Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1152567
J Health Sci Med 2022; 5(5): 1499-1504

Papillary thyroid carcinoma prevalence and its predictors in patients with primary hyperparathyroidism

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Cite this article as: Durmuş ET, Atmaca A, Kefeli M, Çolak R, Durmuş B, Polat C. Papillary thyroid carcinoma prevalence and its predictors in patients with primary hyperparathyroidism. J Health Sci Med 2022; 5(5): 1499-1504.

ABSTRACT

Aim: Papillary thyroid carcinoma (PTC) and primary hyperparathyroidism (PHPT) are among the most common endocrine diseases. Although it has been shown that hyperparathyroidism may be associated with various cancers, the question of whether there is an association between hyperparathyroidism and PTC remains controversial. To evaluate the incidence of concomitant PTC among patients with PHPT and to identify possible risk factors for the development of PTC in these patients.

Material and Method: The data of 543 patients who had been operated on due to PHPT in our institution were reviewed retrospectively. Patients who underwent thyroid surgery in conjunction with parathyroidectomy and patients whose diagnosis of PTC was confirmed histopathologically were compared in terms of their clinical, biochemical, and histopathological features. The prevalence of PTC found in patients with PHPT was compared with national rates to estimate standardized incidence ratios (SIRs).

Results: Of the 456 PHPT patients enrolled in the study, 281 (61.6%) had concomitant thyroid nodules on thyroid ultrasonography, and PTC was detected in 53 (11.6%) patients during their thyroid surgeries. Compared to the general population, the incidence of papillary thyroid cancer was increased in both women and men with PHPT (SIR: 272.2, 95% CI: 201.6-360.0, p<0.001 and SIR: 736.5, 95% CI: 322.1-1457.0, p<0.001, respectively). Patients who were found to have PTC were older than non-PTC patients and had higher serum calcium levels (p=0.026 and p= 0.012, respectively). In multivariate analysis, a high serum calcium level and advanced age were independent predictors of PTC in patients with PHPT (OR: 1.402, 95% CI: 1.046-1.878, p=0.024 and OR: 1.024, 95% CI: 1.001-1.047, p=0.043, respectively).

Conclusion: Our study showed a significant increase in the prevalence of PTC in patients with PHPT compared to the general population in association with both older age and higher levels of serum calcium. Due to their higher levels of risk, such patients should particularly be comprehensively screened for PTC preoperatively, and the indications for thyroid surgery entailing parathyroidectomy should be updated in the current guidelines.

Keywords: Primary hyperparathyroidism, papillary thyroid carcinoma, prevalence, hypercalcemia, advanced age

INTRODUCTION

Among the most commonly seen mineral metabolism disorders, primary hyperparathyroidism (PHPT) occurs as a result of parathyroid hormone (PTH) being abnormally secreted without complete regulation from one or more of the parathyroid glands. Upon determining which glands are hyperactively secreting PTH, the standard treatment is parathyroidectomy (PTX) (1). Although the primary target organs for potential complications of hyperparathyroidism are the skeleton and kidneys, some studies have shown that hyperparathyroidism may also have cancer-promoting potential and that it may be associated with thyroid or non-thyroid cancers (2-7). However, it remains to be determined whether these complications arise primarily as the result of a genetic predisposition to the development of cancer or whether physiological associative effects, be they environmental or intrinsic, are at play. Similarly, it has not yet been established whether this risk is generally related to PHPT or is specifically related to only severe cases and whether the complications are associated more generally with malignancies or with specific types of cancer (4). Because PHPT is one of the most common endocrine disorders

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Received: 01.08.2022 **Accepted:** 19.08.2022

and predominantly affects postmenopausal women, it is important to address these questions and learn more about the disorder's relationship with cancer.

