

Cancer in First-Degree Relatives and Risk of Glioma in Adults

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Abstract

Relatively few studies have examined glioma risk in relation to history of cancer in first-degree relatives. We sought to describe such risks in a large hospital-based case-control study. Histologically confirmed incident adult glioma cases ($n = 489$) were identified at three regional referral hospitals between June 1994 and August 1998. Controls ($n = 799$) admitted to the same hospitals for nonmalignant conditions were frequency-matched on age, sex, race/ethnicity, hospital, and proximity of residence to hospital. Participants received a personal interview, including questions regarding cancer in family members. Odds ratios (ORs) were calculated to estimate the risk of glioma associated with a history of cancer in a first-degree relative using conditional logistic regression and compared with standardized incidence ratios among relatives of cases versus relatives of controls. Among participants reporting a family history of a brain cancer or a brain tumor, risk of glioma was 1.6 [95% confidence interval (CI), 0.5–5.3; $n = 5$] and 3.0 (95% CI, 0.9–10.8; $n = 7$), respectively, in comparison with those without such family histories. Participants who had a family history of stomach (OR, 2.2; 95% CI, 1.0–4.6), colon (OR, 1.4; 95% CI, 0.9–2.2), or prostate cancer (OR, 2.1; 95% CI, 1.1–3.8) or Hodgkin disease (OR, 2.4; 95% CI, 0.9–6.3) had an increased glioma risk. OR estimates were similar to the ratios of standardized incidence ratios for cancer in relatives of cases versus controls. Shared environmental or genetic factors in families may influence glioma risk. Our findings suggest that individuals with a family history of specific cancers other than glioma may have an increased glioma risk.

Introduction

Genetic factors that contribute to glioma etiology are poorly understood. Several rare familial cancer syndromes, such as Li-Fraumeni, hereditary nonpolyposis colon cancer, tuberous sclerosis, and neurofibromatosis (NF) 1 include glioma (1). Segregation analyses and other genetic models suggest that inherited factors may contribute to 5–12% of all brain/central nervous system (CNS) cancers (2, 3), and inheritance is best explained by polygenic or autosomal recessive models (2, 4). However, cancers other than glioma in family members also may be related to glioma risk and usually are not taken into account in heritability estimates. In some (5–8), but not all (9–13), previous case-control studies, risk of glioma has been somewhat elevated among adults who report a relative with a cancer of the brain/nervous system [odds ratio (OR) range, 0.7–3.6]. With one exception (10), glioma risk was not related to family history of cancer of other types, or all cancers combined. Some of these investigations may have been hampered by the diminished recall of persons with brain cancers and reliance on proxy interviews. In cancer registry-based record-linkage studies, individuals with brain cancer have had a greater than expected proportion of first-degree relatives with brain/nervous system cancer (14–19), prostate cancer, colon cancer, and melanoma (14, 16). Persons with cancers at those sites also have had an increased risk of brain/CNS tumors in first-degree relatives (14, 20, 21).

Although family history studies can strengthen and inform genetic investigations of cancer, particularly when previous evidence is sparse, they have some limitations. The probability of having a family history of cancer increases with increasing age and the age and number of relatives, and thus a simple dichotomous measure of the presence/absence of family history (yes/no) can be a biased estimator of cancer aggregation within families in case-control studies (22). Such bias may be reduced by applying an alternative analytic approach, in which relative risk estimates are derived from age-, race-, and cohort-specific disease risks in first-degree relatives (22).

We examined risk of glioma in relation to family history of brain or other cancers in a hospital-based study, using rapid case ascertainment to minimize reliance on proxy interviews. We analyzed the data using two methods and compared the results.

