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Evaluation of the etiological factors of thyroid gland neoplasms: our clinical experience

Tiroid bezi neoplazmalarının etiyolojik faktörlerinin değerlendirilmesi: klinik deneyimimiz

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ABSTRACT

Objective: Thyroid cancer (TC), the most common endocrine malignancy worldwide, has a 10-year survival rate of more than 90% and a better prognosis than other malignancies. However, there are still conflicting data on the stimulators of cancer development, and benign thyroid diseases, such as goiter, benign thyroid nodules, Graves' disease, chronic thyroiditis, breast cancer and various factors including age, gender, consumption of vegetables, fiber food, hypercaloric diet, and tobacco and alcohol use are considered to be responsible. In this study, we aimed to evaluate patients with thyroid neoplasms who underwent surgical treatment in terms of etiological factors discussed in light of the literature.

Material and Method: In our study, patients who underwent surgery with the diagnosis of thyroid gland neoplasms between 2010 and 2020 were evaluated. A total of 371 patients were included in the study. Statistical analyses were performed using IBM SPSS Statistics v. 22.

Results: Of the 371 cases included in the study, 78.16% were female and 21.83% were male. The histopathological distribution of diagnoses was as follows: 76.28% papillary thyroid carcinoma (PTC), 4.31% follicular thyroid carcinoma (FTC), 14.29% follicular adenoma (FA), 0.54% Hurthle cell carcinoma (HCC), 3.77% Hurthle cell adenoma (HCA), and 8.08% medullary thyroid carcinoma (MTC). A total of 567 etiological factors were detected in 371 cases, and the highest factors ratio (1.94) being detected in the FTC group and the lowest (1.49) in the FA group. The most common of these factors was chronic lymphocytic thyroiditis (CLT) (35.31%). While the most common etiological factor in the PTC diagnosis group was thyroid and other non-breast cancers and the history of radiotherapy resulting from their treatment, it was a family history of thyroid cancer in the HCA group. Other systematic organ diseases, CLT, and breast cancer were the most common factors. The body mass index was the highest in the MTC group and the lowest in the PTC group.

Conclusion: Increased human development index, technological developments, greater accessibility of ultrasonography, and better diagnostic sensitivity have led to an increase in the detection of TC. Knowledge of the underlying etiological factors is important for the development of preventive measures and achieving more successful results in terms of diagnosis and treatment.

Keywords: Thyroid cancer, thyroid gland neoplasms, etiological factors

ÖZ

Amaç: Dünya genelinde en sık karşılaşılan endokrin malignite olan tiroid kanserinde (TK) 10 yıllık sağ kalım oranı %90'dan fazla olup diğer malignitelere göre daha iyi bir prognoza sahiptir. Literatürde TK gelişiminde yaş, cinsiyet, sebze ve lifli besin tüketimi, hiperkalorik diyet,tütün ve alkol kullanımı gibi faktörlerin yanında, kanser gelişimi öncesi guatr, iyi huylu tiroid nodülleri, Graves hastalığı, kronik tiroidit gibi benign tiroid hastalıkları ve meme kanseri birlikteliği konusunda tartışmalar devam etmektedir.Çalışmamızda kliniğimizde cerrahi tedavi uyguladığımız tiroid neoplazmlarını literatür eşliğinde etiyolojik faktörler açısından değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda 2010-2020 yılları arasında tiroid bezi neoplazmı tanısıyla cerrahi tedavi uyguladığımız hastalar değerlendirildi. Çalışmaya 371 hasta dahil edildi. İstatistikler IBM SPSS Statistics 22 kullanılarak yapıldı.

