Systematic Reviews and Meta- and Pooled Analyses

Familial Aggregation of Glioma: A Pooled Analysis

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In genome-wide association studies, inherited risk of glioma has been demonstrated for rare familial syndromes and with common variants from 3–5 chromosomal regions. To assess the degree of familial aggregation of glioma, the authors performed a pooled analysis of data from 2 large glioma case-control studies in the United States (MD Anderson Cancer Center, Houston, Texas (1994–2006) and University of California, San Francisco (1991–2004)) and from the Swedish Cancer Registry (1958–2006) to measure excess cases of cancer among first-degree relatives of glioma probands. This analysis included 20,377 probands with glioma and 52,714 first-degree relatives. No overall increase was found in the expected number of cancers among family members; however, there were 77% more gliomas than expected. There were also significantly more sarcoma and melanoma cases than expected, which is supported by evidence in the literature, whereas there were significantly fewer-than-expected cases of leukemia, non-Hodgkin lymphoma, and bladder, lung, pancreatic, prostate, and uterine cancers. This large pooled analysis provided sufficient numbers of related family members to examine the genetic mechanisms involved in the aggregation of glioma with other cancers in these families. However, misclassification due to unvalidated cancers among family members could account for the differences seen by study site.

family; glioma; meta-analysis; neoplasms

Abbreviations: MDACC, MD Anderson Cancer Center; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; UCSF, University of California, San Francisco.

In 2010, approximately 22,020 people in the United States will be diagnosed with a malignant brain tumor, and 13,140 will die from their tumor (1). Over the past decades, epidemiologic studies have not identified strong, consistent risk factors for this deadly cancer, with the exceptions of ionizing radiation to the head and history of allergies. However, 2 recent genome-wide association studies identified and validated inherited variants in 3 chromosomal regions associated with high-grade or any glioma and 2 additional regions associated with any glioma (2, 3). A number of heritable syndromes are associated with increased incidence of brain tumors, such as Li-Fraumeni, neurofibromatosis (types 1 and 2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial polyposis, and von Hippel-Lindau, but these syndromes explain only about 4% of the pediatric cases and even fewer of the adult cases, approximately 1%–2% (4). However, several studies report the clustering of brain tumors in families unaffected by these cancer syndromes, and it seems unlikely that the common glioma risk variants newly discovered by genome-wide association studies are sufficiently penetrant to account for observed familial aggregation of brain tumors.

Several large studies suggest an increased risk of primary brain tumors and other cancers for relatives of glioma cases (5–17). These studies reported the risk of developing cancer at any site to be between 1.0 and 1.8 and the risk of developing a brain tumor to be between 1.0 and 3.0 for individuals with a family history of brain tumors. The variation in the results of these studies may reflect differences in study methodologies, sample sizes, types of relatives included in the study (e.g., first vs. second degree), and ascertainment and validation of the family members’ cancers.
Although the familial aggregation studies suggest a genetic etiology for brain tumors, it is also possible that the aggregation may result from shared environmental exposures.

The purpose of this study was to assemble large data sets from 3 sites of the GLIOGENE Consortium to accurately estimate, in a pooled analysis, the risk of brain tumors and other cancers for first-degree relatives of glioma patients. In this paper, we show the results of a pooled analysis of these 3 studies and discuss the caveats of the different methodologies used to ascertain and calculate standardized incidence ratios (SIRs).