Materials and Methods

Study Setting and Population. A detailed description of the study has been published previously (23). Individuals newly diagnosed with a malignant intracranial glioma between June 1994 and August 1998 and seen at one of three regional referral centers for the diagnosis and treatment of glioma (Brigham and Women's Hospital, Boston, Massachusetts; St. Joseph's Hospital, Phoenix, Arizona; and Western Pennsylvania Hospital, Pittsburgh, PA) were eligible for the study. Included patients also were required to be adults (age ≥ 18 years) who reside within 50 miles of the hospital (or within Arizona if seen at St. Joseph's), speak either English or Spanish, and have received

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care at the participating hospital within 8 weeks of the qualifying diagnosis; 74% were enrolled and interviewed within 3 weeks. Overall, 88% ($n = 489$) of eligible cases participated. All intracranial gliomas were confirmed histologically (International Classification of Diseases for Oncology, 2nd edition, morphology codes 9380–9473 and 9490–9506).

Controls were individuals admitted to the same institutions for nonmalignant conditions within the same time period as cases. Controls were frequency matched to glioma cases (and to meningioma and acoustic neuroma cases not included in this report) according to age (in 10-year age groups), sex, race/ethnicity (non-Hispanic white, Hispanic white, African-American, Asian, or other), and proximity of residence to the admitting hospital (0–5 miles, >5 to 15 miles, >15 to 30 miles, >30 to 50 miles, and >50 miles). Of eligible controls who were approached for an interview, 799 (86%) agreed to participate. The most common diagnostic categories for control admission included injuries and poisoning (25%) and diseases of the circulatory (22%), musculoskeletal (22%), digestive (11%), or nervous (7%) systems. Written informed consent was received from each participant or from his or her proxy before the interview. The study protocol was reviewed and approved by institutional review boards at the three study hospitals and the National Cancer Institute.

Data Collection. A structured computer-assisted interview was administered to participants by a trained research nurse in the hospital. Proxy interviews were necessary for 17% of individuals with glioma and 3% of controls, mostly because of death or severe illness or impairment of the participant. An additional 12% of case interviews and 1% of control interviews were conducted with both the participant and a proxy, usually a spouse. Suspected brain tumor risk factors and routine demographic data were collected. A full census of the first-degree relatives (biological parents, siblings, and offspring) of participants was sought, including the relative's year of birth or current age, vital status, and year or age at death. Respondents were queried about diagnoses of brain tumors in first-degree relatives, including whether the tumor was benign, malignant, or of uncertain malignancy, and about cancer diagnoses at other sites, and the site and age or year of diagnosis. Information regarding the respondent's personal history of cancer also was collected.

Statistical Analysis. As noted above, a simple indicator of the presence/absence of a family history of cancer ("yes/no") can be a biased measure of familial cancer aggregation in case-control studies, particularly with increasing differences in family size or age of relatives between case and control subjects, or with increasing frequency of disease (20). Such bias may be diminished by calculating relative risk estimates based on the expected age- and cohort-specific cancer risks in first-degree relatives. Thus, two analytic strategies were used to assess the risk of glioma in relation to family history of cancer: ORs were estimated using conditional logistic regression; and standardized incidence ratios (SIRs) were calculated.

Conditional logistic regression was used to compute ORs and 95% confidence intervals (CIs) for the relationship between glioma and family history of specific cancers. Respondents who were adopted, could not provide information about first-degree relatives, or who did not complete the family history questions were excluded (21 cases and 31 controls). Thus, this analysis is based on 468 cases and 768 controls. We evaluated possible confounding of the relationship between glioma and family history of cancer by education, income, family size (number of first-degree relatives), and age of each parent and two oldest

siblings, because these relatives are most likely to contribute to a family history of cancer. All analyses were adjusted for the matching variables of age at interview, sex, race/ethnicity, study hospital, and proximity of residence to hospital. Other variables were not included as covariates because they did not alter the OR estimate by $\geq 10\%$. Analyses were stratified by the age (18–49 years, ≥ 50 years) or sex of the study participant, type of respondent (self, proxy/assisted), relative's age at cancer diagnosis (18–49 years, ≥ 50 years), and glioma subtype.

