
# Occurrence of malignant neoplasia in patients with primary hyperparathyroidism

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# Occurrence of malignant neoplasia in patients with primary hyperparathyroidism

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**Abstract**

**Background.** The association between primary hyperparathyroidism (1HPT) and cancer is debated. The present study was aimed to investigate the occurrence of neoplasia in 1HPT.

**Methods**: All consecutive patients (n=1750) referred to our "Osteoporosis and Metabolic Disease" outpatients clinic for osteoporosis or hypercalcemia were eligible for the study. The exclusion criteria were: the finding of osteoporosis and/or altered calcium-phosphorous metabolism in the context of investigations for malignancy, the presence of diseases known to influence the cancer risk and the heavy smoking habit. Eventually, 1606 patients (1407 females, 199 males) were enrolled. In all patients calcium-phosphorous metabolism, PTH and vitamin D levels were measured and the occurrence of cancer during the 10 years prior the study inclusion was recorded.

**Results**: 163 patients had 1HPT while 1443 had not. Patients with and without 1HPT were comparable for age and gender. In 1HPT patients the occurrence of all, breast, kidney and skin cancer was significantly higher (21.5%, 12.2%, 2.5%, 1.8%, respectively) than in patients without 1HPT (12.4%, 6.9%, 0.3%, 0.3%, $p<0.05$ for all comparisons). The 1HPT presence was significantly associated with the occurrence of all neoplasia and of breast, skin and kidney neoplasia (odds ratio, 95% confidence interval, P value: 1.93, 1.27-2.92, 0.002; 1.93, 1.11-3.35, 0.002; 9.18, 2.16-38.8, 0.003; 8.23, 1.71-39.5, 0.008, respectively), after adjusting for age, gender (as appropriate), smoking habit and vitamin D levels.

**Conclusions**: During the 10 years prior the diagnosis of 1HPT, the occurrence of all, breast, skin and kidney neoplasia is increased.

## Introduction

Primary hyperparathyroidism (1HPT) affects at least 1 in 1000 persons and its incidence rises with age, with a peak in the seventh decade (1, 2). The 1HPT risk is 5-fold higher in women than in men after 75 years of age, while it is comparable between sexes before 45 years of age (1). In the majority (i.e. 80-85%) of cases 1HPT is due to a single gland adenoma, with hyperplasia and parathyroid carcinoma accounting for the 10-15% and <1% of cases, respectively (2).

The 1HPT condition is characterized by hypercalcemia, increased urinary calcium excretion and inappropriately high or unsuppressed levels parathyroid hormone (3), and it may lead to osteoporosis, fragility fractures and kidney stones and, possibly, to an increased risk of cardiovascular events and neuro-psychological alterations (4). Besides these consequences, given the evidence of an increased cancer-related mortality in 1HPT (5, 6) and of the possible anti-apoptotic action of the parathyroid hormone (PTH) (7-9), in the past years some authors investigated the possibility of an increased risk of malignancies in this condition (5, 6, 10-18). Interestingly, cancer is now a known feature of chronic kidney disease, which is characterized persistently elevated PTH values (19).

However, while some studies found an increased risk of some malignancies, such as breast, skin, colon, thyroid and kidney cancer (10-16), other investigations were not able to find any association between 1HPT and malignant neoplasia (17, 18). These discordances are probably due to the different designs (i.e. retrospective or prospective), different settings (i.e. national registers- or population-based) and different inclusion criteria (i.e. all patients diagnosed with 1HPT or only surgically treated 1HPT patients) of the available studies. In addition, given that many studies were based on National Registers data, the origin of the 1HPT diagnosis was not reported. This is of utmost importance, since 1HPT is often asymptomatic and its diagnosis is frequently made in the context of routine exams. Therefore, it is not possible to exclude that the increased 1HPT prevalence, that has been described among patients with cancer in some studies, could have been related, in fact, to the increased number of biochemical investigations routinely performed in patients with neoplasia. Finally, a complete characterization of 1HPT patients regarding their disease activity, comorbidities and risk factors for cancer was lacking in all available studies, rendering the results scarcely comparable.

