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Extra-thyroidal Cancers in Euthyroid Hashimoto's Patients Under Levothyroxine Treatment: Outlook A Single Tertiary Center Cases

Levotiroksin Tedavisi Alan Ötiroid Hashimoto Hastalarında Tiroid Dışı Kanserler: Tek Bir Tersiyer Merkezin Hastalarına Bakış

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Abstract: We aimed to investigate the frequency of extra-thyroidal cancer (ETC) in euthyroid Hashimoto's patients under levothyroxine (LT4) treatment. Moreover, we determined whether cancer development could be related to demographic, clinical, biochemical, and metabolic parameters. Consecutive participants in the follow-up above 18 years old diagnosed with hypothyroidism caused by Hashimoto's thyroiditis (HT) in a single tertiary center between 2016 December and 2023 December were included in the study. A total of 577 Hashimoto's patients were analyzed retrospectively. The study population was divided into two subgroups according to presence or absence of ETC. Demographic, clinical, biochemical, and metabolic parameters were compared in patients with and without cancer. Mean age was 52.6±13.5 years. Of the 577 patients, 87.3% were female and 12.7% were male. The most prevalent two comorbidities accompanying HT were metabolic syndrome (36.4%) and obesity (31.2%). The frequency of concomitant appearance of ETC with HT was 13.3%. The most common two cancers were breast (46.2%) and ovary (8.7%). In multivariate analysis, older age (OR 1.030, 95% CI 1.012-1.049, p=0.001), positive family history for cancer (OR 1.859, 95% CI 1.117-3.092, p=0.017), and elevated fasting blood glucose (OR 1.022, 95% CI 1.007-1.037, p=0.005) were found to be significantly positively correlated with increased risk of cancer. This study revealed that the frequency of ETC was 13.3% in euthyroid Hashimoto's patients under LT4 treatment. Breast cancer was the most common cancer affecting study population. Older age, positive family history for cancer and elevated fasting blood glucose were defined as independent risk factors for cancer development.
Keywords: Hashimoto's thyroiditis, hypothyroidism, extra-thyroidal cancers

Özet: Levotiroksin (LT4) tedavisi alan ötiroid Hashimoto hastalarında tiroid dışı kanser (TDK) sıklığını araştırmayı amaçladık. Ayrıca kanser gelişiminin demografik, klinik, biyokimyasal ve metabolik parametrelerle ilişkili olup olmadığını da belirledik. Aralık 2016 ile Aralık 2023 tarihleri arasında tek bir tersiyer merkezde Hashimoto tiroiditi (HT) kaynaklı hipotiroidi tanısı alan 18 yaş üzeri takipteki ardışık katılımcılar çalışmaya dahil edildi. Toplam 577 Hashimoto hastası retrospektif olarak analiz edildi. Çalışma popülasyonu TDK olup olmamasına göre iki alt gruba ayrıldı. Kanserli ve kansersiz hastalarda demografik, klinik, biyokimyasal ve metabolik parametreler karşılaştırıldı.Bulgular: Ortalama yaş 52,6±13,5 yıldı. Beş yüz yetmiş yedi hastanın %87,3'ü kadın, %12,7'si erkekti. HT'ne eşlik eden en sık iki komorbidite metabolik sendrom (%36,4) ve obezite (%31,2) idi. HT ile TDK'in birlikte görülme sıklığı %13,3 idi. En sık görülen iki kanser meme (%46,2) ve over (%8,7) oldu. Çok değişkenli analizde, ileri yaşın (OR 1,030, %95 CI 1,012-1,049, p=0,001), pozitif aile öyküsünün (OR 1,859, %95 CI 1,117-3,092, p=0,017) ve yüksek açlık kan şekerinin (OR) 1,022, %95 CI 1,007-1,037, p=0,005) artan kanser riski ile anlamlı pozitif korelasyona sahip olduğu bulunmuştur. Bu çalışma, LT4 tedavisi alan ötiroid Hashimoto hastalarında TDK sıklığının %13,3 olduğunu ortaya çıkardı. Meme kanseri, çalışma popülasyonunu etkileyen en yaygın kanserdi. İleri yaş, pozitif aile öyküsü ve yüksek açlık kan şekeri, kanser gelişimi için bağımsız risk faktörleri olarak tanımlandı.
Anahtar Kelimeler: Hashimoto tiroiditi, hipotiroidi, tiroid dışı kanserler

