Incidence and familial risks in pituitary adenoma and associated tumors

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Abstract

Reliable data on familial risks are important for clinical counseling and cancer genetics. We wanted to study incidence trends and familial risks for pituitary adenomas and associated tumors through parental and sibling probands, using the nation-wide Swedish Family-Cancer Database on 10.5 million individuals, containing families with parents and offspring. Cancer data were retrieved from the Swedish Cancer Registry from years 1958 to 2002, including 3239 pituitary tumor patients. Familial risk for offspring was defined through standardized incidence ratio (SIR), adjusted for many variables. The incidence of pituitary adenoma has increased moderately from 1958 to the 1990s and declined thereafter. There were only three offspring–parent pairs with a concordant pituitary tumor, the SIR was not significant. Parental skin cancer (SIR 1.60) and leukemia (1.90, chronic lymphatic leukemia 2.59) were associated with offspring pituitary adenoma diagnosed at any age up to 70 years. There was a strong association of pituitary adenomas with nervous system hemangiopericytomas, SIR 182. The only significant association among siblings was between pituitary tumors and breast cancer (1.46). The risk of pituitary adenoma was marginally increased in individuals whose siblings were diagnosed with colorectal cancer. The results suggest an association of pituitary adenomas with nervous system hemangiopericytomas and breast and colorectal cancers, in addition to some other tumor types. Whether these associations can be explained by the recently identified pituitary adenoma predisposing gene, *AIP*, remains to be established.

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Introduction

Pituitary adenomas are indolent tumors, which account for 10–15% of all diagnosed intracranial neoplasms (Asa & Ezzat 2002, DeLellis *et al.* 2004). Small adenomas may occur in up to 15% of pituitary glands examined at autopsy and over 20% in radiological examinations (Ezzat *et al.* 2004). It is believed that with the use of modern imaging techniques the diagnosed cases of pituitary adenoma are increasing (Asa & Ezzat 2002). Being benign tumors, most cancer registration systems do not record pituitary adenomas, whereby the data on the related incidence trends and etiology are limited. Pituitary adenomas can be typed based on their hormone-secreting properties into lactotropic (prolactin secreting, 35%), gonadotropic (follicle-stimulating hormone and luteinizing hormone, 35%), somatotropic (growth hormone, GH,

10–15%) and other tumor types, including tumors with mixed secreting patterns and non-secreting adenomas (Asa & Ezzat 2002, DeLellis *et al.* 2004). According to World Health Organization Classification of tumors in endocrine organs, some 25–30% of the surgically removed pituitary adenomas secrete GH, but in clinical series the incidence is lower due to the inclusion of medically treated tumors (DeLellis *et al.* 2004). GH overproduction may lead to excessive growth, diagnosed as acromegaly or gigantism.

Pituitary adenomas are manifested in two syndromes, multiple endocrine neoplasia 1 (MEN1) and Carney complex (DeLellis *et al.* 2004). MEN1 is characterized by high penetrance of tumors in endocrine glands and by biochemical evidence of hyperparathyroidism in a large majority of the affected individuals. Carney complex is very rare, featuring endocrine, cutaneous, and neural tumors

(DeLellis *et al.* 2004). Recently, Daly *et al.* described a multinational series of 64 families with two or more affected individuals with pituitary adenoma, not belonging to the known syndromes (Daly *et al.* 2006b). Prolactinomas and GH-secreting tumors made up 74% of the cases. In half of the families, the tumors of affected individuals secreted the same hormone, while in the remaining families the tumors showed a different secretion pattern. In another recent study, Vierimaa *et al.* identified germline mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene in patients diagnosed with pituitary adenoma (Vierimaa *et al.* 2006). The tumors were oversecreting GH or prolactin, and the phenotype in the families was acromegaly or gigantism. Many patients lacked a strong family history, suggesting that AIP is a low-penetrance tumor susceptibility gene. Because of the low penetrance, inherited predisposition to AIP may be difficult to detect in families in a clinical setting. None of these studies assessed the presence of associated tumors in families presenting pituitary adenomas.

