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Epidemiology of Brain Tumors

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Brain tumors are classified on the basis of histopathology into the following major histologic groupings: tumors of neuroepithelial tissue (hereafter referred to as glioma, including astrocytoma [grade II], anaplastic astrocytoma [grade III], glioblastoma [grade IV], oligodendroglioma, and ependymoma), tumors of meninges (including meningioma and hemangioblastoma), germ cell tumors, and tumors of sellar region (including pituitary tumors and craniopharyngioma). This article reviews the incidence of brain tumors in terms of temporal, demographic, and geographic variation. The incidence and survival probability of brain tumors are summarized using information from the Central Brain Tumor Registry of the United States (CBTRUS) [1] and the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute [2] and literature is reviewed pertaining to risk and prognostic factors, focusing on compelling and promising lines of research that have emerged from the brain tumor literature and from descriptive comparisons. Because only recent research has considered variation in risk factors according to histologic subtypes,

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we are not always able to report findings in refined histologic categories. Approximately 75% of all primary brain tumors are classified as glioma or meningioma; therefore, this article focuses primarily on these more common brain tumors.

Descriptive epidemiology

During the years 1998 to 2002, the average annual rate of occurrence of incident (newly diagnosed) primary brain tumors in the United States was 14.4 per 100,000 persons [1]. The incidence of brain tumors has increased over time and differs according to gender, age, race and ethnicity, and geography.

Based on nine geographic areas surveyed by the United States SEER program since 1973, the age-adjusted incidence rate for malignant brain tumors has increased among men (from 5.9 per 100,000 men in 1973 to 7.0 per 100,000 men in 2003) and women (from 4.1 per 100,000 women in 1973 to 5.2 per 100,000 women in 2003) [2]. Most, if not all, of this increase probably is attributable to improvements in diagnostic imaging (eg, use of CT and MRI), increased availability of medical care and neurosurgeons, changing approaches in the treatment of older patients, and changes in classifications of specific histologies of brain tumors [3–5].

For all central nervous system (CNS) tumors, of which brain tumors are the majority, the age-adjusted average annual (1998 to 2002) incidence rate for women (15.1 per 100,000 person years) is slightly greater than that for men (14.5 per 100,000 person years) [1]. Table 1 shows average annual (1997 to 2001) age-adjusted incidence rates and median ages at diagnosis for the major histologic groupings and selected common histologic subtypes of brain tumors. As shown in Table 1, glioma and germ cell tumors are more common in men, whereas meningioma is approximately twice as common in women. This gender difference is greater, approximately fourfold, among Polynesians [6].

In the United States, the median age at diagnosis among all patients diagnosed with a primary brain tumor between 1998 and 2002 was 57 years [1]. Average annual incidence rates of the major histologic groupings according to age at diagnosis are shown in Fig. 1. Average annual incidence rates, according to age at diagnosis, for selected histologies common among adults and children/adolescents (ages 0 to 19), respectively, are shown in Figs. 2 and 3. Among adults (see Fig. 2), incidence rates of meningioma and glioblastoma increase with advancing age, except for a decline in the incidence rate of glioblastoma in people ages 85 years and older. (A logarithmic scale is used in Fig. 2, so that variation by histology can be displayed.) Among children/adolescents (see Fig. 3), incidence rates of all non–germ cell histologies decrease through childhood and adolescence, whereas the incidence of germ cell tumors reaches a peak during the adolescent years. Variation in incidence according to histologic type may reflect diagnostic

Table 1
Number of cases, median ages at diagnosis, and age-adjusted average annual (1998–2002) incidence rates of primary brain tumors (major histologic groupings and selected histologic subtypes), according to gender

Histologic group	Number of cases	Median age at diagnosis (years)	Rate	Male rate	Female rate
Tumors of neuroepithelial tissue/glioma	27,776	53	6.42	7.67	5.35
Pilocytic astrocytoma	1465	12	0.33	0.34	0.32
Diffuse astrocytoma	428	46	0.10	0.11	0.08
Anaplastic astrocytoma	2029	51	0.47	0.56	0.38
Glioblastoma	12,943	64	3.05	3.86	2.39
Oligodendroglioma	1559	41	0.35	0.38	0.33
Anaplastic oligodendroglioma	781	48	0.18	0.20	0.16
Ependymoma/anaplastic ependymoma	1126	39	0.26	0.29	0.22
Mixed glioma	722	42	0.16	0.19	0.14
Malignant glioma, not otherwise specified	1668	43	0.38	0.42	0.35
Benign and malignant neuronal/glial, neuronal and mixed	944	26	0.21	0.23	0.19
Embryonal/primitrive/ medulloblastoma	1094	9	0.24	0.29	0.19
Tumors of meninges	19,980	63	4.70	2.95	6.18
Meningioma	19,190	64	4.52	2.75	6.01
Germ cell tumors	397	17	0.09	0.12	0.06
Tumors of sellar region	4496	48	1.03	1.05	1.03

Rates are per 100,000 population, age-adjusted to the 2000 United States (19 age groups) standard and based on cancer incidence data from the following registries: Arizona, Colorado, Connecticut, Delaware, Idaho, Maine, Massachusetts, Minnesota, Montana, New Mexico, New York, North Carolina, Texas, Utah, and Virginia.