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1. Introduction

Various risk factors increase the risk of cancer including family history, genetic mutations, environmental effects, and aging. Low-grade chronic inflammatory condition caused by impaired function of T cells may be also associated with the increased risk of certain types of cancer in different autoimmune disorders [1-4]. Hashimoto's thyroiditis (HT) is the most common autoimmune disease caused by hypothyroidism, which presents lymphocytic infiltration of thyroid gland and elevated autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb). In the literature, the link between HT and papillary thyroid cancer (PTC) was mainly assessed. There were many fine-needle aspiration cytology (FNAC) studies and archival thyroidectomy specimen studies [5,6]. FNAC studies show no significant correlation, whereas many of thyroidectomy specimen studies report a positive correlation [5]. A meta-analysis showed that PTC was more often found in patients with HT than in patients without HT [6]. However, there was a significant heterogeneity among the studies such as different study methods and different patient selection criteria [6]. Therefore, the relationship between HT and PTC has been controversial for decades. On the other hand, the number of studies investigating the link between HT and extra-thyroidal cancer (ETC) is limited [2,7]. A meta-analysis demonstrated that patients with HT had increased risk of developing various types of ETC when compared to people without HT [2]. People with under the effect of chronic inflammatory state are more prone to have several types of ETC, such as breast, liver, colon, bladder, prostate, stomach, ovarian, and skin cancers [3].

The exact mechanisms behind carcinogenesis in patients with HT are still unclear, but there are several hypotheses. Chronic inflammation induced by anti-thyroid antibodies plays an essential role in promoting tumorigenesis. Inflammatory cells release reactive oxygen species (ROS), inflammatory cytokines/chemokines, and growth factors in a chronic inflammatory microenvironment [3]. Oxidative stress causes deoxyribonucleic acid (DNA) damage and induces cell proliferation [3]. Proteins and lipids are damaged by ROS, resulting in their dysfunction [8]. In addition, DNA methylation occurs in tumor suppressor genes. It seems that genetic alterations and molecular abnormalities play a major role in inflammation-induced tumor development [8,9]. Inflammatory microenvironment also leads to angiogenesis, formats new blood vessels, and causes tumor aggressiveness [1]. The thyroid gland and neoplastic organ cells present several structural similarities [10,11]. Cross-reactivity of TPO antibodies with some antigens such as lactoperoxidase and myeloperoxidase may also cause destruction of cells and cancer development [10,11]. The increased expression of the sodium iodide symporter, and thyroid hormone receptors in both thyroid and various other extra-thyroidal tissues could play a role in the relationship between these two diseases [12,13]. Iodination of proteins initiates oxidative stress and may stimulate transformation of normal cells to cancer cells [10]. Cancer development and progression may be also associated with thyroid hormone status. Despite experimental clinical studies, there is contradictory evidence of the relationship between HT and risk of developing malignancy.

Diabetes mellitus (DM) is an important risk factor for developing many types of cancer [14-16]. Cancer development in patients with DM is associated with hyperglycemia, hyperinsulinemia, obesity, and dyslipidemia. These metabolic disorders cause a low-activity chronic inflammatory state and increase oxidative stress [14,15,17]. Hence, they may increase the many types of cancer initiation and progression. Furthermore, patients at pre-diabetes levels have increased risk for cancer development [18]. The relationships between these metabolic disorders and ETC are still unclear in patients with HT.

The aim of this present study was to investigate the frequency of ETC in euthyroid Hashimoto's patients under levothyroxine (LT4) treatment. Moreover, we analyzed whether cancer development could be related to clinical, biochemical, and metabolic parameters.

2. Materials and Methods

Ethical committee approval for this present retrospective cohort study was obtained on March 25, 2024, with decision number 2024.136.IRB2.061. The study was carried out according to the Declaration of Helsinki. Consecutive patients in the follow-up above 18 years old diagnosed with primary hypothyroidism caused by HT in a single tertiary center between 2016 December and 2023 December were included in the study. All patients were in euthyroid status under LT4 treatment.

HT was defined in presence of autoantibodies for either TPO, Tg or both. The positivity of antibodies was verified on two separate measurements for each patient at our single center. Furthermore, thyroid ultrasonography (USG) examination was performed to accurate chronic thyroiditis. The diagnosis of HT was made by roughness of the thyroid parenchyma, hypoechoic, and heterogenous thyroid structure at USG examination. Excluded were patients with <18 years old, pregnancy, breastfeeding, history for Graves' disease, HT in euthyroid status without taking LT4 treatment, serum negative autoimmune thyroiditis, history for subacute thyroiditis, human immunodeficiency virus disease, immune checkpoint inhibitor-induced thyroid dysfunction, taking immunomodulator medications, amiodarone, and lithium. There were 577 patients with eligibility criteria.

