Evaluation of the Relationship Between Thyroid Cancer and the Concurrent Detection of Thyroid Nodules *on the Background of Primary Hyperparathyroidism*

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Abstract

Introduction

Primary Hyperparathyroidism (PHPT) is commonly caused by a benign parathyroid adenoma that results in overactivity of the gland and subsequent hypercalcemia due to elevated parathyroid hormone (PTH). This endocrine pathology is associated with thyroid cancer, specifically Papillary Thyroid Cancer (PTC). However the explanation for their synchronous presentation is unknown. Moreover, it causes diagnostic and treatment challenges that impact patient outcomes.

Aims and Objectives

To critically analyze published research to address the relationship between PHPT and thyroid cancer, the role of ultrasound imaging in detecting sinister thyroid nodules in PHPT patients and the features of PHPT that predispose the risk of thyroid malignancy.

Study Design

Literature Review

Methodology

Electronic database searches of PubMed and CINAHL Plus through EBSCOhost were conducted using the keywords “primary hyperparathyroidism”, “thyroid nodules” and “thyroid cancer”. Following application of filters and removal of duplicates, 627 relevant results remained. Articles were screened for eligibility based on predetermined selection criteria. Following a review of titles and abstracts, 10 peer-reviewed articles were chosen for further analysis. The studies included were critically appraised using the EBL Critical Appraisal Checklist.

Results

10 articles were examined, 2 were prospective cohort studies and 8 were retrospective cohort studies. All studies involved exhaustive medical chart reviews of patients with PHPT, to investigate the concomitance of thyroid malignancy. Six studies established cervical ultrasound as the optimal method of recognition and preoperative localization of thyroid and parathyroid lesions. Overall, the incidence of thyroid cancer among PHPT patients ranged between 2.9% to 32.9%. Four studies established age, gender and PTH levels as risk factors.

Conclusion

The existing literature is consistent with previous studies and purports that individuals with a background of PHPT are at an increased risk of thyroid cancer. Furthermore, the highest likelihood of identifying thyroid cancer is through preoperative localization of parathyroid adenomas by cervical ultrasound, in female patients over the age of 50.

Key Findings

Further research is needed to understand the underlying pathogenesis and genetic mechanisms that encompass the relationship between PHPT and thyroid cancer.

Introduction

The discrete anatomical location of the parathyroid glands remains a challenge in the treatment of its pathologies. Consisting of four small glands located on the posterior aspect of the thyroid gland, they function to maintain calcium homeostasis through the release of Parathyroid Hormone (PTH). The disease aetiology of Primary Hyperparathyroidism (PHPT) is commonly the result of a benign parathyroid adenoma that causes overactivity of the gland and subsequent hypercalcemia due to elevated PTH [1]. It is the third most common endocrine disorder, affecting 0.1-0.4% of the global population [2].

While thyroid disease is associated with PHPT, it is currently unknown whether the concurrent presentation of PHPT and Papillary Thyroid Cancer (PTC) is coincidental or causal, due to their intimate anatomical relationship [3]. Recent studies have determined that the incidence of PTC has risen dramatically in the past few decades, with the frequency of thyroid procedures and incidental findings of thyroid cancer increasing at an average rate of 10% [4-6]. It is known that the incidence of thyroid disorders in PHPT patients is significantly greater than the incidence of PHPT in patients with thyroid disorders, suggesting that the existing association is not bidirectional [7]. Additionally, the issue remains of whether PHPT is a risk factor for thyroid cancer or if cervical ultrasounds are resulting in overdiagnosis.

Routine screening of the parathyroid glands simultaneously incorporates evaluation of the thyroid gland. Preoperative diagnostic imaging for localizing parathyroid adenomas can also detect thyroid nodules [8]. These thyroid lesions are referred to as incidentalomas, which are asymptomatic yet warrant Fine Needle Aspiration Biopsy (FNAB) to rule out malignancy. Further neck exploration through invasive measures are associated with risks that outweigh the benefits if performed unnecessarily.

The existing evidence is inconclusive as to whether increased recognition of thyroid incidentalomas will improve health outcomes or lead to excessive thyroid interventions. Therefore, concurrent thyroid pathology and PHPT can be problematic for the healthcare provider's clinical and surgical decision-making regarding their patients.

The purpose of this literature review is to critically appraise the existing evidence of the relationship between detection of thyroid nodules and incidence of thyroid cancer on the background of PHPT. More importantly, it will provide insight on the impact of over-detection with diagnostic imaging and predictable risk factors on the concomitant pathologies. This is of clinical relevance as the benefits of surgical intervention for thyroid incidentalomas remain controversial. As clinical guidelines for management and treatment remain non-existent [7], it is imperative to determine the factors contributing to the concurrence of thyroid cancer and PHPT, in order to mitigate them.

