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The Prevalence of Malignant Tumours among Women with a History of Hyperthyroidism: St. Petersburg Case-Control Study

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ABSTRACT

Objective: Thyroid diseases are the most common endocrine disorders. The association between thyroid disease and cancer risk remains unclear. Some epidemiological studies have demonstrated an increased risk of cancer in women with history of the hyperthyroidism.
Aim: To assess cancer incidence and to calculate the relative risk (RR) of malignant tumors in patients with history of hyperthyroidism.
Materials and Methods: A randomized, retrospective, case-control study was conducted among women with history of Graves' disease and nodular toxic goiter in 1999–2009. inclusive. the study consisted of 1362 patients with history of hyperthyroidism, a comparison group is used consisting of 1144 patients with eu- and hyperthyroidism. Cancer incidence is estimated for March 31, 2018.
Results: The relative risk of cancer in women with history of hyperthyroidism was 2.36 (95% CI 1.63-3.42, $\chi 2 = 22.16$, $p < 0.01$), the relative risk of hormone-dependent tumors amounted to 2.65 (95% CI 1.7–4.13, $\chi 2 = 20.59$, $p < 0.01$). The relative risk of colorectal cancer and ovarian cancer was increased: RR = 3.53 (95% CI 1.34–9.32, $\chi 2 = 7.4$, $p < 0.01$) and RR = 3.27 (95% CI 1.388–6.76, $\chi 2 = 11.49$, $p < 0.01$) respectively.
Conclusions: We found an increased risk of colorectal and ovarian cancers in women with hyperthyroidism. Women with history of hyperthyroidism should be attributed to the group of increased cancer risk, that requires a set of measures for primary and secondary prevention of cancer.

Keywords
Non-genomic effects of thyroid hormones; Hyperthyroidism; Oncological morbidity; Colorectal cancer; Ovarian cancer

Introduction

Thyroid diseases are the most common human pathology and currently occupy the first place among all diseases of the endocrine system. Moreover, there are significant gender differences in the prevalence of diseases. Women are affected in 3–10 times more often than men [1]. Thyrotoxicosis syndrome is the second most common endocrine disorder after diabetes mellitus [2]. Graves' disease is the most common reason for thyrotoxicosis, followed by nodular toxic goiter. Solitary toxic adenomas and thyroiditis are more rare causes [3]. At the beginning of the 21st century, the theory of dyshormonal carcinogenesis underwent a renaissance due to the discovery and study of the non-genomic effects of thyroid hormones mediated through the membrane receptor integrin αvβ3 (CD51/CD61), demonstrating that iodothyronines, especially in elevated concentrations, are stimulators of tumor growth and angiogenesis [4]. Table 1 shows the non-genomic effects of thyroid hormones induced through effects on CD51/CD61 integrin.

Epidemiological studies at the turn of the twentieth and twenty-first centuries have shown that a history of hyperthyroidism increases the relative risk of ovarian cancer by 80% [5] and breast

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cancer by 45–60% [6]. There are also enough epidemiological studies that have demonstrated that hyperthyroidism, including subclinical, is a risk factor for morbidity and mortality from malignant neoplasms (MN) of different localizations: breast cancer [7, 8], thyroid cancer [9], pancreatic cancer [10] and lung cancer [11]. No previous epidemiological studies have been conducted in the Russian Federation.

Table 1. Non-genomic effects of thyroid hormones (induced through effects on CD51/CD61 integrin)

Effect	Intracellular messenger	Iodothyronines T_4	Iodothyronines T_3
Ion exchange:			
Activity Ca^{2+}–ATP-ase [12,13]	PKC	↑	↑
Activity Na^{+}/K^{+}–ATP-ase [12, 13, 14]	MAPK, PI-3-K	**0**	↑
Activity $Na^{+}/H+$ – antiport [12]	MAPK	↑	↑
Polymerisation of actin [15, 16]	FAK*	↑	0
Translocation of intracellular proteins from the cytoplasm to the nucleus [16]	MAPK	↑	↑
Neoangiogenesis [15, 13, 16]	MAPK	↑	↑
Proliferation of tumour cells [14, 13. 16]	MAPK	↑	↑
Activation of nuclear receptors to oestrogen (in the absence of oestrogen) [17]	MAPK	↑	no data available
Expression of specific genes (HIF-1, ZAKI–4)[18, 21]	PI-3-K	0	↑

Note: PKC–protein kinase C, MAPK–mitogen-activated protein kinase, PI-3-K–phosphotidyl-inositol 3-kinase, FAK–focal adhesion kinase

The purpose of the study is to assess cancer morbidity and calculate the relative risk of malignancy in patients with a history of thyroid disease accompanied by long-term hyperthyroidism (diffuse toxic goiter (DTG) and nodular toxic goiter (UTG).

