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Second primary neoplasms after 19281 endocrine gland tumours: aetiological links?

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Abstract

The nationwide Swedish Family-Cancer Database of 9.6 million individuals was used to analyse the development of second neoplasia after 6909 thyroid and 12 697 other endocrine tumours. Tumour cases were retrieved from the Swedish Cancer Registry from 1958 to 1996. The risk of a second endocrine tumour was markedly increased compared with first endocrine tumour; e.g. the standardised incidence ratios (SIRs) were well over 10 for adrenal tumours after thyroid cancer, and *vice versa*. Familial risks were higher for the development of second compared with first neoplasms, and the SIRs for men were usually higher than those for women. Many increases between different endocrine glands can probably be ascribed to known cancer syndromes. Even cancers at some other sites were increased after the development of primary endocrine tumours. Notably, small intestinal carcinoids were increased after thyroid and other endocrine tumours, and brain menigiomas were increased after parathyroid and pituitary adenomas. These novel associations suggest shared risk factors for these sites. However, many endocrine tumours are benign and the diagnosis of the first tumour may increase the likelihood of a second diagnosis.

Keywords: Thyroid cancer; Adrenal tumours; Parathyroid tumours; Pituitary tumours; Familial cancer; Multiple endocrine neoplasia; Meningioma

1. Introduction

Improvements in cancer survival result in increasing proportions of patients diagnosed with a second primary cancer. Improvements in medical diagnostic and viewing techniques facilitate the detection of second tumours, particularly of asymptomatic tumours that would otherwise escape diagnosis. Second malignancies may have resulted from the treatment given for the first cancer, and/or be caused by the same environmental or genetic factors that caused the first cancer [1]. In some cases, the intense medical scrutiny after the first cancer may lead to an overdiagnosis. However, in the Swedish Cancer Registry practically all the reported cancers are histologically- or cytologically-verified, assuring the correctness of diagnosis. Endocrine gland malignancies are divided into thyroid and other endocrine tumours according to the International Classification of Diseases. The latter encompass parathyroid, adrenal, pituitary and other rarer malignancies. Both adenomas and carcinomas are common, but usually either type predominates at a particular site. Other endocrine tumours account for 1% of male and 2% of female malignancies and they are twice as common as thyroid cancers in Sweden [2]. The female excess is also seen for thyroid cancers. Endocrine tumours are associated with many known cancer syndromes, including multiple endocrine neoplasia (MEN), neurofibromatosis 1 and von Hippel-Lindau (VHL) disease [3]. Typical of all these syndromes is a high risk status and multiple presentation of neoplasia. However, only a small minority of endocrine tumours in a population is associated with these or other familial syndromes, ranging from 3% for pituitary adenomas to 20% for medullary thyroid carcinomas [4]. The familial relative risks for thyroid cancers are the highest, approximately 10, of all of the cancers in the Swedish Family-Cancer Database, and are only partially explained by the incidence of medullary thyroid cancer, which is seen in patients with the MEN 2 syndrome [5–7]. For other endocrine gland tumours, the familial risks are somewhat over 2.0. A limited number of population-based epidemiological studies are available on non-thyroid endocrine neoplasms. However, to

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our knowledge, no systematic study has investigated the occurrence of second tumours after these neoplasms [8].

2. Patients and methods

We used the nationwide Family-Cancer Database on 9.6 million individuals to analyse the occurrence of second tumours in men and women who had been diagnosed with primary neoplasms of the thyroid and other endocrine glands.

The Swedish Family-Cancer Database includes all persons born in Sweden after 1934 with their biological parents [5,9]. Data on neoplasms were retrieved from the nationwide Swedish Cancer Registry from 1958 to 1996. Data on family history were included in the analysis. A large number of cancer sites and histologies were considered which resulted in a comprehensive analysis. It was important to cover these sites as many endocrine glands share familial risk factors. A four-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used. The use of ICD7 with four digits revealed the tumour site for the endocrine neoplasms. Histology codes were used to specify the tumour type. Among the thyroid cancers, a separate code for medullary cancer was introduced in 1985 but the thyroid adenocarcinoma classification is likely to include some medullary cancers before that year [7]. The following ICD-7 codes were pooled: 'oral' cancer codes 161 (larynx) and 140–148 (lip, mouth, tongue, pharynx), except for code 142 (salivary glands). Rectal cancer, ICD-7 code 154 was separated for anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0).

The Swedish Cancer Registry records mainly malignant tumours, but for the non-thyroid endocrine glands, the central nervous system and the urinary tract even benign tumours at these sites are noted; this also includes carcinoid tumours, irrespective of the site. For endocrine tumours, usually either malignant or benign tumours predominate depending on the site. For the thyroid, mainly carcinomas are noted. For the parathyroid, thymus and pituitary sites, adenomas are the overwhelming majority, and they also predominate for the pancreas. For adrenal tumours, adenomas and paragangliomas are the most common type, adenocarcinoma is somewhat rarer, and pheochromocytoma and neuroblastoma (each approximately 7%) are rare tumours. In the analysis, we considered both the site (endocrine gland) and histology, in as much as was possible with regard to the numbers in the subgroups and the practicality of the comparisons. Rare tumours were combined in 'other' groups. However, all statistically meaningful associations were followed. In the initial analysis with non-endocrine sites, all main cancer sites were included. However, because this resulted in tables with too much data, for clarity, the data presented in the tables was based on the criteria given in Results.

Only non-synchronous second tumours were included, i.e. at least 1 month had to elapse between the diagnoses for the first and the second cancer. Family relationships were obtained from the Family-Cancer Database on all first-degree relatives. Standardised incidence ratios (SIR) were calculated by dividing the observed numbers (O) of the second events by the expected (E) ones, calculated as person-years at risk based on age (5-year age-groups)-, period (5-year periods)-, area of residence (two categories, three large cities and rest of the country)-, socio-economic status (four categories)- and sex-specific incidence rates of all women [10]. Confidence intervals (95% CI) were calculated assuming a Poisson distribution [10]. In all combinations of first and second cancers where increased SIRs were observed, cancers in all family members were examined.