Among the various types of thyroid cancer, papillary thyroid carcinoma (PTC) is most commonly seen, with researchers reporting that PTC accounts for roughly 84% to 90% of all cases of malignancies of the thyroid (8,9). Although its general prognosis is very good, PTC spreads to the cervical lymph nodes in 20% to 50% of all cases and distant metastasis is observed in <5% of cases. Thus, early diagnosis is important (10). In the literature, the incidence rate for PTC associated with PHPT has been reported to range between 2% and 17% (6,7,11-14); however, these are mostly reports on small case series, and the identified frequency of PTC has rarely been compared with the general population. Although some studies have sought answers to whether this association is coincidental or related to the more frequent performance of preoperative neck US evaluations for patients with PHPT, the findings remain controversial (3,4).

The objectives of the present study are to determine the prevalence of concomitant PTC in patients with PHPT in our patient population, representing one of the largest case series reported to date; to evaluate whether the frequency of PTC increases in patients with PHPT compared to the general population; and to determine whether there are possible predictors of the development of PTC in patients with PHPT.

MATERIAL AND METHOD

The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 27.12.2019, Decision No: 2019/882). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Characteristics and Study Protocol

We analyzed the data of 543 patients who underwent PTX due to PHPT in our tertiary care hospital between January 2010 and August 2019. A total of 87 patients were excluded because regular follow-up data, operation notes, pathology reports, or preoperative neck US results were unavailable; because they were <18 years of age; because they had previously undergone parathyroid or thyroid surgery; or because they were found to have medullary thyroid carcinoma/multiple endocrine neoplasia. The distinction between multiglandular parathyroid disease and uniglandular parathyroid disease was made according to current guidelines (15). In the preoperative period, it was confirmed that the patients met the biochemical diagnostic criteria for PHPT in the presence of at least one of the indications for the operation (1). Neck ultrasonography (US) was performed for all patients included in the study in order to evaluate whether there was synchronous thyroid disease. For thyroid nodules that yielded suspicious US results based on the guidelines of the American Thyroid Association, thyroid fine-needle aspiration biopsies (FNABs) were conducted, and the results of those biopsies were reported within the framework of the standards of the Bethesda System for Reporting Thyroid Cytopathology (16). In addition, lymph node biopsies were performed for patients who were found to have pathological lymphadenopathy of the neck. In cases where an operation was planned for patients with PHPT due to concomitant synchronous thyroid disease, when there was an indication for thyroid surgery, the patients were evaluated in multidisciplinary meetings attended by an endocrinologist, thyroid/parathyroid surgery specialist, and pathologist, and the type of thyroid surgery to be performed in conjunction with PTX was determined (total thyroidectomy, lobectomy, thyroidectomy with central/lateral lymph node dissection, etc.) (9, 16). All operative procedures were conducted by a surgeon who had over 20 years of experience performing thyroid and parathyroid surgeries. Patients presenting with thyroid nodules underwent intensive exploration of the thyroid during the course of their operations, as well. The final histological diagnosis was based on the histopathologic examination of permanent sections of lesions by the same pathologist.

For all patients enrolled in the study, age and gender were recorded as demographic data. All relevant laboratory findings were also recorded, including the values of intact PTH (iPTH), 25-OH vitamin D3 ($25(OH)D_3$), serum calcium (Ca) and phosphate (P), 24-h urine calcium, glomerular filtration rate (GFR) according to the equation proposed in the Modification of Diet in Renal Disease (MDRD) Study, and serum alkaline phosphate (ALP). The serum values of creatinine, ALP, albumin, Ca and P, and 24-h urine Ca were evaluated spectrophotometrically using a Cobas 8000 Modular Analyzer (C701 Module, Roche Diagnostics). Measurements of iPTH were performed by electrochemiluminescence assay (Cobas 8000 Modular Analyzer, e602 Module, Roche Diagnostics). Levels of $25(OH)D_3$ in plasma were measured using an appropriate instrument for high-performance liquid chromatography (Ultimate 3000, Thermo Scientific). The neck US results of the patients were also evaluated, as were the available thyroid FNAB results, preoperative parathyroid imaging results, type of operations performed (PTX alone or PTX with thyroid surgery), thyroid surgery indications, operation notes, and postoperative histopathology results. Patients were divided into two groups according to whether they were found to have or not have PTC in the presence of PHPT, and these groups were compared in terms of clinical,

biochemical, and histopathological features. For patients who were found to have PTC, histopathological features of PTC such as bilaterality, multifocality, subtype, extrathyroidal extension, lymphatic invasion, vascular invasion, and cervical lymph node metastasis were also recorded and tall cell, columnar cell, and hobnail subtypes were considered as aggressive subtypes based on WHO classification (17).