Materials and Methods

General study design

We conducted a single-stage epidemiological retrospective multicenter randomised clinical comparative case-control study to examine the impact of thyroid disease with long-standing thyrotoxicosis on the risk of cancer in women.

The main group consisted of 1362 patients aged from 40 to 65 years inclusive. Patients were treated in specialised hospitals of St.Petersburg from 1999 to 2009 for thyrotoxicosis due to diffuse toxic goiter (n=1015) and nodular toxic goiter (n=347) during treatment of thyroid disease. According to the medical history, the probable duration of thyrotoxicosis before drug and/or surgical treatment was at least 1 year. The comparison group consisted of 1144 female doctors and nurses of the outpatient department of the same age group, who underwent complex medical examination in 1999–2001 and further in 2004–2007. The examination included thyroid status determination (serum thyrotropic hormone level) with thyroid hyperactivity excluded. It

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should be noted that 189 women in the comparison group, including those with a history of autoimmune thyroiditis (AIT), were on continuous L-thyroxine hormone replacement therapy at a dose of 100 mcg or less.

Study inclusion criteria:

- age between 40 and 65 years inclusive at the time of inclusion in the study;
- history of diffuse toxic goiter or nodular toxic goiter;
- surgical, medical (use of thyrostatics) or combined treatment for thyroid disease.

Study exclusion criteria:

- patients under 40 years of age or over 65 years of age at the time of enrolment;
- presence of malignant neoplasm of any localisation, including ca in situ, and/or oncohematological and/or lymphoproliferative disease, previously diagnosed thyroid disease accompanied by long-standing thyrotoxicosis;
- thromboembolism, acute myocardial infarction, stroke in the anamnesis;
- diabetes mellitus type I and/or other endocrine disorders (excluding thyroid disease), including those requiring the prescription of hormone replacement therapy;
- psychiatric illnesses, algocolitis, drug abuse, malignant neoplasms and/or lymphoproliferative diseases in the anamnesis and/or identified during the study;
- Broca body mass index greater than 34.9 kg/m^2, less than 18.5 kg/m^2;
- HIV-positive patients or patients at high risk of infection receiving antiretroviral therapy, chronic viral hepatitis B and/or C;
- any other significant illnesses which, in the opinion of the investigator, reduce the validity of the research being conducted;
- reluctance of the patient to participate in the study.

Conducting randomization

Randomisation was carried out by assigning an identification number to each patient and then removing every conditional 6th patient in both groups from the study. Thus, after randomisation, the number of women in the study groups was 1135 and 953 patients in the main and comparison groups respectively.

Determination of cancer morbidity in comparison groups

Cancer morbidity in the study groups was assessed using databases of statistical records on the fact of attendance at specialised medical institutions and/or the fact of death. The databases of the local population cancer register were used. The fact of cancer morbidity was also assessed by direct telephone contact with the patients or their relatives in the case of the patient's death and then documented. The results of the study were summarised and calculated using data collected by March 31, 2018.

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Statistical analysis of research results

To determine the odds ratio (OR) and the absolute risk of the disease in persons without a history of thyrotoxicosis (Rc), a four-field contingency table was constructed based on the number of studied groups and signs (Table 2).

Table 2. Contingency table

	Cancer "+"	**Cancer "-"**	**Total**
Hyperthyroidism in anamnesis	a	b	a + b
Eu- and hypothyroidism	c	d	c + d
Total	a + c	b + d	a+b+c+d

Comparison of cancer morbidity in the study groups was made by determining the relative risk (RR), which was calculated according to the formula:

$$RR = \frac{\text{OR}}{(1 - \text{Rc} + (\text{Rc x OR})}$$

where RR is the relative risk.
The confidence interval (CI) limits were defined as
ln(RR) ± 1.96xSe {ln(OR)},
where Se is the standard error equal to ln(OR) that is the logarithm of the odds ratio, defined as

$$\{ln(OR)\} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

the upper and lower limits of the confidence interval were determined according to the formula

$$e^{ln\,(PR)} \pm 1.96 = \sqrt{\frac{b}{a(a+b)} + \frac{d}{c(d+c)}}$$

Statistical validity was determined using non-parametric statistics: Pearson's goodness-of-fit test (chi-square, $\chi 2$) with Yates correction and likelihood adjustment. The correlation between events was determined by Pearson's contingency criterion (C) and Cramer's V-criterion (Vk).

