The association between primary hyperparathyroidism and malignancy: nationwide cohort analysis on cancer incidence after parathyroidectomy

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Abstract

In order to evaluate the link between primary hyperparathyroidism (pHPT) and malignancies, cases subjected to parathyroid adenomectomy (PTX) during 1958–1997 in Sweden were identified by analyzing the National Swedish Cancer Registry. To minimize the influence of confounding by detection, cases with malignant disease diagnosed before or at the same time as pHPT or during the first year after PTX were excluded. Altogether 9782 cases (7642 \textsuperscript{1}) were included and followed for up to 40 years. Thus, the study comprises 89 571 person-years of observation. The incidence of malignancies was compared with that in the Swedish population standardized for age, sex, and calendar year. An increased overall incidence of cancer was demonstrated in both genders (standardized incidence ratio (SIR) 1.43, 95% confidence interval (CI) 1.35–1.52). This remain unchanged beyond 15 years after PTX. Breast cancer contributed a quarter of the cancer incidence in women (SIR 1.44, 95% CI 1.25–1.62). An increased risk of kidney (SIR 2.40, 95% CI 1.72–3.25), colonic (SIR 1.46, 95% CI 1.19–1.77), and squamous cell skin cancer (SIR 2.79, 95% CI 2.25–3.43) was found in both genders. The risk of endocrine and pancreas cancer was increased in the minority of patients who had their PTX before the age of 40. We conclude that pHPT is associated with an increased risk of developing malignancies that persists even after PTX. This suggests a causal disassociation with the biochemical derangements caused by parathyroid adenoma, while potentially common etiological mechanisms may include genetic predisposition or acquired disability to withstand environmental influence.

Introduction

Primary hyperparathyroidism (pHPT) has been associated with various malignancies, as well as with premature death in malignant disorders (Palmer et al. 1988, Hedback et al. 1990, Pickard et al. 2002, Michels et al. 2004, Nilsson et al. 2004, Backlund et al. 2005). Predisposing genetic and environmental risk factors have been suggested but the association between pHPT and malignancies has not been confirmed by all investigators (Wermers et al. 1998, Soreide et al. 1997). It is still unclear whether the excessive risk relates to pHPT in general or only to severe disease and whether it concerns malignancy in general or specific cancer forms. Furthermore, 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 parathyroid adenectomy (PTX). More insight into these matters is important since pHPT is an endocrine disease that affects about 1% of the adult population, predominantly postmenopausal women (Lundgren et al. 1997). Identification of certain risk factors could be of assistance in the management of pHPT. A total of 85% pHPT patients have a single parathyroid adenoma. In the remaining 15%, all four glands may be involved. The aim of the present study was to analyze the association between parathyroid adenoma and cancer, including differences by age, sex or time period, in a population-based setting.
by using the Swedish Cancer Registry, to which all patients operated for parathyroid adenomas are reported since 1958.

Materials and methods

The Swedish Cancer Registry has been in function since 1958 and all malignancies have to be reported by both the treating physician and the pathologist or cytologist who establishes the diagnosis. Besides malignancies, there are a few benign tumors, including parathyroid adenomas, for which reporting is also compulsory. Parathyroid hyperplasia is not reported to the registry. The completeness of the Swedish Cancer Registry has been assessed to be around 97% (Mattsson & Wallgren 1984), although no specific validation has been made for parathyroid adenomas.

The available information in the Swedish Cancer Registry includes date of diagnosis, type of malignancy, and a personal identifier (the National Registration Number assigned to all Swedish residents), which denotes the year, month and day of birth, and sex. All individuals reported to the Swedish Cancer Registry from 1958 through 1997 were included. The seventh revision of the International Classification of Diagnoses (ICD-7) was used, including codes 140–209. The National Registration Number enabled us to identify all the subsequent malignancies occurring among patients with a prior diagnosis of parathyroid adenoma. To minimize the bias of confounding by diagnosis, all cases with malignant disease detected before or at the same time as pHPT or during the first year after PTX were excluded. Altogether 9782 individuals were identified. The numbers of patients included in the cohort in the different time periods are presented in Table 1 and the age distribution of the cohort in Table 2. Linkage to the Swedish Death Registry and the Emigration Registry enabled us to determine for how long any given individual was at risk of developing malignancy. Follow-up was from January 1, 1958 to December 31, 1997.