Aims and Objectives

The primary objective of this paper is to critically analyze and evaluate the existing peer reviewed literature that address the following topics:

1) The relationship between PHPT and thyroid cancer

2) The role of ultrasound imaging in detecting sinister thyroid nodules in PHPT patients

3) The features of PHPT that predispose the risk of developing thyroid cancer

Methodology

Database Search

To obtain the articles for review, an electronic database search using PubMed and CINAHL Plus through EBSCOhost was conducted on January 11th, 2020. The purpose of this was to identify articles that were relevant to the topic of how PHPT is associated with the development of thyroid cancer. Themes incorporated in the primary search were "primary hyperparathyroid-

ism" and "thyroid cancer".

The following keywords were used on CINAHL Plus through EBSCOhost Database:

1) Primary Hyperparathyroidism

2) Thyroid Nodules

3) Thyroid Cancer OR Papillary Thyroid Carcinoma

The following keywords were developed and searched for using PubMed Database:

1) ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])

2) ("thyroid neoplasms"[MeSH Terms] OR ("thyroid"[All Fields] AND "neoplasms"[All Fields]) OR "thyroid neoplasms"[All Fields] OR ("thyroid"[All Fields] AND "cancer"[All Fields]) OR "thyroid cancer"[All Fields]) OR ("Crit Arts"[Journal] OR "CA Cancer J Clin"[Journal] OR "ca"[All Fields])

3) ("thyroid nodule"[MeSH Terms] OR ("thyroid"[All Fields] AND "nodule"[All Fields]) OR "thyroid nodule"[All Fields] OR ("thyroid"[All Fields] AND "nodules"[All Fields]) OR "thyroid nodules"[All Fields])

Application of Filters

The filters applied to both databases after the initial search are presented below in table 1:

Table 1
List of filters applied on EBSCOhost and PubMed .

Filter	Comment
Publication dates	2009-2020
Text Availability	Full Text
Language	English
Age	18+
Species	Humans

Selection Criteria

Table 2
Details the inclusion and exclusion criteria applied for the selection of the studies included in this review.

Inclusion Criteria	Exclusion Criteria
Relevant articles published within the past 10 years and available online with full-text, in English	Articles in other languages that are older than 10 years, without full-text
Peer reviewed articles in academic journals	Articles that are not peer-reviewed, case reports or animal studies
Studies evaluating the imaging results of adults +18 years with PHPT and thyroid nodules	Studies involving patients with MEN or previous thyroidectomy
Studies evaluating the genetic component thyroid cancer in PHPT patients	Studies evaluating the risk of non-thyroid related cancers from PHPT
Studies assessing the histological features of thyroid nodules	Studies evaluating benign thyroid nodules exclusively
Studies evaluating the relationship between PHPT and thyroid cancer	Studies that do not involve patients with PHPT
Studies assessing the diagnostic and prognostic markers of thyroid cancer	Studies assessing the diagnosis and management of PHPT

Quality Assessment

To assess the quality of each study, the EBL Critical Appraisal Checklist was applied to establish validity. The checklist assesses the study population, study design, data collection and results of each study. A score was calculated for the validity of individual sections and the overall paper.

Data Extraction

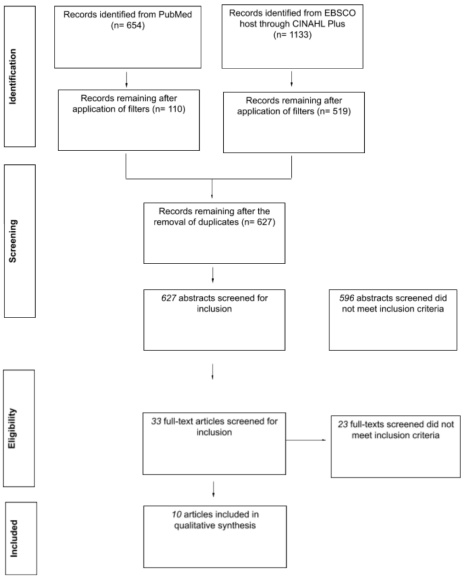
To evaluate each study, the following information was extracted:

I. First author, publication year
II. Title of study
III. Location of study
IV. Study objectives
V. Study design
VI. Sample size
VII. Methodology
VIII. Selection criteria
IX. Key findings
X. Strengths and limitations