Ethical rules and regulations

The study was conducted in accordance with the principles of the World Association of Helsinki Declaration on Ethical Principles of Scientific and Medical Research Involving Human Subjects, the current Procedures and Standards of Medical Care and other applicable regulatory requirements for clinical trials and observational programmes in the Russian Federation. The patient observation protocol and examination programme were approved by the local ethics committee.

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Results of the Study

At the end of the epidemiological study, 101 (8.9%) and 36 (3.8%) patients and/or deaths from malignancy in the main and comparison groups respectively were found (Table 3).

Table 3. Analysis of the incidence of malignancy in patients with a history of thyrotoxicosis

Groups	Registered malignancy	Without a detected melignancy	Total
Group of patients with a history of long-term hyperthyroidism	101 (a)	1034 (b)	1135 (a+d)
Group of patients with eu- and hypothyroidism	36 (c)	917 (d)	953 (c+d)
Total	137 (a+c)	1951 (b+d)	2088 (a+b+c+d)

According to data presented in Table 4, women with a history of long-term hyperthyroidism had a greater than 2-fold risk of malignancy (RR=2.36; 95% CI 1.63-3.42, p<0.01; C=0.102, Vk=0.103), with a hormone-dependent tumour risk (RR=2.65; 95% CI 1.7-4.13, p<0.01; C=0.114, Vk=0.099).

Table 4. Incidence of malignancy in patients with a history of thyrotoxicosis (by nosological forms)

Localisation of malignancy	History of hyperthyroidism (a/b)	Comparison group (c/d)	RR	95% CI	χ2	Plausibility criterion
BC	24/1111	11/942	1.832	0.902-3.72	2.89	p>0.05
OC	35/1100	9/944	3.27	1.58-6.76	11.49	p<0.01
KPP	21/1114	5/948	3.53	1.34-9.32	7.4	p<0.01
CC	16/1119	3/950	4.48	1.31-15.32	6.89	p<0.01
EC	4/1131	2/951	1.68	0.31-9.15	0.37	p>0.05
Total malignancy, *includes: hormone-dependent tumours*	18/1117 3/1132	9/944 8/945	1.68 0.68	0.76-3.72 0.08-1.18	1.67 3.27	p>0.05 p>0.05
Total malignancy, *includes: hormone-dependent tumours*	101/1034 79/1056	36/917 25/928	2.36 2.65	1.63-3.42 1.7-4.13	22.16 20.59	p<0.01 p<0.01

Note:BC–breast cancer, OC–ovarian cancer, CC–colorectal cancer, EC–endometrial cancer.

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When analysing the topical localisation of neoplasms, colorectal cancer (RR=4.48; 95% CI 1.31-15.32, p<0.01) and ovarian cancer (RR=3.27; 95% CI 1.58-6.76, p<0.01) had the most significant increased incidence in women with a history of hyperthyroidism.

Thus, our epidemiological study shows that women with a history of long-term hyperthyroidism have a higher risk of malignancies than women with eu- and hyperthyroidism, with a slightly higher risk of hormone-dependent tumours than the general oncological risk.

Discussion

"The case-control" study has been chosen because it is preferable and more reliable for diseases with a long latency period and for polyetiological and rare diseases [5, 10]. Malignant neoplasms fully satisfy the first two criteria for this type of study, and partially satisfy the third research criterion, yielding to cardiovascular and infectious diseases in terms of prevalence. In our epidemiological study, we obtained colorectal and ovarian cancer in women with a history of thyrotoxicosis.

While an increased risk of ovarian cancer and breast cancer has been found in previous epidemiological studies, an increased risk of colorectal cancer has hardly been described in the epidemiological work of other authors (Table 5).

