

Occurrence of malignant neoplasia in patients with primary hyperparathyroidism

Journal:	<i>European Journal of Endocrinology</i>
Manuscript ID	EJE-17-0028
mstype:	Clinical Study
Date Submitted by the Author:	13-Jan-2017
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Keywords:	Primary hyperparathyroidism, malignancy, breast cancer, vitamin D

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Occurrence of malignant neoplasia in patients with primary hyperparathyroidism

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Short title: Cancer and primary hyperparathyroidism

Keywords: Primary hyperparathyroidism, malignancy, breast cancer, vitamin D

Word count: 3284

Number of figures/tables: 2/3

Disclosure Summary: Authors have nothing to disclose.

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20 **Abstract**

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

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

30 **Results:** 163 patients had 1HPT while 1443 had not. Patients with and without 1HPT were comparable for
31 age and gender. In 1HPT patients the occurrence of all, breast, kidney and skin cancer was significantly
32 higher (21.5%, 12.2%, 2.5%, 1.8%, respectively) than in patients without 1HPT (12.4%, 6.9%, 0.3%, 0.3%,
33 $p<0.05$ for all comparisons). The 1HPT presence was significantly associated with the occurrence of all
34 neoplasia and of breast, skin and kidney neoplasia (odds ratio, 95% confidence interval, P value: 1.93, 1.27-
35 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
36 adjusting for age, gender (as appropriate), smoking habit and vitamin D levels.

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

39 Introduction

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

45 The 1HPT condition is characterized by hypercalcemia, increased urinary calcium excretion and
46 inappropriately high or unsuppressed levels parathyroid hormone (3), and it may lead to osteoporosis,
47 fragility fractures and kidney stones and, possibly, to an increased risk of cardiovascular events and neuro-
48 psychological alterations (4). Besides these consequences, given the evidence of an increased cancer-related
49 mortality in 1HPT (5, 6) and of the possible anti-apoptotic action of the parathyroid hormone (PTH) (7-9), in
50 the past years some authors investigated the possibility of an increased risk of malignancies in this condition
51 (5, 6, 10-18). Interestingly, cancer is now a known feature of chronic kidney disease, which is characterized
52 persistently elevated PTH values (19).

53 However, while some studies found an increased risk of some malignancies, such as breast, skin,
54 colon, thyroid and kidney cancer (10-16), other investigations were not able to find any association between
55 1HPT and malignant neoplasia (17, 18). These discordances are probably due to the different designs (i.e.
56 retrospective or prospective), different settings (i.e. national registers- or population-based) and different
57 inclusion criteria (i.e. all patients diagnosed with 1HPT or only surgically treated 1HPT patients) of the
58 available studies. In addition, given that many studies were based on National Registers data, the origin of
59 the 1HPT diagnosis was not reported. This is of utmost importance, since 1HPT is often asymptomatic and
60 its diagnosis is frequently made in the context of routine exams. Therefore, it is not possible to exclude that
61 the increased 1HPT prevalence, that has been described among patients with cancer in some studies, could
62 have been related, in fact, to the increased number of biochemical investigations routinely performed in
63 patients with neoplasia. Finally, a complete characterization of 1HPT patients regarding their disease
64 activity, comorbidities and risk factors for cancer was lacking in all available studies, rendering the results
65 scarcely comparable.

