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The changing incidence of thyroid carcinoma in Shenyang, China before and after universal salt iodization

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background:
An increase in the prevalence of thyroid disease has been found with increasing iodine intake, since universal salt iodization (USI) was instituted throughout China in 1996. The aim of this study was to analyze the incidence of thyroid carcinoma (TC) before and after USI in Shenyang, a city of northeastern China.

Material/Methods:
The pathology reports were collected from patients with thyroid diseases who underwent surgery in the First Hospital of China Medical University from January 1, 1992 to December 31, 2009. The detection rate, the constituent ratio, the changes of sex, age, and concomitant thyroid diseases of each histological type of TC were analyzed.

Results:
The detection rate of TC, papillary thyroid carcinoma (PTC), and medullary thyroid carcinoma (MTC) increased; that of follicular thyroid carcinoma (FTC) decreased; and that of undifferentiated thyroid carcinoma (UTC) showed no change after USI. The constituent ratio of PTC increased, that of FTC and UTC decreased, and that of MTC showed no change after USI. The mean age of female patients with TC decreased after USI. The incidences of PTC complicated with either nodular goiter or chronic lymphocytic thyroiditis increased after USI.

Conclusions:
The detection rate of TC increased significantly, PTC predominated in the histological types of TC, and the mean age of female patients with TC decreased after USI. The patients with either nodular goiter or chronic lymphocytic thyroiditis under high iodine intake should be followed up.

key words:
thyroid carcinoma • iodine • universal salt iodization

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Background

Thyroid carcinoma (TC) is the most commonly encountered endocrine malignancy. Its incidence is increasing over the years, and constitutes approximately 1% of all the new diagnoses of cancer each year in the United States.

The etiology of TC is multifactorial; both genetic and environmental factors play key roles in modulating TC pathogenesis [1]. A clear relationship between iodine supply to the population and TC incidence has not been proven and is still debated [2]. However, the distribution of TC types (the higher prevalence of PTC in comparison to FTC) is related to higher iodine intake [3].

Universal salt iodization (USI) has been carried out throughout China since 1996, and as a result, iodine intake has increased countrywide. Meanwhile, an increase in the prevalence of thyroid disease has been found with increasing iodine intake [4].

To further investigate the association between iodine intake and risk for TC, we compared the detection rates of TC after USI with the rates before USI in the First Hospital of China Medical University in Shenyang, a city of Northeastern China, which was previously an iodine deficient area.

Material and Methods

A retrospective review of the pathological reports of the patients with thyroid diseases who underwent surgery in the First Hospital of China Medical University from Jan 1, 1992 to Dec 31, 2009 was performed. The WHO international classification was followed for typing the TC. The proportions of the thyroid diseases in all surgically removed specimens were calculated as the detection rates of thyroid diseases. The detection rates and the constituent ratios of each histological type of TC before and after USI were calculated, respectively. The detection rate, the constituent ratio, the changes of sex, age, and concomitant thyroid diseases of each histological type of TC before and after USI were analyzed statistically.

Statistical analysis

All statistical analyses were conducted by using the statistical program SPSS 16.0 for windows (SPSS, Chicago, IL, USA). Data were analyzed using the Student's t test or t' test for continuous variables, and the χ^2 test for nonparametric data. Numerical data are presented as mean ±SD, where appropriate. A P value below 0.05 was considered statistically significant.

Results

A total of 1239 cases of TC were reviewed in the First Hospital of China Medical University between 1992 and 2009. Of these, 961 (78%) were diagnosed in women and 278 (22%) in men. Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), undifferentiated thyroid carcinoma (UTC), and other types of TC were 1061(86%), 68(5%), 45(4%), 30(2%) and 35(3%), respectively. The thyroid microcarcinoma before and after USI were 3.53% (3/85) and 24.26% (280/1154), respectively.

The detection rates of TC before and after USI

The total detection rate of TC after USI (1.31%, 1154/87911) was significantly higher than before USI (0.71%, 85/11903) (χ^2=30.64, P<0.001). As to each histological type of TC, the detection rate of PTC (1.15%, 1009/87911) after USI was significantly higher than before USI (0.44%, 52/11903) (χ^2=50.38, P<0.001), and that of MTC after USI (0.05%, 44/87911) was also higher than before USI (0.01%, 1/11903) (χ^2=4.04, P<0.05), while that of FTC after USI (0.05%, 46/87911) was significantly lower than before USI (0.18%, 22/11903) (χ^2=27.04, P<0.001) and that of UTC showed no significant difference after USI compared with before USI (P>0.05).