Bulgular: Çalışmaya dahil edilen 371 olgunun %78,16'sı kadın, %21,83'ü erkek cinsiyette olup, tanıların histopatolojik olarak dağılımı %76,28'i papiller tiroid karsinomu (PTK), %4,31'i foliküler tiroid karsinomu (FTK), %14,29'u foliküler adenom (FA), %0,54'ü Hurthle hücreli karsinom (HHK), %3,77'si Hurthle hücreli adenom (HHA) ve %8,08'i medüller tiroid karsinomu (MTK) şeklindeydi. Toplamda 371 olguda 567 etiyolojik faktör tespit edilmiş olup,olgu başına düşen etiyolojik faktör oranı en yüksek (1,94) FTK, en düşük (1,49)FA tanı grubundaydı. Bu faktörler arasında en sık görüleni %35,31 ile kronik lenfositik tiroidit (KLT) idi. PTK tanı grubunda en sık görülen etiyolojik faktör tiroid ve meme dışı diğer kanserler ve bunların tedavisinden kaynaklanan radyoterapi öyküsü iken; HHA'da ailede tiroid kanseri öyküsü olmasıydı. Sistematik diğer organ hastalıkları, KLT ve meme kanseri en sık görülen faktörlerdi. Vücut kitle indeksi (VKİ) değeri ise en yüksek MTK, en düşük PTK tanı grubunda gözlendi.

Sonuç: İnsani gelişmişlik indeksinin yükselmesi, teknolojik gelişmeler, ultrasonografinin erişilebilirliği ve tanı duyarlılığındaki yükselme, TK insidansında artışa neden olmaktadır. Bu artışın zemininde yer alan etiyolojik faktörlerin iyi bilinmesi; koruyucu önlemlerin geliştirilmesi, tanı ve tedavi açısından daha başarılı sonuçlar alınması için önemlidir.

Anahtar Kelimeler: Tiroid kanseri, tiroid bezi neoplazmaları, etiyolojik faktörler

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy (1), with an increasing incidence worldwide since the first use of neck ultrasonography for its diagnosis in the 1980s. The 10-year survival rate of TC is more than 90%, and it has a favorable prognosis compared to other malignancies (2). Although the incidence of TC is approximately the same in pre-pubertal males and females, it is seen predominantly in the female gender starting with adolescence. It is two to four times more frequent in women than in men, regardless of age (3, 4). It has a poor prognosis in the elderly and an excellent prognosis in children. Age has a critical effect on tumor development and prognosis (5-7).

Environmental factors and genetic background significantly affect the biological and clinical features of TC (8). The incidence of TC is higher in regions with iodine deficiency, and the risk of developing cancer is inversely proportional to vegetable and fiber consumption, and directly proportional to hypercaloric diet (9). It is considered that ethanol, caffeine and other endogenous factors may be effective in the development of TC (10). Tobacco and alcohol use increases the incidence of TC (11). Genetic inheritance is also thought to play an important role in familial non-medullary cancers, which constitute 5-10% of TC cases (12).

Benign thyroid diseases, such as goiter, benign thyroid nodules, Graves' disease and chronic lymphocytic thyroiditis (CLT) may be seen in the patient before TC occurs (13). Breast cancer and TC are the two most common malignancies in women and may occur metachronously. Women with TC are at high risk for developing breast cancer later (14).

In this study, we evaluated patients with benign and malignant thyroid neoplasms who underwent surgical treatment in our clinic in terms of etiological factors discussed in light of the literature.

MATERIAL AND METHOD

Our study was carried out after obtaining approval from the Clinical Researches Ethics Committee of Gülhane Training and Research Hospital (Date 15.12.2021, Decision No: 2021/90). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, the surgical treatment decision was made at the endocrinology council of our hospital in patients presenting with thyroid gland neoplasms between 2010 and 2020, and the data of those who underwent surgery in our clinic were evaluated using their files. This retrospective study included 371 cases whose files contained complete information concerning the etiological factors that were the subject of the study and whose surgery and pathology reports could be accessed. Cases with missing data were excluded from the study. The statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 371 cases included in the study, 290 (78.16%) were female and 81 (21.83%) were male. The distribution of histopathological diagnoses was as follows: 283 papillary thyroid carcinomas (PTCs), 16 follicular thyroid carcinomas (FTCs), 53 follicular adenomas (FAs), two Hurthle cell carcinoma (HCCs), 14 Hurthle cell adenomas (HCAs), and three medullary thyroid carcinomas (MTCs). The female gender (78.17%) was predominant in all pathological diagnoses. The most dominant group of female gender was found to be FTC at a rate of 81.25%, while the HCA group had the lowest rate of female patients at 64.28%. The male gender was most dominant in the HCA (35.7%) group, and there was no male patient in the HCC group (**Table 1**). During the study period, bilateral total thyroidectomy was the most frequently performed operation, accounting for 270 (78.49%) of all operations. There was no significant difference between the surgical procedures performed according to the tumor types in the distinction made according to the histopathological diagnoses. Lymph node dissection (LND) was performed in a total of 147 cases, among which central + cervical LND was the most common (n=67, 45.58%).

