DOI: 10.17750/KMJ2017-77

Thyroid diseases and the risk of non-thyroidal pathology

R.I. Glushakov[1], E.V. Kozyrko[2,3], I.V. Sobolev[4], S.A. Ermolova[1], O.V. Vlaseva[1], A.A. Kuzin[1], N.I. Tapilskaya[3]

[1]Military Medical Academy named after S.M. Kirov of Russian Federation Ministry of Defense, Saint Petersburg, Russia;
[2]Research Center for Obstetrics, Gynecology and Perinatology named after V.I. Kulakov, Moscow, Russia;
[3]Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russia;
[4]Saint Petersburg Clinical Scientific and Practical Center of Modern Types of Medical Care (Oncology), Saint Petersburg, Russia

Abstract

This review presents generalized epidemiological data regarding the prevalence of non-neoplastic thyroid pathology in developed and developing countries, particularly in iodine-deficient regions, and the effect of mass iodine prophylaxis on reducing the incidence and prevalence of thyroid diseases in these regions. In addition, the review presents data regarding the prevalence of subclinical hypo- and hyperthyroidism, in which according to the averaged data, one clinical manifestation of thyroid insufficiency accounted for 20 cases of unregistered subclinical hypothyroidism and one case of identified thyroid hyperfunction accounted for 15 cases of subclinical hyperthyroidism. Furthermore, this review describes methodological, clinical, and social difficulties in assessing the prevalence of thyroid pathology and presents the main nongenomic actions of thyroid hormones, which originated from the extracellular domains of a cell adhesion protein, integrin αVβ3, resulting in the activation of mitogen-activated protein kinase, phosphatidylinositol-3 kinase, and serine/threonine protein kinases. The cell and tissue response to this stimulation is the activation of cell proliferation, angiogenesis, cell migration, and increased tissue-specific proinflammatory gene expressions, which ultimately lead to the acceleration of cancer development and its natural history. The review reports data from epidemiological studies, which established a correlation between the thyroid status and incidence (prevalence) of malignant neoplasms. Population-based studies have demonstrated that long-term hyperthyroidism increases the risk for developing malignant neoplasms of different localizations, particularly those of the breast, ovary, prostate, and lung.

Keywords: subclinical hyperthyroidism, effects of thyroid hormone, malignant neoplasms**.**

For citation: Glushakov R.I., Kozyrko E.V., Sobolev I.V. et al. Thyroid diseases and the risk of non-thyroidal pathology. *Kazan medical journal.* 2017; 98 (1): 77–84. DOI: 10.17750/KMJ2017-77.

Thyroid gland (TG) disorders are the most frequent human pathology and have varying prevalence in different regions, which primarily depends on the level of iodine consumption. Previous epidemiological studies on TG dysfunction have had a number of restrictions, e.g., defining the concepts of overt and subclinical hypo- or hyperthyroidism, sampling criteria, structure of the population under study (by age, sex, genetic, and environmental characteristics), and methods for determining thyroid hormone levels [42].

Iodine deficiency as a risk factor for developing thyroid pathology

Almost one-third of the world population lives in iodine-deficient regions [44]. An iodine intake of <50 μg/day leads to an endemic distribution of goiter, and that of <25 μg/day may result in patients having hypothyroidism owing to iodine deficiency. The prevalence of goiter in severe iodine-deficient regions can be >80%. Iodine prophylaxis programs have demonstrated effective results in reducing the prevalence of goiter, preventing goiter, and preventing the development of cretinism in children.

Functional TG autonomy may develop in nodular goiter, leading to the development of thyrotoxicosis, whose prevalence in this regard can significantly increase at the beginning of implementing mass iodine prophylaxis programs, particularly among people aged >40 years. In addition, in this context, the prevalence of autoimmune thyroiditis may increase, with hypothyroidism as an outcome of autoimmune thyroiditis.

According to an Iranian study, with the initiation of measures and increased iodine consumption, the prevalence of TG dysfunction can transiently increase in people with multinodular goiter and functional TG autonomy, which develop because of chronic iodine deficiency.

For correspondence: glushakovruslan@gmail.com Received 29.03.2016; accepted 22.06.2016.

Iodine-induced thyrotoxicosis most often develops in people living in severe iodine-deficient regions, particularly if there is a rapid and excessive increase in iodine consumption [4]. This increase in the incidence rate is apparently associated with the transfer of subclinical forms of thyroid status disorders to clinical ones and the subsequent registering of the disease [16, 20, 31].

Considering the importance of eliminating iodine deficiency diseases, in 1991, the World Health Organization Assembly stated that iodine deficiency as a global problem should be eliminated worldwide by 2000; however, it could not be implemented because of various reasons [31, 43].

