



Increase Cancer Risk in Patients with Primary Hyperparathyroidism

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Abstract

Introduction: Primary Hyperparathyroidism (PHPT) affects at least 1 in 1000 individuals and its incidence increases with age, with a peak incidence in the seventh decade of life. It is the third most common endocrine diagnosis. Several studies have identified a relationship between PHPT and an increased risk of developing malignancies such as breast, skin, colon, rectal, thyroid, prostate, and kidney cancers. The aim of this study was to report a cohort of patients with PHPT with concomitant cancer and compared them with PHPT without cancer.

Methods: Retrospective study from a prospectively kept database of patients with PHPT treated by our group between January 2015 and July 2017. The operation performed by our group is, a minimally invasive radio-guided parathyroidectomy, which entails a bilateral neck exploration through a two-centimeter incision. The patients' characteristics were obtained and analyzed from the electronic medical records. Patients without complete medical records were not included in our study. All data were collected in a non-identifiable fashion in accordance with the principles outlined in the declaration of Helsinki and as required for our institutional review board approval.

Results and Discussion: A total of 63 patients with PHPT were included in our study. Eighty percent of our patients were females; the mean age at diagnosis was 56.7 years (range: 29 years to 77 years). There were 23 patients with concomitant cancer (36.5% of the cases). The most frequently encountered malignancy was breast cancer in 14.3% of the cases (nine patients), thyroid cancer 7.9% (five patients), and skin cancer 6.3% (two patients with melanoma, one with basal-cell carcinoma and another one with squamous cell cancer). We did not identify a clinical or statistical difference between the two groups. The patients' demographics were very similar: gender ($p=0.8$), age ($p=0.6$), preoperative calcium levels ($p=0.3$), preoperative PTH levels ($p=0.2$), preoperative vitamin D levels ($p=0.5$) and preoperative urinary calcium levels ($p=0.5$).

Conclusion: The available evidence at this time suggests a possible correlation between PHPT and malignancy. It remains to be clarified whether the risk is due to genetic predisposition to tumor development or a physiological associative effect. We recommend discussing with patients with a diagnosis of PHPT who are considering undergoing a parathyroidectomy about the possible increased risk of cancer seen in patients with PHPT. More studies are needed to determinate the exact relationship between the PHPT and the risk of developing cancer.

Keywords: Primary hyperparathyroidism; Hyperparathyroidism; Breast cancer; Colon cancer; Rectal cancer; Prostate cancer; Renal cancer; Skin cancer; Hipercalcemia

Introduction

In 1852, Sir Richard Owen, the curator of the Natural History Museum, discovered the parathyroid glands when he was dissecting a rhinoceros that had died in the London Zoo [1,2]. In 1903, Askanazy made the association between bone disease and a parathyroid adenoma during an autopsy [1,2]. But in 1925, Mandl was the first to remove a parathyroid tumor with significant improvement of the disease [1,2]. Primary Hyperparathyroidism (PHPT) affects at least 1 in 1000 persons and its incidence rises with age, with a peak in the seventh decade of life [3,4]. It is the third most common endocrine diagnosis [3,4]. The risk of developing PHPT is 5-fold greater in women compared to men after the age 75 years, while it is comparable between genders before the age of 45 years [5]. PHPT is due to a single parathyroid gland adenoma in approximately 85% to 90% of the cases, with multiple gland disease accounting for the remaining 10% to 15% of the cases (double

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adenomas, triple adenomas, or four gland hyperplasia) [6,7]. PHPT arises from an unregulated overproduction of PTH (Parathyroid Hormone) from an abnormal parathyroid gland. PHPT is defined as hypercalcemia or widely fluctuating levels of serum calcium resulting from the inappropriate or autogenously secretion of PTH by one or more parathyroid glands in the absence of a known or recognized stimulus [6].

PHPT is distinguished by having hypercalcemia, normal or increased 24-h urinary calcium excretion and increased or inappropriately normal levels of parathyroid hormone [8]. It may be associated with osteopenia, osteoporosis, fragility fractures, kidney stones, increased risk of cardiovascular events and neuropsychological alterations [9]. Besides these effects and given the available evidence of an increased cancer-related mortality in patients with PHPT and of the possible anti-apoptotic action of the PTH, in the past years some authors investigated the possibility of an increased risk of malignancies in this condition [10,11]. Interestingly, cancer is now a known feature of chronic kidney disease, which is a characterized persistently elevated PTH level [12].

