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Increased thyroid malignancy in patients with primary hyperparathyroidism

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Abstract

Background: Multiple studies have reported the increased incidence of thyroid cancer in patients with primary hyperparathyroidism (PHPT). However, the underlying risk factors of concomitant thyroid cancer in patients with PHPT remain unknown. The primary aim of this study was to examine the records of patients with PHPT to identify characteristics that correlated with the presence of coexisting thyroid nodules, and which may have an implication for the prediction of thyroid cancer.

Methods: Medical records of consecutive patients with PHPT ($n = 318$) were reviewed from January 2010 to September 2020 in two tertiary medical centers in China. Patient clinicopathological and biological data were collected and analyzed.

Results: Of a total of 318 patients with PHPT, 105 (33.0%) patients had thyroid nodules and 26 (8.2%) patients were concomitant with thyroid cancer. A total of 38 thyroid nodules taken from 26 patients were pathologically assessed to be well-differentiated papillary thyroid carcinoma (PTC), with 81% being papillary thyroid microcarcinoma (PTMC). In 79% (30/38) of these cancers, thyroid nodules were considered suspicious following preoperative ultrasound. Multinomial logistic regression analysis revealed that female gender was associated with increased risk of thyroid nodules (OR = 2.13, 95% CI: 1.13–3.99, $P = 0.019$), while lower log-transformed parathyroid hormone levels were an independent predictor of thyroid cancer in patients with PHPT (OR = 0.50, 95% CI: 0.26–0.93, $P = 0.028$).

Conclusion: In conclusion, we observed a relatively high prevalence of thyroid cancer in our cohort of Chinese patients with PHPT. Evaluation of thyroid nodules by preoperative ultrasound may be advisable in patients with PHPT, particularly for females and patients with modestly elevated serum parathyroid hormone levels.

Key Words

- ▶ primary hyperparathyroidism
- ▶ thyroid malignancy
- ▶ parathyroid hormone
- ▶ surgery

Endocrine Connections
(2021) 10, 885–893

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, having a prevalence of 0.04–0.1% in the general population (1). The principal role of parathyroid hormone (PTH) is to maintain (raise) blood calcium levels in three different ways: (i) release of calcium

from the bones via stimulation of osteoclastic activity; (ii) decrease calcium excretion in the kidney; (iii) increase absorption of calcium from the gut (2). However persistent overproduction of PTH in patients with PHPT may damage target organs including bone and kidney, manifesting

as osteoporosis and kidney stones (3). A smaller number of patients may present with acute pancreatitis, gastrointestinal ulcers, or neuropsychiatric symptoms (3, 4). Some studies have also reported an increased risk of malignancies, including hematopoietic, breast, skin, thyroid, and urinary tract carcinoma (5, 6, 7). Previous studies have reported 15–75% of patients with PHPT have concomitant thyroid nodules (8, 9). Moreover, several authors have described a rate of thyroid cancer in patients with PHPT that appears to be higher than the general population (4, 10, 11, 12, 13, 14, 15). A review of data from nine studies, including a total of 2510 patients with PHPT requiring parathyroidectomy, indicated an incidence for thyroid cancer of 5%, compared to international estimates ranging from ~2 to 12 per 100,000 thyroid cancer new cases per year (15). Accordingly, patients with PHPT may be at higher risk of thyroid cancer and the detection of thyroid nodules may be treated with greater suspicion. Although elusive at this time, a more detailed understanding of the risk factors contributing to this pathology would benefit clinical decision-making.

The primary aim of this retrospective study was to explore risk factors for malignancy among a cohort of 318 patients with PHPT, with or without benign or malignant thyroid nodules, presenting to two tertiary medical centers in China between 2010 and 2020.