In order to overcome these pitfalls, we designed a study for comparing the occurrence of malignant neoplasia in patients referred to our "Osteoporosis and Metabolic Disease" outpatient clinic and subsequently diagnosed with or without 1HPT.

**Design of the study, patients and methods**

*Design of the Study and patients*

All Caucasian patients (n=1750, 1532 females, 218 males) referred to the "Osteoporosis and Metabolic Disease" tertiary care outpatient clinic since May 1st, 2014 to May 31st 2016 at Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico in Milan (Italy), for the first report of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels were considered eligible for the study. Since patients affected with osteoporosis may be referred to our outpatient clinic (a tertiary care center for the study of hyperparathyroidism and severe osteoporosis) even for the skeletal consequences of systemic diseases (20), some of which could *per se* influence the cancer risk, the study protocol was designed in order to avoid the foreseeable potential selection bias. Therefore it comprised the following exclusion criteria: I) the finding of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging or follow-up of malignancy; II) the patients' addressing for the need of the prescription of a bone-active drug in the context of aromatase inhibitors therapy, as recommended by our National Guidelines (21); III) the presence of neoplasia in the context of a previously identified familiar and/or hereditary syndrome (i.e. multiple endocrine neoplasia, hereditary breast or ovarian cancer) (22); IV) the presence of diabetes, obesity (i.e body mass index, BMI, ≥ 30 kg/m2), chronic liver diseases or other chronic disorders (i.e renal and hepatic transplant, chronic inflammation diseases) and/or substances and therapies (i.e glucocorticoids, immunosuppressants, alcohol abuse, external radiation) known to increase the cancer risk and/or calcium-phosphorous metabolism (23); V) the presence of heavy smoking habit (≥ 1 pack/day) (24). On the basis of these criteria, 144 patients (n=6, n=6, n=20, n=97 and n=15 fulfilling the criteria I, II, III, IV and V, respectively) did not entry the study, and eventually 1606 patients (1407 females, 199 males) were enrolled (Figure 1)

From all patients, the occurrence of malignant neoplasia during the 10 years prior the study inclusion was recorded. The diagnosis of cancer have been ascertained by verifying the medical reports. This length of

observational period of time has been decided since in 1HPT patients the diagnostic delay may be even of 10 years (25). In addition, from all patients we obtained information regarding the occurrence of fragility fractures (at spine, ribs, wrist, hip, and proximal humerus), cardiovascular events (i.e. myocardial infarction, stroke, transient ischemic attack, angina pectoris, pulmonary embolism, intracerebral hemorrhage, peripheral artery disease), hypertension and dyslipidemia during the 10 years prior the study inclusion. In all patients the diagnosis of osteoporosis or osteopenia was done on the basis of a dual X-ray absorptiometry (DXA) bone mineral density (BMD) assessment and/or of the occurrence of a fragility fracture (26, 27). Subjects were considered current smokers if they smoked more than 5 cigarettes/day and/or 10 packs/year (28).

All patients underwent the biochemical testing for osteoporosis suggested by both the protocol approved in our Centre (20) and our national Guidelines (29), including, in particular, serum calcium, albumin, phosphorous, creatinine, PTH, 25hydroxy-cholecalciferol (25OHVitD), 24-h urine calcium and creatinine excretion levels. All patients with increased albumin-adjusted serum calcium levels, confirmed at least twice, were tested for ionized serum calcium levels. Primary hyperparathyroidism was diagnosed in the presence of hypercalcemia and elevated or inappropriately normal PTH levels, after the evaluation of calcium clearance:creatinine clearance ratio, in order to rule out familial hypocalciuric hypercalcemia (30). Eventually 163 patients (148 females, 15 males) were found to be affected with 1HPT while 1443 (1259 females and 184 males) were not and were used as control group.

We reviewed the medical records preceding the study entry of all 1HPT patients. In 40 patients (37 females, 3 male, age 70.7±11.3 years) we found that the hypercalcemia was already present at least 5 years before the enrolment. In this subgroup of 1HPT patients we assessed the occurrence of malignancies during the period of time between the first finding of hypercalcemia and the study entry. These data were compared with those of 120 age-, and gender-matched subjects without 1HPT, who had been randomly selected from the whole group of control subjects.

