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Factors associated with serum thyroglobulin levels in a population living in Belarus

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SUMMARY

Objective—Serum thyroglobulin (Tg) has been associated with a number of thyroid disorders and has been proposed as an indicator of iodine deficiency in a population. However, few studies have addressed the epidemiology of Tg in a population-based setting or in the context of exposure to radioactive iodine-131 (I-131). Our objective was to evaluate baseline levels of Tg in relation to socio-demographic characteristics, iodine status, and thyroid function for individuals exposed to I-131.

Design—A population-based cohort assembled in Belarus following the Chernobyl accident provided demographic factors, clinical data, and physiological measurements.

Participants—Our analytic sample included 10,344 subjects of whom 7,890 had no thyroid disease and 2,454 had evidence of structural or functional thyroid abnormality.

Measurements—Standardized assays were used to measure serum Tg, urinary iodine, TSH, and antibodies to Tg and thyroid peroxidase. Ultrasound was used to assess the presence of nodules and estimate thyroid volume.

Results—In the fully adjusted model, percent change in Tg was significantly increased among females, smokers, and subjects of older age and Tg increased with decreasing urinary iodine concentration, increasing serum TSH and increasing thyroid volume (p-values for trend < 0.0001), and presence of thyroid nodules (p < 0.05). We found a complex interaction between region of residence, rural/urban living, presence/absence of thyroid abnormalities, and serum Tg (p < 0.0001).

Conclusions—In residents of Belarus, serum Tg is significantly related to presence of thyroid abnormalities as well as indicators of thyroid function and iodine deficiency and, therefore, could

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be used to characterize the iodine status and thyroid function of individuals in the context of epidemiological study.

Keywords

Thyroglobulin; Iodine; Thyroid; Chernobyl Nuclear Accident; Republic of Belarus

Introduction

Thyroglobulin (Tg) is a central protein of the thyroid gland, serving as the storage site of iodine and playing a major role in the coupling reaction necessary to synthesize thyroid hormones.¹ Elevated serum Tg has been proposed as an indicator of iodine deficiency in a population.^{2–4} In addition, changes in serum Tg levels have been associated with a number of thyroid disorders including Graves' disease⁵, subacute thyroiditis^{5, 6}, and thyrotoxicosis factitia.⁷ Although its utility as a predictor of thyroid cancer risk has not been established⁸, serum Tg levels are also used to monitor response to treatment in low-risk patients with papillary or follicular thyroid carcinoma.⁹

Few studies to date have addressed the epidemiology of serum Tg in a large population-based sample^{4, 10}. Most observational studies have focused on small groups of patients with thyroid disease^{5, 7, 9–16}, with comparison and interpretation of results complicated by varying degrees of assay sensitivity, precision, or standardization^{17, 18}. In addition, few epidemiological studies have evaluated potential interference of endogenous Tg antibodies (Tg-Ab) on measurement of serum Tg in healthy subjects⁴. Following the 1986 Chernobyl nuclear accident, in which large amounts of radioactive iodine-131 (I-131) were released into the atmosphere, a population-based Belarus-American Thyroid cohort (BelAm) was assembled to study the effects of I-131 on the thyroid gland based on in-depth clinical screening examinations which included blood samples for analysis of thyroid hormones and antibodies and urine samples for measurement of iodine concentrations.^{19, 20}

The objective of the current analysis was to evaluate baseline levels of serum Tg in relation to socio-demographic characteristics, indicators of iodine status, and thyroid function in subjects with and without thyroid abnormalities. We used data from the first round of screening of the BelAm cohort²⁰, in which biochemical measurements performed with sensitive standardized immunoluminometric assays are available for the majority of individuals, including measurements of Tg-Ab.¹² To our knowledge, this study represents the largest population-based epidemiological analysis to date of serum Tg.

