



Practice of Epidemiology

The Glioma International Case-Control Study: A Report From the Genetic Epidemiology of Glioma International Consortium

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Decades of research have established only a few etiological factors for glioma, which is a rare and highly fatal brain cancer. Common methodological challenges among glioma studies include small sample sizes, heterogeneity of tumor subtypes, and retrospective exposure assessment. Here, we briefly describe the Glioma International Case-Control (GICC) Study (recruitment, 2010–2013), a study being conducted by the Genetic Epidemiology of Glioma International Consortium that integrates data from multiple data collection sites, uses a common protocol and questionnaire, and includes biospecimen collection. To our knowledge, the GICC Study is the largest glioma study to date that includes collection of blood samples, which will allow for genetic analysis and interrogation of gene-environment interactions.

cancer; case-control studies; glioblastoma; glioma; methodology; study profile

Abbreviations: GBM, glioblastoma multiforme; GICC, Glioma International Case-Control; GLOGENE, Genetic Epidemiology of Glioma; WHO, World Health Organization.

Editor's note: *An invited commentary on this article appears on page 92, and the authors' response appears on page 95.*

With an annual incidence rate of 2–3 cases per 100,000 population in the United States, glioma, which comprises approximately 28% of all primary brain tumors, is a rare but highly fatal disease (1–4). Decades of research have established only a few etiological factors (family history, rare genetic cancer predisposition syndromes, ionizing radiation, and 10 independent genetic risk loci) (5–11), partly because glioma is a particularly challenging disease to study. Because it is a rare, highly fatal, and heterogeneous disease (2), it is difficult to accrue

enough cases for large-scale epidemiologic studies (6). Due to potential etiological differences by tumor subtype, large sample sizes are needed to stratify results by histology. Additionally, it is not usually feasible to conduct a prospective study, thus necessitating the use of case-control study designs and retrospective exposure assessments. For these reasons, we opted to develop a consortium structure that integrates data from multiple sites, uses a common protocol and questionnaire, and includes biospecimen collection. Studies conducted by such consortia can help overcome some of the above obstacles and may be able to attain sufficient statistical power for identifying novel risk factors for this enigmatic disease.

To examine the genetic factors underlying *familial* glioma, the Genetic Epidemiology of Glioma International Consortium

(GLOGENE Consortium) was formed in 2006 to recruit families affected by ≥ 2 cases of glioma from 14 institutions across 5 countries (12). Research carried out by this consortium has yielded a number of high-impact discoveries (13, 14). However, because familial glioma accounts for only about 5% of all gliomas (12), the GLOGENE investigators recognized the need to study sporadic glioma, which comprises the remaining 95% of gliomas. Thus, capitalizing upon the infrastructure in place from the GLOGENE familial study, we have launched a large study of glioma that includes biospecimen collection: the Glioma International Case-Control (GICC) Study.

The main goals of the GICC Study are: 1) to identify novel genetic risk variants for glioma, as well as validate variants implicated by previous genome-wide association studies of glioma; and 2) to explore biologically relevant gene-gene and gene-environment interactions in glioma susceptibility. With 4,545 cases and 4,173 controls, the GICC Study confers the opportunity to evaluate both environmental exposures and genetic variation while accounting for tumor subtype. The study's comprehensive questionnaire data will allow for examination of putative risk factors identified from prior literature (i.e., radiation exposure, atopy, childhood infections), which can be reexamined in detail and validated. Additionally, the large study population may enable us to explore gene-environment interactions. Here, we present an overview of the study's structure and methodology, some methodological challenges and solutions, and preliminary demographic data.

THE GICC STUDY: DESIGN AND METHODS

Structure of the GICC Study

There are 14 recruitment sites in the GICC Study: Brigham and Women's Hospital (Boston, Massachusetts), Case Western Reserve University (Cleveland, Ohio), Columbia University (New York, New York), the Danish Cancer Society Research Centre (Copenhagen, Denmark), the Gertner Institute (Tel Hashomer, Israel), Duke University (Durham, North Carolina), the University of Texas MD Anderson Cancer Center (Houston, Texas), Memorial Sloan Kettering Cancer Center (New York, New York), the Mayo Clinic (Rochester, Minnesota), NorthShore HealthSystem (Chicago, Illinois), Umeå University (Umeå, Sweden), the University of California, San Francisco (San Francisco, California), the University of Southern California (Los Angeles, California), and the Institute of Cancer Research (London, United Kingdom).