Materials and Methods

Patients

Clinical data were collected from patients with PHPT undergoing surgery in two large tertiary medical centers (Qilu hospital of Shandong University and the Affiliated Yantai Yuhuangding Hospital of Qingdao University) from January 2010 to September 2020. Patients with confirmed PHPT based on medical history, physical examination, and laboratory tests were eligible for inclusion. All parathyroid lesions were pathologically confirmed as either parathyroid adenoma, parathyroid carcinoma or parathyroid hyperplasia. Patients who had secondary or tertiary HPT, multiple endocrine neoplasia, a history of radiation exposure, and those with familial HPT were excluded from this study. Patients with PHPT diagnosed during the clinical work-up for thyroid nodules were also excluded. This study protocol was reviewed and approved by the Qilu Hospital and Yuhuangding Hospital Ethics Committees. Individual informed patient consent was waived due to the retrospective nature of this study.

Data collection

The data for patients with PHPT included age, gender, chronic disease history (hypertension, diabetes mellitus, and coronary heart diseases), PHPT-related comorbidity (urinary tract stones, osteoporosis, pathological fracture, pancreatitis, etc.), laboratory blood analyses within 1 week prior to surgery (PTH, calcium, 25-hydroxyvitamin D (25(OH)D), albumin, phosphorus, potassium, alkaline phosphatase (AKP), creatinine (Cr), blood urea nitrogen (BUN), thyroid-stimulating hormone (TSH), and thyroid autoantibodies (TPOAb and TgAb)). The reference range of PTH was from 15 to 65 pg/mL. Normality of serum calcium was from 2.11 to 2.52 mmol/L. Serum calcium concentrations were adjusted for serum albumin. Adjusted calcium = 0.02 (40 g/L – serum albumin (g/L)) + measured total serum calcium (mmol/L). All patients underwent preoperative thyroid and parathyroid ultrasound imaging. Surgical options were appropriately chosen according to the 2015 American Thyroid Association guideline. Either partial, subtotal, or near-total thyroidectomy was performed for benign thyroid nodules. Where thyroid cancer was confirmed by frozen section or fine-needle aspiration biopsy (FNAB), lobectomy, near-total, or total thyroidectomy with cervical lymph node dissection was performed. Histopathological sections of parathyroid gland and thyroid nodules were reviewed by two independent pathologists. Notably, final pathological reports of thyroid cancer included the following details: tumor size, histological type, location, bilaterality, multifocality, status of extrathyroidal extension, and cervical lymph node metastasis.

Statistical analysis

Statistical analyses were performed using SPSS (version 23.0; SPSS Inc). Continuous variables were presented as mean ± s.d. for normally distributed data or median (minimum to maximum) for non-normally distributed data except for PTH. Due to its skewed distribution, PTH was also reported as natural log-transformed values (lnPTH) when analyzed as continuous quantities. All categorical variables were presented as proportions. Comparisons of means and proportions were performed with independent samples one-way ANOVA and the chi-square test, respectively. Non-normally distributed variables were compared using the Mann–Whitney *U*-test or Kruskal–Wallis test. Multinomial logistic regression analysis was used to identify potential risk factors for thyroid nodules, including thyroid cancer and benign thyroid nodules, in patients with PHPT. Odds

ratios (OR) and the corresponding 95% CI were calculated for risk factors. A receiver operating characteristic (ROC) analysis was performed to determine the capacity of the clinical and biochemical markers to predict thyroid malignancy in patients with PHPT. A value of $P < 0.05$ was considered as statistically significant.

Results

The inclusion process of patients with PHPT was shown in Fig. 1. A total of 318 patients with PHPT were included in this study. The mean age was 53 ± 13 years with 70.8% ($n=225$) of patients being female. Diagnosis with PHPT was initially based on elevated serum calcium or the presence of parathyroid nodules, primarily evident through regular health check-ups ($n=130$, 41%), followed by urinary tract stones ($n=79$, 25%), musculoskeletal pain ($n=62$, 19%), nausea or vomiting ($n=30$, 9%), fracture ($n=11$, 3%), pancreatitis ($n=3$, 1%) (Fig. 2). The diagnosis of PHPT was always confirmed by biochemical profile, parathyroid ECT (Emission CT) and ultrasound imaging. The baseline demographic and clinical and biochemical characteristics are described in Table 1. Age was comparable between patients with thyroid cancer, benign thyroid nodules, or without thyroid nodules (Table 1). Although elevated compared to the normal range (15–65 pg/mL), serum PTH levels were significantly lower in patients with thyroid cancer than patients without thyroid nodules. A larger proportion of female patients with PHPT had thyroid

nodules compared to those without thyroid nodules. There were no differences observed in serum calcium, phosphorus, potassium, AKP, BUN, TSH, 25(OH)D levels, TPOAb positivity, and TgAb positivity (Table 1).