**MATERIALS AND METHODS**

Case ascertainment at the MD Anderson Cancer Center

Probands with histologically confirmed primary glioma (International Classification of Diseases for Oncology, Third Edition, morphology codes 9380–9481) were recruited from The University of Texas MD Anderson Cancer Center (MDACC) between June 1992 and June 2006. The included probands were aged 18 years or older (cases ascertained between 1992 and 2002 were aged <65 years; cases ascertained between 2002 and 2006 could be ≤75 years of age), self-reported Caucasian, and citizens of the United States. Each proband and/or next of kin was administered an extensive family health questionnaire by trained interviewers to solicit information on the presence of cancer in the proband’s first-degree relatives. When possible, study personnel obtained medical records or death certificates for relatives who reported a possible malignancy to confirm the report. Overall, approximately 50% of all cancers among MDACC relatives included in this pooled analysis were obtained from the proband’s biologic parents, siblings, half-siblings, and children. They were then asked whether any of them had a cancer at any site or a brain tumor and, if so, to specify the primary cancer site(s) and age(s) at diagnosis. Relatives identified as possibly having a brain tumor were sent a separate questionnaire asking them their history of a variety of medical conditions including brain tumor; if the relative was deceased, the closest informant for the relative was sent the questionnaire. For the subjects recruited in 1991–1994, study personnel also attempted to validate reports of any cancer among relatives similarly.

The University of California, San Francisco (UCSF) study attempted validation of only a first-degree relative’s brain tumors but not other cancers; thus, there may have been either under- or overreporting for other cancer sites. The UCSF Committee on Human Research approved the methods for this study (Institutional Review Board approval H6539-04956-21A).

Case ascertainment in Sweden

It is mandatory by law to register all tumors, including all intracranial tumors—both benign and malignant—in the Swedish Cancer Registry. According to recent quality studies, the Swedish Cancer Registry is close to 100% complete for all diagnosed cancers in the country. All unique patients registered with a glioma (International Classification of Diseases, Seventh Revision, code 193, pathology codes 475 and 476) in the Swedish Cancer Registry (diagnosed between 1958 and 1997) were linked to the Swedish Multigenerational Registry. This registry was created to include all individuals aged 15 years or younger in 1947 and their parents. It therefore comprises all citizens of Sweden born since 1932. The registry was linked to the causes of death registry starting in 1961, so data for individuals who died prior to 1961 are truncated in the cohort. The parents, children, and siblings were linked to each proband with glioma. Because of the structure of the registries, we were able to obtain information on the parents and siblings of probands who were aged 65 years or younger at onset of glioma; however, information on the children of all probands was not available.

Calculation of SIRs for the MDACC and UCSF studies

To determine excess cancers in the first-degree relatives, SIRs were computed as the ratio of the observed number of cancer cases among first-degree relatives to the expected number using the Cohort Analysis for Genetic Epidemiology (CAGE) computer program (20). The expected number of cancers was determined by using sex-, age-, and calendar year–specific rates from the Surveillance, Epidemiology, and End Results (SEER) Program, which includes 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 the Cohort Analysis for Genetic Epidemiology program uses first primary cancers from SEER to compute the
expected number of cancers. The SIRs for cancer among first-degree relatives were compared by proband’s gender, age at glioma diagnosis, and histologic grade of glioma (low grade = World Health Organization grade 2; high grade = World Health Organization grades 3 and 4) and the age and sex of the first-degree relative. The 95% confidence intervals for the SIRs were determined by assuming a Poisson distribution for the observed number of cancers among first-degree relatives.

**Calculation of SIRs for the Sweden study**

The SIR was again defined as the ratio between the observed and the expected number of cases among first-degree relatives of glioma cases. The expected number of cancer cases was calculated by multiplying the cancer-specific incidence rate for Sweden by calendar- and age-specific person-years. Cancer incidence in Sweden for the period 1958–1997 was obtained from the Swedish Cancer Registry and was used in the calculations. Person-years were calculated from the date of birth to the first date of the following events: cancer diagnosis, interview, or death. The SIRs for cancer in first-degree relatives were compared by proband’s gender, age at glioma diagnosis, and histologic grade of glioma and the age and sex of the first-degree relative. The 95% confidence intervals for the SIRs were determined by assuming a Poisson distribution for the observed number of cancers among first-degree relatives.

**Calculation of pooled estimates**

To calculate a pooled SIR, we first determined the combined number of observed cancers, \( \hat{O} \), by summing across the 3 studies described above. In a similar fashion, we calculated the combined number of expected cancers, \( \hat{E} \). The pooled SIR was then calculated, \( \text{SIR} = \hat{O}/\hat{E} \). The 95% confidence interval for the pooled SIR was determined by assuming a Poisson distribution using the pooled observed number of cancers, \( \hat{O} \).