Table 1. Mean age and gender of the cases according to pathological diagnoses

Diagnosis/Gender-Age	PTC n (%)	FTC n %)	FA n (%)	HCC n (%)	HCA n (%)	MTC n (%)	Total n (%)
Female n (%)	221 (59.57)	13 (3.50)	43 (11.59)	2 (0.54)	9 (2.43)	2 (0.54)	290(78.17)
Male n (%)	62 (16.71)	3 (0.81)	10 (2.70)	0	5 (1.35)	1 (0.27)	81 (21.83)
Mean age, SD	43.99	47.80	44.15	54.00	46.20	41.5	44.29±12.31
Female	42.24	48.25	44.19	54.40	46.29	52.00	46.07± 13.1
Male	50.21	46.00	44.00	0	46.00	31.00	48.79±11.2
Total	283 (76.28)	16 (4.31)	53 (14.29)	2 (0.54)	14 (3.77)	3 (0.81)	371 (100)

PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma, HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma, SD: Standard Deviation

The mean age was 44.29±12.31 years for the whole sample, 46.07±13.1 years for the female patients, and 48.79±11.2 years for the male patients, with no statistically significant difference according to gender (p=0.234). Since the number of cases in the MTC and HCC groups was not sufficient for a reliable evaluation, the age differences according to the male and female genders were evaluated in the remaining diagnosis groups, and a statistically significant difference was found only for the PTC diagnosis (female: 42.24 years; male: 50.21 years) (p=0.071).

Considering the age distribution of the patients, more than half of the patients were in the 20-45 years group (n=187, 50.40%). There were only six cases of PTC in the 0-20 years group, and there was no patient with another diagnosis in this age group. PTC was the diagnostic group with the highest proportion of cases in the age range of 20-45 years (55.12%). FTC was the diagnosis with the highest proportion of cases in the 45-60 years group (81.25%). There were 49 (13.21%) cases aged ≥60 years, and this group most commonly presented with HCA (21.43%) among all the diagnoses (**Table 2**).

Among the 371 cases evaluated in our study, a total of 567 etiological factors were identified, including 196 secondary or multifactorial factors, and a secondary etiological factor was found in 52.83% of the cases. Since the number of cases with MTC and HCC was very small, these two groups were excluded from the evaluation. The ratio of etiological factors per case was 1.53 in all cases, with the highest ratio being observed in the FTC group (1.94) and the lowest ratio in the FA group at 1.49. The most common etiological factor was CLT (35.31%) and the least common was radiotherapy (RT) (2.16%). CLT association was most frequently observed in patients with FTC (43.75%). The history of RT was present in only eight (2.83%) cases with PTC. Although a family history of thyroid cancer was seen at a frequency of 3.50% in all cases, the highest rate was observed in the HCA group (7.14%). The most common etiological factors accompanying PTC were thyroid and other non-breast cancers (6.71%) and the presence of a history of RT (2.83%) due to their treatment. Breast cancer (6.25%), CLT (43.75%), and other systematic organ diseases (68.75%) were more common in the FTC group. A family history (35.71%), diabetes mellitus (DM) (21.42%), immune system-related diseases (14.29%), hyperlipidemia (21.42%), and hypertension (28.57%) were more common in the HCA group. The mean body mass index (BMI) was 26.05 (18.5-24.9), with the lowest value obtained from the PTC group (25.8) and the highest in the MTC group (28.4) (**Table 3**).

When all the cases were evaluated, the mean thyroid-stimulating hormone (TSH) was 3.35 mIU/mL, with the highest value being observed in the HCA group (6.12 mIU/mL) and the lowest (1.56 mIU/mL) in the MTC group. When graded according to the TSH serum concentrations

Table 2. Age range distribution according to pathological diagnoses

Diagnosis/Age Distribution	PTC	FTC	FA	HCC	HCA	MTC	Total
0-20 years n (%)	6 (2.12)	0	0	0	0	0	6 (1.60)
20-45 years n (%)	156 (55.12)	3 (18.75)	21 (39.62)	1 (50.00)	5 (35.71)	1 (33.33)	187 (50.40)
45-60 years n (%)	86 (30.39)	13 (81.25)	24 (45.28)	1 (50.00)	6 (42.86)	2 (66.67)	132 (35.58)
≥60 years n (%)	38 (13.43)	0	8 (15.09)	0	3 (21.43)	0	49 (13.21)
Total, n	283	16	53	2	14	3	371