From CBTRUS statistical report: Primary Brain Tumors in the United States, 1998–2002.

practices and access to diagnoses in different age groups in addition to actual biologic variations of brain tumors with age.

Gliomas are approximately twice as common among whites as compared with blacks, as are germ cell tumors. From 1998 to 2002, the incidence rate of glioma among whites was 6.8 per 100,000 persons and 3.5 per 100,000 persons among blacks. During this same time, the incidence of glioma among non-Hispanics (6.7 per 100,000 persons) was greater than that of Hispanics (4.9 per 100,000 persons). There are no well-described explanations for the observed race and ethnicity differences; however, genetic differences (as described later) may contribute to race-related incidence differences.

Brain tumor incidence rates vary moderately by geographic region in areas that report to CBTRUS [1]. The lowest age-adjusted average annual (1998 to 2002) incidence of all CNS tumors is found in Virginia (9.6 per

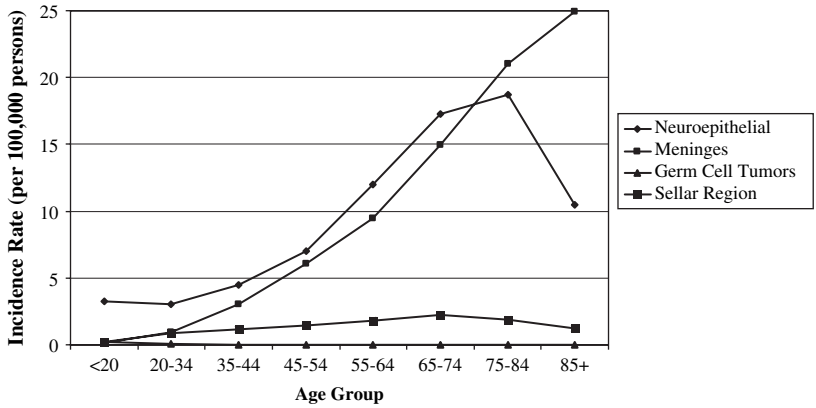


Fig. 1. Age-specific incidence rates of primary CNS tumors, 1998–2002, according to major histologic groupings, CBTRUS. (*Reported in tabular form in* CBTRUS (2005) statistical report: Primary Brain Tumors in the United States, 1998–2002.)

100,000 person years), and the highest is located in Colorado (21.9 per 100,000 person years) [1]. For malignant brain tumors, a similar degree of variation is reported in the geographic SEER regions [2]. There also is worldwide geographic variation in the incidence of brain tumors; for example, malignant brain tumors occur in Japan with less than half the frequency of that in Northern Europe. Countries reporting a high incidence of malignant brain tumors include Australia, Canada, Denmark, Finland, Sweden, New Zealand, and the United States, whereas areas of the world with a lower

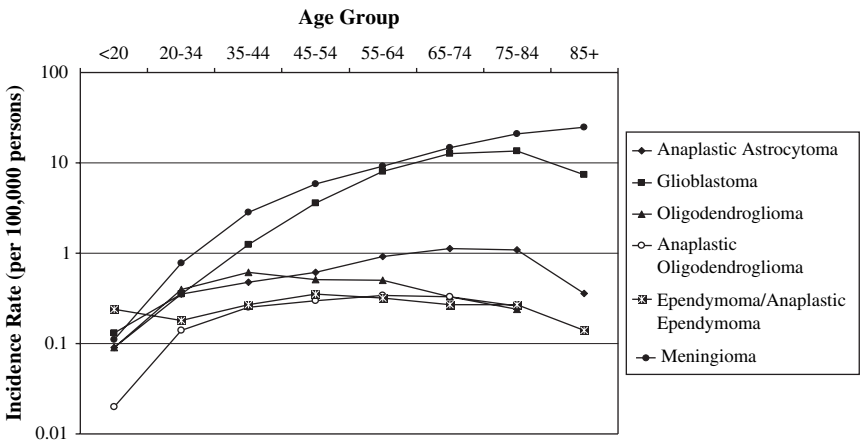


Fig. 2. Age-specific incidence rates of primary neuroepithelial brain tumors and meningioma, 1998–2002, CBTRUS. (*Reported in tabular form in* CBTRUS (2005) statistical report: Primary Brain Tumors in the United States, 1998–2002.)

