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Original Article

Occurrence of malignant neoplasia in patients with primary hyperparathyroidism

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ABSTRACT

Introduction: The association between primary hyperparathyroidism (1HPT) and cancer is debated. The present study was aimed to investigate the occurrence of neoplasia in 1HPT.
Patients and 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: One-hundred-sixty-three 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.
Conclusion: During the 10 years prior the diagnosis of 1HPT, the occurrence of all, breast, skin and kidney neoplasia is increased.

1. 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, normal or increased urinary calcium excretion and increased or inappropriately normal levels parathyroid hormone [3], and it may be associated with 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

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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.

2. Design of the study, patients and methods

2.1. 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/m^2), 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 (Fig. 1).

From all patients, the occurrence of malignant neoplasia during the 10 years prior the study inclusion was recorded. The diagnosis of cancer has been ascertained by verifying the medical reports. This length of observational period of time has been decided since in about 66% of 1HPT patients the diagnostic delay may vary from few months to even 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 presence of osteoporosis or osteopenia was ascertained 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 albumin-adjusted serum calcium levels equal to or above 10 mg/dL, 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 [30,31].

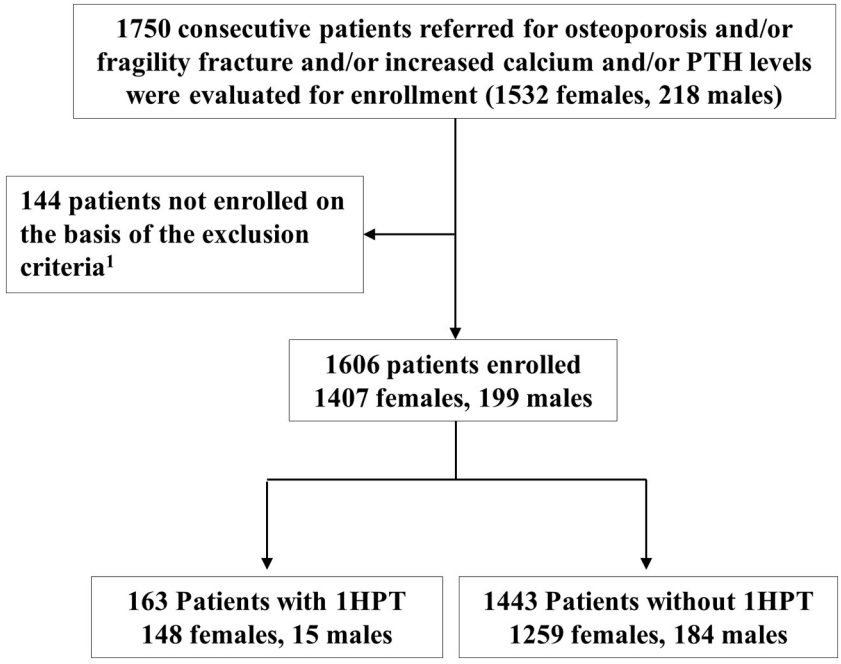

Fig. 1. Design of the study. Exclusion criteria: 1) the finding of osteoporosis and/or fragility fracture and/or increased calcium and/or PTH levels in the context of investigations for the staging or follow-up of malignancy; 2) the patients' addressing for the need of the prescription of an antifracture 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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