The structure of the GICC Study is presented in Figure 1. A steering committee oversees the administration of the study. Data management and statistical analyses are conducted centrally, with oversight by a topic-specific working group. These working groups were formed for each exposure of interest and are led by members of the GLOGENE Consortium.

A common study protocol was developed and is followed as closely as possible at each study site. However, it was not feasible to conduct the study identically at every site due to site-specific differences in infrastructure, resources, institutional policies, and laws and regulations across 14 institutions and 5 countries. Every site administered the same questionnaire

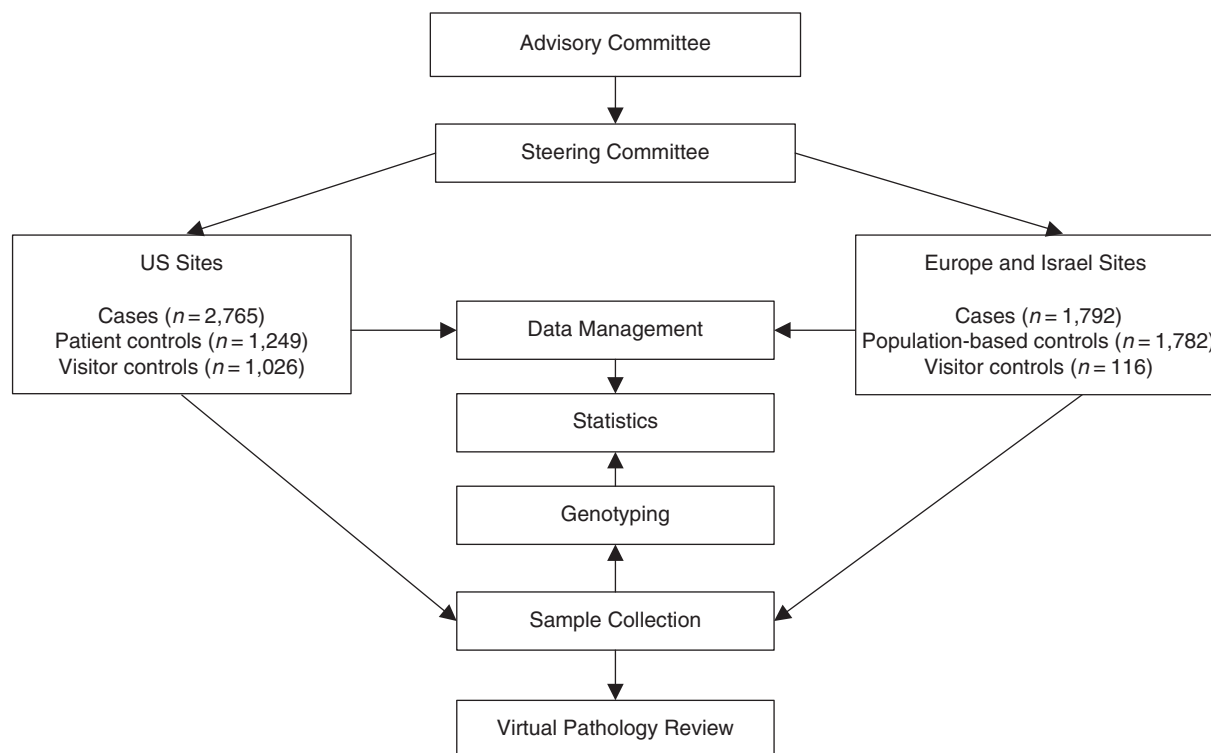


Figure 1. Infrastructure of the Glioma International Case-Control Study (recruitment, 2010–2013).

(either the full version or the abbreviated version) and entered the data into a centralized Web-based database.

Ethical considerations

All participating institutions received institutional review board or ethical board approval to conduct the study. All study staff were trained in human subjects research, and informed consent was obtained from all participants.