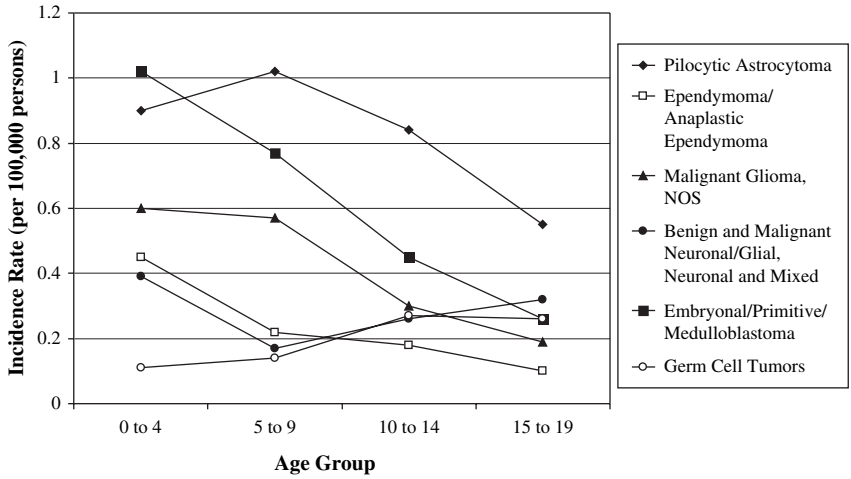


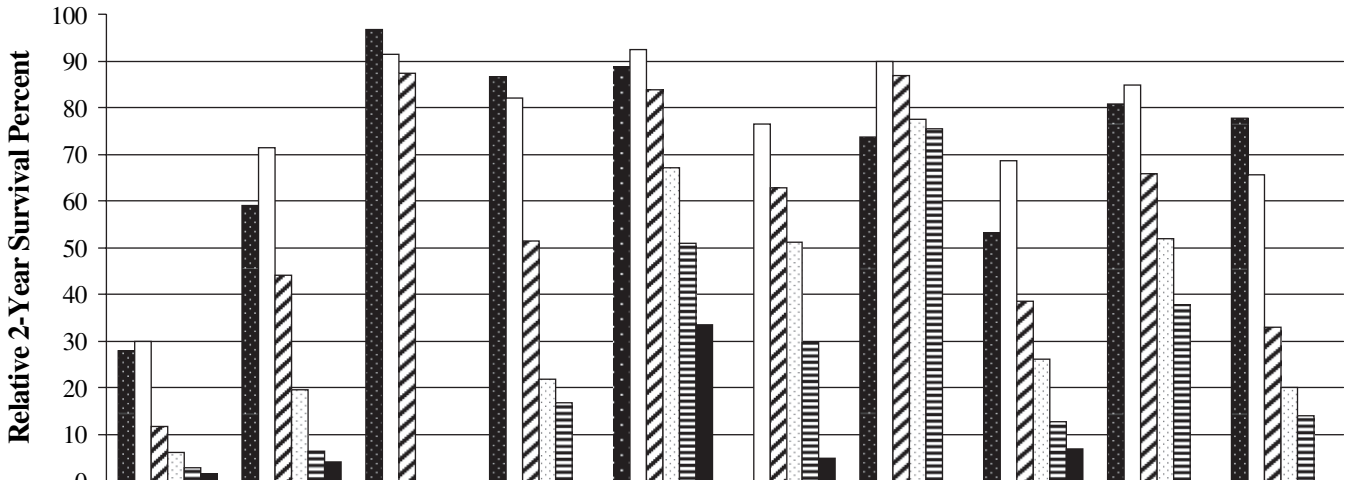
Fig. 3. Age-specific incidence rates of primary CNS histologies more common among children, 1998–2002, CBTRUS. (*Reported in tabular form in* CBTRUS (2005) statistical report: Primary Brain Tumors in the United States, 1998–2002.)

incidence—such as Rizal, Philippines, and Bombay, India—have an incidence approximately one fourth that of the high-incidence countries [5,7]. Differences in diagnostic practices and completeness of brain tumor reporting make all geographic, especially international, comparisons difficult [5]. In addition, higher incidence rates appear in countries (and within the United States—in some states) with greater access to health care and better medical care [5,7]. In one study, although American immigrants had a lower risk for death from all causes, their risk for death from brain tumors was greater than that for their American-born counterparts. This suggests that country of birth alters risk, that exposures occurring early in life may afford protection to the American born, or that potential early exposures in non-American countries increase brain tumor risk [8].

Survival probability and prognostic factors

Glioma and glioma subtypes, including glioblastoma

Survival time after brain tumor diagnosis varies greatly by histologic type and age at diagnosis, as shown in Fig. 4 [1]. For each age group, relative survival probability is lowest for patients who have glioblastoma. In general, survival probability is lower for those in older age groups. The relative 2-year and 5-year survival probabilities associated with primary malignant brain tumors diagnosed between 1998 and 2003 are 37.7% and 30.2%, respectively [2]. For the period 1973 to 2003, the 2-year relative probability of surviving a malignant brain tumor for men (35.2%) was slightly less than



	Glioblastoma	Anaplastic Astrocytoma	Pilocytic Astrocytoma	Diffuse Astrocytoma	Oligo-dendroglioma	Anaplastic Oligo-dendroglioma	Ependymoma/ Anaplastic Ependymoma	Glioma Malignant, NOS	Mixed Glioma	All Neuroepithelial
■0-19	27.9	59	96.7	86.6	88.9		73.6	53.1	80.8	77.7
□20-44	29.8	71.4	91.4	81.9	92.3	76.5	89.9	68.6	84.7	65.6
▨45-54	11.6	44.0	87.4	51.4	83.7	62.8	86.8	38.6	65.8	32.8
□55-64	6.0	19.4		21.7	67.1	51.2	77.5	26.0	51.9	20.0
▤65-74	2.7	6.4		16.7	50.9	29.5	75.5	12.7	37.6	13.8
■75+	1.4	4.1			33.3	4.9		6.9		

Histologic Type

Fig. 4. Two-year relative survival probabilities of primary malignant CNS tumors according to age at diagnosis and histologic type, based on the follow-up of individuals diagnosed between 1973 and 2002, SEER, compiled by CBTRUS. (*Reported in tabular form in* CBTRUS (2005) statistical report: Primary Brain Tumors in the United States, 1998–2002.)

that for women (35.6%) [2]. Although the prognosis is poor for many patients who have malignant brain tumors, 2-year survival probability for patients who have malignant brain tumors has increased from 28.5% in 1975 to 38.7% in 2002 [2]. Much of this increase occurred in patients younger than 65 years of age who were diagnosed with tumors other than anaplastic astrocytoma and glioblastoma. This increase in survival may be an artifact of improved ascertainment of indolent brain tumor subtypes rather than improved clinical management. There has been little change in the survival probability for patients diagnosed with glioblastoma.