Characteristics of the subjects including age, gender, body mass index (BMI), history of smoking, family history for cancer in first degree relatives, presence of ETC, ETC localizations, time of cancer occurrence either before or after the diagnosis of HT, duration of hypothyroidism (years), daily LT4 dose to achieve euthyroid status (mcg), concurrent comorbid diseases [obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, and type 1 diabetes mellitus (T1DM)], laboratory findings [(fasting blood samples for TPOAb, TgAb, thyroid stimulating hormone (TSH), free T4 (FT4), glucose, and estimated glomerular filtration rate (eGFR), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), alanine aminotransferase enzyme (ALT), and 25-hydroxyvitamin D (25OHD)] were reviewed. eGFR was calculated by using Chronic Kidney Disease Epidemiology Collaboration equation. The National Cholesterol Education Programs Treatment Panel III (NCEP ATP III) criteria was used to define metabolic syndrome [19]. Demographic, clinical, biochemical, and radiological findings were obtained from the medical records.

Patients were divided into two subgroups according to presence or absence of ETC. Cancer group was compared to non-cancer group in terms of demographic, clinical, and biochemical parameters.

Assays

Serum TPOAb, TgAb, TSH, FT4, and 25OHD measurements were performed by using electrochemiluminescence immunoassay method. Positive TPOAb was defined as higher than 35 IU/mL and positive TgAb was defined as higher than 115 IU/mL. The minimum and maximum detectable TgAb concentrations were 10 IU/mL and 4000 IU/mL respectively. The minimum and maximum detectable TPOAb concentrations were 9 IU/mL and 600 IU/mL respectively. Enzymatic tests were used to measure serum glucose, LDL, and TG concentrations. Serum HDL level was measured by using a colorimetric assay system. The assessment of ALT enzyme activity was performed by using the International Federation of Clinical Chemistry method. Roche Cobas 503 PRO analyzer device was used for analysis of biochemical parameters. Immunochemistry tests were performed by using Roche Cobas 801 PRO module.

Statistical Analysis

IBM SPSS Statistics (version 28.0, Chicago, USA) program was used for data analysis. Descriptive statistics of variables were defined as percentage (%), frequency, mean±standard deviation, and median. A comparative analysis of independent groups studied by quantitative characteristics was performed using the Mann-Whitney U test. The Chi-Square test was used in the comparison of independent groups by qualitative characteristics. If the Chi-Square test did not meet the criteria Fisher's Exact test was used. The relationship of potential risk factors for the presence of ETC was evaluated by using logistic regression model. Odds ratios (OR) along with the 95% confidence intervals were calculated for predictors of ETC presence. The statistical significance level was defined when the p value was <0.05.

3. Results

This retrospective present study included 577 euthyroid patients with HT under LT4 treatment. Five hundred four (87.3%) patients were female, and 73 (12.7%) patients were male. Mean age was 52.6±13.5 years. Mean BMI was 27.2±4.7 kg/m^2. Of the 577 patients, 159 (27.6%) were smoking. Seventy seven (13.3%) patients had ETC. The results are summarized in Table 1. There were double cancers in 3 patients. A total of 80 malignant tumors were found: 37 (46.2%) were breast cancer, 7 (8.7%) were ovary cancer, 6 (7.5%) were leukemia, 5 were (6.2%) colon cancer, 4 (5%) were pancreas cancer, 3 (3.8) were bladder cancer, 3 (3.8%) were lung cancer, 3 (3.8%) were endometrial cancer, 2 (2.5%) were kidney cancer, and 2 (2.5%) were lymphoma. The remaining 8 (10%) patients had other cancer types: 1 prostate cancer, 1 malign melanoma, 1 testis cancer, 1 parotid cancer, 1 nasopharyngeal cancer, 1 cervix cancer, 1 stomach

cancer, and 1 laryngeal cancer. The classification of ETC types is shown in Table 2. In addition, there were 6 patients (1%) diagnosed with PTC through FNAC in our study population. The mean age at diagnosis for ETC was 50.9±12.8 years. Approximately, 55% of the patients were diagnosed with ETC after the diagnosis of HT. There was a positive family history for cancer in 146 (25.3%) patients. The most prevalent two comorbidities accompanying HT were metabolic syndrome (36.4%) and obesity (31.2%). Mean duration of hypothyroidism was 10.9±7.6 years. Mean daily LT4 dose to achieve euthyroidism was 77.2±35.2 mcg. Median TPOAb and TgAb concentrations were 209.0 IU/mL and 195 IU/mL, respectively. Mean TSH level in euthyroid status was 2.23±1.22 µIU/mL.