To calculate SIRs, person-years of observation for each first-degree relative were accrued beginning with the later of January 1, 1925 or date of birth and continuing to the earlier of either date of death, date of cancer diagnosis of interest, or date of study interview. The Connecticut Tumor Registry, which includes information on all incident cancers diagnosed in the state since 1935, was used to derive expected numbers of cancer cases at each site by birth year, sex, and 5-year calendar period of cancer occurrence for each relative (rates for 1935–1939 were used for 1925–1934). Race-specific expected numbers could not be calculated for nonwhites (7.9% of cases and 8.3% of controls). For some relatives of participants, the date of birth, death, vital status, or age at cancer diagnosis was missing. Data were missing slightly more often among glioma cases (20.7% were missing at least 1 data value in their first-degree family members, of the average of 20 data items per family) than among controls (18.5% were missing at least 1 of 20 data items), or in total, 8.7% of the 3177 case relatives and 7.9% of 5332 control relatives to be included in the SIR analysis had a missing value (which did not affect the OR analysis). To ensure that these relatives were not excluded, thus biasing glioma cases toward smaller families with fewer cancers than controls, we imputed values for missing data using mean values from similar respondents stratified by participant age, relative type (*i.e.*, mother, sister) and relative vital status (24). Expected values were summed, and SIRs (the ratio of the number of observed to expected cancer cases) were calculated separately for relatives of cases and for relatives of controls. SIR estimates also were calculated separately by age of respondent (or age of eligible participant if respondent was a proxy) at interview (18–49 years, ≥ 50 years), sex, type of respondent (self, proxy), and attained age/age at cancer of relative (18–49 years, ≥ 50 years), and the ratio of the case SIR to the control SIR was computed.

Results

Individuals with glioma had a higher education and income, on average, than controls (Table 1). The number of siblings, offspring, or total first-degree relatives differed only slightly between the two groups. Substantial differences were not apparent between cases and controls with regard to the age or birth cohort of their parents or two oldest siblings (data not shown).

SIR risk estimates, calculated separately for relatives of glioma cases and relatives of controls, were less than unity for several cancers. Because the reported history of cancer in relatives of participants seemed to differ from the expected occurrence based on Connecticut Tumor Registry rates, but cases and controls were similar to each other in family size and age of relatives, we also determined the ratio of the SIR for family members of glioma cases to the SIR for family members of controls. Overall, the ratio of the SIRs was quite comparable with the OR estimate derived using logistic regression (Tables 2 and 3), and most of the remainder of the "Results" section focuses on the latter estimate. The SIR for bone cancer was elevated for both relatives of cases and relatives of controls.

Table 1 Characteristics of individuals with glioma and controls

	Glioma N (%)		Controls N (%)	
	(n = 468)		(n = 768)	
Age at interview ^{a,b}				
18–29	57 (12.2)		98 (12.8)	
30–49	170 (36.3)		298 (38.8)	
50–69	161 (34.4)		266 (34.6)	
70+	80 (17.1)		106 (13.8)	
Sex ^b				
Female	205 (43.8)		423 (55.1)	
Male	263 (56.2)		345 (44.9)	
Education				
High school or less	175 (37.4)		323 (42.0)	
1–3 yrs of college	127 (27.1)		238 (31.0)	
College graduate	85 (18.2)		101 (13.2)	
Graduate or professional school	65 (13.9)		85 (11.1)	
Missing	16 (3.4)		21 (2.7)	
Annual household income:				
<\$25,000	115 (24.6)		237 (30.9)	
\$25,000–\$49,999	152 (32.5)		231 (30.1)	
\$50,000–\$74,999	78 (16.7)		143 (18.6)	
\$75,000 or more	102 (21.7)		123 (16.0)	
Missing	21 (4.5)		34 (4.4)	
No. of siblings				
0	44 (9.4)		87 (11.3)	
1–2	215 (45.9)		324 (42.2)	
3–4	122 (26.1)		203 (26.5)	
≥5	87 (18.6)		154 (20.0)	
No. of offspring:				
0	122 (26.1)		194 (25.3)	
1–2	189 (40.4)		317 (41.3)	
3–4	131 (28.0)		183 (23.8)	
5+	26 (5.5)		74 (9.6)	
Glioma histology				
Astrocytoma	9400-21 ^c	100 (21.5)	N.A. ^d	
Glioblastoma multiforme	9440-42 ^c	229 (48.9)		
Oligodendroglioma	9450-60 ^c	54 (11.5)		
Ependymoma	9391-94 ^c	10 (2.1)		
Other glioma	9380-83 ^c , 9422-30 ^c , 9470-73 ^c , 9500-06 ^c	75 (16.0)		

^a Age at interview was within 3 weeks of age at diagnosis for 75% of glioma cases or within 3 weeks of age at hospital admission for 92% of controls.