Patients with cancer who have hypercalcemia can be divided into two major groups: Those with and those without an elevated PTH level. The most common cause of inappropriately elevated PTH in all patients is PHPT [6]. Ninety percent of all cases of hypercalcemia are caused by either PHPT or hypercalcemia of malignancy [13]. Some studies have identified an increased risk of developing certain malignancies, such as breast, skin, colon and rectal, thyroid and kidney cancer, while other studies have not been able to find an association between PHPT and cancer [2,4,10,12-18]. These discordances are probably due to the different designs (i.e. retrospective or prospective), different settings (i.e. national registries or population-based) and different inclusion criteria (i.e. all patients diagnosed with PHPT or only surgically treated PHPT patients) of the available studies.

It is unclear whether the excessive risk relates to the PHPT in general or only to the severity of the disease and whether it concerns malignancy in general or a specific form of cancer. Likewise, it is not clear if the influence is primarily on incidence as opposed to mortality or whether the risk may be reduced by normalizing the biochemical disturbances through parathyroidectomy. A better understanding into these matters is important since PHPT is an endocrine disease that affects around 1% of the adult population, predominantly postmenopausal women [19]. Detection of certain risk factors could be of help in the management of PHPT. The aim of the study was to analyze the association between PHPT and cancer, including differences by age, sex or time period and compare them to patients PHPT without cancer.

Materials and Methods

Study population

In this retrospective study from a prospectively kept database, we identified patients with PHPT operated on at a single institution (Sociedad Quirúrgica at the American British Cowdray Medical Center) from January 2015 to July 2017. The data that was utilized for the study was obtained from the electronic medical records and included age, gender, serum calcium, ionized calcium, PTH, Vitamin D, and urinary calcium; and concomitant diagnosis of malignancy. All data was collected in a non-identifiable fashion in accordance with the principles outlined in the declaration of Helsinki and as

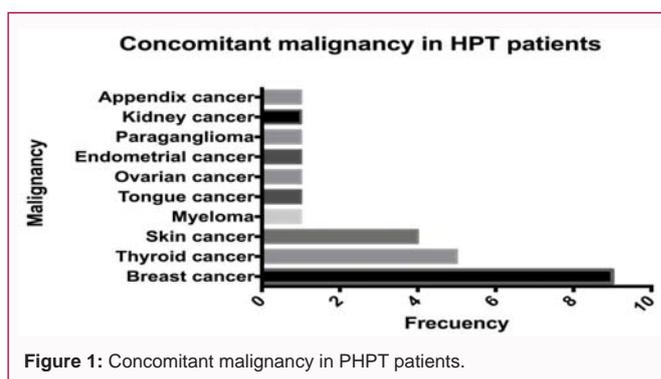


Figure 1: Concomitant malignancy in PHPT patients.

required for our institutional IRB approval [20]. Patients without clinical records or histological confirmation (biopsy or surgery) were not included.

Statistical analysis

Demographic, biochemical and concomitant malignancy data were summarized with descriptive statistics. The patients were divided in two groups: those with concomitant malignancy and those without malignancy. Continuous variables were compared using Student's t-test. Categorical variables were compared using the χ^2 test. Odds Ratios (ORs) and their corresponding 95% confidence intervals were estimated by logistic regression models. Two-tailed probability values were calculated; p values <0.05 were considered to indicate statistical significance. The analysis was conducted using Prism 6 software.

Results

A total of 63 patients with PHPT were included in this study. Eighty percent of the patients were females and twenty percent were males; the mean age of the study was 56.7 (range: 29 years to 77 years). The mean preoperative calcium level was 10.2 mg/dl, the mean preoperative PTH level was 97 pg/dl, the mean preoperative Vitamin D was 27.5 ng/dl, and mean preoperative urinary calcium was 223.1 mg in 24 h (Table 1). There were 23 patients with concomitant malignancy (36.5% of the cases). The most frequently encountered malignancy was breast cancer in 14.3% of the cases (nine patients), thyroid cancer 7.9% (five patients) and skin cancer 6.3% (four patients, two with melanoma, and one with basal-cell carcinoma and another one with epidermoid cancer). The rest of the malignancies are described on Figure 1.

We did not identify any clinical or statistical difference between the two groups. The patients' demographics are very similar: gender (p=0.8), age (p=0.6), preoperative calcium levels (p=0.3), preoperative PTH levels (p=0.2), preoperative vitamin D levels (p=0.5) and preoperative urinary calcium levels (p=0.5).

Discussion

PHPT affects at least one in 1000 individuals and its incidence increases with age, with a peak incidence in the seventh decade of life. The underlying cause of sporadic PHPT is unknown, the majority of cases are non-familial in origin and in less than 1% of the cases the disease is a part of hereditary disorder [14].