Statistical analysis

Standardized incidence ratios (SIRs) were calculated by dividing observed numbers of cases by expected numbers of cases. The expected number of cancer cases was calculated by multiplying the number of cases per year by the relevant gender, age, and region-specific cancer incidence rate for each age group and year of observation. Cancer incidences in the general population were calculated based on the Public Health Cancer Statistics published by the Ministry of Health of the Republic of Turkey, last updated in 2017 (18). While performing descriptive statistical studies, continuous data were given as mean ± standard deviation and categorical data as frequency (percentage). Independent sample t-tests were used in comparing the continuous data of the groups, while chi-square or Fisher exact tests were used to compare categorical data between the groups. As a result of univariate analysis, a binary logistic regression model was created using parameters with significance of $p<0.05$. This model was used to determine independent factors that could predict PTC. In this study, we applied two-way analyses and used $p<0.05$ to indicate statistical significance. IBM SPSS Statistics 25 (IBM Corp.) was used for statistical analysis.

RESULTS

Among the 456 patients with PHPT included in this study, 377 (82.7%) were female and 79 (17.3%) were male. The age at diagnosis was 48±13.3 years for female patients and 49±12.8 years for male patients (p=0.680). The mean duration of follow-up was 24±23.9 months. Twenty-seven of the patients had multiglandular parathyroid disease and 429 had uniglandular parathyroid disease. Of the patients who underwent PTX, 281 (61.6%) had synchronized thyroid nodularity. Among them, 211 (75.1%) patients had multiple thyroid nodules and 70 (24.9%) had solitary nodules. While 353 patients underwent isolated PTX, 103 patients underwent PTX with thyroid surgery. PTC was detected in 53 of the patients who underwent thyroid surgery (F/M=46/7). We assessed SIRs for PTC in female and male patients separately. Among female patients, the incidence of PTC was increased compared to the general population (SIR: 272.2, 95% CI: 201.6-360.0, p <0.001). Among male patients, the incidence of PTC was similarly increased compared to the general population (SIR: 736.5, 95% CI: 322.1-1457.0, p<0.001). **Table 1** presents the SIRs for PTC in PHPT patients compared to the general population and cancer incidence data by gender.

Table 1. Papillary thyroid carcinoma incidence data by gender

	Observed	Expected	SIR (95% CI)	p value
Female (n=377)	46	0.169	272.2 (201.6-360.0)	<0.001
Male (n=79)	7	0.009	736.5 (322.1-1457.0)	<0.001

CI: Confidence interval, SIR: Standardized incidence ratio

The mean age of patients at diagnosis was 52±11.1 years in the PTC group and 48±13.4 years in the non-PTC group, thus being higher in the PTC group (p=0.026). While the mean serum Ca value was 11.7±1.21 mg/dL in the PTC group, it was 11.4±0.83 mg/dL in the non-PTC group, being significantly higher in the PTC group (p=0.012). The groups were similar in terms of gender, serum iPTH, serum P, 25(OH)D_3, serum ALP, GFR, 24-h urine calcium, osteoporosis, kidney stones on imaging, and histopathologic characteristics (**Table 2**). To determine the preoperative predictors of concomitant PTC in the presence of PHPT, a binary logistic regression model was created with variables identified as having significance of $p<0.05$ between the groups in univariate analysis (age at diagnosis, serum Ca; **Table 3**). In multivariate analysis, age at diagnosis and serum Ca were found to be independent factors predicting the presence of PTC in patients with PHPT (OR: 1.024, 95% CI: 1.001-1.047, p=0.043 and OR: 1.402, 95% CI: 1.046-1.878, p=0.024, respectively).