A histopathologic report confirmed the diagnosis in all cases with the final diagnosis of PHPT being parathyroid adenoma in 282 patients (88.68%), atypical parathyroid adenoma in 22 patients (6.92%), oncocytic parathyroid adenoma in 2 patients (0.63%), parathyroid carcinoma in 8 patients (2.52%), and parathyroid hyperplasia in 4 patients (1.26%). Of the total of 318 patients with PHPT, 105 (33.0%) patients had thyroid nodules and 26 (8.2%) patients were concomitant with thyroid cancer (Table 2). Of these 26 cases, all were assessed to be well-differentiated papillary thyroid carcinoma (PTC), namely 21 cases (81%) of papillary thyroid microcarcinoma (PTMC), 3 cases (12%) of conventional PTC, and 2 cases (7%) of a tall-cell variant of PTC (Table 3). Bilaterality, multifocality, extrathyroidal extension, and central lymph node metastasis were found in 7 cases (26.9%), 8 cases (30.8%), 8 cases (30.8%), and 2 cases (7.7%), respectively. Among the 26 patients, a total of 38 malignant thyroid nodules were ultimately confirmed by pathology. Prior to surgery, 30 (79%) hypoechoic thyroid nodules were observed as suspicious by preoperative ultrasound, while 8 (21%) thyroid nodules were neither detected nor suspicious as malignancy by ultrasound (Supplementary Table 1, see section on supplementary materials given at the end of this article).

To further investigate the factors associated with benign thyroid nodules and thyroid cancer being present

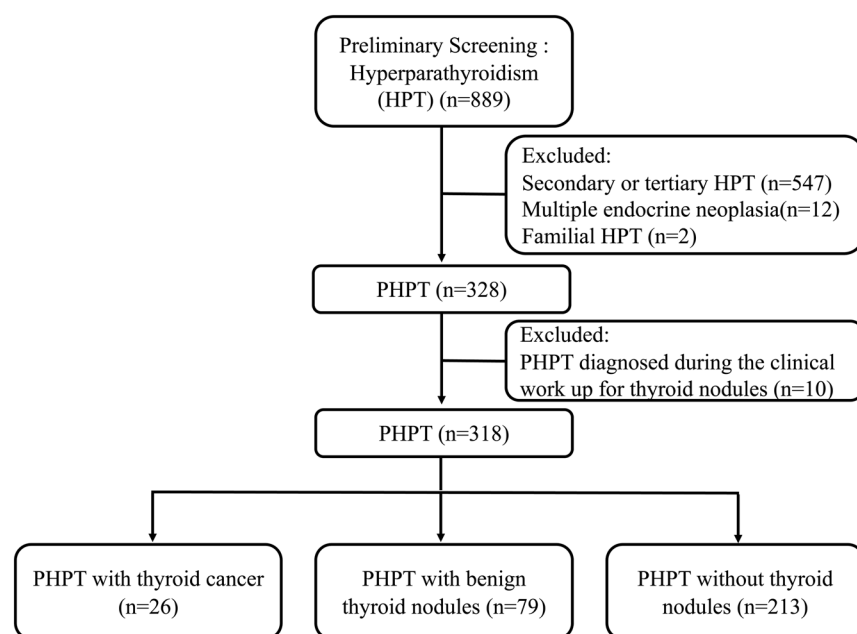
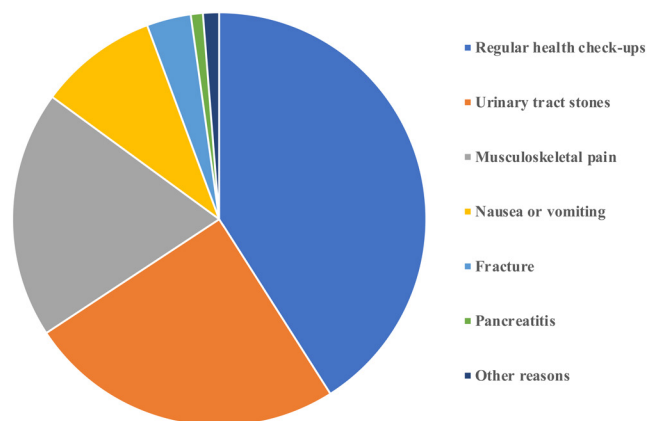