The natural history of some of the different presentations of PHPT remains only partly comprehended with available studies suggesting limited risk of disease progression, while other studies suggesting a more malignant progression of the disease. Some studies have suggested an increased risk of premature death from

Table 1: Characteristics of patients with HPT.

	Total (n=63)	PHPT with Cancer (n=23) (%)	PHPT without Cancer (n=40) (%)	p<0.05
Female	50 (79.4)	18 (78.3)	32 (80)	0.8
Male	13 (20.6)	5 (21.7)	8 (20)	
Age (years)	56.7 ± 11.4	57.8 ± 9.7	56.2 ± 12.3	0.6
Preoperative Calcium	10.2 ± 0.7	10 ± 0.8	10.2 ± 0.7	0.3
Preoperative PTH	97 ± 44.8	86.5 ± 27.1	102.3 ± 51	0.2
Preoperative Vitamin D	27.5 ± 16.4	25.2 ± 9.5	28.5 ± 18.7	0.5
Preoperative Urinary Calcium	223.1 ± 131.5	252.3 ± 145.7	210.3 ± 127.7	0.5

cardiovascular disease and malignancy in patients with mild to moderate hypercalcemia that did not undergo parathyroidectomy. The optimal treatment in this predominant subgroup of patients is mired in controversy with available studies throwing up conflicting results. The question is, should we counsel patients on the need to undergo parathyroidectomy due to an increase incidence of cancer in patients with PHPT?

In vitro models, calcium is generally associated with increased differentiation, decreased proliferation and induction of apoptosis; on the contrary, PTH may have an anti-apoptotic effect and promote cell growth and invasiveness [21]. Recent studies have identified that the Calcium-Sensing Receptor (CaSR) mediates cell fate-regulating processes including hormone secretion, control of proliferation, differentiation, apoptosis and chemotaxis. Interestingly, it could act as an oncogene and a tumor suppressor gene, depending on the site of cancer. In cancers such as prostate, testicular, ovarian and breast cancer it seems to act as an oncogene, by promoting proliferation an inhibiting apoptosis' [22,23]. Reduction or even loss expression of CaSR in malignancies such as parathyroid cancer, colorectal cancer and neuroblastomas leads to the loss of the protective effects of calcium [22-24].

Hypercalcemia can occur in up to 30% of individuals with a malignancy [25]. PHPT is responsible for 6% to 21% of hypercalcemia among patients with cancer, it's more common in those with a history of head and neck irradiation and it has been associated with breast irradiation [13,25-30]. One retrospective study indicated that no cancer causes of hypercalcemia accounted for 97% of patients in remission and 21% of those who had active cancer, with PHPT causing 75% of those cases [27]. Therefore, we recommend that the PTH level should be checked in a patient with cancer and hypercalcemia [13].

Since the 1960s, there have been multiple studies discussing the association between PHPT and cancer (breast, skin, colon, thyroid and kidney cancer) [2,4,10,12-18,21,26,31-34]. Nonetheless, the data has been conflicting. The Swedish Cancer Registry in 1988 published a retrospective study involving 4,163 patients with PHPT who underwent parathyroidectomy and were followed up for 22 years. This study showed a considerably increased relative risk of developing gastrointestinal cancers, endocrine tumors (involving adrenals, thymus, pituitary and pancreas), renal carcinoma and breast cancer [15]. In 1990 another retrospective study from Sweden involving 896 operated patients with PHPT followed up for about 13 years showed the presence of 24 different tumor locations among the 72 patients who died from malignancy with a significant link only with pancreatic adenocarcinoma [35]. An additional retrospective study among 2,425 patients with PHPT using the Danish National Cancer Registry was published in 2002. It showed a 25% increased risk of cancer with (risk being higher in women). Hematopoietic cancers (mainly

multiple myeloma) were significantly more common in patients with PHPT, while patients with unspecified hyperparathyroidism had significantly increased carcinoma of the urinary tract and thyroid gland [36]. Patients with secondary hyperparathyroidism had a trivial overall cancer risk suggesting that malignancies were not due to the PTH itself [36].