The number of person-years at risk was calculated from the date of entry into the cohort up to the diagnosis of malignancy (including a possible second operation for parathyroid adenoma), death, emigration, or end of follow-up (December 31, 1997). A standardized incidence ratio (SIR) was calculated as the ratio of the observed number of malignancies to that expected in the entire Swedish population, standardized for age, gender, and calendar year. A 95% confidence interval (CI) of SIR was calculated on the assumption that the observed number follows a Poisson distribution (Breslow & Day 1987). Various stratification studies were conducted, which include age and calendar year at entry, the duration of follow-up, attained age, gender, and various interactions.

Results

The cohort of 9782 patients undergoing PTX for single parathyroid adenoma during 1958–1997 was dominated by women (n = 7642♀, 2140♂, Table 1). At the time of PTX, most patients were over 60 years of age (n = 5811, 59%) and just a small proportion (n = 698, 7%) were under 40. The cohort was followed for a total of 89 571 person-years.

The overall incidence of subsequent malignancies was higher among cases (SIR 1.43, 95% CI 1.35–1.52) compared with the general population beyond the first postoperative year at all ages and for both sexes (Tables 1–3). This increased risk still held after exclusion of breast cancer (ICD-170), which contributed a quarter of the cancer incidence in women. The increased incidence of colonic cancer (ICD-153) came from patients over 60 years of age. An increased risk of breast cancer, non-melanoma skin cancer (ICD-191), and renal parenchyma cancer (ICD-180) was identified in cases over 40 years of age at PTX (Table 4). Among the minority of patients who had PTX before the age of 40, there was an increased risk of endocrine cancer (malignant neoplasm of endocrine glands other than

Table 1 Parathyroid adenoma cohort by calendar year with total number of individuals registered (TN), observation time in person-years (py), number (n), and standard incidence ratio (SIR) with 95% confidence interval (CI) of individuals with a malignant diagnosis registered 1 year or more after parathyroidectomy

<table>
<thead>
<tr>
<th>Year</th>
<th>TN</th>
<th>py</th>
<th>n</th>
<th>SIR</th>
<th>CI 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958–1964</td>
<td>171</td>
<td>3170</td>
<td>50</td>
<td>2.19</td>
<td>1.62–1.88</td>
</tr>
<tr>
<td>1965–1974</td>
<td>1538</td>
<td>24271</td>
<td>303</td>
<td>1.44</td>
<td>1.28–1.61</td>
</tr>
<tr>
<td>1975–1985</td>
<td>3078</td>
<td>36869</td>
<td>483</td>
<td>1.39</td>
<td>1.27–1.52</td>
</tr>
<tr>
<td>1985–1997</td>
<td>4995</td>
<td>25260</td>
<td>349</td>
<td>1.42</td>
<td>1.28–1.58</td>
</tr>
<tr>
<td>1998–2007</td>
<td>9782</td>
<td>89570</td>
<td>1185</td>
<td>1.43</td>
<td>1.35–1.52</td>
</tr>
</tbody>
</table>

Table 2 The parathyroid adenoma cohort by age distribution, total number of individuals registered (TN), observation time in person-years (py), number (n), and the standard incidence ratio (SIR) with 95% confidence interval (CI) of individuals with a malignancy registered 1 year or more after parathyroidectomy

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>TN</th>
<th>py</th>
<th>n</th>
<th>SIR</th>
<th>CI 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40</td>
<td>698</td>
<td>9658</td>
<td>56</td>
<td>2.44</td>
<td>1.84–3.26</td>
</tr>
<tr>
<td>40–60</td>
<td>3273</td>
<td>38984</td>
<td>423</td>
<td>1.42</td>
<td>1.29–1.56</td>
</tr>
<tr>
<td>60+</td>
<td>5811</td>
<td>40930</td>
<td>706</td>
<td>1.39</td>
<td>1.29–1.50</td>
</tr>
</tbody>
</table>
the thyroid, ICD-195) and pancreas cancer (ICD-157). No increased incidence of thyroid cancer (ICD-194) was found. The risk of cancer was still increased beyond 15 years after PTX (Table 5).

**Discussion**

Very little is known about the underlying causes of a sporadic parathyroid adenoma. In less than 1%, the disease is a part of hereditary disorders, such as multiple endocrine neoplasia involving genes on chromosome 11q and 10q and the gene for the HPT jaw tumor syndrome on 1p (Koch et al. 2001, Chen et al. 2003, Skogseid 2003). The majority of cases are of non-familial origin and in 85% the disorder stems from a single parathyroid adenoma.

