile to the fourth quantile were 0.432, 0.453, 0.326 (P < 0.01); the OR of Na in the second and third quartile was 0.656 and 0.576 (P < 0.05 or 0.01); the OR of P in the fourth quartile was 1.949 (P < 0.01). After further gender stratification analyses, we found that in women, the negative association of serum Mg, CL, Na and positive association of serum P on thyroid nodules with malignant tendency still existed. Compared with the lowest quartile, from the second quantile to the fourth quantile, the ORs of Mg were 0.620, 0.467, 0.263 (P < 0.05 or 0.01); the ORs of CL were 0.470, 0.538, 0.427 (P < 0.01); the ORs of Na in the second and third quartile were 0.576, 0.547 (P < 0.05 or 0.01); the ORs of P in the fourth quartile was 1.696 (P < 0.05). We found that in men, the negative association of serum Mg, CL and positive association of serum P on thyroid nodules with malignant tendency still existed. Compared with the lowest quartile, the ORs of Mg in the third and fourth quartile were 0.335, 0.092 (P < 0.05 or 0.01); the ORs of CL in the third and fourth quartile were 0.227, 0.157 (P < 0.01); the ORs of P in the third quartile were 3.767 (P < 0.05). We observed significant sex interactions in the relationships of Na with thyroid nodules with malignant tendency.

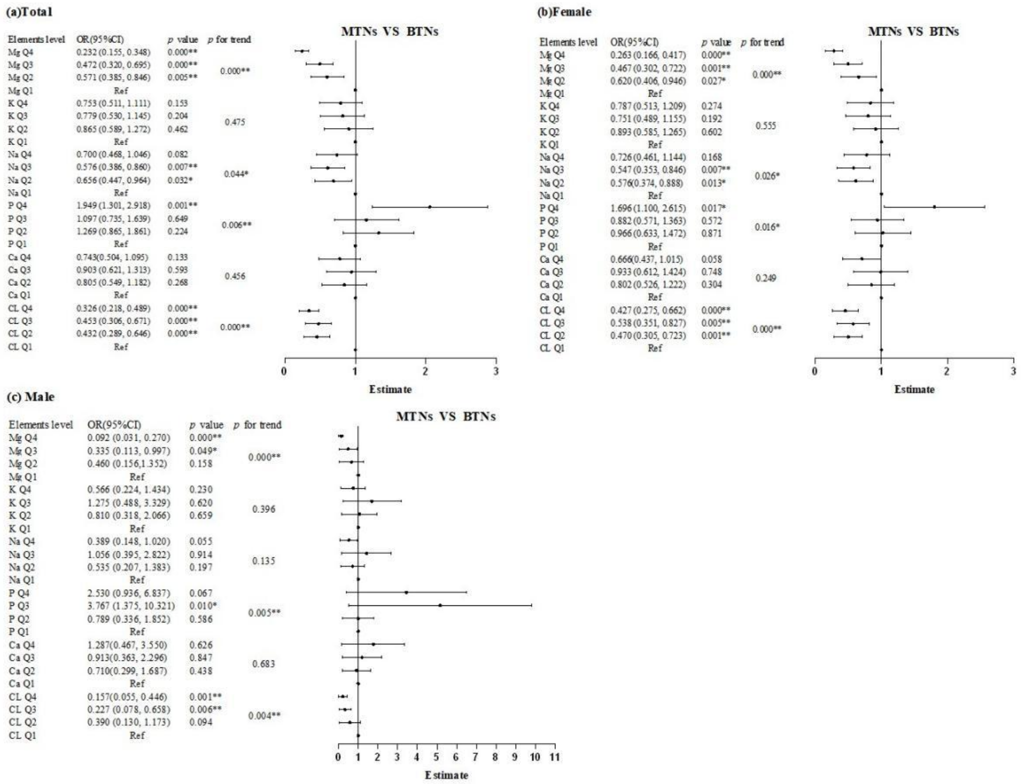

Fig. 1 Relationships between the malignant tendency of thyroid nodules and serum essential elements by logistic analyses in the total population (a), female (b), and male (c). The model was adjusted for age, gender, BMI, smoking, drinking. In the gender-stratified analyses, the model adjusted for all potential confounders except sex. Abbreviations: CL, chlorine; Ca, calcium; P, phosphorus; Na, sodium; K, potassium; Mg, magnesium; BTNs, participants with benign thyroid nodules; MTNs, participants with malignant thyroid nodules.

