

Short Communication

Aggregation of Cancer in First-Degree Relatives of Patients with Glioma

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Abstract

Background: Previous studies have been inconclusive in estimating the risk of different cancer sites among close relatives of glioma patients; however, malignant melanoma has consistently been described.

Methods: We obtained family history information from 1,476 glioma patients under age 75 years who registered at M. D. Anderson Cancer Center between June 1992 and June 2006. The number of observed cancers ($N = 1,001$) among 8,746 first-degree relatives (FDR) was compared with the number expected from age-, sex-, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results Program using standardized incidence ratios (SIR).

Results: The overall SIR for any cancer was 1.21 (95% confidence interval, 1.14-1.29). Among FDRs under 45 years the overall SIR was 5.08, and for relatives >45 years the overall SIR was 0.95. The SIRs were significantly elevated for brain tumors (2.14), melanoma (2.02), and sarcoma (3.83). We observed an excess of pancreatic cancer, which was significantly higher only among mothers. **Conclusion:** We observed an overall 21% increase in cancer among the FDRs of glioma patients including excess cases of brain tumors and melanoma, which could point to similar genetic contributions to these two malignancies. A large international linkage study is under way to examine potential genomic regions important for familial glioma. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2491-5)

Introduction

Brain cancer is lethal to 12,820 persons in the United States and affects the remainder of the 18,820 Americans diagnosed with malignant brain tumors each year (1). Previous studies have contributed little in etiologic understanding, and thus families of patients, in addition to the grief over the death or disability of relatives, bear anxiety about their own risk of the disease. Researchers report that brain tumors are involved in heritable syndromes such as Li-Fraumeni, neurofibromatosis (types 1 and 2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial polyposis, and von Hippel-Lindau, but to what extent is unclear (2). In a definitive, population-based study of malignant glioma, Li et al. (3) found that only slightly more than half (58%) of *p53* mutation-positive patients were likely to have a first-degree relative (FDR) affected with cancer.

Early studies of familial aggregation of brain tumors have been mostly inconclusive; however, recent larger studies suggest an increased risk of primary brain tumors among FDRs of glioma cases (4-10). For individuals with a family history of brain tumors, the risk of developing any cancer has been reported between 1.0-1.8, and 1.0-9.0 for brain tumors (4-8, 10). Such ranges may be the result of differences in study methodologies, sample sizes, types of relatives included in the study, or ascertainment and validation of the cancer. Although findings of familial cancer aggregation suggest a genetic etiology, such aggregation may result from shared familial exposure to environmental agents, which may challenge genetic explanations of familial cancer aggregation.

We tested the genetic explanation of family aggregation by determining whether a large group of FDRs of glioma patients showed increased incidence for cancer overall, brain tumors, and several other sites.

Materials and Methods

Participants included 1,477 primary glioma probands, self-reported Caucasian race, U.S. or Canadian citizens, and registered at The University of Texas M. D. Anderson Cancer Center between June 1992 and June 2006. Each proband and/or next of kin was given an extensive

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Table 1. Demographic and clinical characteristics of glioma probands (N = 1,476)

	n (%)
Age at diagnosis (y)	
0-19	94 (6)
20-29	148 (10)
30-39	280 (19)
40-49	387 (26)
50-59	337 (23)
60-69	30 (2)
70-76	191 (13)
Mean age of probands at diagnosis (SE), 43.7 y (0.39)	
Median age of probands at diagnosis, 45 y	
Gender	
Male	864 (59)
Female	612 (41)
Male/female ratio, 1.4:1	
No. FDRs with cancer per family	
0	667 (45)
1	563 (38)
2	194 (13)
3+	52 (3.5)
No. FDRs with brain tumor per family	
0	1,429 (97)
1	46 (3)
2	1 (0.07)
Histology*	
High grade	691 (47)
Anaplastic	461 (31)
Low grade	288 (20)
Other	35 (2)

NOTE: Anaplastic—aplastic forms of astrocytoma, ependymoma, glioma, mixed (oligoastrocytoma), and oligodendroglioma. Low grade—astrocytoma, pilocytic astrocytoma, subependymal giant cell astrocytoma, ependymoma, ganglioma, juvenile pilocytic astrocytoma, mixed glioma, myxopapillary ependymoma, oligodendroglioma, optic nerve glioma, pleomorphic xanthoastrocytoma, and subependymoma. Other—astroblastoma, dysembryoplastic neuroepithelial tumors, primitive neuroectodermal tumors, and unclassified astrocytoma.

