Brain Tumor Epidemiology: Consensus From the Brain Tumor Epidemiology Consortium

Melissa L. Bondy, PhD
Michael E. Scheurer, PhD
Beatrice Malmer, MD
Jill S. Barnholtz-Sloan, PhD
Faith G. Davis, PhD
Dora Il'yasova, PhD
Carol Kruchko
Bridget J. McCarthy, PhD
Preetha Rajaraman, PhD
Judith A. Schwartzbaum, PhD
Siegal Sadetzki, MD, MPH
Brigitte Schlehofer, PhD
Joseph L. Wiemels, PhD
Margaret Wrensch, PhD
Patricia A. Buffler, PhD

On behalf of the Brain Tumor Epidemiology Consortium

Epidemiologists in the Brain Tumor Epidemiology Consortium (BTEC) have prioritized areas for further research. Although many risk factors have been examined over the past several decades, there are few consistent findings, possibly because of small sample sizes in individual studies and differences between studies in patients, tumor types, and methods of classification. Individual studies generally have lacked samples of sufficient size to examine interactions. A major priority based on available evidence and technologies includes expanding research in genetics and molecular epidemiology of brain tumors. BTEC has taken an active role in promoting understudied groups, such as pediatric brain tumors; the etiology of rare glioma subtypes, such as oligodendroglioma; and meningioma, which, although it is not uncommon, has only recently been registered systematically in the United States. There also is a pressing need for more researchers, especially junior investigators, to study brain tumor epidemiology. However, relatively poor funding for brain tumor research has made it difficult to encourage careers in this area. In this report, BTEC epidemiologists reviewed the group’s consensus on the current state of scientific findings, and they present a consensus on research priorities to identify which important areas the science should move to address.

KEYWORDS: glioma, meningioma, epidemiology, genetics.

Epidemiologic studies of glioma have examined many risk factors over the past several decades; however, there are few consistent findings. The inconclusive results may be because of small sample sizes in individual studies and differences between studies in patients, tumor types, and methods of classification. Individual studies generally have lacked sufficient sample size to examine interactions. A major priority based on available evidence and technologies includes expanding research in genetics and molecular epidemiology of brain tumors (BTs). Because of the small numbers of

© 2008 American Cancer Society
DOI 10.1002/cncr.23741
Published online 17 September 2008 in Wiley InterScience (www.interscience.wiley.com).
patients, BTs have been an orphan disease, and the funding to study these tumors has been relatively limited. The Brain Tumor Epidemiology Consortium (BTEC) convened a group meeting to develop a consensus on research priorities to identify the important areas the science should move to address.

The discussion below addresses the current state of literature and presents the group’s consensus on important research needs to drive the science forward over the next decade. Although the epidemiologic literature on BTs is inconclusive in many areas, there are many promising areas to pursue in future research. Here, we include an overview of the descriptive epidemiology and risk factors, such as inherited susceptibility, ionizing radiation, nonionizing radiation, immune function (including allergies and infections), established neurocarcinogens, and metals.

**Methodology of Review and Assessment of Important Research Areas**

In preparation for the BTEC group meeting, 2 experts who previously had published studies in a specific area were assigned to write an overview of their area of expertise before the meeting in Berkeley, California. Generally, larger studies with conclusive results that were published in the last 25 years were considered as references by searching the PubMed database. The review was not intended as an exhaustive overview of the literature covering all studies that reported inconclusive results; a review of this magnitude was published previously. All background chapters were presented at the meeting, and small discussion groups were formed from the attending delegates. Each research area of interest was discussed in the small groups, and each group prioritized the research topics they considered most important for future studies. Finally, a large room discussion with all 45 delegates was conducted based on the initial recommendations from the small groups. The full discussion of each topic was followed by a vote from the entire group to identify the priority research areas of major interest to the majority of the group.

**Incidence and Mortality**

The annual, global, age-standardized incidence of primary malignant BTs is ≈3.7 per 100,000 for men and 2.6 per 100,000 for women. Rates appear to be higher in more developed countries (men, 5.8 per 100,000; women, 4.1 per 100,000) than in less developed countries (men 3.0 per 100,000; women 2.1 per 100,000). Approximately 21,810 individuals (11,780 men and 10,030 women) were diagnosed with primary malignant BTs in 2008 in the United States (www.cancer.org accessed on March 1, 2008). The incidence of both primary malignant and nonmalignant BTs in the United States is ≈16.5 per 100,000 per year, with Caucasians having the highest rate. Men generally have higher rates of primary malignant BTs, whereas women have higher rates of nonmalignant tumors, primarily meningiomas. The distribution of tumor types varies substantially by age group, and interested readers are referred to the Central Brain Tumor Registry of the United States (CBTRUS) website (www.cbtrus.org accessed on March 1, 2008) for a complete compilation of BT statistics. Data from several national cancer registries support differences in the epidemiology of BTs in children versus adults. For example, in Sweden, medulloblastoma (23.5%) and low-grade glioma (31.7%) are the most common types of tumors in pe-
diagnostic patients aged ≤15 years; which is very different compared with adult patients, in whom high-grade glioma (30.5%) and meningioma (29.4%) are the most common types of adult primary BTs (data from the Swedish Cancer Registry). Data from CBTRUS also support these differences in the United States.