Table 3
Reasons for Article Exclusion after Full-Text Review

Reason for Exclusion	Number
Case Report	15
Did not involve patients with PHPT	4
Evaluation of cancer not related to the thyroid	1
PHPT diagnosis and management	2
Assessment of benign thyroid nodules exclusively	1
TOTAL	**23**

Figure 1
Methodology of literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



Data Selection Process

On EBSCOhost, the initial search generated 1133 results, and was reduced to 519 after the application of filters from Table 1. On PubMed, the initial search produced 654 results, which was reduced to 110 upon application of the same filters. After collating all the results and removal of duplicates, 627 articles remained. Of the 627 abstracts screened, 596 articles did not fulfill the inclusion criteria. The remaining 33 full-text articles were then analyzed in more detail, with the application of the inclusion and exclusion criteria, and 10 articles were selected to be assessed in this literature review. Figure 1 depicts the study selection process.

Results

Association between PHPT and PTC

Nine studies assessed the relationship between PHPT and PTC to determine that there is an increased incidence of thyroid malignancy on the background of the parathyroid disorder [7,9,11-17]. The incidence of the concurrent pathologies ranged from 2.9% in the Yazici et al study [7], to 32.9% in the Scerrino et al study [14]. Thyroid nodules that were identified upon imaging of the parathyroid gland were the primary indicator of thyroid gland dysfunction.

Furthermore, Preda et al determined that the incidence of PTC is similar among PHPT and SHPT cohorts [13].

Table 4
Validity scores determined by the Evidence Based Librarianship (EBL) Checklist for the critical appraisal of peer-reviewed scientific articles

Study	Population Validity	Data Collection Validity	Study Design Validity	Results Validity	Overall Validity
Adler *et al.* 2010	40%	100%	100%	100%	86%
Barbaros *et al.* 2009	60%	100%	100%	67%	80%
Cetin *et al.* 2019	75%	100%	100%	100%	95%
Cuhaci *et al.* 2019	67%	100%	100%	67%	86%
Preda *et al.* 2019	80%	100%	100%	100%	95%
Scerrino *et al.* 2016	80%	80%	100%	50%	76%
Shen *et al.* 2019	60%	80%	100%	67%	76%
Vargas-Ortega *et al.* 2018	60%	100%	100%	83%	86%
Xue *et al.* 2016	60%	100%	100%	83%	85%
Yazici *et al.* 2015	40%	100%	100%	83%	81%

Risk factors of PTC in PHPT patients

Four studies established risk factors for developing PTC on the background of PHPT [11,13,16-17]. Age, gender and elevated PTH levels were determined to be risk factors ($p<0.05$), such that females over the age of 50 were dominant in the PHPT and PTC cohort (11,13,16). In contrast, Yazici et al did not find a meaningful correlation between PTC and age [7].

The role of ultrasound in PTC diagnosis

Six studies concluded that cervical ultrasound was the optimal method of recognition and preoperative localization of suspicious thyroid and parathyroid lesions [7,9-10,12,14-15]. Two studies determined that nuclear imaging with Tc99m sestamibi scintigraphy and ultrasound should be used as complementary diagnostic tools in detecting PTC [12,14]. Adler et al found that routine ultrasound in PHPT patients is beneficial in discovering occult thyroid pathology and determining appropriate interventions [9].

Upon completion of a comprehensive literature search of the EBSCOhost (CINAHL Plus) and PubMed databases, 10 articles were chosen to be analyzed. These articles were peer-reviewed, published in English within the past 10 years, had full-text available, involved human partici-

pants and investigated the relationship between PHPT and thyroid cancer. A total of 2 prospective cohort studies and 8 retrospective cohort studies were included. The validity scores of each paper are elucidated in Table 4 and the key findings from each paper is summarized in Table 5. Additionally, three main themes emerged from the qualitative synthesis of the chosen articles.

The quality of each study was objectively assessed with the EBL Critical Appraisal tool. The validity of each section, in addition to the overall validity was calculated based on a predetermined formula and deemed acceptable within each study.

Discussion

Following a thorough analysis of 10 peer-reviewed articles that were published within the past 10 years, it is evident that PHPT is associated with concomitant thyroid malignancy. The purpose of this literature review was to investigate the relationship between the two diseases, identify the risk factors and explore the influence of diagnostic imaging on the incidence of thyroid cancer with a background of PHPT.

Findings

Nine studies identified thyroid cancer among PHPT patients on the presence of thyroid nodules. In all cases, these nodules were incidental findings that were recognized while investigators were examining parathyroid adenomas. The wide range of incidence can be explained by differences in the size of the cohorts and geographical, environmental and cultural factors in each study. Furthermore, the existing spatial relationship regarding the anatomical location of parathyroid and thyroid lesions warrants further investigation as to whether a temporal relationship exists.