Figure 1 Criteria for including patients with primary hyperparathyroidism (PHPT).

**Figure 2**

The clinical pattern leading to patients initially being diagnosed with PHPT. Regular health check-ups ($n = 130$, 41%); urinary tract stones ($n = 79$, 25%); musculoskeletal pain ($n = 62$, 19%); nausea and vomiting ($n = 30$, 9%); fracture ($n = 11$, 3%); pancreatitis ($n = 3$, 1%); others ($n = 3$, 1%).

in patients with PHPT, multivariate-adjusted logistic regression analyses were performed. Female gender was an independent predictor for thyroid nodules after adjusting for lnPTH (model 1), age, albumin-adjusted serum calcium, and creatinine (model 2). The presence of thyroid cancer was significantly associated with decreased of lnPTH (OR=0.52; 95% CI: 0.32–0.84; $P = 0.008$) after adjusting for gender (model 1). The association remained significant after additional adjustment for age, albumin-adjusted serum calcium and creatinine (OR=0.50; 95% CI: 0.26–0.93; $P=0.028$) (model 2) (Table 4). The ROC analysis revealed that serum PTH levels < 192 pg/mL had a good capacity to differentiate the thyroid malignancy from benign thyroid nodules or without thyroid nodules, with an area under the curve (AUC) of 0.687 ($P=0.002$). This cut-off value for the PTH level had a sensitivity of 69.2% and a specificity of 67.8% for predicting thyroid malignancy in patients with PHPT.

Discussion

The coexistence of thyroid disease in patients with PHPT is a known clinical challenge that remains poorly understood, with highly variable incidence rates being reported and potential risk factors being unclear. The prevalence of thyroid nodules in our cohort of patients with PHPT was 33.0%, being similar to other populations (20–76%) (16, 17). The proportion of female patients with PHPT having thyroid nodules was significantly higher than those without thyroid nodules and is also consistent with epidemiological findings suggesting females are more prone to developing thyroid

nodules (18, 19). Our data did not reflect any differences in gender distribution between patients with thyroid cancer and patients with benign thyroid nodules.

To the best of our knowledge, this was the largest cohort study of thyroid cancer in patients with PHPT in China. The incidence of thyroid cancer we observed in patients with PHPT was 8.2%, similar to two previous Chinese studies that have reported prevalence rates of 7.7% (12/155 patients) and 6.3% (7/112 patients) (12, 14). Taken together, these three studies in Chinese populations report a higher rate of malignancy in patients with PHPT than other similar studies. Two reviews have estimated the incidence of thyroid cancer in patients with PHPT by pooling data from multiple countries, reporting average rates of 3.5% (12) and 5% (15). We also observed an overall rate of malignancy of 25% for thyroid nodules in patients with PHPT, which is higher than the rate reported in the general population with thyroid nodules (7–15%) (20). Noting the highly variable nature of data in this field, these results suggest a higher rate of malignancy in our cohort compared to other similar studies, warranting some discussion of the possible contributing factors. It is striking that the average serum level of 25(OH)D we observed was 10.67 ± 6.34 ng/mL (~25 nmol/L). Such values are not uncommon among clinical populations in China but are approximately half the commonly agreed minimum target level for vitamin D sufficiency (21). To our knowledge, vitamin D status has not been reported in other studies to allow comparison with other cohorts of patients with PHPT. Perhaps significantly, vitamin D deficiency has been increasingly implicated in the initiation and progression of numerous malignancies. However, as with other cancers, the hypothesis that vitamin D status modulates thyroid cancer incidence is equivocal (22). Nevertheless, an analysis of preoperative serum 25(OH)D levels in 548 females undergoing thyroidectomy has revealed lower 25(OH)D levels in patients with a tumor size > 1 cm (23).