PTC: Papillary Thyroid Carcinoma , FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma, HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma

Table 3. Distribution of accompanying diseases according to pathological diagnoses

	PTC n (%)	FTC n (%)	FA n (%)	HCC n (%)	HCA n (%)	MTC n (%)	Total n (%)
Familial history of thyroid cancer, n (%)	9 (3.18)	1 (6.25)	2 (3.77)	0	1 (7.14)	0	13 (3.50)
Diabetes mellitus, n (%)	31 (10.95)	1 (6.25)	6 (11.32)	0	3 (21.43)	0	41 (11.05)
Breast cancer, n (%)	14 (4.95)	1 (6.25)	0	0	0	0	15 (4.04)
*Immunological diseases, n (%)	31 (10.95)	1 (6.25)	3 (5.66)	1 (50.00)	2 (14.29)	0	38 (10.24)
Chronic lymphocytic thyroiditis, n (%)	98 (34.63)	7 (43.75)	21 (39.62)	1 (50.00)	3 (21.43)	1 (33.33)	131 (35.31)
Hyperlipidemia, n (%)	46 (16.25)	3 (18.75)	11 (20.75)	0	3 (21.43)	0	63 (16.98)
Hypertension, n (%)	61 (21.55)	4 (25.00)	15 (28.30)	1 (50.00)	4 (28.57)	0	85 (22.91)
Radiotherapy history, n (%)	8 (2.83)	0	0	0	0	0	8 (2.16)
**Other cancer history, n (%)	19 (6.71)	0	0	0	0	0	19 (5.12)
***Others, n (%)	71 (20.09)	11 (68.75)	14 (26.42)	1 (50.00)	2 (14.29)	0	99 (26.68)
Total	430 (75.84%)	31 (5.47%)	79 (13.93%)	4 (0.7%)	22 (3.88%)	1 (0.18%)	567 (100%)
Factor ratio per case	1.52	1.94	1.49	2.0	1.57	0.33	1.53
BMI	25.8	26.2	26.9	27.2	27.1	28.4	26.05
Total	283	16	53	2	14	3	371

PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma *Immunological: Autoimmune, Rheumatological or Allergic Disease, **Other Cancer: Thyroid and History of Non-Mammary Cancer, **Others: Cardiac, Neurological, Lung, Kidney, Coagulopathy; Cases with Vasculitis, Smoking and Graves' Disease. BMI: Body Mass Index

as undertaken by Lun et al. (15), it was seen that only one case with HCA had a TSH value of ≥4.95 Since TSH was ≥10 mIU/mL in this case, the mean value of this group was higher compared to the remaining diagnoses. When the TSH range of 0-0.35 was evaluated, 14.82% of all cases were found to have a value within this range, and the FTC group had the highest proportion (18.75%) among all the diagnosis groups. The TSH range of 0.36-1.35 was detected in 21.02% of all cases, with the FA group having the highest rate (28.30%). The TSH range of 1.36-1.90 was observed in 19.95% of all cases and had the highest rate in the FTC group (31.25%). The TSH range of 1.91-4.94 had the highest number of cases (n=133 cases, 35.84%), and most (43.75%) were in the FTC group. Lastly, 8.36% of all cases and 9.54% of the PTCs had a TSH value of ≥4.95, (**Table 4**).