Subjects and Methods

Study sample

A detailed description of the study population has been previously published.²⁰ Briefly, our analytic sample was drawn from the BelAm cohort that is comprised of 11,611 subjects living in Belarus who were 18 years at the time of the Chernobyl accident on April 26, 1986.²¹ For the analyses presented here, we used data from the 1st or baseline screening examination conducted mainly from 1997 to 2001. We excluded cohort members with a diagnosis of thyroid cancer (n=86), self-reported history of any thyroid disease prior to the 1st screening, or intake of thyroid hormones at 1st examination (n=611). To reduce potential interference with serum Tg measurements, we excluded subjects with elevated Tg-Ab levels (greater than 60 IU/mL) (n=491). Subjects were also excluded if information on their serum Tg levels or presence of thyroid nodules was not available (n=74). To eliminate potential inter-assay variation in performance, we excluded five subjects whose serum measurements

of Tg were performed using a different assay. After these exclusions, the final analytic dataset contained 10,344 subjects.

Subjects with and without thyroid abnormalities ('abnormal' and 'normal' groups, respectively) were analyzed separately. The abnormal group included cohort members who, at 1st screening, were found to have at least one of the following: enlarged thyroid (diffuse goiter) either at palpation or ultrasound examination; thyroid nodules at ultrasound; decreased or increased levels of thyroid-stimulating hormone (TSH; <0.3 mIU/L and 4 mIU/L, respectively). Of 10,344 subjects, 7,890 (76%) were classified into the normal group and 2,454 (24%) into the abnormal group. A sensitivity analysis was performed to separately examine the two most common thyroid conditions of diffuse goiter (n=1,781) and presence of thyroid nodules (n=358). It found that the levels of Tg and trends across factors under investigation (sex, age, year, etc.) were largely similar to those in the overall abnormal thyroid group (not shown).

Study subjects or accompanying guardians for minors provided written informed consent for the study. The study was approved by institutional review boards in Belarus and the United States.

Data collection

The screening protocol is described in detail in Stezhko and colleagues.²⁰ In brief, participants were administered questionnaires regarding demographic characteristics and dietary and lifestyle habits around the time of the accident relevant for thyroid dose estimation. An endocrinologist conducted a physical examination of the thyroid gland and obtained a detailed medical history. Study participants underwent a second thyroid palpation and ultrasound examination by a trained ultrasonographer. The thyroid gland was examined using 7.5-MHz probes (Toshiba 240, Tokyo, Japan; Sigma or Logic200) with the subject supine and neck extended. Information on presence and characteristics of thyroid nodules as well as on overall thyroid echostucture and echogenicity was recorded. Thyroid volume was calculated based on the volume of an ellipsoid as described by Brunn and colleagues.²²

Subjects also provided blood and spot urine samples throughout the day (with 75% of these collected between 8:00 am and 12:00 pm). Serum Tg, TSH, anti-thyroid peroxidase antibodies (ATPO-Ab), and Tg-Ab were largely measured with LUMitest immunochemiluminescence assays (BRAHMS Diagnostica, GMBH, Henningsdorf, Germany) using a Bertholdt 953 luminometer (Berthold Technologies, GmbH & Co. KG, Bad Wildbad, Pforzheim, Germany). For about 30% of serum samples, TSH was measured using IMx immunochemiluminescence assays (ABBOTT, USA) and Tg-Abs were measured using radioimmunoassays (RIA, BRAHMS Diagnostica, GMBH, Henningsdorf, Germany). No systematic differences in TSH distributions were observed for the two different assays (BRAHMS and ABBOT) so they were combined. Iodine concentration was measured in urine specimens using the method of Dunn and colleagues.²³

Statistical analysis

Variables potentially associated with serum Tg based on evidence from previous studies were considered in current analyses. These variables included socio-demographic characteristics (sex, age, calendar year of examination, oblast or state of residence, urbanicity) as well as smoking status and indicators of iodine intake and/or thyroid function (urinary iodine concentration, thyroid volume, levels of serum TSH, ATPO-Ab, Tg-Ab, and presence of thyroid nodules). We first tested the association of serum Tg with socio-demographic and physiological factors individually, and calculated serum Tg means and

medians according to different categories of each factor. We used the Kruskal-Wallis test to test the heterogeneity of median Tg levels across categories of a factor under investigation.

