

# Is Primary Hyperparathyroidism a Risk Factor for Papillary Thyroid Cancer? An Exemplar Study and Literature Review

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## Abstract

**Introduction** Primary hyperparathyroidism (PHPT) is associated with several cancer types, including papillary thyroid carcinoma (PTC).

**Objective** To explore further the relation between PHPT and PTC.

**Methods** By considering patients with PHPT as extra-suspicious for PTC, we studied an exemplar group of patients with PHPT with a small ( $\leq 1$  cm) thyroid nodule, which was negative in preoperative cytologic examination. During parathyroidectomy, a frozen section biopsy of the thyroid nodule confirmed PTC, as did the final surgical specimen, revealing that the preoperative cytology was false-negative. Additionally, relevant reports retrieved from the English literature addressing thyroid cancer and hyperparathyroidism were reviewed and processed.

**Results** Four patients with PHPT were studied. Three had a multifocal thyroid disease, and three had neck lymph node metastasis. Processing previous report data supported an association between PHPT and PTC. Although thyroid nodularity among patients with PHPT was similar to the general population, PTC incidence was higher. This was true also for patients with secondary hyperparathyroidism.

**Conclusions** This study emphasized that PHPT should be considered as a noteworthy risk factor for PTC. Fine needle aspiration of a thyroid nodule is the most valuable diagnostic procedure for thyroid cancer. Yet, false-negative results were reported in up to 10% of cases, especially in small, subcentimeter nodules. In line with our data and the literature, patients with PHPT should have both a detailed ultrasound addressing the thyroid and cytology of any thyroid nodule, including small subcentimeter lesions. Moreover, surgical flexibility, allowing intraoperative thyroid nodule sampling, should be considered even for “innocent” nodules.

## Keywords

- hyperparathyroidism
- parathyroid adenoma
- thyroid nodule
- thyroid cancer
- parathyroidectomy

## Introduction

The coexistence of thyroid nodule and primary hyperparathyroidism (PHPT) presents a clinical diagnostic and management challenges. Previous investigations have reported a relatively high, but versatile, incidence of 12 to 52% of thyroid nodules in patients with PHPT<sup>1–3</sup> and 5 to 26% among

patients with PHPT with thyroid disease requiring surgery.<sup>3</sup> Frequent thyroid nodules have also been detected by ultrasound (US) in patients with secondary hyperparathyroidism (SHPT).<sup>4</sup> Other observations have indicated an increased risk for cancer in patients with PHPT, mainly of hematopoietic, breast, and urinary tract malignancies, but also endocrine neoplasms.<sup>5,6</sup> With the exception of familial

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endocrinopathies, the association between hyperparathyroidism and thyroid cancer has neither frequently reported nor widely discussed. Therefore, the clinical significance of concomitant thyroid cancer and hyperparathyroidism remains unclear.

The objective of this study was to explore the presumed association between PHPT, thyroid nodularity, and thyroid cancer by conducting an exemplar case series study, specifically addressing small ( $\leq 1$  cm), otherwise “innocent,” non-suspicious thyroid nodules (by preoperative US and cytology) copresenting in patients with PHPT scheduled for parathyroidectomy that intra- and postoperative surgical pathology revealed as papillary thyroid carcinoma (PTC). Additionally, relevant observations retrieved from the English literature addressing thyroid cancer and hyperparathyroidism (both PHPT and SHPT) were reviewed, processed, and presented.

Methods

This work has been approved by the local Institutional Review Board. An exemplar group of patients diagnosed with PHPT was studied. All had both a preoperative 99m Tc-MIBI (methoxyisobutyl isonitrile) scan and neck US suggesting a single parathyroid adenoma and were scheduled for an elective parathyroidectomy. In addition, all preoperative US studies demonstrated a small, benign-appearing thyroid nodule. US-guided fine needle aspiration (FNA) results from these thyroid nodules were also reported to be benign (II, according to the Bethesda system for reporting thyroid cytopathology).<sup>7</sup>

All the patients were otherwise healthy, and none had any risk factors related to thyroid cancer according to the American Thyroid Association (ATA) 2009 guidelines (i.e., prior thyroid cancer, family history, or exposure to external irradiation).<sup>8</sup>

All patients underwent surgery in which a parathyroid adenoma was excised. By addressing these patients with PHPT as extra-suspicious for PTC, the thyroid lesion was sent for an intraoperative frozen section pathologic examination, which confirmed PTC. Thus, as planned and discussed before surgery, with consent given, total thyroidectomy was performed in addition to the parathyroidectomy.

