Analysis of the correlation between high iodized salt intake and the risk of thyroid nodules: a large retrospective study

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Abstract

Background: Currently, whether daily excess iodized salt intake increases the risk of thyroid nodules and even thyroid cancer remains controversial. Our research group aimed to provide a theoretical basis for the clinical guidance of daily iodized salt intake and the prevention of thyroid nodules through a retrospective analysis of the correlation between daily iodized salt intake and the risk of thyroid nodules and thyroid cancer in Hunan, China.

Methods: This study retrospectively analyzed the data of subjects who underwent a physical examination at the Health Management Center, Third Xiangya Hospital of Central South University, between January 1, 2017, and December 31, 2019. Subjects enrolled in this study underwent thyroid ultrasonography and tests to urine routines and liver and kidney function, and all subjects completed a questionnaire survey. The daily iodized salt intake of the study subjects was estimated based on spot urine methods (Tanaka). A multivariate logistic regression model was used to analyze the relationship between daily iodized salt intake and thyroid nodules and thyroid cancer.

Results: Among the 51,637 subjects included in this study, the prevalence of thyroid nodules was 40.25%, and the prevalence of thyroid cancer was 0.76%; among all enrolled subjects, only 3.59% had a daily iodized salt intake less than 5 g. In addition, we found that a daily intake of more than 5 g of iodized salt was not only an independent risk factor for the occurrence of thyroid nodules (odds ratio (OR): 2.08, 95% confidence interval (CI): 1.86–2.31, \( p < 0.001 \)) but also an independent risk factor for the occurrence of thyroid cancer (OR: 5.81, 95% CI: 1.44–23.42, \( p = 0.012 \)). A pooled analysis showed a significantly higher risk of thyroid nodules in subjects aged > 60 years with a daily iodized salt intake of more than 5 g compared to subjects aged < 60 years with a daily iodized salt intake of no more than 5 g (OR: 4.88, 95% CI: 4.29–5.54, \( p < 0.001 \)); the risk of thyroid cancer was not significantly different between subjects aged > 60 years with a daily iodized salt intake of more than 5 g and those aged < 60 years with a daily iodized salt intake of no more than 5 g (OR: 2.15, 95% CI: 0.52–8.95, \( p = 0.281 \)). The risk of thyroid nodules was not increased in physically active subjects with a daily iodized salt intake of more than 5 g compared to physically inactive subjects with a daily iodized salt intake of no more than 5 g (OR: 1.12, 95% CI: 0.97–1.28, \( p = 0.111 \)). The same protective effect of physical activity was observed for thyroid cancer in subjects whose daily iodized salt intake exceeded 5 g. The risk of thyroid nodules was reduced for subjects with an education level of postgraduate and above, even when the daily iodized salt intake exceeded 5 g, compared to those with high school education and below and a daily iodized salt intake of no more than 5 g (OR: 0.79, 95% CI: 0.66–0.93, \( p = 0.005 \)); however, a protective effect of...
education level on the occurrence of thyroid cancer was not observed. Independent risk factors affecting daily iodized salt intake greater than 5 g included age, triglycerides, family history of tumors, physical activity, and marital status.

Conclusions: Daily intake of more than 5 g of iodized salt increased the risk of thyroid nodules and thyroid cancer, while increased physical activity and education level reduced the risk of thyroid nodules and thyroid cancer caused by iodized salt intake.

Keywords: Thyroid nodules, Thyroid cancer, Iodized salt, Risk factor

Introduction
Thyroid nodules are frequently detected in healthy individuals undergoing physical examinations [1, 2]. The detection rate of thyroid nodules by simple physical examination is 5–7%, and the detection rate of thyroid nodules by combined ultrasound examination can be as high as 20–76% [3]. Based on pathological characteristics, thyroid nodules can be divided into benign nodules and malignant nodules [4]. The majority of thyroid nodules found during a physical examination are benign, and a few are malignant; a small number of benign nodules may further develop into malignant lesions [5, 6]. Many factors, including sex and ionizing radiation, may affect thyroid nodule formation and malignancy [7]. However, whether excessive daily iodized salt increases the risk of thyroid nodules and thyroid cancer remains controversial [8, 9].

Iodine is an essential trace element involved in the synthesis of thyroid hormone. Iodine deficiency disorders affect various stages of human growth and development and cause different clinical manifestations [10]. In particular, iodine deficiency in pregnant women can affect fetal neurodevelopment, leading to mental retardation in newborns. Since 1995, China has implemented a universal salt iodization program. Ten years later, the rate of goiter in Chinese students aged 7–14 decreased from 20.4% to less than 5%; thyroid-related diseases caused by iodine deficiency, including simple goiter, cretinism, mental disorders and neuronal development disorders, were also greatly reduced [11]. During that same time period, some scholars observed an increasing trend in the incidence of thyroid nodules and thyroid cancer, and they suggested that salt iodization was a risk factor for the occurrence and development of thyroid nodules [12, 13]. However, some scholars offered different viewpoints [14]. Chen et al. found that even with salt iodization, the intake of iodine in Zhoushan, China, is still insufficient, and salt iodization is necessary for inland areas [9]. Given that it is unclear whether the daily intake of excess iodized salt will increase the risk of thyroid nodules and thyroid cancer, more clinical data are needed for follow-up studies.