The study complies with the Declaration of Helsinki and it has been approved by the Ethical Committee of Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, Milan, Italy. An informed consent has been obtained from each patient.

*Methods*

Serum and urinary calcium, albumin, and phosphate were measured by standard colorimetric techniques. Total calcium was corrected for serum albumin according to the formula: total calcium (mg/dL)+(4.4−albumin (mg/dL))*0.8 (31) (reference interval 8.4–10.2 mg/dl). Serum intact PTH levels were measured by a two-step automated sandwich chemiluminescent immunoassay (DiaSorin), with intra- and interassay coefficients of variation <10% (reference interval 6.5– 36.8 pg/mL). The serum 25OHVitD concentration was measured by radioimmunoassay (Diasorin), with intra and interassay of 7.2% and <12%, respectively (normal levels above 30 ng/mL).

Data regarding BMD were obtained by DXA scans at the spine and hip, performed at our Hospital (Hologic Discovery, Waltham MA, USA) at lumbar spine (LS; in vivo precision 1.0%), total femur (FT, in vivo precision 1.7%) and femoral neck (FN, in vivo precision 1.8%) in the 77% of patients and at other centers (Hologic Discovery and Lunar GE) in the 23% of patients. Conventional spinal radiographs in lateral and anteroposterior projection (T4–L4) were obtained at baseline in all subjects with standardized technique. Vertebral fractures were diagnosed on visual inspection using the semiquantitative visual assessment previously described by Genant and coauthors. (32).

*Statistical analysis*

Statistical analysis was performed by SPSS version 21.0 statistical package (SPSS, Inc.). The normality of distribution was checked by Kolmogorov–Smirnov test. The results are expressed as mean±standard deviation if not differently specified. The comparison of continuous variables between patients with and without 1HPT was performed using Student's t-test or Mann–Whitney U test, as appropriate. The categorical variables were compared by $\chi^2$ test.

The logistic regression analysis assessed the association between the 1HPT diagnosis and the presence of all neoplasia and of the neoplasia that were significantly more frequent in 1HPT patients than in controls, after adjusting for variables that might influence the cancer risk, such as, age, gender (as appropriate), low 25OHVitD levels and smoking habit.

Values of $p<0.05$ were considered significant.

**Results**

The clinical characteristics of the whole sample of patients (n=1606) are reported in table 1. During the 10 years prior the study entry, a malignant neoplasia occurred in 412 (26.2%) patients, with the breast, prostate and thyroid cancers being the most frequent ones. The other cancers occurred at colon, uterus, lung, kidney, skin, ovary, liver and pancreas in decreasing order. Breast and uterus cancer were reported only in female subjects.

A condition of 1HPT was found in 163 patients, while 1443 patients were not affected with 1HPT (Figure 1). Among these latter, 47 patients showed a secondary hyperparathyroidism (i.e. elevated PTH in the presence of frankly normal calcium levels) due to hypovitaminosis D. The comparisons between the clinical characteristics of patients with and without 1HPT are reported in table 2. Patients with and without 1HPT were comparable as far as age, gender, prevalence of hypertension, cardiovascular events, dyslipidemia and osteopenia or osteoporosis was concerned. The fragility fracture prevalence and the smokers were significantly more prevalent among patients without 1HPT. As expected, in 1HPT patients serum and urinary calcium, total alkaline phosphatase and PTH levels were higher, while phosphorous and 25OHVitD lower, than in patients without 1HPT. In 1HPT patients the overall occurrence of cancer and the occurrence of breast, kidney and skin cancer was significantly higher (1.7-, 1.8-, 8.3- and 6-fold increased, respectively) than in patients without 1HPT. For the other types of cancer a statistically significant difference was not found.

