Familial Risks in Nervous System Tumors

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Abstract

We used the nationwide Swedish Family-Cancer Database to analyze the risk for nervous system tumors in offspring through parental and sibling probands. Among 0–68-year-old offspring, close to 11,000 patients with a nervous system tumor were identified in years 1961 to 2000, among whom 199 had a parent diagnosed with a nervous system tumor. Brain tumors constituted 86% of all tumors, and astrocytoma was the main histological type, representing half of all cases. Standardized incidence ratios (SIRs) for familial risk were only increased for brain tumors of meningioma, astrocytoma, and hemangioblastoma histology. When parents were diagnosed with tumors of the same histology, the SIRs for offspring were 3.06, 2.19, and 165 for meningioma, astrocytoma, and hemangioblastoma, respectively. Among siblings, the SIRs were 4.41, 3.20, and 61. Age-specific analysis of familial astrocytoma revealed three distinct components, one < 10 years, the second ~age 30 years, and the third at age >60 years. The kappa test was used to assess the likelihood of an identical histology in two family members. The occurrence of hemangioblastoma was completely determined among the siblings, and the kappa value was 1.00. Meningiomas were also moderately ordered among the siblings, but astrocytomas were less determined. Many syndromes are known in which nervous system tumors are manifestations, including hemangioblastoma, recognized as part of von Hippel-Lindau disease. Yet, it is likely that many brain astrocytoma, meningioma, and mixed families represent yet unknown heritable conditions.

Introduction

According to the ICD[3] version 7, tumors of the nervous system are divided by anatomical location to those of brain, spine, and peripheral nerves. The incidence of these tumors in Sweden is ~10, 0.8, and 0.3/100,000, respectively (1). Histologically, the most common brain tumors are (in this order) astrocytomas of different kinds, meningiomas, neurinomas (schwannomas), ependymomas, and medulloblastomas; spinal tumors are meningiomas and neurinomas; peripheral nerve tumors are neurinomas, neurofibrosarcomas, and neuroblastomas (2). In Sweden, brain tumors are the most common childhood neoplasia, constituting some 7% of all diagnosed brain tumors (1). Brain tumors of children and young adults are preferentially pilocytic and diffuse astrocytomas, medulloblastomas, and ependymomas (2). Therapeutic irradiation and family history are the only established risk factors of nervous system tumors (3). Nervous system tumors are manifested in many rare cancer syndromes such as Li-Fraumeni, neurofibromatosis 1 and 2, von Hippel-Lindau, Turcot, and Gorlin (2, 4–6). It is not known how large a fraction of nervous system tumors these syndromes account for; for childhood brain tumors, identified genetic conditions were thought to cover some 2% (7). Population-based family studies have mainly covered brain cancers or all nervous system tumors combined; familial risks in adults have been ~1.8–1.9 in Sweden (8–12) and Utah (13). However, no increase in familial glioma has been found in Iceland (14). No increased risk of brain cancer has been observed in parents of childhood brain cancer patients (15) nor among offspring of survivors of childhood brain cancer (16).

Here, we analyze the risk of familial nervous system tumors of any age and of defined histological type using the newest update of the nationwide Swedish Family-Cancer Database (17). Compared with previous brain cancer studies from this Database, an extended population (offspring from year 1932 onwards compared with year 1935 earlier), more cancer cases (follow-up, including year 2000 compared with year 1996), and a more refined histological classification (covering 8 years compared with 4 years) are being used, allowing analysis by age of onset through parental and sibling probands. In the Database, family relationships and cancers were obtained from registered sources of practically complete coverage, reducing chances for bias.

Subjects and Methods

Statistics Sweden maintains a "Multigeneration Register" where children, offspring, born in Sweden in 1932 and later, are registered with their parents (those pleading parenthood at birth), and they are organized as families (17). Information on the database is also available at the Nature Genetics web site as "Supplementary Information" to Ref. 18. The data on families and cancers have a complete coverage, barring some groups of deceased offspring, which affect those born in the 1930s and who died before 1991. Although this small group of offspring with missing links to parents has negligible effect on the estimates of familial risk (19), we limited the present study to offspring whose parents were known to eliminate possibility of bias. This register was linked by the individually unique national registration number to the Cancer Registry from years 1958–2000. Cancer registration is considered to be close to 100% currently (1). Only the first primary nervous system

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[3] The abbreviations used are: ICD, International Classification of Diseases; SNOMED, Systematized Nomenclature of Medicine; SIR, standardized incidence ratio; CI, confidence interval; IR, incidence rate.