^b Age and sex matching are not exact because some controls also were matched to meningioma and acoustic neuroma cases not included in this analysis.

^c International Classification of Diseases for Oncology, 2nd edition, Morphology codes.

^d Not applicable.

Participants reporting a family history of brain cancer or brain tumors did not have a significantly increased risk of glioma. However, both estimates were based on a limited number of observations (Table 2). A family history of brain cancer remained unrelated to glioma risk among participants age 18–49 years or those ≥50 years at interview, and when only first-degree relatives with adult brain cancer (diagnosis age ≥ 18 years) were considered (data not shown).

Overall, risk of glioma was elevated at least 2-fold among individuals with a history of stomach cancer, prostate cancer, or Hodgkin's disease in first-degree relatives (Table 3). Glioma risk also was modestly increased (1.4-fold) among persons who reported a family history of colon cancer. Among participants age 18–49 years, risk of glioma was increased at least 2-fold among those who had a family history of colon (OR, 2.3; 95% CI, 1.0–5.4; 16 cases and 11 controls) or prostate cancer (OR,

3.1; 95% CI, 1.2–8.4; 12 cases and 7 controls), compared with those without such family histories (data not shown). Among older participants (≥50 years), glioma risk was elevated among those who had a family history of stomach cancer (OR, 3.4; 95% CI, 1.3–9.1; 14 cases and 6 controls) or Hodgkin's disease (OR, 2.9; 95% CI, 0.9–9.3; 7 cases and 5 controls). No strong differences in relative risk were evident when data were analyzed according to the age that the relative's cancer occurred (18–49 years, ≥50 years). Risk of glioma was slightly elevated (OR, 1.4; 95% CI, 0.9–1.9) among those who reported two or more family members with cancer (75 cases and 98 controls), compared with those who did not report any cancer in relatives. However, the OR estimate declined to 1.2 (95% CI, 0.8–1.9) when a family history of stomach, colon, or prostate cancer, or Hodgkin's disease was deleted. The relative risks of glioma associated with the family histories noted above were generally higher in women than in men, but differences were compatible with chance (data not shown). In analyses that excluded imputed data or proxy interviews, each previously noted family history was a stronger risk factor for glioma or remained unchanged, except that after proxy exclusion, a family history of stomach cancer was no longer related to glioma risk (data not shown). Risks of the two largest glioma subtypes, glioblastoma multiforme (*n* = 227) and astrocytoma (*n* = 100), did not differ meaningfully from previous results, although persons with a breast cancer family history had an increased astrocytoma risk (OR, 2.1; 95% CI, 1.0–4.3; 11 cases and 53 controls).

Relative risk of glioma was not increased among participants with a personal medical history of a previous cancer or a benign tumor (data not shown). Five glioma cases and no controls reported a personal history of NF. Four cases (including one who had a personal history of NF) and no controls reported a family member with NF.

Discussion

In the present study, risk of glioma was not elevated among participants who had a first-degree relative with a brain cancer, although there was a suggestion of an increased risk among those with a family history of a benign brain tumor. Both estimates were imprecise because of the small number of observations. Persons who had a first-degree relative with stomach, colon, or prostate cancer or Hodgkin's disease had 1.4–3.4-fold increased risks, suggesting that if heritable factors are contributing to risk of glioma, they may be identifiable among families in whom glioma co-occurs with more common cancers.