The Swedish Cancer Registry has recorded even benign intracranial tumors throughout its existence, since 1958. These data give us a possibility to follow national incidence trends for pituitary adenoma. Additionally, based on the nation-wide Swedish Family-Cancer Database, we have the possibility to assess familial risks for pituitary adenoma and examine whether these tumors would be associated with other tumors in families. Based on the assumption that colorectal cancer is increased in acromegaly patients (Webb *et al.* 2002, Bogazzi *et al.* 2006, Jenkins *et al.* 2006), we examine specifically the familial associations between pituitary adenomas and colorectal cancer.

Materials and methods

The Swedish Cancer Registry was established in 1958. According to the instructions by the National Board of Health and Welfare, all physicians in hospitals and other establishments for medical treatment in Sweden must report all cases of cancer and benign intracranial tumors (clinical report) to the Cancer Registry. Furthermore, pathologists and cytologists report every cancer diagnosis on surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates, and autopsies (pathology report) to the Registry. Thus the majority of cases are notified twice, in separate reports; cancer registration is currently considered to be close to 100% for invasive tumors (Center for Epidemiology 2004). The initial

notifications are received by six regional oncology centers, which control the quality of the reports. Some 100 pituitary adenomas are reported annually, compared with a total of some 50 000 cancers; thus, tumor-type specific features, such as hormonal correlates of pituitary adenomas have not been separately recorded. Incidences of pituitary adenomas, standardized according to the Swedish standard population as of December 31, 2000, were available in the Swedish Cancer Registry from years 1958 to 2003.

Statistics Sweden maintains a 'Multigeneration Register' where children, offspring, born in Sweden in 1932 and later (maximally 70 years old) are registered with their biological parents and are organized as families. False paternity cannot be excluded, but, if present, results would be biased towards null. The 'Multigeneration Register' was linked using the individually unique national registration number to the Cancer Registry to establish the Swedish Family-Cancer Database (Hemminki *et al.* 2001b). All data in the Family-Cancer Database were accrued by register linkages and thus reporting bias, common in interview studies, cannot be present. The Database was last updated in 2004, and included cancer cases from 1958 to 2002. A four-digit diagnosis code according to the seventh revision of the International Classification of Diseases (ICD-7) has been used. Basal cell carcinoma of the skin is not registered in the Cancer Registry. Only the first primary pituitary adenoma was considered in the present study. Information on family history was collected on all first-degree relatives (parents and siblings). Standardized incidence ratios (SIRs) were used to measure the cancer risks for offspring according to the occurrence of cancers in their families. The follow-up was started for each offspring at birth, immigration, or on 1 January, 1961, whichever was the latest time. Follow-up was terminated at the diagnosis of first cancer, death, emigration, or the closing date of the study on 31 December, 2002. Parents' ages were not limited, but offspring were 0–70 years of age. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, gender-, tumor type-, period-, and socioeconomic status- (six groups) specific standard incidence rates for all offspring lacking a family history (Esteve *et al.* 1994). Confidence intervals (95% CIs) were calculated assuming a Poisson distribution, and they were rounded to the nearest two decimals (Esteve *et al.* 1994). Risks for siblings were calculated using the cohort method in this study, which considers each sibling separately and is practically independent of the number of siblings (Hemminki *et al.* 2001a).

Results

The incidence trends of pituitary adenomas for men and women are shown in Fig. 1, based on the data from the Swedish Cancer Registry. The male incidence increased from 0.9/100 000 in years 1958–1959 to a maximum of 1.9/100 000 in years 1995–1999, and it has decreased to 1.3/100 000 in the last period of 2000–2003. The female incidence was initially very similar to the male rate but since then it has been lower. The age-incidence curves for pituitary adenomas are shown in Fig. 2, based on a total of 3239 pituitary tumor patients identified from the Family-Cancer Database. The female incidence was higher than the male one for ages below 30 years, but at the higher age groups the incidence rates were reversed. The male incidence reached a sharp maximum around age 70–74 years compared with a flatter female curve.

Familial risks for offspring pituitary adenomas are shown in Table 1, when their parents were diagnosed with any cancers. There were only three offspring–parent pairs with a concordant pituitary tumor (SIR 1.77, 95%CI 0.33–5.25). Parental skin cancer (SIR 1.60) and leukemia (1.90) associated with offspring pituitary adenoma diagnosed at any age up to 70 years. Skin cancers were mainly squamous cell carcinomas. The association of offspring pituitary tumors and parental colorectal cancer was of borderline significance (1.20, 0.97–1.48). Early onset (<30 years) pituitary tumors in offspring associated with parental endocrine gland tumors and leukemia; pituitary tumors, diagnosed at ages 30–45 years were in excess in offspring whose mothers were diagnosed with breast cancer. In order to examine the possible role of MEN1 or Carney complex, in the noted associations when all families with endocrine gland tumors, other than pituitary adenomas, were excluded; all the noted significant associations were essentially unchanged.