Table 1 Number of cases of offspring nervous system tumors, 1961–2000

Subsites and histological types	All cases			Familial cases[a]		
	No.	%	IR[b]	No.	%	IR
Subsites						
Brain	9414	85.6	8.2	172	86.4	16.8
Intraspinal	688	6.3	0.6	13	6.5	0.6
Peripheral nerves	448	4.1	0.2	6	3.0	0.3
Multiple parts	9	0.1	0.0	0	0.0	0.0
Part unspecified	438	4.0	0.6	8	4.0	0.5
All	10997	100.0	9.6	199	100.0	18.2
Histological types of brain cancer						
Medulloblastoma	356	3.8	0.1	3	1.7	0.1
Neurinoma	830	8.8	0.8	17	9.9	2.8
Meningioma	1845	19.6	2.1	37	21.5	5.9
Astrocytoma	4469	47.5	4.0	88	51.2	7.0
Ependymoma	336	3.6	0.2	4	2.3	0.2
Hemangioblastoma	293	3.1	0.2	8	4.7	0.3
Others	1285	13.6	0.8	15	8.7	0.6
All	9414	100.0	8.2	172	100.0	16.8

[a] Parent with nervous system tumor.
IR/100,000.

Table 2 Familial SIR for subsites of nervous system tumors in offspring when parents or siblings are probands[a]

Proband age (yrs) at diagnosis	Brain				Intraspinal				Peripheral nerves				Part unspecified				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Parent																				
0–14	24	**1.98**	**1.27**	**2.95**	1	1.47	0.00	8.41	1	0.68	0.00	3.92	1	6.83	0.00	39.13	27	**1.87**	**1.23**	**2.73**
15–29	29	**1.74**	**1.17**	**2.50**	4	2.32	0.60	5.99	3	3.47	0.65	10.28	1	3.93	0.00	22.51	37	**1.90**	**1.33**	**2.61**
30–44	52	**1.63**	**1.22**	**2.14**	7	**2.70**	**1.07**	**5.60**	1	1.56	0.00	8.91	3	2.21	0.42	6.53	63	**1.73**	**1.33**	**2.21**
45–59	51	**1.44**	**1.07**	**1.89**	1	0.48	0.00	2.74	1	2.01	0.00	11.51	3	1.10	0.21	3.24	56	**1.37**	**1.04**	**1.78**
≥60	16	**3.11**	**1.77**	**5.06**	0				0				0				16	**2.62**	**1.49**	**4.26**
All	172	**1.70**	**1.45**	**1.97**	13	1.74	0.92	2.99	6	1.70	0.61	3.72	8	1.59	0.68	3.16	199	**1.70**	**1.47**	**1.95**
Sibling																				
0–14	9	**2.27**	**1.03**	**4.33**	0				0				0				9	1.91	0.86	3.63
15–29	18	**3.38**	**2.00**	**5.35**	1	1.74	0.00	9.98	3	**10.00**	**1.89**	**29.61**	0				22	**3.50**	**2.19**	**5.31**
30–44	30	**2.69**	**1.81**	**3.84**	2	2.15	0.20	7.89	1	4.02	0.00	23.06	0				33	**2.58**	**1.77**	**3.63**
45–59	17	1.13	0.65	1.81	0				0				1	0.88	0.00	5.07	18	1.04	0.61	1.64
≥60	8	**3.30**	**1.41**	**6.53**	0				0				0				8	**2.80**	**1.20**	**5.54**
All	82	**2.16**	**1.72**	**2.68**	3	1.08	0.20	3.19	4	3.14	0.82	8.12	1	0.52	0.00	2.97	90	**2.05**	**1.64**	**2.52**

[a] Bold type: 95% CI does not include 1.00. O, observed.

tumors were considered. A four-digit diagnostic code according to the ICD-7 was used; the code 1930 was used for brain cancer, 1931 for spinal tumors, and 1933 for peripheral nerve tumors. The histological classification of brain tumors was used, as present in the Cancer Registry, to define astrocytoma (pathology codes 471–476), medulloblastoma (436), neurinoma (451–456), ependymoma (481–486), meningioma (461–466), and hemangioblastoma (501). These codes have been used since the start of cancer registration in Sweden (WHO/HS/CANC/24.1 Histology Code). From year 1993 onwards, ICD-O-2/ICD with histopathological data according to the SNOMED[4] was used; we refer to this classification as SNOMED.

