ORIGINAL ARTICLE

Effect of Iodine Intake on Thyroid Diseases in China

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ABSTRACT

BACKGROUND

Iodine is an essential component of thyroid hormones; either low or high intake may lead to thyroid disease. We observed an increase in the prevalence of overt hypothyroidism, subclinical hypothyroidism, and autoimmune thyroiditis with increasing iodine intake in China in cohorts from three regions with different levels of iodine intake: mildly deficient (median urinary iodine excretion, 84 μg per liter), more than adequate (median, 243 μg per liter), and excessive (median, 651 μg per liter). Participants enrolled in a baseline study in 1999, and during the five-year follow-up through 2004, we examined the effect of regional differences in iodine intake on the incidence of thyroid disease.

METHODS

Of the 3761 unselected subjects who were enrolled at baseline, 3018 (80.2 percent) participated in this follow-up study. Levels of thyroid hormones and thyroid autoantibodies in serum, and iodine in urine, were measured and B-mode ultrasonography of the thyroid was performed at baseline and follow-up.

RESULTS

Among subjects with mildly deficient iodine intake, those with more than adequate intake, and those with excessive intake, the cumulative incidence of overt hypothyroidism was 0.2 percent, 0.5 percent, and 0.3 percent, respectively; that of subclinical hypothyroidism, 0.2 percent, 2.6 percent, and 2.9 percent, respectively; and that of autoimmune thyroiditis, 0.2 percent, 1.0 percent, and 1.3 percent, respectively. Among subjects with euthyroidism and antithyroid antibodies at baseline, the five-year incidence of elevated serum thyrotropin levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. A baseline serum thyrotropin level of 1.0 to 1.9 mIU per liter was associated with the lowest subsequent incidence of abnormal thyroid function.

CONCLUSIONS

More than adequate or excessive iodine intake may lead to hypothyroidism and autoimmune thyroiditis.

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Salt has been iodized throughout China since 1996, and as a result, iodine intake has increased countrywide. Data from the Ministry of Health of China indicate that the median urinary iodine excretion — a surrogate measure for iodine intake — increased from 165 μg per liter in 1995 to 330 μg per liter in 1997 and stabilized at a similar level (306 μg per liter) in 1999.[1] In fact, according to the guidelines of the World Health Organization (WHO), the United Nations Children's Fund, and the International Council for Control of Iodine Deficiency Disorders,[2] after iodization measures were instituted, the levels of iodine intake of some residents of China were more than adequate (median urinary iodine excretion, 200 to 299 μg per liter) or excessive (median urinary iodine excretion, >300 μg per liter). During the same period, we have observed increasing numbers of patients with thyroid disorders.

In order to understand the effect of increased iodine intake on thyroid health, a project to investigate iodine-induced thyroid diseases was initiated in 1999 in cohorts in three regions with different levels of iodine intake.[3-6] Median urinary iodine excretion was 84 μg per liter in Panshan, a region with mildly deficient iodine intake; 243 μg per liter in Zhangwu, a region with more than adequate iodine intake; and 651 μg per liter in Huanghua, a region of excessive iodine intake. In 1999 (at baseline), the prevalence of overt hypothyroidism was 0.3 percent, 0.9 percent, and 2.0 percent in the regions with mildly deficient, more than adequate, and excessive levels of iodine intake, respectively. The prevalence of subclinical hypothyroidism was 0.9 percent in Panshan, 2.9 percent in Zhangwu, and 6.1 percent in Huangha, and the prevalence of autoimmune thyroiditis was 0.5, 1.7, and 2.8 percent, respectively. The prevalences of all three thyroid diseases appeared to increase as the iodine intake rose. We conducted a five-year follow-up study to evaluate the effect of persistent regional differences in iodine intake on the incidences of these thyroid diseases and to report changes from baseline in the three regions studied.

METHODS

SUBJECTS

In 1999, three representative communities with different levels of iodine intake were chosen for study, as previously described.[4] These three regions included Panshan, a county in northeastern China in which the local inhabitants traditionally consumed locally produced salt (iodine content, less than 3.4 mg per kilogram) and thus had a long-term mild deficiency in iodine intake. Residents of Zhangwu — another county in northeastern China — had mildly deficient levels of iodine intake before 1995, but the intake increased after salt iodization was instituted, so that the iodine intake of local inhabitants had been more than adequate since 1996. Data from the Endemic Department of Liaoning Province show that the mean urinary iodine excretion in the 1980s and 1990s was between 70 and 90 μg per gram of creatinine among residents in both Panshan and Zhangwu until 1996 but that it had increased in Zhangwu after 1996.[7] Huanghua, a county close to the Bo Hai Sea, is a region in which residents have excessive iodine intake owing to the high iodine content in the drinking water[8] (96 to 228 μg per liter; mean urinary iodine excretion from the 1970s to 1980s, 509 to 757 μg per gram of creatinine).