Hunan is located in the hilly area of central China. The residents consume iodized salt, and most residents have a preferred dietary taste for and a large daily intake of iodized salt. Therefore, this study aimed to investigate the correlation between daily iodized salt intake and thyroid nodules and thyroid cancer by retrospectively analyzing the risk factors for thyroid nodules and thyroid cancer in the Hunan region. The risk factors for daily salt intake were further explored to provide scientific suggestions for clinical guidance on daily iodized salt intake and the prevention and treatment of thyroid nodules and thyroid cancer.

Materials and methods
Research design
This was a cross-sectional study based on data obtained during physical examinations. The information and test results for all individuals who underwent a physical examination at the Health Management Center, Third Xiangya Hospital of Central South University, between January 1, 2017, and December 31, 2019, were collected. Potential bias was controlled by including all physical examination data recorded for that time period rather than conducting random sampling.

Study subjects
This study retrospectively collected data of 53,784 healthy subjects who underwent physical examinations at the Health Management Center, Third Xiangya Hospital of Central South University, between January 1, 2017, and December 31, 2019. A total of 2147 subjects had missing clinical data and, thus, were excluded; therefore, the data for 51,637 subjects were included in the final analyses. The subjects included were long-term residents of the Hunan region. This study received ethics approval from the Third Xiangya Hospital of Central South University, and all patients signed informed consent forms.

Clinical and laboratory data collection
The clinical and laboratory data of each subject, including general information such as body weight and height; laboratory tests, such as fasting blood glucose, blood
lipids, and urine sodium; and special tests, such as thyroid ultrasound, were collected by physicians. Body mass index (BMI) was calculated as body weight (kg) divided by square of height (m) (kg/m\(^2\)). Body mass index (BMI) was classified into four grades [15]: BMI < 18.5 was defined as underweight, BMI 18.5–23.9 was defined as normal weight, BMI 24.0–27.9 was defined as overweight, and BMI > 28.0 was defined as obese.

Questionnaire
In addition to the physical examination and laboratory tests, we also designed a questionnaire based on the National Physical Examination Questionnaire [16]. The questionnaire included general information, such as sex, age, family history of tumors, history of exposure to hazardous substances, marital status and education level, as well as lifestyle information, such as smoking history, drinking history, physical activity, work hours and sleep duration. The history of exposure to toxic substances included noise, vibration, geomagnetic radiation, chemical pollution, dust, air pollution, cooking fumes, etc. Smokers were defined as those with continuous or cumulative smoking for more than 6 months [17]; drinkers were defined as those whose alcohol intake exceeded 10 g per day [18]; and physical activity was defined as being physically active, at a moderate intensity or higher, 3 or more times per week, lasting at least 30 min each session [19].

Fig. 1 Analysis the risk factors of thyroid nodules and thyroid cancer. A Distribution of iodized salt intake for all medical examiners. B Risk factors for thyroid nodules. C Independent risk factors for thyroid nodules. D Distribution of iodized salt intake for patients with thyroid nodule. E Risk factors for thyroid cancer. F Independent risk factors for thyroid cancer.
### Table 1: Clinicopathologic characteristics among people with or without thyroid nodule

| Variables                                      | Non-nodule (n = 30,853) | Nodule (n = 20,784) | p     |
|------------------------------------------------|-------------------------|---------------------|-------|
| Age (y)                                        | 43.75 ± 11.51           | 48.68 ± 12.16       | 0.001 |
| FBG (mmol/L)                                   | 5.53 ± 1.28             | 5.69 ± 1.50         | < 0.001 |
| TAG (mmol/L)                                   | 1.84 ± 1.78             | 1.84 ± 1.84         | 0.200 |
| TCH (mmol/L)                                   | 5.01 ± 0.97             | 5.10 ± 1.01         | < 0.001 |
| HDL (mmol/L)                                   | 1.33 ± 0.30             | 1.34 ± 0.30         | 0.228 |
| LDL (mmol/L)                                   | 2.84 ± 0.82             | 2.91 ± 0.85         | < 0.001 |
| Estimate iodized salt intake                   | 8.08 ± 1.95             | 8.75 ± 1.98         | < 0.001 |
| Sex [n (%)]                                     |                         |                     | < 0.001 |
| Male                                           | 19,459 (63.1)           | 10,383 (50.0)       |       |
| Female                                         | 11,394 (36.9)           | 10,401 (50.0)       |       |
| Family history of cancer [n (%)]               |                         |                     | 0.175 |
| No                                             | 29,975 (97.2)           | 20,234 (97.4)       |       |
| Yes                                            | 878 (2.8)               | 550 (2.6)           |       |
| History of exposure to hazardous substances [n (%)] |                       |                     | < 0.001 |
| No                                             | 16,518 (53.5)           | 10,718 (51.6)       |       |
| Yes                                            | 14,335 (46.5)           | 10,066 (48.4)       |       |
| Smoking [n (%)]                                 |                         |                     | 0.024 |
| No                                             | 23,337 (75.6)           | 15,539 (74.8)       |       |
| Yes                                            | 7516 (24.4)             | 5245 (25.2)         |       |
| Drinking [n (%)]                               |                         |                     | < 0.001 |
| No                                             | 21,077 (68.3)           | 13,874 (66.8)       |       |
| Yes                                            | 9776 (31.7)             | 6910 (33.2)         |       |
| Exercising [n (%)]                             |                         |                     | < 0.001 |
| No                                             | 11,306 (36.6)           | 8758 (42.1)         |       |
| Yes                                            | 19,547 (63.4)           | 12,026 (57.9)       |       |
| Estimate salt intake [n (%)]                   |                         |                     | < 0.001 |
| ≤ 5 g                                          | 1393 (4.5)              | 462 (2.2)           |       |
| > 5 g                                          | 29,460 (95.5)           | 20,322 (97.8)       |       |
| BMI [n (%)]                                     |                         |                     | 0.001 |
| ≤ 18.5                                         | 6106 (19.8)             | 4376 (21.1)         |       |
| 18.5–24                                        | 21,730 (70.4)           | 14,524 (69.9)       |       |
| 24–28                                          | 2538 (8.2)              | 1588 (7.6)          |       |
| > 28                                           | 479 (1.6)               | 296 (1.4)           |       |
| Educational status [n (%)]                     |                         |                     | < 0.001 |
| Senior high school and below                   | 10,110 (32.8)           | 9489 (45.9)         |       |
| Undergraduate college                           | 15,479 (50.1)           | 9256 (44.5)         |       |
| Postgraduate and above                          | 5264 (17.1)             | 2039 (9.9)          |       |
| Marital status [n (%)]                         |                         |                     | < 0.001 |
| Single                                         | 2686 (8.6)              | 1203 (5.8)          |       |
| Married                                        | 27,331 (88.6)           | 18,905 (91.0)       |       |
| Divorced                                       | 603 (2.0)               | 400 (1.9)           |       |
| Windowed                                       | 233 (0.8)               | 276 (1.3)           |       |
Daily iodized salt intake assessment
Based on literature and previous studies [16, 20, 21], we calculated 24-h urinary sodium excretion using the Tanaka formula to estimate daily iodized salt intake. The calculation formula was as follows: Estimated 24-h urinary sodium excretion =21.98 × ((Naspot÷Crspot) × Pr24hCr)0.392. Pr24hCr = 14.89 × weight + 16.14 × height-2.04 × age-2244.45. Naspot = spot urinary sodium (mmol/l); Crspot = spot urinary creatinine (mmol/l); Iodized salt = NaCl = Estimated 24-h urinary sodium excretion× 2.55. The urinary sodium test was examined by an ion selective electrode method.