SIRs were used to measure the cancer risks for offspring according to occurrence of cancers in their families. SIRs were calculated for offspring whose parent or sibling had the same concordant cancer, *i.e.*, using parents or sibling as probands. Follow-up was started for each offspring at birth, immigration, or January 1, 1961, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration, or the closing date of the study, December 31, 2000. When >2 affected offspring were found in any family, they were counted as independent event; however, this applied only to three families and had minimal effect on the results.

Parents' ages were not limited but offspring were 0–68 years of age. All tumor IRs were based on the data in the Family-Cancer Database, and they are essentially similar to rates in the Swedish Cancer Registry. Rates were standardized to the European population. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, sex-, tumor type-, period- (5-year bands), socioeconomic status- (six groups), and residential area- (three groups) specific standard IRs for all offspring lacking a family history (20). Because >98% of all offspring lacked family history, the reference rate was essentially that for the whole population. CIs (95% CI) were calculated assuming a Poisson distribution (20). Risks for siblings were calculated using the cohort method, described and discussed elsewhere (21). In this method, sibships of two or more are included and all siblings contribute to cases and person

[4] Internet address: http://snomed.org.

years. Families with multiple affected individuals are ascertained at multiple times, and they are not independent, leading to too narrow CIs (approximately by a factor of 1.4; Ref. 22); no correction was done in the present article.

The kappa statistic was used as the measure of agreement between histologies: (observed proportion in agreement − expected proportion in agreement)/(1 − expected proportion in agreement; Ref. 22). The kappa can assume values between −1 and 1; 0 shows a complete chance occurrence, and −1 or 1 show a complete concordance or discordance. Values between 0.40 and 0.60 are considered moderately concordant. We only present positive values of the kappa because only the concordance of histological types is relevant in this context.

Results

The Family-Cancer Database covered years 1961–2000 from the Swedish Cancer Registry and included 10997 cases of nervous system cancer in 0−68-year-old offspring (Table 1). Brain tumors accounted for 85.6% of all tumors, with an age-standardized IR of 8.2/100,000. A parental family history of nervous system cancer was found for 199 cases (1.81%). The most common histological types were astrocytoma, almost one-half of all, meningioma, and neurinoma. The incidence of familial cases was almost twice as high as that of all cases.

Age-specific familial risk for nervous system neoplasms was analyzed using parents or siblings as probands (Table 2); the age of the probands was not stratified. The overall SIRs were 1.70 and 2.05, respectively. Because of the largest number of cases, only brain tumors showed a significant overall familial risk: 1.70 when a parent and 2.16 when a sibling was diagnosed with nervous system tumor. Brain tumors diagnosed in childhood (<15 years) showed marginally higher SIRs than the total SIRs. SIR for intraspinal tumors was increased in one age group, similar to peripheral nerve neoplasms. Among the familial intraspinal tumors, neurinoma and meningioma were the most common histologies; neurofibrosarcomas accounted for most spinal tumors.

Analysis was carried out by specific subtype of brain tumor in offspring using parents or siblings as probands (Table 3). The overall SIRs were significant for meningioma, astrocytoma, and hemangioblastoma (only from parental probands). Astrocytoma risks showed a U-shaped age dependence; familial hemangioblastoma affected only young individuals, whereas neurinoma and meningioma affected preferentially those >60 years of age, but the number of neurinoma cases was small. Among the 8 hemangioblastoma patients of affected parents, 1 had an insulinoma and another a renal cancer as a second neoplasm, and a third patient had a sibling with paraganglioma. Among parents, 5 had hemangioblastoma. The affected offspring were diagnosed between ages 12 and 32 years.