The period of time between the study entry and the occurrence of neoplasia was lower in patients with 1HPT (56.3±23.1 months, range 36-116 months) than in those without 1HPT (89.0±33.6 months, range 24-120 months). The prevalence of subjects in whom the neoplasia occurred at least 5 years before the study entry was higher in 1HPT patients (26/35, 74.3%) than in controls (40/179, 22.3%, $p < 0.0001$). In the 40 patients with 1HPT, in whom the hypercalcemia was already evident within 5 years before the study entry, the occurrence of neoplasia during this period of time tended to be higher (9/40 cases, 22.5%) than that in the 120 subjects without 1HPT randomly selected as controls (14/120 cases, 11.7%, $p=0.06$).

The logistic regression analysis showed that the occurrence of all neoplasia and of breast, skin and kidney neoplasia was significantly associated with the condition of 1HPT even after adjusting for age, gender (only for all cancers and skin cancer), smoking habit and hypovitaminosis D (table 3). Finally, in the

47 patients with secondary hyperparathyroidism, the prevalence of all cancers was comparable with that of patients with normal PTH levels (12.8% vs 12.4%) and reduced as compared with 1HPT patients (12.8% vs 21.5%, p=0.005).

**Discussion**

The present study shows that the occurrence of cancer, and in particular of breast, skin and kidney cancer is increased during the 10 years before the diagnosis of 1HPT even after adjusting for possible confounders such as age, gender, presence of hypovitaminosis D and smoking habit.

The previous studies investigating the occurrence of neoplastic diseases in 1HPT gave discordant results. Indeed, while some data suggested that the 1HPT condition could be associated with an increased risk of breast, skin, colon, thyroid and kidney cancer (10-16), others did not (17, 18). The limits of these investigations were related to their retrospective design and to the fact that the origin of the 1HPT and cancer diagnoses was not clearly reported. Therefore, the 1HPT diagnosis could have been done in the context of cancer staging or, *viceversa*, cancer diagnosis in the context of 1HPT workup. To overcome these pitfalls, in some of these studies the neoplasia that had occurred before the 1HPT diagnosis were excluded (11, 13). This, however, could have introduced a further bias, since in 1HPT patients the diagnostic delay may be even of 10 years (25). Finally, in all previous studies a complete characterization of subjects with and without 1HPT regarding their comorbidities and risk factors for cancer was lacking, rendering the finding of an increased cancer risk in 1HPT not clearly demonstrated.

The design of the present study consented us to overcome most of these pitfalls. Indeed, the inclusion criteria (i.e. the referral to our "Osteoporosis and Metabolic Disease" outpatient clinic) have been the same for patients with and without 1HPT. By excluding patients with the finding of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging or follow-up of malignancy, we avoided the risk that an increased 1HPT finding in patients with cancer could have been due to the increased number of exams performed in these patients. Similarly, the exclusion of patients with heavy smoking habit, diabetes, obesity and chronic disorders and/or therapies known to increase the cancer risk consented to avoid that a different occurrence of cancer in patients with and without 1HPT could be related to the different healthy status of the subjects included in the study.

In the present study the independent association between the all cancer occurrence and the female gender is probably related to high frequency of breast cancer. The high prevalence of 1HPT patients and the increased prevalence of smokers and of fractured patients among patients without 1HPT is not surprising. Indeed, in our tertiary care outpatient clinic patients are referred by their general practitioners generally for

an inadequate response to a bone-active drug and/or for the occurrence of a fragility fracture, which are both associated with the smoking habit (33), or for high calcium and/or PTH levels, while rarely for densitometric osteoporosis as unique reason. On the other hand, the finding that the prevalence of hypertension, dyslipidemia and cardiovascular events was comparable between patients with and without 1HPT somewhat confirms that the healthy status was similar between the two groups of patients. Therefore, in the absence of these possible confounding factors, the present study strongly suggests that the condition of 1HPT is associated with an increased occurrence of cancer, and, in particular, of breast, skin and kidney cancer, during the 10 years before the 1HPT diagnosis.

It is evident, however, that the cross-sectional design of the present study does not consent to draw conclusions about causality. In addition, we have no certain information about the temporal distance between the onset of the parathyroid disease and the appearance of the malignancy. However, in 1HPT patients the period of time between the diagnosis of cancer and of 1HPT was lower than in subjects without 1HPT and, at variance with these latter, in the majority of 1HPT patients the neoplasia occurred less than five years before the 1HPT diagnosis (Figure 2). Importantly, in the subgroup of 1HPT patients, in whom the hypercalcemia was already evident at least 5 years before the study entry, the occurrence of neoplasia during this period of time tended to be higher than in controls. Overall these findings are in keeping with the hypothesis of a relationship between the cancer and the 1HPT occurrence.