Few studies have assessed the prevalence of autoimmune TG diseases in iodine-deficient regions [31, 42, 43]. For example, a Sicilian study investigated the prevalence of functional TG autonomy depending on the iodine deficiency of the region. The prevalence of functional TG autonomy was significantly higher in iodine-deficient zones (4.4% of total patients) than in iodine-rich zones (2.7%). In addition, a higher proportion of patients with nodular toxic goiter (NTG) were observed in iodine-deficient zones (1.3%) [8].

In 2014, a study ($n = 6,252$) conducted in Sardinia (a mild and moderate iodine-deficient region) reported the prevalence of goiter to be 22.1%, that of overt hyper- and hypothyroidism to be 0.4% and 0.7%, respectively, and that of subclinical hypo- and hyperthyroidism to be 4.7 and 2.4%, respectively [13].

In most cases, regions with normal iodine consumption report autoimmune TG diseases such as primary atrophic hypothyroidism, Hashimoto thyroiditis (autoimmune thyroiditis), and Graves' disease.

Population-based studies conducted in Europe, the USA, and Japan have investigated the prevalence of hyper- and hypothyroidism, as well as the prevalence of antibody-carriers in various ethnic populations, predominantly Caucasian populations [42]. A cross-sectional population study ($n = 25,862$), which was started in 1995 in Colorado, USA (with a population of 3,655,714), aimed to assess the prevalence and early detection of socially significant diseases (e.g., arterial hypertension, colorectal cancer, and glaucoma) in healthy people aged >18 years to determine thyroid-stimulating hormone (TSH) levels in all participants. The results revealed that the prevalence of hypo- and hyperthyroidism with clinical manifestations in participants without previously diagnosed TG disease was 0.4% and 0.1%, respectively, and that of subclinical hypo- and hyperthyroidism was 9.0% and 2.2%, respectively. The research data reveal that 20 cases of subclinical hypothyroidism accounted for one unregistered clinical manifestation of TG insufficiency and 15 cases of subclinical hyperthyroidism accounted for one detected case of TG hyperfunction [11].

The multistage, multiethnic study, National Health and Nutrition Examination Survey III (NHANES III), which was conducted from 1988 to 1994 in the USA and involved a sample ($n = 17,353$ over the age of 12 years) corresponding to the demographic distribution of the general US population (population at the beginning of the study, 205,562,185) with each person representing a mathematically weighted ratio of people in the population, determined the prevalence of TG diseases by recording the average levels of TSH, total thyroxine (T_4), and antibodies against thyroid peroxidase and thyroglobulin.

According to a study, the prevalence of hypothyroidism in the general population was 4.6% (overt, 0.3%; subclinical, 4.3%), which accounted for >9,500,000 people with unrecorded TG insufficiency, and that of hyperthyroidism was 1.3% (overt, 0.5%; subclinical, 0.7%), which accounted for 2,600,000 people with unrecorded hyperthyroidism [21].

Thyrotoxicosis syndrome is one of the most common conditions in endocrinology, with 80%–90% of adult thyrotoxicosis cases and 95% of pediatric cases presenting with diffuse toxic goiter (DTG) [38].

Regarding prevalence, the most common cause of thyrotoxicosis is Graves' disease, followed by a multinodular toxic goiter and rarer causes such as solitary toxic adenoma and thyroiditis. However, in a prospective multicenter study (17 centers across six European countries), among all thyrotoxicosis cases, 9.2%, 59.6%, and 31.2% of patients were diagnosed as having autonomic adenoma of TG, Graves' disease, and unclassified hyperthyroidism, respectively. According to the study, autonomic adenoma of TG was more common in iodine-deficient regions (10.1%) than in iodine-sufficient regions (3.2%) [32].

Although the peak incidence of Graves' disease occurs between 20 and 49 years of age, in some ethnic groups, it occurs in the older age (after 60 years) [9, 31, 42]. In epidemiological studies, individual causes of thyrotoxicosis are rarely considered separately, usually they are all combined together. The officially

reported incidence rate of TG hyperactivity in males is 2.1 and 22.0 per 100,000 people per year in Spain and Scotland, respectively, and that in females is 23.4 and 99.0 per 100,000 people per year in New Zealand and Scotland, respectively. These data only approximate the actual picture and depend on the availability of the population register and/or the university clinic dealing with this issue, as well as the state or foundation programs [31].

In addition, in studies different points of distribution/separation of patients depending on the TSH level were used, which ranges from 0.1 to 0.5 mU/L and affects the intermediate and final results of the studies.

Furthermore, the provision of regions with iodine is crucial because even its moderate deficit leads to a manifold increase in thyrotoxicosis caused by NTG, and this difference manifests itself in the older age groups (≥50 years) [42].