Several studies have explored the potential role of elevated PTH and calcium levels in thyroid diseases in patients with PHPT but have reported conflicting results (3, 14). One previous study involving a total of 59 PHPT cases indicated that high PTH levels were significantly associated with the development of thyroid cancer (3), while another two studies found no correlation between thyroid cancer and serum PTH levels (14, 24). In contrast, we have observed in our relatively large patient cohort that preoperative serum PTH levels were significantly lower in patients with thyroid cancer than in patients without thyroid nodules. Furthermore, a low value for log-transformed PTH was found to be an independent predictor for the presence

Table 1 Clinical and biologic characteristics between PHTP with and without benign or malignant thyroid nodules.

	Total PHPT (n = 318)	Thyroid carcinoma (n = 26)	Benign thyroid nodule (n = 79)	Without thyroid nodules (n = 213)
Age	53 ± 13	53 ± 7	56 ± 10 ^a	52 ± 14
Sex				
Male	93 (29.2%)	4 (15.4%)	15 (19.0%)	74 (34.7%)
Female	225 (70.8%)	22 (84.6%) ^a	64 (81.0%) ^b	139 (65.3%)
Comorbidity				
Hypertension	85 (26.7%)	7 (26.9%)	21 (26.6%)	57 (26.8%)
Diabetes mellitus	27 (8.5%)	1 (3.8%)	7 (8.9%)	19 (8.9%)
Coronary heart disease	22 (6.9%)	1 (3.8%)	6 (7.6%)	15 (7.0%)
Urinary tract stones	99 (31.1%)	4 (15.4%) ^a	14 (17.7%) ^b	81 (38.0%)
Osteoporosis	60 (18.9%)	4 (15.4%)	21 (26.6%)	35 (16.4%)
Pathological fracture	11 (3.5%)	1 (3.8%)	1 (1.3%)	9 (4.2%)
Pancreatitis	3 (0.9%)	0 (0.0%)	2 (2.5%)	1 (0.5%)
Malignant tumor history	10 (3.1%)	1 (3.8%)	4 (5.1%)	5 (2.3%)
Gastrointestinal ulcer	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Biological features				
PTH (pg/mL)	284.9 (30.63–5000.0)	143.85 (30.6–3576.0) ^b	275.3 (73.15–3545.0)	336.0 (65.8–5000.0)
lnPTH	5.88 ± 1.05	5.34 ± 1.19 ^b	5.81 ± 0.95	5.97 ± 1.04
Serum calcium (mmol/L)	3.02 ± 0.48	2.93 ± 0.45	2.95 ± 0.49	3.06 ± 0.47
Adjusted serum calcium (mmol/L)	2.97 ± 0.50	2.86 ± 0.47	2.90 ± 0.50	3.01 ± 0.49
Serum phosphorus (mmol/L)	0.79 ± 0.24	0.81 ± 0.17	0.82 ± 0.31	0.77 ± 0.21
Serum potassium (mmol/L)	4.11 ± 0.49	4.10 ± 0.46	4.14 ± 0.50	4.10 ± 0.49
AKP (U/L)	125 (22–2540)	99 (56–734)	119 (53–1447)	136 (22–2540)
Cr (μmol/L)	69.36 ± 36.41	65.22 ± 22.70	61.87 ± 31.19 ^a	72.65 ± 39.10
BUN (mmol/L)	5.05 ± 2.50	4.44 ± 1.55	4.81 ± 2.61	5.21 ± 2.54
TSH (μIU/mL)	1.66 (0.003–25.59)	2.21 (0.003–4.43)	1.87 (0.006–6.33)	1.50 (0.05–25.59)
25(OH)D (ng/mL) ^c	10.67 ± 6.34 (135)	12.46 ± 7.28 (14)	10.25 ± 5.65 (28)	10.53 ± 6.42 (93)
TPOAb positivity ^c	26.6% (53/199)	25.0% (5/20)	28.1% (16/57)	26.2% (32/122)
TgAb positivity ^c	32.5% (63/194)	35.0% (7/20)	31.6% (18/57)	32.5% (38/117)

^a*P* value < 0.05 as compared to patients with PHPT without thyroid nodules; ^b*P* value < 0.01 as compared to patients with PHPT without thyroid nodules; ^cData were available in a smaller cohort and number of cases with available data are listed in brackets.