The constituent ratios of TC before and after USI

The constituent ratio of PTC after USI was significantly higher than before USI (87.44% *vs.* 61.18%, χ^2=44.37, P<0.001), while that of FTC was significantly lower than before USI (3.99% *vs.* 25.88%, χ^2c=69.02, P<0.001), that of UTC was lower than before USI (2.08% *vs.* 7.06%, χ^2c=6.33, P<0.05), and that of MTC showed no significant difference after USI compared with before USI (P>0.05).

Sex distribution in TC before and after USI

Except for MTC, the detection rates of female patients with PTC, FTC, and UTC were all higher than in male patients before and after USI. However, the female/male ratio of each histological type of TC showed no significant difference before and after USI (P>0.05) (Table 1.)

Mean age distribution in TC before and after USI

The mean age of the patients with TC after USI was lower than before USI (t'=2.48, P<0.05), that of female patients after USI was lower than before USI (t'=2.10, P<0.05), but that of male patients showed no significant difference before and after USI (t=1.43, P>0.05). The mean ages of both female and male patients with each histological type of TC showed no significant difference before and after USI (P>0.05) (Table 2.)

Table 1. Sex distribution in TC before and after USI.

Histologic types	Before USI			After USI			P
	F	M	F:M	F	M	F:M	
PTC	36	16	2.25:1	800	209	3.83:1	NS
FTC	19	3	6.33:1	39	7	5.57:1	NS
MTC	1	0	—	22	22	1.00:1	NS
UTC	6	0	—	19	5	3.80:1	NS

TC – thyroid carcinoma; USI – universal salt iodization; PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; MTC – medullary thyroid carcinoma; UTC – undifferentiated thyroid carcinoma; F – female; M – male; F:M – female to male ratio; NS – not significant (>0.05).

Table 2. Mean age distribution in TC before and after USI (year).

Histologic types	Before USI			After USI			P
	F	M	Total	F	M	Total	
PTC	50.75±16.72	45.14±15.23	46.87±15.76	44.00±13.64	42.89±13.21	43.14±13.31	NS
FTC	51.33±11.02	47.11±15.64	47.68±14.95	47.71±20.46	44.62±14.70	45.09±15.48	NS
MTC	—	46.00± 0.00	46.00±0.00	47.55±14.19	53.05±11.43	50.30±13.03	NS
UTC	—	68.00±9.40	68.00±9.40	50.20±7.86	66.47±10.84	63.08±12.18	NS
Total	**49.95±15.80**	**47.98±16.09**	**48.45±15.9**	**45.26±13.96**	**43.68±13.71**	**44.03±13.78**	**<0.05***

TC – thyroid carcinoma; USI – universal salt iodization; PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; MTC – medullary thyroid carcinoma; UTC – undifferentiated thyroid carcinoma; F – female; M – male; NS – not significant (>0.05).
<0.05 * – The mean age of both the total patients and female patients with thyroid carcinoma after USI was lower than before USI (P<0.05) and that of male patients was NS.

Table 3. The incidences of TC complicated with other thyroid diseases before and after USI [%].

Histologic types	Nodular goiter			Chronic lymphocytic thyroiditis			Adenoma		
	Before USI	After USI	P	Before USI	After USI	P	Before USI	After USI	P
PTC	7.69	49.26	<0.001	0.00	9.91	<0.05	7.69	4.66	NS
FTC	9.09	28.26	NS	0.00	4.35	NS	4.55	8.70	NS
MTC	0.00	40.91	NS	100.00	9.09	NS	0.00	2.27	NS
UTC	0.00	29.17	NS	0.00	0.00	NS	0.00	0.00	NS

TC – thyroid carcinoma; USI – universal salt iodization; PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; MTC – medullary thyroid carcinoma; UTC – undifferentiated thyroid carcinoma; NS – not significant (>0.05).

The incidences of TC complicated with other thyroid diseases before and after USI

The incidence of PTC complicated with nodular goier after USI was significantly higher than before USI (χ^2=34.28, P<0.001) and that of PTC complicated with chronic lymhocytic thyroiditis was also higher than before USI (χ^2c=4.59, P<0.05), while that of each histological type of TC complicated with thyroid adenoma showed no significant difference before and after USI (P>0.05) (Table 3.)

Table 4. Epidemiologic studies dealing with the influence of iodine deficiency and iodine supplementation on the distribution of the different histological types of TC.

