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The prevalence of malignancy in nodular goiter in endemic and non-endemic regions

Endemik ve endemik olmayan bölgelerde nodüler guatrda malignite prevelansı

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ABSTRACT

Aim: The aim of the study was to investigate the incidence of thyroid cancer and the impact of uncontrolled iodine prophylaxis on the development of thyroid cancer in patients with single-nodular and multinodular goiter in endemic and non-endemic regions of the Republic of Azerbaijan.

Material and Methods: The study comprised 352 patients who underwent thyroid surgery for nodular goiter between 2015 and 2022. Patients were categorized into two groups and two subgroups based on endemic (n=126) and non-endemic (n=226) regions. Also according to the number of thyroid nodules 2 subgroups were defined as solitary nodular goiter (169) and multinodular goiter (183).

Results: Although there was a general decrease in the incidence of goiter disease in endemic regions due to iodine prophylaxis, an increase in the incidence of MNG was recorded (56.4%). Thyroid malignancy was detected in 20 patients (15.9%) in the endemic nodular goiter group. There were 11 (8.7%) patients with solitary nodular goiter (SNG) and 9 (7.1%) with multinodular goiter (MNG) (p≥0,05). Histopathologic evaluation revealed classical variant of papillary cancer in 19 of them (15.1%) and the follicular variant of papillary cancer in 1 (0.8%) patient. In non-endemic regions, thyroid cancer was detected in 47 cases (20.8%) with 23 (10.2%) MNG and 24 (10.6%) SNG patients. Follicular cancer was detected in 2 patients (0.7%), classical type papillary cancer in 36 patients (15.9%), microcarcinoma in 7 patients (3.1%) and medullary cancer in 2 patients (0.9%) (p≥0,05).

Conclusions: Based on the data collected from endemic regions, the uncontrolled use of iodine prophylaxis has led to a decrease in the prevalence of follicular thyroid cancer and an increase in the incidence of papillary thyroid carcinoma. Avoiding the use of iodized table salt under in regions by endemically monitored sanitary-epidemiological conditions can lead to a reduced likelihood of developing follicular cancer.

Keywords: Lodine deficiency, endemic goiter, multinodular goiter, singular nodular goiter, papillary thyroid carcinoma, follicular thyroid carcinoma.

ÖZ

Amaç: *Bu çalışmada, Azerbaycan'ın endemik ve endemik olmayan bölgelerinde nodüler guatrı olan hastalarda tiroid kanseri prevalansını ve kontrolsüz iyot profilaksisinin tiroid kanseri gelişimi üzerindeki etkisini incelemek amaçlanmıştır.*

Gereç ve Yöntem: *Çalışmaya 2015-2022 yılları arasında nodüler guatr nedeniyle opere edilen 352 hasta dahil edildi. Hastalar endemik (n=126) ve endemik olmayan (n=226) bölgelere göre iki gruba ve iki alt gruba ayrıldı. Ayrıca tiroitde olan nodül sayısına göre: soliter nodüler guatr (169) ve multinodüler guatr (183) sınıflandırıldı.*

Bulgular: *İyot profilaksisi nedeniyle endemik bölgelerde genel olarak guatr görülme sıklığında azalma olmasına rağmen, multinodüler guatr (MNG) görülme sıklığında artış (%56,4) kaydedildi. Endemik nodüler guatr hastalarının %15,9'unda tiroid malignitesi saptandı.*

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Soliter nodüler guatr (SNG) hastalarının 11'inde (%8,7), MNG hastalarının dokuzunda (%7,1) malignite tanısı mevcuttu (p≥0,05). Histopatolojik sonuçları bu grubun 19'unda (%15,1) papiller kanserin klasik varyantı ve birinde (%0,8) foliküler varyantı şeklindeydi. Endemik olmayan bölgelerde tiroit kanseri saptanan 47 olgunun (%20,8), 23'ünde (%10,2) MNG, 24'ünde (%10,6) SNG alt grubu izlendi. Endemik olmayan bölgelerde iki hastada (%0,7) foliküler kanser, 36 hastada (%15,9) klasik tip papiller kanser, yedi hastada (%3,1) mikrokarsinom ve iki hastada (%0,9) medüller kanser saptandı (p≥0,05).