Because of the poor prognosis for patients who have glioblastoma—less than one third survive longer than 1 year [2]—investigators have sought to determine factors associated with survival probability and survival time from glioblastoma. Based on previous findings, the following are known to be related to glioblastoma prognosis: age, Karnofsky Performance Status score, extent of resection, capacity for complete resection, degree of necrosis, enhancement on preoperative MRI studies, volume of residual disease, therapeutic approach, pre- and postoperative tumor size, noncentral tumor location (defined as infiltration of splenium, basal ganglia, thalamus, or midbrain), patient deterioration, patient condition before radiation therapy, and presurgical serum albumin level [9–12]. Recent efforts to identify prognostic factors for glioblastoma and other glioma subtypes have focused on genetic factors and molecular markers. For oligodendroglioma, it is now well established that the combined loss of 1p and 19q confers a more favorable prognosis [13]. Although results are inconsistent, and effects may be modified by other factors, such as age, there is some evidence that the following are prognostic indicators for glioblastoma and other glioma subtypes: p53 mutation and expression [14–23], overexpression or amplification of epidermal growth factor receptor (EGFR) [15,17,18,20–22], CDKN2A alterations and deletions [15,17,20], and MDM2 amplifications [14,17,20,22,24]. Simmons and colleagues [25] demonstrated the complex relationship of survival with age at diagnosis, p53, and EGFR in patients who have glioblastoma. They found that in patients younger than the median age, there was a shorter survival time in patients whose tumors overexpressed EFGR but had normal p53 immunohistochemistry [25]. In interpreting their findings, it should be remembered that post-hoc subgroup analysis increases the risk for false-positive findings [26]. Age-dependent associations between glioblastoma survival and 1p and CDKN2A also have been demonstrated [15]. p53 protein expression probably decreases with advancing age [15,25], and the association between p53 expression and survival from glioblastoma may be hidden when confounding by age is adjusted statistically. Loss of heterozygosity (LOH) on chromosome 10q is associated with shorter duration of survival from glioblastoma [23,27], and the combined LOH on 1p and 19q may afford a more favorable prognosis to patients who have glioblastoma [23]. There may be a strong association between different genotypes of human telomerase MNS16A

and glioblastoma survival time (24.7 months median survival time for the SS genotype, compared with 14.0 months and 13.1 months for the SL and LL genotypes, respectively) [28]. These results are promising because human telomerase MNS16A may be exploitable as a biomarker of treatment success.

Recently, Wrensch and colleagues [22] reported that glutathione S-transferases (GST) theta (T)1 deletion afforded a less favorable glioma prognosis, whereas higher glioma survival probability was afforded to patients who had glioma and who had the ERCC1 (a DNA excision repair gene) C8092A polymorphism. EGFR expression in patients who had anaplastic astrocytoma was associated with nearly threefold poorer survival [22]. Patients who had glioblastoma and who had elevated IgE lived 9 months longer compared with those who had lower or normal IgE levels [22]. This finding may implicate immunologic factors in glioblastoma prognosis [22]. Patients who have glioblastoma and who have higher IgE levels may have better antitumor defenses or less aggressive tumors with weaker anti-immunologic effects; alternatively, IgE itself may have antitumor activity through direct activity on glioma or other nearby cells [22]. Associations between glioma prognosis in relation to atopic allergy, in which IgE is increased, should be studied. As discussed later, there is consistent and compelling evidence of protection against glioma as the result of allergies and immune-related conditions. Further suggesting the importance of immunologic factors in glioblastoma prognosis, a recent report indicates that amplification of interleukin (IL)-6, a cytokine that may promote glioblastoma, is associated significantly with decreased glioblastoma survival [29]. Analyses of atopy, IgE, and cytokines in relation to glioma prognosis may help understand better the complex nature of immunologic response to gliomagenesis, including secreted tumor-specific factors and host immune responses, and such investigations also may have implications for immunologic therapy for glioma. In addition, brain tumors, like all cancers, must evade immune rejection with mechanisms presumably similar to any foreign tissue growth. Future studies also should include the examination of T-cell activities, such as that of T-regulatory cells, which are associated with tissue graft acceptance and brain tumor prognosis [30,31].