Table 1
Number and familial proportion of all patients with first primary endocrine tumour and of patients who developed a second tumour

Sex	First tumour site	With first tumour			With second tumour		
		Sporadic (%)	Familial (%)[a]	Total	Sporadic (%)	Familial (%)	Total
Men	Thyroid gland	1852 (97.6)	45 (2.4)	1897	88 (89.8)	10 (10.2)	98
	Adrenal	507 (97.1)	15 (2.9)	522	40 (93.0)	3 (7.0)	43
	Parathyroid	1766 (98.7)	24 (1.3)	1790	117 (99.2)	1 (0.9)	118
	Pituitary	1397 (98.9)	16 (1.1)	1413	55 (96.5)	2 (3.5)	57
	Other	459 (97.0)	14 (3.0)	473	36 (94.7)	2 (5.3)	38
	All	5981 (98.1)	114 (1.9)	6095	336 (94.9)	18 (5.1)	354
Women	Thyroid gland	4906 (97.9)	106 (2.1)	5012	288 (96.6)	10 (3.4)	298
	Adrenal	626 (97.4)	17 (2.6)	643	60 (87.0)	9 (13.0)	69
	Parathyroid	6119 (98.9)	69 (1.1)	6188	407 (97.6)	10 (2.4)	417
	Pituitary	1142 (99.2)	9 (0.8)	1151	70 (100.0)	0 (0.0)	70
	Other	507 (98.1)	10 (1.9)	517	48 (92.3)	4 (7.7)	52
	All	13300 (98.4)	211 (1.6)	13511	873 (96.4)	33 (3.6)	906

Synchronous primary tumours were not included if diagnosed less than 1 month after the first tumour.
[a] Family history refers to a first-degree relative affected with an endocrine or thyroid gland tumour.

3. Results

Male thyroid and female parathyroid tumours were the most common of the individual endocrine tumours diagnosed as a primary neoplasm (Table 1). The female excess of all endocrine tumours was clear, with a total number of 13 300 female to 5981 male tumours. The familial proportion among first endocrine neoplasms varied from 0.8% for female pituitary to 2.9% for male adrenal tumours. A total of 873 female and 336 male non-synchronous (>1 month since the first diagnosis) second malignancies were recorded, including endocrine tumours and cancers at any site. The familial proportion was clearly increased compared with first malignancies, reaching 13.0% for female adrenal tumours.

The site-specific risks of male and female second endocrine tumours are shown in Table 2. The risks were very high compared with the risks of first tumours. At male concordant sites, the SIR for second adrenal tumour after a first adrenal tumour was 68.6. At discordant sites after thyroid cancer, the SIR was 40.7 for adrenal and 9.9 for parathyroid neoplasms. The highest SIR of 122.5 was for thyroid cancer following an adrenal tumour. Similar analysis for female malignancies also showed high SIRs, but most risks were lower than those for the men (Table 2). After thyroid cancer, female adrenal and parathyroid tumours had SIRs of 25.0 and 2.5, clearly below the male rates. After adrenal tumours, the SIR for thyroid cancer was 26.1 and the 95% CIs did not overlap with those of the male SIR of 122.5.

Histologically defined, both all and familial second endocrine tumours are presented in Table 3, combined for men and women. Adrenal paraganglioma showed a risk of 721.1 after medullary thyroid cancer, and this was increased to 1601.7 when a family member was affected with an endocrine (thyroid or other endocrine) tumour. In the reverse order, medullary thyroid cancer following an adrenal paraganglioma or other histologies, the risks were also increasingly high. More than one half of the cases with these tumours had an affected family member with the same kind of tumour. It should be noted that the code for medullary thyroid carcinoma was instituted in the Swedish Cancer Registry since 1985; before that time medullary cancers were probably classified mainly under ''anaplastic tumour''. However, it cannot be excluded that some medullary tumours also were classified under 'adenocarcinoma' [7]. Because more than one half of first thyroid adenocarcinomas in Table 3 were diagnosed before 1985, there is no absolute

Table 2
SIR for second endocrine tumours

First tumour site	Second tumour site	Men			Women		
		O	E	SIR (95% CI)	O	E	SIR (95% CI)
Thyroid gland	Thyroid gland	1	0.6	1.8 (0.0–6.9)	5	4.2	1.2 (0.4–2.5)
	Adrenal	6	0.1	**40.7 (14.6–79.7)**	14	0.6	**25.0 (13.6–39.8)**
	Parathyroid	6	0.6	**9.9 (3.6–19.4)**	19	7.7	**2.5 (1.5–3.7)**
	Pituitary	1	0.4	2.5 (0.0–9.7)	4	0.9	**4.2 (1.1–9.4)**
	Other endocrine		0.1		1	0.5	1.9 (0.0–7.4)
Adrenal	Thyroid gland	9	0.1	**122.5 (55.5–215.5)**	8	0.3	**26.1 (11.2–47.3)**
	Adrenal	2	0.0	**68.6 (6.5–196.8)**		0.1	
	Parathyroid		0.1		1	0.6	1.8 (0.0–6.9)
	Pituitary		0.1		2	0.1	**27.4 (2.6–78.5)**
	Other endocrine	1	0.0	43.3 (0.0–169.7)		0.0	
Parathyroid	Thyroid gland	2	0.6	3.1 (0.3–8.9)	8	4.7	1.7 (0.7–3.1)
	Adrenal	1	0.2	5.5 (0.0–21.4)	2	0.7	3.0 (0.3–8.6)
	Parathyroid	4	0.8	**4.8 (1.2–10.6)**	4	12.4	0.3 (0.1–0.7)
	Pituitary	1	0.5	2.0 (0.0–8.0)	4	1.0	3.9 (1.0–8.6)
	Other endocrine	3	0.2	**15.8 (3.0–38.7)**	4	0.7	**5.4 (1.4–11.9)**
Pituitary	Thyroid gland		0.5		1	0.9	1.1 (0.0–4.3)
	Adrenal		0.1		1	0.1	8.0 (0.0–31.3)
	Parathyroid	5	0.6	**9.1 (2.9–18.8)**	6	1.7	**3.4 (1.2–6.8)**
	Pituitary	3	0.4	**7.8 (1.5–19.1)**	5	0.2	**21.1 (6.7–43.6)**
	Other endocrine		0.1			0.1	
Other endocrine	Thyroid gland	2	0.1	**21.3 (2.0–61.0)**		0.3	
	Adrenal		0.0		1	0.0	23.5 (0.0–92.2)
	Parathyroid	1	0.1	9.1 (0.0–35.7)	1	0.7	1.5 (0.0–6.0)
	Pituitary	1	0.1	13.3 (0.0–52.3)		0.1	
	Other endocrine	1	0.0	28.2 (0.0–110.5)	2	0.0	**40.1 (3.8–115.1)**