Patients with ETC were compared to those without cancer. The results of patients with or without ETC are shown in Table 3. Mean age was significantly higher in patients with cancer (p=0.000). Individuals with a first-degree family history for cancer had a higher risk of developing cancer than those without a family history (p=0.007). Rate of T2DM was higher in patients who had cancer (p=0.027). Duration of hypothyroidism was longer in patients without cancer (p=0.028). The TgAb titers were higher in cancer group compared with the non-cancer group (p=0.036). People with cancer had significantly higher fasting blood glucose (FBG) concentrations than those without cancer (p=0.000). The comparison of patients with and without cancer showed that mean eGFR was significantly lower in cancer group (p=0.001). Mean serum TG levels were elevated in patients with cancer in comparison with subjects without cancer (p=0.046). Compared with cancer group, the mean 25OHD level was lower in non-cancer group (p=0.007).

As shown in Table 4, univariate and multivariate data analyses were performed to identify significant predictors of cancer development. Independent risk factors related to increased risk of cancer were older age (OR 1.030, 95% CI 1.012-1.049, p=0.001); positive family history for cancer (OR 1.859, 95% CI 1.117-3.092, p=0.017); and elevated fasting blood glucose (OR 1.022, 95% CI 1.007-1.037, p=0.005).

Table 1. Demographic, clinical, metabolic, and biochemical features of the study population

Parameters	**Total (n=577)**
Age, years, mean±SD	52.6±13.5
Gender, n (%)	
Female	504 (87.3)
Male	73 (12.7)
BMI, kg/m^2, mean±SD	27.2±4.7
Current smoker, n (%)	159 (27.6)
Cancer, n (%)	77 (13.3)
Age at diagnosis (cancer), years, mean±SD	50.9±12.8
Cancer diagnosis, n (%)	
Before HT	35 (45.5)
After HT	42 (54.5)
Positive family history for cancer, n (%)	146 (25.3)
Comorbid conditions, n (%)	
None	311 (53.9)
Metabolic syndrome	210 (36.4)
Obesity	180 (31.2)
T2DM	57 (9.9)
T1DM	16 (2.8)
Duration of hypothyroidism, years, mean±SD	10.9±7.6
Daily levothyroxine dose to achieve euthyroidism, mcg, mean±SD	77.2±35.2
TPOAb, IU/mL, median	209.0
TgAb, IU/mL, median	195.0
TSH, µIU/mL, mean±SD	2.23±1.22
FT4, ng/dL, mean±SD	1.26±0.21
FBG, mg/dL, mean±SD	101.0±14.6
eGFR, mL/min/1.73 m^2, mean±SD	95.7±20.9
LDL, mg/dL, mean±SD	135.6±39.6
HDL, mg/dL, mean±SD	59.8±15.0
TG, mg/dL, mean±SD	132.3±73.4
ALT, U/L, mean±SD	20.3±9.7

25OHD, ng/mL, mean±SD	34.1±14.5

HT: Hashimoto's thyroiditis, SD: standard deviation, BMI: body mass index, T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, TPOAb: thyroid peroxidase antibody. TgAb: thyroglobulin antibody, TSH: thyroid stimulating hormone, FT4: free T4, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, 25OHD: 25-hydroxyvitamin D

Table 2. Classification of cancer types

Cancer locations	**80 malignant tumors in 77 patients, n (%)**
Breast	37 (46.2)
Ovary	7 (8.7)
Leukemia	6 (7.5)
Colon	5 (6.2)
Pancreas	4 (5)
Bladder	3 (3.8)
Lung	3 (3.8)
Endometrial	3 (3.8)
Kidney	2 (2.5)
Lymphoma	2 (2.5)
Others	8 (10)

Table 3. Demographic, clinical, biochemical, and metabolic characteristics of the patients with and without cancer