From the retrospective chart reviews, 4 studies identified that sex, age, hormone levels and size of thyroid nodules are risk factors for the development of PTC in PHPT patients. Specifically, Vargas-Ortega et al observed an increase in the incidence of thyroid cancer among females older than 50 years with elevated PTH levels [16]. A stepwise multivariate logistic regression analysis was conducted to validate this correlation between clinical and biochemical characteristics and thyroid cancer. Conversely, the Yazici et al study did not support these findings [7]. Therefore, there is the possibility of selection bias regarding the medical records that were chosen for review.

All studies involved the use of cervical U/S in various capacities. However, 6 studies investigated its role as the primary tool for screening and diagnostic purposes. Adler et al [9], found that the high-resolution ultrasound imaging has greater specificity than sensitivity for detecting parathyroid adenomas. This conclusion was further supported by the Barbaros et al [10], study, which discovered that false positive results increase with larger thyroid nodules that are posteriorly located. However, the limitation of using ultrasound imaging is that it cannot detect nodules less than 1 cm. Despite requiring a FNAB to confirm the presence of thyroid malignancy with histopathology, Shen et al [15] discovered that lesions identified on imaging positively correlate with sinister findings. This advantage of early detection is not without the disadvantage of over-diagnosis. It is established in literature that routine U/S for PHPT patients can mitigate unnecessary thyroid interventions (9). In contrast, the concurrent detection of papillary microcarcinoma, a small sized and non-invasive type of PTC, has led to an increase in thyroidectomies [7]. This is controversial because there were no accompanying clinical symptoms to warrant gland excision and the risks of the procedure outweigh no intervention. Although it may be efficient and accurate, the information obtained from ultrasound imaging should always be considered in the context of the complete clinical picture.

Quality and Validity

The EBL Critical Appraisal Checklist was used to determine that the studies included in this literature review are of good to high quality, as the overall validity scores ranged between 76% to

95%. Among individual categories, population validity varied considerably. This is due to the relatively small sample size in most of the retrospective cohort studies. Consequently, the validity of the results was affected, and the statistical power was reduced.

Strengths and Limitations

A major strength of this literature review is that it provides a wholistic summary of the topic of study. Firstly, the 10 selected articles were chosen from 2 different online sources, which reduced database bias and allowed for a broader scope of scientific publications to be incorporated. Secondly, the studies were conducted in various geographical medical centers and similar trends between PHPT and thyroid cancer were identified, thereby minimizing location bias. Thirdly, most of the studies highlighted the involvement of an individual or small team of medical technicians and pathologists to obtain diagnostic data from the patients. This minimized user bias and strengthened the validity of the results. Finally, the credibility of the findings in each study were further supported by the use of appropriate statistical tests. Specifically, all studies assessing categorical variables used Fischer's chi-square test with a p-value of less than 0.05 to establish statistical significance.

Equally important in this review are the limitations presented in the studies. Given the nature of the research question, the predominant implementation of the retrospective cohort study design posed certain restrictions. Although it is ethical and feasible, these observational studies can only determine correlations, rather than causal links between variables. Furthermore, extracting patient data from their medical records are prone to information bias and confirmation bias. Researchers cannot control for confounding variables and differences in the methods by which patients underwent clinical examinations or thyroid surgery. Notably, most studies were limited to a small sample size of PHPT patients. This is disadvantageous because it minimizes the reliability and external validity of the clinical outcomes. Thus, these factors must be considered when identifying trends in chart reviews, in order to obtain objective conclusions.

Future Research

Although the existing research concludes that an association between both diseases exist, it fails to explore the mechanisms by which PHPT and thyroid cancer are related. This provides an avenue for future research regarding the pathogenesis or genetic factors that may be implicated. This would be beneficial in determining whether the concurrent pathologies are incidental or predictable. Thus, the existing hypothesis generating retrospective study designs need to be supported with evidence from prospective clinical studies.

Conclusion

The existing evidence suggests that individuals with a background of PHPT are at an increased risk of thyroid cancer. This literature review not only focuses on this relationship, but also analyzes the use of ultrasonography in diagnosis and potential risk factors. The clinical importance of these findings is that it will aid in predicting the occurrence of thyroid cancer in PHPT patients, thereby enabling future physicians to prevent its occurrence rather than cure it. Therefore, the impact of detecting incidental thyroid lesions prior to any clinical manifestations must be further investigated to determine the best course of action that beneficiates patient outcomes.

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