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O, observed; E, expected.
Bolding shows that 95% CIs do not cross 1.00 (taken with two decimals).

guarantee that the SIR calculated for the second tumour were for cases with a primary that was a pure adenocarcinoma. On the other hand, almost all cases where thyroid adenocarcinoma is given as a second neoplasia, were diagnosed after 1985 and should be true adenocarcinomas. A separate analysis for thyroid cancer before and after 1985 is not useful because of the different and short follow-up times and the small number of cases. The risk for pituitary adenoma was 45.1 when it was observed after primary adrenal tumours.

The second cancers at various sites after thyroid cancer are shown in Table 4 by follow-up time. The sites were selected in Table 4 because they were either significantly increased or they were increased after other endocrine tumours, as shown in Table 5. Very high SIRs were observed for the second thyroid and other endocrine tumours shortly after the first diagnosis. Prostate cancer was increased after adenocarcinoma. For prostate cancer the time from thyroid cancer diagnosis was longer than for any other second cancer. There was no evidence that diagnosis of a second prostate cancer occurred earlier in the 1990s, from for example increased vigilance, than in the 1980s (i.e. the mean time from diagnosis of a primary thyroid to diagnosis of a second tumour of the prostate was 10 years in the 1980s and 14 years in the 1990s; however these figures are not fully comparable because the study period is truncated). Small intestinal and renal cancers were increased after thyroid cancer.

A similar analysis was carried out for second cancers following other endocrine gland tumours (Table 5). The highest SIRs were noted after adrenal tumours, particularly for thyroid (SIR 52.5) and other endocrine (14.8) tumours, but even for renal (8.5), nervous system (5.2) and liver (4.0) cancers. Among the seven nervous system tumours, two were neurinomas (schwannomas), one was menigioma, one hemangiomas and the remaining tumours were of unspecified histology. The SIR for small intestinal cancers was increased after all endocrine tumours (3.2). Even the SIR for breast cancer was significant although the absolute increase was small. Leukaemia was not in excess with an SIR of 1.1 ($n=28$)

We wanted to investigate in detail the type of small intestinal cancers that were increased after endocrine tumours (Table 6). Most of the increase was due to carcinoids with an overall SIR of 4.2; the SIR was 3.4

Table 3
SIR of second endocrine tumours in men and women combined by histology

First tumour		Second tumour		All			Familial		
Site	Histology	Site	Histology	O	E	SIR (95% CI)	O (%)	E	SIR (95% CI)
Thyroid	Adenocarcinoma	Thyroid	Adenocarcinoma	2	3.3	0.6 (0.1–1.7)			
			Medullary	2	0.7	2.8 (0.3–8.0)			
		Adrenal	Paraganglioma	7	0.2	**41.2 (16.3–77.3)**	4 (57.1)	0.0	**139.9 (36.4–310.6)**
			Other	3	0.4	**7.6 (1.4–18.7)**			
		Parathyroid	Adenoma	18	7.7	**2.3 (1.4–3.6)**			
		Pituitary	Adenoma	5	1.1	**4.6 (1.4–9.5)**			
	Medullary	Thyroid	Adenocarcinoma	2	0.2	8.2 (0.8–23.6)			
		Adrenal	Paraganglioma	10	0.0	**721.1 (343.4–1237.3)**	6 (60.0)	0.0	**1601.7 (576.5–3139.8)**
		Parathyroid	Adenoma	5	0.7	**7.4 (2.3–15.2)**	2 (40.0)	0.1	**44.4 (4.2–127.2)**
Adrenal	Paraganglioma	Thyroid	Adenocarcinoma	2	0.1	**16.7 (1.6–47.8)**	1 (50.0)	0.0	89.2 (0.0–349.7)
			Medullary	12	0.0	**513.3 (264.0–844.9)**	9 (75.0)	0.0	**1196.9 (542.7–2106.6)**
		Adrenal	Paraganglioma						
			Other	1	0.0	56.5 (0.0–221.5)			
	Other	Thyroid	Adenocarcinoma	1	0.2	5.6 (0.0–21.8)			
			Medullary	2	0.0	**187.2 (17.7–536.6)**	1 (50.0)	0.0	410.3 (0.2–1608.7)
		Adrenal	Paraganglioma						
			Other	1	0.0	75.0 (0.0–294.0)			
		Parathyroid	Adenoma	1	0.4	2.6 (0.0–10.1)			
		Pituitary	Adenoma	2	0.0	**45.1 (4.3–129.2)**			
Parathyroid	Adenoma	Thyroid	Adenocarcinoma	9	4.1	**2.2 (1.0–3.9)**			
			Medullary	1	1.1	0.9 (0.0–3.7)			
		Adrenal	Paraganglioma						
			Other	3	0.6	4.7 (0.9–11.5)			
		Parathyroid	Adenoma	7	13.1	0.5 (0.2–1.0)			
		Pituitary	Adenoma	5	1.4	**3.7 (1.2–7.6)**			
Pituitary	Adenoma	Adrenal	Paraganglioma	1	0.0	40.7 (0.0–159.6)			
		Parathyroid	Adenoma	9	1.8	**5.0 (2.3–8.8)**	1 (11.1)	0.0	86.6 (0.0–339.5)
		Pituitary	Adenoma	4	0.5	**8.9 (2.3–19.7)**			

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O, observed; E, expected.
Family history refers to a first-degree relative affected with a thyroid or endocrine gland tumour.
Bolding shows that 95% CIs do not cross 1.00.

after parathyroid tumours and 6.5 after pituitary tumours. Only one carcinoid was diagnosed in patients with adrenal tumours (data not shown). In families where small intestinal carcinoids were diagnosed as a second cancer, no excess of other cancers was found.