Parameters	**Without cancer (n=500)**	**With cancer (n=77)**	**P value**
Age, years, mean±SD	51.8±13.4	58.3±13.1	**0.000^{m}**
Gender, n (%)			
Female	436 (87.2)	68 (88.3)	0.785^{X2}
Male	64 (12.8)	9 (11.7)	
BMI, kg/m^2, mean±SD	27.2±4.6	27.4±4.9	0.918^{m}
Current smoker, n (%)	141 (28.2)	18 (23.4)	0.378^{X2}
Positive family history of cancer, n (%)	117 (23.4)	29 (37.7)	**0.007^{X2}**
Comorbid conditions, n (%)			
None	274 (54.8)	37 (48.1)	0.269^{X2}
Metabolic syndrome	177 (35.4)	33 (42.9)	0.205^{X2}
Obesity	158 (31.6)	22 (28.6)	0.593^{X2}
T2DM	44 (8.8)	13 (16.9)	**0.027^{X2}**
T1DM	12 (2.4)	4 (5.2)	0.164^{X2}
Duration of hypothyroidism, years, mean±SD	11.0±7.4	9.8±8.4	**0.028^{m}**
Daily levothyroxine dose to achieve euthyroidism, mcg, mean±SD	77.2±34.5	77.1±39.4	0.822^{m}
TPOAb, IU/mL, median	215.5	174.0	0.330^{m}
TgAb, IU/mL, median	184.0	261.0	**0.036^{m}**
TSH, µIU/mL, mean±SD	2.24±1.23	2.16±1.12	0.684^{m}
FT4, ng/dL, mean±SD	1.26±0.21	1.27±0.22	0.765^{m}
FBG, mg/dL, mean±SD	100.2±14.1	106.4±16.5	**0.000^{m}**
eGFR, mL/min/1.73 m^2, mean±SD	97.0±20.6	86.2±22.8	**0.001^{m}**
LDL, mg/dL, mean±SD	136.0±39.6	133.1±39.6	0.726^{m}
HDL, mg/dL, mean±SD	59.6±14.7	60.5±16.9	0.586^{m}
TG, mg/dL, mean±SD	130.9±73.1	141.0±74.8	**0.046^{m}**
ALT, U/L, mean±SD	20.1±9.6	21.8±10.4	0.084^{m}
25OHD, ng/mL, mean±SD	33.6±14.7	37.3±12.8	**0.007^{m}**

HT: Hashimoto's thyroiditis, SD: standard deviation, BMI: body mass index, T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, TPOAb: thyroid peroxidase antibody. TgAb: thyroglobulin antibody, TSH: thyroid stimulating hormone, FT4: free T4, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, 25OHD: 25-hydroxyvitamin D. ^{m}Mann-Whitney U test / ^{X2}Chi-Square test (Fischer test)

Table 4. Logistic regression analysis of the variables associated with cancer development

Parameters	Univariate analysis			Multivariate analysis		
	OR	**95% Cl**	**P**	**OR**	**95% Cl**	**P**
Age	1.036	1.018-1.055	**0.000**	1.030	1.012-1.049	**0.001**
Positive family history of cancer	1.978	1.193-3.278	**0.008**	1.859	1.117-3.092	**0.017**
Duration of hypothyroidism	0.976	0.942-1.010	0.169			
T2DM	1.451	1.037-2.030	**0.030**			
TgAb	1.000	1.000-1.001	**0.010**			
FBG	1.025	1.010-1.039	**0.001**	1.022	1.007-1.037	**0.005**
eGFR	0.975	0.964-0.987	**0.000**			
TG	1.002	0.999-1.005	0.266			
25OHD	1.016	1.001-1.032	**0.040**			

OR: odds ratio, Cl: confidence level, HT: Hashimoto's thyroiditis, T2DM: type 2 diabetes mellitus, TgAb: thyroglobulin antibody, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, TG: triglyceride, 25OHD: 25-hydroxyvitamin D

4. Discussion

This present retrospective cohort study included 577 euthyroid Hashimoto's patients under LT4 treatment showed that the frequency of concomitant appearance of ETC was 13.3%. The most common 3 concurrent cancers were breast (46.2%), ovary (8.7%), and leukemia (7.5%). In multivariate analysis, older age, positive family history for cancer, and elevated fasting blood glucose level were independently associated with the increased risk of cancer.