We then examined the relationship between serum levels of Tg and significant predictors that emerged from univariate analyses, in multivariable models. In these models, we used the natural log transformation of the response variable Tg which closely followed the normal distribution. We tested for potential pairwise interactions between the factors of interest and presence or absence of thyroid abnormalities using likelihood ratio tests, adjusting for other predictors that were significant in multivariable analyses. If there was no evidence of a statistically significant interaction or difference in the relationships for serum Tg with a factor of interest between the two groups (normal and abnormal), these were combined; otherwise, the results are presented separately. For ease of interpretation, regression coefficients, β_j , were converted to percent changes (PCs) according to the equation,

$$\% \Delta Tg = 100 \frac{E(Tg_1) - E(Tg_0)}{E(Tg_0)} = 100(\exp(\beta_j) - 1),$$

where $E(Tg_1)$ is the expected serum Tg for an individual subject in category 1 of some factor and $E(Tg_0)$ is the expected serum Tg in the referent category. The PC is a unitless measure that represents the percent change in the geometric mean of Tg comparing one category of a factor to the referent category after adjusting for all other factors. Trend tests were conducted by treating the categorical variables as ordinal in regression models. Statistical tests were two-sided with a specified type I error of 0.05. P-values and 95% confidence intervals (CIs) were estimated by maximum likelihood procedures. Kruskal-Wallis tests were performed using the NPAR1WAY procedure and regression analyses were conducted with the GENMOD procedure using SAS software V9.2 (SAS Institute, Inc.).

Results

The distribution of serum Tg concentration both in the normal and abnormal thyroid groups varied significantly across many demographic characteristics (Table 1). In the normal group, median Tg levels were statistically significantly elevated in females and smokers. Median Tg increased with increasing age at examination, decreased with increasing calendar year at examination, and varied significantly by oblast (higher in Mogilev and others) and rural/urban residence (higher in rural areas within each oblast). In the abnormal group, median Tg showed similar trends, except it did not vary significantly by sex. Overall, median serum Tg levels in the abnormal group were higher than in the normal thyroid group for each of the factors examined.

The distributions of mean and median Tg levels across indicators of iodine intake and thyroid function are shown in Table 2 separately for the normal and abnormal groups. Median serum Tg increased significantly with decreasing urinary iodine concentration, increasing TSH level, and increasing thyroid volume in both groups. No statistically significant heterogeneity in median serum Tg according to ATPO-Ab or Tg-Ab levels was found, except for the RIA assay in the abnormal group ($p_{\text{trend}}=0.004$). Similarly, no statistically significant difference in median Tg was found between subjects with and without ultrasound detected thyroid nodules ($p=0.421$) in the abnormal group.

In multivariable analyses, the relationship between serum Tg and place of residence defined at oblast and urbanicity level was significantly different between normal and abnormal thyroid groups ($p<0.0001$, 8 degrees of freedom, Table 3). Although higher levels of Tg in

rural compared to urban places of residence were observed in all oblasts for both normal and abnormal groups, in Gomel, the median of Tg was significantly higher in rural compared to urban residents only in the abnormal group (PC=16.15%, 95% CI: 6.59%–26.56%). Additional adjustment for I-131 thyroid dose did not change this association (not shown).

Since there were no significant differences between normal and abnormal groups in the relationships with the remaining factors significant in multivariable models, Table 4 shows combined results. We found a 21% increase in serum Tg levels for females compared to males and similarly large increase for the age range of 26–33 years compared to the reference group of 10 to 17 years at 1st examination. Percent change in serum Tg declined sharply in more recent calendar years. During the short span of 7 years, the geometric mean of serum Tg decreased by 34%. Smokers had almost 14% higher levels of serum Tg compared to non-smokers. After controlling for all other factors, serum Tg levels strongly increased with decreasing urinary iodine levels, increasing TSH level, and increasing thyroid volume (p trend for each <0.0001). The presence of nodules was associated with about 15% increase in serum Tg.

Discussion

In this large study of residents of Belarus, aged 18 years or younger at the time of the Chernobyl accident, baseline levels of serum Tg were evaluated in relation to socio-demographic characteristics and physiological parameters of the thyroid gland after taking into account potential interference of Tg-Ab. Analyses were conducted both in subjects with and without thyroid abnormalities.

