

Hyperparathyroidism and Subsequent Cancer Risk in Denmark

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BACKGROUND. There is increasing evidence that hyperparathyroidism (HPT), a condition that leads to elevated serum calcium levels, is associated with endocrine and other malignancies, suggesting a possible causal link between HPT and carcinoma.

METHODS. To investigate the relation of HPT to subsequent cancer risk, the authors conducted a record-linkage study among 2425 patients who were diagnosed with HPT in Danish hospitals. Patients were identified in hospital discharge records, and records were then linked with the Danish National Cancer Registry for the years 1977–1993 to identify cancer incidence. To estimate cancer risk, standardized incidence ratios (SIRs) were computed.

RESULTS. After excluding patients who were diagnosed in the first year of follow-up, a total of 219 malignancies were observed, resulting in an SIR of 1.25 (95% confidence interval [95%CI], 1.1–1.4). Cancer risk among women was higher than among men. Among those with primary (idiopathic) HPT, hematopoietic malignancies were elevated significantly (SIR, 1.88; 95%CI, 1.0–3.2; based on 13 patients), with the excess derived primarily from 4 observed patients with multiple myeloma. Patients with secondary HPT had an insignificantly increased risk of overall cancers. Patients who were diagnosed with other or unspecified types of HPT had significant increases in carcinoma of the urinary tract (SIR, 2.71; 95%CI, 1.2–5.3; based on 8 patients) and carcinoma of the thyroid gland (SIR, 21.19; 95%CI, 4.3–61.9; based on 3 patients).

CONCLUSIONS. Future studies should monitor whether specific endocrine alterations associated with HPT may affect the long-term risk of hematopoietic, thyroid, and urinary tract carcinomas. *Cancer* 2002;95:1611–7.

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Hyperparathyroidism (HPT) is defined by overproduction of the parathyroid hormone, which regulates serum calcium levels, thus leading to hypercalcemia. The incidence of primary, or idiopathic, HPT is approximately 28 per 100,000 population, with a female-to-male ratio of 2:1, and it occurs most frequently in women age \geq 60 years, for whom the prevalence is estimated at 2 per 1000 population.¹ In about 85% of patients with primary HPT, the condition is the result of adenoma in one or more of the four parathyroid glands, whereas the remaining patients have HPT that is attributable mostly to multiple tumors. Secondary and tertiary HPT also can occur. Secondary HPT is the result of biochemical conditions (low serum calcium), which chronically stimulate the parathyroid gland to increase the production of parathyroid hormone; tertiary HPT is the continued,

chronic overproduction of parathyroid hormone once the biochemical stimulus of low calcium has been resolved.

Parathyroid adenomas can occur with a complex of other malignancies in one of two hereditary conditions known as multiple endocrine neoplasia 1 (MEN1) and MEN2. MEN1 usually is characterized by parathyroid tumors as well as enteropancreatic and anterior pituitary tumors, and it occurs in approximately 3–20 per 100,000 population. In the less common MEN2, parathyroid tumors can be accompanied by medullary thyroid carcinomas and pheochromocytomas.²

Increasing evidence suggests a possible common biochemical link between HPT and the risk of developing malignant disease outside of a hereditary pathway. In early studies on the topic, significant correlations were found between parathyroid adenomas and previous, concurrent, and subsequent gastrointestinal, breast, thyroid, genitourinary, and respiratory malignancies³ as well as nonmedullary thyroid carcinomas.⁴ Later cohort studies addressed the hypotheses that either the biologic correlates of HPT or the associated hypercalcemia may be associated with an increased risk of developing malignant disease. A prospective study in the late 1980s using the Swedish National Cancer Registry followed a cohort of 4163 patients who underwent surgery for HPT for up to 22 years and found higher than expected rates of malignant disease.⁵ After eliminating patients who were diagnosed during the first year of follow-up, a 40% increased risk of malignancy was observed, with excesses seen for gastrointestinal, endocrine, kidney, and breast carcinoma. However, conflicting evidence of the association between HPT and carcinoma does exist. In a population-based study in Rochester, Minnesota, that followed 435 patients with HPT over a 28-year period, carcinoma and cardiovascular mortality were significantly lower than expected.⁶ Screening techniques may have allowed detection of patients with milder HPT in that study. It was notable that patients in the highest quartile of serum calcium levels had significantly higher overall mortality rates compared with patients in the lower three quartiles.