Sonuç: *Endemik bölgelerde elde ettiğimiz verilere göre kontrolsüz iyot profilaksisi kullanılması nedeniyle foliküler tiroit karsinom prevalansında azalma gözlemlenirken, papiller tiroit karsinom sıklığında artış olmuştur. Epidemiyolojik takip koşullarında iyotlu sofra tuzunun bölgelerin endemik özelliklerine göre kontrol altında tutulması foliküler kanser riskinin azalmasına yol açabilir.*

Anahtar Sözcükler: *İyot eksikliği, endemik guatr, multinodüler guatr, soliter nodüler guatr, papiller tiroit karsinom, foliküler tiroit karsinom.*

INTRODUCTION

Multinodular goiter (MNG) occurs in approximately 5-15% of the population, but in endemic regions with the increased use of neck ultrasound, this prevalence exceeds 50%. Some environmental factors, such as age, iodine intake, gender, lifestyle, and head and neck irradiation may affect the risk of thyroid nodules (1). Some studies have also shown that excessive iodine intake might contribute to nodule development, though this association remains unclear (2).

In the pathogenesis of endemic goiter, as a result of iodine deficiency, the increase in TSH level leads to follicular cell hyperplasia and eventually diffuse and nodular growth of the thyroid gland. Autonomous nodules also may develop later. Iodine deficiency, which affects approximately two billion people worldwide, is particularly problematic in some parts of the world with a natural lack of iodine and its unavailability, such as Africa, Southeast Asia, and the Western Pacific region. Azerbaijan is also iodine deficient, as indicated by a survey conducted in 1996 (in 35 districts and cities of the Azerbaijan Republic by WHO and with the participation of local specialists) revealed a 98-100% prevalence of endemic goiter among 8-14 years old school children, in endemic zones and 77-86% in non-endemic regions based on ultrasound examination. As an iodine deficient country, table salt is iodized in Azerbaijan. However, it has been determined that uncontrolled iodine prophylaxis in regions without iodine deficiency can lead to the development of goiter. This process, influenced by exogenously iodine intake, induces the pathogenesis of goiter, causing functional and morphological changes (3, 5). Several authors have suggested that thyroid tumors caused by iodine deficiency are due to chronic TSH overstimulation, possibly interacting with epidermal growth factor and insulin-like growth factor I (4).

Thyroid cancer incidence exhibits geographic variations depending on the environment and genetic factors (6). Prolonged state of TSH elevation due to thyroid dysfunction increases the risk of thyroid cancer. Recent studies indicate a higher malignancy rate in patients with multinodular goiter when compared to single nodular goiter. (7, 17, 22). The occurrence of malignancy in MNG cases ranges from 7-17% of cases. (17, 22). According to the 2009 State Statistics Committee, 16,986 patients with thyroid diseases were registered in the Republic of Azerbaijan, 53 of them were with thyroid neoplasms. Of those registered cases there were 3251 diffuse goiter, 2730 nodular goiter, 5443 thyrotoxicosis, 3363 hypothyroidism and 1060 thyroiditis (8). Preoperative diagnosis of thyroid cancer is mainly provided by minimally invasive fine needle aspiration biopsy (FNAB) examination (7, 9). FNAB, while provides crucial information for the biologic nature of the thyroid, has also been inaccurate in determining malignancy at around 25% in extensive series (10). The challenge arises when dealing with numerous nodules, as taking biopsies from each one is practically impossible in MNG cases, limiting the ability to assess the entire gland’s morphological structure (11). Additionally, even with negative cytological results from FNAB, the possibility of malignancy cannot be completely ruled out with complete accuracy (3, 6, 21). Furthermore, the relationship between MNG, malignancy, and iodine deficiency, has not been fully investigated (7). Papillary cancer malignancy is extensively documented in the relevant literature (7, 9, 15).

The aim of the current study was to investigate the incidence of thyroid cancer and the impact of uncontrolled iodine prophylaxis on thyroid cancer development of in patients with single nodular and multinodular goiter in both endemic and non-endemic regions of the Republic of Azerbaijan.

MATERIALS and METHODS

The study population included 352 patients (age 9-76) who underwent thyroid surgery for nodular goiter during 2015-2022 at the Educational Surgical Clinic of Azerbaijan Medical University and "Real hospital" (Baku city). There were 309 women (87.8%). Patients were divided into 2 groups based on the endemic and non-endemic regions, as well as into 2 subgroups according to the number of thyroid nodules as single-nodular and multinodular goiter. Thyroid functional status was assessed by routine physical examinations, thyroid hormones levels (TSH, fT3, fT4) and ultrasound examination of the gland, FNAB was performed when indicated. In patients with a suspicion of malignancy on FNAB, total thyroidectomy was performed by the same surgical team. Clinical details were reviewed considering age, gender, surgical method and histopathologic results. Patients with Graves' disease was excluded. All data were statistically analyzed (SPSS, version 20.0) using Pearson X2 (xi) and Student's t-test, respectively ($p \leq 0.05$).