25(OH)D, 25-hydroxyvitamin D; AKP, alkaline phosphatase; IBUN, blood urea nitrogen; Cr, creatinine; ln, natural logarithm; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

of thyroid cancer in patients with PHPT after adjusting for other confounding factors. A possible correlation between serum calcium levels and various cancers in the general population, such as colorectal and breast, remains controversial (25, 26, 27). One study from a Chinese group found a significant negative correlation between the albumin-corrected serum calcium level and the presence of thyroid cancer in patients with PHPT (14). Our data suggest adjusted serum calcium levels may be lower in PHPT patients

with thyroid cancer, although no statistical difference was observed compared to patients with benign nodules, or without nodules (*P* = 0.129). A small cross-sectional study consisting of 40 medullary thyroid cancer patients and 40 healthy controls showed a low serum calcium level was a potent risk factor for medullary thyroid cancer (28). And a case-control study including 1092 participants, indicated that lower serum calcium levels were an independent predictor of thyroid nodules among patients with type 2

Table 2 Association of benign and malignant thyroid nodules with PHTP.

	Total (n = 318) (%)	Not concomitant with thyroid nodules (n = 213) (%)		Concomitant with thyroid nodules	
				Benign (n = 79) (%)	Malignant (n = 26) (%)
Parathyroid adenoma	282 (88.68)	184 (86.38)	72 (91.14)	26 (100)	
Atypical parathyroid adenoma	22 (6.92)	19 (8.92)	3 (3.80)	0 (0)	
Oncocytic parathyroid adenoma	2 (0.63)	2 (0.94)	0 (0)	0 (0)	
Parathyroid carcinoma	8 (2.52)	7 (3.29)	1 (1.27)	0 (0)	
Parathyroid hyperplasia	4 (1.26)	1 (0.47)	3 (3.80)	0 (0)	

Table 3 Characteristics of patients with PHPT and thyroid carcinoma.

Case	Age	Sex	Location of tumor	Number of tumor	Tumor type	Tumor size (cm)	PTH (pg/mL)	Extrathyroidal extension	Central lymph node metastasis
1	53	Female	Left	2	PTMC	0.4, 0.1	1813.0	No	No (0/5)
2	55	Female	Left	1	Conventional PTC	1.1	77.1	Yes	No (0/10)
3	63	Male	Right	1	PTMC	0.4	321.3	Yes	No (0/3)
4	43	Female	Left	1	PTMC	0.8	1039.0	No	No (0/6)
5	54	Female	Bilateral	2	PTMC	0.5, 0.6	66.1	No	Yes (2/10)
6	57	Female	Right	1	PTMC	1	111.9	No	No (0/2)
7	44	Male	Left	1	PTMC	0.7	3576.0	No	No (0/2)
8	52	Male	Left	1	PTMC	0.5	396.5	No	No (0/6)
9	45	Female	Bilateral	2	Conventional PTC	0.6, 1.5	115.8	Yes	Yes (6/12)
10	63	Female	Bilateral	2	PTMC	0.1, 0.4	159.2	No	No (0/4)
11	58	Female	Bilateral	3	PTMC	1.0, 0.7, 0.6	190.6	No	NA
12	41	Female	Right	1	PTMC	0.3	1548.0	No	NA
13	54	Male	Left	1	PTMC	1	1430.0	No	NA
14	66	Female	Right	1	PTMC	0.9	149.9	Yes	No (0/9)
15	54	Female	Left	1	Conventional PTC	1.1	103.8	Yes	No (0/15)
16	43	Female	Right	1	PTMC	0.4	30.6	No	NA
17	47	Female	Bilateral	4	Tall-cell variant of PTC	0.6, 0.5, 0.3, 0.06	171.2	Yes	No (0/10)
18	67	Female	Right	1	Tall-cell variant of PTC	1.3	85.3	Yes	No (0/1)
19	52	Female	Bilateral	3	PTMC	0.6, 0.3, 0.3	128.3	Yes	No (0/11)
20	52	Female	Right	1	PTMC	0.5	373.2	No	No (0/3)
21	57	Female	Left	1	PTMC	0.4	80.7	No	No (0/1)
22	60	Female	Right	1	PTMC	0.6	146.5	No	No (0/6)
23	52	Female	Left	1	PTMC	0.5	141.2	No	No (0/6)
24	59	Female	Left	1	PTMC	0.5	98.2	No	No (0/4)
25	46	Female	Bilateral	2	PTMC	0.4, 0.3	103.6	No	No (0/2)
26	46	Female	Left	1	PTMC	0.7	100.4	No	No (0/2)