The results obtained in our study can be explained either by the characteristics of the study population (inclusion criteria for patients with long-standing manifest disease, ethnicity and gender composition) or by the lack of screening programmes for early detection of CRC in many countries. Also noteworthy is the increased risk of hormone-dependent tumours, which may be due to the ability of TG to affect the cell membrane and activate the α-isoform of the estrogen receptor (ER-α) through enzyme-dependent mechanisms in the absence of a specific ligand [17]. In an earlier experimental study on a transplanted culture of ovarian cancer, induction of hypothyroidism resulted in at least a two-fold increase in rat survival [14].

On one side, in the framework of the scholastic theory of tumor development, the accumulated epidemiological and clinical data on prooncogenic properties of thyroid hormones mediated by genomic and non-genomic effects and caused by activation of their pro-proliferative and pro-angiogenic action on cells suggest an acceleration of the "natural history of tumor development", namely, the transfer of disease from preclinical to clinical stage [13, 16]. Also, the systemic proinflammatory and immunomodulatory effects of thyroid hormones in terms of the hierarchical theory of tumor development cannot be overlooked and may explain the acceleration of tumor dissemination and progression due to the formation of "prenisks" for "tumor stem cells" [12].

Iodine prophylaxis in iodine-deficient regions is a separate issue in the prevention of thyroid disorders and, therefore, in the reduction of cancer risks in the population [27]. Nodular goiter can develop functional thyroid autonomy leading to thyrotoxicosis, the prevalence of which may increase significantly at the start of mass iodine prophylaxis programmes, particularly in those over 40 years of age [3]. According to the Iranian study, the prevalence of thyroid dysfunction may transiently increase in persons with multinodular goiter and functional thyroid autonomy due to chronic iodine deficiency. Iodine-induced thyrotoxicosis develops most frequently in regions

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of severe iodine deficiency, especially in cases of episodic increased iodine intake [28]. Such increase in incidence appears to be related to the progression of subclinical hyperthyroidism to clinical hyperthyroidism with subsequent disease registration [8].Understanding the importance of elimination of iodine deficiency diseases, the WHO Assembly in 1991 decided that iodine deficiency, as a global problem, should be eliminated worldwide by 2000, but due to a combination of many reasons it did not happen [27].

Table 5. Epidemiological evidence on the impact of thyroid status on malignancy

Year of publication	Author (s)	Research design	Topical localization	Relative risk of malignancy with		95% CI
				History of hyperthyroidism	History of hypothyroidism	
2000	Ness et al. [5]	Retrospective comparative of "case-control" type	Ovarian cancer	1.8		no data
2007	Ko, Wang and Holly [10]	Retrospective comparative of "case-control" type	Thyroid cancer	2.1	-	1.0–4.2
2009	Hellevik et al. [11]	Prospective observational	Total of malignancy: Lung cancer Pancreatic cancer	1.34 2.34 1.97		1.06–1.69 1.24–4.4 1.04–3.76
2010	Shu et al. [21]	Longitudinal cohort	Total of malignancy: Malignancy of head and neck	1.13 (1.66)1 1.56		1.07–1.19 (1.14–2.35)1 1.08–2.2
2012	Mondul et al. [23]	Prospective randomised of cross-over type	PC2	-	0.48	0.28–0.81
2013	Tosovic et al. [8]	Prospective observational study	BC	2.803		1.26–6.25
2015	Ryödi et al. [24]	Retrospective cohort	Lung cancer Stomach cancer	1.46 1.64		1.05–2.02 1.01–2.68
2016	Søgaard et al. [26]	Prospective cohort study	BC5	1.13	0.94	1.08–1.19 0.88–1.00

Note: 1– With burdened oncological heredity; 2 – PC – prostate cancer; 3 – OR at "normally elevated" T3: level is within the "upper" quartile of the reference values; 4 – CRC–colorectal cancer; 5 – BC– breast cancer.

Completely unexplored issues that relate to thyroid status and require separate consideration and further study are the quality of life and cardiological risks of cancer patients and conventionally

healthy populations with hypo- and hyperthyroidism.

Conclusion

1. Women with a history of long-term hyperthyroidism have a higher risk of malignancy compared with eu- and hyperthyroid women.

2. Women with a history of long-term hyperthyroidism should be classified as a high-risk group for cancer, requiring a set of measures for primary (long-term use of combined oral contraceptives, low-dose acetylsalicylic acid, folate fortification, etc.) and secondary prevention of malignancies (screening and early detection of malignant neoplasms).

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