Worldwide, age-standardized mortality for primary malignant BTs is ≈2.8 per 100,000 population for men and 2.0 per 100,000 population for women.² Like incidence rates, the estimated mortality is higher in more developed countries (men, 4.1 per 100,000; women, 2.7 per 100,000) than in less developed countries (men, 2.2 per 100,000; women, 1.6 per 100,000). US mortality rates for primary malignant BTs are 5.6 per 100,000 for men and 3.7 per 100,000 for women. In the United States, the 5- and 10-year survival rates are ≈29.1% and 25.3% according to data from the American Cancer Society (ACS) website (www.cancer.org accessed on March 1, 2008), respectively, and those rates differ significantly by histology and age. For example, patients with glioblastoma multiforme (GBM) have a 5-year survival rate of 3.3%, whereas patients with lower grade gliomas, such as pilocytic astrocytoma, oligodendroglioma, and ependymoma, have 5-year survival rates of >70%; whereas patients with astrocytoma (not otherwise specified), anaplastic astrocytoma, malignant glioma, and lymphoma have 5-year survival rates <40%. Overall, and for most histologies, the 5-year survival rate decreases with age (data from www.cbtrus.org). However, there are some histologic types for which survival is poorer among children and the elderly (e.g., GBM and ependymoma). Conflicting reports, some with methodologic problems, have indicated variations in survival by race/ethnicity.⁵⁻⁹ Caucasians reportedly had a 5-year relative survival rate of 33.5%, whereas African Americans had a 5-year relative survival rate of 37.0%. Similar analyses using data from the Surveillance, Epidemiology, and End Results Program indicated that African Americans had similar or poorer survival than Caucasians,⁷ but those results were adjusted incompletely for important prognostic factors (e.g., age at diagnosis, treatment patterns, and tumor histologies). After adjustment, African Americans had a 13% higher risk of death for primary malignant BTs and a 40% higher risk of death from low-grade tumors compared with non-Hispanic whites.⁶

In summary, progress in diagnostic technologies and ascertainment, particularly for nonmalignant BTs, may account for much of the modest increase in incidence. Changes in tumor classification and coding likely are responsible for some of the increases in incidence for BTs histologies, such as oligodendroglioma and astrocytoma, and not otherwise specified. Further diagnostic advances will produce rising incidence in specific diagnoses. The influence of sex on BT incidence rates is consistent over time and geographic area, with a preponderance of glioma among men and meningioma among women.

**Risk Factors**

Table 1 summarizes the associations observed for a variety of factors with adult glioma and meningioma. There is consensus among BT epidemiologists that variations in study designs, population characteristics, information sources, measurement, and classification have limited the ability to make conclusive associations of specific types of adult BTs with individual risk factors. In addition, studies have varied in their reliance on proxy and historic information and on standards of precision and completeness for data sources used. With respect to environmental exposures, future studies should pay greater attention to whether or not suspect agents can cross the blood-brain barrier (BBB) or whether they can reach the brain by other routes.

**Genetic susceptibility: Genetic syndromes**

Studies of syndromes, familial aggregation, linkage, and mutagen sensitivity in adults suggest genetic susceptibility to gliomas. Although the genetic syndromes caused by rare inherited mutations and associated with higher risk of BTⁱ⁰ account for few cases, they provide an important starting point for identifying candidate genes and pathways for gliomagenesis. Syndromes, including gliomas or medulloblastoma, with gene names and chromosome location, are neurofibromatosis 1 (NF1) (17q11) and NF2 (22q12), tuberous sclerosis 1 (TSC1) (9q34) and TSC2 (16p13), retinoblastoma 1 (RB1) (13q14), Li-Fraumeni (TP53) (17p13), and Turcot syndrome and multiple hamartoma (the adenomatous polyposis coli gene APC, 5q21; the human mut-L homolog 1 gene hMLH1, 3p21.3; hMSH2, 2p22-21; the postmeiotic segregation increased 2 gene PMS2, 7p22; and the phosphatase and tensin homolog gene PTEN, 10q23.3). The roles of more common variants in many of these genes (and related pathways) in sporadic gliomas are unknown to date.