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

69

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

71 *Design of the Study and patients*

72 All Caucasian patients (n=1750, 1532 females, 218 males) referred to the “Osteoporosis and
73 Metabolic Disease” tertiary care outpatient clinic since May 1st, 2014 to May 31st 2016 at Fondazione IRCCS
74 Cà Granda-Ospedale Maggiore Policlinico in Milan (Italy), for the first report of osteoporosis and/or fragility
75 fracture and/or increased calcium and/or PTH levels were considered eligible for the study. Since patients
76 affected with osteoporosis may be referred to our outpatient clinic (a tertiary care center for the study of
77 hyperparathyroidism and severe osteoporosis) even for the skeletal consequences of systemic diseases (20),
78 some of which could *per se* influence the cancer risk, the study protocol was designed in order to avoid the
79 foreseeable potential selection bias. Therefore it comprised the following exclusion criteria: I) the finding of
80 osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of
81 investigations for the staging or follow-up of malignancy; II) the patients’ addressing for the need of the
82 prescription of a bone-active drug in the context of aromatase inhibitors therapy, as recommended by our
83 National Guidelines (21); III) the presence of neoplasia in the context of a previously identified familiar
84 and/or hereditary syndrome (i.e. multiple endocrine neoplasia, hereditary breast or ovarian cancer) (22); IV)
85 the presence of diabetes, obesity (i.e body mass index, BMI, ≥ 30 kg/m²), chronic liver diseases or other
86 chronic disorders (i.e renal and hepatic transplant, chronic inflammation diseases) and/or substances and
87 therapies (i.e glucocorticoids, immunosuppressants, alcohol abuse, external radiation) known to increase the
88 cancer risk and/or calcium-phosphorous metabolism (23); V) the presence of heavy smoking habit (≥ 1
89 pack/day) (24). On the basis of these criteria, 144 patients (n=6, n=6, n=20, n=97 and n=15 fulfilling the
90 criteria I, II, III, IV and V, respectively) did not entry the study, and eventually 1606 patients (1407 females,
91 199 males) were enrolled (Figure 1)

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

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

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

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

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

120

121

122 *Methods*

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

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

138 *Statistical analysis*

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

144 The logistic regression analysis assessed the association between the 1HPT diagnosis and the presence of all
145 neoplasia and of the neoplasia that were significantly more frequent in 1HPT patients than in controls, after
146 adjusting for variables that might influence the cancer risk, such as, age, gender (as appropriate), low
147 25OHVitD levels and smoking habit.

148 Values of $p < 0.05$ were considered significant.

149 Results

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

155 A condition of 1HPT was found in 163 patients, while 1443 patients were not affected with 1HPT
156 (Figure 1). Among these latter, 47 patients showed a secondary hyperparathyroidism (i.e. elevated PTH in
157 the presence of frankly normal calcium levels) due to hypovitaminosis D. The comparisons between the
158 clinical characteristics of patients with and without 1HPT are reported in table 2. Patients with and without
159 1HPT were comparable as far as age, gender, prevalence of hypertension, cardiovascular events,
160 dyslipidemia and osteopenia or osteoporosis was concerned. The fragility fracture prevalence and the
161 smokers were significantly more prevalent among patients without 1HPT. As expected, in 1HPT patients
162 serum and urinary calcium, total alkaline phosphatase and PTH levels were higher, while phosphorous and
163 25OHVitD lower, than in patients without 1HPT. In 1HPT patients the overall occurrence of cancer and the
164 occurrence of breast, kidney and skin cancer was significantly higher (1.7-, 1.8-, 8.3- and 6-fold increased,
165 respectively) than in patients without 1HPT. For the other types of cancer a statistically significant difference
166 was not found.

167 The period of time between the study entry and the occurrence of neoplasia was lower in patients
168 with 1HPT (56.3±23.1 months, range 36-116 months) than in those without 1HPT (89.0±33.6 months, range
169 24-120 months). The prevalence of subjects in whom the neoplasia occurred at least 5 years before the study
170 entry was higher in 1HPT patients (26/35, 74.3%) than in controls (40/179, 22.3%, p <0.0001). In the 40
171 patients with 1HPT, in whom the hypercalcemia was already evident within 5 years before the study entry,
172 the occurrence of neoplasia during this period of time tended to be higher (9/40 cases, 22.5%) than that in the
173 120 subjects without 1HPT randomly selected as controls (14/120 cases, 11.7%, p=0.06).