Table 2. Clinical features of PHPT patients with/without papillary thyroid carcinoma

	Non-PTC (n= 403)	PTC (n=53)	p value
Age at diagnosis (years) (mean ± SD)	48±13.4	52±11.1	0.026
Gender (Female n%)	331 (82.1)	46 (86.8)	0.400
Serum iPTH (pg/mL)	219±159.9	208±146.5	0.622
Serum Ca (mg/dL)	11.4±0.83	11.7±1.21	0.012
Serum P (mg/dL)	2.5±0.5	2.7±0.5	0.056
25-OH vitamin D (µg/L)	16.4±11.5	15.7±11.5	0.688
Serum ALP (U/L)	120±90.3	108±44.4	0.344
24hr urine Ca (mg/day)	402±387.9	387±219.6	0.815
GFR (MDRD)	97±28.0	95±23.6	0.709
Osteoporosis*	117 (47.3)	17 (48.6)	0.893
Kidney stones **	98 (31.7)	16 (37.2)	0.471
Thyroid nodularity	229 (56.8)	52 (98.1)	NA
Histopathologic examination			
Uniglandular parathyroid disease	378 (93.8)	51 (96.2)	NA
Multiglandular parathyroid disease	25 (6.2)	2 (3.8)	
Follow-up period (months)	23±22.9	36±27.9	<0.001

25-OH vitamin D: 25-hydroxy vitamin D, ALP: Alkaline phosphatase, Ca: Calcium, iPTH: Intact parathyroid hormone, GFR: Glomerular filtration rate, MDRD: Modification of Diet in Renal Disease, P: Phosphate, PHPT: Primary hyperparathyroidism *Bone densitometry was performed in 282 patients **Kidney imaging was performed on 352 patients

Table 3. Predictive factors of papillary thyroid carcinoma by multivariable analysis

	OR (95% CI)	p value
Age at diagnosis (years)	1.024 (1.001-1.047)	0.043
Serum calcium	1.402 (1.046-1.878)	0.024

CI: Confidence interval, OR: Odds ratio

Of the 103 patients who underwent thyroid surgery with PTX, 65 (63.1%) underwent PTX with total thyroidectomy and 38 (36.9%) underwent PTX with thyroid lobectomy. Indications for thyroid surgery performed in conjunction with PTX are shown in **Table 4**. PTC was found in 39 (60%) of the patients who underwent total thyroidectomy, in 14 (36.8%) of the patients who underwent lobectomy, and in 53 (51.5%) of the patients who underwent PTX with thyroid surgery. PTC was detected incidentally in 37 (69.8%) of 53 patients who were found to have PTC, and 36 (67.9%) of these cases involved papillary microcarcinoma. Five (9.4%) of the patients with PTCs had aggressive subtypes, 4 (7.5%) had lymphatic invasion and/or vascular invasion, and 3 (5.7%) had cervical lymph node metastases. Other histopathological features of PTCs are shown in **Table 5**.

Table 4. Indications for simultaneous parathyroidectomy and thyroid surgery for patients with PHPT

Indications for thyroid surgery (n=103)	n (%)
Nontoxic guatr with compression symptoms	57 (55.3%)
Thyroid FNAB results	30 (29.1%)
Bethesda I (recurrent)	2 (1.9%)
Bethesda III (recurrent)	12 (11.7%)
Bethesda IV	7 (6.8%)
Bethesda V	4 (3.9%)
Bethesda VI	5 (4.9%)
Graves disease	2 (1.9%)
Toxic multinodular goiter	6 (5.8%)
Toxic adenoma	3 (2.9%)
Cosmetic reasons due to goiter	2 (1.9%)
Suspicion of thyroid cancer on intraoperative inspection	2 (1.9%)
Concomitant parathyroid carcinoma	1 (1%)