DISCUSSION

The incidence of TC is higher in countries with a high human development index compared to those with a low human development index (16). In a study by Lee et al. (17), 75.5% of the patients with PTCs were women. In our study, a similar rate of women was observed both for all cases and for those with a PTC diagnosis. Considering all the cases in the current study, the female patients were younger than the male patients, but the age difference according to gender was not statistically significant (p=0.071); however, proportionally the most significant difference was observed in cases with PTC. It has been suggested that age-related genetic background of thyroid tissue has a significant effect on tumor development and critical impact on prognosis (5). TC has a high recurrence rate in patients older than 45 years even if their tumor size is small. Mazzaferri et al. (18) found that the recurrence rate was the highest at the most extreme ages (<20 years and >59 years), and <15 years and >45 years constituted a high risk for TC recurrence and death from cancer. Sharon et al. (19) found that 53.8% of patients with well-differentiated thyroid carcinomas (WDTCs) were in the 20-45 age range. In our study, although there was no statistically significant difference between the diagnosis groups in terms of the mean age (p=0.234), the highest proportion of cases were in the 20-45 years group. It was noteworthy that proportionally, the highest rate of PTC cases was in the 20-45 years group, and the cases of FTC were in the 45-60 years group. While 13.21% of all cases were found in the age group of ≥60 years, the diagnosis with the highest rate of cases in this age group was HCA. In a study by Won Gu Kim et al. (20), patients with HCC were found to be significantly older and have more lymphovascular invasion compared to the FTC group. In our study, although only two cases were diagnosed with HCC, the highest mean age among all cases was 54.40 years in this diagnosis group. While the mean age of the patients with FTC was 43±14 years in the previous study, we found it to be 47.80 years in our group.

In our study, it was observed that more than one etiological factor coexisted in 52.83% of the cases, and the factor ratio per case was 1.53 at the mean age of all cases (44.29±12.3 years). It was also determined that PTC was the most similar diagnosis group in terms of the mean age and factor ratio. Although patients with PTC constituting 76.28% of all cases included in our study was considered to be effective in this similarity, a factor of 1.94 was observed in the FTC group with a higher mean age and a lower factor (1.49) in the FA group with a lower mean age. When all the cases and diagnoses were evaluated, it was determined that there might be a correlation between the mean age and factor ratio.

TC is among the cancers with the highest hereditary predisposition (21), but more than 90% of cases are sporadic due to somatic genetic changes (22). Apart from familial medullary cancer with a high hereditary transmission rate, approximately 3-9% of TCs are familial non-medullary thyroid carcinomas. In our study, a family history was present in 3.50% of all cases and most frequently observed in the HCA group, which is consistent with the literature.

In the literature, it has been shown that high TSH levels stimulate follicular proliferation and support the development of PTC, and the risk of malignancy is associated with abnormally increased serum TSH concentrations (23). In a previous study, it was stated that the risk of PTC increased by 53% in patients with a TSH of ≥2.00 uIU/ml compared to those with a TSH of <2.00 uIU/ml (24). It is considered that long-term TSH stimulation and BRAF mutations in PTC may play a role in this mechanism (25). Although serum TSH levels have been shown to be correlated with the rates of PTC, it has been hypothesized that TSH facilitates breast carcinogenesis both independently and in combination with estrogen (26, 27). When we evaluated the TSH concentration in our study by dividing it into levels as described by Lun et al. (15), although 85.2% of the cases had a TSH value within the normal range, the TSH range with the highest number of cases was 1.91-4.94. FTC was the diagnosis group with the highest rate of patients with a TSH value in this range. A TSH value of ≥4.95, which is also the limit of hypothyroidism, was both numerically and proportionally the highest in the PTC group. Although the cases in the PTC group had normal TSH values, most being in the range of 1.91-4.94 may explain why the association of breast cancer is mostly seen in cases with PTC. In our study, we observed that the cases of carcinoma predominantly had TSH values in the range of 1.91-4.94, while patients with benign neoplasms had a more homogeneous distribution in terms of TSH.

In this study, the most common etiological factor was CLT (35.31%) and the least common was a history of RT (2.16%). The formation of TC can also be induced by the production of proinflammatory cytokines and oxidative stress in autoimmune thyroiditis (25). Lun et al. (15) observed a significant difference in TSH concentrations between patients with PTC and Hashimoto's thyroiditis and those without thyroiditis, and they reported that elevated TSH concentrations associated with Hashimoto's thyroiditis might increase the risk of PTC. In a study conducted by Uhlirova et al. (28), Hashimoto's thyroiditis was detected in 15% of the cases. In contrast, although CLT was observed in 35.3% of all our cases and 34.63% of the PTC cases, the highest rate of CLT was observed in the FTC group at a rate of 43.75%. We also determined that 35.1% of the cases had CLT coexistence and this coexistence was seen at a higher rate in follicular origin cancer and benign neoplasms than in Hurthle cell neoplasms.