*High grade: glioblastoma, gliosarcoma, ependymoblastoma.

family health questionnaire to solicit information on the presence of cancer in the proband's FDRs. When possible, we obtained medical records or death certificates for relatives who reported a possible malignancy to confirm the report. Dates of birth, death, and cancer diagnosis were verified for those diagnosed and treated at a U.S. or Canadian hospital. Cancers were coded according to the International Classification of Diseases for Oncology (ICD-O-3; ref. 11).

To determine excess cancers in the FDRs, we computed standardized incidence ratios (SIR) as the ratio of the observed number of cancer cases among FDRs to the expected number using the Cohort Analysis for Genetic Epidemiology computer program (12). The expected number of cancers was determined using sex-, age-, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results (SEER) Program, including population-based registry data since 1975. For reported cancer diagnoses before 1975, the first year of record for SEER, we used the rates for 1975 to estimate number of expected cancers. We excluded cervical carcinoma *in situ* and nonmelanoma skin cancers, which are also excluded in SEER. Person-years were calculated from the date of birth to the first

date of the following events: cancer diagnosis, interview, or death. Person-years were calculated to the first primary cancer because Cohort Analysis for Genetic Epidemiology uses first primary cancers from SEER to compute the expected number of cancers. The SIRs for cancer among relatives were compared by proband's gender, age of glioma diagnosis, and histologic grade of glioma, and the age and sex of the FDR. The 95% confidence intervals (95% CI) for the SIRs were determined assuming a Poisson distribution for the observed number of cancers among FDRs.

The project was approved by the Institutional Review Board of M. D. Anderson Cancer Center. Each proband was given a questionnaire by trained interviewers.

Results

A total of 1,476 Caucasian probands (Table 1) and their FDRs were included in this analysis. This group is highly representative of the 1,907 Caucasian glioma patients seen at M. D. Anderson during that time period. All enrolled probands participated in the study; however, one proband and his FDRs were excluded because of a Li-Fraumeni-like pattern of cancers within the pedigree. Among the probands, 24% were proxy reported. The median age of the probands at presentation was 45 years; 6% were <20 years old at diagnosis. Among the probands, the male to female ratio was 1.4:1, and 47% were diagnosed with a high-grade glioma.

From a total of 8,858 FDRs, 8,746 (99%) were included in this analysis, contributing 391,784 person-years of follow-up (Table 2). The 112 FDRs were excluded due to missing information needed for the analysis (year of birth, sex, or age at cancer diagnosis). Among the FDRs, 17 (0.2%) were missing sex, and 163 (2%) were missing year of birth for which we imputed using the pedigree and birth order data. A previous validation study from our group showed that self-reported cancers were 85% accurate (13); in the current analysis, 84% of validated

Table 2. SIRs by proband characteristics (age, tumor histology), relative age at diagnosis, and relationship for all cancers in FDRs