Genetic causes of BTs apart from well known syndromes have yet to be clarified; however, BTs aggregate in families.¹¹ In addition, a segregation study suggested multifactorial inheritance, and linkage studies have pointed to the 15q23 region.¹²,¹³ Large collections of glioma families for more extensive linkage analyses are being collected in the international GLIOGENE study of familial glioma (www.gliogene.org accessed on March 1, 2008).
Genetic susceptibility: Specific genetic polymorphisms

Researchers have studied several polymorphisms in relation to glioma, most commonly in DNA repair, carcinogen metabolism, and immune function genes, either because of their plausible relation to carcinogenesis or from consistently observed associations between allergies and glioma (see below). Although some promising results have been reported, as noted below, too few studies have been conducted of any polymorphisms to assure consistency. Inherited vari-
ation in DNA repair represents a major category of genes that have been studied extensively with respect to cancer because of their importance in maintaining genomic integrity. Glioma and/or glioma subtypes have been associated significantly with variants in the excision repair cross-complementing 1 and 2 genes (ERCC1 and ERCC2, respectively); the nearby gene glioma tumor suppressor candidate of unknown function (GLTSCR1); the protein kinase, DNA-activated catalytic polypeptide gene PRKDC (also known as x-ray repair cross-complementing group 7 (XRCC7)); methylguanine-DNA methyltransferase (MGMT); and, most recently, the chromatin assembly factor 1, subunit A gene CHAF1A.\textsuperscript{14-19} Ataxia telangiectasia mutated haplotypes have been associated with meningioma, and cell cycle genes have been associated more weakly with glioblastoma.\textsuperscript{20,21} Recently, a polymorphism in the breast cancer 1 (BRCA1)-interacting protein 1 (BRIP-1) was associated with meningioma, which may provide a functional link to the previously described association with breast cancer.\textsuperscript{22} Intragenic single-nucleotide polymorphisms in the Ki-ras and ERCC2 genes were associated with a 1.7-fold increase in meningioma risk, and a significant interaction was reported between radiation and cyclin D1 and p16 single-nucleotide polymorphisms.\textsuperscript{23} Simultaneous consideration of DNA repair with other relevant (eg, inflammation or cell cycle control) pathways would allow proper evaluation of larger sets of polymorphisms. For example, most gliomas exhibit dysregulation of p53 whether through mutation or some other mechanism, and the transformed 3T3 cell double-minute 2 gene MDM2 is a key guard in this pathway. The few established, exogenous, environmental causes of glioma are therapeutic or high-dose chemotherapy for cancers at sites other than the brain.\textsuperscript{24-27} Genetic factors determine the degree of risk from these exposures. Children who are treated with cranial irradiation and intensive antimetabolite therapy for acute lymphocytic leukemia and those with germ line polymorphisms that lead to low or absent thiopurine methyltransferase activity are significantly more likely than children without such polymorphisms to develop BT. Metabolizing enzymes, such as glutathione transferases, have been investigated in several studies with inconsistent results.\textsuperscript{28,29}

Abundant evidence suggests that inherited susceptibility acts in glioma risk, but describing its forms is challenging. The 2 main, possibly complementary, research efforts are familial linkage studies currently undertaken in the Gliogene study and disease association studies. Although large-scale, genome-wide association studies of glioma have much to commend them, for BTs, there are serious limitations of relatively small sample sizes and heterogeneity within and between types of gliomas and other primary BTs. These increase the chances of both false-positive and false-negative results. Consequently, it will be important to continue to prioritize polymorphisms based on biologic knowledge to develop strong prior hypotheses for testing subsets of pathways, genes, and polymorphisms. Several groups now plan large-scale association studies, including the University of California-San Francisco (UCSF) Adult Glioma study, a European-M. D. Anderson Cancer Center Consortium, and a Mayo study of oligodendroglioma. UCSF also is developing a website to catalog and prioritize genes and polymorphisms of interest with glioma etiology and prognosis (www.snplogic.org accessed on March 1, 2008).

Tumor studies have provided valuable information both for categorizing tumors and suggesting chromosomal regions important in glioma pathogenesis. Cytogenetic and array-based comparative genomic hybridization studies of gliomas have identified copy number changes (deletions, amplifications, gains) in several regions. Deletions and loss of heterozygosity suggest tumor suppressor genes, whereas amplifications and gains may point to genes involved in tumor initiation or progression. The more regularly observed of these, which may vary by histologic type, include gains and deletions in 1p; deletion of 4q; amplifications and gains of 7; deletions of 9, 10, and 11; and loss of 13, 19, and 22. Coincidentally, several well known tumor suppressor genes and oncogenes occur in these regions. These also indicate substantial genetic and gene expression heterogeneity within and between tumor grades and between histologic types.\textsuperscript{30} However, the degree to which the mature tumor is independent of the ‘causal’ environmental or genetic pathways is unknown. It also is not known whether variability of dysregulated pathways among tumors reflects different causes. In addition to these histologic differences, GBM can be separated further into ‘secondary’ GBM, which theoretically has progressed from lower grade tumors, and ‘primary’ or ‘de novo’ GBM with no clinically apparent precursor. It is noteworthy that mutation of the tumor protein p53 gene TP53 and amplification of the epidermal growth factor receptor gene \textit{EGFR} correlate with the type of GBM.\textsuperscript{30} Tumors with \textit{TP53} mutations more often are secondary GBM, whereas \textit{de novo} GBM more likely harbors \textit{EGFR} amplification. Despite some inconsistencies between studies, case-control findings support smaller case series hypothesizing that astrocytic
tumors arise through different pathways and reflect different causal mechanisms. Therefore, molecular subtyping is likely to be useful in the future as an adjunct to histology for tumor classification.