Problems in diagnosing DTG

DTG is one of the most common TG diseases that affect females 7–10 times more often than males. The prevalence of DTG in the general population is quite high and reaches up to 2%–5% depending on the region; the incidence rate is 5–7 per 100,000 people per year [42]. However, according to cohort studies, 1–3 cases of subclinical hyperthyroidism account for one case of overt hyperthyroidism, reaching a prevalence of 1%–6% in the general population [29, 35, 45].

The challenges in diagnosing TG include the special aspects of detecting antibodies against the TSH receptor, for which radioreceptor and biological methods are used. The radioreceptor assay is based on the suppression of patients' serum by binding the radioactive TSH to its receptor under the action of these antibodies. The advantages of the currently available radioreceptor methods for detecting antibodies against the TSH receptor are their sensitivity, specificity, relatively low cost, and the speed of obtaining the results.

However, the radioreceptor method does not provide any data regarding the type of antibodies, such as whether they are stimulating, blocking, or neutral, which is crucial for diagnosing DTG [30].

Although biological methods are highly sensitive and specific for detecting thyroid-specific antibodies in scientific research, their results in routine clinical practice are quite variable. Thus, the sensitivity of techniques used for determining thyroid-specific antibodies was 56%–91% when biological methods were used in multicenter studies [17].

Prevalence of subclinical forms of TG diseases

According to official statistics, the prevalence of thyrotoxicosis among females in regions with normal iodine consumption is 0.5%–2%, which among males is 10 times less [5].

In the paradigmatic Whickham Survey published in 1977, according to randomly selected samples from 2,779 adults who matched the UK population with regard to age, sex, and social class, the prevalence of undiagnosed thyrotoxicosis was 4.7 cases per 1,000 females. Diagnosed and/or previously treated thyrotoxicosis was observed in 20 per 1,000 females or in 27 per 1,000 if the possible unaccounted cases were considered. Likewise, the rate for males was 1.6–2.3 per 1,000; previously undiagnosed cases of thyrotoxicosis were not identified among males of the Whickham cohort, and the average age of diagnostics was 48 years.

After 20 years, researchers reexamined 1,877 survivor patients of this study to determine the risk factors and mortality causes; however, except the female sex, no other significant risk factors were identified for thyroid pathology [41].

In the Copenhagen crossover study, 4,073 randomly enrolled participants included 65% of the registered (2,656 males and females) aged 41–71 years. The prevalence of hyperthyroidism before the study was 1.4%, whereas that after the study was 3.3%; 1.9% of hyperthyroidism cases were detected, of which 1.3% were subclinical hyperthyroidism cases [24].

In a Japanese study that screened 1,818 healthy adults (804 males and 1,014 females; mean age, 51.3 ± 9.0 years), hypothyroidism was observed in 12 (0.7%) patients, subclinical hypothyroidism in 105 (5.8%), clinical thyrotoxicosis in 13 (0.7%), and subclinical thyrotoxicosis in 39 (2.1%). In addition, elevated titers of antithyroid antibodies were recorded in 17.7% of males and 31.4% of females. The prevalence of positive test results for antithyroid antibodies without thyroid enlargement was 14.8% among males and 23.4% among females. The authors concluded that the incidence rate of TG dysfunction in Japanese adults, who did not demonstrate changes in the thyroid status, was up to 10% of the total adult population [22].

A large population study conducted in Tyneside, Scotland, revealed 620 new thyrotox-

icosis cases, with the incidence of new cases at 0.77 per 1,000 females [95% confidence interval (CI), 0.7–0.84] and 0.14 per 1,000 males (95% CI, 0.12–0.18) per year [16]. The incidence rate of new thyrotoxicosis cases increased with age and was 2–8 times higher among females than among males. A recent additional analysis of the Thyroid Epidemiology, Audit and Research Study revealed that the incidence rate of new thyrotoxicosis cases is increasing among females because of the rise in autoimmune diseases among the general population [28].

As early as in 1984, epidemiological research data published with a subtotal coverage of the adult population of 12 cities in England and Wales revealed that the incidence rate of thyrotoxicosis, mainly caused by NTG, correlated with the prevalence of endemic goiter in these regions [7].

Furthermore, a Danish comparative study of the incidence of hyperthyroidism in East Jutland (iodine-deficient region) and Iceland (iodine-sufficient region) serves as a confirmation of the influence of iodine availability in the region. The study demonstrated that hyperthyroidism was more common in East Jutland than in Iceland because of a much higher incidence rate of multinodular toxic goiter, and most patients with these diseases were aged >50 years. Conversely, the prevalence of Graves' disease was significantly higher in Iceland than in East Jutland, and this difference was most pronounced in younger age groups, where hyperthyroidism in Iceland was more than two times as frequent as that in East Jutland [27].