The average rate of PTC among patients with HT was 1.2% in FNAC studies and ranged from 27.5% to 40.1% in thyroidectomy studies [5,6]. Researchers predominantly show that PTC patients with HT had a better prognosis and a lower risk of recurrence than those without HT [20]. However, there is not enough available data whether the coexistence of HT impacts on ETC frequency, characteristics and prognoses. Based on the ETC in the literature, most studies evaluated a link between HT and breast cancer. A meta-analysis included 28 studies that demonstrated increased breast cancer development in patients with chronic autoimmune thyroid disorder [21]. Two studies confirmed increased cancer risk in patients with HT [22,23]. A recent meta-analysis showed that patients with HT had a significantly increased risk of several types of ETCs including breast, lung, urogenital, digestive system, and blood cancers [2]. The frequency of ETCs in patients with HT ranged from 2% to 11%, with a mean rate of 6.5% [2]. Increased cancer risk and incidence are still under debate in patients with HT. A study conducted by Sarlis et al. [24] showed no relationship between breast cancer and HT. Prinzi et al. [25] evaluated ETCs in women with different benign and malign thyroid diseases. The most common ETC was breast in their study population. However, they found that lack of thyroid autoimmunity was associated with increased risk of ETC development [25]. According to our center's experience, the frequency of ETC was 13.3%. Moreover, approximately half of the malignant tumors were observed in breast tissue followed by ovarian and bone marrow. There may be a link between HT and breast cancer. Increased breast and ovarian cancer development may be related to female gender preponderance in patients with all autoimmune diseases. It is considered that there is an association between various autoimmune diseases and hematological malignancies such as leukemia, Hodgkin/non-Hodgkin lymphoma and myeloma [26].The underlying mechanisms include genetic, environmental factors, medical treatments of autoimmune diseases, and irregular immune function [26]. The incidence of acute leukemia and chronic myeloid leukemia was significantly higher among patients with autoimmune diseases when compared to general population [26]. Furthermore, primary familial autoimmune disease was a possible etiological factor in childhood acute leukemia [27]. Although there is an increased association between Hashimoto/hypothyroidism and non-Hodgkin lymphoma [26], it is not clear whether there is a possible link between HT and leukemia. This issue needs to be further investigation with larger sample size prospective studies.

Chiappa C et al. [23] showed a significant association between HT and cancer diagnosed with younger than 45 years old in both women and men. The other study showed that there was a link between ETC development and chronic autoimmune thyroiditis, especially in patients at young age [25]. In contrast to these study results, Chen et al. [22] reported that older age was associated with higher cancer risk in Hashimoto's patients. We confirmed this data. The mean age at diagnosis for cancer was

nearly 51 years old in our study. Moreover, more than one-half of cases were diagnosed with cancer after the diagnosis of HT. Hence, we suggest that patients in follow-up with HT, especially after the age of 50 should be screened for the development of several cancer types.

There is limited available data for the relationship between ETC and family history of cancer in patients with HT. A study did not find a statistically significant association between breast cancer and family history [23]. There was a positive correlation between HT and presence of ETC in our present study. Hence, based on our study results, we think that Hashimoto's patients with a family history of cancer should be followed up more closely for certain cancer types.

Most studies in the literature explored TPOAb concentration in cancer patients with autoimmune thyroid disorders. Studies were especially conducted on patients with breast cancer [7]. Some authors reported that there was a stronger correlation between breast cancer risk and presence of thyroid autoimmunity [28]. According to a study's results, TPOAb and TgAb levels were significantly higher in patients with breast cancer than in control group [29]. Patients with TPOAb and/or TgAb positivity had an increased risk for several types of cancer, such as melanoma, breast cancer and hematological cancers [25]. In contrast, some studies found that patients with absence of thyroid autoimmunity revealed higher risk for all types of ETC [25]. Tosovic et al. [30] showed that women with high levels of TPOAb had low breast cancer risk. This issue is still under debate. In our present study, TgAb titers were higher in cancer group. However, when this data was analyzed using multivariate statistics, there was no correlation between TgAb and development of cancer.