**Ionizing radiation exposure**

Certain forms and doses of ionizing radiation are generally accepted causes of BTs. A-bomb studies, nuclear test fall-out data, therapeutic radiation for cancer and benign conditions, and occupational and environmental studies have connected ionizing radiation to tumorigenesis. The first conclusive evidence of an association between ionizing radiation and BTs came from a follow-up study of Israeli children who were receiving radiation therapy for tinea capitis with a mean dose to the brain from 1 gray (Gy) to 6 Gy. The cohort included 10,834 irradiated individuals with both matched population and sibling control groups. With follow-up, meningiomas increased strikingly (relative risk [RR], 9.5; 95% confidence interval [CI], 3.5-25.7) and gliomas increased marginally (RR, 2.6; 95% CI, 0.8-8.6). A later follow-up of the cohort indicated that showed the excess RR/Gy for the irradiated group was 4.63 (95% CI, 2.43-9.12) and 1.98 (95% CI, 0.73-4.69) for benign meningiomas and malignant BT, respectively, with an inverse trend observed for age at irradiation noted only for malignant BTs. For both tumors, the risk was elevated after a latency of ≥30 years and was dose responsive, but it was not associated with sex or origin.

The high meningioma incidence of A-bomb survivors was reported for residents of Nagasaki and Hiroshima. The difference between the Japanese and Israeli studies may arise from A-bomb survivors’ lower radiation exposure compared with the tinea capitis cohort, and A-bomb radiation mainly affected adults, whereas tinea capitis radiation primarily affected children. A 6.5-fold increase in the risk of meningioma among exposed versus unexposed populations of Hiroshima survivors also was reported. The latest study reported a statistically significant dose-response for all nervous system tumors combined, indicating that exposure to even moderate doses (<1 Sievert) of radiation is associated with elevated incidence of central nervous system tumors.

A follow-up study of childhood nasopharyngeal radium exposure (345 cases and 1158 controls) reported an RR for BTs of 3.09 for the children who were exposed. The Childhood Cancer Survivor Study (CCSS) of 5-year survivors of childhood cancer (n = 14,361) identified subsequent primary CNS tumors among 116 members, most often meningioma (n = 66) and glioma (n = 40), that occurred a median of 17 years and 9 years, respectively, after the original diagnosis. Exposure to radiation therapy as treatment for the primary cancer was associated with odds ratios (ORs) of 6.78 (95% CI, 1.5-30), 9.94 (95% CI, 2.2-45.6), and 7.07 (95% CI, 2.8-18.1) for glioma, meningioma, and all CNS tumors combined, respectively. A limitation of the CCSS and some survival studies is that data on the survival of children with cancer who received radiation during the first 5 years after diagnosis and treatment are not included, and some treatment-related BTs may arise during this first 5 years after diagnosis.

Cohort studies of nuclear industry workers, radiologists, and x-ray technologists have reported the effects of occupational ionizing radiation on the risk of leukemia but not the risk of BT. A study of US radiology technologists from 1983 to 1998, reported on 53 patients with BT, yielding a standardized incidence ratio of 0.95. A case-control study of patients with newly diagnosed CNS tumors aged 25 to 74 years reported an RR of 2.1 (95% CI, 1.0-4.3) for developing meningioma in individuals who received dental radiography at least annually, compared with individuals who received dental radiography less than every fifth year. However, most studies of diagnostic ionizing radiation and BT risk reported no association. Alternatively, a high rate of meningioma was reported in families in which additional siblings were irradiated, thus, lending support for the role of genetic susceptibility in these tumors.

**Nonionizing radiation: Electromagnetic fields and radiofrequency cell phones**

The association of exposure to nonionizing radiation, specifically exposures in the radiofrequency range (RF) or electromagnetic fields in the extremely-low-frequency range, and the development of primary BTs remains unresolved. Of particular interest is the questionable correlation between both gliomas and meningiomas and cellular phone use. These exposures are ubiquitous, and recent research focuses principally on mobile phones, because these RF exposures occur near the head and brain. The possible influence of currently acceptable low-level RF exposures on carcinogenesis has been suggested by some studies and warrants further investigation.