In the baseline study, home visits were made in each of the three regions to all 16,287 inhabitants who were older than 13 years of age and who had been living in the community for more than 10 years. An oral questionnaire was administered to each person. The questionnaire elicited personal information and data on the economic status of the family, eating habits, type of salt used, amount of salt ingested per day, and the personal or family history of thyroid diseases (including time of diagnosis and therapy undertaken). Among those receiving home visits, 3761 participated in the baseline study (1103 in Panshan, 1584 in Zhangwu, and 1074 in Huanghua). Pregnant women and women receiving oral contraceptives were excluded. Both palpation and B-mode ultrasonography of the thyroid were performed, and samples of urine and blood were obtained from each subject after an overnight fast.

The follow-up study used the same protocol as the baseline study and included 3018 of the 3761 original subjects (80.2 percent): 884 of the 1103 subjects in Panshan (80.1 percent), 1270 of the 1584 subjects in Zhangwu (80.2 percent), and 864 of the 1074 subjects in Huanghua (80.4 percent).

Research protocols were approved by the medical ethics committee of China Medical University. All subjects provided written informed consent after the research protocols were carefully explained to them.

ASSAYS

Both the baseline and follow-up studies used the same assay methods and assay kits. The laboratory instrumentation and personnel were also the same at baseline and follow-up.

Serum levels of thyrotropin, thyroid peroxidase antibody, thyroglobulin antibody, and thyroglobulin were measured in all subjects. Serum levels of free thyroxine, free triiodothyronine, and thyrotropin receptor antibody were measured in subjects with abnormal serum thyrotropin levels (less than 0.3 mIU per liter or greater than 4.8 mIU per liter). The chemiluminescence immunoassay for thyrotropin, thyroid peroxidase antibody, thyroglobulin antibody, thyroglobulin, free thyroxine, and free triiodothyronine was from Diagnostic Products Corporation, and the radioreceptor assay for thyrotropin receptor antibody was from Diasorin.

The reference range for the serum thyrotropin level (0.3 to 4.8 mIU per liter) was derived from 2.5th to 97.5th percentile values for the 2503 subjects without known clinical thyroid disease, without a family history of thyroid disease, without antithyroid antibodies, and without goiter or nodules on B-mode ultrasonography in the three cohorts. The limit of detection of serum thyrotropin was 0.002 mIU per liter. At follow-up, the intraassay and interassay coefficients of variation for serum variables were between 1.2 and 9.4 percent. Thirty blood samples tested at baseline were retested in 2004 for each thyroid hormone and for antithyroid antibodies, and the interassay coefficients of variation were less than 9 percent.

Urinary iodine excretion was determined in all subjects at baseline and follow-up with the use of the colorimetric ceric ion–arsenious acid ash method, based on the Sandell–Kolthoff reaction.[9] Thyroid ultrasonography was also performed[10] by trained observers using the same equipment (model SA600 with 7.5-MHz linear transducers, Medsion) in both studies. Goiter was defined as a thyroid volume exceeding 19.4 ml for women and 25.6 ml for men. This definition was derived from the mean (+2 SD) thyroid volume in 392 subjects without thyroid disease, without a family history of thyroid disease, without antithyroid antibodies, and without goiter or nodules on B-mode ultrasonography from one region (median urinary iodine excretion, 126 μg per liter [25th to 75th percentile, 112 to 188]). The diagnostic criteria for thyroid diseases are listed in Table 1.

Table 1. Diagnostic Criteria for Thyroid Diseases.

Thyroid Disease	Diagnostic Criteria*
Overt hypothyroidism	Thyrotropin >4.8 mIU/liter, free T_4 <10.3 pmol/liter
Subclinical hypothyroidism	Thyrotropin >4.8 mIU/liter, free T_4 within the normal range
Autoimmune thyroiditis	TPOAb >100 IU/ml with overt or subclinical hypothyroidism
Hashimoto's thyroiditis	With goiter
Atrophic thyroiditis	Without goiter
High serum autoantibody values	TPOAb ≥50 IU/ml or TgAb ≥40 IU/ml
Overt hyperthyroidism	Thyrotropin <0.3 mIU/liter; free T_4 >24.5 pmol/liter, free T_3 >6.3 pmol/liter, or both
Subclinical hyperthyroidism	Thyrotropin <0.3 mIU/liter, free T_3 and free T_4 within the normal ranges
Graves' disease	Overt hyperthyroidism, a diffuse goiter or normal thyroid volume on B-mode ultrasonography, and TRAb >2 IU/liter or TPOAb >100 IU/ml
Goiter	Thyroid volume >19.4 ml (women) or >25.6 ml (men)
Diffuse	Goiter without nodules
Nodular	Goiter with nodules >10 mm in diameter
Single nodule	Single nodule >5 mm in diameter, thyroid volume within the normal range
Multiple nodules	≥2 Nodules >5 mm in diameter, thyroid volume within the normal range

* The reference range for free thyroxine (T_4) is 10.3 to 24.5 pmol per liter; for free triiodothyronine (T_3), 2.3 to 6.3 pmol per liter; for thyroid peroxidase antibody (TPOAb), 7 to 50 IU per milliliter; for thyroglobulin antibody (TgAb), 10 to 40 IU per milliliter; and for thyrotropin receptor antibody (TRAb), ≤2 IU per liter. To convert values for free T_4 to nanograms per deciliter, multiply by 12.87.