An epidemiological study in Pescopagano (the Lucan Apennines, Italy, which is an iodine-deficient region in the absence of iodine prophylaxis; population, 2,248 people) examined 1,411 residents, including 419 children (215 boys and 204 girls) aged 1–14 years, accounting for 94.1% of the population in this age group, and 992 adults (573 females and 419 males), accounting for 72.5% of the population in this age group. The results revealed that the prevalence of endemic goiter was 16.0% among children and 59.8% among adults. In addition, the prevalence of hyperthyroidism, including functional autonomy of TG ($n=31$) and DTG ($n=36$), was 4.7%, and more than half of the DTG cases were detected for the first time. Of note, although functional thyroid autonomy was not observed in children, its proportion gradually increases with age, reaching 15.4% in the elderly (>75 years). The prevalence of clinical and subclinical hypothyroidism in adults amounted to 0.2% and 3.8%, respectively. Elevated levels of autoantibodies against TG and thyroperoxidase were found in 12.6% of patients. The authors of the study concluded that iodine-deficient regions reported a gradual increase in the age-related prevalence of endemic goiter, NTG, and DTG. The frequency of hyperthyroidism was two times higher in iodine-deficient regions than in iodine-sufficient regions, primarily because of a significant increase in the specific gravity of NTG [3].

Furthermore, a Chinese study ($n=3,018$) demonstrated the difference in the prevalence of hyperthyroidism among three regions with different iodine consumption levels; subclinical hyperthyroidism was observed in 3.7% and 3.9% of cases in two iodine-deficient regions and 1.1% in the iodine-sufficient region [39].

In developing countries, only a small number of studies were conducted on the epidemiology of thyroid diseases [31]. For example, a study was conducted on the prevalence of thyroid pathology in an urban community of Teheran at 6–7 years after examining patients ($n=1,999$) with a previously reported absence of thyroid pathology by determining the levels of TSH and antibodies against thyroid peroxidase (TLGS study). The prevalence of TG functional abnormalities in 808 randomly selected patients without a thyroid disease history was as follows: clinical hypothyroidism, 0.28% in females and 0.21% in males; subclinical hypothyroidism, 11.59% in females and 4.69% in males; clinical hyperthyroidism, 1.4% in females and 0.21% in males; and subclinical hyperthyroidism, 5.72% in females and 3.62% in males [14].

A Mexican two-center study of the adult population aged 18–71 years reported the prevalence of undiagnosed hypothyroidism and hyperthyroidism to be 4.98% and 1.8%, respectively [33].

The only data on the population of the Negroid race was obtained in a Johannesburg study (Republic of South Africa), where a 10-fold lower incidence of thyrotoxicosis was found among ethnic Africans than among ethnic Europeans (0.09 per 1,000 females and 0.007 per 1,000 males per year) [31, 42].

Since the introduction of new food quality standards in Switzerland in 1980, iodide levels in table salt were increased from 7.5 to 15 mg/kg. By 1989, an investigation of the change in the incidence of hyperthyroidism in the population of approximately 109,000 people revealed that the incidence rate decreased by 56%, which was associated with a decline in

the incidence rate of UTZ (decrease by 73%) and a lower incidence of Graves' disease (decrease by 33%). Notably, in the first 1–2 years, the registration of new hyperthyroidism cases increased by >20%, which is mainly attributed to the manifestation of subclinical forms of diseases [5].

Thus, according to existing literature, the general prevalence of subclinical hyperthyroidism, excluding the unregistered overt thyrotoxicosis cases whose prevalence is 1.5–2 times higher than that in official statistics according to the minimum calculations, ranges from 1.0% to 9.7% depending on the region, and it is the highest among people aged >50 years. Among risk factors, only female sex can be implicitly defined because females are 5–10 times more likely to be diagnosed as having autoimmune diseases than males [9, 23, 42].

Hyperthyroidism and risk of cardiovascular pathology

Hyperthyroidism, particularly subclinical hyperthyroidism, is a significant risk factor for the progression of cardiovascular diseases, mainly because of rhythm and conductivity disorders, as well as osteoporosis owing to the disorder of calcium metabolism [23]. Based on the Beijing cohort study, subclinical hyperthyroidism occurs in only 7.1% of patients with cardiomyopathy and is indicated by an independent risk factor for death owing to cardiovascular diseases, which increases the risk by 38.2% [29].

A Danish study conducted from 2000 to 2009 revealed an increase in mortality owing to all causes in the case of clinical and subclinical hyperthyroidism, with their related risk (RR) reported to be 1.25 (95% CI, 1.15–1.36) and 1.23 (95% CI, 1.16–1.30), respectively, compared with euthyroidism. In addition, the risk of an adverse cardiovascular event in clinical and subclinical hyperthyroidism was 1.16 (95% CI, 1.05–1.27) and 1.09 (95% CI, 1.02–1.16), respectively. A decline in mortality owing to all causes was observed in subclinical hypothyroidism (TSH level, 5–10 mIU/L), with RR reported to be 0.92 (95% CI, 0.86–0.98) [35].