Results

The preoperative workup and intraoperative courses of the four patients are summarized in ►Table 1 and ►Table 2, respectively. The postoperative recovery and follow-up were uneventful in all patients; postoperative parathyroid hormone and calcium blood levels returned to normal values. Surgical pathology of all the thyroid lesions was reported as PTC, classical variant, without evidence for an extracapsular spread (►Table 2). Patient 3 had an uneventful completion thyroidectomy 2 weeks after the first surgery, whereas patient 4 decided not to have completion thyroidectomy. Patients 1, 2, and 3 were later referred for ablative iodine 131 treatment.

The MEDLINE electronic database was searched to identify relevant studies. For this purpose, we used the following

Table 1 Preoperative workup in four patients with primary hyperparathyroidism

Characteristics	Patient			
	1	2	3	4
Age (y)	32	55	39	49
Gender	Male	Female	Female	Female
Preoperative PTH level <sup>a</sup>	75	120	120	121
Preoperative calcium level <sup>b</sup>	11	11.2	11.2	11
Parathyroid adenoma localizing studies <sup>c</sup>	Adjacent to the right thyroid lobe, lower pole	Lateral and deep to the right thyroid lobe	Near the inferior pole of the right thyroid lobe	Deep and posterior to the right thyroid lobe
Other neck ultrasound findings	10 × 7-mm, right thyroid lobe hypoechoic nodule, with regular borders, without calcifications, no lymphadenopathy	5-mm nodule with fine calcifications in the right thyroid lobe and 3 smaller foci (<2 mm) in the left thyroid lobe	7.5 × 5-mm hypoechoic nodule with regular borders in the right thyroid lobe, no lymphadenopathy	9-mm nodule in the left thyroid lobe, with some fine calcifications, no lymphadenopathy
Preoperative thyroid FNA report	Benign-appearing follicular cells	Colloid and benign-appearing follicular cells	A few benign follicular cells and some red blood cells	Follicular cells and colloid

Abbreviations: FNA, fine needle aspiration; PTH, parathyroid hormone.  
<sup>a</sup>Normal PTH level range: 10–65 pg/mL.  
<sup>b</sup>Normal serum calcium range: 8.5–10.3 mg/dL.  
<sup>c</sup>99m Tc-MIBI scan and neck ultrasound study.

**Table 2** Intraoperative course of four patients with PHPT

	Patient			
	1	2	3	4
Operative findings in the thyroid field	Firm nodule in the right thyroid gland upon palpation	Firm nodule in the right thyroid gland upon palpation, ill-looking ipsilateral lymph nodes in levels III, IV	Firm nodule in the right thyroid gland upon palpation	Firm nodule in the right thyroid gland upon palpation
Frozen section report	PTC	PTC	Suspected PTC	Suspected PTC
Surgeon's decision	Total thyroidectomy + level VI neck dissection	Total thyroidectomy + level VI neck dissection + right levels III, IV selective neck dissection	Hold thyroidectomy; wait for final pathological result	Right hemithyroidectomy; wait for final pathologic result

Abbreviation: PTC, papillary thyroid carcinoma.

free-text terms: “hyperparathyroidism” with “thyroid cancer” or “risk factor” or “hypercalcemia,” and limited to “human.” In addition, relevant studies were also extensively searched for by hand. Time and language limitations were applied to the years 1900 to 2014 and English, respectively. Data regarding the occurrence of thyroid nodules among patients with PHPT were reported to match the general population.<sup>9,10</sup> However, processing reported information regarding PTC among patients with PHPT who were operated for parathyroid adenoma suggested a 5% incidence rate of coexistence of thyroid cancer and PHPT.<sup>1,2,9–15</sup> The range varies between 3.3 and 15% (► **Table 3**).