STATISTICAL ANALYSIS

All statistical analyses were performed with SPSS software (version 11.5). Comparison of the proportions for the three cohorts was performed with the use of the chi-square test ($\alpha = 0.05$); if the null hypothesis was rejected, then pairwise comparisons were performed ($\alpha' = 0.0125$). Analysis of variance (by means of the Student–Newman–Keuls test) was used to compare the mean ages among the cohorts. Serum thyroglobulin values were compared among the three cohorts with the use of the Student–Newman–Keuls test after logarithmic transformation, because the data had a log-normal distribution rather than a normal distribution. Risk factors were analyzed with the use of logistic regression. The level of significance was set at 5 percent for the Student–Newman–Keuls test and logistic regression.

RESULTS

SUBJECTS

Levels of urinary iodine excretion and salt intake at baseline and follow-up were stable in each cohort (Table 2). Except for their different levels of iodine intake, the three cohorts were similar in age and sex, economic status, and health care received. Iodine intake was also essentially the same at baseline and at follow-up.

SERUM THYROGLOBULIN

Serum thyroglobulin values were not available for subjects with high levels of thyroglobulin antibody (≥40 IU per milliliter). Values were thus available for 3335 subjects in 1999 (990 in Panshan, 1435 in Zhangwu, and 910 in Huanghua) and 2679 subjects in 2004 (795 in Panshan, 1132 in Zhangwu, and 752 in Huanghua). Serum thyroglobulin levels differed significantly among the three cohorts both in 1999 ($F = 11.7$, $P < 0.001$) and in 2004 ($F = 24.6$, $P < 0.001$). The levels also differed significantly between the cohorts in 1999 (Panshan vs. Zhangwu, $P < 0.001$; Panshan vs. Huanghua, $P = 0.007$; and Zhangwu vs. Huanghua, $P = 0.002$) and in 2004 (Panshan vs. Zhangwu, $P < 0.001$; Panshan vs. Huanghua, $P < 0.001$; and Zhangwu vs. Huanghua, $P = 0.008$).

HYPOTHYROIDISM

During the follow-up period, 11 subjects received a diagnosis of overt hypothyroidism, 7 of whom (64 percent) were considered to have autoimmune thyroiditis. The prevalence of the disease at baseline differed significantly for all comparisons (among all three cohorts, $\chi^2 = 15.2$, $P < 0.001$; Panshan vs. Zhangwu, $\chi^2 = 4.5$, $P = 0.04$; Panshan vs. Huanghua, $\chi^2 = 14.1$, $P < 0.001$; and Zhangwu vs. Huanghua, $\chi^2 = 4.9$, $P = 0.03$). In addition, 60 subjects received a diagnosis of subclinical hypothyroidism; 20 of these subjects (33 percent) had high levels (≥50 IU per milliliter) of thyroid peroxidase antibody. The prevalence of the disease differed significantly among the cohorts (all three cohorts, $\chi^2 = 47.1$, $P < 0.001$; Panshan vs. Zhangwu, $\chi^2 = 12.7$, $P < 0.001$; Panshan vs. Huanghua, $\chi^2 = 43.3$, $P < 0.001$; and Zhangwu vs. Huanghua, $\chi^2 = 15.9$, $P < 0.001$). The cumulative incidence of subclinical hypothyroidism was significantly higher in Zhangwu (with iodine intake that was more than adequate) and Huanghua (with excessive intake) than in Panshan (with mildly deficient intake) (all three cohorts, $\chi^2 = 20.1$, $P < 0.001$; Panshan vs. Zhangwu, $\chi^2 = 18.3$, $P < 0.001$; Panshan vs. Huanghua, $\chi^2 = 20.4$, $P < 0.001$; and Zhangwu vs. Huanghua, $\chi^2 = 0.17$, $P = 0.68$) (Table 3).

Of the 121 subjects who received a diagnosis of subclinical hypothyroidism in 1999, 100 (82.6 percent) participated in the 2004 follow-up study; none had received thyroxine therapy during this period. Of these 100 subjects, 29 (29.0 percent) had persistent subclinical hypothyroidism (3 of 7 in Panshan [42.9 percent], 17 of 42 in Zhangwu [40.5 percent], and 9 of 51 in Huanghua [17.6 percent]). There were more cases of persistent hypothyroidism in Zhangwu than in Huanghua ($P = 0.02$). Five of the 100 subjects with subclinical hypothyroidism in 1999 had overt hypothyroidism in 2004 (4 of 42 in Zhangwu [9.5 percent] and 1 of 51 in Huanghua [2.0 percent]). The remaining 66 subjects had become euthyroid by 2004.