While Although the relative rarity of primary BTs necessitates a case-control study design, these studies experience severe limitations with exposure assessment because of their reliance on personal recall of cases and controls of their RF exposures (ie, cell phone use). The INTERPHONE study, which was coordinated by the International Agency for Research
Allergies, atopic diseases, and systemic infections

Meta-analyses of an extensive literature based on numerous case-control studies and two cohort studies indicate that there is an inverse association between self-reported allergies and glioma that is unlikely to be caused by chance or methodological biases alone. However, because recall bias could affect the self-reporting of allergies and because the presence of the tumor itself could affect postdiagnostic IgE levels, investigators of a subsequent study recently examined whether inherited polymorphisms in genes that have a positive association with allergies (interleukin 13 [IL-13], IL-4, and IL-4 receptor-alpha [IL-4Ralpha]) may be associated inversely with glioma. Such results (if produced) would argue against recall bias and reverse causality as the explanations for the associations between allergies, IgE levels, and glioma. Although definitive results from such studies are elusive, some consistent associations with survival and/or case-control status were reported for an IL-13 polymorphism and an IL-4R haplotype, both of which are linked with allergies.

It remains unclear whether allergies protect against tumors or whether immunosuppressive gliomas inhibit allergies, because the results from 2 additional studies on IgE and glioma were not consistent with the aforementioned results. First, the presence of atopic disorders at the time of diagnosis, and not prior history, was associated with a reduced risk of glioma in an additional study. Second, it was demonstrated that a cohort of patients initially tested for total serum IgE levels and subsequently linked to a population-based cancer registry exhibited no association between IgE levels with subsequent cancer (however, glioma was not addressed specifically in that study). The original article on IgE and glioma also reported that non-IgE-related allergies were related inversely to glioma, suggesting that IgE per se may not be on the causal pathway driving the association but, rather, another related immune factor may be responsible.

If the inverse associations between allergies, IgE, relevant polymorphisms, and glioma are real and are not caused by bias or possible reverse causality, then what mechanisms could explain the associations? Known tumor immunology is based on cell-mediated immune mechanisms that are controlled by Th1-CD4-positive cells. These cells enhance cytotoxic T-cell and natural killer cell activation through interferon-gamma (IFN-gamma) and suppress T-helper 2 (Th2)-CD4-positive T cells, which are critical for enhancing allergic phenotypes and depend on IL-4 and IL-13. However, gliomas are known for expressing high amounts of cytokines that inhibit both Th1 and Th2 immunity and are secreted by T-regulatory (Treg), CD4-positive cells. Patients with glioma who do exhibit Th2-type phenotypes are protected against glioma, as discussed above, which may result from the attraction of eosinophils to the tumor site. Another possibility is that immunosuppressive Treg cells (Tregs) may be the vehicle for inhibition of antitumor immunity, and allergy is a clinical manifestation that is correlated with hyperallergic immunity (Th2) and enhanced cellular immunity (Th1), both of which help inhibit tumors. Evidence of the Treg inverse association with IgE is strengthened by the observation that a mutation in the forkhead box P3 gene FOXP3, which is central to Treg function, leads to high serum levels of IgE and intense allergic inflammation. Moreover, atopic conditions are characterized by relatively low levels of Tregs, and allergic desensitization (treatment-induced immunosuppression of allergic conditions) is mediated by Tregs.

One possible mechanism for protection against glioma conferred by allergies is that individuals with allergies have lower levels of Tregs and, thus, may be better able to mount an antitumor response than individuals without allergies. A corollary to this exists with regard to tissue transplantation, in which infiltration by Tregs is necessary for successful grafts of foreign tissue. Similarly, a tumor is a foreign tissue that would engraft more successfully with the inhibition of immune rejection afforded by more Tregs. Higher Treg levels that are produced in response to
symptoms associated with elevated IgE levels (eg, asthma exacerbations) have an anti-inflammatory effect that inhibits early glioma development by blocking T-cell activation and angiogenesis, mechanisms that may be enhanced by the use of nonsteroidal anti-inflammatory drugs, which also have been linked to a lower risk of glioma. In addition, Tregs help determine whether infections will be chronic or acute by accumulating at sites of chronic infection, hampering immunity, and allowing pathogens to persist. Acute infections are related to decreased cancer risk at several sites, including gliomas; whereas chronic infections are associated with an increased cancer risk. A history of infections and colds is also associated with reduced glioma risk (OR, 0.3; 95% CI, 0.1, 0.8). Individuals who report at least 1 febrile episode in the 10 years before diagnosis of glioblastoma have a lower risk than individuals who report none. Also, the observed inverse association between antivaricella zoster virus (anti-VZV) IgG levels and glioma (described below) may be accounted for by an inadequately modulated Treg response, resulting in the extinguishing of viral latency in patients who then have a higher future risk of glioma. Individuals (among the controls without tumors) who have a productive Treg response are likely to strike a balance between VZV maintenance and suppression and react similarly in a productive manner against a nascent BT. However, any findings related to the immune system and glioma based on case-control studies may reflect preclinical immune-suppressive effects of the glioma.