Age-specific incidence of brain astrocytoma and familial SIR are shown in Fig. 1*A* for offspring of parents with nervous system tumors; Fig. 1*B* shows the same curves for brain astrocytoma in siblings. The data on SIRs are modified from Table 3. The curves for SIRs resemble each other, independent of the proband status, although the middle incidence peak occurs at an earlier age among siblings. An early onset maximum was noted for ages < 10 years and perhaps a late onset maximum at ages > 60 years. We analyzed all cancers in the families constituting the three incidence peaks in Fig. 1 to find evidence on known cancer syndromes. The astrocytoma cases had 161 siblings who had only four cancers, all of different types; however, 1 person diagnosed for astrocytoma at the age of 48 years had a sibling with colon cancer diagnosed at the age of 36,

Table 3 SIR for histological types of brain tumor in offspring when parents or siblings are probands[a]

Proband age (yrs) at diagnosis	Medulloblastoma			Neurinoma			Meningioma			Astrocytoma			Ependymoma			Hemangioblastoma			All		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Parent																					
0–14	1	0.62	0.00 3.56	1	14.37	0.01 82.36	0			16	**2.58**	**1.47 4.20**	3	2.66	0.50 7.87	1	7.28	0.00 41.72	24	**1.98**	**1.27 2.95**
15–29	2	4.34	0.41 15.96	3	2.08	0.39 6.16	3	2.10	0.40 6.21	9	1.09	0.49 2.08	1	1.74	0.00 9.99	6	**6.10**	**2.19 13.36**	29	**1.74**	**1.17 2.50**
30–44	0			4	1.05	0.27 2.71	14	1.77	0.97 2.98	26	**1.78**	**1.16 2.62**	0			1	0.77	0.00 4.40	52	**1.63**	**1.22 2.14**
45–59	0			6	1.35	0.49 2.97	15	1.26	0.70 2.08	29	**1.86**	**1.25 2.68**	0			0			51	**1.44**	**1.07 1.89**
≥60	0			3	**8.73**	**1.65 25.83**	5	**3.33**	**1.05 7.84**	8	**2.69**	**1.15 5.33**	0			0			16	**3.11**	**1.77 5.06**
All	3	1.23	0.23 3.64	17	1.68	0.98 2.70	37	**1.61**	**1.13 2.22**	88	**1.85**	**1.48 2.28**	4	1.38	0.36 3.58	8	**2.47**	**1.06 4.90**	172	**1.70**	**1.45 1.97**
Sibling																					
0–14	1	1.90	0.00 10.92	1	41.84	0.02 239.84	0			5	2.48	0.78 5.82	1	2.74	0.00 15.73	0			9	**2.27**	**1.03 4.33**
15–29	0			1	2.11	0.00 12.07	1	2.10	0.00 12.01	7	**2.69**	**1.07 5.57**	1	5.40	0.00 30.94	2	6.34	0.60 23.33	18	**3.38**	**2.00 5.35**
30–44	0			2	1.47	0.14 5.42	6	2.06	0.74 4.52	17	**3.44**	**2.00 5.53**	1	4.24	0.00 24.33	0			30	**2.69**	**1.81 3.84**
45–59	0			3	1.60	0.30 4.75	8	1.59	0.68 3.15	5	0.75	0.24 1.75	0			0			17	1.13	0.65 1.81
≥60	0			0			3	4.19	0.79 12.40	3	2.17	0.41 6.42	0			0			8	**3.30**	**1.41 6.53**
All	1	1.25	0.00 7.19	7	1.79	0.71 3.72	18	**1.96**	**1.16 3.10**	37	**2.10**	**1.48 2.89**	3	3.02	0.57 8.93	2	1.74	0.16 6.41	82	**2.16**	**1.72 2.68**

[a] Bold type: 95% CI does not include 1.00. O, observed.