Logistic-regression analysis indicated that a serum thyrotropin level above 6 mIU per liter (odds ratio, 3.4; 95 percent confidence interval, 1.1 to 10.5), high levels of antithyroid antibody (thyroid peroxidase antibody ≥50 IU per milliliter or thyroglobulin antibody ≥40 IU per milliliter) (odds ratio, 5.3; 95 percent confidence interval, 1.8 to 15.7), and a shift in iodine intake from mildly deficient to more than adequate (odds ratio, 8.0; 95 percent confidence interval, 2.5 to 25.4) were risk factors for continued subclinical hypothyroidism. Separate logistic analysis showed that a serum thyrotropin level greater than 2 mIU per liter (odds ratio, 6.6; 95 percent confidence interval, 3.1 to 14.1), high antithyroid antibody levels (odds ratio, 3.0; 95 percent confidence interval, 1.6 to 5.6), a shift in

Table 2. Demographic Characteristics and Iodine Intake at Baseline (1999) and at Follow-up (2004).*

Characteristic	Panshan (Mildly Deficient Iodine Intake)		Zhangwu (More Than Adequate Iodine Intake)		Huanghua (Excessive Iodine Intake)	
	1999 (N=1103)	2004 (N=884)	1999 (N=1584)	2004 (N=1270)	1999 (N=1074)	2004 (N=864)
Sex (M:F)	1:2.88	1:3.16	1:3.22	1:3.37	1:2.91	1:3.26
Age (yr)						
Mean	36±13	42±12	39±13	45±12	37±13	42±12
Range	14–88	19–81	14–95	19–84	14–79	19–83
Urinary iodine excretion (μg/liter)						
Schoolchildren†						
Median	84	88	243	214	651	634
Interquartile range	33–99	37–102	167–479	189–458	521–844	511–897
Study cohort						
Median	103	97	375	350	615	635
Interquartile range	61–188	46–137	237–562	213–505	470–768	427–745
Iodine in drinking water (μg/liter)						
Median	8.2	10.0	4.6	7.8	201.8	201.8
Interquartile range	1.4–17.0	8.1–12.4	2.4–13.9	6.6–10.0	174.7–260.5	167.6–205.7
Iodine in salt (mg/kg)	<3.4	<3.4	54.5±3.6	45.6±5.9	23.3±5.6	25.0±10.0
Serum thyroglobulin (ng/ml)						
Median	7.7	11.7	6.0	9.1	6.4	10.2
Interquartile range	4.4–13.4	6.6–21.6	3.3–10.7	4.8–17.2	3.6–11.4	5.9–20.4

* Plus–minus values are means ±SD. Data for 1999 are from Yang et al.[4] and Li et al.[11]
† Values were obtained for reference in 60 schoolchildren 8 to 10 years of age.

iodine intake from mildly deficient to more than adequate (odds ratio, 10.7; 95 percent confidence interval, 1.4 to 79.7), and excessive iodine intake (odds ratio, 9.1; 95 percent confidence interval, 1.2 to 69.7) were risk factors for subclinical hypothyroidism at follow-up among subjects with normal thyroid function at baseline.

AUTOIMMUNE THYROIDITIS AND THYROID AUTOANTIBODIES

The prevalence of autoimmune thyroiditis differed significantly among the three cohorts ($\chi^2=18.4$, P<0.001) and between Panshan (mildly deficient intake) and Zhangwu (more than adequate intake) ($\chi^2=8.7$, P=0.003) and Huanghua (excessive intake) ($\chi^2=18.8$, P<0.001) but not between Zhangwu and Huanghua ($\chi^2=3.6$, P=0.06). The cumulative incidence of autoimmune thyroiditis differed significantly among the three cohorts ($\chi^2=6.3$, P=0.04) and was significantly higher in Zhangwu (1.0 percent of subjects who participated in the follow-up) and Huanghua (1.3 percent) than in Panshan (0.2 percent) (Panshan vs. Zhangwu, $\chi^2=4.8$, P=0.03; Panshan vs. Huanghua, $\chi^2=6.5$, P=0.01; Zhangwu vs. Huanghua, $\chi^2=0.29$, P=0.59) (Table 3). In contrast, no significant difference was found in the cumulative incidence of high levels of thyroid peroxidase antibody and thyroglobulin antibody among the three cohorts (Table 3).

The prevalence of Hashimoto's thyroiditis differed significantly among the three cohorts ($\chi^2=7.4$, P=0.03) and between Panshan and Huanghua ($\chi^2=7.6$, P=0.006) but not between Zhangwu and Panshan ($\chi^2=3.7$, P=0.06) or Huanghua ($\chi^2=1.2$, P=0.29). The prevalence of atrophic thyroiditis differed significantly among the three cohorts ($\chi^2=11.7$, P=0.003) and between Panshan and Zhangwu ($\chi^2=5.3$, P=0.02) and Panshan and Huanghua ($\chi^2=11.7$, P=0.001) but not between Zhangwu and Huanghua ($\chi^2=2.5$, P=0.11).