A secondary analysis of the study revealed that subclinical hyperthyroidism is a risk factor for atrial fibrillation (RR, 1.41; 95% CI, 1.25–1.59), whereas hypothyroidism reduced the risk of atrial fibrillation [34].

A prospective South Korean cohort study (n = 212,456) with a median follow-up of 4.3 years, conducted from 2002 to 2009, enrolled urban residents who did not have a thyroid history and had registered normal thyroid hormone levels. The analysis of mortality (730 deaths, including 335 owing to malignant tumors and 112 owing to cardiovascular diseases) revealed that the free T_4 level was inversely proportional to the overall mortality risk (RR, 0.77; 95% CI, 0.63–0.95; p = 0.01), and the free triiodothyronine (T_3) level was inversely proportional to mortality owing to malignant tumors (RR, 0.62; 95% CI, 0.45–0.85; p = 0.001), particularly that owing to hepatocellular carcinoma [45].

Nongenomic effects of thyroid hormones

At the end of the twentieth century, Davis et al. discovered and subsequently assessed nongenomic mechanisms of TG action that was initiated by the receptors of plasma membranes for T_3 and T_4, located on the $\alpha V\beta 3$ integrin [12], which is expressed on the surface of leukocytes, platelets, and epithelial and endothelium cells, providing interaction between cells and leukocytes with biological surfaces.

Nongenomic mechanisms include TG stimulation without the participation of gene transcription of mitogen-activated protein kinase, phosphatidylinositol-3-kinase, and serine-threonine kinase, thereby promoting tumor progression, namely angiogenesis, cell proliferation, and cell migration [1, 2, 12]. In addition, iodothyronines can stimulate tissue-specific proinflammatory gene expressions in a dose-dependent manner, thereby providing a systemic proinflammatory effect, which at the tissue and organ level results in an immunopathological process. Given the systemic proinflammatory effect of TG, prolonged hyperthyroidism may contribute to the onset of a chronic inflammatory reaction that makes cells more susceptible to malignancy [1, 2].

Hyperthyroidism and risk of malignant neoplasms

Epidemiological studies conducted in the last decades of the twentieth century on the North American continent demonstrated that a hyperthyroidism history increases the relative risk of ovarian cancer by 80% and that of breast cancer by 45%–60%, adjusted for risk factors (e.g., sex, age, race, use of oral contraceptives, body mass index, smoking, and glucose metabolism disorder) [1].

A retrospective case–control study (San Francisco, USA) conducted among patients with pancreatic cancer (n = 532) between 1995 and 1999 demonstrated that compared with the control group (n = 1,701), the group with

a history of thyroid disease and hyperthyroidism has an increased risk of developing malignant TG tumors [odds ratio (OR), 2.2; 95% CI, 1.1–4.2 and OR, 2.1; 95% CI, 1.0–4.2] [25].

The 30-year follow-up data obtained from females (Massachusetts, USA) with TG diseases ($n = 7{,}338$) demonstrated that a hyperthyroidism history (95% CI, 0.8–1.4) increases the relative risk of death owing to malignant neoplasm by 1.2 times, that owing to pancreatic cancer by 2.6 times (95% CI, 1.4–4.3), that owing to lung cancer by 2.2 times (95% CI, 1.3–3.5) [18].

A prospective, randomized, crossover study was conducted in Finland from 1985 to 1989 among smokers ($n = 29{,}133$) aged 50–59 years who were diagnosed as having malignant tumors as of 2005 according to the National Cancer Registry (patients with prostate cancer, 401; people in the control group, 800) and the hormonal examination performed at the enrollment; the study results revealed a correlation between the thyroid status and the subsequent risk of prostate cancer. A lower risk of prostate cancer was observed in patients with euthyroidism having a relatively high TSH level (tendency to hypothyroidism) than in those having a low TSH level, namely TSH levels of ≥2.2 mIU/mL and TSH levels of <2.2 mIU/mL, respectively (RR, 0.70; 95% CI, 0.51–0.97; $p = 0.03$). In this study, patients with laboratory-diagnosed hypothyroidism had a lower risk of developing prostate cancer than those with euthyroid (RR, 0.48; 95% CI, 0.28–0.81; $p \leq 0.006$) [26].

A noteworthy prospective study (Malmö Preventive Project) with an average follow-up of 19.3 years and a total study power of 51,989 person-years, which was conducted among 2,696 females, demonstrated that T_3 basic levels within the reference values (0.9–3.2 mmol/L) correlated with the risk of breast cancer.

In 1983-1984 and 1990–1992, the serum T_3 level was determined depending on the birth year of patients, and the incidence rate of breast cancer was determined according to the Swedish Cancer Registry.