Figure 1 Incidence trends of pituitary adenomas for men and women, based on the data from the Swedish Cancer Registry from year 1958 to 2003.

Figure 2 Age-incidence curves for pituitary adenomas, based on a total of 3239 pituitary tumor patients identified from the Family-Cancer Database.

A separate analysis was carried out for the risk of pituitary adenoma when a sibling presented with any cancer (Table 2). No sibling pairs with concordant pituitary tumors were found. The only significant association was between pituitary tumors and breast cancer (1.46), particularly with early onset (below 41 years) pituitary tumors (1.73). Late onset pituitary tumors were also associated with sibling's kidney cancer (four adenocarcinomas and two transitional cell carcinomas) and Hodgkin's disease. The risk of pituitary adenoma was marginally increased in individuals whose siblings were diagnosed with colorectal cancer (1.65, 0.92–2.73).

The risk for pituitary adenoma is shown in Table 3 according to a specific type of leukemia in parents. Although pituitary adenomas showed SIRs above unity when parents were diagnosed with many leukemia subtypes, the only significant association was with parental chronic lymphatic leukemia (2.59), particularly for adenomas diagnosed after age 40 years (2.96); however, this type of leukemia also showed the most cases.

We analyzed in more detail the associations of pituitary adenomas with other nervous system tumors. No association was found with any of the main tumor types, astrocytoma, meningioma, ependymoma, and neurinoma; however, hemangiopericytoma associated with pituitary tumors, and the SIR was excessive, 182 ($N=2$, 95%CI 17–670, diagnostic ages 52 and 54 years). Remarkably, only 15 nervous system hemangiopericytomas were found in the whole database, and 2 of them associated with pituitary tumors in families.

Discussion

Thanks to the registration of pituitary adenomas in the Swedish Cancer Registry, we were able to follow the

Table 1 Familial risk for pituitary tumors in offspring diagnosed at different ages when parents were affected with cancers

Familial site	All age				<30 Years				30–45 Years				>45 Years			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	12	0.81	0.42	1.42	5	1.89	0.60	4.44	5	0.85	0.27	1.99	2	0.32	0.03	1.17
Stomach	26	0.82	0.54	1.21	3	0.67	0.13	2.00	9	0.77	0.35	1.46	14	0.91	0.49	1.53
Small intestine	5	1.77	0.56	4.17	0				2	1.75	0.17	6.45	3	2.57	0.48	7.60
Colon	55	1.14	0.86	1.49	8	1.01	0.43	2.00	24	1.26	0.80	1.87	23	1.09	0.69	1.63
Rectum	37	1.33	0.94	1.84	9	1.92	0.87	3.66	13	1.18	0.63	2.03	15	1.24	0.69	2.05
Liver	18	0.90	0.53	1.43	3	0.97	0.18	2.88	11	1.43	0.71	2.56	4	0.43	0.11	1.12
Pancreas	21	1.06	0.66	1.62	5	1.60	0.50	3.76	8	1.05	0.45	2.07	8	0.89	0.38	1.75
Lung	46	1.00	0.73	1.34	5	0.59	0.19	1.40	20	1.06	0.65	1.64	21	1.13	0.70	1.72
Breast	78	1.12	0.88	1.40	13	0.89	0.47	1.52	41	1.44	1.03	1.95	24	0.90	0.58	1.34
Cervix	13	0.97	0.51	1.66	2	0.76	0.07	2.78	6	1.10	0.40	2.41	5	0.94	0.30	2.20
Endometrium	22	1.28	0.80	1.93	4	1.27	0.33	3.29	7	0.99	0.39	2.05	11	1.57	0.78	2.81
Ovary	20	1.31	0.80	2.03	4	1.39	0.36	3.60	10	1.63	0.78	3.01	6	0.96	0.35	2.11
Prostate	89	0.97	0.78	1.19	12	0.76	0.39	1.34	39	1.05	0.75	1.44	38	0.97	0.69	1.34
Kidney	16	0.76	0.43	1.23	3	0.82	0.15	2.42	7	0.83	0.33	1.72	6	0.66	0.24	1.44
Urinary bladder	25	0.81	0.53	1.20	4	0.74	0.19	1.91	12	0.97	0.50	1.69	9	0.70	0.32	1.33
Melanoma	20	1.32	0.80	2.04	7	1.85	0.73	3.82	8	1.25	0.53	2.47	5	1.00	0.32	2.36
Skin	37	1.60	1.13	2.21	6	1.66	0.60	3.64	14	1.54	0.84	2.59	17	1.64	0.95	2.63
Nervous system	17	0.96	0.56	1.55	2	0.53	0.05	1.95	10	1.39	0.66	2.57	5	0.75	0.24	1.76
Thyroid gland	7	1.42	0.56	2.95	2	1.89	0.18	6.97	3	1.53	0.29	4.53	2	1.06	0.10	3.88
Endocrine glands	16	1.53	0.87	2.49	7	3.20	1.27	6.64	3	0.69	0.13	2.06	6	1.51	0.54	3.31
Pituitary cancer	3	1.77	0.33	5.25	2	5.00	0.47	18.37	1	1.43	0.00	8.22	0			
Connective tissue	3	0.74	0.14	2.18	0				2	1.23	0.12	4.51	1	0.60	0.00	3.46
Non-Hodgkin's lymphoma	18	1.01	0.59	1.59	6	1.74	0.63	3.81	5	0.69	0.22	1.62	7	0.97	0.39	2.02
Hodgkin's disease	4	1.35	0.35	3.49	0				1	0.87	0.00	5.00	3	2.46	0.46	7.28
Myeloma	15	1.51	0.84	2.49	4	2.45	0.64	6.34	4	1.03	0.27	2.66	7	1.58	0.62	3.27
Leukemia	34	1.90	1.31	2.66	8	2.56	1.09	5.07	12	1.70	0.87	2.97	14	1.82	0.99	3.06
All	506	1.03	0.94	1.12	99	1.07	0.87	1.31	212	1.07	0.93	1.22	195	0.97	0.84	1.12