Diagnosis of thyroid nodules and thyroid cancer
The diagnosis of thyroid nodules relies on thyroid ultrasound through a direct scan with a linear array or trapezoidal high-frequency probe. The probe frequency was 7 ~ 10 MHz, and the size, number and nature of thyroid nodules was evaluated. The diagnosis of thyroid cancer relies on a pathological diagnosis.

Data analysis
The clinical data and laboratory results of the subjects are expressed as the mean ± standard deviation. The χ2 test was used to compare categorical variables, and analysis of variance was used to compare continuous variables. Logistic regression analysis was performed to evaluate the risk factors for thyroid nodules and thyroid cancer; the results are expressed as ORs and 95% confidence intervals (CIs). Logistic regression analysis was performed to assess the risk factors for daily iodized salt intake in all physical examination subjects and thyroid nodule patients; the results are presented as ORs and 95% CIs. Multivariate linear regression analysis was performed to determine the risk factors for thyroid nodules, thyroid cancer, and daily iodized salt intake; for all enrolled subjects, the final risk assessment model was constructed using a stepwise method. SPSS 20.0 (IBM, Chicago, IL, USA) was used for statistical analyses. P < 0.05 was considered statistically significant.

Results
General data of the subjects
Among the 51,637 included subjects, 20,784 were found to have thyroid nodules, accounting for 40.25% of the total (Supplemental Figure 1A). A total of 390 subjects were ultimately diagnosed with thyroid cancer, accounting for 0.76% of the total (Supplemental Figure 1B). Currently, the World Health Organization (WHO) recommends that daily salt intake should be less than 5 g [22], but only 3.59% of the subjects met this criterion (Supplemental Figure 1C). Compared with those subjects without thyroid nodules, age, fasting blood glucose (FBG), triglyceride (TAG), total cholesterol (TCH), sex, history of exposure to hazardous substances, smoking and drinking history, estimate iodized salt intake, BMI, education level, marital status, sleep duration and working hours were the risk factors of thyroid nodules (Fig. 1A-B, Table 1). The independent risk factors were estimate iodized salt intake, age, FBG, and LDL (Fig. 1C).

On the basis of the above results, we conducted a telephone follow-up with 20,784 patients with thyroid nodules and found that 390 of them were eventually diagnosed with thyroid cancer. Compared with subjects with noncancerous nodules, subjects diagnosed with thyroid cancer were of a lower age and had lower fasting blood glucose levels. Other relevant factors included daily iodized salt intake, sex, smoking, physical activity, BMI, education level, and working hours (Fig. 1D-E, Table 2). The independent risk factors were estimate iodized salt intake and age (Fig. 1F).

Table 1 Clinicopathologic characteristics among people with or without thyroid nodule (Continued)

| Variables                  | Non-nodule (n = 30,853) | Nodule (n = 20,784) | p    |
|----------------------------|-------------------------|---------------------|------|
| Sleeping time [n (%)]      |                         |                     |      |
| < 5 h                      | 2929 (9.5)              | 1954 (9.4)          | 0.006|
| 5-7 h                      | 19,162 (62.1)           | 13,199 (63.5)       |      |
| 7-9 h                      | 8411 (27.3)             | 5422 (26.1)         |      |
| > 9 h                      | 351 (1.1)               | 209 (1.0)           |      |
| Working time [n (%)]       |                         |                     | 0.007|
| < 4 h                      | 3585 (11.6)             | 2625 (12.6)         |      |
| 4-6 h                      | 4931 (16.0)             | 3267 (15.8)         |      |
| 6-8 h                      | 14,024 (45.5)           | 9338 (44.9)         |      |
| > 8 h                      | 8313 (26.9)             | 5554 (26.7)         |      |

