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Factors associated with serum thyroglobulin in a Ukrainian cohort exposed to iodine-131 from the accident at the Chernobyl Nuclear Plant

Kamau O. Peters[a,*], Mykola Tronko[b], Maureen Hatch[a], Valeriy Oliynyk[b,1], Galyna Terekhova[b], Ruth M. Pfeiffer[a], Victor M. Shpak[c], Robert J. McConnell[d], Vladimir Drozdovitch[a], Mark P. Little[a], Lydia B. Zablotska[e], Kiyohiko Mabuchi[a], Alina V. Brenner[a], Elizabeth K. Cahoon[a]

[a] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States
[b] Department of Fundamental and Applied Problems of Endocrinology, State Institution 'V.P. Komisarenko Institute of Endocrinology and Metabolism of Academy of Medical Sciences of Ukraine', Kiev, Ukraine
[c] Department of Medical Consequences of the Chernobyl accident and International Cooperation, State Institution 'V.P. Komisarenko Institute of Endocrinology and Metabolism of Academy of Medical Sciences of Ukraine', Kiev, Ukraine
[d] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, United States
[e] Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, CA, United States

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ABSTRACT

Background: Serum thyroglobulin (Tg) is associated with the presence of thyroid disease and has been proposed as a biomarker of iodine status. Few studies have examined factors related to serum Tg in populations environmentally exposed to ionizing radiation and living in regions with endemic mild-to-moderate iodine deficiency.
Methods: We screened 10,430 individuals who were living in Ukraine and under 18 years of age at the time of the 1986 Chernobyl Nuclear Power Plant accident for thyroid disease from 2001 to 2003. We estimated the percent change (PC) in serum Tg associated with demographic factors, iodine-131 thyroid dose, and indicators of thyroid structure and function using linear regression. We also examined these relationships for individuals with and without indications of thyroid abnormality.
Results: Mean and median serum Tg levels were higher among participants with abnormal thyroid structure/function. Percent change in serum Tg increased among females, smokers and with older age (p-values < 0.001), and Tg increased with increasing thyroid volume, and serum thyrotropin (p-values for trend < 0.001). We found no evidence of significant associations between iodine-131 thyroid dose and Tg. Serum Tg levels were inversely associated with iodized salt intake (PC $= -7.90$, 95% confidence interval: -12.08, -3.52), and over the range of urinary iodine concentration, the odds of having elevated serum Tg showed a U-shaped curve with elevated Tg at low and high urinary iodine concentrations.
Conclusion: Serum Tg may be a useful indicator of population iodine status and a non-specific biomarker of structural and functional thyroid abnormalities in epidemiological studies.

1. Introduction

Insufficient iodine intake in approximately 1.9 billion people worldwide is primarily due to environmental conditions, low levels of iodine in soils distant from coastal areas and in regions with frequent flooding (Ahad and Ganie, 2010). Iodine deficiency increases the risk of developing thyroid diseases (such as goiter, hypothyroidism and hyperthyroidism) and can result in impaired mental function and congenital abnormalities in children born to iodine deficient mothers (WHO et al., 2007). Despite the clinical importance of measuring iodine deficiency, commonly used indicators have a number of limitations in their ability to reliably assess current iodine status. Urinary iodine concentration (UIC) from spot urine reflects recent dietary iodine intake (hours to days) and can have high daily variability (Vejbjerg et al.,

Abbreviations: ATg, antibodies to thyroglobulin; ATPO, antibodies to thyroid peroxidase; CI, confidence interval; FDR, false discovery rate; Gy, Gray; ^{131}I, iodine-131; PC, percent change; Tg, thyroglobulin; TSH, thyrotropin (thyroid stimulating hormone); UIC, urinary iodine concentration

* Correspondence to: Radiation Epidemiology Branch, DCEG, National Cancer Institute, NIH, DHHS, 9609 Medical Center Dr., Rm 7E528, MS 9778, Bethesda, MD 20892-9778, United States.
E-mail address: kamau.peters@nih.gov (K.O. Peters).

[1] Deceased

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2009; Zimmermann et al., 2006). In contrast, high thyroid volume is an indicator of long-term iodine deficiency that may persist for years after iodine repletion (Zimmermann et al., 2006). Serum thyroglobulin (Tg), a thyroid protein that facilitates the uptake and storage of iodine in the thyroid gland, has been proposed as a biomarker of intermediate-term population iodine nutrition status (weeks to months) based on associations with UIC (Knudsen et al., 2001; Krejbjerg et al., 2016; Swanson et al., 2012; Vejbjerg et al., 2009), and sensitivity to changes in iodine status following iodine supplementation (Gordon et al., 2009; Ma and Skeaff, 2014; Skeaff and Lonsdale-Cooper, 2013; Vejbjerg et al., 2009; Zimmermann et al., 2006).

Most studies of serum Tg have been conducted among individuals with clinical manifestations of thyroid disease, such as subacute thyroiditis (Hidaka et al., 1994), Graves' disease (Izumi and Larsen, 1978), and thyrotoxicosis factitia (Mariotti et al., 1982), or among people with a history of thyroid cancer (Ericsson et al., 1984; Haugen et al., 2016; Heemstra et al., 2007; McGrath et al., 2015; Molinaro et al., 2013; Rosario et al., 2013; Trimboli et al., 2015). While several epidemiologic studies have examined factors related to serum Tg in large population-based settings (Krejbjerg et al., 2016; Ma and Skeaff, 2014), only one other study has examined factors related to Tg in a radiation exposed population with mild-to-moderate iodine deficiency (Cahoon et al., 2013). In addition, studies reporting serum Tg concentrations often fail to assess assay interference by serum autoantibodies (Spencer et al., 2011), and may use different measurement assays without proper inter-study assay standardization, complicating both quantification of serum Tg concentration and comparability to other studies (Demers and Spencer, 2002; Spencer et al., 1998).