Since the 1960s, there have been several reports on an association between pHPT and malignancies and an increased risk of premature death (Dent & Watson 1964, Palmer et al. 1988, Hedback et al. 1990, Michels et al. 2004, Nilsson et al. 2004, Backlund et al. 2005). However, the data have been conflicting. In two studies from North America, long-term survival in pHPT was not decreased and in one study the overall survival was even better than expected (Soreide et al. 1997, Wermers et al. 1998). The strength of our study lies in the large number of identified subjects during the specified time period and the completeness of the Swedish Cancer Registry. The explored cohort of patients subjected to extirpation of histologically verified parathyroid adenoma was followed for up to 40 years. A cohort of this size is necessary to achieve sufficient statistical power to assess risks and the possible influence of PTX. A potential weakness is the inclusion of only surgically treated pHPT, which does not reflect the entire pHPT population in Sweden. The available data in the registries are limited and hospital records for individual patients would need to be analyzed to obtain relevant information about the degree of hypercalcemia and the type of symptoms. There may be a selection of patients with an advanced stage of disease, especially among cases registered before the introduction of automated methods for serum calcium measurement in the mid-1970s. However, most of the cases (n=8073) in the cohort were registered after 1975 and in recent decades.

**Table 3** Standard incidence ratio (SIR) with 95% confidence interval (CI) and incidence of malignant (n) 1 year or more after parathyroidectomy by sex and ICD-related disease (ICD-7)

<table>
<thead>
<tr>
<th>Gender</th>
<th>All malignancies</th>
<th>Breast cancer</th>
<th>Large intestine cancer</th>
<th>Non melanoma skin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR</td>
<td>CI 95</td>
<td>n</td>
</tr>
<tr>
<td>♂♂</td>
<td>909</td>
<td>1.46</td>
<td>1.36–1.56</td>
<td>220</td>
</tr>
<tr>
<td>♀♀</td>
<td>276</td>
<td>1.36</td>
<td>1.20–1.53</td>
<td>0</td>
</tr>
</tbody>
</table>

- Renal parenchyma cancer
- Pancreatic cancer
- Endocrine cancer excluding thyroid
- Thyroid cancer

**Table 4** Standard incidence ratio (SIR) with 95% confidence interval (CI) and number of observations (n) 1 year or more after parathyroidectomy for malignancy (n) 1 year or more after parathyroidectomy by age and ICD-related disease (ICD-7)

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>All malignancies</th>
<th>Breast cancer</th>
<th>Large intestine cancer</th>
<th>Non melanoma skin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR</td>
<td>CI 95</td>
<td>n</td>
</tr>
<tr>
<td>20–40</td>
<td>56</td>
<td>2.44</td>
<td>1.84–3.16</td>
<td>10</td>
</tr>
<tr>
<td>40–60</td>
<td>423</td>
<td>1.42</td>
<td>1.29–1.56</td>
<td>84</td>
</tr>
<tr>
<td>60+</td>
<td>706</td>
<td>1.39</td>
<td>1.29–1.50</td>
<td>126</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Renal parenchyma cancer</th>
<th>Pancreatic cancer</th>
<th>Endocrine cancer excluding thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR</td>
<td>CI 95</td>
</tr>
<tr>
<td>20–40</td>
<td>0</td>
<td>0.00</td>
<td>0.00–7.35</td>
</tr>
<tr>
<td>40–60</td>
<td>22</td>
<td>3.14</td>
<td>1.97–4.75</td>
</tr>
<tr>
<td>60+</td>
<td>19</td>
<td>1.98</td>
<td>1.19–3.09</td>
</tr>
</tbody>
</table>
even mild pHPT has been surgically treated to a large degree (Hedback et al. 1995, Lundgren et al. 1997, Valdemarsson et al. 1998, Hagstrom et al. 2002). Indeed, in the present registry, 12% of the patients had a normal calcium level the day before PTX (Bergenfelz et al. 2003).