Abbreviations: FBG fasting blood glucose, TAG Triglyceride, TCH total cholesterol, HDL high density lipoprotein, LDL Low density lipoprotein.
| Variables                                      | Non-cancer \(n = 20,394\) | Cancer \(n = 390\) | \(p\)     |
|-----------------------------------------------|-----------------------------|--------------------|----------|
| Age (y)                                        | 48.72 ± 12.18               | 46.54 ± 11.11      | 0.036    |
| FBG (mmol/L)                                   | 5.69 ± 1.50                 | 5.58 ± 1.06        | 0.038    |
| TAG (mmol/L)                                   | 1.84 ± 1.85                 | 1.81 ± 1.53        | 0.621    |
| TCH (mmol/L)                                   | 5.10 ± 1.01                 | 4.97 ± 0.94        | 0.435    |
| HDL (mmol/L)                                   | 1.34 ± 0.30                 | 1.33 ± 0.29        | 0.528    |
| LDL (mmol/L)                                   | 2.91 ± 0.85                 | 2.81 ± 0.83        | 0.877    |
| Estimate iodized salt intake                   | 8.72 ± 1.96                 | 10.11 ± 2.09       | 0.045    |
| Sex \([n (%)]\)                               |                             |                    | 0.003    |
| Male                                          | 10,217 (50.1)               | 166 (42.6)         |          |
| Female                                        | 10,177 (49.9)               | 224 (57.4)         |          |
| Family history of cancer \([n (%)]\)          |                             |                    | 0.136    |
| No                                            | 19,859 (97.4)               | 375 (96.2)         |          |
| Yes                                           | 535 (2.6)                   | 15 (3.8)           |          |
| History of exposure to hazardous substances \([n (%)]\) | | | | 0.750 |
| No                                            | 10,520 (51.6)               | 198 (50.8)         |          |
| Yes                                           | 9874 (48.4)                 | 192 (49.2)         |          |
| Smoking \([n (%)]\)                           |                             |                    | 0.021    |
| No                                            | 15,267 (74.9)               | 272 (69.7)         |          |
| Yes                                           | 5127 (25.1)                 | 118 (30.3)         |          |
| Drinking \([n (%)]\)                          |                             |                    | 0.311    |
| No                                            | 13,623 (66.8)               | 251 (64.4)         |          |
| Yes                                           | 6771 (33.2)                 | 139 (36.4)         |          |
| Exercising \([n (%)]\)                        |                             |                    | < 0.001  |
| No                                            | 8510 (41.7)                 | 248 (63.6)         |          |
| Yes                                           | 11,884 (58.3)               | 142 (36.4)         |          |
| Estimate salt intake \([n (%)]\)              |                             |                    | 0.021    |
| \(\leq 5\) g                                  | 460 (2.3)                   | 2 (0.5)            |          |
| \(> 5\) g                                     | 19,934 (27.7)               | 388 (99.5)         |          |
| BMI \([n (%)]\)                               |                             |                    | 0.019    |
| \(\leq 18.5\)                                 | 4269 (20.9)                 | 107 (27.4)         |          |
| 18.5–24                                       | 14,273 (70.0)               | 251 (64.4)         |          |
| 24–28                                         | 1560 (7.7)                  | 28 (7.2)           |          |
| > 28                                          | 292 (1.4)                   | 4 (1.0)            |          |
| Educational status \([n (%)]\)                |                             |                    | < 0.001  |
| Senior high school and below                  | 9476 (45.5)                 | 213 (54.6)         |          |
| Undergraduate college                          | 9117 (44.7)                 | 139 (35.6)         |          |
| Postgraduate and above                         | 2001 (9.8)                  | 38 (9.6)           |          |
| Marital status \([n (%)]\)                   |                             |                    | 0.318    |
| Single                                        | 1183 (5.8)                  | 20 (5.1)           |          |
| Married                                       | 18,542 (90.9)               | 363 (93.1)         |          |
| Divorced                                      | 397 (1.9)                   | 3 (0.8)            |          |
| Windowed                                      | 272 (1.3)                   | 4 (1.0)            |          |
Correlation between daily iodized salt intake and thyroid nodules and thyroid cancer

To further investigate the correlation between daily iodized salt intake and thyroid nodules and thyroid cancer, variables were introduced through stepwise logistic regression analysis. Compared with that in subjects without thyroid nodules, when only daily iodized salt intake was included as a variable for analysis of subjects with thyroid nodules, the OR was 2.072 [95% CI: 1.863–2.305, \(p < 0.001\) (Model 1, Table 3)]. With the introduction of other variables, daily iodized salt intake was always a risk factor that increased the risk of thyroid nodules (Model 2–8, Table 3).

In the subjects with thyroid cancer, compared with those with thyroid nodules but without cancer, when only daily iodized salt intake was included as a variable for analysis, the OR was 4.477 [95% CI. 1.112–18.019, \(p = 0.035\) (Model 1, Table 4)]. After introducing other variables stepwise, daily iodized salt intake was always a risk factor for thyroid cancer (Model 2–7, Table 4).

Because daily iodized salt intake is not only an independent risk factor for thyroid nodules but also an independent risk factor for thyroid cancer, we further evaluated the feasibility of daily iodized salt intake as a novel indicator for the clinical diagnosis of thyroid nodules and thyroid cancer. Notably, daily iodized salt intake can be used as an important reference indicator for the diagnosis of both thyroid nodules and thyroid cancer, with areas under the ROC curve (AUCs) of 0.600 and 0.693, respectively ((Fig. 2A-B).