Table 3. Prevalence and Cumulative Incidence of Thyroid Diseases in the Three Regions.*

Thyroid Disease	Panshan (Mildly Deficient Iodine Intake)	Zhangwu (More Than Adequate Iodine Intake)	Huanghua (Excessive Iodine Intake)
	number of cases (percent)		
Overt hypothyroidism			
Prevalence†	3 (0.3)	15 (0.9)	21 (2.0)
Incidence	2 (0.2)	6 (0.5)	3 (0.3)
Subclinical hypothyroidism			
Prevalence†	10 (0.9)	46 (2.9)	65 (6.1)
Incidence	2 (0.2)	33 (2.6)	25 (2.9)
Autoimmune thyroiditis			
Prevalence	5 (0.5)	27 (1.7)	30 (2.8)
Incidence	2 (0.2)	13 (1.0)	11 (1.3)
Hashimoto's thyroiditis			
Prevalence	4 (0.4)	16 (1.0)	16 (1.5)
Incidence	0	4 (0.3)	4 (0.5)
Atrophic thyroiditis			
Prevalence	1 (0.1)	11 (0.7)	14 (1.3)
Incidence	2 (0.2)	9 (0.7)	7 (0.8)
Overt hyperthyroidism			
Prevalence‡	18 (1.6)	32 (2.0)	13 (1.2)
Incidence	12 (1.4)	12 (0.9)	7 (0.8)
Subclinical hyperthyroidism			
Prevalence‡	41 (3.7)	62 (3.9)	12 (1.1)
Incidence	12 (1.4)	25 (2.0)	9 (1.0)
Graves' disease			
Prevalence‡	15 (1.4)	20 (1.3)	12 (1.1)
Incidence	7 (0.8)	7 (0.6)	5 (0.6)

Among the 213 subjects with euthyroidism who had high levels of thyroid peroxidase antibody in 1999, 184 (86.4 percent) participated in the 2004 follow-up. Of these, 146 (79.3 percent) continued to have high levels (47 of 56 in Panshan [83.9 percent], 67 of 79 in Zhangwu [84.8 percent], and 32 of 49 in Huanghua [65.3 percent]), with the rate of continued euthyroidism significantly higher in Panshan and Zhangwu than in Huanghua ($P=0.03$ and $P=0.01$, respectively). In addition, the higher the level of thyroid peroxidase antibody, the higher the percentage of subjects with continued euthyroidism (54.8 percent of subjects with a level of 50 to <100 IU per milliliter, 80.5 percent with a level of 100 to <500 IU per milliliter, and 93.9 percent with a level 500 IU per milliliter or above). The same trend was found in those with high levels of thyroglobulin antibody.

The cumulative incidence of supranormal levels of thyrotropin (greater than 4.8 mIU per liter) among subjects with euthyroidism who also had high levels of either thyroid peroxidase antibody or thyroglobulin antibody increased with increasing iodine intake in all three cohorts (Fig. 1). The cumulative incidence among subjects with high levels of thyroid peroxidase antibody differed significantly among the three cohorts ($\chi^2=9.3$, $P=0.01$) and between Panshan and Huanghua ($\chi^2=8.3$, $P=0.004$) but not between Zhangwu and either Panshan ($\chi^2=1.2$, $P=0.26$) or Huanghua ($\chi^2=3.4$, $P=0.07$). The cumulative incidence among subjects with high levels of thyroglobulin antibody

Table 3. (Continued.)

Thyroid Disease	Panshan (Mildly Deficient Iodine Intake)	Zhangwu (More Than Adequate Iodine Intake)	Huanghua (Excessive Iodine Intake)
	number of cases (percent)		
High TPOAb level			
Prevalence§	101 (9.2)	155 (9.8)	113 (10.5)
Incidence	25 (2.8)	52 (4.1)	32 (3.7)
High TgAb level			
Prevalence§	99 (9.0)	142 (9.0)	101 (9.4)
Incidence	29 (3.3)	49 (3.9)	44 (5.1)
Diffuse goiter			
Prevalence¶	159 (19.5)	205 (13.5)	54 (5.1)
Incidence	48 (7.1)	53 (4.4)	57 (6.9)
Nodular goiter			
Prevalence¶	30 (3.7)	52 (3.4)	26 (2.5)
Incidence	34 (5.0)	29 (2.4)	7 (0.8)
Single nodule			
Prevalence¶	72 (8.8)	125 (8.3)	43 (4.1)
Incidence	27 (4.0)	69 (5.7)	46 (5.6)
Multiple nodules			
Prevalence¶	31 (3.8)	29 (1.9)	71 (6.7)
Incidence	3 (0.4)	15 (1.2)	8 (1.0)

* The prevalence was calculated at baseline (1999); incidence is the cumulative incidence between 1999 and 2004. The total numbers of cases on which prevalence and incidence percentages for all thyroid disease except goiter or nodule were based are 1103 and 884 for Panshan, 1584 and 1270 for Zhangwu, and 1074 and 864 for Huanghua, respectively. The total numbers of cases on which prevalence and incidence percentages for goiter and nodule were based are 815 and 678 for Panshan, 1514 and 1204 for Zhangwu, and 1056 and 826 for Huanghua, respectively. TPOAb denotes thyroid peroxidase antibody, and TgAb thyroglobulin antibody.
† Prevalence data are from Shan et al.[3]
‡ Prevalence data are from Yang et al.[4]
§ Prevalence data are from Li et al.[12]
¶ Prevalence data are from Hu et al.[13]

differed significantly among the three cohorts ($\chi^2=7.2$, P=0.03) and between Panshan and Huanghua ($\chi^2=5.8$, P=0.02) and Zhangwu ($\chi^2=4.6$, P=0.04) but not between Zhangwu and Huanghua ($\chi^2=0.8$, P=0.36).