RESULTS

Patients were divided into 2 groups: endemic (35.8%, n=126) and non-endemic (64.2%, n=226). Within the endemic group, subgroups were formed: SNG accounted for 43.6% (n=55) and MNG constituted 56.4% (n=71). While there were 17 men (13.5%), 86.5% were women (n=109). Clinically, 19.1% of cases (n=24) were hyperthyroid, 9.5% (n=12) were hypothyroid and 71.4% (n=90) were euthyroid. The FNAB was performed on all radiologically "suspicious" nodules and the results were classified by the Bethesda system (Table-1).

In non-endemic regions 26 patients (11.5%) were men, 200 (88.5%) were women. MNG constituted 49.5% (n=112), while SNG constituted 50.5% (n=114). Before surgery, 81% of patients (n=183) were euthyroid, 11.1% (n=25) were hyperthyroid, and 7.9% (n=18) were hypothyroid.

Results summarizing the analysis to determine the benign and malignant nature of 126 patients operated on in the endemic region are presented in Table-2.

According to the data presented in Table-2, malignant pathohistological result was 42.1% in nodes with a size of 20-29.9 mm, and 34.2% in benign ones. There was no statistical difference between the number of patients with benign and malignant forms according to the size of the nodules ($\chi 2emp=4.09$, $p \geq 0.05$).

In non-endemic regions, malignancy was most common in nodules with a 10-19.9 mm. The details of this group are presented in Table-3. Statistical analysis showed significant difference between the number of patients with benign and malignant nodules according to the size ($\chi 2emp=14.8$, $p \leq 0.05$).

In group I, thyroid cancer was detected in 20 patients (15.9%) during postoperative pathohistological examination. Eleven of them (8.7%) were on SNG patients, while 9 (7.1%) were in MNG disease. Of those cases 19 (15.1%) were classic papillary cancer, and only 1 (0.8%) patient had follicular variant of papillary cancer. There was no significant statistical difference between the groups (p=0.220) (Table-4).

Table-1. The result of FNAB in endemic and non-endemic regions.

Bethesda	Region					
	Non-endemic		Endemic		Total	
	n	%	n	%	n	%
1	0	0%	2	4%	2	1.6%
2	37	38.5%	15	30%	42	33.3%
3	4	4.2%	6	12%	10	7.9%
4	27	28.1%	13	26%	30	23.8%
5	21	21.9%	11	22%	32	25.4%
6	7	7.3%	3	6%	10	7.9%

In group II, pathohistological examinations revealed thyroid cancer in 47 patients (20.8%). Malignancy rate was similar in both SNG and MNG disease as 10.6% and 10.2% respectively in SNG and MNG cases. There were 2 cases with follicular and 36 cases with papillary cancers. (p=0,220) (Table-4).

Table-2. The size of the nodules and their pathohistological results in endemic regions.

Size of nodule	Patohistology					
	Benign		Malign		Total	
	n	%	n	%	n	%
< 10 mm	2	2.7%	2	10.5%	4	4.3%
10-19.9 mm	21	28.8%	6	31.6%	27	29.3%
20-29.9 mm	25	34.2%	8	42.1%	33	35.9%
≥ 30 mm	25	34.2%	3	15.8%	28	30.4%

Table-3. The size of the nodules and their pathohistological results in non-endemic regions.

Size of nodule	Pathohistology					
	Benign		Malign		Total	
	n	%	n	%	n	%
< 10 mm	3	1.7%	2	4.3%	5	2.2%
10-19.9 mm	39	21.8%	20	42.6%	59	26.1%
20-29.9 mm	57	31.8%	17	36.2%	74	32.7%
≥ 30 mm	80	44.7%	8	17%	88	38.9%

Table-4. The details of pathohistological diagnosis and incidence of thyroid cancer by regions.