ETE, extrathyroidal extension; NA, not available; PHPT, primary hyperparathyroidism; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma.

diabetes mellitus (adjusted OR=1.98, 95% CI 1.66–2.84) (29). Collectively, the association between serum calcium or PTH levels and the presence of thyroid cancer in patients with PHPT remains unclear, requiring further studies with a larger sample size.

The rate of multifocality of thyroid cancer was three times as high (7 out of 18) in PHPT patients with relatively lower PTH levels (<192 pg/mL) than patients with higher PTH levels (1 out of 8) (>192 pg/mL) (Table 3). Furthermore, 4 cases with thyroid cancers larger than 1 cm exclusively belonged to patients with PTH levels <192 pg/mL, which is consistent with a previous study suggesting tumor size was larger in PHPT patients with lower preoperative PTH levels than in secondary hyperparathyroidism with higher PTH levels (30). One hypothesis for this observation is that hyperparathyroidism with modestly elevated PTH levels is more likely to be asymptomatic, thus extending the occult period and prolonging the exposure of thyroid cells to a microenvironment that stimulates transformation to malignancy. However, the underlying mechanism warrants further investigation.

Molecular analyses indicate that mitogen-activated protein kinase (MAPK) pathway activation is crucial for the initiation of PTC, particularly in patients with *BRAF V600E* mutation or *RET/PTC* rearrangements (31). In addition, the Wnt/ β -catenin signaling pathway plays a critical role in driving the development and progression of PTC by promoting cell proliferation and invasion (32, 33). Previous studies have indicated that PTH exerts antiapoptotic or proliferating actions by activating Wnt/ β -catenin or MAPK signaling pathways in osteoblastic cells, demonstrating its mitogenic effects (34, 35). We hypothesize that PTH may potentiate the intrinsic MAPK signaling pathway in patients harboring *BRAF V600E* mutation or *RET/PTC* rearrangements. Unfortunately, genetic profiles of patients with PTC included in our study were unavailable.

Currently, there are no guidelines to manage the coexistence of thyroid nodules in patients with PHPT. For thyroid cancer, lobectomy or total thyroidectomy with cervical lymph node dissection is recommended according to 2015 ATA (American Thyroid Association) guidelines (20). For PHPT, the surgical approach has transitioned from bilateral

Table 4 Risk of thyroid nodules, benign thyroid nodules, and thyroid cancer by serum PTH.