To investigate further the correlation of HPT to the subsequent risk of developing carcinoma, we conducted a record linkage study among patients with hospital-diagnosed HPT in Denmark. Patients were identified from hospital discharge records and were linked to the Danish National Cancer Registry using personal identification (ID) numbers.

MATERIALS AND METHODS

The Hospital Discharge Register, a nationwide registry of hospital discharges for Denmark covering the years

1977–1993, was used to identify patients who were hospitalized for HPT.⁷ Each record in the Register includes the population ID number (a unique identifier assigned to every Danish citizen and to noncitizens who hold residence permits), dates of admission and discharge for the hospitalization, codes for surgical procedures performed, and up to 20 discharge diagnoses. Discharge diagnoses were coded according to a Danish version of the International Classification of Diseases (ICD-8).⁸ A total of 2817 patients who had one or more discharges for HPT (ICD-8 code 252.00-09) were identified.

The population ID number was used to link the roster of individuals ascertained from the Discharge Register with the Central Population Register file to obtain information about vital status and validity of the ID number. After the linkage was performed, 83 patients were excluded because of death before hospital discharge, 16 patients were excluded due to invalid ID numbers, and 8 patients were excluded because of foreign residency. Thus 2710 patients remained in the cohort. The roster was linked with records of the Danish Cancer Registry for the years 1977–1993 to identify cancer incidence. The Cancer Registry was established in 1942, and the reporting of cancer to the Registry is mandated by law.⁹ Because malignancies that are diagnosed during the first year of follow-up may reflect surveillance bias, analyses included only patients with disease that was diagnosed after this period; 2425 patients had follow-up > 1 year. A total of 14,703 person-years (PY) were accumulated beginning with the first day of the month after 1 year after the first hospital discharge for HPT and continuing until the earlier of 1) the date of death, 2) the date of emigration, or 3) the end of the study (December 31, 1993). Multiple tumors per patient were recorded.

Expected numbers of diagnosed malignancies were calculated based on Danish multiple cancer incidence rates and the observed distribution of PY, with adjustment for gender, age, and calendar year (in 5-year intervals). The standardized incidence ratio (SIR) was estimated as the number of malignancies observed divided by the number expected. The 95% confidence interval (95%CI) for each SIR was calculated based on the assumption that the observed number was distributed as a Poisson random variable.

ICD diagnosis codes for HPT delineate primary HPT, secondary HPT, and *other* or *unspecified* causes of HPT, including hyperparathyroid crisis, generalized osteitis fibrosa cystica, nephrocalcinosis from hyperparathyroidism, and hyperparathyroidism otherwise defined or unspecified. Because the clinical significance of these conditions can be very different, we

stratified most analyses by primary HPT (ICD8 252.00 and 252.01), secondary HPT (ICD8 252.02), or other HPT (ICD8 252.03, 252.04, 252.05, 252.08, and 252.09). Because parathyroid surgery is used mainly to treat patients with primary HPT and not other HPT types, patients with one of the other HPT ICD8 codes who also underwent parathyroid surgery were classified with primary HPT for the purposes of this study. These patients were switched from other HPT to primary HPT at the time they underwent parathyroid surgery, with PY before surgery contributing to the category *other HPT* and PY after surgery contributing to the category *primary HPT*.

An analysis of the cancer incidence for the entire cohort was undertaken first. Subsequent analyses were conducted separately for patients with primary HPT, secondary HPT, and other HPT. These analyses were stratified by gender, age, whether patients had ever undergone parathyroid surgery, whether HPT was the only discharge diagnosis in the initial HPT hospitalization, whether patients had been hospitalized for HPT only once or more frequently, and time from the initial diagnosis of HPT to the initial diagnosis of malignant disease (latency). For analysis by hospitalization, PY after the first hospitalization and before the second hospitalization for HPT were allocated to the first hospitalization stratum. PY accumulation starting from the date of the second HPT hospitalization was allocated to the *two or more hospitalizations* category.

RESULTS

In total, 1767 patients (72.9%) in the study were females, and 658 patients (27.1%) were males. The average age at which patients were diagnosed with HPT was 58.2 years (range, 0–95 years), and the average age at which patients first were diagnosed with malignant disease was 67.2 years (range, 2–101 years). There were 1643 patients (67.8%) with primary HPT, 1044 of these patients diagnosed with primary HPT, and 599 patients diagnosed with other HPT and undergoing parathyroid surgery. There were 399 patients with primary HPT who underwent surgery within the first year of follow-up, and these patients were excluded from surveillance. There were 822 patients who were diagnosed with primary HPT or other HPT who were switched that underwent surgery after the first year of follow-up. There were 312 patients (12.9%) with secondary HPT and 470 patients (19.4%) with other HPT. Some of the diagnoses in the other HPT group included uremia, calculi of the kidney or ureter, and diabetes mellitus.