**RESULTS**

A total of 20,377 probands with glioma were available for analysis. Probands with the following diagnoses were not included in the current analysis: astroblastoma, glioma not otherwise specified, and unclassified astrocytoma. Therefore, the analysis included 1,440 glioma probands from MDACC and 1,090 glioma probands from UCSF in the United States, and 17,847 glioma probands from the Swedish Cancer Registry. Probands with known familial cancer syndromes were not included in the analyses. One proband and the first-degree relatives were excluded from both the MDACC and the UCSF series because of a Li-Fraumeni–like pattern of cancers within the pedigrees; no such cases were found in the Swedish data. The demographic characteristics (Table 1) between the 3 groups of probands were remarkably similar; however, the MDACC probands were 10 years younger than the other 2 groups because the age criteria in the early years of the study included younger cases. The UCSF site did not include cases under the age of 20 years. The overall male-to-female ratio (1.3:1) is consistent with the reported literature for glioma. The proportion of high-grade tumors was similar between MDACC and UCSF (80%); however, this proportion was slightly higher than in Sweden (73%).

A total of 52,714 first-degree relatives were included in the pooled analysis: 8,587 from MDACC, 6,125 from UCSF, and 38,002 from Sweden. During follow-up, 3,891 malignant cancers were observed and 3,934.51 were expected (SIR = 0.99, 95% confidence interval: 0.96, 1.02) among the first-degree relatives. However, increased SIRs were detected for specific cancers, as described below.

The SIRs for glioma among the first-degree relatives of our glioma probands (Table 2) did not differ significantly by age of the proband at each site. Family members of probands with high-grade glioma experienced 70% more cases of cancer than expected in the MDACC and Swedish data and 90% more in the UCSF data. Younger first-degree relatives (less than age 45 years) experienced greater numbers of cases of cancer in all series, with the effects being greater for the MDACC and UCSF series. A higher SIR for siblings was evident in the Swedish and UCSF data but not for the MDACC site; however, there were far fewer cancer cases among siblings from this site.

Pooled estimates for glioma (Table 3) showed a more than 2-fold increase in the number of glioma cases if either the proband or his or her first-degree relative developed a glioma at a younger age. There was very little difference in the SIRs for glioma if the proband had a high-grade or low-grade glioma; both showed approximately 75% excess cases of glioma in the first-degree relatives. The pooled estimate for glioma among siblings of probands showed an overall 2.6-fold increase.

Cancer-specific estimates (Table 4) revealed interesting trends for both increased and decreased numbers of cases among first-degree relatives of glioma probands. Overall, pooled estimates showed greater-than-expected numbers of sarcoma, brain tumors, and melanoma. There was evidence of significantly decreased numbers of leukemia, non-Hodgkin lymphoma, and lung, bladder, pancreas, prostate, and uterine cancers. These cancer-specific estimates varied somewhat by study site; however, the trends mostly held across the sites.

**DISCUSSION**

In this 3-site pooled analysis, we found an increase in the number of brain tumors among first-degree relatives of glioma patients (SIR = 1.77, 95% confidence interval: 1.56, 2.00); however, no overall increase in expected cancer cases was observed in the first-degree relatives of glioma cases. We found that this increase in glioma among first-degree relatives was particularly high for the probands’ siblings (SIR = 2.56, 95% confidence interval: 1.18, 3.85). Across the 3 studies included in this pooled analysis, the SIRs for glioma among first-degree relatives of the probands ranged from 1.67 (Sweden) to 2.12 (MDACC).