Bethesta: System for Reporting Thyroid Cytopathology, Bethesda I: nondiagnostic or unsatisfactory; Bethesda II: benign; Bethesda III: atypia of undetermined significance or follicular lesion of undetermined significance; Bethesda IV: follicular neoplasm or suspicious for a follicular neoplasm; Bethesda V: suspicious for malignancy; Bethesda VI: malignant, PHPT: Primary hyperparathyroidism,

Table 5. Histopathological characteristics of PTC in patients with PHPT

PTC (n=53)	n (%)
Incidental	37 (69.8)
Tumor size (mm) (mean ± SD)	11.3±12.9
≤ 10	36 (67.9)
> 10	17 (32.1)
Bilaterality	13 (24.5)
Multifocality	22 (41.5)
Subtypes	
Follicular	26 (49.1)
Classic	15 (28.3)
Oncocytic	7 (13.2)
Tall cell	5 (9.4)
Extrathyroidal extension	1 (1.9)
Lymphatic invasion	2 (3.8)
Vascular invasion	2 (3.8)
Cervical LNM	3 (5.7)

LNM: Lymph node metastasis, PHPT: Primary hyperparathyroidism, PTC: Papillary thyroid carcinoma

DISCUSSION

This study showed that the prevalence of PTC is significantly higher in patients with PHPT compared to the general population and that PHPT is a risk factor for the development of PTC. This study also showed that advanced age and high Ca levels may be predictors for the development of PTC in patients with PHPT. Our results suggest that the current guidelines should include additional recommendations on the treatment of patients with PHPT and synchronized thyroid disease; the indications for thyroid surgery with PTX for patients with PHPT should not be the same as those applied for other thyroid patients. Our results also emphasize the importance of conducting routine and comprehensive preoperative thyroid assessments for all patients with PHPT.

Previous studies have reported the association of PHPT with multiple types of cancer, including breast cancer, hematopoietic cancer, thyroid cancer, urinary tract carcinomas, colon cancer, and squamous cell skin cancer, with this association recently being considered as a risk factor for the occurrence of PTC (2-7). For example, one previous study found thyroid malignancy to be the most prevalent type of cancer (SIR: 21.19, 95% CI: 4.3-61.9) among patients presenting with PHPT as the primary disorder (5). Some studies have suggested that this relationship between PHPT and cancer reflects the existence of a genetic predisposition to cancer with disturbed vitamin D receptor alleles triggering poor regulation of the parathyroid glands together with defective processes of apoptosis and higher rates of preneoplastic lesions (19, 20). Other findings of previous research suggest that increased levels of PTH, decreased levels of vitamin D, and the presence of hypercalcemia are involved in thyroid carcinogenesis because of their ability to promote the release of vascular endothelial growth factor and fibroblast growth factor, with these growth factors possibly impacting the thyroid follicular cells via mitogenic and differential effects while impacting endothelial cells via angiogenic effects (3,21-23). Although the underlying mechanism has yet to be clarified, previous studies generally support the hypothesis that the association between these two diseases is not accidental and that there is a strong relationship between them.

According to many researchers, concomitant thyroid nodules are observed in 15% to 75% of all cases of PHPT, while PTC presenting in association with PHPT has been found to have incidence rates ranging from 2% to 17% (6,7,11-14). In our large case series, we found that the frequency of thyroid nodularity was 61.6% while the frequency of PTC was 11.6% in patients with PHPT, and these results are consistent with the literature. Among

patients with PHPT, thyroid nodules were found to have an overall malignancy rate of 18.5%, which was higher than the previously reported malignancy rate of thyroid nodules in the general patient population (5-15%) (24). These results suggest that PHPT may be a risk factor for the development of malignancies in thyroid nodules. The wide ranges indicated in reports on the PHPT-PTC association are likely due to the fact that reports are generally created based on small case series or the higher rates of confirmed PTC among patients with PHPT as these patients undergo neck US more frequently for the preoperative determination of synchronized thyroid disease. However, the increase in the accessibility of thyroid US as a result of the development of health services over the years has increased the incidence of not only PTCs detected in the presence of PHPT but also that of latent PTCs in the general population. Therefore, comparing PHPT patients with the general population while evaluating the prevalence of PTC may give more accurate results. In our study, in comparison to the general population, both male and female patients with PHPT had significantly higher risks of PTC. We think that all patients with PHPT should be evaluated with comprehensive preoperative neck US to ensure the early diagnosis of PTC and prevent the complications that may develop in the event of a second surgery.