Table 1 shows that a total of 219 malignancies were observed, resulting in an SIR of 1.25 (95%CI,

1.1–1.4). The risk of many malignancies was elevated nonsignificantly, including malignancies of the pancreas and corpus uteri, non-Hodgkin lymphoma, multiple myeloma, brain malignancies, and malignancies in connective tissue. Significant increases were limited to malignancies of the urinary system (SIR, 1.78; 95%CI, 1.1–2.7; based on 23 patients), which included the bladder (SIR, 1.78; 95%CI, 1.0–2.9) and the kidneys (SIR, 1.77; 95%CI, 0.8–3.5), and to thyroid carcinoma (SIR, 6.37; 95%CI, 1.5–4.5; based on 4 patients). Among the bladder tumors, there were six bladder papillomas, one transitional cell papilloma, seven transitional cell carcinomas (four of which were papillary carcinomas), and one bladder sarcoma. All four thyroid tumors were diagnosed among female patients, resulting in a gender specific SIR of 7.46 (95%CI, 2.0–19.1). Among the patients with thyroid carcinoma, two patients with follicular adenocarcinoma, one patient with papillary and follicular adenocarcinoma, and one patient with papillary carcinoma were observed. Female patients also had a significantly excessive rate of bladder carcinoma (SIR, 2.27; 95%CI, 1.0–4.3; based on 9 patients).

Primary HPT

Among all patients with primary HPT, there were 155 malignant neoplasms, yielding an SIR of 1.24 (95%CI, 1.1–1.5). Selected results are shown in Table 2. Included were 25 patients with breast carcinoma (SIR, 1.42; 95%CI, 0.9–2.1) and 13 patients with lymphatic and hematopoietic malignancies (SIR, 1.88; 95%CI, 1.0–3.2), with the excess primarily deriving from 4 observed patients with multiple myeloma.

When analysis of the primary HPT cohort was stratified by gender, no significant elevations in malignancies occurred in male patients. Female patients had a significant increase in all malignancies (SIR, 1.32; 95%CI, 1.1–1.6) as well as multiple myeloma (SIR, 4.31; 95%CI, 1.2–11.0). Breast carcinoma rates were elevated nonsignificantly in female patients with an SIR of 1.43 (95%CI, 0.9–2.1).

Total malignancies were elevated in patients age < 50 years (SIR, 1.61; $n = 20$ patients) and age ≥ 65 years (SIR, 1.21; $n = 83$ patients), patients who underwent parathyroid surgery (SIR, 1.29), patients who had HPT concurrently with another diagnosis (SIR, 1.33), patients who had only one hospital visit with an HPT diagnosis (SIR, 1.39), and patients who had more than one visit (SIR, 1.19) (see Table 2). Elevations in breast carcinoma rates generally followed the same pattern on stratification as overall malignancies. Urinary carcinoma rates were elevated nonsignificantly across all stratifications. Multiple myeloma rates were unique in that they were elevated significantly in patients who

TABLE 1
Standardized Incidence Ratios (SIR) of Selected Malignancies with > 1 Year Latency among 2425 Patients Diagnosed with Hyperparathyroidism in Denmark, 1977–1993