This finding is consistent with the estimates reported in the literature. Using the Swedish registry data, Malmer et al.
reported a 2-fold (SIR = 2.12, 95% confidence interval: 1.18, 3.49) increase in glioma cases among first-degree relatives of probands with astrocytoma. The specificity of the increased risk with tumor histology was also reported later. Malmer et al. found that the risk of low-grade gliomas was highest for first-degree relatives when the proband also had a low-grade tumor, and they found the same for high-grade tumors (21). They also reported a higher risk of glioma for the siblings of probands, as was found in our current analysis. Using a case-control methodology, Wrensch et al. (17) compared the medical histories of first-degree relatives of glioma patients with those of controls and found no difference in family histories of cancer overall but an increased odds of brain tumors (2.3, 95% confidence interval: 1.0, 5.8) in the proband’s relatives. This result supports the increase in cases of glioma among the first-degree relatives of probands in the current pooled analysis; however, it is important to note that these subjects were also included in this pooled analysis.

A consistent increase in the number of melanoma cases among first-degree relatives of glioma probands was observed. The association between glioma and melanoma has been previously reported in aggregation studies (7, 11, 13, 22) and is supported by linkage of melanoma to regions of chromosome 9 (23, 24), which have been reported to be deleted or mutated in gliomas (25–27). Furthermore, recent genome-wide association studies of both glioma (2, 3) and melanoma (28) have identified variants in chromosome 9p21 near the cyclin-dependent kinase inhibitor genes, CDKN2A (p16) and CDKN2B (p15), and other genes. Although the variants identified for melanoma and glioma are not in the same linkage block, the results indicate that it is plausible that deletions or other chromosomal modifications in the region might account for some familial aggregation of glioma and melanoma. The melanoma-neural system tumor syndrome, in which affected families have increased risk of melanoma and astrocytomas, was recently linked to loss of both the p16 and p14 genes located on chromosome 9 (20). In addition, p16 regulation has been linked to sensitivity to ionizing radiation, the only consistently associated environmental risk factor for glioma (29). Therefore, deletion of a common tumor suppressor gene may explain the association of glioma with melanoma found in our study, with p14, p15, and p16 being obvious candidates for further investigation in these families. This effect could also be due to the effects of low-penetrance genetic variants.


<table>
<thead>
<tr>
<th>Age at diagnosis, years</th>
<th>MDACC (n = 1,440)</th>
<th>UCSF (n = 1,090)</th>
<th>Sweden (n = 17,847)</th>
<th>Total (N = 20,377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19</td>
<td>76 5.3</td>
<td>0 0</td>
<td>1,466 8.2</td>
<td>1,542 7.5</td>
</tr>
<tr>
<td>20–29</td>
<td>142 9.9</td>
<td>61 5.6</td>
<td>923 52.2</td>
<td>1,126 5.5</td>
</tr>
<tr>
<td>30–39</td>
<td>276 19.3</td>
<td>134 12.3</td>
<td>1,602 9.0</td>
<td>2,012 9.9</td>
</tr>
<tr>
<td>40–49</td>
<td>381 26.6</td>
<td>200 18.4</td>
<td>2,433 13.6</td>
<td>3,014 14.8</td>
</tr>
<tr>
<td>50–59</td>
<td>336 23.5</td>
<td>234 21.5</td>
<td>3,846 21.5</td>
<td>4,416 21.6</td>
</tr>
<tr>
<td>60–69</td>
<td>190 13.3</td>
<td>219 20.1</td>
<td>4,583 27.7</td>
<td>4,992 24.5</td>
</tr>
<tr>
<td>≥70</td>
<td>30 2.1</td>
<td>242 22.2</td>
<td>2,994 16.8</td>
<td>3,266 16.0</td>
</tr>
<tr>
<td>Mean (standard error)</td>
<td>44.1 (0.39)</td>
<td>55.5 (0.48)</td>
<td>52.2 (0.14)</td>
<td>51.7 (0.20)</td>
</tr>
<tr>
<td>Median</td>
<td>45</td>
<td>56</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>849 59.0</td>
<td>616 56.5</td>
<td>9,967 55.8</td>
<td>11,432 56.0</td>
</tr>
<tr>
<td>Female</td>
<td>591 41.0</td>
<td>474 43.5</td>
<td>7,880 44.2</td>
<td>8,945 44.0</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1.4:1</td>
<td>1.3:1</td>
<td>1.3:1</td>
<td>1.3:1</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low gradea</td>
<td>288 20.0</td>
<td>223 20.5</td>
<td>4,796 26.9</td>
<td>5,307 26.0</td>
</tr>
<tr>
<td>High gradeb</td>
<td>1,152 80.0</td>
<td>867 79.5</td>
<td>13,051 73.1</td>
<td>15,070 74.0</td>
</tr>
</tbody>
</table>