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

177 47 patients with secondary hyperparathyroidism, the prevalence of all cancers was comparable with that of
178 patients with normal PTH levels (12.8% vs 12.4%) and reduced as compared with 1HPT patients (12.8% vs
179 21.5%, $p=0.005$).

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180 Discussion

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

184 The previous studies investigating the occurrence of neoplastic diseases in 1HPT gave discordant
185 results. Indeed, while some data suggested that the 1HPT condition could be associated with an increased
186 risk of breast, skin, colon, thyroid and kidney cancer (10-16), others did not (17, 18). The limits of these
187 investigations were related to their retrospective design and to the fact that the origin of the 1HPT and cancer
188 diagnoses was not clearly reported. Therefore, the 1HPT diagnosis could have been done in the context of
189 cancer staging or, *viceversa*, cancer diagnosis in the context of 1HPT workup. To overcome these pitfalls, in
190 some of these studies the neoplasia that had occurred before the 1HPT diagnosis were excluded (11, 13).
191 This, however, could have introduced a further bias, since in 1HPT patients the diagnostic delay may be even
192 of 10 years (25). Finally, in all previous studies a complete characterization of subjects with and without
193 1HPT regarding their comorbidities and risk factors for cancer was lacking, rendering the finding of an
194 increased cancer risk in 1HPT not clearly demonstrated.

195 The design of the present study consented us to overcome most of these pitfalls. Indeed, the
196 inclusion criteria (i.e. the referral to our “Osteoporosis and Metabolic Disease” outpatient clinic) have been
197 the same for patients with and without 1HPT. By excluding patients with the finding of osteoporosis and/or
198 fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging
199 or follow-up of malignancy, we avoided the risk that an increased 1HPT finding in patients with cancer
200 could have been due to the increased number of exams performed in these patients. Similarly, the exclusion
201 of patients with heavy smoking habit, diabetes, obesity and chronic disorders and/or therapies known to
202 increase the cancer risk consented to avoid that a different occurrence of cancer in patients with and without
203 1HPT could be related to the different healthy status of the subjects included in the study.

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

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

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

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

236 A limit of the present study is related to the lack of reliable data on the vitamin D status during the
237 10 years prior to diagnosis and even at the time of the study inclusion. Indeed, since our patients were mainly
238 referred to our tertiary care center for osteoporosis and/or fragility fractures, we could not exclude that some
239 of them were taking vitamin D supplements at the time of the diagnosis. This could explain the relatively low
240 prevalence of secondary hyperparathyroidism in our sample. The lack of reliable information on vitamin D
241 status in the patients may be of importance since hypovitaminosis D is associated with an increased risk of
242 neoplasia (35) and in the 1HPT condition the 25OHVitD levels are often reduced (1-4), as suggested even by
243 the present study. Notwithstanding these considerations, the association between the 1HPT condition and the
244 increased occurrence of neoplasia has been confirmed even after adjusting for the vitamin D status.

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

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

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

258 **Declaration of interest**

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

261

262 **Funding**

263 This research did not receive any specific grant from any funding agency in the public, commercial or not-
264 for-profit sector. No author has been paid by pharmaceutical companies or other agencies.

265

266 **Individual contributions**

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

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

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

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

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

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

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

274

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

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371 **Legend to Figure 1**372 **Title:** Design of the study

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

380

381 **Legend to Figure 2**

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

384 The neoplasia occurred within 5 years before the study entry in the 74.3% of 1HPT patients with cancer and
385 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 events¹	110 (6.8)
Dyslipidemia	233 (14.5)
Osteoporosis²	1375 (85.6)
Osteopenia³	209 (13.0)
Fragility fractures⁴	1103 (68.7)
Smokers	308 (19.2)
Calcium (mg/dL)	9.6 ± 0.6 (8.1-13.2)
Phosphorous (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 cancer⁵	105 (7.5) ⁴
Prostate cancer⁶	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.