Type of malignancy	Total > 1 yr			Females > 1 yr			Males > 1 yr		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All malignancies	219	1.25	1.1–1.4	166	1.31	1.1–1.5	53	1.08	0.8–1.4
Buccal cavity and pharynx	1	0.36	0.0–2.0	1	1.66	0.0–3.7	0	—	0.0–2.9
Colon	19	1.19	0.7–1.9	14	1.14	0.6–1.9	5	1.35	0.4–3.2
Rectum	9	1.19	0.5–2.3	6	1.18	0.4–2.6	3	1.2	0.2–3.5
Pancreas	8	1.54	0.7–3.0	7	1.80	0.7–3.7	1	0.76	0.0–4.2
Lung (primary)	16	0.84	0.5–1.4	6	0.57	0.2–1.3	10	1.17	0.6–2.2
Breast	32	1.31	0.9–1.8	32	1.31	0.9–1.9	0	—	—
Corpus uteri	10	1.60	0.8–2.9	10	1.60	0.8–2.9	0	—	—
Urinary system	23	1.78	1.1–2.7	13	1.85	1.0–3.2	10	1.69	0.8–3.1
Kidney	8	1.77	0.8–3.5	4	1.30	0.4–3.3	4	2.75	0.7–7.1
Bladder	15	1.78	1.0–2.9	9	2.27	1.0–4.3	6	1.35	0.5–2.9
Skin (nonmelanoma)	35	1.35	0.9–1.9	24	1.30	0.8–2.0	11	1.44	0.7–2.6
Thyroid	4	6.37	1.5–4.5	4	7.46	2.0–19.1	0	—	0.0–40.1
Other endocrine glands	0	—	0.0–30.2	0	—	0.0–44.5	0	—	0.0–30.2
Lymph and hematopoietic	14	1.43	0.8–2.4	11	1.6	0.8–2.9	3	0.99	0.0–2.9
Non-Hodgkin	6	1.60	0.6–3.5	5	1.9	0.6–4.3	1	0.96	0.0–5.3
Multiple myeloma	4	2.16	0.6–5.5	4	3.1	0.8–7.8	0	0.00	0.0–6.7
Leukemia	4	1.07	0.3–2.8	2	0.8	0.1–2.9	2	1.62	0.2–5.9
Brain and nervous system	7	1.83	0.7–3.8	6	2.1	0.8–4.6	1	0.99	0.0–5.5
Connective tissue	2	4.56	0.5–16.5	2	6.7	0.8–24.2	0	—	0.0–26.2
Other disease sites ^a	39	—	—	—	—	—	—	—	—

Obs: observed; SIR: standardized incidence ratio; 95% CI: 95% confidence interval.

^a Other malignancies observed include the following: stomach (4), small intestine (2), liver-primary (3), liver-other (2), gallbladder (1), peritoneum and not otherwise specified (NOS) (2), lung-pleura (1), cervix (3), ovary (4), NOS female (1), prostate (4), testis (1), melanoma (5), eye (2), secondary and NOS (4).

had never undergone parathyroid surgery (SIR, 11.4) and in patients who had concomitant diagnoses (SIR, 4.87). Malignancies also were stratified by latency (time from index diagnosis to diagnoses with carcinoma), with numbers that were too small to analyze trends.

Secondary HPT

Patients with secondary HPT had a nonsignificant elevated risk of cancer overall (SIR, 1.49; 95%CI, 0.9–2.4). Two patients with metastases were the only significant finding, with an SIR of 12.15 (95%CI, 1.4–43.9; based on 3 patients). Nonsignificant elevations also occurred in carcinoma of the breast (SIR, 1.76; 95%CI, 0.4–5.1) and the corpus uteri (SIR, 4.94; 95%CI, 0.6–17.8; based on 2 patients). There was one patient with bladder carcinoma, and no patients had thyroid carcinoma or multiple myeloma.

Other HPT Types

Among the patients who were diagnosed with other and unspecified types of HPT, the overall cancer risk was 1.19 (95%CI, 0.88–1.59; based on 47 patients; data not shown). The overall cancer risk was elevated nonsignificantly among women (SIR, 1.24), among pa-

tients age < 65 years (SIR, 1.20 for patients age < 50 years and 1.46 for patients age 50–64 years), and among patients with more than one hospital visit (SIR, 1.29). Breast carcinoma rates were not elevated. Malignancies of the urinary system (including both bladder and renal carcinoma) were elevated significantly overall (SIR, 2.71; 95%CI, 1.2–5.3; $n = 8$ patients), among women (SIR, 3.78; $n = 6$ patients), among patients age ≥ 65 years (SIR, 4.87; $n = 8$ patients), among patients with concomitant diagnoses (SIR, 3.55; $n = 8$ patients), and among patients with more than one visit to the hospital for HPT (SIR, 3.40; $n = 6$ patients). The rates of thyroid were elevated significantly overall (SIR, 21.19; 95%CI, 4.3–61.9; $n = 3$ patients), among women (SIR, 24.88; $n = 3$ patients); in patients age > 65 years (SIR, 24.93; $n = 2$ patients), and in patients who had more than one hospital visit with an HPT diagnosis (SIR, 36.50; $n = 3$ patients).