Breast cancer and TC are the two most common malignancies in women and often occur metachronously. Women with TC are at increased risk for breast cancer. Similarly, women with breast cancer have an increased incidence of subsequent TC development. In the literature, it is reported that while women with breast cancer are twice more likely to develop TC in future, women with TC have a 67% higher risk of developing breast cancer compared to the general population (14). Chung et al. (29) reported that the rate of TC detection was 2.6% when patients were screened simultaneously for breast cancer with ultrasound and fine-needle aspiration biopsy. Studies have shown that aggressive FTC is detected more frequently than PTC in patients with a history of breast cancer (30). The co-occurrence of these two diseases is even more common in men, with those having a history of TC being 29 times more likely to develop breast cancer. Metachronous thyroid cancer is also more common when the first breast tumor is HER2-positive (31). Studies have stated that familial characteristics are important in the association of these cancers, and they suggested that mutations in PTEN (32) and germline mutations in PARP4 (33) may be effective. In our study, breast cancer was seen only in WDTC cases, mostly PTC. In addition to this, it was seen in 4.04% of all cases. Breast cancer was not observed in other diagnostic groups.

Numerous studies have associated endocrine disrupting chemicals (EDCs) with obesity, developmental disorders, and hormone-dependent cancers (34). EDCs can stimulate the development of TC and breast cancer through estrogenic signaling. Behaviorally driven environmental factors including obesity, sedentary lifestyle, alcohol consumption, and tobacco use have been shown to increase the risk of cancer (35). A pooled analysis of five prospective studies also reported a higher risk of TC in obese subjects (36). Insulin regulates thyroid gene expression and stimulates thyrocyte proliferation, differentiation and transformation. In a previous study, insulin resistance was present in 50% of patients with PTC and 10% of matched controls (37). In another study, BMI at the time of diagnosis was found to be directly related to the risk of TC in women (38). Insulin-like growth factor1 (IGF-1), which has structural homology to insulin, binds to the IGF-1 receptor and acts as a potent growth factor stimulating malignant transformation, tumor progression, and metastasis (39). Zhao et al. (24) found the BMI of WDTCs as 25.18 and Cortney et al. (16) reported the BMI of PTCs as 29.4 (±5.3). In our study, the mean BMI was 26.05 (range, 18.5-24.9) for all cases, and the lowest BMI value was observed in the PTC group (25.8) and the highest in the MTC group (28.4). Therefore, the BMI of our cases was in a similar range to the values given in the literature. The cases with PTC with the lowest mean age had the lowest BMI, while those with other diagnoses presenting with a higher mean age had higher BMI values.

In the literature, physical inactivity and diabetes have been closely associated with obesity, which is also related to the risk of TC (40, 41). It has been shown that there is a significant positive association between diabetes and TC risk. Diabetes affects carcinogenesis in numerous biological ways, including hyperglycemia, hyperinsulinemia, and chronic inflammation (42). In our study, the frequency of DM was 11.05% for all cases, and the highest rate was seen in cases with HCA.

There are studies suggesting that a low-calorie diet is a preventive factor for TC (43). It is considered that hyperlipidemia may play a role in the increase in the incidence of TC (44). In a recent study conducted in the People's Republic of China, it was found that people with hypercholesterolemia had a 1.33 times higher risk of TC than those without this condition (24). In the current study, hyperlipidemia was present in 16.98% of all our cases, and the highest rate was observed among those with HCA.

Although radiotherapy is a good option for the treatment of many cancers, especially breast cancer, it is also a risk factor for the development of cancer, especially TC (45, 46). Many recent clinical studies have shown that the thyroid's ability to produce hormones changes following radiotherapy (47, 48). Most cases of TC that occur with irradiation are PTCs (49). When the patients who had received radiotherapy treatment for various diseases were evaluated in our study, it was observed that only the PTC group had a history of RT. In addition, all cases with a history of "breast cancer" or "thyroid and

other non-breast cancer", except for one patient, had PTC. Similarly, we observed that all the cases that had previously undergone radiotherapy presented with PTC. In light of the literature, we considered that radiotherapy, which may be used in the treatment of diseases that occur in other areas of the body, may also contribute to the development of PTC, although the neck is not directly irradiated.