The combined effects of daily iodized salt intake and age, physical activity, and education level on the risk of thyroid nodules and thyroid cancer

In previous studies, we found that daily iodized salt intake, age, physical activity, and education level were all...
independent risk factors for thyroid nodules and thyroid cancer. Therefore, we further attempted to use these indicators in a combined analysis (Tables 5, 6). Compared with subjects younger than 60 years old with a daily intake of iodized salt not exceeding 5 g, regardless of an increase in age or daily iodized salt increase, subjects older than 60 years old with a daily intake of iodized salt not exceeding 5 g had a higher risk of thyroid nodules; the risk of thyroid nodules was highest among those who were older than 60 years old and whose daily iodized salt intake exceeded 5 g (OR: 4.88, 95% CI: 4.29–5.54, p < 0.001). In the combined analysis with thyroid cancer, an increased risk of cancer was observed only when daily iodized salt intake exceeded 5 g (OR: 3.84,

Table 5 Joint association between estimate iodized salt intake and age/exercising/educational status on risk of thyroid nodule

| Estimate iodized salt intake and Age | Non-nodule n (%) | Nodule n (%) | OR (95% CI) | p |
|-------------------------------------|------------------|--------------|-------------|---|
| **Estimate iodized salt intake ≤5 g** |                  |              |             |   |
| Age ≤ 60y                            | 1270 (4.12)      | 368 (1.77)   | 1.00        |   |
| Age > 60y                            | 123 (0.40)       | 94 (0.45)    | 2.64 (1.97–3.53) | < 0.001 |
| **Estimate iodized salt intake > 5 g** |                  |              |             |   |
| Age ≤ 60y                            | 27,144 (87.98)   | 17,050 (82.03) | 2.16 (1.92–2.43) | < 0.001 |
| Age > 60y                            | 2316 (7.51)      | 3272 (15.74) | 4.88 (4.29–5.54) | < 0.001 |
| **Estimate iodized salt intake and exercising** |                  |              |             |   |
| Estimate iodized salt intake ≤5 g    |                  |              |             |   |
| No                                  | 576 (1.87)       | 327 (1.57)   | 1.00        |   |
| Yes                                 | 817 (2.65)       | 135 (0.65)   | 0.29 (0.23–0.37) | < 0.001 |
| **Estimate iodized salt intake > 5 g** |                  |              |             |   |
| No                                  | 10,730 (34.78)   | 8431 (40.56) | 1.38 (1.21–1.59) | < 0.001 |
| Yes                                 | 18,730 (60.71)   | 11,891 (57.21) | 1.12 (0.97–1.28) | 0.111 |
| **Estimate iodized salt intake and educational status** |                  |              |             |   |
| **Estimate iodized salt intake ≤5 g** |                  |              |             |   |
| Senior high school and below        | 429 (1.39)       | 217 (1.04)   | 1.00        |   |
| Undergraduate college                | 724 (2.35)       | 200 (0.96)   | 0.55 (0.44–0.69) | < 0.001 |
| Postgraduate and above               | 240 (0.78)       | 45 (0.22)    | 0.37 (0.26–0.53) | < 0.001 |
| **Estimate iodized salt intake > 5 g** |                  |              |             |   |
| Senior high school and below        | 9681 (31.38)     | 9272 (44.61) | 1.89 (1.60–2.24) | < 0.001 |
| Undergraduate college                | 14,755 (47.82)   | 9056 (43.57) | 1.23 (1.03–1.43) | 0.022 |
| Postgraduate and above               | 5024 (16.28)     | 1994 (9.59)  | 0.79 (0.66–0.93) | 0.005 |

Fig. 2 Value of daily iodized salt intake in the diagnosis of thyroid nodules and thyroid cancer. A Thyroid nodules. B Thyroid cancer.
95% CI: 1.95–15.46, \( p = 0.042 \). Compared with those who did not exercise and had a daily iodized salt intake of no more than 5 g, those who did regularly participate in physical activity exhibited a reduced risk of thyroid nodules. Therefore, although the daily intake of more than 5 g of iodized salt increased the risk of thyroid nodules, the risk of thyroid nodules associated with a daily intake of iodized salt greater than 5 g can be partially offset by physical activity in this population (OR: 1.12, 95% CI: 0.97–1.28, \( p = 0.111 \)); similar results were also observed in the combined thyroid cancer analysis. Compared with those who had an education level of high school or below and daily iodized salt intake no more than 5 g, those with higher education levels exhibited a reduced risk of thyroid nodules; however, a daily intake of iodized salt greater than 5 g increased the risk of thyroid nodules. Therefore, compared with that in subjects with a high school education or lower, the risk of thyroid nodules was lower among those subjects with a postgraduate education or higher and with a daily iodized salt intake greater than 5 g (OR: 0.79, 95% CI: 0.66–0.93, \( p = 0.005 \)), indicating that the increased risk of thyroid nodules caused by daily iodized salt intake greater than 5 g can be offset by education level. In the combined analysis with thyroid cancer, daily iodized salt intake and education level were not statistically significant.