DISCUSSION

Overall, the incidence of cancer in this cohort was higher than expected, with a crude 25% excess in the risk of all cancers combined. Women appeared to be affected more than men. Among patients who were

TABLE 2
Standardized Incidence-ratios of Significant Malignancies with > 1 Year Latency among 1643 Patients with Primary Hyperparathyroidism in Denmark, 1977–1993

Characteristic	All malignancies		Breast		Urinary system		Multiple myeloma	
	No.	SIR	No.	SIR	No.	SIR	No.	SIR
Overall	155	1.24 ^a	25	1.42	14	1.52	4	3.03
Gender								
Female	119	1.32 ^a	25	1.43	6	1.20	4	4.31 ^a
Male	36	1.04	0	—	8	1.91	0	—
Age (yrs)								
< 50	20	1.61 ^a	5	1.61 ^a	1	1.59	0	—
50–64	52	1.19	5	0.75	7	2.18	1	2.26
65+	83	1.21 ^a	15	1.89 ^a	6	1.12	3	3.75
Surgery								
Ever	119	1.29 ^a	18	1.39	11	1.61	0	—
Never	36	1.10	7	1.53	3	1.28	4	11.40 ^a
Concomitant diagnoses								
Only HPT	53	1.10	7	1.07	8	2.18	0	—
Concomitant	102	1.33 ^a	18	1.63	6	1.09	4	4.87 ^a
No. of hospital visits								
1	45	1.39 ^a	12	2.66 ^a	6	2.51	1	3.00
1+	110	1.19 ^a	13	1.00	8	1.18	3	3.04
Latency (yrs)								
1–2	22	1.28	4	1.58	1	0.80	0	—
3–4	39	1.31	7	1.64	4	1.83	3	9.50 ^a
5–9	55	1.06	10	1.38	5	1.30	1	1.81
10+	39	1.50	4	1.15	4	2.08	0	—

SIR: standardized incidence ratio; HPT: hyperparathyroidism.

^a Significant at the $\alpha = 0.05$ level.

diagnosed with primary HPT and other HPT, the main elevations observed were for malignancies of the urinary tract system and the thyroid, whereas the group of patients who were diagnosed with secondary HPT was too small to analyze by disease types.

We attempted to separate patients with clinical primary HPT from other patients. In patients with primary HPT, plasma calcium is elevated, and plasma parathyroid hormone levels are elevated moderately. These changes usually are due to an idiopathic change in a clone or a group of parathyroid cells, and surgery often offers successful treatment. In secondary or other types of HPT, however, patients generally have normal or low plasma calcium levels and high parathyroid hormone levels due to a condition, such as vitamin D deficiency or chronic renal failure. Thus, primary HPT and other types of HPT are characterized by clinically distinct parathyroid and serum calcium levels, which may have different effects on cancer risk.

Several associations were found in our cohort of patients with primary HPT, including multiple myeloma. There are accumulating numbers of case reports noting comorbidity among patients with myeloma who have primary HPT and hypercalcemia,^{10–14}

although, to our knowledge, there are no other studies documenting a possible association of myeloma with HPT. Two of the sites that have been linked most consistently with primary HPT have been the colon^{15,16} and the breast.^{5,17} Although a slight elevation was observed in our study for breast carcinoma, the risk was nonsignificant and was difficult to interpret given the absence of information on important potential confounders, including menstrual and reproductive characteristics. In the current study, we found little evidence of alteration in the risk for colorectal carcinoma despite reasonable power to detect an association if it existed. Some studies suggest that elevated serum calcium levels may be associated with prostate carcinoma;¹⁸ however, there was no evidence of elevated rates of prostate carcinoma among our patients. In eliminating the first year of follow-up, we attempted to reduce increased surveillance for the observed malignancies that may have been initiated by the diagnosis of HPT.

In parallel with the results from patients with primary HPT, the overall risk of developing malignant disease was elevated moderately for patients with secondary HPT. No specific disease types contributed to

the overall excess, which may have been the result of a lack of power to detect alterations in risk for individual malignancies. Alternatively, because patients with this type of HPT generally exhibit higher levels of serum parathyroid hormone, the lack of elevated malignancies in this group may indicate that malignancies among patients with secondary HPT are not associated with the parathyroid hormone itself.