Several factors should be considered in the interpretation of our study results. The proportion of proxy respondents in our study was smaller than in most previous glioma case-control studies. Proxy respondents are likely to be less knowledgeable than subjects regarding the history of malignant or benign tumors in the participant's family. In analyses excluding proxy interviews, most relationships between family history and glioma risk persisted. Some glioma cases who completed the interview could also have had impaired recall. We did not validate the brain or other cancers reported in first-degree relatives or the respondents' personal history of cancer. In two previous glioma validation studies, a high proportion of reported cancers in relatives (75% and 84%) were confirmed by medical records (8, 25). Glioma cases and controls enrolled through large referral hospitals may not be representative of the general population, but a hospitalized population was selected to obtain direct interviews promptly, and, in fact, 75% of cases (excluding proxy subjects) were interviewed within 3 weeks of

Table 2 Family history of brain tumors and risk of glioma: risks estimated by standardized incidence ratios (SIRs) and odds ratios (ORs), overall and by age at interview

Family history of	Cases N (%) (n = 468)	Controls N (%) (n = 768)	SIR glioma ^a	SIR glioma/ SIR controls	OR (95% CI) ^{b,c}
Overall					
Brain cancer	5 (1.1)	6 (0.8)	0.7 (0.2–1.7)	1.1	1.6 (0.5–5.3)
Benign brain tumors	7 (1.5)	4 (0.5)	– ^d	– ^d	3.0 (0.9–10.8)
Brain tumor (unknown if benign or malignant)	11 (2.4)	27 (3.5)	– ^d	– ^d	0.7 (0.3–1.4)
Age 18–49 yrs at interview	n = 227	n = 396			
Brain cancer	3 (1.3)	4 (1.0)	1.4 (0.3–4.0)	1.4	1.4 (0.5–12.3)
Benign brain tumor	5 (2.2)	2 (0.5)	– ^d	– ^d	3.7 (0.7–20.6)
Brain tumor (unknown if benign or malignant)	5 (2.2)	5 (1.3)	– ^d	– ^d	0.9 (0.3–3.1)
Age ≥50 yrs at interview	n = 241	n = 372			
Brain cancer	2 (0.8)	2 (0.5)	0.4 (0.1–1.6)	1.0	1.4 (0.2–10.4)
Benign brain tumor	2 (0.8)	2 (0.5)	– ^d	– ^d	0.6 (0.1–8.9)
Brain tumor (unknown if benign or malignant)	6 (2.5)	22 (5.9)	– ^d	– ^d	0.3 (0.1–0.9)

^a Glioma only, no controls.

^b The reference group for each odds ratio estimate was comprised of study participants without a family history of the particular cancer of interest and can be obtained by subtracting from the total of 468 cases and 768 controls. CI, confidence interval.

^c Odds ratio estimates were adjusted for age at interview (continuous), race (white, nonwhite), sex, study hospital, proximity of residence to hospital (<15 miles, ≥15 miles).

^d Standardized incidence ratios were not calculated because the expected numbers of cases of benign brain tumors or those of unknown behavior (benign or malignant) were not available from the Connecticut Tumor Registry.

diagnosis. Prompt interviews, a lower proportion of proxy respondents, and high response rates were strengths of this study.

OR estimates derived from logistic regression models generally were similar to the ratios of the SIR estimates for relatives of cases and controls. Variations in risk estimates between the two methods may be attributable, in part, to cancer at the same site in two or more first-degree relatives of the same participant, because each affected relative is counted separately in the SIR estimate, but only the presence/absence of family history is counted in the OR estimate. Cancer is a reportable

disease in Connecticut; thus, the expected cancer rates that contribute to the SIR may represent a more complete ascertainment of cancer occurrence than the observed cases in relatives reported during the study interview. However, when reported history of cancer in first-degree relatives has been compared with population-based registry records, the proportion of false positive reports has exceeded that of false negative reports (26). The elevated SIR for a family history of bone cancer among glioma cases and controls may be related to the reporting of metastases, which were not clearly distinguished in the interview.