We also wanted to examine the types of nervous system tumours that were increased after endocrine tumours (Table 7). After thyroid cancer, the increase in nervous system tumours was due to brain and spinal astrocytomas and neurinomas (data not shown). By contrast, brain meningiomas were increased after other endocrine tumours, particularly after pituitary neoplasms (SIR 11.9). The SIRs for meningioma were highest within the first year of diagnosis of an endocrine tumour; e.g. the SIR of brain meningiomas were 22.05 ($n=8$, 95% CI: 9.42–39.98), 3.55 ($n=16$, 95% CI: 2.02–5.50), and 4.37 ($n=10$, 95% CI: 2.08–7.50) after <1, 1–10 and >10 years of follow-up. The respective SIRs for brain meningioma after pituitary adenoma were 119.90 ($n=5$, 95% CI: 37.83–248.04), 7.26 ($n=4$, 95% CI: 1.89–16.12) and 8.04 ($n=4$, 95% CI: 2.09–17.85). The family members of patients with a second meningioma had few other cancers. Yet 2/45 families had a patient with a carcinoid tumour (one gastric and the other colonic). The risk of haemangioblastoma was also markedly increased.

4. Discussion

Diagnosis of second tumours may differ from that of first tumours in a number of ways that may make the incidence rates for the two poorly comparable. First, it may be impossible to distinguish second tumours as independent primaries. The Swedish Cancer Registry has clear instructions about the reporting of multiple primary malignancies and a re-evaluation of 209 multiple primary tumours found 98% of second malignancies to be correctly classified [11]. Second, reporting may differ systematically between the first and second neoplasms resulting in either higher or lower risks for the second tumour compared with first tumour. Overreporting should not be possible because practically all diagnoses are histologically- or cytologically-verified [2]. Neither does underreporting appear likely because in a

Table 4
SIR for second tumours after thyroid cancer

First thyroid tumour	Second tumours	Follow-up interval (years)											
		>10			1–10			>10			All		
		O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Adenocarcinoma	Small intestine	1	0.1	15.6 (0.0–61.3)	2	0.8	2.4 (0.2–6.8)	2	0.9	2.2 (0.2–6.4)	5	1.8	2.8 (0.9–5.7)
	Breast	5	3.3	1.5 (0.5–3.1)	49	50.7	1.0 (0.7–1.3)	59	58.4	1.0 (0.8–1.3)	113	112.4	1.0 (0.8–1.2)
	Prostate	4	1.4	2.9 (0.7–6.4)	19	14.5	1.3 (0.8–2.0)	27	11.7	**2.3 (1.5–3.3)**	50	27.6	**1.8 (1.3–2.3)**
	Kidney	8	0.5	**15.1 (6.5–27.4)**	6	7.2	0.8 (0.3–1.6)	13	7.4	1.8 (0.9–2.8)	27	15.1	**1.8 (1.2–2.5)**
	Nervous system	3	0.6	**5.3 (1.0–13.0)**	11	8.0	1.4 (0.7–2.3)	15	7.9	**1.9 (1.1–3.0)**	29	16.5	**1.8 (1.2–2.5)**
	Thyroid	12	0.2	**52.5 (27.0–86.4)**	0	2.8		2	2.3	0.9 (0.1–2.5)	14	5.3	**2.6 (1.4–4.2)**
	Endocrine	43	0.4	**112.4 (81.3–148.5)**	15	5.8	**2.6 (1.4–4.1)**	8	6.6	1.2 (0.5–2.2)	66	12.7	**5.2 (4.0–6.5)**
	Leukaemia	2	0.4	4.5 (0.4–12.8)	10	5.9	1.7 (0.8–2.9)	17	6.2	**2.7 (1.6–4.2)**	29	12.5	**2.3 (1.5–3.2)**
	All tumours	98	14.7	**6.7 (5.4–8.1)**	244	200.6	**1.2 (1.1–1.4)**	268	210.5	**1.3 (1.1–1.4)**	610	425.8	**1.4 (1.3–1.5)**
Medullary	Small intestine	0	0.0		1	0.1	10.8 (0.0–42.5)	0	0.1		1	0.2	5.3 (0.0–20.7)
	Breast	2	0.8	2.5 (0.2–7.0)	5	4.4	1.1 (0.4–2.4)	2	4.1	0.5 (0.0–1.4)	9	9.3	1.0 (0.4–1.7)
	Prostate	0	0.7		2	2.0	1.0 (0.1–2.9)	2	1.5	1.3 (0.1–3.9)	4	4.1	1.0 (0.3–2.2)
	Kidney	1	0.2	5.4 (0.0–21.0)	2	0.8	2.6 (0.2–7.4)	1	0.7	1.5 (0.0–5.7)	4	1.7	2.4 (0.6–5.4)
	Nervous system	1	0.1	7.0 (0.0–27.5)	0	0.8		0	0.6		1	1.5	0.7 (0.0–2.6)
	Thyroid	6	0.1	**106.8 (38.4–209.3)**	2	0.2	8.3 (0.8–23.9)	0	0.2		8	0.5	**16.9 (7.2–30.7)**
	Endocrine	13	0.1	**126.5 (67.1–204.5)**	9	0.5	**17.0 (7.7–29.8)**	2	0.5	4.0 (0.4–11.4)	24	1.1	**21.1 (13.5–30.5)**
	Leukaemia	0	0.2		1	0.6	1.5 (0.0–6.0)	2	0.6	3.4 (0.3–9.7)	3	1.4	2.1 (0.4–5.3)
	All tumours	27	5.1	**5.3 (3.5–7.5)**	36	20.9	**1.7 (1.2–2.3)**	23	18.0	1.3 (0.8–1.8)	86	44.0	**2.0 (1.6–2.4)**
All	Small intestine	1	0.1	11.6 (0.0–45.4)	3	0.9	3.2 (0.6–7.9)	2	1.0	2.1 (0.2–5.9)	6	2.0	**3.0 (1.1–5.9)**
	Breast	7	4.1	1.7 (0.7–3.2)	54	55.1	1.0 (0.7–1.3)	61	62.5	1.0 (0.7–1.2)	122	121.7	1.0 (0.8–1.2)
	Prostate	4	2.1	1.9 (0.5–4.3)	21	16.5	1.3 (0.8–1.9)	29	13.2	**2.2 (1.5–3.1)**	54	31.8	**1.7 (1.3–2.2)**
	Kidney	9	0.7	**12.6 (5.7–22.1)**	8	7.9	1.0 (0.4–1.8)	14	8.1	1.7 (0.9–2.8)	31	16.7	**1.9 (1.3–2.6)**
	Nervous system	4	0.7	**5.7 (1.5–12.6)**	11	8.8	1.3 (0.6–2.1)	15	8.5	1.8 (1.0–2.8)	30	18.0	**1.7 (1.1–2.3)**
	Thyroid	18	0.3	**63.2 (37.4–95.8)**	2	3.0	0.7 (0.1–1.9)	2	2.5	0.8 (0.1–2.3)	22	5.8	**3.8 (2.4–5.6)**
	Endocrine	56	0.5	**115.4 (87.1–147.6)**	24	6.3	**3.8 (2.4–5.5)**	10	7.1	1.4 (0.7–2.4)	90	13.9	**6.5 (5.2–7.9)**
	Leukaemia	2	0.6	3.3 (0.3–9.5)	11	6.5	1.7 (0.8–2.8)	19	6.8	**2.8 (1.7–4.2)**	32	13.9	**2.3 (1.6–3.2)**
	All tumours	125	19.8	**6.3 (5.3–7.5)**	280	221.5	**1.3 (1.1–1.4)**	291	228.5	**1.3 (1.1–1.4)**	696	469.8	**1.5 (1.4–1.6)**