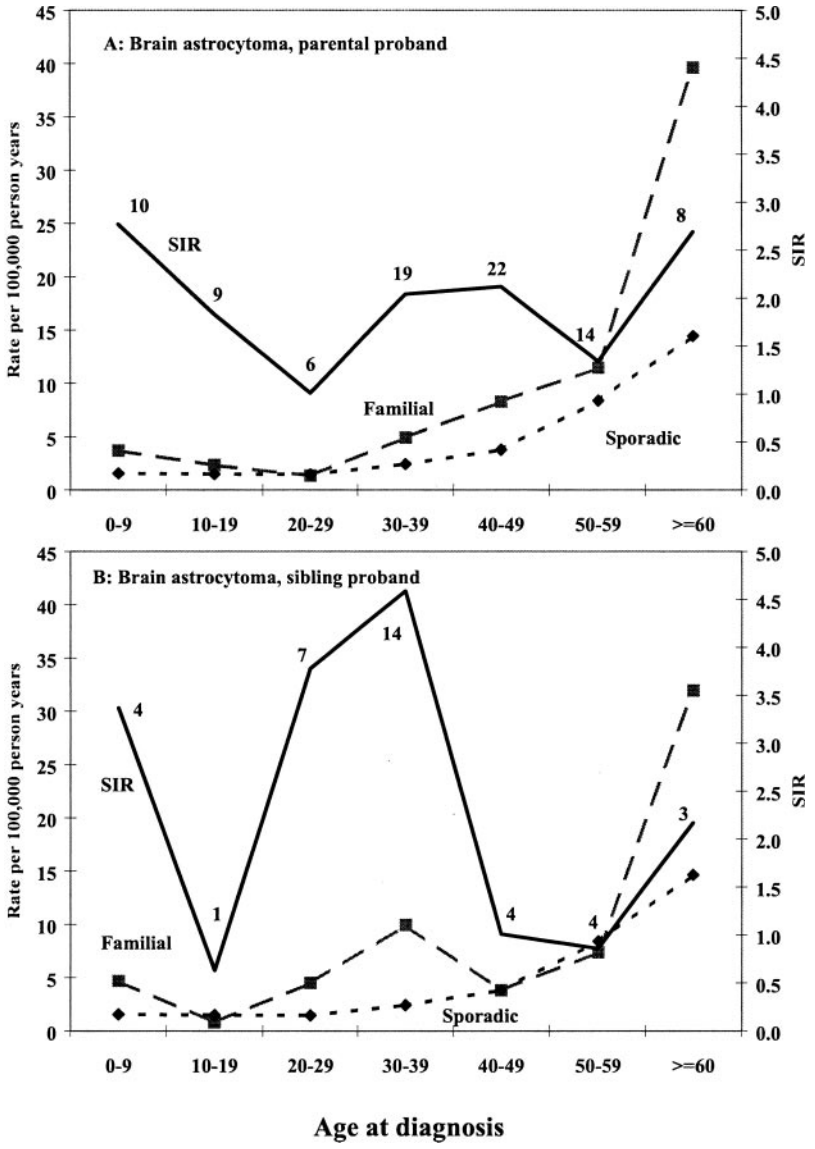

Fig. 1. Age-specific incidence and SIR for brain astrocytoma in offspring of parents (*A*) or among siblings (*B*) when the proband was diagnosed with a nervous system tumor. The data are modified from Table 3. The figures above the SIR curves indicate the number of cases. All data points with >6 cases have lower CIs at over 1.00.

suggesting Turcot syndrome. Parents of the childhood cases (<19 years) had different tumors, 7 (39%) had astrocytoma, 6 (33%) meningioma, 3 neurofibrosarcoma, and 2 neurinoma, diagnosed between ages 29 and 81 years. In astrocytomas diagnosed at a higher age, parental tumors were mainly astrocytomas (close to 65%) and meningiomas (30%).

Analysis was extended to specific histological types in offspring using parents or siblings as probands (Table 4). The numbers of cases were small for any combinations of specific histologies, and only some concordant histologies showed significantly increased SIRs. Risk for concordant meningioma was 3.06 among offspring and parents and 4.41 among siblings. For hemangioblastoma, the SIRs were 165 and 60, respectively. We searched all cancers in the concordant meningioma families and found 40 siblings to the affected individuals; they had three cancers of different type.

Analysis was also carried out using the SNOMED histopathology, which was available only from year 1993 onwards, and thus, less cases were retrieved (data not shown). Familial glioblastoma showed an age maximum at 45–59 years, and the overall risk was equal to that of astrocytoma when a parent had a nervous system tumor (glioblastoma, $n = 17$, SIR = 2.19, 95% CI = 1.27–3.51; astrocytoma, $n = 24$, SIR = 2.16, 95% CI = 1.38–3.22). Neurilemmoma showed a high risk at ages > 60 years ($n = 3$, SIR = 5.94, 95% CI = 1.12–17.58).