	No.	P-Y	Obs	Exp	SIR (95% CI)
Proband age (y)					
<35	1,664	59,031	108	74.80	1.44 (1.18-1.74)
35-50	3,327	139,382	356	269.31	1.32 (1.19-1.47)
>50	3,755	193,371	537	481.37	1.12 (1.02-1.21)
Proband's histology					
High grade	4,377	209,204	564	480.39	1.17 (1.08-1.28)
Anaplastic	2,646	112,745	277	216.83	1.28 (1.13-1.44)
Low grade	1,555	64,060	148	118.99	1.24 (1.05-1.46)
Relative's age (y)					
<45	4,514	123,334	262	51.55	5.08 (4.49-5.74)
≥45	4,232	268,450	739	773.93	0.89 (0.89-1.03)
Relationship					
Fathers	1,418	90,451	352	297.98	1.18 (1.06-1.31)
Mothers	1,436	93,487	341	295.22	1.16 (1.04-1.28)
Siblings	3,345	148,941	277	210.17	1.32 (1.17-1.48)
Offspring	2,547	58,905	31	22.12	1.40 (0.95-1.99)
Total	8,746	391,784	1,001	825.48	1.21 (1.14-1.29)

Table 3. Cancer-specific SIRs for FDRs by gender of proband

	Total			Male proband		
	Obs	Exp	SIR (95% CI)	O	E	SIR (95% CI)
All malignancies	1,001	825.48	1.21 (1.14-1.29)	610	492.71	1.24 (1.14-1.34)
Bladder	29	46.16	0.63 (0.42-0.90)	17	27.96	0.61 (0.35-0.97)
Sarcoma	9	2.35	3.83 (1.75-7.26)	5	1.39	3.61 (1.16-8.41)
Brain	46	21.45	2.14 (1.57-2.86)	27	12.73	2.12 (1.40-3.09)
Breast (female)	160	150.31	1.06 (0.91-1.24)	98	88.94	1.10 (0.89-1.34)
Colorectal	104	85.89	1.21 (0.99-1.47)	58	51.94	1.12 (0.85-1.44)
Hodgkin's	15	12.03	1.25 (0.70-2.06)	11	7.07	1.56 (0.78-2.78)
Leukemia	38	32.74	1.16 (0.82-1.59)	26	19.6	1.33 (0.87-1.94)
Lung	109	145.41	0.75 (0.62-0.90)	65	87.64	0.74 (0.57-0.95)
Melanoma	72	35.69	2.02 (1.58-2.54)	55	21.08	2.61 (1.97-3.40)
Non-Hodgkin's	30	37.84	0.79 (0.53-1.13)	21	22.58	0.93 (0.58-1.42)
Pancreas	32	23.34	1.37 (0.94-1.94)	21	14.14	1.49 (0.92-2.27)
Prostate	86	96.40	0.89 (0.71-1.10)	55	58.39	0.94 (0.71-1.23)
Stomach	17	18.58	0.91 (0.53-1.46)	6	11.31	0.53 (0.19-1.16)
Thyroid	12	16.4	0.73 (0.38-1.28)	6	9.64	0.62 (0.23-1.35)
Uterine	27	40.76	0.66 (0.44-0.96)	16	24.44	0.65 (0.37-1.06)

reported cancers were in agreement with the self-report. During follow-up, 1,001 cancers were observed and 825 were expected (SIR, 1.21; 95% CI, 1.14-1.29) among the FDRs. Overall SIRs were significantly higher among parents and siblings and nonsignificantly elevated for the offspring of the probands.

The data partitioned by proband's age at diagnosis showed the highest SIR in relatives of probands diagnosed with glioma under age 35 years; however, the SIR was elevated regardless of the proband's diagnosis age (Table 2). SIRs for all cancers were similar in relatives regardless of tumor histology of the proband; however, FDRs of probands with anaplastic tumors had the highest SIR (Table 2). FDRs were five times as likely to develop cancer at an earlier age (<45 years) than expected (SIR, 5.08; 95% CI, 4.49-5.74).

Table 3 shows cancer site-specific SIRs among FDRs for 15 cancers, stratified by the proband's gender and age of the FDR at diagnosis. The FDRs of both male and female probands had elevated SIR for brain tumors and sarcoma. Melanoma was more common among relatives of male probands, and pancreatic cancer showed a borderline-significant increased SIR among relatives of male probands. Colorectal cancer incidence was elevated among relatives of female probands; however, the SIR was of borderline significance. None of the other cancers showed a significant risk increase. Whereas the increase in colorectal cancer among FDRs was not large for any one group of FDRs, the SIR was 9.78 for relatives who developed colorectal cancer at a young age (<45 years). This increase among young FDRs was also seen for pancreas, prostate, and stomach cancer, although these findings were based on small numbers of observed cases.