### 3.4 Thyroid function indexes of MTNs and BTNs

In this study, a total of 6 thyroid function indexes (TSH, FT4, FT3, Tg, TPOAb and TGAb) were detected in blood samples (Table 3). In general, the level of TSH in MTNs was higher than that of in BTNs, but the level of Tg in MTNs was lower than that of in BTNs ($P < 0.01$). Based on gender differences, women with MTNs were found to have lower serum levels of FT3, Tg and higher level of TSH than those in BTNs ($P < 0.01$). Men with MTNs had lower serum level of Tg than those in BTNs ($P < 0.01$).

Table 3 Thyroid function indexes in subjects with benign and malignant thyroid nodules

| Characteristic | Total | | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|---|---|
| | MTNs（n = 509） | BTNs（n = 454） | P | MTNs（n = 152） | BTNs（n = 63） | P | MTNs（n = 357） | BTNs（n = 391） | P |
| TSH | 2.32（1.62-3.41） | 2.05（1.30-3.15） | 0.000** | 2.15（1.17-3.14） | 2.06（1.32-3.09） | 0.955 | 2.54（1.79-3.46） | 2.05（1.32-3.15） | 0.000** |
| FT4 | 16.45（15.06-18.15） | 16.45（14.85-17.89） | 0.312 | 17.18（15.68-18.91） | 17.62（15.70-19.07） | 0.501 | 16.18（14.65-17.43） | 16.41（14.89-17.93） | 0.052 |
| FT3 | 4.86（4.46-5.38） | 4.90（4.43-5.41） | 0.709 | 5.42（4.93-5.73） | 5.38（4.86-5.83） | 0.931 | 4.68（4.32-5.08） | 4.83（4.40-5.31） | 0.003** |
| Tg | 18.36（9.13-37.14） | 93.36（28.75-500） | 0.000** | 16.96（8.72-33.98） | 100.10（41.55-379.95） | 0.000** | 19.26（9.42-37.63） | 91.13（27.48-500） | 0.000** |
| TPOAb | 10.88（8.18-14.27） | 11.38（8.20-16.19） | 0.130 | 10.69（8.33-13.36） | 11.27（7.29-16.15） | 0.608 | 10.90（8.16-14.74） | 11.38（8.35-16.19） | 0.241 |
| TGAb | 15.55（12.88-19.11） | 14.90（11.36-18.99） | 0.082 | 15.43（12.88-18.12） | 14.14（11.11-17.64） | 0.165 | 15.64（12.95-19.55） | 15.09（11.41-19.19） | 0.115 |

* $P < 0.05$, ** $P < 0.01$, compared with the BTNs. BTNs = benign thyroid nodules, FT3 = free triiodothyronine, FT4 = free thyroxine, MTNs = malignant thyroid nodules, Tg = thyroglobulin, TGAb = thyroglobulin antibody, TPOAb = thyroperoxidase antibodies, TSH = thyroid-stimulating hormone.

### 3.5 Correlation between electrolyte and thyroid function indexes

The partial correlation analysis of electrolyte and thyroid function indexes were conducted (Fig 2A-B). There were significant positive correlations in women between Na and FT3， between K and TGAb ($P < 0.05$); there were significant positive correlations in men between CL，Na and Tg ($P < 0.05$).