Kappa test was applied to assess the histological concordance of brain tumors (data not shown). Hemangioblastoma showed the highest kappa, 0.85 between offspring and parents and 1.00 between siblings. Kappa values of meningioma and astrocytoma among offspring and parents were not histology specific and they ranged between 0.28 and 0.36. However, among siblings, histology-specific tumors showed the highest kappa values, 0.46 for meningioma and 0.37 for astrocytoma. Among offspring and parents, kappa values were 0.27 for neurinoma and meningioma.

In the Database, five families had a parent and 2 offspring affected by nervous system tumors. In two families, all patients had an astrocytoma; in the remaining three families, the af-

Table 4 SIR for histological types of brain tumor in offspring when parents or siblings are probands[a]

Proband histological types	Neurinoma			Meningioma			Astrocytoma			Ependymoma			Hemangioblastoma			All		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Parent																		
Neurinoma	2	3.77	0.35 13.85	2	1.76	0.17 6.48	5	1.78	0.56 4.18	0			0			11	1.88	0.93 3.38
Meningioma	4	1.49	0.39 3.85	19	**3.06**	**1.84 4.79**	17	1.39	0.81 2.22	1	1.42	0.00 8.11	0			47	**1.79**	**1.32** 2.38
Astrocytoma	6	1.39	0.50 3.05	10	1.04	0.50 1.92	45	**2.19**	**1.60 2.93**	2	1.58	0.15 5.81	1	0.71	0.00 4.07	68	**1.57**	**1.22** 1.99
Ependymoma	0			0			0			1	28.99	0.01 166.15	0			3	2.88	0.54 8.54
Hemangioblastoma	0			0			0			0			6	**165.75**	**59.65 363.15**	7	**6.68**	**2.65 13.84**
All	14	1.52	0.83 2.57	34	**1.63**	**1.13 2.28**	75	**1.74**	**1.37 2.18**	4	1.55	0.40 4.00	7	2.39	0.95 4.95	149	**1.63**	**1.38 1.91**
Sibling																		
Neurinoma	0			0			3	2.14	0.40 6.35	0			0			4	1.31	0.34 3.39
Meningioma	0			10	**4.41**	**2.10 8.14**	5	1.36	0.43 3.21	0			0			17	**2.10**	**1.22 3.37**
Astrocytoma	3	2.00	0.38 5.93	5	1.44	0.45 3.38	22	**3.20**	**2.01 4.86**	0			0			33	**2.24**	**1.54 3.15**
Ependymoma	0			0			0			0			0			3	3.56	0.67 10.52
Hemangioblastoma	0			0			0			0			2	**60.98**	**5.75 224.24**	2	1.99	0.19 7.33
All	4	1.21	0.31 3.12	17	**2.18**	**1.27 3.50**	33	**2.22**	**1.53 3.12**	3	3.58	0.67 10.59	2	2.07	0.19 7.60	70	**2.18**	**1.70 2.76**

[a] Bold type: 95% CI does not include 1.00. O, observed.

fected individuals had tumors of different histologies, two of which included one spinal tumor. No unambiguous assignment of these patients to a known syndrome was possible.

Discussion

The problems of inaccurate reporting of cancers in family members, a weakness in many case-control studies (23), can be avoided when registered sources of medically verified cases are used, as in the present study from the Swedish Family-Cancer Database. The reporting of nervous system tumors may be particularly problematic because of common metastasis in the brain. However, even unbiased population-based studies cannot distinguish cancer syndromes that account for a small proportion of familial aggregation for a particular type of histology. Another inherent limitation is that in the Swedish Cancer Registry, the detailed SNOMED histology-topology was taken to use in year 1993, and it could usually cover no more than one recent familial case. Because of these limitations, it was not possible to single out families with many known syndromes affecting the nervous system, including neurofibromatosis 1 and 2, although for these conditions, intraspinal and peripheral nerve tumors of defined histological types suggested identity. Hemangioblastoma was an exception because it is a manifestation in a syndrome in which many rare tumors show high penetrance. In families with hemangioblastoma, second tumors and tumors in siblings indicated that the cause was von Hippel-Lindau disease (23, 24).

The overall familial risk for nervous system tumors of 1.70 in offspring of parental nervous system tumor patients is in line with earlier publications on brain tumors from this and other sources (8–13, 25). Although the present study was the largest yet published, we were unable to note overall familial risks for intraspinal and peripheral nerve tumors. In the discussion below, we only take up the new findings of the present study and refer a general discussion to our earlier publications.