HYPERTHYROIDISM

There were no significant differences in the cumulative incidence of either overt hyperthyroidism or Graves' disease among the three cohorts (Table 3). Graves' disease was the main cause of overt hyperthyroidism, accounting for 58.3 percent of cases in Panshan, 58.3 percent in Zhangwu, and 71.4 percent in Huanghua.

The prevalence of subclinical hyperthyroidism differed significantly among the three cohorts ($\chi^2=19.2$, P<0.001) and between Huanghua and Panshan ($\chi^2=15.5$, P<0.001) and Zhangwu ($\chi^2=18.5$, P<0.001) but not between Panshan and Zhangwu ($\chi^2=0.07$, P=0.79). Of 115 subjects with subclinical hyperthyroidism at baseline, 92 (80.0 percent) participated in the follow-up in 2004, and none had received treatment for the disease. At follow-up, 5 (5.4 percent) had overt hyperthyroidism, 18 (19.6 percent) continued to have subclinical hyperthyroidism, and 66 (71.7 percent) had become euthyroid. There was no significant difference in these proportions among the three cohorts.

Logistic-regression analysis indicated that a thyrotropin level below 0.3 mIU per liter (odds ratio, 5.7; 95 percent confidence interval, 2.1 to 15.0),

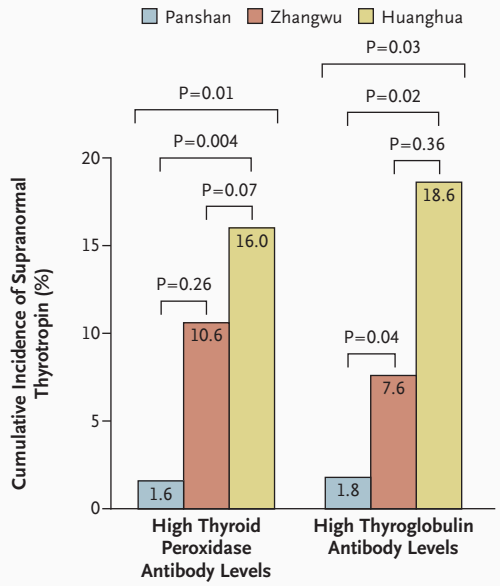

Figure 1. Cumulative Incidence of Supranormal Thyrotropin Levels among Subjects with Euthyroidism and High Levels of Thyroid Peroxidase Antibody or Thyroglobulin Antibody.

Iodine intake was mildly deficient in Panshan, more than adequate in Zhangwu, and excessive in Huanghua. The cumulative incidence increased with increasing iodine intake.

a high level of thyroid peroxidase antibody (odds ratio, 3.8; 95 percent confidence interval, 1.7 to 8.8), and the presence of any kind of goiter (odds ratio, 3.1; 95 percent confidence interval, 1.4 to 6.8) were risk factors for overt hyperthyroidism.

GOITER

The prevalence of diffuse goiter differed significantly for all comparisons (among all three cohorts, $\chi^2=91.7$, P<0.001; Panshan vs. Zhangwu, $\chi^2=14.0$, P<0.001; Panshan vs. Huanghua, $\chi^2=94.9$, P<0.001; and Zhangwu vs. Huanghua, $\chi^2=49.3$, P<0.001). The cumulative incidence of diffuse goiter also differed significantly for all comparisons (among all three cohorts, $\chi^2=8.1$, P=0.01; Panshan vs. Zhangwu, $\chi^2=6.1$, P=0.01; Panshan vs. Huanghua, $\chi^2=0.02$, P=0.89; and Zhangwu vs. Huanghua, $\chi^2=6.0$, P=0.01), with a higher incidence in Panshan and Huanghua than in Zhangwu. In contrast, the cumulative incidence of nodular goiter decreased with increasing iodine intake and differed significantly for all comparisons (among all three cohorts, $\chi^2=26.8$, P<0.001; Panshan vs. Zhangwu, $\chi^2=10.4$, P=0.001; Panshan vs. Huanghua, $\chi^2=24.4$, P<0.001; and Zhangwu vs. Huanghua, $\chi^2=6.2$, P=0.01).

The prevalence of a single nodule in the thyroid gland differed significantly among the three cohorts ($\chi^2=21.5$, P<0.001) and between Huanghua and Panshan ($\chi^2=9.7$, P=0.002) and Zhangwu ($\chi^2=8.9$, P=0.003) but not between Panshan and Zhangwu ($\chi^2=0.24$, P=0.63). The prevalence of multiple nodules differed significantly for all comparisons (among all three cohorts, $\chi^2=38.7$, P<0.001; Panshan vs. Zhangwu, $\chi^2=7.5$, P=0.006; Panshan vs. Huanghua, $\chi^2=7.6$, P=0.006; and Zhangwu vs. Huanghua, $\chi^2=38.5$, P<0.001). No significant differences among cohorts were found in the cumulative incidence of either single or multiple nodules (Table 3).