**Viruses**

Polyomaviruses, including the JC virus, the BK virus, and simian virus 40, have been identified in human glioma tissues and have induced BTs in animals. In a nested case-control study, no statistically significant associations were observed between viral IgG for these viruses and glioma, but those results were based on a small sample. A study of contaminated polio vaccine indicated that there was a lower risk of gliomas in birth cohort members who were exposed to contaminated vaccine in childhood or infancy than in unexposed members; however, that cohort effect may have been caused in part by improved BT diagnostic technology.

Because some herpes viruses can establish latency in the nervous system, they also have been plausible candidates for research. One report showed that glioma tissue from 27 tumors expressed multiple human cytomegalovirus (HCMV) gene products in contrast to control and normal tissues. Three additional studies failed to replicate these findings; however, 2 newer reports support the original findings related to HCMV. Inflammatory stimuli can activate HCMV gene transcription and can induce malignant transformation and transactivate other oncogenic viruses associated with malignant gliomas, such as the JC virus. Two independent case-control series reported inverse correlations between serum IgG antibodies to VZV and glioma. Consistent with these inverse associations are those between self-reported history of chicken pox in the same individuals, and there was an inverse dose-response relation between higher IgG levels and lower glioma risk. In contrast, to our knowledge, there is no evidence for an association between glioma and antibodies to herpes simplex, Epstein-Barr virus, or cytomegalovirus.

**Neurocarcinogens and metals**

Previous studies of associations between primary BTs and chemical and physical agents previously were reviewed extensively. Despite decades of research, the only environmental agent that is associated conclusively with BT risk is ionizing radiation. Risks from specific neurocarcinogens have yet to be identified; however, the continued occurrence of BT clusters leaves open the question of the effect and extent of their exposures. Early studies focused on nitroso compounds and polycyclic aromatic hydrocarbons because of their ability to induce BTs in animal models, but studies have yet to link BTs conclusively with exposure to these or other neurocarcinogenic compounds (aliphatic and alicyclic hydrocarbons, methylene chloride, mercury, glycerol polyglycidyl, polychlorinated biphenyls, and epichlorohydrine exposures) possibly because of small numbers, tumor heterogeneity, unknown latency period or period of vulnerability of the brain to these compounds, recall difficulties, and other methodological issues. Observations of an association between drinking water and BTs suggest that ingestion of an environmental contaminant has an impact, perhaps from chlorinated sources like chloroethane, a byproduct of the treatment of sewage and wastewater, or nitrate/nitrite contamination leeching into drinking water supplies. In addition, 1 occupational study reported an elevated risk of glioma, especially low-grade gliomas, associated with exposure to metals.

Cadmium is a type I carcinogen that as been associated with human lung, renal, bladder, breast, liver, and stomach cancers and ranks first among suspect metals for BTs. It is used commonly in the production of common consumer goods and can be found in the environment. The major sources
of personal exposure are occupation, smoking, and diet. \textsuperscript{111,112,123} Studies support the carcinogenic effects of cadmium\textsuperscript{116,124} and have demonstrated its effects on increasing the permeability of the BBB\textsuperscript{125}; however, only 1 epidemiologic study (an occupational cohort study of 413,877 Finnish women) reported weak evidence for an association between cadmium and BTs, that study but neglected to control for cadmium in tobacco smoke and diet.\textsuperscript{100}

Lead also occurs widely in the environment and is classified as a probable human carcinogen, although evidence is weak for CNS tumors.\textsuperscript{126} Most studies of lead-exposed human populations report chromosomal toxicity and interference with repair of DNA damage\textsuperscript{127,128} leading to increased in vitro mutagenicity.\textsuperscript{129} Despite limitations with exposure assessment, the direction of risk in most cohort studies of lead exposure has been positive.\textsuperscript{130} In addition, most,\textsuperscript{131-133} but not all,\textsuperscript{134,135} case-control studies of occupational exposures to lead report a slight increased risk of BTs in the highest levels of lead exposure.\textsuperscript{133} Studies of lead and meningioma risk consistently report a statistically significant, positive association,\textsuperscript{133,134,136,137} and one study produced suggestive evidence of effect modification by a common polymorphism in the delta-aminolevulinic acid dehydratase gene \textit{ALAD}.\textsuperscript{134}

Prognostic Factors

Glioma survival and prognostic information comes primarily from clinical trials and population registry data. Clinical trial groups provide useful, oftentimes more complete information on prognostic factors from cases in which the pathology has been reviewed centrally. However, it still is unfortunate that the majority of adult patients do not have access to or are not enrolled in clinical trials, limiting the representativeness of the sample. Alternatively, survival estimates based on population registry data have the advantage of representing the full spectrum of glioma patients but the disadvantage that pathologic diagnoses vary considerably, depending on the neuropathologist, the time and site of diagnosis, and the diagnostic criteria used.\textsuperscript{138-140}