Bold type, 95%CI does not include 1.00.

incidence trends of these tumors since the start of the registration 1958. The registration primarily covers clinically recognized tumors, which is a small proportion of all pituitary adenomas (Ezzat *et al.* 2004). An extensive discussion on the incidence and prevalence rates of pituitary adenomas was recently published (Daly *et al.* 2006a). The Swedish Cancer Registry actually also includes tumors found at autopsy, but pituitary adenomas appear to be almost completely overlooked because the autopsy material provides few new cases (Center for Epidemiology 2004). The reason may be that in a routine autopsy there are no resources to carry out detailed analyses in order to verify whether any suspected finding is really a tumor. In this vein, only one percent of prostate cancer is reported from autopsies, a negligible addition to some 8000 clinically recognized tumors (Center for Epidemiology 2004). There has been a moderate increase in the incidence, particularly of male adenomas, up to the 1990s, but since then the incidence appears to have declined. The increase in

incidence in the early period may be related to an increase in active reporting, and in the later period to improved diagnostic techniques (Asa & Ezzat 2002). The apparent decline after year 2000 has a number of speculative explanations: notification activity may have declined for unknown reasons or, perhaps, because imaging techniques have replaced traditional histological examinations. Moreover, the introduction of effective tools for early diagnostics is initially increasing the incidence of the disease and later decreasing the incidence towards a steady-state level, as shown for mammographic screening (IARC 2002).

The overall incidence of recorded pituitary adenomas, 1/100 000 was quite similar to the rate in the Central Brain Tumor Registry of the United States (www.cbtrus.org). The age-incidence patterns showed a typical high risk at old age; the female excess at ages before 35 years has been ascribed to prolactinomas because of their earlier presentation in women (Ciccarelli *et al.* 2005). One may argue that if this

Table 2 Familial risk for pituitary tumors in offspring diagnosed at different ages when siblings were affected with cancers