Table 3 Family history of cancer and risk of glioma: risks estimated by standardized incidence ratios (SIRs) and odds ratios (ORs)

Family history of cancer ^a	Cases N (%) (n = 468)	Controls N (%) (n = 768)	SIR glioma ^b	SIR glioma/ SIR controls	OR (95% CI) ^{c,d}
Lip, oral cavity, pharynx	6 (1.3)	10 (1.3)	0.5 (0.2–1.0)	0.9	0.9 (0.3–2.6)
Stomach	17 (3.6)	13 (1.7)	1.4 (0.8–2.2)	1.9	2.2 (1.0–4.6)
Colon	37 (7.9)	40 (5.1)	1.1 (0.8–1.4)	1.4	1.4 (0.9–2.2)
Lung	33 (7.1)	56 (7.3)	0.7 (0.5–1.0)	1.0	1.0 (0.6–1.6)
Bone	7 (1.5)	8 (1.0)	6.0 (2.4–12.4)	1.4	1.1 (0.3–2.7)
Melanoma	5 (1.1)	6 (0.8)	0.5 (0.2–1.2)	1.4	1.3 (0.4–4.5)
Nonmelanoma					
Skin	6 (1.3)	8 (1.0)	– ^e	– ^e	1.3 (0.4–3.9)
Breast	38 (8.1)	54 (7.0)	0.7 (0.5–0.9)	1.1	1.2 (0.8–1.9)
Cervix	5 (1.1)	5 (0.7)	0.7 (0.2–1.5)	1.5	1.5 (0.4–6.2)
Endometrial/uterine not otherwise specified	6 (1.3)	12 (1.6)	0.4 (0.2–1.0)	0.7	0.8 (0.3–2.4)
Ovary	8 (1.7)	16 (2.1)	0.9 (0.4–1.7)	0.7	0.8 (0.3–2.0)
Prostate	24 (5.1)	20 (2.6)	0.9 (0.6–1.3)	1.8	2.1 (1.1–3.8)
Bladder	6 (1.3)	7 (0.9)	0.3 (0.1–0.7)	1.1	1.4 (0.4–4.0)
Non-Hodgkin's disease					
Lymphoma	11 (2.4)	17 (2.2)	0.9 (0.5–1.6)	1.0	0.8 (0.4–1.8)
Hodgkin's disease	10 (2.1)	7 (0.9)	2.3 (1.1–4.2)	2.3	2.4 (0.9–6.3)
Leukemia	9 (1.9)	17 (2.2)	0.9 (0.4–1.6)	0.9	0.7 (0.3–1.7)
Any malignancy	200 (42.7)	281 (36.6)	0.7 (0.6–0.8)	1.1	1.2 (0.9–1.6)

^a Only cancers reported by at least five cases and five controls are included in the analysis, or sites that were *a priori* of interest because of previous findings.

^b Glioma only, no controls.

^c The reference group for each odds ratio estimate was comprised of study participants without a family history of the cancer of interest and can be obtained by subtracting from the total of 468 cases and 768 controls.

^d All odds ratio estimates were adjusted for age at interview (continuous), race (white, nonwhite), sex, study hospital, and proximity of residence to hospital (<15 miles, ≥15 miles).

^e Standardized incidence ratios were not calculated because the expected numbers of nonmelanoma skin cancers was not available from the Connecticut Tumor Registry.

A family history of brain tumors (malignant or benign) has been related to an increased risk of adult glioma inconsistently in case-control studies (5–13). Familial aggregation has been estimated to occur in 5% of glioma cases (2), and inherited factors have been deemed to contribute to 12% of brain/CNS cancers (3). Relatives with cancers at sites other than brain/CNS were not considered in these estimates. The identification of excess cancer risks in glioma families may have been hindered by several factors. For example, diminished recall among some glioma cases and reliance on proxy interviews would tend to introduce misclassification in family cancer history. In addition, if particular histological subtypes are associated with different family cancer histories, pooling of all participants with brain/CNS tumors may obscure specific relationships. Similarly, participants' reports of a "brain cancer" in a relative may include benign tumors, childhood brain cancers (which may be etiologically distinct), or brain metastases from other primary cancers. Shared environmental factors within families, in contrast, could create the spurious appearance of genetic clustering of otherwise unrelated tumors.