¹myocardial infarction, stroke, transient ischemic attack, angina pectoris, pulmonary embolism, intracerebral hemorrhage, peripheral artery disease. ²Bone mineral density at any site expressed as T-score below -2.5 and/or presence of fragility fractures. ³Bone mineral density at any site expressed as T-score between -1.0 and -2.0. ⁴Clinical fragility fracture spine, ribs, wrist, hip, and proximal humerus and/or morphometric vertebral fractures. ⁵Percentage in female patients. ⁶Percentage 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 events¹	15 (9.2)	95 (6.6)	0.210
Dyslipidemia	20 (12.3)	213 (14.8)	0.392
Osteoporosis²	123 (75.5)	1252 (86.8)	0.875
Osteopenia³	18 (11.0)	191 (13.2)	0.875
Fragility fractures⁴	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
Phosphorous (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 cancer⁵	18 (12.2)	87 (6.9)	0.021
Prostate cancer⁶	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.

¹myocardial infarction, stroke, transient ischemic attack, angina pectoris, pulmonary embolism, intracerebral hemorrhage, peripheral artery disease. ²Bone mineral density at any site expressed as T-score below -2.5 and/or presence of fragility fractures. ³Bone mineral density at any site expressed as T-score between -1.0 and -2.0. ⁴Clinical fragility fracture spine, ribs, wrist, hip, and proximal humerus and/or morphometric vertebral fractures. ⁵Percentage in female patients. ⁶Percentage 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

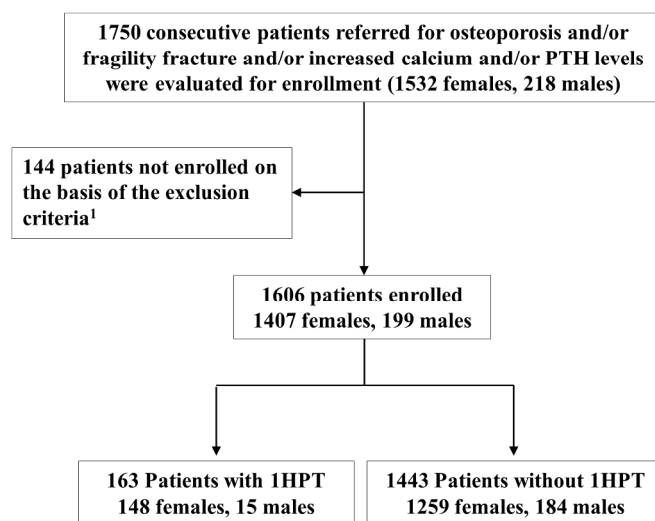


Figure 1: Design of the study

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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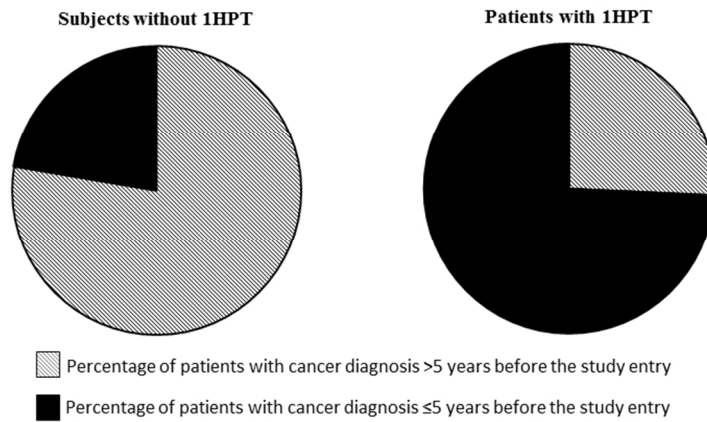


Figure 2: Percentage of subjects with the occurrence of cancer within 5 years before the study entry among patients with cancer and primary hyperparathyroidism (1HPT) and controls with cancer. The neoplasia occurred within 5 years before the study entry in the 74.3% of 1HPT patients with cancer and in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

254x190mm (96 x 96 DPI)