Familial site	All age				≤40 Years				>40 Years			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	4	1.45	0.38	3.74	3	2.91	0.55	8.62	1	0.58	0.00	3.30
Stomach	5	2.42	0.76	5.69	2	2.72	0.26	10.00	3	2.25	0.42	6.67
Small intestine	1	1.82	0.00	10.44	1	4.89	0.00	28.03	0			
Colon	9	1.53	0.69	2.92	4	1.86	0.48	4.80	5	1.34	0.42	3.16
Rectum	6	1.62	0.58	3.56	2	1.52	0.14	5.58	4	1.68	0.44	4.35
Liver	1	0.58	0.00	3.35	1	1.60	0.00	9.15	0			
Pancreas	1	0.56	0.00	3.19	1	1.57	0.00	8.98	0			
Lung	11	1.62	0.80	2.90	6	2.53	0.91	5.55	5	1.13	0.36	2.65
Breast	38	1.46	1.03	2.01	17	1.73	1.00	2.77	21	1.30	0.80	1.99
Cervix	4	0.94	0.25	2.44	2	1.08	0.10	3.96	2	0.84	0.08	3.09
Endometrium	2	0.52	0.05	1.92	0				2	0.79	0.07	2.92
Ovary	4	0.92	0.24	2.37	2	1.20	0.11	4.43	2	0.74	0.07	2.72
Prostate	10	1.30	0.62	2.40	3	1.22	0.23	3.62	7	1.33	0.53	2.76
Kidney	7	2.20	0.87	4.56	1	0.85	0.00	4.87	6	3.00	1.08	6.56
Urinary bladder	7	1.62	0.64	3.36	4	2.63	0.68	6.81	3	1.07	0.20	3.18
Melanoma	8	0.95	0.40	1.87	3	0.83	0.16	2.47	5	1.03	0.32	2.42
Skin	1	0.40	0.00	2.32	0				1	0.64	0.00	3.68
Nervous system	6	0.81	0.29	1.76	3	0.90	0.17	2.68	3	0.73	0.14	2.15
Thyroid gland	0				0				0			
Endocrine glands	4	1.07	0.28	2.76	0				4	1.79	0.47	4.63
Connective tissue	2	1.64	0.16	6.05	1	1.88	0.00	10.79	1	1.46	0.00	8.37
Non-Hodgkin's lymphoma	3	0.63	0.12	1.87	1	0.54	0.00	3.09	2	0.69	0.07	2.54
Hodgkin's disease	4	2.72	0.71	7.04	0				4	5.40	1.40	13.96
Myeloma	1	0.83	0.00	4.77	0				1	1.28	0.00	7.31
Leukemia	2	0.55	0.05	2.02	1	0.61	0.00	3.47	1	0.50	0.00	2.89
All	75	1.14	0.90	1.43	30	1.15	0.77	1.64	45	1.14	0.83	1.52

Bold type, 95%CI does not include 1.00.

were correct, the female excess should be seen throughout the reproductive period. The counterargument is that, the number of cases being constant, are shifted into one age group leaves a deficit in another group. Pituitary tumors were found to be in excess in female, and to a lesser extent in male same-sex twins; this was speculated to be related to the postnatal growth period, during which twins catch up the weight of singletons but the hypothesis may not be correct

because the effect was not seen in different sex twins (Hemminki & Chen 2005).

Multiple comparisons are a major source of spurious results in the present kinds of studies. A formal approach to deal with the problem is to adjust the CIs to the number of comparisons; however, because there is no agreement on how the adjustment should be made, we emphasize the value of high SIRs and 95%CIs extensively deviating from the borderline value of 1.00.

Table 3 Familial risk for pituitary tumors when parents were affected with leukemia

Leukemia subtypes	All age				≤40 Years				>40 Years			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Acute lymphatic leukemia	2	2.90	0.27	10.68	1	3.29	0.00	18.87	1	2.60	0.00	14.89
Chronic lymphatic leukemia	17	2.59	1.51	4.16	6	2.11	0.76	4.62	11	2.96	1.47	5.31
Acute myeloid leukemia	6	1.64	0.59	3.58	4	2.38	0.62	6.16	2	1.01	0.09	3.70
Chronic myeloid leukemia	2	1.07	0.10	3.92	1	1.22	0.00	7.00	1	0.95	0.00	5.42
Polycythaemia vera	5	2.08	0.66	4.89	3	2.95	0.56	8.74	2	1.44	0.14	5.29
Myelofibrosis	2	2.70	0.25	9.93	1	2.81	0.00	16.11	1	2.60	0.00	14.91
Other leukemia	2	1.96	0.18	7.19	0				2	3.29	0.31	12.09
All leukemia	34	1.90	1.31	2.66	15	1.91	1.07	3.16	19	1.89	1.14	2.96

Bold type, 95%CI does not include 1.00.