A subsequent statistical processing of the data of 2,185 patients, with T_3 levels determined within the framework of the preexisting prevention program in Sweden, enrolled 10,902 participants (study power 52,579 person-years; average follow-up, 24.1 years) as of December 31, 2010; it revealed that the risk of breast cancer in patients with T_3 levels within the upper quartile of the reference values was 2.80 (95% CI, 1.26–6.25). However, the risk of death owing to breast cancer in this group was significantly different only among postmenopausal females (RR, 3.73; 95% CI, 1.69–8.22; $p \leq 0.001$).

Based on regression analysis, the authors concluded a positive correlation between the T_3 level and the risk of death owing to breast cancer, but they also found that the T_3 level did not affect the risk of death owing to other causes [40].

In 1995, a prospective study in Norway with a median follow-up of 9 years enrolled 29,691 patients (19,710 females and 9,980 males) from 92,936 people in the Northern Trondelag province to investigate TSH levels. TSH levels were determined in all females aged ≥40 years, randomly in 50% of males aged >40 years, and in 5% of males and females aged 20–40 years. The exclusion criteria of the study were previously diagnosed malignant neoplasms and/or any thyroid disease and lack of data regarding harmful habits.

The results revealed that subclinical hyperthyroidism increases the relative risk of developing malignant neoplasms by 1.34 times (95% CI, 1.06–1.69), particularly lung cancer by 2.34 times (95% CI, 1.24–4.4), prostate cancer by 1.97 times (95% CI, 1.04–3.76), colon cancer by 1.38 times (95% CI, 0.7–2.73), and breast cancer by 1.2 times (95% CI, 0.67–2.16) [19].

A longitudinal cohort epidemiological study was conducted in Sweden with the objective of investigating the cancer incidence rate among patients who were diagnosed as having Graves' disease ($n = 18{,}156$) between 1964 and 2006. The study results revealed that a malignant neoplasm was diagnosed in 1,495 (8.2%) patients with an average age of 17 years (from 0 to 42 years). The study excluded patients in whom a neoplasm was simultaneously diagnosed with a thyroid disease, resulting in 1,259 patients with cancer (1,018 females and 241 males). Thus, compared with the general population, the relative risk of developing malignant neoplasms was 1.13 (95% CI, 1.07–1.19), and with a burdened general oncological heredity, the relative risk was 1.66 (95% CI, 1.14–2.35). In addition, the relative risk of developing malignant neoplasms of the head and neck was 1.56 (95% CI, 1.08–2.2), whereas that of developing malignant neoplasms of the breast was 1.14 (95% CI, 1.03–1.26) [36].

Conclusions

A sufficient number of experimental and clinical data are currently accumulated regarding the pro-cancer-inducing properties of thyroid

hormones, which are mediated because of the combination of genomic and nongenomic effects and the activation of their pro-proliferative, proangiogenic, and genotoxic effects on cells so that, when considering action of iodothyronines within a stochastic theory of tumor development, it leads to acceleration of the "natural history of tumor development."

With regard to the hierarchical theory of tumor development, systemic proinflammatory and immunomodulatory action of thyroid hormones can elucidate the acceleration of tumor dissemination and progression by the formation of "pre-niches" and "niches" for stem tumor cells.

Existing epidemiological and clinical studies suggest that hyperthyroidism, including subclinical hyperthyroidism, may be a risk factor for the occurrence of malignancies. In addition, it is an independent prognostic factor of response to treatment and the risk of disease recurrence in patients with malignant tumors.

Currently, there is considerable evidence that DTG is a genetically determined disease that is associated with polymorphism and/or mutation of several genes, including those encoding proteins of the major histocompatibility complex and pro- and antiinflammatory interleukins [36, 43]. Moreover, it is essential to understand that known external agents, which are known risk factors of malignancies (e.g., smoking and use of talc), can trigger autoimmune processes because of epigenetic regulation, which in turn, can be a risk factor for DTG [37]. In view of this, there arises a rather logical question regarding the role of polymorphism (mutation) of genes and/or disorders epigenetically mediated by these genes, associated with DTG and/or other autoimmune pathology in carcinogenesis.

In contrast, considering the significant role of iodothyronines in neurogenesis and the metabolism of neural tissues, even subclinical insufficiency of the thyroid endocrine function becomes a risk factor for developing neuropsychic diseases. Sufficient clinical and epidemiological data currently suggest that subclinical hypothyroidism is a risk factor for the development and progression of depression and other bipolar personality disorders [6, 31].

Because no current studies assess the impact of the thyroid status on the quality of life of patients with malignant neoplasms, futures studies should assess the quality of life of patients with cancer and thyroid dysfunction.