However, the possible role, if any, of PTH in the cancer development remains unclear. The fact that the cancer risk may persist even after the recovery from 1HPT is against the hypothesis of a causative role of the PTH excess in the cancer pathogenesis (13). In keeping, in the present study we found that patients with secondary hyperparathyroidism (i.e. with increased PTH levels together with normal calcium levels) did not show an increased occurrence of neoplasia as compared with patients with normal PTH and calcium levels. Even if we have no information regarding the length of the secondary hyperparathyroidism, that could have influenced the results, this finding is in keeping with a previous study suggesting that patients with secondary hyperparathyroidism had an insignificant overall cancer risk (11). In addition, a previous study suggested a possible role of the increased calcium level, in the breast cancer development (34). Overall, these data suggest that in 1HPT the increased calcium levels, rather than PTH levels, may act as a contributor in the cancer pathogenesis.

A limit of the present study is related to the lack of reliable data on the vitamin D status during the 10 years prior to diagnosis and even at the time of the study inclusion. Indeed, since our patients were mainly referred to our tertiary care center for osteoporosis and/or fragility fractures, we could not exclude that some of them were taking vitamin D supplements at the time of the diagnosis. This could explain the relatively low prevalence of secondary hyperparathyroidism in our sample. The lack of reliable information on vitamin D status in the patients may be of importance since hypovitaminosis D is associated with an increased risk of neoplasia (35) and in the 1HPT condition the 25OHVitD levels are often reduced (1-4), as suggested even by the present study. Notwithstanding these considerations, the association between the 1HPT condition and the increased occurrence of neoplasia has been confirmed even after adjusting for the vitamin D status.

A further possible explanation of the increased risk of neoplasia associated with 1HPT is that both these conditions could be related to the same genetic predisposition. For example, given the possible effect of vitamin D in influencing the cell proliferation, in particular at the parathyroid glands, it is not possible to exclude that vitamin D status and metabolism and some genetic polymorphic variations in vitamin D metabolism, may have played a role in inducing a predisposition to the development of both parathyroid and neoplastic cells (36).

Finally, even if patients with the most common risk factors for cancer (i.e. alcohol abuse, cancer-causing substances, chronic inflammation, immunosuppression, obesity, diabetes, radiation, tobacco abuse), have been excluded, there are a number of other factors that could influence the development of cancer (for example the dietary habits and the sun exposure), that have not been assessed.

Notwithstanding these limitations, the present study strongly suggest that during the 10 years prior the diagnosis of a 1HPT condition the occurrence of neoplasia, and in particular of breast, kidney and skin cancer, is increased.

**Declaration of interest**

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

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**Individual contributions**

Serena Palmieri: literature search, data collection and analysis, revision of the manuscript

Letizia Roggero: literature search, data collection and analysis, drafting of the manuscript

Elisa Cairoli: data analysis and interpretation, revision of the manuscript

Valentina Morelli: data analysis and interpretation, revision of the manuscript

Alfredo Scillitani: study design, data interpretation, revision of the manuscript

Iacopo Chiodini: study design, data analysis and interpretation, writing of the manuscript

Cristina Eller-Vainicher: study design, data interpretation, revision of the manuscript

All authors approved the final version of the manuscript and are accountable for all aspects of the work. The corresponding author (Iacopo Chiodini) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Legend to Figure 1**

**Title:** Design of the study

**Footnotes:** Exclusion Criteria: 1) the finding of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging or follow-up of malignancy; 2) the patients' addressing for the need of the prescription of an antifracture drug in the context of aromatase inhibitors therapy; 3) the presence of neoplasia in the context of a previously identified familiar and/or hereditary syndrome; 4) the presence of diabetes, obesity, chronic liver diseases or other chronic disorders and/or therapies and/or substances (i.e. glucocorticoids, immunosuppressants, alcohol, external radiation) known to increase the cancer risk; 5) the presence of heavy smoking habit (≥1 pack/day)

**Legend to Figure 2**

**Title:** Percentage of subjects with the occurrence of cancer within 5 years before the study entry among patients with cancer and primary hyperparathyroidism (1HPT) and controls with cancer.