Factors associated with estimated iodized salt intake
The above studies showed that a daily iodized salt intake greater than 5 g was an independent risk factor for both thyroid nodules and thyroid cancer. Therefore, we further investigated the risk factors that could influence daily iodized salt intake. First, we analyzed which factors were related to a daily iodized salt intake greater than 5 g. The results showed that age, triglycerides, total cholesterol, history of exposure to hazardous substance, physical activity, and marital status were risk factors for a daily iodized salt intake greater than 5 g can be partially offset by physical activity in this population (OR: 1.12, 95% CI: 0.97–1.28, \( p = 0.111 \)); similar results were also observed in the combined thyroid cancer analysis. Compared with those who had an education level of high school or below and daily iodized salt intake no more than 5 g, those with higher education levels exhibited a reduced risk of thyroid nodules; however, a daily intake of iodized salt greater than 5 g increased the risk of thyroid nodules. Therefore, compared with that in subjects with a high school education or lower, the risk of thyroid nodules was lower among those subjects with a postgraduate education or higher and with a daily iodized salt intake greater than 5 g (OR: 0.79, 95% CI: 0.66–0.93, \( p = 0.005 \)), indicating that the increased risk of thyroid nodules caused by daily iodized salt intake greater than 5 g can be offset by education level. In the combined analysis with thyroid cancer, daily iodized salt intake and education level were not statistically significant.
### Table 7 Clinicopathologic characteristics among all people grouped by estimate iodized salt intake

|                        | Salt intake (≤ 5 g, n = 1855) | Salt intake (> 5 g, n = 49,782) | p     |
|------------------------|--------------------------------|---------------------------------|-------|
| Age (y)                | 43.70 ± 13.44                  | 45.82 ± 11.96                   | < 0.001|
| FBG (mmol/L)           | 5.69 ± 1.96                    | 5.59 ± 1.35                     | < 0.001|
| TAG (mmol/L)           | 1.64 ± 1.55                    | 1.84 ± 1.82                     | < 0.001|
| TCH (mmol/L)           | 4.92 ± 1.05                    | 5.05 ± 0.98                     | 0.003  |
| HDL (mmol/L)           | 1.36 ± 0.32                    | 1.34 ± 0.30                     | < 0.001|
| LDL (mmol/L)           | 2.79 ± 0.85                    | 2.87 ± 0.83                     | 0.283  |
| Sex [n (%)]            |                                 |                                 |       |
| Male                   | 968 (52.2)                     | 28,874 (58.0)                   |       |
| Female                 | 887 (47.8)                     | 20,908 (42.0)                   |       |
| Family history of cancer [n (%)] |                  |                                 | < 0.001|
| No                     | 1750 (94.3)                    | 48,459 (97.3)                   |       |
| Yes                    | 105 (5.7)                      | 1323 (2.7)                      |       |
| History of exposure to hazardous substances [n (%)] |                                 |                                 | < 0.001|
| No                     | 1623 (87.5)                    | 25,613 (51.5)                   |       |
| Yes                    | 232 (12.5)                     | 24,169 (48.5)                   |       |
| Smoking [n (%)]        |                                 |                                 | 0.339  |
| No                     | 1414 (76.2)                    | 37,462 (75.3)                   |       |
| Yes                    | 441 (23.8)                     | 12,320 (24.7)                   |       |
| Drinking [n (%)]       |                                 |                                 | 0.326  |
| No                     | 1275 (68.7)                    | 33,676 (67.6)                   |       |
| Yes                    | 580 (31.3)                     | 16,106 (32.4)                   |       |
| Exercising [n (%)]     |                                 |                                 | < 0.001|
| No                     | 903 (48.7)                     | 19,161 (38.5)                   |       |
| Yes                    | 952 (51.3)                     | 30,621 (61.5)                   |       |
| BMI [n (%)]            |                                 |                                 | 0.815  |
| ≤ 18.5                 | 379 (20.4)                     | 10,103 (20.3)                   |       |
| 18.5–24                | 1302 (70.2)                    | 34,952 (70.2)                   |       |
| 24–28                  | 151 (8.1)                      | 3975 (8.0)                      |       |
| > 28                   | 23 (1.2)                       | 752 (1.5)                       |       |
| Educational status [n (%)] |                              |                                 | 0.015  |
| Senior high school and below | 646 (34.8)                    | 18,953 (38.0)                   |       |
| Undergraduate college  | 924 (49.8)                     | 23,811 (47.8)                   |       |
| Postgraduate and above | 285 (15.4)                     | 7018 (14.1)                     |       |
| Marital status [n (%)] |                                 |                                 | < 0.001|
| Single                 | 254 (13.7)                     | 3635 (7.3)                      |       |
| Married                | 1544 (83.2)                    | 44,692 (89.8)                   |       |
| Divorced               | 42 (2.3)                       | 961 (1.9)                       |       |
| Windowed               | 15 (0.8)                       | 494 (1.0)                       |       |
| Sleeping time [n (%)]  |                                 |                                 | 0.894  |
| < 5 h                  | 167 (9.0)                      | 4716 (9.5)                      |       |
| 5-7 h                  | 1174 (63.3)                    | 31,187 (62.6)                   |       |
| 7-9 h                  | 493 (26.6)                     | 13,340 (26.8)                   |       |
| >9 h                   | 21 (1.1)                       | 539 (1.1)                       |       |
education level, and marital status (Fig. 3B). On this basis, we also conducted a subgroup analysis of subjects with thyroid nodules. We found that age, triglycerides, physical activity, and marital status were risk factors for a daily iodized salt intake greater than 5 g, whereas fasting blood glucose, high-density lipoprotein (HDL), LDL, sex, and family history of tumors were protective factors against a daily iodized salt intake greater 5 g (Table 8, Fig. 3C, Suppl Fig 3). Linear regression analysis indicated that the independent risk factors for a daily iodized salt intake greater than 5 g in patients with thyroid nodules were age, triglycerides, family history of tumors, physical activity, and marital status (Fig. 3D). These results indicated that independent of the specific population with

| Working time [n (%)] | ≤ 5 g, n = 1855 | > 5 g, n = 49,782 | p |
|---------------------|----------------|------------------|---|
| < 4 h               | 241 (13.0)     | 5969 (12.0)      | 0.602 |
| 4-6 h               | 294 (15.8)     | 7904 (15.9)      |     |
| 6-8 h               | 822 (44.3)     | 22,540 (45.3)    |     |
| > 8 h               | 498 (16.8)     | 13,369 (26.9)    |     |