	Model 1, OR (95% CI)	P value	Model 2, OR (95% CI)	P value
Thyroid nodules (n = 105)				
ln (PTH) (1/ln (pg/mL))	0.79 (0.62–1.00)	0.052	0.88 (0.65–1.20)	0.884
Women	2.39 (1.33–4.30)	0.004	2.13 (1.13–3.99)	0.019
Adjusted serum calcium (1/mmol/L)	–	–	0.83 (0.41–1.68)	0.609
Cr (1/μmol/L)	–	–	1.00 (0.99–1.01)	0.222
Age	–	–	1.02 (0.99–1.04)	0.102
Benign thyroid nodules (n = 79)				
ln (PTH) (1/ln (pg/mL))	0.88 (0.68–1.15)	0.354	1.04 (0.75–1.44)	0.835
Women	2.31 (1.21–4.43)	0.011	1.98 (0.98–3.98)	0.056
Adjusted serum calcium (1/mmol/L)	–	–	0.76 (0.35–1.66)	0.490
Cr (1/μmol/L)	–	–	0.99 (0.98–1.00)	0.132
Age	–	–	1.03 (1.00–1.05)	0.038
Thyroid cancer (n = 26)				
ln (PTH) (1/ln (pg/mL))	0.52 (0.32–0.84)	0.008	0.50 (0.26–0.93)	0.028
Women	2.66 (0.87–8.09)	0.086	2.69 (0.83–8.75)	0.100
Adjusted serum calcium (1/mmol/L)	–	–	1.25 (0.35–4.50)	0.734
Cr (1/μmol/L)	–	–	1.00 (0.99–1.02)	0.855
Age	–	–	1.00 (0.96–1.03)	0.834

Multinomial adjusted logistic regression analyses for 318 patients with PHPT. Patients with primary hyperparathyroidism without thyroid nodules were used as a reference group. Model 1 is adjusted for gender. Model 2 is further adjusted for age, creatinine (Cr), and albumin-adjusted serum calcium. ln, natural logarithm; PTH, parathyroid hormone.

neck exploration to minimally invasive parathyroidectomy (10). However, it should be cautioned that this minimally invasive approach may lead to concomitant thyroid disease being missed. In agreement with previous reports (14, 24, 30), 22 out of 26 cases (84.6%) we observed were TMC and rarely involved any local lymph node or distant metastasis. Thyroid cancer in 19 out of 26 cases (73%) was confined to a single lobe, thus lobectomy and not total thyroidectomy should be recommended for low-risk thyroid cancer to minimize surgery-associated complications (36, 37). Due to the indolent nature of PTMC, active surveillance instead of immediate surgical intervention may be an alternative feasible option for low-risk PTMCs (38, 39). Our observation was that a small proportion of malignant thyroid nodules were undetected or neglected by preoperative ultrasound, but identified through intraoperative exploration. However, it is of note that a large proportion of thyroid nodules that were suspicious by preoperative ultrasound were pathologically confirmed as thyroid cancer. Thus, evaluation of thyroid diseases by preoperative ultrasound and FNAB for larger thyroid nodules should be recommended in patients with PHPT.

A limitation of this study was that serum PTH and calcium levels were measured at a single point within 1 week prior to surgery, and these data may have varied at other time points. Although the low serum 25(OH) D levels measured in a subset of patients are intriguing, these data were not sufficient to test for an association between vitamin D deficiency and risk of malignancy.

Moreover, a small set of patients with asymptomatic PHPT not undergoing surgery were excluded from our analysis, leading to a potential selection bias.

Conclusions

Both benign and malignant thyroid nodules may be commonly encountered in patients with primary hyperparathyroidism. We have observed a relatively high prevalence of thyroid malignancy in our cohort of Chinese patients with PHPT. Our analyses suggest that evaluation of thyroid nodules by preoperative ultrasound is warranted in patients with PHPT, particularly for female patients and those with modestly elevated serum parathyroid hormone levels.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0217>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81802642; Grant recipient: Lei Sheng) and Shandong Provincial Natural Science Foundation of China (Grant No. ZR2019PH082; Grant recipient: Weili Liang).

Ethics approval

This study protocol was reviewed and approved by the Qilu Hospital and Yuhuangding Hospital Ethics Committees. Individual informed patient consent was waived due to the retrospective nature of this study.

Author contribution statement

L L, B L, and L S designed the study. B L, W L, Q Z, and B Z collected the data and performed the analyses. All authors discussed the results, wrote and approved the submission of the manuscript.

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Received in final form 4 July 2021

Accepted 14 July 2021

Accepted Manuscript published online 14 July 2021