The neoplasia occurred within 5 years before the study entry in the 74.3% of 1HPT patients with cancer and in the 22.3% of non-1HPT patients with cancer ($p < 0.0001$).

**Table 1:** Clinical characteristics of the whole sample of subjects included in the study

| | **All patients (n= 1606)** |
|---|---|
| **Age (years)** | 65.4 ± 11.0 (42-93) |
| **Gender (females)** | 1407 (87.6) |
| **Hypertension** | 450 (28.0) |
| **Cardiovascular events**[1] | 110 (6.8) |
| **Dyslipidemia** | 233 (14.5) |
| **Osteporosis**[2] | 1375 (85.6) |
| **Osteopenia**[3] | 209 (13.0) |
| **Fragility fractures**[4] | 1103 (68.7) |
| **Smokers** | 308 (19.2) |
| **Calcium (mg/dL)** | 9.6 ± 0.6 (8.1-13.2) |
| **Phosporous (mg/dL)** | 3.5 ± 0.6 (1.9-4.8) |
| **Parathyroid hormone (pg/mL)** | 34.4 ± 41.3 (9.4-806.0) |
| **24-h urine calcium (mg/day)** | 196.4 ± 119.9 (60-980.0) |
| **25OHVitamin D (ng/mL)** | 41.3 ± 18.9 (2.0-133.0) |
| **All cancers** | 214 (13.3) |
| **Breast cancer**[5] | 105 (7.5)[4] |
| **Prostate cancer**[6] | 7 (3.5)[5] |
| **Thyroid cancer** | 32 (2.0) |
| **Colon cancer** | 17 (1.1) |
| **Uterus cancer** | 13 (0.9) |
| **Lung Cancer** | 8 (0.5) |
| **Kidney Cancer** | 8 (0.5) |
| **Skin cancer** | 7 (0.4) |
| **Ovary cancer** | 4 (0.3)[4] |
| **Liver cancer** | 4 (0.2) |
| **Pancreas cancer** | 3 (0.2) |

The results are expressed as mean±SD or absolute number, with range or percentage in parentheses. [1]myocardial infarction, stroke, transient ischemic attack, angina pectoris, pulmonary embolism, intracerebral hemorrhage, peripheral artery disease. [2]Bone mineral density at any site expressed as T-score below -2.5 and/or presence of fragility fractures. [3]Bone mineral density at any site expressed as T-score between -1.0 and -2.0. [4]Clinical fragility fracture spine, ribs, wrist, hip, and proximal humerus and/or morphometric vertebral fractures. [5]Percentage in female patients. [6]Percentage in male patients. Smoker: patient who smokes more than 5 cigarettes/day and/or 10 packs/year

**Table 2**. Comparison between the clinical and biochemical characteristics and the prevalence of cancer in patients with 1HPT and without 1HPT