Brain cancer risk in relation to family history of cancer has been investigated by linking genealogical information to population-based cancer registries in Utah (14), Iceland (18), and Sweden (15–17), using analytic methods that account for the family size and age of relatives. Individuals who had a first-degree relative with a brain/CNS cancer had a glioma risk that was elevated 2-fold in the Utah Population Database (14), 1.6-fold in the Icelandic Cancer Registry (18), and 1.7-fold in the Swedish Family Cancer Database (17), compared with that expected. Risk was particularly elevated among women (4-fold) and those diagnosed before age 50 years (9-fold) in the Utah population, whereas risk of adult astrocytoma was 2–3-fold higher among those who had a first-degree relative with astrocytoma in the Swedish family cancer data (15, 16).

Our data are similar to one study (27) and are supported weakly by a second (16) in suggesting that risk of glioma may be increased among individuals who report benign brain tumors in first-degree relatives, although our numbers of affected case and control families were limited. The small number of cases with NF in our study did not report benign brain tumors in family members.

Among first-degree relatives of persons with brain/CNS cancer, risk of stomach cancer was elevated almost 2-fold in the Utah Population Database, and 3.6-fold if the brain/CNS cancer was diagnosed before age 50 years (14). Brain cancer risk was not increased in the families of those with stomach cancer in the Swedish family cancer database (16, 28). Inherited cancer syndromes that involve an excess risk of both glioma and stomach cancer include hereditary nonpolyposis colon cancer (29) and probably Li-Fraumeni syndrome (30).

Relative risks of both colon cancer and glioma are known to be increased in carriers of germ-line alterations in DNA mismatch repair genes [hereditary nonpolyposis colon cancer (29, 31)] and possibly the *adenomatous polyposis coli* gene (32). In the Swedish family cancer database, persons with a CNS tumor had a 2-fold increased risk of colorectal cancer in offspring if both were diagnosed at younger ages (21). However, in another Swedish study, risk of astrocytoma was decreased among those with a colon cancer family history (15).

An increased risk of brain tumors in the families of men with prostate cancer has been noted in the Utah Population Database (14) and in two studies of families with multiple prostate cancer cases (33, 34), but not in a third such study (35). Multiplex prostate cancer families that include members with brain tumors may be etiologically distinct from other families

with multiple prostate cancer cases, and the former have been associated with the chromosome *1p36* [also known as *CAPB* (36)] and *1q42.2–43* [*PCAP* (37)] regions in linkage studies.

Brain cancer risk was somewhat increased in families of Hodgkin's disease cases compared with relatives of controls in one study (38). Risk of second primary brain/CNS tumors was elevated after diagnosis of Hodgkin's disease in another investigation, but the effects of Hodgkin's disease treatment on risk cannot be excluded as an explanation (39).

Although our study findings are generally consistent with reports from cancer registry studies, multiplex cancer families, and rare cancer syndromes, we did not find an elevated risk of glioma among individuals with a family history of melanoma (14, 16, 27) or pancreatic (14), breast, endometrial, or thyroid cancers (16), as has been suggested in previous studies.

A family history of cancer may be attributable, in part, to shared environmental factors and is also thought to be an indicator of inheritance of rare, highly penetrant mutations that have little effect on cancer risk in the general population. However, some genes known to have highly penetrant rare mutations also have common variants [such as the codon 72 polymorphism in *tp53* and common polymorphisms in *xeroderma pigmentosum complementation group D* (*XPD*)] that have been related to increased risk of cancer (40, 41), including glioma (42), in population-based studies. These studies imply that investigations of family history of cancer may serve to inform and strengthen hypotheses regarding the etiology of both rare hereditary glioma and more common sporadic glioma (43). Our findings suggest that a family history of benign brain tumors or specific cancers in addition to glioma should be considered among the factors that may shed light on the genetics of glioma etiology.

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