Abbreviations: FBG fasting blood glucose, TAG Triglyceride, TCH total cholesterol, HDL high density lipoprotein, LDL Low density lipoprotein
|                          | Salt intake (≤ 5 g, n = 462) | Salt intake (> 5 g, n = 20,322) | p     |
|--------------------------|------------------------------|---------------------------------|-------|
| Age (y)                  | 47.91 ± 14.52                | 48.69 ± 12.10                   | < 0.001|
| FBG (mmol/L)             | 5.98 ± 2.43                  | 5.69 ± 1.47                     | < 0.001|
| TAG (mmol/L)             | 4.97 ± 1.10                  | 5.10 ± 1.00                     | 0.041 |
| TCH (mmol/L)             | 1.63 ± 1.53                  | 1.84 ± 1.85                     | 0.057 |
| HDL (mmol/L)             | 1.36 ± 0.34                  | 1.34 ± 0.30                     | < 0.001|
| LDL (mmol/L)             | 2.83 ± 0.93                  | 2.91 ± 0.84                     | 0.032 |
| Sex [n (%)]              |                              |                                 |       |
| Male                     | 208 (45.0)                   | 10,175 (50.1)                   |       |
| Female                   | 254 (55.0)                   | 10,147 (49.9)                   |       |
| Family history of cancer [n (%)] |                      |                                 | < 0.001|
| No                       | 400 (86.6)                   | 19,834 (97.6)                   |       |
| Yes                      | 62 (13.4)                    | 488 (2.4)                       |       |
| History of exposure to hazardous substances [n (%)] |        |                                 | 0.438 |
| No                       | 230 (49.8)                   | 10,488 (51.6)                   |       |
| Yes                      | 232 (50.2)                   | 9834 (48.4)                     |       |
| Smoking [n (%)]          |                              |                                 | 0.173 |
| No                       | 358 (77.5)                   | 15,181 (74.7)                   |       |
| Yes                      | 104 (22.5)                   | 5141 (25.3)                     |       |
| Drinking [n (%)]         |                              |                                 | 0.889 |
| No                       | 307 (66.5)                   | 13,567 (66.8)                   |       |
| Yes                      | 155 (33.5)                   | 6755 (33.2)                     |       |
| Exercising [n (%)]       |                              |                                 | < 0.001|
| No                       | 327 (70.8)                   | 8431 (41.5)                     |       |
| Yes                      | 135 (29.2)                   | 11,891 (58.5)                   |       |
| BMI [n (%)]              |                              |                                 | 0.064 |
| ≤ 18.5                   | 102 (22.0)                   | 4274 (21.0)                     |       |
| 18.5–24                  | 303 (65.6)                   | 14,221 (70.0)                   |       |
| 24–28                    | 47 (10.2)                    | 1541 (7.6)                      |       |
| > 28                     | 10 (2.2)                     | 286 (1.4)                       |       |
| Educational status [n (%)] |                            |                                 | 0.841 |
| Senior high school and below | 217 (47.0)                | 9272 (45.6)                     |       |
| Undergraduate college    | 200 (43.3)                   | 9056 (44.6)                     |       |
| Postgraduate and above   | 45 (9.7)                     | 1994 (9.8)                      |       |
| Marital status [n (%)]   |                              |                                 | < 0.001|
| Single                   | 50 (10.8)                    | 1153 (5.7)                      |       |
| Married                  | 395 (85.5)                   | 18,510 (91.1)                   |       |
| Divorced                 | 9 (1.9)                      | 391 (1.9)                       |       |
| Windowed                 | 8 (1.7)                      | 268 (1.3)                       |       |
| Sleeping time [n (%)]    |                              |                                 | 0.744 |
| < 5 h                    | 39 (8.4)                     | 1915 (9.4)                      |       |
| 5-7 h                    | 295 (63.9)                   | 12,904 (63.5)                   |       |
| 7-9 h                    | 125 (27.1)                   | 5297 (26.1)                     |       |
| > 9 h                    | 3 (0.6)                      | 206 (1.0)                       |       |
thyroid nodules, age, triglycerides, and family history of tumors, physical activity, and marital status were independent risk factors for a daily iodized salt intake greater than 5 g. Improvements in these areas of daily life can help reduce daily iodized salt intake.

**Discussion**

Through a retrospective analysis of data of 51,637 individuals who underwent a physical examination in the Hunan region, this study found that the daily iodized salt intake of most subjects in this region was significantly higher than the recommended intake by the WHO and that a daily iodized salt intake greater than 5 g is an independent risk factor for the occurrence of thyroid nodules and even thyroid cancer. Factors such as age, triglycerides, family history of tumors, physical activity, and marital status were all independent risk factors affecting daily iodized salt intake, both in general subjects who underwent a physical examination and in subjects with thyroid nodules.