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O, observed; E, expected.
Bolding shows that 95% CIs do not cross 1.00.

study on 630 000 second neoplasms from Sweden, practically all the SIRs for second cancers even at discordant sites were over unity [12]. One exception was cancers with a poor survival, such as pancreas and lung, where underreporting was noted [12]. Third, improvements in medical viewing and imaging techniques is likely to increase the number of second tumours and particularly of indolent ones, such as carcinoid tumours [13–15]. We were likely to see some evidence of this type of incidental diagnosis as discussed later.

We analysed systematically second tumours after endocrine gland tumours in order to find aetiological

Table 5
SIR for second tumours after non-thyroid endocrine gland tumours

First thyroid tumour	Second tumours	Follow-up interval (years)											
		>10			1–10			>10			All		
		O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Adrenal	Small intestine	1	0.0	65.4 (0.0–256.2)	0	0.1		0	0.1		1	0.2	5.4 (0.0 21.2)
	Liver	1	0.1	9.0 (0.0–35.1)	3	0.6	4.7 (0.9–11.6)	1	0.5	2.0 (0.0–7.9)	5	1.2	**4.0 (1.3 8.4)**
	Pancreas	0	0.1		1	0.6	1.6 (0.0–6.4)	0	0.5		1	1.2	0.9 (0.0–3.3)
	Breast	0	0.4		3	3.7	0.8 (0.2–2.0)	4	2.8	1.4 (0.4–3.2)	7	6.9	1.0 (0.4 1.9)
	Kidney	10	0.1	**88.(1 42.0–151.2)**	0	0.7		1	0.5	2.1 (0.0–8.1)	11	1.3	**8.5 (4.2 14.2)**
	Nervous system	4	0.1	**38.5 (10.0–85.5)**	3	0.8	3.9 (0.7–9.7)	0	0.5		7	1.4	**5.2 (2.1 9.7)**
	Thyroid	9	0.0	**318.0 (144.2–559.7)**	7	0.2	**32.2 (12.8–60.4)**	4	0.1	**29.7 (7.7–65.8)**	20	0.4	**52.5 (32.0 78.1)**
	Endocrine	8	0.1	**110.5 (47.2–200.3)**	3	0.5	**6.0 (1.1–14.7)**	3	0.4	**8.1 (1.5 19.8)**	14	0.9	**14.8 (8.1 23.6)**
	All tumours	40	3.4	**11.9 (8.5–15.9)**	34	21.2	**1.6 (1.1–2.2)**	27	15.7	**1.7 (1.1–2.4)**	101	40.3	**2.5 (2.0 3.0)**
Parathyroid	Small intestine	1	0.2	6.6 (0.0–25.8)	4	2.0	2.0 (0.5–4.4)	3	1.0	3.0 (0.6–7.5)	8	3.2	**2.5 (1.1 4.6)**
	Liver	3	1.2	2.5 (0.5–6.0)	27	16.7	**1.6 (1.1–2.3)**	11	8.0	1.4 (0.7–2.3)	41	25.9	**1.6 (1.1 2.1)**
	Pancreas	2	1.1	1.8 (0.2–5.2)	13	14.9	0.9 (0.5–1.4)	10	7.1	1.4 (0.7–2.4)	25	23.1	1.1 (0.7 1.5)
	Breast	5	6.4	0.8 (0.2–1.6)	101	82.9	1.2 (1.0–1.5)	47	36.0	1.3 (1.0–1.7)	153	125.3	**1.2 (1.0 1.4)**
	Kidney	7	1.1	**6.6 (2.6–12.4)**	23	13.9	**1.7 (1.0–2.4)**	15	6.3	**2.4 (1.3 3.7)**	45	21.3	**2.1 (1.5 2.8)**
	Nervous system	6	1.0	**6.1 (2.2–11.9)**	20	12.7	1.6 (1.0–2.3)	11	5.4	**2.0 (1.0–3.4)**	37	19.1	**1.9 (1.4 2.6)**
	Thyroid	39	0.3	**135.2 (96.1–180.9)**	5	3.6	1.4 (0.4–2.9)	1	1.4	0.7 (0.0–2.7)	45	5.3	**8.4 (6.2 11.1)**
	Endocrine	11	0.9	**12.7 (6.3–21.3)**	14	10.8	1.3 (0.7–2.1)	8	4.9	1.6 (0.7–3.0)	33	16.6	**2.0 (1.4 2.7)**
	All tumours	101	36.1	**2.8 (2.3–3.4)**	498	485.1	1.0 (0.9–1.1)	258	234.0	1.1 (1.0–1.2)	857	755.1	**1.1 (1.1 1.2)**