Meningioma

For benign brain tumors, such as meningioma, there currently are no estimates of American population-based survival probabilities, because these tumors were not registered as part of the SEER program until recently. Population-based data suggest, however, that survival time for patients diagnosed with meningioma in Norway improved between 1963 and 1992 [32] and in Finland between 1953 and 1984 [33]. McCarthy and colleagues [34] estimated that the 5-year survival probability was 69% for meningioma, and 81% among patients ages 21 to 64 years at diagnosis but only 56% among those 65 years of age or older at diagnosis [34]. Patients who had

benign meningioma had a 5-year survival probability of 70%, whereas the 5-year survival probability for patients who had malignant meningioma was 55% [34]. Prognostic factors for patients who had meningioma have not been studied thoroughly. Results from a large study of 9000 cases revealed the following prognostic factors for benign meningioma: age, tumor size, and surgical and radiation treatments. In contrast, for malignant meningioma, the prognostic factors included only age and surgical and radiation treatments [34]. Abnormalities of chromosome 14 also may affect meningioma prognosis [35].

Risk factors

Risk factors for brain tumors are discovered by conducting analytic epidemiologic studies, which usually compare either brain tumor risk in participants with or without certain characteristics (cohort studies) or the histories of participants with or without brain tumors (case–control studies). Results from a cohort study can provide evidence that a modifiable or varying cause (risk factor) preceded the brain tumor, whereas results from a case–control study usually cannot address temporality (the major exception being studies of germline characteristics that clearly precede environmental exposures and brain tumor diagnoses). Epilepsy or seizure disorder (which is associated consistently with glioma risk) is not discussed in this article, because it probably is a result of glioma rather than a cause [36]. Compelling and promising lines of research that have emerged from the brain tumor literature and from descriptive comparisons are discussed.

Reproductive and menstrual factors

Women have a lower glioma risk (shown in Table 1). Incidence rates from the New York State Cancer Registry suggest that this protection occurs between the approximate ages of menarche and menopause and decreases in postmenopausal age groups [37]; however, as shown in Fig. 5 (which shows the male-to-female ratios of average annual glioma incidence rates according to age group), incidence rates derived from the SEER program suggest increased glioma risk among men within each age group, with the exception of infants; further, the rates among men remain at least 40% greater than those among women for all age groups 30 years and older. Age-adjusted comparisons of postmenopausal women, whose menopause was not induced surgically, with premenopausal women show that postmenopausal women are at greater risk for glioma and acoustic neuroma [38] than are premenopausal women. Results pertaining to parity and glioma risk are mixed, suggesting lower risk among parous women [39,40] or no association [38,41,42]. Two recent studies [41,42] suggest a possible increase in glioma risk as the result of later (14 years or older versus younger than 12 years) age at menarche. Meningioma is approximately twice as common in

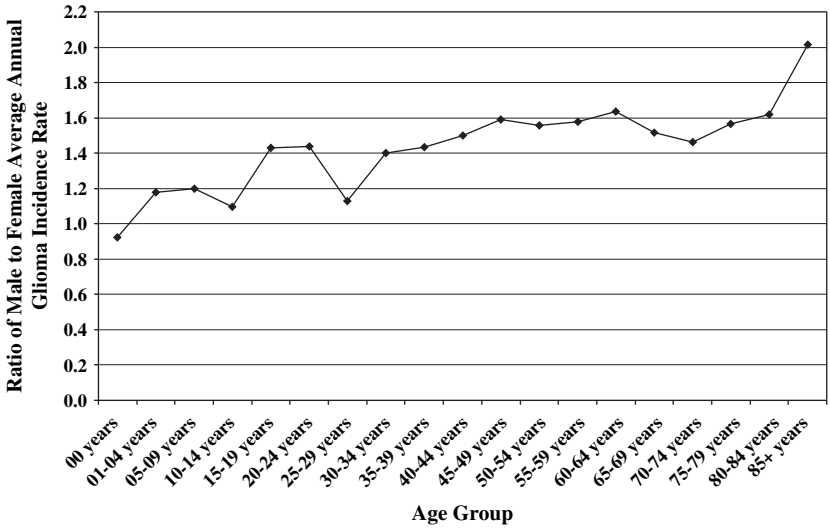


Fig. 5. Ratios of male-to-female average annual glioma incidence rates according to age group. (*Data from* SEER Program. SEER*Stat Database: incidence - SEER 9 Registries Public-Use, Nov 2005 Sub (1973–2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.)

women as in men. Some meningioma tumors express progesterone receptors, and this expression occurs to a greater degree in women [43]. In general, there are consistent results suggesting that, among women of the same age, those who are premenopausal have greater meningioma risk than are those who are postmenopausal. Studies of meningioma risk and age at menarche and parity have produced conflicting results [38,44]. For example, some results concerning parity and age at menarche suggest that estrogen or other reproductive or menstrual hormones may decrease meningioma risk. Further study is required to understand hormone-related factors, especially because some of the findings are opposite of those expected and because menstrual and reproductive factors alone are insufficient to classify lifetime estrogen or other hormonal exposure accurately. Moreover, inconsistent results pertaining to oral contraceptive use and hormone replacement therapy and both glioma [41,42,45] and meningioma [42,45] risks encourage the continued study of the relationships between brain tumor risks and endogenous and exogenous estrogen exposures. Cohort studies of reproductive factors and brain tumor risk among women who have and have not taken estrogen replacement therapy should be conducted.

Environmental and behavioral risk factors

Because they may be modifiable and because there are strong associations between some modifiable factors (such as tobacco smoking) and cancers of

other anatomic sites (such as lung cancer), investigators have examined potential associations between brain tumor risk and environmental and behavioral factors. Only one such factor is associated consistently with brain tumor risk—exposure to therapeutic doses of ionizing radiation.