Logistic-regression analysis showed that female sex (odds ratio, 2.7; 95 percent confidence interval, 1.7 to 4.4), mildly deficient iodine intake (odds ratio, 1.8; 95 percent confidence interval, 1.3 to 2.6), excessive iodine intake (odds ratio, 1.5; 95 percent confidence interval, 1.0 to 2.1), and high levels of thyroid autoantibodies (odds ratio, 1.7; 95 percent confidence interval, 1.1 to 2.5) were the risk factors for goiter in normal subjects.

Of the 418 subjects with diffuse goiter at baseline, 344 (82.3 percent) participated in the follow-up. Of these 344, 128 (37.2 percent) still had diffuse goiter: 53 of 132 (40.2 percent) in Panshan, 59 of 170 (34.7 percent) in Zhangwu, and 16 of 42 (38.1 percent) in Huanghua. Twenty-eight of the 344 subjects (8.1 percent) had nodular goiter: 16 of 132 (12.1 percent) in Panshan, 9 of 170 (5.3 percent) in Zhangwu, and 3 of 42 (7.1 percent) in Huanghua. Significantly more subjects had nodular goiter in the region in which intake was deficient (Panshan) than in the region in which intake was more than adequate (Zhangwu) (P=0.03). Thyroid size reverted to normal in 123 of the 344 subjects (35.8 percent): 48 of 132 (36.4 percent) in Panshan, 70 of 170 (41.2 percent) in Zhangwu, and 5 of 42 (11.9 percent) in Huanghua. Nodular goiter reverted to normal in significantly more subjects in Panshan and Zhangwu than in Huanghua during the follow-up period (P=0.003 and P<0.001, respectively). Of the 108 subjects who initially had nodular goiter, 88 (81.5 percent) participated in the follow-up; 61 (69.3 percent) still had nodular goiter in 2004: 20 of 25 (80.0 percent) in Panshan, 28 of 44 (63.6 percent) in Zhangwu, and 13 of 19 (68.4 percent) in Huanghua.

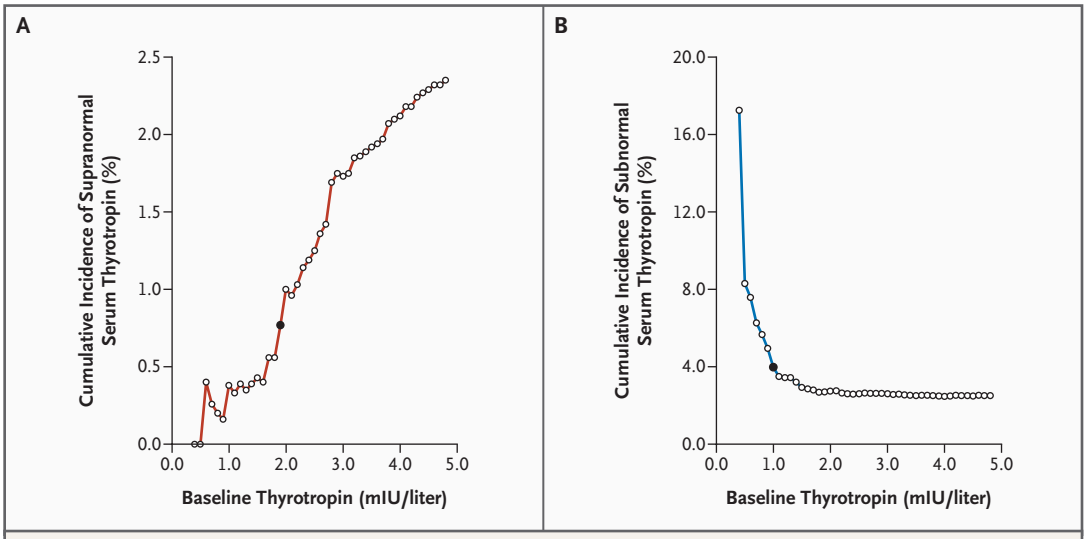

Figure 2. Cumulative Incidence of Abnormal Levels of Serum Thyrotropin at Five Years among 2727 Subjects Who Had Normal Levels of Serum Thyrotropin at Baseline.

The relation between the baseline thyrotropin levels in 1999 and the cumulative incidence in 2004 of supranormal serum thyrotropin levels (above 4.8 mIU per liter) (Panel A) or subnormal serum thyrotropin levels (below 0.3 mIU per liter) (Panel B) is shown. A serum thyrotropin level above 1.9 mIU per liter (solid symbol in Panel A) was associated with an increased incidence of a supranormal thyrotropin level; a drop in serum thyrotropin level below 1.0 mIU per liter (solid symbol in Panel B) was associated with an increased incidence of a subnormal thyrotropin level.

THYROID CANCER

No cases of thyroid cancer were identified in Panshan or Zhangwu at baseline; however, 10 subjects (1 man and 9 women) were found to have papillary thyroid carcinoma in Huanghua, the region with excessive intake of iodine.[14] Between 1999 and 2004, 13 cases of papillary thyroid cancer were diagnosed in Huanghua (in 2 men and 11 women) but none were diagnosed in the other two regions.