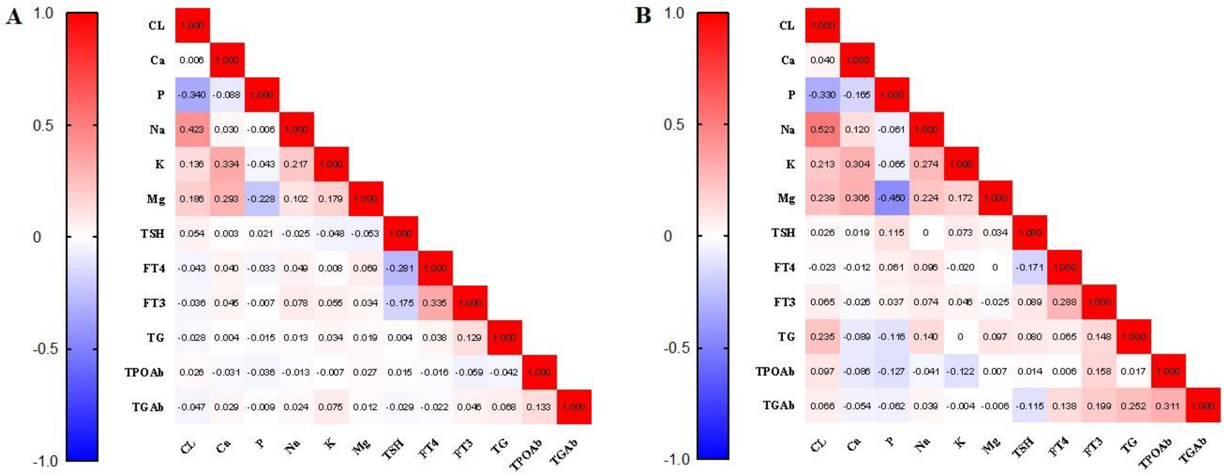


Fig. 2 The correlations between serum trace elements (CL, Ca, P, Na, K, Mg) and thyroid function indexes (TSH, FT4, FT3, Tg, TPOAb and TGAb) in the female (A) (n = 748)and male (B) (n = 215) subjects analysed using partial correlation analysis adjusted for age, gender, BMI, smoking, alcohol intake. The colour of each section is proportional to the correlation coefficient (blue, negative correlation; red, positive correlation). Rows, columns: serum essential elements and thyroid function indexes.

## 4 Discussion

At present, no studies have investigated the relationship between electrolyte and the malignant tendency of thyroid nodules. This study found that Mg, CL, and Na are potential influencing factors related to malignant tendency of thyroid nodules, and the imbalance of Na elements in females may disturb the balance of thyroid function.

Our study found that in the general population, the detection concentrations of Mg, CL, and Na were significantly decreased in the MTNs compared with the BTNs. On this basis, the serum Mg, CL, and Na concentrations were negatively correlated with the malignant tendency of thyroid nodules through logistic regression analysis. It showed that low serum Mg, CL, and Na concentrations emerged as consistent risk factors for thyroid nodules malignant tendency. Hyponatremia is a common condition among individuals with cancer (62% of cases), along with hypokalemia (40%), hypophosphatemia (32%), hypomagnesemia (17%), and hypocalcemia (12%).4 Small cell lung cancer (SCLC) is the most common malignancy associated with hyponatremia typically, affect nearly a quarter of patients with this diagnosis. This is followed by head and neck cancers due to a similar pathogenesis. Hypomagnesemia can raises the risk for lymphomas and other malignancies. In malignancy, hypomagnesemia, hypochloremia, and hyponatremia can be apresenting finding, it will be interesting to investigate the mechanisms involved.