Examination of the SIRs by type of relative revealed that excess cases of brain cancer concentrated in fathers, brothers, and sisters, whereas the aggregation of sarcoma was among mothers and daughters (data not presented). Mothers, fathers, and sisters exhibited significant increases in melanoma, and mothers showed a significant increase in pancreatic cancer. Brothers had a greater occurrence of leukemia, and daughters showed no other increases at the other sites.

Discussion

This analysis of cancer in FDRs of glioma patients is among the largest done to date, apart from one study describing the Swedish population (7, 8). Because cancer incidence varies among Caucasians in different parts of the world, it is important to conduct well-designed cohort studies in different populations. We sought to determine whether a patient's family faced increased risk of cancer and showed that this was true for certain cancer sites and was often gender and age specific. Given that rates of glioma incidence are highest for Whites and the registry data from SEER are more complete for Whites, we focused on this group for the current analysis. We anticipate further analyses for our African American ($n = 58$) and Hispanic ($n = 114$) probands using the race/ethnic-specific rates available from SEER.

We found an overall 16% to 32% increase in expected cases for all malignancies in the FDRs of glioma cases. We also found an increase in the number of brain tumors among FDRs of glioma patients (SIR, 2.14; 95% CI, 1.57-2.86). Malmer et al. (7, 8) observed a similar SIR (2.12; 95% CI, 1.18, 3.49) among FDRs of probands with astrocytoma in Sweden. They later showed that the risk of low-grade gliomas was highest among FDRs with a family member who also had a low-grade glioma; similarly, those family members with high-grade gliomas were at highest risk if the proband also had a high-grade glioma (14). They reported a high risk for glioma among siblings, which we also found (SIR, 2.75). Paunu et al. (15) showed a 4-fold increased incidence of central nervous system tumors among families that included two or more glioma cases. In addition, they showed that the incidence of central nervous system tumors was higher for relatives of late-onset glioma cases. We also observed the highest SIR for brain tumors in the FDRs of glioma probands who were diagnosed after age 35 years. By comparing the medical histories of FDRs of 462 glioma patients with those of 443 controls, Wrensch et al. (10) found similar family histories of cancer overall but an increased odds ratio for brain tumors (2.3; 95% CI, 1.0-5.8) in the proband's relatives. They concluded that a family history of brain tumors might be a risk factor for

Table 3. Cancer-specific SIRs for FDRs by gender of proband (Cont'd)