Abbreviations: MDACC, MD Anderson Cancer Center; UCSF, University of California, San Francisco.

a Astrocytoma, pilocytic astrocytoma, subependymal giant cell astrocytoma, ependymoma, ganglioma, juvenile pilocytic astrocytoma, mixed glioma, myxopapillary ependymoma, oligodendroglioma, optic nerve glioma, pleomorphic xanthoastrocytoma, subependymoma.

b Glioblastoma, gliosarcoma, ependymoblastoma, anaplastic astrocytoma, anaplastic ependymoma, anaplastic glioma not otherwise specified, anaplastic oligoastrocytoma (mixed), anaplastic oligodendroglioma.
The highest SIRs among first-degree relatives at the MDACC and UCSF study sites were observed for sarcoma. To our knowledge, an increase in sarcomas among family members of glioma probands has been reported in only one other series (12). This finding could be due to the small number of observed cases in these 2 series; the larger

Table 2. Standardized Incidence Ratios by Proband Characteristics (Age, Tumor Histology), Relative’s Age at Diagnosis, and Relationship for Glioma in First-Degree Relatives, 1994–2006 (MDACC), 1991–2004 (UCSF), and 1958–1997 (Sweden)

<table>
<thead>
<tr>
<th>MDACC</th>
<th>UCSF</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Observed</td>
<td>SIR 95% CI</td>
<td>No. Observed</td>
</tr>
</tbody>
</table>

Proband’s age, years
- ≤19
  - 302 0 2.13 1.32, 3.26
- 20–50
  - 4,788 21 1.99 0.95, 3.67
- >50
  - 3,497 24 1.87 1.21, 2.76

Proband’s histology
- High grade
  - 7,029 31 1.73 1.18, 2.46
  - 4,926 30 1.94 1.31, 2.77
- Low grade
  - 1,558 14 4.29 2.34, 7.19
  - 1,199 5 1.71 0.55, 4.00

Relative’s age, years
- <45
  - 4,283 21 6.01 3.72, 9.18
  - 2,373 12 5.68 2.93, 9.93
- ≥45
  - 4,304 24 1.36 0.87, 2.02
  - 3,744 23 1.42 0.90, 2.13

Relationship
- First-degree relatives
  - 8,587 45 1.79 1.22, 2.60
  - 6,125 35 1.90 1.32, 2.65
- Siblings
  - 2,505 2 1.12 0.13, 4.04
  - 2,323 15 2.20 1.23, 3.64

Abbreviations: CI, confidence interval; MDACC, MD Anderson Cancer Center; SIR, standardized incidence ratio; UCSF, University of California, San Francisco.

The highest SIRs among first-degree relatives at the MDACC and UCSF study sites were observed for sarcoma. To our knowledge, an increase in sarcomas among family members of glioma probands has been reported in only one other series (12). This finding could be due to the small number of observed cases in these 2 series; the larger

Table 3. Pooled Standardized Incidence Ratios by Proband Characteristics (Age, Tumor Histology), Relative’s Age at Diagnosis, and Relationship for Glioma and Any Malignancies in First-Degree Relatives, 1994–2006 (MDACC), 1991–2004 (UCSF), and 1958–1997 (Sweden)

<table>
<thead>
<tr>
<th>Glioma</th>
<th>Any Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Observed</td>
<td>No. Expected SIR 95% CI</td>
</tr>
</tbody>
</table>

Proband’s age, years
- <19
  - 86 37.61 2.29 1.83, 2.82
  - 85 40.68 2.09 1.67, 2.58
- 20–50
- >50