Therapeutic doses of ionizing radiation

Exposure to therapeutic doses of ionizing radiation is the only established potentially modifiable brain tumor risk factor [5,46]. Ionizing radiation used to treat tinea capitis and skin hemangioma in children or infants is associated with relative risks as high as 18 for nerve sheath tumors, 10 for meningioma, and 3 for glioma [5,46]. Children irradiated for treatment of tinea capitis also have a greater risk for pituitary adenoma [47]. There are mixed results concerning exposure to diagnostic and therapeutic readiographs of the head and neck [48,49]; however, radiographs performed 15 to 40 years preceding diagnosis seem to increase meningioma risk [50], as do radiographs performed before age 20 or taken before the year 1945 [51]. A study in a Finnish population showed that second primary brain tumors occur more frequently than expected among patients treated previously for brain tumors with radiation therapy [52]. Survivors of the atomic bombing of Hiroshima have a high incidence of meningioma correlating with the dose of radiation to their brain [53]. These atomic bomb survivors also have higher incidences of glioma, schwannoma, and pituitary tumors, although there is no increased risk for brain tumors among those who were exposed in utero [46]. There are homogenous and strong results suggesting associations between ionizing radiation and brain tumor risk; however, because exposure to high levels of ionizing radiation is rare, these exposures account for only a small percentage of brain tumors.

Cellular telephone use

Most early studies of the association between cell phone use and glioma risk generally provide no evidence for this relationship [54]. If the latency period is at least 5 years long, however, then these early studies did not have sufficient numbers of long-term cell phone users to evaluate this relationship adequately. In contrast, several recent studies provide some evidence for an association between long-term cell phone use and glioma that also may be attributed to recall or selection bias [55,56]. The largest population-based case–control study reported to date (1522 glioma cases and 3301 controls) conducted in five Nordic Countries and the United Kingdom [57] found no consistent evidence overall for increased risk for glioma related to use of cell phones nor did they find increased glioma risk in the most highly exposed group. Only one subgroup, that consisting of individuals indicating ipsilateral use (same side of the head as the brain tumor) 10 or more years before the reference date, had an increased risk for glioma, and there was an increasing trend with years since first use on

the ipsilateral side. Over the past 2 decades, there have been decreasing levels of nonionizing radiation from cell phones and these levels vary across cell phone types. Further studies are needed to determine whether or not the observed risk represents a biologic effect of nonionizing radiation from cell phones on glioma risk or merely is an artifact. As the number of long-term cell phone users increases, it will be possible to identify increasing numbers of patients who have glioma who are long-term cell phone users and, thus, conduct studies with sufficient statistical power to provide definitive answers to this important public health question.

Additional environmental and behavioral risk factors with inconclusive, minimal, or no compelling evidence of association with brain tumor risk

Several environmental and behavioral risk factors may alter brain tumor risk, but there is inconclusive, minimal, or no evidence to establish causality for the following associations: head injury and trauma (for intravascular brain tumors) [58]; head injury and trauma (for nonintravascular brain tumors) [5,58–62]; dietary calcium intake (for glioma) [63,64]; dietary N-nitroso compound intake (for glioma and meningioma) [65–68]; dietary antioxidant intake (for glioma); [64–67]; dietary maternal N-nitroso compound intake (for childhood brain tumors) [5,62]; dietary maternal and early life antioxidant intake (for childhood brain tumors); maternal folate supplementation (for primitive neuroectodermal tumors) [62,69]; tobacco smoking (for glioma and meningioma) [62,66,70]; alcohol consumption (for glioma, meningioma, and childhood brain tumors) [46,71]; and exposure to electromagnetic fields (for childhood and adult brain tumors) [62]. In addition, the literature on occupational risk factors is vast and inconclusive; Wrensch and colleagues [5] summarized this literature; however, there has been no comprehensive review of occupational factors associated with brain tumor risk since 1986. Possible explanations for failure to find consistent and statistically significant findings for the factors listed include the following: small study sample sizes; false-positive results (related to small sample sizes and lack of precise research hypotheses); invalid or imprecise exposure measures (resulting from use of proxy respondents when patients who have brain tumor are unavailable, from errors in exposure history recall, or from lack of validation of verifiable exposures); inherited or developmental variation in metabolic and repair pathways; unaccounted-for protective exposures or conditions (such as allergies, described later); differential diffusion of chemicals across the blood-brain barrier; differentially expressed metabolic and repair pathways in the brain; and disease heterogeneity. It also is possible that failure to find strong and consistent environmental risk factors for brain tumors (except for therapeutic ionizing radiation) may be attributable to the absence of true strong environmental associations. Nonetheless, low brain tumor survival probabilities dictate the continued search for environmental factors that might be altered to prevent disease.

Genetic factors

Many investigators have turned attention away from environmental and behavioral risk factors and toward genetic risk factors, in part because of the abundance of null or inconclusive findings related to potentially modifiable environmental factors, in part because there is increasing knowledge of the molecular pathology of brain tumors, especially glioma, and in part because of new technologies for examining associations between genotypes and diseases. Although familial aggregation of glioma has been demonstrated, it can be difficult to distinguish shared environmental exposures from inherited characteristics. Grossman and colleagues [72] showed that brain tumors occur in families with no known predisposing hereditary disease and that the pattern of occurrence in many families suggests environmental causes. Results presented by Malmer and coworkers [73], however, suggest that first-degree relatives, and not spouses, have a significantly increased brain tumor risk.