Study population

Case eligibility and recruitment. Case recruitment began in April 2010 at all sites. Eligibility criteria for cases were as follows:

- Diagnosis of histologically confirmed, supratentorial, intracranial glioma (World Health Organization (WHO) grades II–IV): fibrillary astrocytoma (*International Classification of Diseases, Ninth Revision*, code 9420/3), protoplasmic astrocytoma (code 9410/3), gemistocytic astrocytoma (code 9411/3), oligodendroglioma (code 9450/3), oligoastrocytoma (code 9382/3), anaplastic astrocytoma (code 9401/3), anaplastic oligodendroglioma (code 9451/3), anaplastic oligoastrocytoma (code 9382/3), or glioblastoma (code 9440/3)
- Age 18–80 years at diagnosis
- Ability to speak the local language

Cases were recruited within 1 year of diagnosis and consented to participation at their clinic visits. Blood/saliva samples and interviews were obtained or scheduled at that time. Interviews were conducted in person (52.5%) or by telephone (21.8%), or the questionnaire was self-administered (mailed to the respondent) (21.3%). At European and Israeli sites, cases were recruited nationwide through the university clinics that had neuro-oncology centers. The consent process for all centers involved written permission to abstract data from medical records and to obtain pathology slides for confirmation of the glioma diagnosis. If the case patient had neurological or other health deficits, we asked an appropriate proxy to assist with questionnaire completion.

Control eligibility and recruitment. Like cases, controls were eligible for the study if they were between 18 and 80 years of age and could speak the local language. Investigators at each site chose which control recruitment method to use based on feasibility and their existing infrastructure.

Seven sites recruited visitors accompanying cancer patients as controls, 4 sites recruited clinic-based controls, and 3 sites used population-based controls (Figure 1). It was not feasible for all sites to recruit controls using identical methods. Ideally, control selection would capture members of the underlying source population for the cases (15, 16). However, there is no ideal method for recruiting such a control population for any case-control study (16), particularly one involving several large referral centers, where the source population includes a mix of both national and international patients and cannot therefore be easily defined. Our goal was to accrue either visitors accompanying non-brain-tumor patients or patients at general medical clinics as controls or, alternatively, population-based controls, to optimize participation at as many sites as possible. Sites

with population-based case recruitment accrued population-based controls (Sweden, Denmark, Israel). Most US sites are tertiary-care and/or referral centers and thus used visitor or general clinic-based controls, depending on what was most feasible and/or cost-effective.

There are advantages of using visitor controls. Hospital visitors generally tend to derive from the same hypothetical population as cases, and are likely to be included as cases if they were to develop glioma (17, 18). Published reports also support the use of hospital/clinic visitors for control recruitment in studies with underlying populations that are difficult to define (18–20). Many of the consortium investigators have previously used this method to accrue controls for several ongoing case-control studies.

However, visitors accompanying non-brain-tumor patients may be more likely to report higher prevalences of exposures, such as family history of cancer (18), or to devote more effort to recalling details during questionnaire response than the general population, potentially as a result of being a close contact of someone with cancer. General medical clinic-based controls may be more likely to report comorbid conditions (e.g., allergies/asthma) or medication use (e.g., antihistamine use) than the general population, which could bias a potential association between such factors and glioma towards the null. For these reasons, we will conduct sensitivity analyses by examining each exposure-outcome relationship of interest by control type (discussed below).

Centralized pathology review. Pathology slides from a subset of the cases recruited during the first year of the GICC Study (total $n = 588$) were subjected to centralized review to ensure that misclassification of tumor type was minimal across sites. Some studies of reviews by independent pathologists have shown large interindividual variability (up to 50% between histopathological entities for both major and minor changes) (21–23).

Our pathology team met in October 2011 to design our pathology review protocol. To ensure a high participation rate, the decision as to whether the original slides from initial diagnosis or freshly cut slides were sent to our team was left to the discretion of the individual study center, according to each country's or hospital's local guidelines. The corresponding pathology reports were also collected. All non-glioblastoma multiforme (GBM) cases ($n = 509$) and 10% of GBM cases ($n = 79$) available on that date were selected for review, because GBMs are classified according to established diagnostic criteria (WHO scheme) and have previously been shown to be subject to a very low rate of diagnostic discrepancy (24).