Our main objective was to evaluate the relationship between serum Tg and commonly used measures of iodine intake in epidemiological studies including urinary iodine. While we relied on measurements of iodine concentration in spot urine samples, known to have large within-subject variation, we found a significant independent increase in serum Tg with decreasing concentration of urinary iodine. Similar associations have been reported in other studies, particularly those conducted among iodine deficient populations.^{2, 4, 24} A recent study by Hatch *et al.* in this cohort which focused on assessing the effect of government iodization initiatives in Belarus reported that at 1st screening examination (largely corresponding to the period prior to iodization program), the median urinary iodine concentration and prevalence of diffuse goiter were consistent with a mild level of iodine deficiency (65.3 µg/L and 16%, respectively).²⁵

Compared to the iodine concentration in spot urine samples, serum Tg levels may be more suitable for characterizing an individual's iodine intake due to the lower within-subject variability.^{26, 27} In addition, serum Tg has the advantage of capturing iodine intake over a longer time period (weeks to months rather than days).³ Since intake of radioactive iodine is influenced by concentrations of iodine in thyroid tissue, using serum Tg concentration as a more stable measure of an individual's iodine level may provide better insight into how individual iodine status might modify the dose-response relationship between radioactive I-131 exposure and risk of thyroid cancer. While no effect modification was found for I-131 and individual levels of iodine in spot urine samples in the BelAm cohort or a parallel cohort in Ukraine,²¹ our findings suggest the potential value of using serum Tg to examine this interaction in future analyses.

It has been proposed that elevated serum Tg in iodine deficient populations might result from changes in thyroid metabolism and/or amount of thyroid tissue.²⁸ In agreement with this idea, we found independent increases in serum Tg with increasing thyroid volume, presence of thyroid nodules, and increasing levels of TSH. Correlation between serum Tg

and thyroid volume is the most consistently reported association in iodine deficient populations. In fact, in a Danish study conducted in the area of mild-to-moderate iodine deficiency, thyroid volume emerged as the most important predictor of serum Tg. The same study also reported positive associations with presence of thyroid nodules and suppressed TSH levels (<0.2 mU/L).⁴ While our findings concerning thyroid nodules are consistent with the above mentioned study, the TSH findings are not. We found a strong, monotonic increase in serum Tg with increasing levels of TSH that was not due to associations with mild hypo- or hyperthyroidism (TSH 4.0 mIU/L and TSH <0.3 mIU/L, respectively). This trend was apparent within the normal TSH range. The reasons for discrepancies between the two studies with regards to TSH are not clear, but perhaps relate to the younger age of our population.

Indicators of iodine status and thyroid function often exhibit geographical variation. Our finding that individuals living in rural areas tended to have higher median Tg levels than those living in urban areas (Table 1) is consistent with the observation by Hatch and colleagues that within Belarus, populations in rural areas had lower median urinary iodine concentrations than their urban counterparts.²⁵ These associations were particularly pronounced in the abnormal thyroid group, even after adjusting for socio-demographic and physiological variables related to serum Tg (Table 4). Urban/rural differences within oblast and between the oblasts probably point to the importance of food origin, supply, distribution, and consumption preferences. The significant interaction between oblast and rural/urban residence and normal/abnormal thyroid status on median levels of serum Tg, which was primarily due to the Gomel data, is difficult to interpret. Residents from Gomel oblast generally had higher exposure to radioactive iodine,²⁹ but adjustment for I-131 dose had no effect on the observed interaction. Reasons for the interactive effect are not clear and might represent a chance finding, iodine intake differences not fully captured by Tg, or some unidentified factor prevalent in Gomel.

Relatively few studies have addressed the epidemiology of serum Tg for basic demographic characteristics. Some studies examining serum Tg in healthy subjects found no sex or age-related differences, while others did.^{4, 10, 30–34} A study of healthy residents of Denmark found no sex-related differences in serum Tg for the 20–39 year age group, but did find a significantly higher serum Tg concentration in females compared to males for the 60 years and older group.³¹ A recent study of serum Tg reference values in healthy subjects with normal thyroid ultrasound also found significantly higher Tg measurements in females as compared to males (median values of 6.7 ng/mL and 8.10 ng/mL, respectively).³² Our findings (Table 4) also support higher levels of serum Tg in females both with and without thyroid abnormalities.