CONCLUSION

The frequency of the diagnosis of micropapillary cancer is increasing as a result of conditions such as improvement in the socioeconomic situation worldwide, continuing increase in the human development index, increased diagnostic sensitivity of ultrasound with technological developments, widespread use of neck ultrasound (even for screening purposes in some countries), and increased use of iodine in the diet. This situation leads to the continuation of the increasing trend in the incidence of thyroid carcinoma. Knowing epidemiological factors underlying this increased incidence of TC is important for the development of preventive measures and achieving more successful results in terms of diagnosis and treatment.

ETHICAL DECLARATIONS

Ethical Committee Approval: Our study was carried out after obtaining approval from the Clinical Researches Ethics Committee of Gülhane Training and Research Hospital (Date 15.12.2021, Decision No: 2021/90).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing? Curr Opin Oncol 2015; 27: 1-7.
2. Acquaviva G, Visani M, Repaci A, et al. Molecular pathology of thyroid tumours of follicular cells: a review of genetic alterations and their clinicopathological relevance. Histopathology 2018; 72: 6-31.
3. Lupoli GA, Fonderico F, Colarusso S, et al. Current management of differentiated thyroid carcinoma. Med Sci Monit 2005; 11: Ra368-73.
4. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. Br J Cancer 1987; 55: 191-5.
5. Haymart MR. Understanding the relationship between age and thyroid cancer. Oncologist 2009; 14: 216-21.
6. Prasad ML, Vyas M, Horne MJ, et al. NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States. Cancer 2016; 122: 1097-107.
7. Nixon IJ, Wang LY, Migliacci JC, et al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. Thyroid 2016; 26: 373-80.
8. Ito Y, Nikiforov YE, Schlumberger M, Vigneri R. Increasing incidence of thyroid cancer: controversies explored. Nat Rev Endocrinol 2013; 9: 178-84.
9. Markaki I, Linos D, Linos A. The influence of dietary patterns on the development of thyroid cancer. Eur J Cancer 2003; 39: 1912-9.
10. Büttel I, Fechter A, Schwab M. Common fragile sites and cancer: targeted cloning by insertional mutagenesis. Ann N Y Acad Sci 2004; 1028: 14-27.
11. Cho YA, Kim J. Thyroid cancer risk and smoking status: a meta-analysis. Cancer Causes Control 2014; 25: 1187-95.
12. Bonora E, Tallini G, Romeo G. Genetic predisposition to familial nonmedullary thyroid cancer: an update of molecular findings and state-of-the-art studies. J Oncol 2010; 2010: 385206.
13. Ríos A, Rodríguez JM, Canteras M, Galindo PJ, Balsalobre MD, Parrilla P. Risk factors for malignancy in multinodular goitres. Eur J Surg Oncol 2004; 30: 58-62.
14. Bolf EL, Sprague BL, Carr FE. A linkage between thyroid and breast cancer: a common etiology? Cancer Epidemiol Biomarkers Prev 2019; 28: 643-9.
15. Lun Y, Wu X, Xia Q, et al. Hashimoto's thyroiditis as a risk factor of papillary thyroid cancer may improve cancer prognosis. Otolaryngol Head Neck Surg 2013; 148: 396-402.
16. Khatami M. Inflammation, aging, and cancer: tumoricidal versus tumorigenesis of immunity: a common denominator mapping chronic diseases. Cell Biochem Biophys 2009; 55: 55-79.
17. Lee CY, Snyder SK, Lairmore TC, Dupont SC, Jupiter DC. Utility of surgeon-performed ultrasound assessment of the lateral neck for metastatic papillary thyroid cancer. J Oncol 2012; 2012: 973124.
18. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001; 86: 1447-63.
19. Cushing SL, Palme CE, Audet N, Eski S, Walfish PG, Freeman JL. Prognostic factors in well-differentiated thyroid carcinoma. Laryngoscope 2004; 114: 2110-5.
20. Kim WG, Kim TY, Kim TH, et al. Follicular and Hurthle cell carcinoma of the thyroid in iodine-sufficient area: retrospective analysis of Korean multicenter data. Korean J Intern Med 2014; 29: 325-33.
21. Bonnefond S, Terry F Davies TF. Thyroid cancer—risks and causes. Oncol Hematol Rev 2014; 10: 144–51.
22. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer 2013; 13: 184-99.
23. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006; 91: 4295-301.
24. Zhao J, Tian Y, Yao J, et al. Hypercholesterolemia is an associated factor for risk of differentiated thyroid cancer in Chinese population. Front Oncol 2020; 10: 508126.