Eight pathologists were randomized into teams of 2, with 1 European pathologist and 1 US pathologist per team. The pathologists were blinded to the primary diagnosis. The teams and the group as a whole employed the WHO general guidelines for typing and grading (25). If the twin team of pathologists did not reach consensus, the case was taken forward to a final panel for a decision by all of the pathologists. A change of diagnosis was defined as a change from low WHO grade to high WHO grade or a complete histological change from oligodendroglioma to astrocytoma or vice versa.

Overall, there was a change of grade from lower to higher in only 4% of glioma cases, and there was a change in both grade and histology in only 2.8% of cases. Given the small

proportions of gliomas that were reclassified, we believe that misclassification of tumor type is unlikely to represent a major source of bias in our study.

Data and specimens

The GICC risk factor questionnaire included questions on demographic characteristics, exposure to ionizing radiation, medical and medication history, and occupational exposure history. The family history section of the questionnaire documents the numbers of and dates of birth and death for all first- and second-degree relatives and all cancer diagnoses in the family. The questionnaire has a fixed script, including transition statements where necessary. The consortium utilized previously validated scales and questions (i.e., the Charlson Comorbidity Index (26) and tobacco use questions from the WHO's Global Adult Tobacco Survey (<http://www.who.int/tobacco/surveillance/gats/en/>)) for as many sections of the questionnaire as possible. Two versions of the questionnaire were utilized: a full version and an abbreviated version. The abbreviated version excluded only detailed questions on brain tumor symptoms, seizures, medical history, immunosuppressant use, dental x-rays, and physical activity. The study sites that administered the abbreviated version (due to time constraints) were: Duke University; Memorial Sloan Kettering Cancer Center; the University of California, San Francisco; the Institute of Cancer Research; and the University of Southern California.

Data collection procedures were similar at each site. All study coordinators attended an initial 2-day central training session to ensure site-to-site homogeneity in protocols and data collection procedures. The study manager conducted site visits to ensure that appropriate procedures were being followed. Staff from all recruitment centers participated in monthly conference calls that focused on data collection, eligibility, and study procedures.

Each participant was asked to submit to venipuncture (30 mL of blood) or, if unable/unwilling to do so, to provide a saliva sample. Each site stored an aliquot of whole blood (or saliva) from each participant and extracted DNA from the remaining blood/saliva using standard methods. The US sites then submitted 10 µg of DNA per participant to the Mayo Clinic's Biospecimen Accessioning and Processing Core for central long-term storage.

Data reliability. One study site, the Mayo Clinic, utilized clinic-based controls from the Mayo Clinic Biobank, which collects medical records and questionnaire data. Controls for this site were selected from the 50,000 available biobank participants, frequency-matched to cases, and recontacted for participation in the GICC Study. Approximately 60% of controls consented to GICC participation about a year after being entered into the biobank. Because these individuals ($n = 453$) completed both questionnaires in a relatively short period of time, we were able to assess concordance between certain variables that were ascertained through similar questions, and we calculated the percentage of concordance between the responses. Only 1 of the 51 variables examined had less than 90% concordance (see Web Table 1, available at <http://aje.oxfordjournals.org/>).

Genotyping. Illumina's Infinium OncoArray-500K BeadChip array (Illumina Inc., San Diego, California) was used for genotyping. We customized the array to include an addi-

tional 37,000 bead types. Customized content included genes previously implicated in glioma etiology. We plan to provide additional details related to the GICC genetic data in a future publication.

Plan of analysis

Statistical analysis. Due to both innate heterogeneity (i.e., geographic/cultural) and differences in study conduct/methodology between sites, a multipronged analytical approach is planned for each exposure of interest. All estimates will be calculated and presented for all gliomas, as well as separately for GBMs and non-GBMs. First, we will compare exposure proportions/means between cases and controls across the 14 study sites. Then site-specific crude and adjusted odds ratios will be calculated for each exposure-outcome relationship, using logistic regression. All 14 sets of site-specific odds ratios, their corresponding 95% Wald confidence intervals, and P values will be presented in each manuscript to show the potential variability in results across sites. These odds ratios and 95% confidence intervals will be compared with each other; specifically, if 1 (or 2) of the site-specific odds ratios are in opposite directions and have nonoverlapping confidence intervals, we will conduct a series of sensitivity analyses to help explain why this odds ratio is outside of the observed range. These sensitivity analyses will vary based on the exposure of interest (behavioral, occupational, etc.).