Rare mutations in penetrant genes and familial aggregation

Brain tumors are believed to develop through the progressive accumulation of genetic or epigenetic alterations that permit cells to evade normal regulatory mechanisms or escape destruction by the immune system. There is strong epidemiologic evidence that genetic factors are associated with brain tumor risk. First, several diseases or syndromes associated with rare mutations in highly penetrant genes (including tuberous sclerosis complex, neurofibromatosis types 1 and 2, nevoid basal-cell carcinoma syndrome, syndromes related to adenomatous polyps, and Li-Fraumeni cancer family syndrome) increase brain tumor risk [5,74]. In a study of 500 patients who had glioma, however, fewer than 1% had a known hereditary syndrome [75]. Although genetic predisposition is considered influential in few brain tumors (5% to 10%), the proportion may be underestimated because some hereditary syndromes are not diagnosed readily and because patients who have brain tumors are not referred routinely to a clinical geneticist. Second, patterns of glioma risk in families, case–control studies, and six Swedish cohorts with overlapping populations are consistent in suggesting potential inheritance. For example, results from one study suggest that approximately 2% of glioma cases may be explained by an autosomal recessive gene [76]; however, a low penetrant dominant gene, and not an autosomal recessive gene, was the more likely explanation for familial clustering in another study [77]. A greater proportion of familial glioma cases overexpress p53 based on immunohistochemistry [78]. The first molecular genetic evidence for familial aggregation of glioma recently was submitted by Paunu and colleagues [79], whose results suggest a novel low-penetrance locus at 15q23-q26.3 among people who have familial glioma in Western Finland. Malmer and colleagues [80] report that glioma and meningioma risks are associated significantly with the CC-CG-CC genotype combination formed

by three polymorphims in p53 but only when cases of a family history of cancer are included; however, these results are based on a small number of cases and controls. Familial aggregation of meningioma has been suggested [81,82] but not demonstrated consistently and should be validated through additional studies.

In addition to rare mutations and familial aggregation, Bondy and coworkers [83,84] found that lymphocyte mutagen sensitivity to gamma radiation increases glioma risk; however, these results should be verified because they may be confounded by age, solar exposure, diet, and glioma treatment and because it was not possible to determine whether or not chromatid breaks increased brain tumor risk or whether or not they represented a systemic effect of the brain tumors themselves.

Because only a small proportion of primary brain tumors seems to result from effects of environmental or behavioral factors or from inherited rare mutations in highly penetrant genes, investigators have turned their attention to common polymorphisms in genes that might influence susceptibility to brain tumors in concert with environmental exposures. Genetic alterations that affect detoxification of carcinogens, DNA stability and repair, and cell cycle regulation conceivably could confer genetic susceptibility to brain tumors.

Glioma and polymorphisms affecting detoxification, DNA stability and repair, and cell cycle regulation

Cytochrome p450 s (CYP) and GST are involved in the metabolism of many electrophilic compounds, including carcinogens, mutagens, cytotoxic drugs, metabolites and products of reactive oxidation. Studies of CYP and GST have produced mixed results. For example, although one case–control study found that CYP2D6 increased astrocytoma and meningioma risks more than fourfold [85], another found no association [86]. Results from a recent meta-analysis of eight studies, including 1630 glioma cases, 245 meningioma cases, and 7151 controls, suggest that, although the T1 null genotype is associated with nearly double meningioma risk (odds ratio [OR] 1.95; 95% CI, 1.02–3.76), there were no associations between any of the GSTP1 105 and GSTP1 114 single- nucleotide polymorphisms (SNPs) and glioma risk; however, none of the investigators whose work was summarized had conducted haplotype analyses. Wrensch and colleagues [87] found little evidence for a general association of GST polymorphisms with glioma but did show an association of GSTT1 deletion for glioma with p53 mutations. In a large Nordic and British population-based, case–control study (725 glioma cases, 546 meningioma cases, and 1612 controls), Schwartzbaum and colleagues [88] reported no associations between the GSTM3, GSTP1 NQ01, CYP1A1, GSTM1, or GSTT1 polymorphisms and adult brain tumor risk; however, they found a weak association between the G-C (Val-Ala) GSTP1 105/114 haplotype and glioma (OR 0.73; 95% CI, 0.54–0.99).