Hunan is located inland in China, and the intake of seafood is relatively low; the intake of iodine is almost entirely from iodized salt. In other studies, daily iodized salt intake was often determined through the subjective feelings of taste (light, normal, and salty) [23, 24], and the data did not reflect the actual situation. In this study, daily salt intake was estimated by the spot urine sample, result in more accurate data. And previous studies have shown that the values obtained by spot urine methods correlated highly with daily salt intake, can be used to estimate daily iodized salt intake [25, 26].

Excessive daily salt intake is closely related to diseases such as hypertension, calcium loss, and kidney diseases [27, 28]. Therefore, the daily salt intake recommended by the WHO is less than 5 g. Whether the intake of iodized salt increases the risk of thyroid nodules and the risk of thyroid cancer remains controversial in academia [29, 30]. In this study, a retrospective analysis of big data indicated that when daily iodized salt intake exceeds 5 g, there was an increased risk of thyroid nodules and thyroid cancer. This result supports the scientific validity of the WHO recommendations.

In this study, patients with thyroid nodules had higher blood glucose and blood lipid levels, indicating that patients with thyroid nodules were more prone to metabolic disorders. In the population with thyroid nodules, the average age of the patients with noncancerous nodules was 48.72 years, and the average age of patients with cancerous nodules was 46.54, indicating a trend toward a younger age, which is consistent with the trend for thyroid disease, i.e., presentation a younger ages. In addition, we found that with the increase in education level, salt intake decreased, and the incidence of thyroid nodules also decreased. Thus, a higher education level is conducive to acquiring relevant health knowledge, paying more attention to one's own health, and moderating salt intake, which demonstrates, from a different perspective, that controlling salt intake is very beneficial for the prevention of thyroid nodules, in addition to reducing the occurrence of hypertension and kidney disease. In the combined analysis of daily iodized salt intake and education level, with the same daily intake of iodized salt, with an increase in education level, the risk of thyroid nodules was reduced, suggesting that education can reduce the risk of thyroid nodules through other factors, in addition to influencing daily iodized salt intake. Marriage status showed a different trend: in all populations who underwent a physical examination and in those with thyroid nodules, married people always tended to have a greater intake of iodized salt, but the incidence of thyroid nodules decreased. We speculate that this is caused by other confounding factors. Finally, we observed that individuals with a family history of tumors tended to have lower daily iodized salt intake, a result that might be related to the fact that families of cancer patients are more likely to choose healthy lifestyles, including decreasing daily iodized salt intake. In the combined analysis of daily iodized salt intake and other factors, we found that physical activity could partially eliminate the increased risk of thyroid nodules and thyroid cancer associated with excessive daily iodized salt intake; therefore, we strongly recommend moderate exercise.

Although this study had a large sample size, there are still limitations. This study is a single-center...

Table 8 Clinicopathologic characteristics among patients with thyroid nodule grouped by estimate iodized salt intake (Continued)

| Working time [n (%)] | Salt intake (≤ 5 g, n = 462) | Salt intake (> 5 g, n = 20,322) | p     |
|---------------------|-------------------------------|-------------------------------|-------|
| < 4 h               | 55 (11.9)                     | 2570 (12.6)                   | 0.367 |
| 4-6 h               | 84 (18.2)                     | 3183 (15.7)                   |       |
| 6-8 h               | 211 (45.7)                    | 9127 (44.9)                   |       |
| > 8 h               | 112 (24.2)                    | 5442 (26.8)                   |       |

Abbreviations: FBG fasting blood glucose, TAG Triglyceride, TCH total cholesterol, HDL high density lipoprotein, LDL Low density lipoprotein
retrospective cross-sectional analysis, and the observed number of thyroid cancer cases was small, only 390, which may affect the reliability of the results to some extent. In addition, the limited enrollment may affect the general applicability of the results to a certain extent. Nevertheless, we can still conclude that currently, the vast majority of the population in inland hilly areas of China have a daily iodized salt intake that is excessive, and the excessive intake of iodized salt will increase the risk of thyroid nodules and thyroid cancer. Limiting salt is imperative; improvements in lifestyles such as salt-restricted diets, moderate exercise, and health knowledge can reduce the risk of thyroid nodules and thyroid cancer.

Abbreviations
GR: Odds ratio; CI: Confidence interval; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Supplementary Information
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Additional file 1: Suppl Fig 1. General data of the subjects. A. The proportion of thyroid nodules. B. The proportion of thyroid cancer. C. The proportion of daily iodized salt intake.

Additional file 2: Suppl Fig 2. Daily iodized salt intake in medical examiners.

Additional file 3: Suppl Fig 3. Daily iodized salt intake in patients with thyroid nodule.

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Authors’ contributions
Yaohui Wang and Jianguang Wang, Experimental design and Data collection. Zhilong Chen, Statistical analysis. Min Ma and Changwei Lin, Case review. Qingnan He and Mingzhu Ye, Supervision, Funding acquisition, Investigation, Zhihen Chen, Statistical analysis. Min Ma and Changwei Lin, Case review. Yaohui Wang and Jiangang Wang, Experimental design and Data collection.

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Availability of data and materials
The data and materials of this study are available from the corresponding author for reasonable requests.

Declarations
Consent to publication
Not applicable.

Ethics approval and consent to participate
Studies involving human participants were approved by the ethical board of Third Xiangya Hospital of Central South University and performed in accordance with relevant guidelines and regulations. Informed consent was obtained from all patients.

Competing interests
The authors declare that they have no conflict of interest.

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