We will then use meta-analysis methods to quantify potential site-specific heterogeneity. We will combine site-specific estimates through a random-effects model to consider variability within and between studies (27). Final combined meta-analysis odds ratios, calculated by both a 1-stage and a 2-stage meta-analysis approach, will be provided. The 1-stage approach synthesizes the individual-level data from all sites simultaneously, while also accounting for clustering of subjects within sites. The 1-stage approach consists of a multilevel logistic regression model with random effects. We will use the adaptive Gauss-Hermite quadrature approximation method (28). In the 2-stage approach, we will use a maximum likelihood estimate to summarize the exposure-outcome association for each study site in the first stage and maximum likelihood estimation/restricted maximum likelihood to combine those aggregate data across study sites in the second stage. To formally measure statistical heterogeneity, we will calculate Cochran's Q statistic and the I^2 statistic to assess the inconsistency of results (29).

Forest plots will be provided as a simple representation of the site-specific and overall summary (meta-analysis) estimates and of the variation between study results (30). Additionally, for each association, we will examine the differences in effect estimates between sites with different types of controls (visitor, clinic, or population-based) to ensure that no patterns by control type are present. In addition, when we are examining exposures for which geographic differences may be meaningful (e.g., allergies/asthma), our analyses will be stratified and results presented accordingly.

Other methodological and analytical challenges and solutions. Two key methodological challenges are related to differences in questionnaire administration methods and the accuracy of proxy-reported information.

Table 1. Characteristics of the Study Population, Glioma International Case-Control Study, 2010–2013

Characteristic	Cases		Controls	
	No.	%	No.	%
Total	4,545	100	4,173	100
Sex				
Male	2,679	58.9	2,350	56.3
Female	1,866	41.1	1,823	43.7
Race/ethnicity				
Missing data	17	0.4	4	0.1
White	4,174	91.8	3,692	88.5
Black	71	1.6	140	3.4
Asian	84	1.9	87	2.1
Hispanic	161	3.5	224	5.4
Other	38	0.8	26	0.6
Age at diagnosis/ enrollment, years ^a				
18–29	307	6.8	294	7.1
30–39	526	11.6	474	11.4
40–49	816	18.0	680	16.3
50–59	1,157	25.5	1,079	25.9
60–69	1,238	27.2	1,098	26.3
70–80	501	11.0	548	13.1
Education				
Missing data	477	10.5	120	2.9
High school or less	1,125	24.8	912	21.9
Some college	1,105	24.3	1,292	31.0
Bachelor's degree	1,026	22.6	958	23.0
Advanced degree	812	17.9	891	21.4

Table continues

Questionnaire administration methods differed by site (Web Table 2). To assess whether reporting bias may exist by questionnaire administration method, we will calculate site-specific odds ratios for each exposure and will assess potential heterogeneity between sites by primary method of questionnaire administration (in-person interview, telephone interview, mixed methods (by phone and in person), or self-administration; see example in Web Table 3). Differences in questionnaire administration are less likely to be causing a major bias in the results if clear patterns do not emerge in the odds ratios by category.

As an additional sensitivity analysis, we will investigate the association between questionnaire administration method and the probability of reporting a positive response for each exposure of interest, using logistic regression (see example in Web Table 4). This analysis will allow us to determine whether the questionnaire administration method is resulting in misclassification of the factor of interest and whether that misclassification is nondifferential or differential by case-control status. If we find differential misclassification by questionnaire administration method, we will consider weighting our future analyses accordingly. Unfortunately, we cannot simply