Other pointers are biological plausibility and agreement with previous hypotheses and results, all of which will be evoked in the discussion below.

Among a total of 3239 pituitary tumor patients, only 3 concordant parent–offspring pairs were identified and although the familial SIR was clearly above unity (1.77), it was not significant. However, the proportion of familial cases may not be substantially smaller than that in the European study by [Daly et al. \(2006b\)](#). The size of the covered population was not given in that study but two of the participating 22 clinics were able to provide a sporadic population of 2600 pituitary adenoma patients diagnosed after age 34 years. One can assume that the population covered by all the 22 clinics thus far exceeded the population covered by the Swedish Database. Furthermore, being clinically based, the European study could identify affected family members back in history ([Daly et al. 2006b](#)).

Colorectal cancer is the only cancer type considered to be increased in acromegaly patients ([Jenkins et al. 2006](#)). Since only some 25–30% of the surgically removed pituitary adenomas secrete GH ([DeLellis et al. 2004](#)) and since our Database contains no details on the hormone-secreting properties of the tumors, we decided to test whether an indication of GH adenoma involvement could be found through a possible association of pituitary adenomas with colorectal cancer in families. Indeed, the risk of pituitary adenoma was marginally increased in individuals whose parents or siblings were diagnosed with colorectal cancer. Although we cannot definitely exclude contribution by other syndromes with a pituitary involvement, such as MEN1 and Carney complex ([DeLellis et al. 2004](#)), the results were identical when the analyses were repeated after the removal of all families presenting with any endocrine tumors other than pituitary adenomas. The Database contains no information on cancer syndromes but these can be deduced from pathognomonic presentation of tumors. We have reported elsewhere that, according to the Family-Cancer Database, the risk for a second pituitary tumor after an initial pituitary tumor is increased ([Hemminki & Jiang 2001](#)); in the most recent follow-up, the risk was 15.0 (8.2–25.2, $N=14$); pituitary tumors were also in excess in patients first diagnosed with colorectal cancer (SIR 2.2, 1.5–3.1, $N=30$; [Hemminki et al. 2006](#)). These data were considered to provide population-level support to the notion that GH-secreting pituitary adenomas constitute an inherited cancer predisposition with a low risk and perhaps many apparently sporadic cases ([Daly et al. 2005a,b](#), [Vierimaa et al. 2006](#)).

The novel findings of the present study concerned the associated tumors, most notably hemangiopericytoma, with a familial association of 182. Although only two nervous system hemangiopericytomas were diagnosed in families presenting with pituitary adenoma, there were no more than 15 cases of these tumors in the Family-Cancer Database, covering a population base of 10.5 million. Being extremely rare tumors, the literature on hemangiopericytomas is limited. The WHO Pathology and Genetics series refers to a case report on one family with three affected individuals ([Kleihues & Cavenee 2000](#)). Interestingly, hemangiopericytomas, as many other tumors, are thought to be rich in insulin-like growth factor receptors, thus potentially mechanistically linking these tumors to the GH-pathway ([Elias et al. 2002](#)).

Among the tumors that associated with pituitary adenoma in families, breast cancer could also possibly be linked to GH overproduction, as suggested in some previous studies ([Webb et al. 2002](#), [Bogazzi et al. 2006](#), [Jenkins et al. 2006](#)). Moreover, there is a strong evidence associating prolactin overproduction with an increased risk of postmenopausal breast cancer and prolactin genotypes with familial breast cancer ([Tworoger & Hankinson 2006](#), [Tworoger et al. 2006](#), [Vaclavicek et al. 2006](#)). The associations of pituitary adenoma with breast cancer were obtained among parents and offspring, and among siblings, strengthening the evidence. The other associated neoplasms, chronic lymphatic leukemia, kidney and skin cancers and Hodgkin's disease were detected either through parental or sibling probands, but not with both, and they need to be confirmed in other settings. Interestingly, all these associations tended to be stronger in older pituitary tumor patients.

This nationwide study on familial pituitary adenomas suggested an association with nervous system hemangiopericytomas and breast and colorectal cancers, in addition to some other tumor types. These associated tumors have not been reported as manifestations in MEN1 or Carney complex. Whether they are linked to the recently characterized AIP mutations remains to be established.

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