Cancer development could be related to thyroid function tests. A study showed that thyroid hormone receptor expression altered in breast cancer patients [31]. Thyroid hormone may bind and stimulate estrogen receptor levels and estrogen production in breast cancer cells [31]. Thyroid hormones may also cause proliferative effects on breast cells [31], and they have important regulator effect on hematopoiesis [32]. Hypothyroidism was an independent risk factor for developing breast cancer in women [33]. Breast cancer risk may be associated with different nationalities or geographical areas in patients with hypothyroidism [34]. A meta-analysis reported decreased cancer risk in the European population, and similar cancer risk in the non-European population [34]. Hypothyroidism was associated with slightly increased gynecological cancer risk [35]. There is controversial data for colorectal cancer. An elevated risk of colorectal cancer was reported in patients with hypothyroidism [36]. Increased cancer risk may be related to gender [37]. Gastric cancer was associated with male gender in patients with hypothyroidism [37]. There are studies which found decreased cancer risk in patients with hypothyroidism [38-42]. Hypothyroidism was related to a lower risk of breast cancer [38], rectal cancer [39], lung cancer [40], prostate cancer [41], and hepatocellular cancer [42]. LT4 treatment was associated with a reduced risk of breast cancer [43] and colorectal cancer [44]. Wang et al. [45] found no association between endometrial cancer and autoimmune hypothyroidism. Breast and ovary cancers were the most frequent two cancer types in our cohort. These study results might be explained with female predominance and subsequent occurrence of estrogen-related cancers. We included euthyroid HT patients under LT4 therapy in this present study. We are closely monitoring the thyroid function tests to avoid under or over treatment. LT4 replacement may decrease the risk of other cancer types. We think that Hashimoto's patients should be followed up carefully to keep them in euthyroid status.

A large study included 159.033 patients demonstrated that patients with DM had a higher risk of several types of ETC such as esophagus, breast, lung, pancreas, liver, endometrium, and colon [15]. In addition, patients with T1DM have also increased risk for cancer development [16]. There is no available data for DM, DM-related diseases and their relationship with ETC development in patients with HT. Our study results indicated that the most common concurrent cancers were breast, ovary, leukemia, colon, and pancreas, respectively. The presence of T2DM was not associated with cancer development, however, FBG levels were significantly positively correlated with cancer development in our multivariate analysis data. Hence, we should give priority to early diagnosis of DM and focus on the management of hyperglycemia to prevent ETC in Hashimoto's patients.

It is known that there is potential relationship between obesity and autoimmunity [17]. Elevated expression of pro-inflammatory cytokines such as leptin may be main factor of occurrence of autoimmunity in obese people [17]. Waring et al. showed that hypothyroidism was associated with increased metabolic syndrome risk [46]. Hypothyroidism is also associated with obesity [47].

Obesity and metabolic syndrome are remarkably associated with insulin resistance. Hyperinsulinemia increases cancer risk via triggering pro-inflammatory pathways and mitogenic activity [14]. A study reported increased cancer risk at several anatomic sites, including esophagus (adenocarcinoma), stomach, breast, pancreas, gallbladder, liver, colon, corpus uteri, and kidney in overweight and obese patients [48]. In our present study, nearly one-third of the patients had either metabolic syndrome or obesity but there was no correlation between these two metabolic disorders and ETC development in patients with HT. Dyslipidemia described as elevated LDL cholesterol concentration, high serum TG concentration and low HDL cholesterol concentration were associated with different cancer types [49]. Lipotoxicity caused by increased levels of free fatty acids plays an essential role in the development of insulin resistance and DM. This hyperlipidemic environment supports cancer cell growth and survival [14]. However, we found no difference in terms of plasma cholesterol levels in euthyroid HT patients with and without cancer.

Our study had several limitations. It was a retrospective single center study with a small sample size. The absence of non-HT age- and gender-matched control group is the other limitation of our study. More prospective cohort studies involving large sample size, multiple geographical regions, multiple ethnicities, long-term follow-up, and control group are needed to clarify the relationship between HT and ETC occurrence or outcomes of the ETCs in Hashimoto's patients in the future. We think that our study results are important. Because we evaluated many risk factors related to cancer. According to our study results euthyroid HT patients had increased risk for certain types of cancer. Although genetic susceptibility could not be changed, early diagnosis may be possible with screening especially in patients with positive family history of cancer. The number of risk factors may be decreased with more tight glucose control. Our findings could be useful for early diagnosis for common malignancies in patients with HT. We suggest that patients with HT should be monitored closely especially in the presence of above mentioned risk factors.

In conclusion, it seems that euthyroid Hashimoto's patients under LT4 therapy are more prone to develop certain types of cancer. In our study, breast cancer was the main cancer type associated with HT. Older age, positive family history for cancer and elevated fasting blood glucose were defined as independent risk factors for cancer development in patients with HT.

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