Pituitary	Small intestine	0	0.0		3	0.4	**7.3 (1.4–17.9)**	1	0.4	2.6 (0.0–10.2)	4	0.8	**4.8 (1.3–10.7)**
	Liver	1	0.2	4.9 (0.0–19.2)	4	2.6	1.6 (0.4–3.5)	0	2.6		5	5.4	0.9 (0.3–1.9)
	Pancreas	3	0.2	**13.(8 2. 6 33.8)**	5	2.7	1.9 (0.6–3.8)	3	2.6	1.2 (0.2–2.9)	11	5.5	2.0 (1.0–3.4)
	Breast	0	0.7		11	10.3	1.1 (0.5–1.8)	9	9.9	0.9 (0.4–1.6)	20	20.9	1.0 (0.6–1.4)
	Kidney	3	0.2	**12.0 (2.3–29.5)**	5	3.2	1.6 (0.5–3.3)	6	2.7	2.3 (0.8–4.4)	14	6.1	**2.3 (1.3–3.7)**
	Nervous system	8	0.2	**34.6 (14.8–62.7)**	11	3.0	**3.7 (1.8–6.2)**	5	2.3	2.2 (0.7–4.5)	24	5.5	**4.3 (2.8–6.3)**
	Thyroid	1	0.1	16.7 (0.0–65.6)	1	0.8	1.3 (0.0–5.1)	0	0.6		2	1.4	1.4 (0.1–4.1)
	Endocrine	5	0.1	**35.4 (11.2–73.1)**	9	1.7	**5.2 (2.4–9.2)**	10	1.5	**6.5 (3.1–11.1)**	24	3.4	**7.0 (4.5–10.1)**
	All tumours	34	6.8	**5.0 (3.4–6.8)**	119	86.1	**1.4 (1.1–1.6)**	85	80.6	1.1 (0.8–1.3)	238	173.6	**1.4 (1.2–1.6)**
Other	Small intestine	1	0.0	60.2 (0.0–236.2)	0	0.1		0	0.1		1	0.2	4.2 (0.0–16.3)
	Liver	0	0.1		0	0.9		1	0.7	1.5 (0.0–6.0)	1	1.7	0.6 (0.0–2.3)
	Pancreas	1	0.1	8.9 (0.0–34.8)	1	0.9	1.1 (0.0–4.3)	1	0.6	1.7 (0.0–6.5)	3	1.6	1.8 (0.3–4.5)
	Breast	2	0.4	4.5 (0.4–13.0)	2	4.3	0.5 (0.0–1.3)	6	2.7	2.2 (0.8–4.3)	10	7.5	1.3 (0.6–2.3)
	Kidney	2	0.1	**16.7 (1.6–47.8)**	3	1.0	3.1 (0.6–7.7)	3	0.6	5.2 (1.0–12.8)	8	1.7	**4.8 (2.1–8.8)**
	Nervous system	1	0.1	9.4 (0.0–36.9)	1	0.9	1.1 (0.0–4.4)	3	0.5	**6.0 (1.1–14.8)**	5	1.5	**3.3 (1.0–6.9)**
	Thyroid	0	0.0		2	0.2	8.4 (0.8–24.1)	0	0.1		2	0.4	5.0 (0.5–14.5)
	Endocrine	0	0.1		5	0.6	**8.0 (2.5–16.6)**	2	0.4	5.4 (0.5–15.5)	7	1.1	**6.6 (2.6–12.3)**
	All tumours	14	3.5	**4.0 (2.2–6.4)**	46	29.6	**1.6 (1.1–2.0)**	34	19.0	**1.8 (1.2–2.4)**	94	52.1	**1.8 (1.5–2.2)**
All	Small intestine	3	0.2	**13.8 (2.6–33.9)**	7	2.7	**2.6 (1.0–4.9)**	4	1.5	2.6 (0.7–5.8)	14	4.4	**3.2 (1.7–5.1)**
	Liver	5	1.6	3.0 (1.0–6.3)	34	20.8	**1.6 (1.1–2.2)**	13	11.7	1.1 (0.6–1.8)	52	34.2	**1.5 (1.1–2.0)**
	Pancreas	6	1.5	**3.9 (1.4–7.7)**	20	19.1	1.0 (0.6–1.6)	14	10.7	1.3 (0.7–2.1)	40	31.4	1.3 (0.9–1.7)
	Breast	7	8.0	0.9 (0.3–1.6)	117	101.2	1.2 (1.0–1.4)	66	51.5	1.3 (1.0–1.6)	190	160.6	**1.2 (1.0–1.4)**
	Kidney	22	1.5	**14.3 (8.9–20.8)**	31	18.7	**1.7 (1.1–2.3)**	25	10.1	**2.5 (1.6–3.6)**	78	30.3	**2.6 (2.0–3.2)**
	Nervous system	19	1.4	**13.3 (8.0–20.0)**	35	17.3	**2.0 (1.4–2.7)**	19	8.7	**2.2 (1.3–3.3)**	73	27.4	**2.7 (2.1–3.3)**
	Thyroid	49	0.4	**121.6 (89.9–158.1)**	15	4.8	**3.1 (1.7–4.9)**	5	2.3	2.2 (0.7–4.6)	69	7.5	**9.2 (7.2–11.5)**
	Endocrine	24	1.2	**20.8 (13.3–29.9)**	31	13.6	**2.3 (1.5–3.1)**	23	7.2	**3.2 (2.0–4.6)**	78	22.0	**3.5 (2.8–4.4)**
	All tumours	189	49.8	**3.8 (3.3–4.4)**	697	622.0	**1.1 (1.0–1.2)**	404	349.3	**1.2 (1.0–1.3)**	1290	1021.1	**1.3 (1.2–1.3)**

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O, observed; E, expected.
Bolding shows that 95% CIs do not cross 1.00.