Several other noteworthy associations with serum Tg emerged from our study. The oldest subjects at 1st examination (26–33 years) had the highest serum Tg. This pattern persisted after controlling for other factors and did not vary by presence or absence of thyroid abnormalities. Serum Tg increased with age among women in an iodine deficient area of Italy¹⁰ and in subjects living in iodine deficient areas of Denmark⁴. In general, these trends may reflect changes in dietary habits with age. In Belarus, older subjects may have been less likely to participate in the iodization programs in schools and work cafeterias that were initiated around 2000. The decrease in serum levels of Tg with calendar time, especially pronounced in 2001–2003, corroborates findings of increased urinary iodine concentration due to iodization programs reported by Hatch *et al.*²⁵ Our study also adds to the evidence that smoking might be associated with increased levels of serum Tg, particularly in iodine deficient areas, as first reported by the Danish study.³⁵ We further demonstrated that the association with smoking seems to be independent of other factors and present in subjects with and without thyroid abnormalities.

The strengths of this study include its large sample size (over 10,000 subjects), availability of data on a number of demographic factors, standardized clinical examination, and availability of biochemical indicators of iodine status and thyroid function measured by sensitive assays. Our study is also strengthened by a standardized approach to measuring serum Tg with concurrent assessment of endogenous Tg-Abs that allowed us to evaluate potential interference with Tg measurements. Several study limitations should also be borne in mind. Although a Tg-Ab level of 60 IU/mL is the cutoff for autoimmune disease diagnosis, this does not necessarily translate into ideal exclusion criteria for interference with Tg measurements. Since no assays, including recovery tests, were performed in this cohort as is often done with patients being monitored for recurrence of thyroid cancer, we accounted for potential residual interference or confounding by adjusting for Tg-Ab levels among Tg-Ab negative individuals in our multivariable models. While serum Tg is a sensitive indicator of thyroid abnormalities, it lacks specificity. With this in mind, grouping subjects with different thyroid disorders in the abnormal group seems justifiable and supported by our sensitivity analysis. The data from the 1st screening cycle is cross-sectional in nature and, therefore, it is not always possible to establish the temporal sequence of the observed associations. We were not able to evaluate the relationship between serum Tg and intake of iodine rich-foods because nutritional data were not available.

In summary, among residents of Belarus aged 18 years or younger at the time of the Chernobyl accident, levels of serum Tg significantly related to indicators of iodine status and thyroid function. Our results support and expand previous findings and serve as important background data for post-Chernobyl studies of thyroid cancer and other thyroid diseases.

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Table 1

Mean and median Tg (µg/L) by socio-demographic characteristics for those with normal and abnormal thyroid

Characteristic	Normal thyroid (N=7890)				Abnormal thyroid (N=2454)			
	N	Mean Tg	Median Tg	P-value ^{a,b}	N	Mean Tg	Median Tg	P-value ^{a,c}
Sex								
Male	4229	11.03	7.6	<0.0001	1086	15.1	10.15	0.635
Female	3661	13.03	8.7		1368	15.82	10	
Age at screening, years^d								
[10,17)	1836	11.32	7.9	<0.0001	684	14.88	9.9	<0.0001
[17,21)	1945	10	7.1		517	14.1	8.3	
[21,26)	2186	11.63	8.4		650	15.39	10.4	
[26,33]	1923	14.92	9.1		603	17.52	12	
Calendar year at exam								
1996–1997	597	13.87	10	<0.0001	501	17.07	11.3	0.0001
1998	1327	11.65	8.2		486	15.39	9.5	
1999	1669	11.74	8.4		461	16.07	10.3	
2000	3067	11.09	7.9		776	14.32	10	
2001–2003	1230	13.81	7.1		230	15.16	8.5	
Oblast of residence at screening								
Gomel urban	2437	11.54	7.6	<0.0001	688	11.97	8.3	<0.0001
Gomel rural	2385	11.97	8.2		739	14.97	10	
Minsk urban	1990	10.97	7.6		556	13.96	9.55	
Minsk rural	252	13.91	10.15		150	24.63	15.25	
Mogilev urban	258	12.81	9.95		84	15.7	12.7	
Mogilev rural	309	15.79	11.5		93	22.98	17.4	
Others urban	149	14.5	10.9		80	20.95	15.15	
Others rural	110	18.11	11.45		64	33.62	25.3	
Smoking status								
Yes	2576	12.04	8.5	<0.0001	665	17.12	11.1	0.002
No	5286	11.94	8		1779	14.92	9.8	
Missing	28	6.95	5.75		10	11.94	6.55	

Abbreviation: Tg=thyroglobulin concentration.