Investigators currently try to identify and understand tumor markers or patient characteristics that influence survival or response to treatment.\textsuperscript{17,141-154} Histologic type and grade, age, extent of resection, tumor location, radiation therapy, and some chemotherapy protocols have been linked consistently and convincingly to survival in both clinical trials and population registry data.\textsuperscript{155-163} Karnofsky performance status at diagnosis and other measures of mental and physical functionality also predict survival for patients with GBM and anaplastic astrocytoma.\textsuperscript{156,160-162}

One difficulty in identifying prognostic factors in rapidly fatal glioblastoma is the limited survival time of nearly all patients. Until the advent of treatment with temozolomide, the median survival after diagnosis for patients with glioblastoma was 6 to 7 months and had not improved in over 20 years. Temozolomide treatment has improved the average survival to 12 to 14 months. There is a very strong and consistent, inverse correlation between age and survival for the various histologic subtypes of glioma (www.cbtrus.org accessed March 1, 2008), and younger patients benefit more from radiation therapy than older patients.\textsuperscript{164} In addition, combined loss of chromosomes 1p and 19q in oligodendrogliomas is a consistent, favorable prognostic indicator\textsuperscript{142,165-173}, whereas, in astrocytic tumors, amplification/overexpression of \textit{EGFR} is common in older patients, especially those with anaplastic astrocytomas.\textsuperscript{18,174,175} \textit{EGFR} amplification also may be associated with poorer survival in younger adults (ages 55-60 years) with GBM.\textsuperscript{152,176} A recent, large, prospective trial of newly diagnosed GBM suggested that methylation of the \textit{MGMT} promoter in GBM tumor samples marked improved outcome,\textsuperscript{177} especially among patients who received frontline temozolomide.\textsuperscript{16}

Recent studies assessing glioma prognosis from expression profiles demonstrated a correlation between survival and the abnormal expression of neurogenesis genes, cell proliferation and mitosis genes, and extracellular matrix genes.\textsuperscript{143,147} In addition, gene expression changes across the genome accompanied loss of chromosome 10 and copy number loss of 10 and gains of 7, 19, and 20.\textsuperscript{147} Small sample sizes, which are typical of expression array studies, make these findings preliminary; however, genome-wide screens invite possible validation in larger studies.

A few studies have provided potentially fruitful areas of discovery of genetic variation related to glioma survival, eg, signaling pathways for growth factors, cell cycle regulators, modifiers of drug metabolism, and radiation and immune response. Common gene polymorphisms influence response to cancer therapies, prognosis, and survival,\textsuperscript{178,179} including \textit{EGF}, glutathione S-transferase P1 (\textit{GSTP1}) and M1 (\textit{GSTM1}), human leukemic antigen A*32 (HLA-A*32) and HLA-B*55, \textit{GLTSCR1} S397S, and \textit{ERCC2} D711D.\textsuperscript{159,141,148,153}

Neurocognitive impairment commonly is associated with primary BTs: Ninety-one percent of patients experience at least 1 area of deficit compared with the normal population, and 71% demonstrate at
least 3 deficits. Even subtle cognitive deficits can limit a patient’s daily life significantly, and if it goes unrecognized, may impact a patient’s ability to adhere to a therapeutic regimen without significant assistance. Standardized neurobehavioral measures may be used as an index for determining treatment outcomes for patients with BT. In fact, improvement in neurocognitive functioning or delay in neurocognitive impairment are acceptable endpoints for clinical trials, and neurocognitive functioning has been demonstrated to predict tumor progression and survival in patients with CNS tumors. However, studies observe wide variation in the incidence of cognitive dysfunction, perhaps from underlying differences in host genetic susceptibility. For example, individuals with no known neurologic disease perform more poorly on tests of memory and executive function if they carry an ‘at-risk’ allele in the apolipoprotein E gene APOE, the catechol-O-methyltransferase gene COMT, and the brain-derived neurotrophic factor gene BDNF. These genes may mediate cognitive reserve, putting individuals with the variant alleles at greater risk for treatment-related symptoms that affect neurocognitive functioning and quality of life, but none of these genetic factors have been explored in patients with BT.

Conclusions
Although the epidemiologic literature on BTs is inconclusive in many areas (Table 1), there are many promising areas to pursue in future research (Table 2). One primary area of prioritization is to develop and identify additional funding sources for the epidemiologic investigation of BTs; this is particularly important for childhood BTs. Because of the rarity of these tumors, it is difficult for any single institution to gather the appropriate number of cases; therefore, collaborative grants are necessary and more difficult to fund because of the large budget associated with these multi-institution studies. Researchers are eager to leverage funds from many sources, including federal granting agencies and private foundations, to bring about such studies. The GLIOGENE study is the first of such efforts to come out of BTEC. A second priority for the group was to enhance collaborative science with data that already exist by pooling datasets from completed studies that examined similar research questions. This is another way to overcome the power issues from individual studies. However, pooling data is an arduous task that takes time, effort, and money to complete. One way BTEC identified to overcome these hurdles is to identify junior investigators within the group to partner with senior investigators and lead a pooled analysis of an interesting topic. To help in this endeavor, several investigators volunteered to initiate a questionnaire that was designed to aid in the pooling of datasets, and potentially of biospecimens, for such projects. A third priority area identified at the meeting was the inclusion of a research agenda related to nonmalignant BTs (eg, meningioma), which make up a good proportion of all BTs. To date, very few epidemiologic studies have been completed on this tumor; and the majority were from the tinea capitis cohorts in Israel. However, another collaborative grant that originated from BTEC investigators has been funded to focus on meningiomas. Again, the main obstacle to overcome was obtaining a sufficient number of cases to perform a meaningful analysis. A fourth area of interest was the development of a better understanding of the biology related to exposure in the brain. This topic, in particular, cuts across most of the individual research topics and relates more to the honing of our tools of exposure assessment. One essential challenge in this effort is the lack of extensive information on how exposures interact with and bypass the BBB. Related to this is the challenge of obtaining good measures of exposure for certain agents; for