Proband’s histology
- High grade
  - 175 98.17 1.78 1.53, 2.07
  - 154 107.58 1.81 1.53, 2.09
- Low grade
  - 81 46.44 1.74 1.39, 2.17
  - 65 58.65 1.68 1.39, 1.97

Relative’s age, years
- <45
  - 118 52.83 2.23 1.85, 2.67
  - 138 91.83 1.50 1.26, 1.78
- ≥45
  - 118 52.83 2.23 1.85, 2.67
  - 138 91.83 1.50 1.26, 1.78

Relationship
- First-degree relatives
  - 256 145.02 1.77 1.56, 2.00
  - 39 15.26 2.56 1.82, 3.49

Abbreviations: CI, confidence interval; MDACC, MD Anderson Cancer Center; SIR, standardized incidence ratio; UCSF, University of California, San Francisco.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>MDACC</th>
<th>UCSF*</th>
<th>Sweden</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Observed</td>
<td>No. Expected</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Bladder</td>
<td>29</td>
<td>45.68</td>
<td>0.63</td>
<td>0.43, 0.91</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>9</td>
<td>2.32</td>
<td>3.88</td>
<td>1.77, 7.37</td>
</tr>
<tr>
<td>Brain b</td>
<td>45</td>
<td>21.18</td>
<td>2.12</td>
<td>1.55, 2.84</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>157</td>
<td>148.87</td>
<td>1.05</td>
<td>0.90, 1.23</td>
</tr>
<tr>
<td>Colorectal</td>
<td>103</td>
<td>85.05</td>
<td>1.21</td>
<td>0.99, 1.47</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>15</td>
<td>11.86</td>
<td>1.27</td>
<td>0.71, 2.09</td>
</tr>
<tr>
<td>Leukemia</td>
<td>38</td>
<td>32.35</td>
<td>1.17</td>
<td>0.83, 1.61</td>
</tr>
<tr>
<td>Lung</td>
<td>107</td>
<td>143.91</td>
<td>0.74</td>
<td>0.61, 0.90</td>
</tr>
<tr>
<td>Melanoma</td>
<td>72</td>
<td>35.26</td>
<td>2.04</td>
<td>1.60, 2.57</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>29</td>
<td>37.42</td>
<td>0.78</td>
<td>0.52, 1.11</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32</td>
<td>23.11</td>
<td>1.38</td>
<td>0.95, 1.96</td>
</tr>
<tr>
<td>Prostate</td>
<td>86</td>
<td>95.32</td>
<td>0.90</td>
<td>0.72, 1.11</td>
</tr>
<tr>
<td>Stomach</td>
<td>17</td>
<td>18.39</td>
<td>0.92</td>
<td>0.54, 1.48</td>
</tr>
<tr>
<td>Thyroid</td>
<td>11</td>
<td>16.20</td>
<td>0.68</td>
<td>0.34, 1.22</td>
</tr>
<tr>
<td>Uterine</td>
<td>27</td>
<td>40.37</td>
<td>0.67</td>
<td>0.44, 0.97</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MDACC, MD Anderson Cancer Center; SIR, standardized incidence ratio; UCSF, University of California, San Francisco.

The UCSF study attempted validation of only first-degree relative’s brain tumors but not other cancers; thus, these other cancers may be either under- or overreported. For primary brain tumors in relatives, 31/35 (89%) were independently verified, and the remaining 4 appeared probable based on details given by the respondent.

Only malignant brain tumors were included in this analysis.
Swedish series showed no increase in the number of sarcoma cases among the first-degree relatives. However, there is evidence to support similar environmental and genetic risk factors for sarcoma and glioma. The strongest evidence of an environmental risk factor for both of these tumor types is with exposure to ionizing radiation (4, 30). The link between these 2 tumors will have to be further investigated in larger samples and in various populations, including the use of case-control data.