## Discussion

This study questioned whether patients with PHPT have a higher risk for PTC in comparison with the general population. All the same, to date the ATA guidelines do not consider PHPT a risk factor for thyroid cancer. An increased awareness

and earlier diagnosis of PHPT has been partially attributed to the popular routine automated biochemical testing, in addition to targeting middle-aged women with blood calcium screening in an aging society.<sup>16</sup> Furthermore, other reports suggested that patients with PHPT may have an elevated risk to encounter cancer including thyroid cancer.<sup>5,6</sup> Concurrently, thyroid cancer incidence has been reported to increase worldwide. The reasons are not clear, yet an increased US detection rate of thyroid lesions is probably only a partial explanation.<sup>17–21</sup> When based on physical examination alone, the incidence of thyroid nodularity was estimated to be 6.4% among female subjects and 1.5% in male subjects, and the incidence of thyroid nodules was 37 to 57% in autopsies series, with similar figures when detected by US.<sup>22</sup>

Contemporarily, FNA is the most valuable diagnostic procedure for PTC; however, false-negative results may be as high as 10%, especially in small, subcentimeter nodules.<sup>23–25</sup> This issue has been addressed by the revised ATA management guidelines for patients with thyroid nodules and differentiated thyroid cancer. These recommendations concluded that “routine FNA is not recommended for sub-centimeter nodules . . . patients for whom consideration of FNA of a sub-centimeter nodule may be warranted include those with a higher likelihood of malignancy (high risk history), i.e., family history of PTC, history of external beam radiation exposure as a child, exposure to ionizing radiation in childhood or adolescence, history of prior hemithyroidectomy with discovery of thyroid cancer, and 18FDG-PET [fluorine-18 fluorodeoxyglucose positron emission tomography]-positive thyroid nodules.”<sup>8</sup>

Regarding “size,” the current study presented four patients with PHPT, without any ATA-recognized risk factors for thyroid cancer, who presented with a small, unsuspecting thyroid nodule, which would not have been studied otherwise but nevertheless proved to harbor PTC in the postoperative pathologic examination. Roti et al reported that tumors ≤10 mm accounted for 39% of all thyroid cancers, and local lymph node invasion occurred in 0.8% of tumors < 5 mm and in 1.6 to 3.3% of patients with nodules 6 to 10 mm in size.<sup>26</sup>

Recent worldwide data reported the incidence of thyroid cancer to be ~2 to 12 per 100,000 per year new cases, and the

**Table 3** Papillary thyroid cancer among patients with PHPT undergoing parathyroidectomy

Author	No. of PHPT patients	No. of patients with thyroid cancer	%
Attie and Vardhan <sup>2</sup>	948	31	3.3
Cinamon and Turcotte <sup>11</sup>	582	25	4.3
Strichartz and Giuliano <sup>12</sup>	308	11	3.5
Morita et al <sup>1</sup>	200	12	6
Rivo Vázquez et al <sup>13</sup>	124	6	4.8
Masatsugu et al <sup>9</sup>	109	19	17.4
Arciero et al <sup>14</sup>	94	6	6.4
Ogawa et al <sup>10</sup>	85	9	10
Gul et al <sup>15</sup>	60	9	15
Total	2,510	128	5

Abbreviation: PHPT, primary hyperparathyroidism.

estimated lifetime risk for developing thyroid among the general population was reported to be 1:842 for men and 1:324 for women (in the United Kingdom).<sup>17–21</sup> Our original assessment of previously reported data suggested a high (5%) rate of thyroid cancer among patients with PHPT undergoing parathyroidectomy (ranging 3.3 to 15%, 128 thyroid carcinoma cases among 2,510 patients with PHPT; **Table 3**).<sup>1,2,9–15</sup> Although expressed in incomparable statistical measures, this rate suggests significance. Noteworthy are reports associating SHPT and thyroid cancer, thus contributing an additional argument that hyperparathyroidism may indeed predispose for thyroid cancer.<sup>27–29</sup>

Finally, a nontraditional operative approach (i.e., obtaining an intraoperative biopsy of a small thyroid nodule with a benign preoperative cytology) in a high-risk patient (with PHPT) has been shown to be rewarding. It is important to note that the intraoperative examinations of the thyroid nodules have been proven to be reliable, as described in the same context.<sup>30</sup>

## Conclusion

Larger population studies are required to determine if hyperparathyroidism is a significant risk factor for PTC. At this time, we suggest that patients with PHPT should be regarded as extra-suspicious for PTC. Therefore, a comprehensive preoperative thyroid workup, including FNA, should be performed in all patients with PHPT, even for small thyroid nodules ( $\leq 1$  cm). Despite an otherwise innocent preoperative evaluation of a thyroid nodule in patients with PHPT, flexible surgical planning with optional intraoperative thyroid tissue sampling should be considered during surgery.

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