Furthermore, decompensated hypothyroidism is a risk factor for the progression of already existing cardiovascular diseases because of mediated hyperhomocysteinemia, dyslipidemia, and endothelial dysfunction [15, 16]. Despite the fact that extensive population studies do not state hypothyroidism to be a risk factor for death owing to cardiovascular diseases [5, 10, 11, 23, 34], subsequent assessment of the influence of iodothyronine levels on the survival rate of patients with cancer should investigate the "pumping causes of death" because of increased mortality owing to cardiovascular diseases. In contrast, the cardiovascular diseases prevention system is stratified by risk factors and is relatively simple and sufficiently studied. Hence, the effect of the thyroid status on cancer and somatic risk, the quality of life of a patient with cancer, and their interrelationship warrant further investigation.

The study was supported by a grant from the Government of St. Petersburg.

REFERENCES

1. Glushakov R.I., Vlas'eva O.V., Sobolev I.V. et al. Thyroid status as prognostic factor in oncology. *Zlokachestvennye opukholi*. 2015; 2 (13): 13–20. (In Russ.)

2. Glushakov R.I., Proshin S.N., Tapilskaya N.I. The role of thyroid hormones in the regulation of the angiogenesis and cells proliferations. *Geny i kletki*. 2011; 6 (4): 26–33. (In Russ.)

3. Aghini-Lombardi F., Antonangeli L., Martino E. et al. The spectrum of thyroid disorders in an iodinedeficient community: The pescopagano survey. *J. Clin. Endocrinol. Metab.* 1999; 84: 561–566.

4. Azizi F., Hedayati M., Rahmani M. et al. Reappraisal of the risk of iodineinduced hyperthyroidism: an epidemiological population survey. *J. Endocrinol. Invest.* 2005; 28: 23–29.

5. Baltisberger B.L., Minder C.E., Bürgi H. Decrease of incidence of toxic nodular goitre in a region of Switzerland after full correction of mild iodine deficiency. *Eur. J. Endocrinol*. 1995; 132 (5): 546–549.

6. Barbero J.D., Gutiérrez-Zotes A., Montalvo I. et al. Free thyroxine levels are associated with cognitive abilities in subjects with early psychosis. *Schizophr. Res*. 2015; 166 (1–3): 37–42.

7. Barker D.J., Phillips D.I. Current incidence of thyrotoxicosis and past prevalence of goitre in 12 British towns. *Lancet*. 1984; 2 (8402): 567–570.

8. Belfiore A., Sava L., Runello F. et al. Solitary autonomously functioning thyroid nodules and iodine deficiency. *J. Clin. Endocrinol. Metab.* 1983; 56 (2): 283–287.

9. Biondi B., Cooper D.C. The clinical significance of subclinical thyroid dysfunction. *Endocr. Rev.* 2008; 29: 76–131.

10. Boekholdt S.M., Titan S.M., Wiersinga W.M. et al. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. *Clin. Endocrinol. (Oxf.).* 2010; 72: 404–410.

11. Canaris G.J., Manowitz N.R., Mayor G., Ridgway E.C. The Colorado thyroid disease prevalence study. *Arch. Intern. Med*. 2000; 160: 526–534.

12. Davis P.J., Glinsky G.V., Lin H.Y. et al. Cancer cell gene expression modulated from plasma membrane

integrin $\alpha_v\beta_3$ by thyroid hormone and nanoparticulate tetrac. *Front. Endocrinol. (Lausanne)*. 2015; 5: 240.

13. Delitala A.P., Pilia M.G., Ferreli L. et al. Prevalence of unknown thyroid disorders in a Sardinian cohort. *Eur. J. Endocrinol*. 2014; 171 (1): 143–149.

14. Delshad H., Mehran L., Tohidi M. et al. The incidence of thyroid function abnormalities and natural course of subclinical thyroid disorders, Tehran, I.R. Iran. *J. Endocrinol. Invest*. 2012; 35 (5): 516–521.

15. Faber J., Selmer C. Cardiovascular disease and thyroid function. *Front. Horm. Res*. 2014; 43: 45–56.

16. Flynn R.V., MacDonald T.M., Morris A.D. et al. The thyroid epidemiology, audit and research study; thyroid dysfunction in the general population. *J. Clin. Endocrinol. Metab*. 2004; 89: 3879–3884.

17. Glaser N.S., Styne D.M. Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. *Pediatrics*. 2008; 121 (3): e481–e488.

18. Goldman M.B., Monson R.R., Maloof F. Cancer mortality in women with thyroid disease. *Cancer Res*. 1990; 50 (8): 2283–2289.

19. Hellevik A.I., Asvold B.O., Bjøro T. et al. Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol. Biomarkers Prev*. 2009; 18 (2): 570–574.

20. Hetzel B.S. The nature and magnitude of the iodine deficiency disorders. In: *Towards the global elimination of brain damage due to iodine deficiency*. B. Hetzel et al. eds. New Delhi: Oxford University Press. 2004; 1–22.