Abnormal thyroid criteria: thyroid volume>25 mL for males, thyroid volume>18 mL for females, thyroid nodules, TSH<0.3 mIU/L, or TSH 4 mIU/L

^a P-values from Kruskal-Wallis Test for heterogeneity of medians

^b P-values for trend are <0.0001 for age group and calendar year in the normal group

^c P-values for trend are 0.004 for age group and 0.0002 for calendar year in the abnormal group

^d Cutoff values based on quartiles in the thyroid normal group

Table 2
Mean and median Tg (µg/L) by iodine status and thyroid function for those with normal and abnormal thyroid

Parameter	Normal thyroid (N=7890)				Abnormal thyroid (N=2454)			
	N	Mean Tg	Median Tg	P-value ^{ab}	N	Mean Tg	Median Tg	P-value ^{ac}
Urinary iodine concentration, µg/L								
[0.1,20)	795	17.14	12.1	<0.0001	355	24.92	16.9	<0.0001
[20,50)	2047	13.3	9.7		655	18.03	13	
[50,100)	2248	11.03	8		681	13.33	9.7	
[100,2120]	2706	10.19	6.6		739	10.75	7.2	
Missing	94	11.89	8.85		24	15.14	11.1	
Thyroid-stimulating hormone, mIU/L								
[0.0,3)				<0.0001	117	12.56	5.9	<0.0001
[0.3,1.7)	4650	11.7	7.7		1235	13.44	9.5	
[1.7,2.9)	2691	12.17	8.6		653	17.83	11.4	
[2.9,4.0)	549	13.05	9.2		157	20.18	13.5	
[4.0,156.4]					292	17.68	11.1	
Thyroid volume, mL ^d								
[2.3,9)	1579	10.66	7.7	<0.0001	336	12.59	9.05	<0.0001
[9,11)	1647	10.94	7.9		337	13.05	8.4	
[11,13)	1656	11.93	8		385	14.17	9.1	
[13,15)	1259	11.84	8.2		337	16.8	10.3	
[15,56.5]	1695	14.33	8.9		1050	17.32	11.3	
Missing	54	9.84	7.8		9	11.58	8.1	
Anti-thyroglobulin (LUMI), IU/mL ^e								
[0,0.2]	1818	11.08	8.1	0.451	553	15.37	10.8	0.731
(0.2,11.4]	1994	13.26	8.1		536	15.88	10.1	
(11.4,59.9]	1856	12.09	7.9		569	16.42	10.3	
Anti-thyroglobulin (RIA), IU/mL ^e								
[0,6.3]	732	11.04	8.25	0.793	281	15.73	10.7	0.003
(6.3,14]	759	11.25	8		267	13.46	8.9	
(14,59.7]	731	11.92	8.4		248	14.81	8.65	

Parameter	Normal thyroid (N=7890)				Abnormal thyroid (N=2454)			
	N	Mean Tg	Median Tg	P-value ^{a,b}	N	Mean Tg	Median Tg	P-value ^{a,c}
Anti-thyroid peroxidase, IU/mL ^f								
[0,4.9]	1971	10.88	8	0.366	652	15.68	10.2	0.444
(4.9,13.2]	1994	13.06	8.1		567	14.78	9.9	
(13.2,22.1]	1953	11.46	8		548	15.2	9.5	
(22.1,11867]	1972	12.41	8.2		687	16.16	10.6	
Presence of nodule at screening								
No	7890	11.96	8.1		1896	15.74	9.9	0.421
Yes					558	14.68	10.75	

Abbreviation: Tg=thyroglobulin concentration.