Patients in the other HPT category had elevated thyroid and urinary tract malignancies. Medullary thyroid carcinoma in conjunction with HPT may be associated with MEN2.¹⁹ In our data, we were unable to determine whether the patient had ever been diagnosed with MEN. However, none of the patients with thyroid carcinoma who were diagnosed after 1 year of latency in this cohort had medullary disease, as confirmed by histologic examination. Given the relatively small size of the cohort, MEN diagnoses would be unexpected. Long-term exposure to elevated calcium, acting on the thyroid as a goitrogen, has been proposed as the mechanism for the association.⁴ Alternatively, radiation exposure has been recognized as a risk factor for both HPT and thyroid carcinoma.²⁰⁻²⁷ Hospital patients may have higher exposure to certain types of radiation, such as X-rays. Malignancies that are associated with MEN1 in patients with HPT, such as pancreatic carcinoma, also were observed; however, the numbers were extremely small.

Urinary tract carcinoma also was of interest in the other cohort of patients with HPT. We were unable to control for smoking, which may contribute to the risk of urinary carcinoma. However, in this population, the incidence of lung carcinoma and other smoking-related disease was not elevated. It has been noted previously that renal carcinoma occurs synchronously^{28,29} and subsequently³⁰ among patients who are diagnosed with HPT. This cohort exhibited symptoms of renal distress, including primary diagnoses of uremia (8% of primary diagnoses), calculi (5% of primary diagnoses), and dialysis procedures (> 250 procedures on index visit). This may relate to the fact that renal colic and stones are a frequent occurrence among patients with HPT, with a Mayo Clinic study documenting an 8% prevalence rate of these conditions among patients with HPT.³¹ Many studies have noted increased urologic malignancies in patients with kidney disease and/or uremia.³²⁻³⁴ Thus, the possibility of urinary tract-related problems confounding the observed risk for renal carcinoma cannot be ruled out. Similarly, an elevation in the risk of bladder carcinoma, also noted in an Italian study of patients with HPT,³⁵ may reflect the irritative influence of hypercalcemia on microstones or macrostones. However, we would expect these conditions to be associated with secondary HPT,

and we saw no elevations in urinary carcinomas among patients who were diagnosed with secondary HPT. Furthermore, surgery and other procedures occurring on the index visit, including dialysis with artificial kidney, cystoscopy, and dialysis peritoneal, may have affected cancer risk independently.

The linkage of nationwide hospital and cancer registries in Denmark to examine cancer outcomes for patients with HPT has important advantages. By including only patients who were diagnosed with carcinoma subsequent to their diagnosis of HPT, a temporal sequence could be established. Because information was gathered from registry records, there was no recall bias. Excluding patients who were diagnosed with cancer within the first year of follow-up limited detection bias. However, because much of the cohort received surgery for HPT more than 1 year after diagnosis, some malignancies may have been detected due to increased surveillance of hospitalized patients or to underlying conditions or surgery, rather than to the direct effects of HPT.

The results of the current study present evidence of a moderately increased overall risk of cancer among patients with HPT. In this study, the association with specific malignancies was dependent on the type of HPT. This may be an important consideration in evaluation the effect of HPT on cancer risk. Future studies should monitor whether specific endocrinologic alterations associated with HPT may impart an independent effect on the long-term risk of thyroid, urinary tract, and hematopoietic malignancies.

REFERENCES

1. National Institute of Diabetes and Kidney and Digestive Diseases. Endocrine and metabolic diseases: hyperparathyroidism. NIH publication no. 95-3425. Available from URL: <http://www.niddk.nih.gov/health/endo/pubs/hyper/hyper.htm> [accessed February 12, 1998]. Bethesda: National Institutes of Health, 1995.
2. Eng C. RET proto-oncogene in the development of human cancer. *J Clin Oncol*. 1999;17:380-393.
3. Kaplan L, Katz AD, Ben-Isaac C, Massry SG. Malignant neoplasms and parathyroid adenoma. *Cancer*. 1971;28:401-407.
4. LiVolsi VA, Feind CR. Parathyroid adenoma and nonmedullary thyroid carcinoma. *Cancer*. 1976;38:1391-1393.
5. Palmer M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of malignant diseases after surgery for primary hyperparathyroidism. *Am J Epidemiol*. 1988;127:1031-1040.
6. Wermers RA, Khosla S, Atkinson EJ, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med*. 1998;104:115-122.
7. Danish National Board of Health. The activity in the hospital care system [in Danish]. Copenhagen: Danish National Board of Health, 1981.
8. Danish National Board of Health. Classification of diseases [in Danish]. Copenhagen: Danish National Board of Health, 1976.