21. Hollowell J.G., Staehling N.W., Flanders W.D. et al. Serum TSH, T_4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab*. 2002; 87: 489–499.

22. Kasagi K., Takahashi N., Inoue G. et al. Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. *Thyroid*. 2009; 19 (9): 937–944.

23. Kim Y.A., Park Y.J. Prevalence and risk factors of subclinical thyroid disease. *Endocrinol. Metab. (Seoul)*. 2014; 29 (1): 20–29.

24. Knudsen N., Jørgensen T., Rasmussen S. et al. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin. Endocrinol. (Oxf.)*. 1999; 51: 361–367.

25. Ko A.H., Wang F., Holly E.A. Pancreatic cancer and medical history in a population-based case-control study in the San Francisco Bay Area, California. *Cancer Causes Control*. 2007; 18 (8): 809–819.

26. Mondul A.M., Weinstein S.J., Bosworth T. et al. Circulating thyroxin, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. *PLoS One*. 2012; 7 (10): e47730.

27. Laurberg P., Pedersen K.M., Vestergaard H., Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *J. Intern. Med*. 1991; 229 (5): 415–420.

28. Leese G.P., Flynn R.V., Jung R.T. et al. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: The Thyroid Epidemiology, Audit and Research Study (TEARS). *Clin. Endocrinol. (Oxf.)*. 2008; 68: 311–316.

29. Li X., Yang X., Wang Y. et al. The prevalence and prognostic effects of subclinical thyroid dysfunction in dilated cardiomyopathy patients: a single-center cohort study. *J. Card Fail*. 2014; 20 (7): 506–512.

30. Lytton S.D., Kahaly G.J. Bioassays for TSH-receptor autoantibodies: an update. *Autoimmun. Rev*. 2010; 10 (2): 116–122.

31. McGrogan A., Seaman H.E., Wright J.W., de Vries C.S. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clin. Endocrinol*. 2008; 69: 687–696.

32. Reinwein D., Benker G., König M.P. et al. The different types of hyperthyroidism in Europe. Results of a prospective survey of 924 patients. *J. Endocrinol. Invest*. 1988; 11 (3): 193–200.

33. Robles-Osorio M.L., Zacarías-Rangel V., García-Solís P. et al. Prevalence of thyroid function test abnormalities and anti-thyroid antibodies in an open population in Central México. *Rev. Invest. Clin*. 2014; 66 (2): 113–120.

34. Selmer C., Olesen J.B., Hansen M.L. et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ*. 2012; 345: e7895.

35. Selmer C., Olesen J.B., Hansen M.L. et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. *J. Clin. Endocrinol. Metab*. 2014; 99 (7): 2372–2382.

36. Shu X., Ji J., Li X. et al. Cancer risk in patients hospitalized for Graves' disease: a population-based cohort study in Sweden. *Br. J. Cancer*. 2010; 102 (9): 1397–1399.

37. Stefan M., Wei C., Lombardi A. et al. Genetic-epigenetic dysregulation of thymic TSH receptor gene expression triggers thyroid autoimmunity. *Proc. Natl. Acad. Sci. USA*. 2014; 111 (34): 12 562–12 567.

38. Smith B.R., Sanders J., Furmaniak J. TSH receptor antibodies. *Thyroid*. 2007; 17 (10): 923–938.

39. Teng W., Shan Z., Teng X. et al. Effect of iodine intake on thyroid diseases in China. *N. Engl. J. Med*. 2006; 354: 2783–2793.

40. Tosovic A., Bondeson A.G., Bondeson L. et al. Triiodothyronine levels in relation to mortality from breast cancer and all causes: a population-based prospective cohort study. *Eur. J. Endocrinol*. 2013; 168 (4): 483–490.

41. Tunbridge W.M.G., Evered D.C., Hall R. et al. The spectrum of thyroid disease in the community: the Whickham survey. *Clin. Endocrinol*. 1977; 7: 481–493.

42. Vanderpump M.P.J. The epidemiology of thyroid diseases. In: Braverman L.E., Utiger R.D. eds. *Werner and Ingbar's. The thyroid: A fundamental and clinical text*. 9-th edn. Philadelphia: J.B. Lippincott-Raven. 2005; 398–406.

43. Wiersinga W.M. Thyroid autoimmunity. *Endocr. Dev*. 2014; 26: 139–157.

44. Zimmermann M.B., Jooste P.L., Pandav C.S. Iodine-deficiency disorders. *Lancet*. 2008; 372: 1251–1262.

45. Zhang Y., Chang Y., Ryu S. et al. Thyroid hormones and mortality risk in euthyroid individuals: the Kangbuk Samsung health study. *J. Clin. Endocrinol. Metab*. 2014; 99 (7): 2467–2476.