Abnormal thyroid criteria: thyroid volume>25 mL for males, thyroid volume>18 mL for females, thyroid nodules, TSH<0.3 mIU/L, or TSH 4 mIU/L

^aP-values from Kruskal-Wallis Test for heterogeneity of medians

^bP-values for trend are <0.0001 for iodine category, thyroid volume quintile, and TSH category; p-values for trend for Tg-Ab LUMI, Tg-Ab RIA, and ATPO-Ab are not significant in the normal group

^cP-values for trend are <0.0001 for iodine category, thyroid volume quintile, and TSH category and 0.004 for Tg-Ab RIA; p-values for trend for Tg-Ab LUMI and ATPO-Ab are not significant in the abnormal group

^dCutoff values based on quintiles in the thyroid normal group

^eCutoff values based on tertiles in the thyroid normal group

^fCutoff values based on quartiles in the thyroid normal group

Table 3

Percent change in Tg (µg/L) and 95% confidence intervals for those with normal and abnormal thyroid^a

Oblast of residence at screening ^b	Normal		Abnormal	
	Percent Change	95% CI	Percent Change	95% CI
Gomel urban	ref		ref	
Gomel rural	1.70	-2.97 6.60	16.15	6.59 26.56
Minsk urban	7.82	2.58 13.33	23.87	12.91 35.90
Minsk rural	17.05	5.08 30.38	71.36	48.19 98.16
Mogilev urban	12.07	0.87 24.53	36.41	13.17 64.43
Mogilev rural	24.64	12.92 37.57	59.76	33.59 91.06
Others urban	24.36	8.53 42.50	39.37	15.39 68.34
Others rural	31.60	12.60 53.80	122.82	80.16 175.58

Abbreviations: Tg=thyroglobulin concentration; CI=confidence interval.

Abnormal thyroid criteria: thyroid volume>25 mL for males, thyroid volume>18 mL for females, thyroid nodules, TSH<0.3 mIU/L, or TSH 4 mIU/L

^a Adjusted for sex, age at exam, calendar year, smoking status, iodine, TSH, thyroid volume, Tg-Ab titer, and nodules

^b P-value for oblast interaction by thyroid normal/abnormal group is <0.0001 (degrees of freedom=8)

Table 4

Percent change in Tg ($\mu\text{g/L}$) and 95% confidence intervals for those with normal and abnormal thyroid combined

Parameter	Percent Change ^{ab}	95% CI	
Sex			
Male	ref		
Female	21.02	16.73	25.47
Age at exam ^c			
[10,17)	ref		
[17,21)	−8.58	−13.02	−3.91
[21,26)	5.42	0.19	10.93
[26,33]	21.32	14.93	28.06
Calendar year at exam			
1996–1997	ref		
1998	−16.38	−21.58	−10.85
1999	−16.60	−21.74	−11.13
2000	−25.68	−30.13	−20.95
2001–2003	−34.16	−38.70	−29.29
Smoking status			
No	ref		
Yes	13.89	9.58	18.38
Urinary iodine concentration, µg/L			
[0,20)	ref		
[20,50)	−18.61	−23.11	−13.85
[50,100)	−32.70	−36.43	−28.75
[100,2120]	−42.86	−46.01	−39.53
Thyroid-stimulating hormone, mIU/L			
[0,0.3)	−20.38	−31.95	−6.85
[0.3,1.7)	ref		
[1.7,2.9)	12.73	8.79	16.80
[2.9,4.0)	26.93	18.89	35.51
[4.0,156.4]	26.12	13.50	40.13
Thyroid volume, mL ^d			
[2.3,9)	ref		
[9,11)	4.22	−1.18	9.91
[11,13)	8.64	2.82	14.79
[13,15)	14.30	7.67	21.34
[15,56.5]	25.21	18.12	32.73
Anti-thyroglobulin, tertile ^e			
Tertile 1	ref		
Tertile 2	−0.76	−4.57	3.21
Tertile 3	−3.33	−7.10	0.60

Parameter	Percent Change ^{ab}	95% CI	
Presence of nodule at screening			
No	ref		
Yes	14.79	5.88	24.46

Abbreviations: Tg=thyroglobulin concentration; CI=confidence interval.

^a Adjusted for all variables in table and oblast interaction with thyroid normal/abnormal status

^b P-values for trend are <0.0001 for age group, calendar year, iodine category, thyroid volume quintile, and TSH category; p-value for trend for Tg-Ab tertile is 0.09

^c Cutoff values for age based on quartiles in the thyroid normal group

^d Cutoff values for thyroid volume based on quintiles in the thyroid normal group

^e Cutoff values based on tertiles in the thyroid normal group are 0.2 and 11.4 for LUMI and 6.3 and 14 for RIA