Pathohistological diagnosis	Non- endemic	Endemic
Benign	179 (79.2%)	106 (84.1%)
Malign	47 (20.8%)	20 (15.9%)
Macro-microfollicular nodular, colloid-adenomatous goiter	146 (64.6%)	83 (65.9%)
Autoimmune thyroiditis, macro-microfollicular nodular, colloid-adenomatous goiter	5 (2.2%)	8 (6.3%)
Macro-microfollicular nodular, colloidal adenomatous tumor on Hashimoto's thyroiditis	16 (7.1 %)	9 (7.1%)
Hurtle cell (oncocytic) adenoma	3 (1.3 %)	0
Follicular adenoma	9 (4%)	6 (4.8%)
Follicular variant of papillary cancer	1 (0.4 %)	1 (0.8%)
Follicular cancer	2 (0.9%)	0
Microcarcinoma	7 (3.1%)	0
A classic variant of papillary cancer	35 (1.5%)	19 (15.1%)
Medullar cancer	2 (0.9%)	0

P>0.05, no significant statistical difference between the groups

DISCUSSION

The epidemiology of thyroid disease is profoundly influenced by various environmental factors, where even minor disparities in population iodine intake can significantly impact the occurrence and progression of thyroid abnormalities and diseases. Monitoring and regulating iodine intake, particularly in endemic regions, represent crucial elements of preventive medicine (8). Endemic iodine deficiency is identified in various geographical regions worldwide, primarily affecting mountainous and foothill areas (10, 21). Iodine deficiency plays a pivotal role in goitrogenesis and ensuring adequate iodine intake through table salt or drinking water in endemic regions has proven to prevent deficiency and positively impact glandular diseases. However, implementing iodine prevention programs faces substantial technical and socio-economic challenges. Lack of information regarding certain causes of endemic goiter impedes the development of effective measures for disease eradication, even in regions with prolonged iodine addition to food sources (8).

In iodine-deficient regions like ours, iodized table salt is employed to combat iodine deficiency, eliminating it in the new generation but leading to notable morphological changes in already formed diffuse and nodular goiter in the older generation (8). Studies in iodine-deficient regions, such as one in Germany, revealed thyroid nodules or diffuse goiter in 33% of men and 32% of women during ultrasound examinations (12). Childhood head or neck radiation elevates malignancy risk and iodine deficiency in endemic regions has been associated with increased malignancy risk (13). Our study aligns with these findings, detecting thyroid cancer in 15.9% of patients in endemic regions, with a prevalence of papillary carcinoma (13, 14).

Global literature presents varying thyroid cancer prevalence among goiter surgery patients in endemic regions, ranging from 6.2% to 20.3% (15, 16). Our findings indicate thyroid cancer in 15.9% of patients from endemic regions, with a male/female ratio of 1/18. Non-endemic regions showed thyroid cancer in 20.8%, revealing diverse malignancy patterns compared to endemic areas, suggesting the interplay of genetic and environmental factors in malignancy development.

Follicular cancer frequency is reportedly elevated in thyroid cancer subtypes in iodine-deficient regions (17). Our study also supports this, detecting follicular cancer in 0.7% of cases in endemic areas. Long-term studies, like Harach et al.'s 40-year investigation in Argentina, highlight iodine intake's role in altering thyroid cancer subtypes (18). Recent literature emphasizes the importance of optimizing population iodine intake for preventive healthcare, linking iodine deficiency correction to a shift towards less malignant forms of thyroid cancer (19).

Additionally, complex relationships between iodine intake and thyroid tumors, including factors like delayed effects, dose thresholds, and interactions with ionizing radiation, have been reported (20.). Our findings align with these complexities, demonstrating thyroid carcinoma in 15.9% of endemic cases. Despite limitations, such as incomplete patient registration, our study provides valuable insights. The increased use of ultrasound facilitates early thyroid nodule detection. Although technology development and increased technological tool usage are common factors in the rise of papillary cancer, our study finds no statistical difference between groups, attributing this to the absence of specific radiation exposure.

In summary, our study reveals a decrease in single nodular goiter incidence and an increase in multinodular goiter due to iodine prophylaxis in endemic regions. Uncontrolled iodine prophylaxis, particularly in non-endemic regions, is associated with an increased goiter prevalence. While there's a decline in cancer incidence linked to iodine intake, there's a concurrent rise in papillary cancer. Endemic regions exhibit different malignancy patterns, with malignancy primarily found in single nodular goiter in non-endemic areas and multinodular goiter in endemic regions.

CONCLUSION

In conclusion, data from endemic regions demonstrate that uncontrolled iodine prophylaxis reduces follicular cancer prevalence but increases papillary carcinoma incidence. Restricting iodized table salt use, under controlled sanitary-epidemiological conditions in endemic regions, may decrease follicular cancer risk.

Conflict of interest: The authors declare no conflict of interest.

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