Table 6
SIR for second small intestinal cancers after endocrine tumours

First tumour	Histology of second small intestinal cancer	O	E	SIR (95% CI)
Thyroid	Carcinoid	4	1.1	**3.7 (1.0–8.1)**
	Other	2	0.9	2.2 (0.2–6.3)
	All	6	2.0	**3.0 (1.1–5.9)**
Other endocrine	Carcinoid	11	2.4	**4.5 (2.2–7.6)**
	Other	3	2.0	1.5 (0.3–3.7)
	All	14	4.4	**3.2 (1.7–5.1)**
Parathyroid	Carcinoid	6	1.8	**3.4 (1.2–6.7)**
	Other	2	1.4	1.4 (0.1–4.1)
	All	8	3.2	**2.5 (1.1–4.6)**
Pituitary	Carcinoid	3	0.5	**6.5 (1.2–16.0)**
	Other	1	0.4	2.7 (0.0–10.7)
	All	4	0.8	**4.8 (1.3–10.7)**
Other	Carcinoid	2	0.2	8.6 (0.8–24.6)
	Other	0	0.2	
	All	2	0.4	4.7 (0.4–13.5)
All	Carcinoid	15	3.5	**4.2 (2.4–6.7)**
	Other	5	2.9	1.7 (0.5–3.6)
	All	20	6.4	**3.1 (1.9–4.6)**

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O,

clues for the aggregation of neoplasia between these sites. In first endocrine tumours, a family history of any endocrine tumour in a first-degree relative was found in 1–3% of cases. The familial proportion was higher in the second cancers, being 10% or more for male thyroid and female adrenal tumours. Endocrine tumours occur in a number of known cancer syndromes, including MEN, VHL and NF1 (Table 8). The first question is obviously to what extent the increases in second tumours can be explained by these syndromes. Among these, MEN1 and NF1 are approximately 10 times more prevalent than the others. MEN1 is characterised by the presence of parathyroid, pituitary and pancreatic tumours, and more rarely carcinoids [8]. In our study, associations of pituitary and parathyroid tumours and intestinal carcinoids suggest that MEN1 is involved. NF1 would give raise to adrenal pheochromocytomas, intestinal carcinoids and diverse gliomas [16]. Only one carcinoid was observed after an adrenal tumour, which was an adenoma and not a pheochromocytoma. Even though nervous system cancers were in excess after adrenal tumours ($n=7$), only two brain schwannomas could possibly be associated with NF1. Thus there was no strong evidence for the presence of NF1 among the patients with endocrine tumours. Medullary thyroid carcinomas associated with adrenal paragangliomas (which is histologically similar to pheochromocytoma [4]) and parathyroid adenomas, point to an association with MEN2. Haemangioblastomas and renal cancers were found in excess as second tumours, suggesting an involvement of VHL, previously identified from the Database [17].

Meningiomas were found to be in excess after different types of endocrine tumours, particularly after pituitary adenomas (SIR 11.9). However, the increase in meningioma after pituitary tumours was most pronounced in tumours that were diagnosed within the year of the first diagnosis. Meningiomas are slowly growing tumours and it is likely that application of cranial imaging techniques for diagnosis of pituitary tumours facilitated their diagnosis. However, the increased SIRs at long follow-up times and even after parathyroid tumours suggest that an incidental diagnosis is not the only reason for the observed association. Case reports have been published on the coexistence of pituitary adenomas and meningiomas and second meninigiomas as late effects of radiation therapy [18,19]. We analysed the risk of a second meningioma by time since the diagnosis of the first endocrine tumour as a control for the radiation effects. Brain meningioma showed the highest risks during the first year of follow-up, ruling out radiation as the main contributor to the observed association. Even after pituitary adenomas, the increase in brain meningiomas was mainly observed in the early follow-up, allowing only a small contribution from the radiation effects. Multiple meningiomas are described as a hallmark manifestation in NF2, but this syndrome is not known to involve endocrine glands [16]. An association of carcinoids, thyroid cancers and nervous system tumours has been described earlier which is consistent with our results on carcinoids in two family members of meningioma patients and on the excess of carcinoids after thyroid cancer [20]. This population-based study found no familial effects in carcinoid tumours even though previous literature, based on case reports, has described a familial carcinoid syndrome [4]. Carcinoids are neuroendocrine tumours and their association with other endocrine tumours, commonly with neuroendocrine function, may thus not be surprising although previous literature on the association is largely lacking [8].

The treatment for thyroid cancer frequently involves the use of radioactive iodine. The late effects of this treatment have been the subject of many studies. A follow-up study on 2968 thyroid cancer patients from Sweden found an increase in kidney, endocrine and nervous system tumours, but no increase in leukaemias or breast cancer [21]. Our study covered more than twice the number of thyroid cancer patients (6909) and we could confirm the risks at the three sites and additionally found a risk for small intestinal, prostate and thyroid cancers and for leukaemia. The SIR for breast cancer was 1.00, excluding any large contribution by Cowden's syndrome, featuring the presence of breast and thyroid cancers in patients [3]. Even though we have no information on the use of iodine among the patients, the persistence of a risk for leukaemia, even 10 years after the diagnosis of thyroid cancer, suggests the presence of a radiation effect.