Because of the large numbers, we were able to describe age-specific familial risks to some extent. In all nervous system cancer, the risk was maximal in the twenties among siblings. In offspring of affected parents, the maximum was broader, covering ages 10–39 years and a late onset maximum at ages $>$ 60 years. In astrocytoma, three maxima were noted, one in childhood, $<$10 years, the second $\sim$30–39 years, and the third one at $>$60 years. These distinct components could imply three different underlying causes. Astrocytomas occur early in tuberous sclerosis, and this condition may contribute to the childhood familial risk; however, because parental tumors were diagnosed at an older age and include also neurinomas and neurofibrosarcomas, the etiology is likely to be heterogeneous (2). Li-Fraumeni syndrome is characterized by occurrence of astrocytomas in the early thirties as the mean age but with a wide distribution, and it is probably part of the second familial component; Turcot syndrome could also contribute to this or the late onset familial component (2). Data from the Swedish glioma cohort suggest different etiologies for low- and high-grade gliomas (9). Furthermore, the familial risk was higher in low-grade glioma compared with the high-grade disease, a finding that we have also observed when analyzing familial risks in histology specific cancers (19).

The kappa test was used to study consistency of occurrence of a defined histology in tumors of different family members between offspring and parents and between siblings. The test statistic will approach 1.00 if the pairs of individuals always present with the identical histological type of tumor, *i.e.*, the histology is completely determined for reasons such as

heritability. Hemangioblastoma offered a proof of the principle. It showed a high kappa value of 0.85 between offspring and parents and 1.00 between siblings, supporting nonrandom, heritable causation. A kappa value 0.4 is considered of a moderately ordered occurrence, and among siblings, meningioma showed a value of 0.46 and astrocytoma 0.37. Between offspring and parents, concordant meningioma gave a kappa of 0.28 and astrocytoma 0.29, but a higher kappa, 0.36, was noted when these two histologies appeared in the same families. Lower kappa values between offspring and parents than between siblings, also noted for hemangioblastoma, may be attributable to a more defined disease phenotype within one generation than between two generations, relating to age and calendar time differences. The data suggest that familial meningioma has a heritable etiology and neurofibromatosis 2 is a known cause of such a clustering (2). However, in this condition, gliomas are located primarily in the spine and not in the brain, as the present results show, suggesting other contributing causes. In the present study, concordant meningiomas showed a higher familial risk than concordant astrocytomas, 3.06 and 2.19 through parental and 4.41 and 3.20 through sibling probands, respectively. The data suggest furthermore that some meningiomas and astrocytomas share a heritable etiology, although the kappa values were low among siblings, but these were based to small numbers. A co-occurrence of these tumors has also been observed in a Finnish study (26).

In summary, the present data suggest discrete familial components in brain astrocytoma and meningioma and familial coaggregation of these tumors in the same families. However, to what extent the familial aggregation can be explained by known heritable causes cannot be solved by epidemiological means alone and mutation analysis in the affected families is required. Overall, the clustering of many types of nervous system tumors in single families suggests that nervous system tumors present in multiple phenotypes, in analogy to the known syndromes and the complex results from segregation analysis on glioma (9, 27). Multiple phenotypes and heterogeneous etiologies are major challenges to gene identification efforts.

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References

1. Centre for Epidemiology. Cancer incidence in Sweden 2000. Stockholm: The National Board of Health and Welfare, 2002.

2. Kleihues, P., and Cavenee, W. (eds.). Tumors of the Nervous System. Lyon: IARC, 2000.

3. Stewart, B., and Kleihues, P. (eds.). World Cancer Report. Lyon: IARC Press, 2003.

4. Li, F. Phenotypes, genotypes, and interventions for hereditary cancers. Cancer Epidemiol. Biomark. Prev., *4:* 579–582, 1995.

5. Fearon, E. R. Human cancer syndromes: clues to the origin and nature of cancer. Science (Wash. DC), *278:* 1043–1050, 1997.

6. Huson, S. Neurofibromatosis type 1: historical perspective and introductory overview. *In:* M. Upadhyaya and D. Cooper (eds.), Neurofibromatosis Type 1, pp. 1–20. Oxford: BIOS, 1998.