9. Danish National Board of Health. Cancer incidence in Denmark, 1996. Copenhagen: Danish National Board of Health, 1999.
10. Goto S, Yoshioka M, Nagai K, et al. Primary hyperparathyroidism associated with multiple myeloma. *Int Med*. 1995;34:988–991.
11. Dagleish AG, Gatenby PA. Refractory hypercalcemia: parathyroid adenoma or multiple myeloma? *Med J Aust*. 1984;140:99–100.
12. Stone MJ, Lieberman ZH, Chakmakjian ZH, Matthews JL. Coexistent multiple myeloma and primary hyperparathyroidism. *JAMA*. 1982;247:823–824.
13. Francis RM, Bynoe AG, Gray C. Hypercalcemia due to the coexistence of parathyroid adenoma and myelomatosis. *J Clin Pathol*. 1982;35:732–736.
14. Jackson RM, Orland MJ. Parathyroid adenoma in a patient with multiple myeloma. *South Med J*. 1979;72:1336–1337.
15. Feig DS, Gottesman IS. Familial hyperparathyroidism in association with colonic carcinoma. *Cancer*. 1987;60:429.
16. Kawamura YJ, Kazama S, Miyahara T, Masaki T, Muto T. Sigmoid colon cancer associated with primary hyperparathyroidism: report of a case. *Surg Today*. 1999;29:789–790.
17. Vichayanrat A, Avramides A, Gardner B, et al. Primary hyperparathyroidism and breast cancer. *Am J Med*. 1976;61:136–139.
18. Chan JM, Giovannucci E, Andersson S-O, Yuen J, Adami H-O, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). *Cancer Causes Control*. 1998;9:559–566.
19. Shan L, Nakamura Y, Nakamura M, Yokoi T, Kakudo K. Genetic alterations in primary and secondary hyperparathyroidism. *Pathol Int*. 1998;48:569–74.
20. Refetoff S, Harrison J, Karanfilski BT, et al. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. *N Engl J Med*. 1975;292:171–175.
21. Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery*. 1998;124:1106–1113.
22. Favus MJ, Schneider AB, Stachura ME, et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation: evaluation of 1056 patients. *N Engl J Med*. 1976;294:1019–1025.
23. Maxon HR, Thomas SR, Saenger EL, et al. Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. *Am J Med*. 1977;63:967–978.
24. Hedman I, Tisell L-E. Associated hyperparathyroidism and non-medullary thyroid carcinoma: the etiologic role of radiation. *Surgery*. 1984;95:392–397.
25. Tisell L-E, Carlsson S, Lindberg S, et al. Autonomous hyperparathyroidism: a possible late complication of neck radiotherapy. *Acta Chir Scand*. 1976;142:367–373.
26. Christesson T. Hyperparathyroidism and radiation therapy. *Ann Intern Med*. 1978;89:216–217.
27. Russ JE, Scanlon EF, Sener SF. Parathyroid adenomas following irradiation. *Cancer*. 1979;43:1078–1083.
28. Read JM, Lang CC. Coexisting renal carcinoma and primary hyperthyroidism. *Br J Urol*. 1988;62:88.
29. Purnell DC, Scholz DA, van Heerden JA. Primary hyperparathyroidism associated with hypernephroma: a diagnostic challenge. *Mayo Clin Proc*. 1982;57:694–698.
30. Safe AF, Cooper S. Primary hyperparathyroidism and renal cell carcinoma in an elderly patient: a rare association. *Br J Clin Pract*. 46:136–137.
31. Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. *N Engl J Med*. 1980;302:189–193.
32. Akizawa T, Kinugasa E, Koshikawa S. Increased risk of malignancy and blood-membrane interactions in uraemic patients. *Nephrol Dial Transplant*. 1994;9(S2):162–164.
33. Chen K-S, Lai M-K, Huang C-C, Chu S-H, Leu M-L. Urologic cancers in uremic patients. *Am J Kidney Dis*. 1995;25:694–700.
34. Levine E. Renal cell carcinoma in uremic acquired renal cystic disease: incidence, detection, and management. *Urol Radiol*. 1992;13:203–210.
35. Pizzolitto S, Barbone F, Rizzi C, Scott AC, Piemonte M, Beltrami CA. Parathyroid adenomas and malignant neoplasms: coincidence or etiological association? *Adv Clin Pathol*. 1997;1:275–280.