FOLLOW-UP INTERVAL FOR MEASURING THYROTROPIN

Follow-up data were obtained for 2727 subjects who had normal thyrotropin levels at baseline. At follow-up, 68 of these subjects (2.5 percent) had a serum thyrotropin level below 0.3 mIU per liter (20 subjects had overt hyperthyroidism, and 48 had subclinical hyperthyroidism); 64 (2.3 percent) had a serum thyrotropin level above 4.8 mIU per liter (5 had overt hypothyroidism, and 59 had subclinical hypothyroidism). Figure 2 shows the cumulative incidence of abnormal serum thyrotropin levels plotted against baseline thyrotropin levels. These data suggest that an increase in serum thyrotropin above 1.9 mIU per liter is associated with an increased incidence of subsequent supranormal thyrotropin level and that a decrease in serum thyrotropin level below 1.0 mIU per liter is associated with an increased incidence of subsequent subnormal thyrotropin level (Fig. 2). Thus, persons with baseline thyrotropin levels above 1.0 mIU per liter but below 1.9 mIU per liter may have the lowest incidence of abnormal thyrotropin levels five years later.

DISCUSSION

Our results suggest a link between increased iodine intake and hypothyroidism. Similar results were reported in small-scale comparative epidemiologic studies by Laurberg et al.[15] and Szabolcs et al.[16] No significant difference in the cumulative incidence of overt hypothyroidism was observed among the three cohorts. This finding may relate to the short interval between the baseline and follow-up studies and the long latency period for hypothyroidism. As compared with regions such as Panshan, in which inhabitants have a mildly deficient long-term intake of iodine, there appears to be a higher incidence of both overt and subclinical hypothyroidism in regions such as Zhangwu, where iodine intake increased from being mildly deficient before salt iodization to more than adequate afterward. Moreover, the highest

rate of progression from subclinical hypothyroidism to overt hypothyroidism also occurred in Zhangwu. These results suggest that iodine supplementation to a level that is more than adequate in a region in which iodine intake was previously mildly deficient may accelerate the development of subclinical hypothyroidism to overt hypothyroidism.

High iodine intake has been reported to initiate and exacerbate infiltration of the thyroid by lymphocytes in genetically susceptible BB/W rats[17] and NOD.H-2h4 mice.[18] Our results suggest that both more than adequate and excessive levels of iodine intake may increase the incidence and prevalence of autoimmune thyroiditis in humans. Autoimmune thyroiditis appeared to be the main cause of overt hypothyroidism in this observational study. High iodine intake may trigger and exacerbate autoimmune thyroiditis, increasing the likelihood of overt hypothyroidism. In the cross-sectional baseline study in 1999, the prevalence of hypothyroidism (as defined by a thyrotropin level above 4.8 mIU per liter) in subjects with high levels of thyroid peroxidase antibody increased with increasing iodine intake in the three cohorts.[12] In addition, the follow-up study showed that, among subjects who had high levels of thyroid peroxidase antibody or thyroglobulin antibody at baseline, the rate of progression to hypothyroidism correlated directly with iodine intake. Therefore, we infer that both more than adequate levels and excessive levels of iodine intake may drive thyroid function from a state of potential autoimmune impairment to overt hypothyroidism.

It has been reported that the incidence of hyperthyroidism increases among persons with chronic, severe iodine deficiency who suddenly increase their iodine intake. Such an increased incidence has been shown to revert to baseline in the continued presence of iodine supplementation three to five years later.[19-21] Our findings did not confirm this observation. It is possible that iodine-induced hyperthyroidism peaked between 1996 (when salt iodization began in China) and 1999, but in a retrospective study by our group, no significant difference was found in the incidence of overt hyperthyroidism between 1990–1996 and 1997–1999 in the three communities.[4] Our current results further confirm that iodine supplementation in regions in which iodine deficiency is mild (not severe) would not increase the incidence of overt hyperthyroidism or Graves' disease.

There has been recent controversy about whether to change the reference range for thyrotropin, especially its upper limit.[22,23] Data from the 20-year follow-up of the Whickham study indicate that an increase in thyrotropin above 2 mIU per liter was associated with an increased probability of hypothyroidism.[24] We obtained natural-history data on subjects with normal thyrotropin levels (0.3 to 4.8 mIU per liter) at baseline and at follow-up. Our data suggest that even within the normal range, a thyrotropin level of 1.0 to 1.9 mIU per liter is safe. Although both higher and lower thyrotropin levels appeared to predict an increased risk of subsequent dysfunction, we recommend monitoring patients with abnormal levels for clinical manifestations rather than changing the reference range for thyrotropin and treating the patients.

In conclusion, although iodine supplementation should be implemented to prevent and treat iodine-deficiency disorders, supplementation should be maintained at a safe level. Levels that are more than adequate (median urinary iodine excretion, 200 to 299 μg per liter) or excessive (median urinary iodine excretion, >300 μg per liter) do not appear to be safe, especially for susceptible populations with either potential autoimmune thyroid diseases or iodine deficiency. Supplementation programs should be tailored to the particular region. No iodine supplementation should be provided for regions in which iodine intake is sufficient, whereas salt in regions in which iodine intake is deficient should be supplemented with iodine according to the degree of iodine deficiency.

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