Another weakness may be the validity of the data in the nationwide registries and the risk of misclassification. In a paper by Hedback & Oden (2003), 754 cases from the Swedish cohort of surgically treated pHPT that were registered with a single adenoma at the first operation, were studied regarding recurrence of pHPT. Of these, re-operation due to a second single adenoma was performed in only 5/754 (0.7%). Thus, extrapolated to the present study, around 65 patients (0.7%) could potentially have been registered twice for parathyroid adenoma. This low number would not influence our results. Some patients with a true adenoma may not have been recorded because they were judged to have parathyroid hyperplasia, just as some with parathyroid hyperplasia may have been classified as having an adenoma. The rate of this misclassification is not known. However, since only a minority of patients were under 40 years of age at PTX and the stratified analyses by age at diagnosis showed an increased risk in all age groups, confounding due to inclusion of hereditary forms of pHPT in the present cohort should be a minor problem. Moreover, renal dysfunction leading to hypercalcemic hyperparathyroidism is usually clinically evident, and very rarely accompanied by single parathyroid adenoma.

The key findings include verification of an increased risk of malignancies following treatment of pHPT, which applied to the entire period, both sexes, all age groups and persisted beyond 15 years after PTX. Certain cancer forms were clearly overrepresented, for example, breast cancer, large intestine cancer, renal cancer, and squamous cell skin cancer. It was already observed in the 1970s that pHPT should be considered in patients with diagnosed cancer and hypercalcemia (Samaan et al. 1976). With today’s sensitive methods for parathyroid hormone determination, the presence of levels inappropriately elevated in relation to the level of calcium is diagnostic for pHPT.

Breast cancer contributed a quarter of the malignancies in women. An increased frequency of parathyroid adenoma has been documented in patients treated for breast cancer, as well as a simultaneous occurrence of breast cancer diagnosed after PTX (Katz et al. 1970, Palmer et al. 1988, Fierabracci et al. 2001, Michels et al. 2004). It was also reported that breast cancer patients without evidence of pHPT had significantly higher serum calcium and parathyroid hormone levels (unrelated to clinical staging or anti-tumor therapy) compared with healthy controls (Fierabracci et al. 2001). The association reported earlier between parathyroid adenoma and thyroid cancer was not confirmed in this study (Hickey et al. 1991; Table 3). A simultaneous occurrence of thyroid cancer may be a detection bias. To minimize this bias of confounding in the present study, all cases with malignant diseases detected at the same time as pHPT or during the first year after PTX were excluded (Palmer et al. 1987). Interestingly, patients below 40 years of age had a higher incidence of endocrine-related cancer (malignant neoplasm of endocrine glands other than the thyroid) and pancreatic cancer, which may reflect that some male patients were falsely included in the cohort. However, the number of cases was too small to permit further analysis.
With the available data, we can only speculate about possible etiologic risk factors, and various genetic and/or environmental factors may contribute to the correlation between pHPT and certain malignancies. The risk does not seem to be linked to the biochemical derangements caused by parathyroid adenoma, since it was similar during the entire period and persisted beyond 15 years after PTX. Being overweight seems to be a risk factor for cancer at several organ sites, including the malignancies that were overrepresented in our study, except for squamous cell skin cancer (Bianchini et al. 2002, Bolland et al. 2004). Vitamin D regulation may be a key factor in the link between pHPT and elevated cancer risk. Vitamin D receptors (VDR) are expressed in the intestine, bone, kidney, and parathyroid glands. VDR are also expressed in most immune cell types and in most breast, colonic, and skin cancer cell lines (Bikle et al. 2005, Giovannucci 2005). The active metabolite of vitamin D3 (1,25-(OH)2D3) has anti-proliferative, prodifferentiative, and immunomodulatory effects, besides the traditional calcium-related effects (Giovannucci 2005). A genetic predisposition due to disturbances in the VDR alleles may cause impaired regulation of parathyroid glands as well as defective apoptosis and increased incidence of preneoplastic lesions (Carling et al. 1998, 2000, Giovannucci 2005). In this context, the link between pHPT and squamous skin cancer may seem intriguing. The incidence is linked to u.v.-light exposure but 1,25(OH)2D3 may also be involved in the regulation of the differentiation of keratinocytes (Bikle et al. 2005).

The present study confirms the earlier findings of a connection between pHPT and certain malignancies. Since this risk continues unchanged 15 years after PTX and beyond, the association seems to be unrelated to the biochemical disturbances caused by pHPT. It remains to be elucidated whether the risk is due to genetic predisposition to tumor development as such, or if there is a physiological associative effect, intrinsic or environmental.

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References