The similarities and differences in the SIRs for the various tumor sites beg a comparison of the studies that constituted this pooled analysis. The overall results were similar, but there are inconsistencies, as shown in Table 4. The differences could be due to differences in case ascertainment; the MDACC cases were recruited through a hospital-based case-control study, the UCSF cases were recruited via a population-based case-control study, and the Swedish cases were ascertained by using a cohort study through the Swedish registries encompassing the entire country. Furthermore, there could be distinct differences related to the various histologic groups that make up “gliomas.” The percentages of high-grade cases in all 3 series were similar; however, there was a slightly higher proportion of lower grade tumors in the Swedish registry than in the MDACC and UCSF groups.

The UCSF sample was population based and drew from the Northern California Cancer Registry represented in SEER, primarily by the San Francisco–Oakland Registry. We were interested in comparing the SEER incidence rates, which were used for the SIR calculations, with those for the California population. The rates of cancer reported by the San Francisco–Oakland Registry were compared with the combined SEER rates; the rates overall and for specific cancers were representative. The age-adjusted rate for whites with all malignancies in SEER is 477.6 per 100,000, whereas the rate in the San Francisco–Oakland Registry is 466.1 per 100,000. The rates were even more similar for brain tumors (incidence rate difference = −0.1), melanoma (incidence rate difference = −1.4), and pancreatic cancer (incidence rate difference = −0.2). This finding increases our confidence about using SEER incidence rates to calculate the SIRs, especially for this population. Furthermore, since the San Francisco–Oakland population is similar to that of the Houston, Texas, area, we are confident that the overall SEER incidence rates closely approximate those of the MDACC catchment area for which there is no direct comparison to SEER. This is important when comparing the SIRs to the Swedish data with robust case ascertainment and calculations based on the whole Swedish population.

This study has a number of strengths. To our knowledge, this large pooled analysis is the first to examine the associations between characteristics of glioma probands and cancer in their first-degree relatives. We were able to confirm the association of glioma risk in families and confirm the aggregation of glioma with other specific cancers in families. By pooling data from these 3 large data sets, we were able to more accurately determine the familial association in younger probands and younger relatives and by histologic type of the proband’s tumor and to begin to understand the specific relatives at greatest risk of these aggregated cancers. All of these facts point to the need to study families when assessing risk of cancers that tend to aggregate in families, such as glioma. The GLIOGENE linkage study (31) was established to examine these rare familial cases of glioma to gain greater insight into the genetic factors driving their etiology.

There are 3 primary limitations of this study. First is the degree of validation of the cancer diagnosis in the first-degree relatives. Validation varies by cancer location; for example, tumors in the abdomen are generally less valid by self-report or family report. Therefore, the lower SIRs reported by some study sites could be due to a dilution of power with tumors that are poorly validated, hence driving the association toward the null value. However, previous validation analyses of our study families showed that 78%-84% of self-reported tumors among family members were validated by medical record review (17, 32). Therefore, we did not validate all tumors among family members included in this pooled analysis.

Second is the issue of left truncation within the Swedish cohort design (33, 34). Left truncation for early lethal cancers such as melanoma could explain the decreased risks reported here for those cancers.

Third is the limited number of studies available for pooling and the overwhelming effect of the Swedish cohort for some cancer sites. Because the Swedish registry had the most weight because of its much larger sample size, the SIRs obtained by the meta-analysis method would be influenced more by the Swedish data. However, overall results using the weighted meta-analysis were not substantially different from those using the pooled method (results not shown here). Furthermore, we tested for heterogeneity of effects among the studies and, after removing overly influential studies for certain cancer sites, found that the effects were often stronger and more significant (results not shown here). Therefore, the results of the pooled analysis without weighting, which included all 3 studies for all cancer sites, are presented here.

In summary, this pooled analysis of 3 large series of glioma cases showed an increase in the number of gliomas among first-degree relatives of glioma patients. In addition, a variety of other cancer sites were over- or underrepresented among the relatives. Furthermore, the SIRs varied somewhat by study, possibly indicating that some other population characteristic(s) may also be at play. These findings should be validated when other large studies are available for pooling to capture the more rare cancers and to enable better assessment of the heterogeneity of the effect across populations. In addition, the use of different study designs, such as the case-control design, would enable calculation of familial risk by adding controls and their familial data.

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