7. Narod, S., Stiller, C., and Lenoir, G. An estimate of the heritable fraction of childhood cancer. Br. J. Cancer, *63:* 993–999, 1991.

8. Malmer, B., Grönberg, H., Bergenheim, A., Lenner, P., and Henriksson, R. Familial aggregation of astrocytoma in northern Sweden: an epidemiological cohort study. Int. J. Cancer, *81:* 366–370, 1999.

9. Malmer, B., Iselius, L., Holmberg, E., Collins, A., Henriksson, R., and Gronberg, H. Genetic epidemiology of glioma. Br. J. Cancer, *84:* 429–434, 2001.

10. Malmer, B., Henriksson, R., and Gronberg, H. Different aetiology of familial low-grade and high-grade glioma? A nationwide cohort study of familial glioma. Neuroepidemiology, *21:* 279–286, 2002.

11. Hemminki, K., Vaittinen, P., and Kyyrönen, P. Age-specific familial risks in common cancers of the offspring. Int. J. Cancer, *78:* 172–175, 1998.

12. Hemminki, K., Li, X., and Collins, V. Parental cancer as a risk factor for brain tumors (Sweden). Cancer Causes Control, *12:* 195–199, 2001.

13. Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A., and Skolnick, M. H. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J. Natl. Cancer Inst. (Bethesda), *86:* 1600–1607, 1994.

14. O'Neill, B. P., Blondal, H., Yang, P., Olafsdottir, G. H., Sigvaldason, H., Jenkins, R. B., Kimmel, D. W., Scheithauer, B. W., Rocca, W. A., Bjornsson, J., and Tulinius, H. Risk of Cancer among relatives of patients with glioma. Cancer Epidemiol. Biomark. Prev., *11:* 921–924, 2002.

15. Olsen, J. H., Boice, J. D., Seersholm, N., Bautz, A., and Fraumeni, J. J. F. Cancer in the parents of children with cancer. N. Engl. J. Med., *333:* 1594–1599, 1995.

16. Sankila, R., Olsen, J. H., Anderson, H., Garwicz, S., Glattre, E., Hertz, H., Langmark, F., Lanning, M., Moller, T., Tulinius, H. Risk of cancer among offspring of childhood-cancer survivors. N. Engl. J. Med., *338:* 1339–1344, 1998.

17. Hemminki, K., Li, X., Plna, K., Granström, C., and Vaittinen, P. The nationwide Swedish Family-Cancer Database: updated structure and familial rates. Acta Oncol., *40:* 772–777, 2001.

18. Hemminki, K., and Granström, C. Risk for familial breast cancer increases with age. Nat. Genet., *32:* 233, 2002.

19. Hemminki, K., and Li, X. Familial risk of cancer by site and histopathology. Int. J. Cancer, *103:* 105–109, 2003.

20. Esteve, J., Benhamou, E., and Raymond, L. Statistical Methods in Cancer Res. IARC Scientific Publication. Lyon: IARC, 1994.

21. Hemminki, K., Vaittinen, P., Dong, C., and Easton, D. Sibling risks in cancer: clues to recessive or X-linked genes? Br. J. Cancer, *84:* 388–391, 2001.

22. Armitage, P., and Berry, G. Statistical Methods in Medical Research. Oxford: Blackwell, 1994.

23. Hemminki, K., Li, X., and Collins, V. A population-based study of familial central nervous system hemangioblastomas. Neuroepidemiology, *20:* 257–261, 2001.

24. Friedrich, C. Von Hippel-Lindau syndrome. A pleomorphic condition. Cancer (Phila.), *86:* 2478–2482, 1999.

25. Wrensch, M., Lee, M., Miike, R., Newman, B., Barger, G., Davis, R., Wiencke, J., and Neuhaus, J. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am. J. Epidemiol., *145:* 581–593, 1997.

26. Paunu, N., Pukkala, E., Laippala, P., Sankila, R., Isola, J., Miettinen, H., Simola, K. O., Helen, P., Helin, H., and Haapasalo, H. Cancer incidence in families with multiple glioma patients. Int. J. Cancer, *97:* 819–822, 2002.

27. de Andrade, M., Barnholtz, J. S., Amos, C. I., Adatto, P., Spencer, C., and Bondy, M. L. Segregation analysis of cancer in families of glioma patients. Genet. Epidemiol., *20:* 258–270, 2001.