Mg plays a central role in thyroid disease and may influence carcinogenic effects through two mechanisms. First, Mg is related to the stabilization of the structure of nucleic acids and seems involved in DNA replication, transcription, and repair. Therefore, any Mg deficiency can lead to the development of tumors through DNA mutations. Second, Mg may influence the development of cancer through its association with inflammation and/or free radicals, which may lead to DNA oxidative damage and cancer formation. CL channels regulate cell volume by an efflux of chloride ions in response to osmotic stresses. Alterations of cell volume played a vital role in both cell proliferation and cell apoptosis. The signals for cell proliferation required an increase of cell volume at some stage, while cell apoptosis was paralleled by cell shrinkage. When the efflux of CL ions is reduced, the decrease in the concentration of CL ions in the extracellular fluid leads to an increase in cell volume and thus cell proliferation, which has been shown to play a role in cancer invasion.

Hyponatremia is associated to increased cancer growth by activating molecular mechanisms that promote proliferation, angiogenesis and invasivity. The expression of CD34, proliferating cell nuclear antigen (PCNA) and Heme Oxygenase-1 (HMOX-1) were more intense in the tumor lesions from hyponatremic mice. CD34 has been utilized as a biomarker to assess angiogenesis in malignancies. PCNA is a nuclear protein, which is involved in DNA replication, elongation and repair. It is worth mentioning that HMOX-1 has been associated to several functions that overall create a microenvironment that favors tumor growth. In particular, it has been shown to promote carcinogenesis, cell proliferation, angiogenesis and invasion. It has been also demonstrated that HMOX-1 can induce chemoresistance by limiting Reactive Oxygen Species-mediated oxidative damage, promoting apoptosis resistance and activating protective autophagy. Hyponatremia might be a marker of occult neoplasms. These findings, which need to be confirmed by additional studies, suggest that a correct [Na+] balance might be seen in the future also as a prevention measure against cancer, in addition to a marker of prognosis.

Uniquely, TC is the only nonreproductive cancer with striking female predominance with three- to four-fold higher incidence among females. The current researches summarize emerging evidence for the importance of sex in the pathogenesis, progression, and response to treatment in differentiated TC with emphasis on the role of sex hormones, genetics, and the immune system. However, the associated causes of these differences are not fully understood. Our study found that in female, serum concentrations of Na and FT3 were significantly lower in the MTNs than in the BTNs, and there was a significant correlation between Na and FT3 by partial correlation analysis and multiple linear regression. Na element imbalance was associated with the malignant tendency of thyroid nodules in female, which may be caused by disturbing the balance of thyroid function. There was a negative association between FT3 and the risk of TC, especially in individuals with benign thyroid disease.5 One of the possible mechanisms may involve the upregulation of TSH by low FT3 levels, TSH has been reported to act like a growth factor in TC, it was positively associated with the risk of TC. Another possibly due to disturbed expression of type 1 iodothyronine deiodinase in the development of thyroid malignancies, thus reducing the transition rate from an inactive FT4 state to an active FT3 state.5 This study provides a new view of the potential relationships between thyroid-related hormones and the risk of TC, namely Na, which may play an important role in the prevention of TC.

In this study, we conducted a case-control study based on the epidemiology of thyroid malignant and benign nodules, and the sample size was large enough to have certain representative significance. Secondly, we stratified the samples by sex to demonstrate the association between electrolyte and thyroid hormone and malignant tendency of thyroid nodules. However, there are still some limitations, the first is the dietary factors could influence electrolyte， this study did not investigate the diet of the patients at that time, but the surveyed people were from the same area, with little difference in diet structure, and the patients were found to have good nutritional status through BMI. Studies should consider dietary assessments and statistical adjustments to control for these factors in the future. The second is this study could not confirm the causal relationship between electrolyte and the malignant tendency of thyroid nodules, which will be further explored to clarify the mechanism of action.

## 5 Conclusions

Electrolyte (Mg, CL, Na) is negatively associated with an increased risk of TC, and have a protective effect on TC. Low level of Na increase the malignant tendency of thyroid nodules in female, which may be associated with disturbing the balance of FT3. This study provides an effective reference for studying the etiology and pathogenesis of malignant tendency of thyroid nodules.

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