	Female proband			FDR <45 y old			FDR ≥45 y old		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
All malignancies	391	332.77	1.17 (1.06-1.30)	262	51.55	5.08 (4.49-5.74)	739	773.93	0.95 (0.89-1.03)
Bladder	12	18.20	0.66 (0.34-1.15)	3	0.56	5.37 (1.08-15.70)	26	45.6	0.57 (0.37-0.84)
Sarcoma	4	0.97	4.14 (1.11-10.60)	5	0.75	6.69 (2.16-15.61)	4	1.61	2.49 (0.67-6.38)
Brain	19	8.71	2.18 (1.31-3.41)	21	3.58	5.87 (3.63-8.97)	25	17.87	1.40 (0.91-2.07)
Breast (female)	62	61.4	1.01 (0.77-1.29)	38	6.40	5.93 (4.20-8.15)	122	143.91	0.85 (0.70-1.01)
Colorectal	46	33.96	1.35 (0.99-1.81)	9	0.92	9.78 (4.46-18.56)	95	84.97	1.12 (0.90-1.37)
Hodgkin's	4	4.96	0.81 (0.22-2.07)	9	3.48	2.58 (1.18-4.91)	6	8.54	0.70 (0.26-1.53)
Leukemia	12	13.14	0.91 (0.47-1.60)	20	4.00	5.01 (3.06-7.73)	18	28.74	0.63 (0.37-0.99)
Lung	44	57.76	0.76 (0.55-1.02)	4	1.03	3.90 (1.05-9.98)	105	144.38	0.73 (0.59-0.88)
Melanoma	17	14.61	1.16 (0.68-1.86)	30	5.11	5.88 (3.69-8.39)	42	30.59	1.37 (0.99-1.86)
Non-Hodgkin's	9	15.25	0.59 (0.27-1.12)	10	3.25	3.07 (1.47-5.65)	20	34.58	0.58 (0.35-0.89)
Pancreas	11	9.2	1.20 (0.60-2.14)	2	0.14	14.20 (1.59-51.27)	30	23.20	1.29 (0.87-1.85)
Prostate	31	38.01	0.82 (0.55-1.16)	2	0.05	44.15 (4.96-159.39)	84	96.35	0.87 (0.70-1.08)
Stomach	11	7.27	1.51 (0.75-2.71)	5	0.19	26.22 (8.45-61.19)	12	18.39	0.65 (0.34-1.14)
Thyroid	6	6.77	0.89 (0.32-1.93)	7	2.96	2.36 (0.95-4.87)	5	13.44	0.37 (0.12-0.87)
Uterine	11	16.32	0.67 (0.34-1.21)	14	0.61	23.14 (12.64-38.83)	13	40.15	0.32 (0.17-0.55)

glioma. In addition, Hill et al. (6) showed that glioma patients had an increased odds of having an FDR with Hodgkin's lymphoma, stomach, colon, or prostate cancer compared with controls.

The highest SIRs among FDRs were observed for sarcoma. This is similar to the results for bone cancer by Hill et al. (6). In our study, the majority (55%) of the sarcomas were in the bone; this could account for the slightly lower SIR in our study than in Hill et al.'s. We also observed a significant nearly 2-fold excess of pancreatic cancer in the male probands' mothers. Although this might be a chance finding, the presence of a cancer predisposing mutation influenced by imprinting could result in an increase in pancreatic cancer in women. Our observed increased risk of melanoma is supported by linkage of melanoma to regions of chromosome 9 (16, 17), for which deletions have also been described in gliomas (18, 19). The melanoma-neural system tumor syndrome, in which affected families have increased risk of melanoma and astrocytomas, was recently linked to loss of both *p16* and *p14* genes that are present on chromosome 9 (20). Therefore, deletion of a common tumor suppressor gene may explain the association of glioma and melanoma found in our study, with *p16* as an obvious candidate gene for further investigation in these families. Our results are comparable with the studies by Malmer et al. (7) and Paunu et al. (15), which included whole nuclear families and showed an association with melanoma.

The deficit of bladder, lung, and uterine cancers in FDRs in our study is similar to what was reported by Hill et al. (6). We found a slight increase in colorectal cancer in our cohort compared with decreases of colon and breast cancer reported by Malmer et al. (7) in a recent study from Sweden. Wrensch et al. (10) showed an increased risk of brain tumors among cases with a family history of breast cancer, and Hemminki et al. (5) showed an aggregation of ependymomas, but not astrocytomas, in cases with a family history of breast cancer. An advantage of our study is that it comprised whole nuclear families, whereas the cohorts from the Swedish multigeneration registry excluded siblings born before 1932 and persons who died before 1961. Patients die young from diseases like glioma, which

might have biased the results in those studies toward the null (5, 8).

This large study confirms that family members of glioma patients experience cancer, including brain tumors, at rates in excess of the general population, indicating that there must be genetic factors contributing to the increased risk. These data provided support to initiate the Gliogene study, an international consortium to study familial glioma. The study includes 15 research groups in North America, Europe, and Israel to characterize genes in glioma families using a genome-wide single-nucleotide polymorphism approach and to conduct linkage analysis to identify new genomic regions or loci that could harbor genes important for gliomagenesis.

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