25. Vukasović A, Kuna SK, Ostović KT, Prgomet D, Banek T. Diffuse sclerosing variant of thyroid carcinoma presenting as Hashimoto thyroiditis: a case report. Coll Antropol 2012; 36: 219-21.
26. Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab 2008; 93: 809-14.
27. Nielsen SM, White MG, Hong S, et al. The breast-thyroid cancer link: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2016; 25: 231-8.
28. Uhliarova B, Hajtman A. Hashimoto's thyroiditis - an independent risk factor for papillary carcinoma. Braz J Otorhinolaryngol 2018; 84: 729-35.
29. Chung WY, Chang HS, Kim EK, Park CS. Ultrasonographic mass screening for thyroid carcinoma: a study in women scheduled to undergo a breast examination. Surg Today 2001; 31: 763-7.
30. Kuo JH, Chabot JA, Lee JA. Breast cancer in thyroid cancer survivors: An analysis of the Surveillance, Epidemiology, and End Results-9 database. Surgery 2016; 159: 23-9.
31. Van Fossen VL, Wilhelm SM, Eaton JL, McHenry CR. Association of thyroid, breast and renal cell cancer: a population-based study of the prevalence of second malignancies. Ann Surg Oncol 2013; 20: 1341-7.
32. Ngeow J, Sesock K, Eng C. Clinical Implications for Germline PTEN Spectrum Disorders. Endocrinol Metab Clin North Am 2017; 46: 503-517.
33. Ikeda Y, Kiyotani K, Yew PY, et al. Germline PARP4 mutations in patients with primary thyroid and breast cancers. Endocr Relat Cancer 2016; 23: 171-9.
34. Gore AC, Chappell VA, Fenton SE, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev 2015; 36: E1-e150.
35. Weiderpass E. Lifestyle and cancer risk. J Prev Med Public Health 2010; 43: 459-71.
36. Kitahara CM, Platz EA, Freeman LE, et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev. 2011; 20: 464-72.
37. Rezzónico JN, Rezzónico M, Pusiol E, Pitoia F, Niepomniszcze H. Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. Metab Syndr Relat Disord 2009; 7: 375-80.
38. Mijović T, How J, Pakdaman M, et al. Body mass index in the evaluation of thyroid cancer risk. Thyroid 2009; 19: 467-72.
39. Zhao S, Jia X, Fan X, et al. Association of obesity with the clinicopathological features of thyroid cancer in a large, operative population: A retrospective case-control study. Medicine (Baltimore) 2019; 98: e18213.
40. Zhao ZG, Guo XG, Ba CX, et al. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. J Int Med Res 2012; 40: 2041-50.
41. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008; 371: 569-78.
42. Schmid D, Behrens G, Jochem C, Keimling M, Leitzmann M. Physical activity, diabetes, and risk of thyroid cancer: a systematic review and meta-analysis. Eur J Epidemiol 2013; 28: 945-58.
43. Xiao Q, Park Y, Hollenbeck AR, Kitahara CM. Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 2014; 23: 1102-8.
44. Hung SH, Lin HC, Chung SD. Statin use and thyroid cancer: a population-based case-control study. Clin Endocrinol (Oxf) 2015; 83: 111-6.
45. Sinnott B, Ron E, Schneider AB. Exposing the thyroid to radiation: a review of its current extent, risks, and implications. Endocr Rev 2010; 31: 756-73.
46. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995; 141: 259-77.
47. Tunio MA, Al Asiri M, Bayoumi Y, Stanciu LG, Al Johani N, Al Saeed EF. Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. J Cancer Res Ther 2015; 11: 684-9.
48. Wolny-Rokicka E, Tukiendorf A, Wydmański J, Roszkowska D, Staniul BS, Zembroń-Łacny A. Thyroid function after postoperative radiation therapy in patients with breast cancer. Asian Pac J Cancer Prev 2016; 17: 4577-81.
49. Inskip PD. Thyroid cancer after radiotherapy for childhood cancer. Med Pediatr Oncol 2001; 36: 568-73.