The incidence of thyroid and other endocrine tumours is approximately twice as high for women as for men in

Sweden [2], but exactly the opposite is the case for the familial risk of thyroid cancer, which is twice as high for men as for women [5]. This phenomenon of a strong familial effect for the gender with a low background incidence has been previously described for pyloric stenosis by Carter and has been denoted as "the Carter effect" [22,23]. In the present study we observed a higher risk for all second endocrine tumours among men compared with women, with the exception of associations involving pituitary adenomas (Table 2); e.g. for thyroid/adrenal (first/second) the male SIR was 40.7 compared with a female SIR of 25.0. Similarly, thyroid/parathyroid was 9.9 and 2.5, adrenal/thyroid 122.5 and 26.1, and parathyroid/parathyroid 4.8 and 0.3. In the last two comparisons, the 95% CIs did not overlap between the male and female SIRs, while they did in the other comparisons. Due to the relatively small number of cases, the data were not conclusive, but they suggest that the Carter effect may also affect the risk of developing a second neoplasia.

In summary, we showed consistent and strong increases in second endocrine tumours after any other endocrine tumours. Some of the risks between the first and the second endocrine gland tumours were remarkably high suggesting that the patients were affected by one of the known cancer syndromes with endocrine gland manifestations, particularly MEN 1, MEN2 and VHL. The development of related cancers in family members supported such an assertion. In addition to endocrine tumours, thyroid cancer caused an increase in

Table 7
SIR for second nervous system tumours after thyroid and other endocrine tumours

	Second tumour				
First tumour	Sites	Histology	O	E	SIR (95% CI)
Thyroid	Nervous system	Meningioma	9	5.0	1.8 (0.8–3.2)
		Haemangioblastoma	1	0.1	19.1 (0.0–74.8)
		Other	20	9.7	**2.1 (1.3–3.1)**
	Brain	Meningioma	8	4.3	1.8 (0.8–3.3)
		Haemangioblastoma	1	0.1	19.9 (0.0–77.9)
		Other	15	9.0	1.7 (0.9–2.6)
Other endocrine	Nervous system	Meningioma	37	9.3	**4.0 (2.8–5.3)**
		Haemangioblastoma	3	0.1	**33.3 (6.3–81.5)**
		Other	33	18.0	**1.8 (1.3–2.5)**
	Brain	Meningioma	34	7.7	**4.4 (3.1–6.0)**
		Haemangioblastoma	3	0.1	**38.7 (7.3–94.9)**
		Other	32	16.7	**1.9 (1.3–2.6)**
Parathyroid	Nervous system	Meningioma	21	6.9	**3.0 (1.9–4.5)**
		Haemangioblastoma	1	0.1	18.6 (0.0–73.0)
		Other	15	12.1	1.2 (0.7–1.9)
	Brain	Meningioma	18	5.8	**3.1 (1.8–4.7)**
		Haemangioblastoma	1	0.0	22.0 (0.0–86.2)
		Other	15	11.3	1.3 (0.7–2.1)
Pituitary	Nervous system	Meningioma	13	1.3	**10.2 (5.4–16.4)**
		Haemangioblastoma	1	0.0	43.5 (0.0–170.5)
		Other	10	3.9	**2.5 (1.2–4.4)**
	Brain	Meningioma	13	1.1	**11.9 (6.3–19.3)**
		Haemangioblastoma	1	0.0	48.8 (0.0–191.2)
		Other	10	3.6	**2.8 (1.3–4.7)**
Other	Nervous system	Meningioma	3	0.9	3.4 (0.6–8.2)
		Haemangioblastoma	1	0.0	74.1 (0.0–290.4)
		Other	8	1.9	**4.1 (1.8–7.4)**
	Brain	Meningioma	3	0.8	3.9 (0.7–9.5)
		Haemangioblastoma	1	0.0	87.0 (0.0–340.9)
		Other	7	1.8	**3.9 (1.5–7.3)**
All	Nervous system	Meningioma	46	14.4	**3.2 (2.3–4.2)**
		Haemangioblastoma	4	0.1	**27.1 (7.1–60.2)**
		Other	53	27.7	**1.9 (1.4–2.5)**
	Brain	Meningioma	42	12.3	**3.4 (2.5–4.5)**
		Haemangioblastoma	4	0.1	**31.3 (8.1–69.5)**
		Other	47	25.7	**1.8 (1.3–2.4)**

SIR, standardised incidence rate; 95% CI, 95% confidence interval; O, observed; E, expected.
Bolding shows that 95% CIs do not cross 1.00.

Table 8
Prevalence and tumour presentation in some known cancer syndromes

	MEN1	MEN2A	MEN2B	VHL	NF1	NF2
Prevalence/10^5	15	ca. 1	ca. 2	2	20	2
Thyroid	Medulla	Medulla	Medulla			
	Hyperplasia	Carcinoma	Carcinoma			
Adrenal	Cortical	Medulla	Medulla	Medulla	Medulla	
	Hyperplasia	Pheochr[a]	Pheochr	Pheochr	Pheochr	
Parathyroid	Hyperplasia	Hyperplasia				
	Adenoma					
Pituitary	Adenoma					
Pancreas islet	Adenoma			Adenoma		
	Carcinoma			Carcinoma		
Paraganglioma		Present	Present	Present		
Meningioma						Present
Schwannoma						Optic
Kidney				Present		
Hemangioblastoma				Present		
Carcinoid	G.i. tract[b]				Duodenal	

MEN1, multiple endocrine neoplasia 1; VHL, von Hippel–Lindau; NF1, neurofibromatosis 1; ca. approximately. Refs. [3,4,16].
[a] Pheochromocytoma.
[b] Gastro-intestinal tract.

small intestinal, prostate, kidney and nervous system cancers and leukaemias. Small intestinal, liver, breast, kidney and nervous system cancers were in excess after non-thyroid endocrine gland tumours. Small intestinal carcinoids and brain meningiomas were the main contributors to the observed increase, suggesting as yet unidentified shared susceptibilities between these and endocrine tumours. However, a part of these increases may due to incidental diagnoses.

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