The objective of this study is to examine demographic characteristics, indicators of thyroid structure and function, and other factors in relation to serum Tg concentration in the Ukrainian-American Cohort Study of Thyroid Cancer and Other Thyroid diseases (UkrAm), 15–17 years after the Chernobyl accident. This study population may be particularly susceptible to thyroid diseases due to environmental exposures to ^{131}I and endemic mild-to-moderate iodine deficiencies.

2. Materials and methods

2.1. Study population

Our study population includes 12,379 individuals in Ukraine who were exposed as children and adolescents (< 18 years of age) to radiation from the Chernobyl accident on April 26, 1986 (Tronko et al., 2012). Measurements of serum Tg and antibodies to thyroglobulin (ATg) were made for individuals participating in the second biennial screening cycle (2001–2003), which was 15–17 years after the accident. We excluded 57 individuals with a history of thyroid cancer, 64 with thyroid cancer at the 2nd cycle, 24 with follicular adenoma, 827 who reported a history of thyroid disease (nodular or diffuse goiter, thyroiditis, hyperthyroidism or hypothyroidism), 2 who reported thyroid surgery, 26 who reported intake of thyroid hormones prior to the 2nd cycle; and 1 who did not have a thyroid gland. To reduce possible assay interference, we excluded 673 subjects with serum ATg concentrations > 60 IU/mL. We also excluded 236 subjects without serum Tg values and 39 with Tg equal to zero. Our final study sample consisted of 10,430 subjects. Study subjects or accompanying guardians for minors provided written informed consent for the study. The study was evaluated and approved by the institutional review boards in Ukraine and the United States National Cancer Institute.

2.2. Screening examination

The details of the screening examination procedure have been previously described (Stezhko et al., 2004; Tronko et al., 2012). Screening consisted of ultrasonography with 7.5-MHz ultrasound probes and thyroid palpation by a trained ultrasonographer, and independent clinical examination and palpation by an endocrinologist. Blood and spot urine samples were collected to measure serum thyroid hormones and antibody concentrations, and urinary iodine concentration. Standardized questionnaires assessing sociodemographic characteristics, residential history, dietary and medical history, and thyroid dose estimation were administered by study personnel. Tg, thyrotropin (TSH), ATg, and anti-thyroid peroxidase (ATPO) concentrations were measured in serum samples with LUMItest immunochemiluminescence assays (Brahms Diagnostica GMBH, Heningsdorf, Germany) using a Berthold 953 luminometer (Berthold Technologies, GmbH & Co. KG, Bad Wildbad, Germany) (McConnell et al., 2007). Urinary iodine content was measured using the Sandell-Kolthoff reaction, as described by Dunn and colleagues (Dunn et al., 1993). Thyroid volume was calculated based on the volume of an ellipsoid, as described by Brunn and colleagues (Brunn et al., 1981).

2.3. Dosimetry

Detailed methods for ^{131}I thyroid dose reconstruction have been described by Likhtarov and colleagues (Likhtarov et al., 2014). Briefly, assessment of thyroid doses from ^{131}I was based on direct readings (readings of gamma radiation from radiation detectors placed on the neck), age- and sex-specific thyroid masses derived for the Ukrainian population from the results of ultrasound measurements done in 1991–1996, questionnaires on residential history, dietary and lifestyle habits, and environmental transfer models. One thousand individual stochastic doses were calculated for each cohort member accounting for shared and unshared errors. The distribution of dose estimates was close to lognormal with geometric standard deviations (GSD) ranging from 1.6 to 5.4 among cohort members (Likhtarov et al., 2014). The arithmetic mean of 1000 individual stochastic dose realizations was used for this analysis. The arithmetic mean (geometric mean) for these individual ^{131}I stochastic doses was 0.67 (0.20) Gray (Gy). Only thyroid doses due to ^{131}I intake were considered in this study, as other exposure pathways (intake of short-lived ^{132}I and ^{133}I, external irradiation and ingestion of long-lived isotopes of cesium) typically account for no more than 5–10% of the total thyroid dose (Likhtarov et al., 2014).

2.4. Statistical analysis

In this exploratory analysis evaluating the relationship between factors associated with Tg and serum Tg concentration, linear regression analyses were used to compute change in log serum Tg and 95% confidence intervals (CIs). Based on previously associations with serum Tg concentration, we considered the following factors potential predictors of serum Tg in this study: sex, age at examination, calendar year of examination, age at exposure, oblast (an administrative subdivision similar to a state or province) of residence, urban or rural residence, smoking status, ^{131}I thyroid dose, serum TSH, ATg and ATPO, UIC, thyroid volume, ultrasound detected thyroid nodules, season, vitamin use, and self-reported intake of iodine rich foods (herring, fish other than herring, and seaweed), use of iodized salt, and iodine supplementation. Missing values for smoking, oblast, UIC and use of iodized salt were coded as separate categories and included as indicator variables in the models. Criteria for inclusion of covariates was based on forward selection with $\alpha = 0.05$. Variables that were initially excluded in forward selection model were evaluated individually for model influence. The variable was left in the model if any of the parameter estimates of the forward selection model changed by more than 10% after adding the variable to the model. The final model included sex, age at examination (15–18, 19–22, 23–26, 27–34 years), calendar year at examination, smoking status, oblast and urban/rural residence at examination, thyroid volume quintiles, the presence of thyroid nodules, serum TSH (≤ 0.3 (the lower limit of the reference range), 0.4–1.6, 1.7–2.8, 2.9–3.9, ≥ 4.0 (the upper limit of the reference range)) (Ostroumova et al., 2013), ATg tertiles and ATPO quartiles, ^{131}I thyroid