| | Patients with 1HPT (n=163) | Patients without 1HPT (n=1443) | p |
|---|---|---|---|
| **Age (years)** | 66.5 ± 12.4 (42-90) | 65.2 ± 10.8 (42-93) | 0.152 |
| **Gender (females)** | 148 (90.8) | 1259 (87.2) | 0.192 |
| **Hypertension** | 54 (33.1) | 396 (27.4) | 0.125 |
| **Cardiovascular events**[1] | 15 (9.2) | 95 (6.6) | 0.210 |
| **Dyslipidemia** | 20 (12.3) | 213 (14.8) | 0.392 |
| **Osteporosis**[2] | 123 (75.5) | 1252 (86.8) | 0.875 |
| **Osteopenia**[3] | 18 (11.0) | 191 (13.2) | 0.875 |
| **Fragility fractures**[4] | 83 (50.9) | 1020 (70.7) | 0.001 |
| **Smokers** | 10 (6.1) | 298 (20.7) | 0.001 |
| **Calcium (mg/dL)** | 10.7 ± 0.6 (10-13.2) | 9.5 ± 0.4 (8.1-10.4) | 0.001 |
| **Phosporous (mg/dL)** | 2.7 ± 0.5 (1.9-4.3) | 3.6 ± 0.5 (2.7-4.8) | 0.001 |
| **Parathyroid hormone (pg/mL)** | 124.2 ± 85.5 (30.0-806.0) | 24.3 ± 8.0 (9.4-134.0) | 0.001 |
| **24-h urine calcium (mg/day)** | 291.1 ± 157.5 (90.0-980.0) | 185.5 ± 109.8 (60.0-975.0) | 0.001 |
| **25OHVitamin D (ng/mL)** | 36.2 ± 17.7 (4.0-88.0) | 41.8 ± 18.9 (4.0-133.0) | 0.001 |
| **All cancers** | 35 (21.5) | 179 (12.4) | 0.001 |
| **Breast cancer**[5] | 18 (12.2) | 87 (6.9) | 0.021 |
| **Prostate cancer**[6] | 0 (0.0) | 7 (3.8) | 1.000 |
| **Thyroid cancer** | 6 (3.7) | 26 (1.8) | 0.104 |
| **Colon cancer** | 1 (0.6) | 12 (0.8) | 1.000 |
| **Uterus cancer** | 1 (0.7) | 12 (1.0) | 1.000 |
| **Lung Cancer** | 2 (1.2) | 6 (0.4) | 0.191 |
| **Kidney Cancer** | 4 (2.5) | 4(0.3) | 0.005 |
| **Skin cancer** | 3 (1.8) | 4(0.3) | 0.026 |
| **Ovary cancer** | 1(0.7) | 3 (0.2) | 0.359 |
| **Liver cancer** | 0 (0.0) | 4(0.3) | 1.000 |
| **Pancreas cancer** | 1 (0.6) | 2 (0.1) | 0.275 |

The results are expressed as mean±SD or absolute number, with range or percentage in parentheses. [1]myocardial infarction, stroke, transient ischemic attack, angina pectoris, pulmonary embolism, intracerebral hemorrhage, peripheral artery disease. [2]Bone mineral density at any site expressed as T-score below -2.5 and/or presence of fragility fractures. [3]Bone mineral density at any site expressed as T-score between -1.0 and -2.0. [4]Clinical fragility fracture spine, ribs, wrist, hip, and proximal humerus and/or morphometric vertebral fractures. [5]Percentage in female patients. [6]Percentage in male patients. Smoker: patient who smokes more than 5 cigarettes/day and/or 10 packs/year.

**Table 3.** Association between the presence of all cancer (panel A), skin cancer (panel B), kidney cancer (panel C) and breast cancer (panel D) with the presence of 1HPT, after adjusting for hypovitaminosis, smoking habit, gender and age.

| | Odds ratio | P value | 95% CI |
|---|---|---|---|
| **Panel A: All Cancer** | | | |
| **Age (1 year increase)** | 1.029 | 0.000 | (1.015-1.042) |
| **Female gender** | 1.837 | 0.031 | (1.058-3.191) |
| **Hypovitaminosis D (yes)** | 1.354 | 0.082 | (0.963-1.903) |
| **Smoker (yes)** | 1.066 | 0.742 | (0.729-1.558) |
| **1HPT diagnosis (yes)** | 1.928 | 0.002 | (1.270-2.929) |
| **Panel B: Skin Cancer** | | | |
| **Age (1 year increase)** | 1.013 | 0.682 | (0.952-1.037) |
| **Female gender** | 1.387 | 0.765 | (0.162-11.904) |
| **Hypovitaminosis D (yes)** | 3.368 | 0.270 | (0.389-21.192) |
| **Smoker (yes)** | 1.012 | 0.991 | (0.116-8.849) |
| **1HPT diagnosis (yes)** | 8.236 | 0.008 | (1.717-39.509) |
| **Panel C: kidney cancer** | | | |
| **Age (1 year increase)** | 1.025 | 0.429 | (0.964-1.091) |
| **Hypovitaminosis D (yes)** | 1.563 | 0.592 | (0.306-7.981) |
| **Smoker (yes)** | 1.035 | 0.975 | (0.120-8.928) |
| **1HPT diagnosis (yes)** | 9.184 | 0.003 | (2.155-38.825) |
| **Panel D: Breast cancer** | | | |
| **Age (1 year increase)** | 1.024 | 0.013 | (1.005-1.043) |
| **Hypovitaminosis D (yes)** | 1.432 | 0.139 | (0.890-2.306) |
| **Smoker (yes)** | 1.153 | 0.590 | (0.688-1.932) |
| **1HPT diagnosis (yes)** | 1.930 | 0.020 | (1.112-3.352) |