A retrospective study published in 2004 from Demark involving 1,578 patients with PHPT found a total of 77 cases of death from malignancy with significantly increased mortality from oral and esophageal cancer, as well as hematological malignancy in men and colonic cancer in women [34]. In 2006, a Swedish prospective cohort study (7,847 women), serum calcium levels showed an opposite association with breast cancer risk in premenopausal women in a dose-response manner but a positive association in overweight peri/post-menopausal women [37]. A retrospective cohort study using the Swedish cancer registry published in 2007, involving 9,782 operated patients with PHPT showed an augmented overall risk of cancers in both genders with risk persisting beyond 15 years after parathyroidectomy [14]. Breast cancer accounted approximately 25% of the cancer incidence in women and an increased risk of renal, colonic and squamous cell cancer was found in both genders [14]. The risk of pancreatic and endocrine cancer was increased in the small subgroup that was operated on before 40 years of age [14]. A study from Scotland involving 3,039 patients with PHPT showed an increased incidence and mortality from cancers in both surgically and conservatively managed patients with the commonest cancers being those of the skin (non-melanoma), breast, colon and lung. Parathyroidectomy was found to defer but not reduce the incidence of cancers [38]. Nonetheless, it is relevant to note that as the absolute number of organ-specific cancers in all the studies mentioned above is small, organ-specific malignancy data need to be interpreted with cautiousness.

In our study we found that the most common malignancy identified was breast cancer in 14.3% of the patients. Interestingly, it is important to notice that in our patient population the women were slightly younger compared to other studies [4,16,39]. Hypercalcemia occurs in up to 40% of patients with breast cancer and has generally been attributed to osteolytic bone metastasis. In the minority of cases, the hypercalcemia is mediated by humoral mechanism involving the secretion of parathyroid-like peptide by malignant cells [39-41]. The reported frequency of PHPT in patients with breast cancer is around 7% to 14% of the cases is very close to our patient population. An increased incidence of parathyroid adenoma has been recognized in patients treated for breast cancer, as well as a simultaneous occurrence of breast cancer diagnosed after parathyroidectomy [15,40,42]. Breast cancer patients without evidence of PHPT have significantly higher serum calcium and PTH (unrelated to clinical staging or anti-tumor

therapy) compared with healthy controls [40].

In 1998, a case of simultaneous papillary thyroid carcinoma and parathyroid adenoma with a raised calcitonin level was reported [32]. A simultaneous occurrence of thyroid cancer and PHPT may be a detection bias. Worldwide data reports that the incidence of thyroid cancer to be 2% to 12% per 100,000 per year. The association between PHPT and thyroid cancer has not been frequently reported, a 12% to 57% incidence of thyroid nodules in patients with PHPT is reported and 9.7% of those cases were malignant [31,32,43]. Non-medullary thyroid cancer occurs in approximately 3% of PHPT cases [32,44]. Recent papers have reported a global incidence of 5% (range 3.3% to 15%) of thyroid cancer among patients with PHPT undergoing parathyroidectomy [2,31,45-49]. We reported an incidence of 7.9% in our cohort.

With the available evidence, we can only speculate about possible etiologic risk factors, and various genetic and/or environmental factors that may contribute to the correlation between PHPT and certain malignancies. The risk does not seem to be linked to the biochemical derangements caused by the parathyroid adenoma [14]. Being overweight seems to be a risk factor for cancer at several organ sites, including the malignancies that have been associated with PHPT, except for squamous cell of the skin [50,51]. Vitamin D regulation may be an important factor in the link between PHPT and the elevated cancer risk [14]. Vitamin D receptors are expressed in the intestine, bone, kidney, and parathyroid glands. Vitamin D receptors are also expressed in most immune cell types and in most colonic, breast, and skin cancer cell lines [52,53]. Vitamin D₃ (1,25-(OH)₂D₃) has anti-proliferative, prodifferentiative, and immunomodulatory effects, in addition to the traditional calcium-related effects [53]. An inherited predisposition due to disturbances in the vitamin D receptors alleles may cause abnormal regulation of the parathyroid glands as well as defective apoptosis and increased incidence of preneoplastic lesions [53-55]. In this setting, the association between PHPT and squamous cell skin cancer may seem fascinating. The incidence is related to ultraviolet light exposure but 1,25(OH)₂D₃ may also be involved in the regulation of the differentiation of keratinocytes [52].

Our study adds to the literature suggesting a connection between PHPT and certain cancers. The association seems to be separate to the biochemical disturbances caused by the PHPT. It remains to be clarified whether the risk is due to genetic susceptibility to tumor development as such, or if there is a physiological associative effect, intrinsic or environmental. Further larger population-based studies are required to determine if PHPT is a significant risk factor for cancer.

Conclusion

The available evidence at this time suggests a possible correlation between PHPT and malignancy. It remains to be clarified whether the risk is due to genetic predisposition to tumor development or a physiological associative effect. We recommend discussing with patients with a diagnosis of PHPT who are considering undergoing a parathyroidectomy about the possible increased risk of cancer seen in patients with PHPT. More studies are needed to determinate the exact relationship between the PHPT and the risk of developing cancer.

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