In the literature, there are very few studies arguing for a relationship between PHPT and PTC and identifying the risk factors for that relationship, and their results are contradictory (6,25,26). In a study conducted with 318 patients, moderate elevations of serum PTH independently predicted thyroid cancer among patients with PHPT (25). Conversely, in another study conducted with a similar population, decreased serum PTH measurements were obtained for patients with both PHPT and PTC in comparison to patients diagnosed with benign thyroid lesions (26). In another study conducted with 155 patients, a significant inverse association was identified between nonmedullary thyroid carcinoma and levels of preoperative serum Ca in cases of PHPT, similarly to the research reported by Liu et al. (6,26). Contrary to those findings, our study, conducted with a much larger patient population compared to previous studies, showed that high serum Ca levels and advanced age were independent risk factors for PTC. In the literature, the carcinogenic effects of significantly extended exposure to higher levels of Ca have been reported as a result of the goitrogenic effects of calcium with inhibited thyroxine synthesis occurring due to higher levels of kidney iodine clearance, and this supports the results of our study (3). The current guidelines set forth the same indications for thyroid surgery combined with PTX for both patients with concomitant thyroid disease and PHPT and patients presenting with isolated thyroid disease (27). Our finding that PHPT patients with high serum Ca levels and older patients with PHPT have significantly increased risks of PTC will hopefully contribute to these indications in the guidelines, and we think that the criteria for thyroid surgery in the guidelines should be customized, particularly for these patients. Our opinion is supported by the finding that 69.8% of the detected cases of PTC were incidental in our study despite the fact that we complied with the current guideline recommendations for the indications of thyroid surgery performed in conjunction with PTX.

In the literature, it has been reported that approximately 10% to 15% of all thyroid cancers are aggressive subtypes (28). In our study, we found this rate to be 9.4% in cases of PTCs accompanying PHPT, which is similar to the rates for isolated PTCs reported in the literature. Some studies have suggested that PTC detected in patients with PHPT may be more aggressive than cases of isolated PTC due to features such as high rates of tumor capsule invasion and multicentricity (29) or high lymph node ratio (number of metastatic lymph nodes divided by number of lymph nodes removed) (30). However, it remains necessary to determine whether PHPT is seen in association with cases of more invasive PTC according to morbidity rates, tumor pathology, and prognosis.

The limitations of our study arose from its retrospective nature. In addition, the rate of co-occurrence of PHPT and PHPT may reflect detection bias. On the other hand, our study is one of the largest case series in the literature, and it is also one of the rare studies comparing the prevalence of PTC in PHPT patients with the prevalence of PTC in the general population. We have also shown that the risk of PTC in patients with PHPT is associated with only advanced age and high serum Ca levels among the many other variables considered in this study. We hope that these findings will contribute to the current guidelines and that the upcoming guideline updates will ensure that these patients are not evaluated in the same way as patients who need other thyroid surgeries.

CONCLUSION

Since patients with PHPT, and particularly the elderly and patients with high Ca levels, have significantly higher risks of PTC, the indications for performing thyroid surgery in conjunction with PTX should be revised considering the benefits of early clinical diagnosis of PTC for patients and the complications that a second surgery may cause. We believe that PTC may have an important place in the early diagnosis and treatment of these patients and our results may change the surgical procedures to be performed in clinical practice, particularly for high-risk patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 27.12.2019, Decision No: 2019/882).

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

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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