1HPT: primary hyperparathyroidism. Smoker: patient who smokes more than 5 cigarettes/day and/or 10 packs/year. Hypovitaminosis D: 25-hydroxy-vitamin D levels below 30 ng/mL

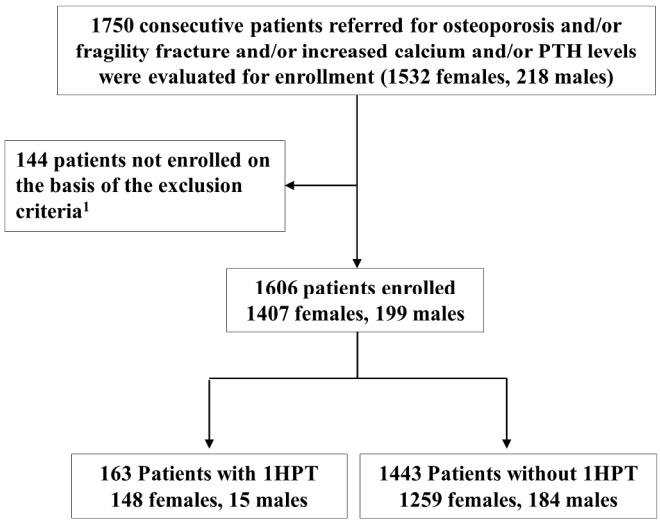


Figure 1: Design of the study
Exclusion Criteria: 1) the finding of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging or follow-up of malignancy; 2) the patients' addressing for the need of the prescription of an antifracture drug in the context of aromatase inhibitors therapy; 3) the presence of neoplasia in the context of a previously identified familiar and/or hereditary syndrome; 4) the presence of diabetes, obesity, chronic liver diseases or other chronic disorders and/or therapies and/or substances (i.e. glucocorticoids, immunosuppressants, alcohol, external radiation) known to increase the cancer risk; 5) the presence of heavy smoking habit (≥1 pack/day)

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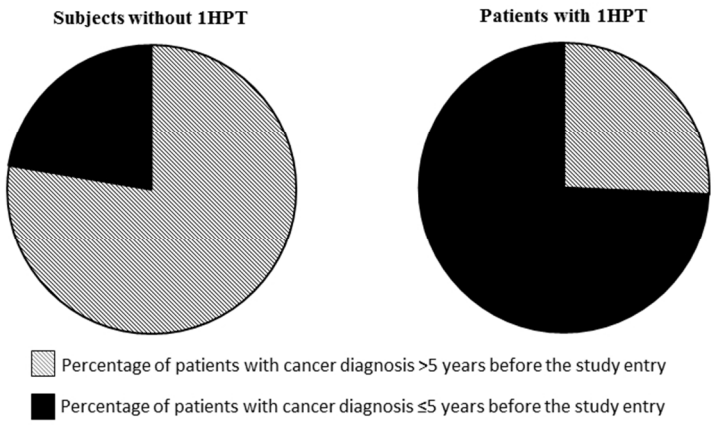


Figure 2: Percentage of subjects with the occurrence of cancer within 5 years before the study entry among patients with cancer and primary hyperparathyroidism (1HPT) and controls with cancer.
The neoplasia occurred within 5 years before the study entry in the 74.3% of 1HPT patients with cancer and in the 22.3% of non-1HPT patients with cancer (p <0.0001).

254x190mm (96 x 96 DPI)