### TABLE 2

<table>
<thead>
<tr>
<th>Research Areas and Priorities for Further Investigation in Brain Tumor Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop and identify sources of funds for research on pediatric populations</td>
</tr>
<tr>
<td>Conduct large-scale genotyping studies (genome-wide association studies; whole genome enriched for candidates)</td>
</tr>
<tr>
<td>Perform pooling of data from existing studies to address research questions not powered by previous individual studies</td>
</tr>
<tr>
<td>Develop research in the role of immunology, infectious agents, viruses, methylation, epigenetics, and imprinting</td>
</tr>
<tr>
<td>Conduct epidemiologic research in meningioma</td>
</tr>
<tr>
<td>Understand routes of exposure: Biology related to the blood-brain barrier: are there other routes through which substances make their way into the brain?</td>
</tr>
<tr>
<td>Communicate and translate research findings: How can this be done better?</td>
</tr>
<tr>
<td>Identify additional sources of funding for brain tumor research</td>
</tr>
<tr>
<td>Study designs and methods:</td>
</tr>
<tr>
<td>Improve exposure assessment—incorporate biomarkers along with exposure history</td>
</tr>
<tr>
<td>Large-scale case-control studies on an international level</td>
</tr>
<tr>
<td>Impact on response to treatment</td>
</tr>
<tr>
<td>Define the most appropriate subgroups for analysis in a way that is consistent across studies to better allow for comparison and pooling of results</td>
</tr>
<tr>
<td>Identify and use the most informative and appropriate markers to reflect racial/ethnic/ancestral differences</td>
</tr>
<tr>
<td>Cohort studies: Look at existing data sources, such as NHANES, EPIC, Cohort Consorts, etc; there is a need to obtain exposure data before disease occurs; prediagnostic phenotypes, consider immune and exposure</td>
</tr>
<tr>
<td>Integrate molecular classification of tumors into approaches—wholly new opportunities</td>
</tr>
</tbody>
</table>

NHANES indicates the National Health and Nutrition Examination Survey; EPIC, European Prospective Investigation for Cancer.
example, whether systemic measures of exposure have the same meaning in the brain or how to measure chemical exposures with relatively short half-lives but long-term effects on the brain. The group has identified experts in BBB biology and in environmental exposure assessment to contribute knowledge and practical experience to BTEC. These continued collaborations will be key in moving the science forward and identifying biomarkers of exposure to physical and chemical agents to complement more traditional self-reported exposures as far as possible.

In addition to prioritizing specific research topics, the future research agenda for BTs requires more comprehensive communication and collaboration among the scientific community than has been achieved. This reality is valid for all BTs but particularly for childhood BTs, in which the numbers to conduct a sufficiently large study are greatly limited in single geographic areas, especially considering the myriad types of childhood BTs. Large, collaborative efforts will be needed to study the many factors that may have etiologic importance for childhood BTs, such as viruses, inherited susceptibility, immune response, or host immunologic status. The roles of genetic, developmental, and environmental factors in both adult and childhood BTs will be understood better with large-scale genetic and epigenetic analyses along with rapidly evolving bioinformatics and data analytic methods and improved exposure assessments. Given the relative rarity of any individual type of BT, increased collaboration and communication among interested researchers with mechanisms to bring in junior investigators are among the highest priorities.

The fundamental challenges inherent in the study of BTs are no longer insurmountable in the age of high-speed electronic communications, genomics, and bioinformatics. We believe it is time to consider comprehensive collaborations at the national and international levels that would not have been possible for earlier generations. Not unlike the efforts to accumulate worldwide human experience in combating climate change, there is a real opportunity to gather comprehensive information. Such collaborative studies are essential to enable us to compare information gathered in the same fashion from patients across the nation and the globe.

REFERENCES


111. Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M.
110. Lanes SF, Rothman KJ, Soden KJ, Amsel J, Dreyer NA.
97. 1966 CANCER Supplement October 1, 2008 / Volume 113 / Number 7