Table 1. Continued

Characteristic	Cases		Controls	
	No.	%	No.	%
Glioma grade				
Not applicable	0	0	4,173	100
Grade II	870	19.1	0	0
Grade III	819	18.0	0	0
Grade IV	2,784	61.3	0	0
Unclassified	72	1.6	0	0
Marital status	475	10.5	117	2.8
Missing data				
Married/living with partner	3,161	69.6	3,017	72.3
Divorced/separated	324	7.1	325	7.8
Widowed	131	2.9	131	3.1
Never married	454	10.0	583	14.0
Interview type				
Missing data	19	0.4	0	0
Self-reported	3,993	87.9	4,173	100
Equally self- and proxy-reported	163	3.6	0	0
Proxy-reported	370	8.1	0	0
Questionnaire administration				
Missing data	155	3.4	79	1.9
By telephone	1,194	26.3	646	15.5
In person	2,182	48.0	2,520	60.4
Both by phone and in person	98	2.2	42	1.0
Self-administered	916	20.2	886	21.2

^a The mean age was 53.4 (standard deviation, 13.8) years in cases and 53.8 (standard deviation, 14.2) years in controls; the median age was 55 (range, 18–80) years in cases and 56 (range, 18–80) years in controls.

adjust for questionnaire administration method in our final models, because of the distribution of administration methods within sites and by case-control status (Web Table 2).

Because glioma may affect the patient's cognitive functioning (or patients may die after giving consent), proxy responses for cases are sometimes necessary. The impact of proxy responses may differ by exposure of interest, partly because some exposures may be less likely to be accurately reported by a proxy than others (e.g., severe allergies in adulthood vs. ages at common childhood illnesses). The proportion of proxy-only respondents in our study is relatively low (7.8% of respondents overall; Table 1), and most proxy respondents are cohabitants of the case, including spouses (approximately 50%). Cases who used proxy respondents at recruitment were more likely to be older and male and more likely to have a high-grade tumor than cases who self-reported (data not shown). As a result, we will compare odds ratios for each exposure including and excluding proxy responses. If the results are similar, proxy responses will be included in the final analyses of that exposure. If they differ, both estimates will be reported. We cannot adjust for proxy response in our regression models, since proxies were not used for controls.

PRELIMINARY RESULTS: DEMOGRAPHIC PROFILE OF THE GICC POPULATION

Demographic characteristics of the GICC study population are summarized in Table 1 (data are shown by site in Web Table 2). The median ages at diagnosis/enrollment for cases and controls were 55 (standard deviation, 13.8) years and 56 (standard deviation, 14.2) years, respectively. Approximately 59% of cases were male, as compared with 56% of controls, and the majority of the study population was non-Hispanic white (91.8% of cases; 88.5% of controls). Among cases, 61.3% had high-grade (WHO grade IV) gliomas. This demographic profile is consistent with previous studies of adult glioma (31).

SUMMARY

Limitations

As a study conducted by an international multi-institution consortium, the GICC Study is subject to some limitations. Site-to-site heterogeneity in control selection and other differences in study conduct can influence our findings, but we have carefully planned our analyses to consider these differences as much as possible. Additional geographic and cultural heterogeneity across international sites may convolute some associations, necessitating that both site-specific and overall meta-regression results be reported for each exposure. Nevertheless, such challenges are unavoidable in large consortium studies, partly due to differences in infrastructure and resources, institutional policies, and national regulations.

Planned analyses

The initial set of GICC analyses will focus on validating previously implicated epidemiologic risk factors for glioma (viral exposures, atopy, antihistamine use, nonsteroidal anti-inflammatory drug use, family history, radiation exposure) in our large study population. Future analyses will include a genome-wide association study and will explore the roles of gene-environment and gene-gene interactions in glioma etiology.

Conclusions

To our knowledge, the GICC Study is the largest case-control study of glioma to date that includes both epidemiologic data and biospecimens, allowing for the evaluation of genetic variants and environmental factors and the exploration of gene-environment interactions. The study includes detailed data on key suspected risk factors for glioma, permitting us to examine these factors in an international context. Many previous glioma studies have been hampered by problems related to small sample sizes, lack of generalizability, and issues regarding exposure assessment. We hope that our consortium study can help overcome some of these challenges.

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The Glioma International Case-Control Study is being conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each study subject or from his/her guardian. Approval from local institutional review boards was received at each institution participating in the Genetic Epidemiology of Glioma International Consortium.

Conflict of interest: none declared.

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