Author/year	Country/province	Iodine deficiency	Iodine supplementation
Belfiore [10], 1987	Italy/Catania	UTC + FTC ↑	UTC+ FTC=>PTC
Langsteger [11], 1993	Switzerland	FTC ↑	FTC=>PTC
Harach [12], 1995	Argentina	—	FTC=>PTC
Pettersson [13], 1996	Sweden	FTC ↑	FTC=>PTC
Segovia [14], 2000	Australia/Carinthia	PTC ↑	FTC=>PTC
Farahati [15], 2004	German/lower Franconia	—	FTC=>PTC
Guan [16], 2006	China/Liaoning	PTC ↑	FTC=>PTC
Kasagi [17], 2007	Japan	—	UTC + FTC=>PTC
Cui [18], 2008	China/Jilin	PTC ↑	FTC=>PTC

TC – thyroid carcinoma; PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; UTC – undifferentiated thyroid carcinoma; ↑ – high proportion of; => – shift to.

Discussion

In the present investigation we noted a significant rise in the total incidence of TC after USI, which largely resulted from an increasing incidence of PTC. Whether the total incidence of TC is influenced by iodine intake is still controversial. In Italy, the incidence of TC was higher in an iodine-deficient area compared to that in an iodine-sufficient region [5]. In China, the prevalence and incidence of TC in iodine-excessive areas were much higher than those in the other 2 iodine-deficient and iodine-sufficient areas [6]. Moreover, some of the highest incidence rates of TC were found in Iceland and Hawaii, both known to have long-standing high iodine intake, although exposure to volcanic activity (and natural radiation) has been suggested as an explanation for the high incidence in these 2 areas [7,8]. However, several other countries [Tyrol (Austria), lower Franconia (Germany), Geneva (Switzerland), Sweden and Salta (Argentina)] introducing iodinated salt programs have observed increasing trends in PTC [9]. Effective iodine prophylaxis programs also lead to a decrease in the frequency of MTC, as well as its more malignant counterpart, FTC [10]. The incidence of ATC decreased after higher iodination of salt [11].

There are many problems in assessing possible changes in TC incidence rates in relation to iodine intake. Factors such as screening programs, clinical practice, and pathological criteria, may show significant variations with time, particularly in iodine-deficient areas before and after USI. Indeed, the change in the incidence of TC after USI is the combined result of multiple factors and it is unlikely that a certain single factor accounts for this result completely. Fortunately, the majority of increased TC was PTC with good prognosis, a striking proportion of which were microcarcinoma. As a result, despite the incidence of TC increasing significantly, the mortality remained stable in recent years [12].

Available evidence from animal experiments and epidemiological studies, as well as from the introduction of iodine prophylaxis, has demonstrated a relationship between iodine intake and the types of thyroid carcinoma [2,13–22]. Consistent with the literature, our results showed there was a change in the distribution of its main histological subtypes of TC, especially the ratio of PTC to FTC after USI. Animal experiments suggested that iodine deficiency and iodine excess could induce carcinomas derived from thyroid follicular cells through different mechanisms (Table 4). A clear increase in the incidence of thyroid epithelial cell carcinomas after prolonged iodine deficiency leading to a situation of the thyroid gland by thyrotropin and possibly other growth factors was observed in the iodine-deficient animals where the malignancies reported were FTC and PTC, whereas the mechanism in which iodine excess-induced TC is still not clear. Only PTC was found in experimental animals fed with an iodine-adequate and iodine-rich diet [2,13].Clinical studies revealed that high iodine intake seemed to be a significant risk factor for the occurrence of BRAF mutation, which occurred uniquely in PTC among various TC and was most important for the initiation of PTC among genetic alterations. The increased PTC incidence may result from BRAF mutation induced by high iodine intake, which may therefore be a risk factor for the development of PTC [23–25]. It has also been suggested that iodine can prevent the progression of differentiated thyroid carcinoma to anaplastic carcinoma by interfering with oncogene

expression or the mutation of tumor suppressor genes such as BRAF, ERK, RAS, and p53 [26,27].

In the present study neither increased nor decreased female/male ratio of the patients with TC was found with increasing iodine intake, although the female/male ratio of each histological type of TC changed slightly before and after USI, demonstrating increasing iodine intake did not influence the female/male ratio of the patients with TC, consistent with the result of Cui et al. [22]. A shift to younger age with female incidence was also noted in the present study and may relate to the contributions of estrogen to the development of TC.

Our results showed that the incidence of PTC complicated with nodular goiter increased after USI, indicating iodine may be a risk factor for a shift from nodular goiter to TC, especially to PTC. In addition, a high dietary intake of iodine may be associated

with a high frequency of PTC and thyroiditis; thyroiditis is more commonly associated with PTC than with other types of TC [28]. Our results showed that the incidence of PTC complicated with chronic lymphocytic thyroiditis increased after USI.

Conclusions

In conclusion, the detection rate of TC increased significantly, PTC predominated in the histological types of TC, and the mean age of female patients with TC decreased after USI. The patients with either nodular goiter or chronic lymphocytic thyroiditis under high iodine intake should be followed up.

Declaration of interest

The authors declare no conflicts of interests.

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