Because DNA repair is important in maintaining DNA integrity, inherited variation in components of DNA repair pathways has been studied extensively with respect to cancer. Associations with glioma are reported for variants in ERCC1 [89,90], ERCC2 [89,91,92], the nearby gene GLTSCR1 (glioma tumor suppressor candidate of unknown function) [91], PRKDC (also known as XRCC7—a gene involved in nonhomologous end-joining double-strand break repair) [93], and O^6methylguanine–DNA methyltransferase (MGMT), a DNA repair enzyme [94,95], but there are too few studies to assess consistency. The AA or AC versus CC genotype in nucleotide 8092 of ERCC1 is shown to increase oligoastrocytoma risk [91], whereas the AA genotype (C to A polymorphism [R156R]) of ERCC2 was more prevalent than the CC or CA genotypes in cases of glioblastoma, astrocytoma, or oligoastrocytoma than in controls [92]. The ERCC2-exon-22 T allele prevalence was 35% in a group of oligodendroglioma cases compared with 18% for controls, and alterations in GLTSCR1 (or a closely linked gene) are associated with oligodendroglioma risk [91]. Wang and colleagues [93] found that the TT genotype of XRCC7 was more common in glioma cases compared with controls. Regarding the MGMT gene, results presented by Wiencke and colleagues [94] suggest that an inherited factor involving the repair of methylation and other alkylation damage may be associated with the development of glioma that have neither TP53 mutations nor TP53 protein overexpression. The combined heterozygote of V1 and a wild allele of the MGMT gene may contribute to the de novo occurrence of glioblastoma [95]. DNA repair is complex, involving more than 130 known genes; therefore, studies focusing on constellations of variants involved in DNA repair pathways and their interactions might help elucidate the roles of variants in gliomagenesis and progression.

Dysregulation of the cell cycle (control of proliferation and apoptosis) is a hallmark feature of most glioma [96], and MDM2 is a key molecule in maintaining the fidelity of this process. In one study [97], the G variant of SNP309 in the MDM2 promoter led to higher expression of MDM2 with concomitant reduced expression of TP53 and was associated significantly with earlier age of tumor development and multiple tumor sites in participants who had Li-Fraumeni syndrome, of which brain tumors are one component. MDM2 seems to regulate TP53 expression negatively [98], and the inverse association between TP53 and MDM2 expression is reported by Wiencke and colleagues [94], among others. The associations between MDM2, TP53, and EGFR remain poorly understood, however, and should be examined in studies with large sample sizes because of the potential need for smaller subgroup analyses.

Inconsistencies in genetic polymorphism studies may result from false-positive associations based on inadequate sample sizes [26] (especially in subgroup analyses) and from confounding by genes with similar functions not accounted for in the analyses. Another possible explanation for

inconsistencies is that study populations may consist of different proportions of types of tumors, and genetic risk for certain subtypes could be masked by lack of risk among other subtypes. When these issues are addressed, the potential interaction between genetic polymorphisms with other genetic characteristics and environmental factors can be evaluated properly.

Glioma, allergy, allergic conditions, infections, and associated immunologic factors

Persuasive evidence has accumulated over the past decade that immunologic factors related to allergy, allergic conditions, and infections have an impact on glioma and glioblastoma risk. Reduced glioma or glioblastoma risk has been attributed to allergy and allergic conditions [99–105], autoimmune diseases [99,105], reported history of varicella-zoster virus (VZV) infections, and positive IgG to VZV [106–108].

Many studies support that glioma risk is decreased as a result of allergies and immune-related conditions. For example, in a large population-based study (965 glioma cases and 1716 controls) in the United Kingdom, Schoemaker and colleagues [102] report reduced glioma risk as the result of a history of asthma (OR 0.71; 95% CI, 0.54–0.92), hay fever (OR 0.73; 95% CI, 0.59–0.90), eczema (OR 0.74; 95% CI, 0.56–0.97), or other allergies (OR 0.65; 95% CI, 0.47–0.90), and these estimates are similar to those reported in earlier studies. Although the mechanism governing potential protection has not been identified, it may arise from the anti-inflammatory effects of cytokines involved in allergic and autoimmune disease [109]. It also may result from increased tumor immunosurveillance in those who have allergies and autoimmune disease [110] or from suppression of the immune system by the brain tumor [102]. Wiemels and colleagues [103] found that total IgE levels were lower in glioma cases than in controls (OR 0.37; 95% CI, 0.22–0.64); these, along with earlier results [100], support the notion that the relation between allergic disease and glioma risk is complex and varies by allergen and allergic pathology. A problem with the case–control studies used to examine the glioma-allergy association is that because of the low survival probability from glioblastoma, investigators have used many proxy respondents to ascertain information concerning allergic conditions. Confirming the suggestion that proxy reports may not be reliable, Schwartzbaum and colleagues [105] found that proxy respondents reported fewer allergic conditions for index subjects than did self-reporting respondents. In a cohort study where information on allergic conditions was obtained on average 19 years or more before diagnosis of a brain tumor, however, Schwartzbaum and colleagues [105] reported an association between allergies and glioma risk (hazard ratio [HR] 0.45; 95% CI, 0.19–1.07)—excluding low-grade glioma—and between immune-related hospital discharges and glioma risk (HR 0.46; 95% CI, 0.14–1.49).

Moreover, results submitted by Schwartzbaum and colleagues [101] confirmed the inverse association between asthma and glioblastoma; they examined five SNPs in three genes, IL-4 receptor alpha (IL-4RA), IL-13, and ADAM33. The IL-4RA SNP T478C TC, CC and A551G AG, AA were significantly positively associated with glioblastoma (ORs were 1.64 [95% CI, 1.05–2.55] and 1.61 [95% CI, 1.05–2.47]), respectively, whereas the IL-13 SNP C1112T CT, TT was associated inversely with glioblastoma (OR 0.56, 95% CI, 0.33–0.96). It is possible that IL-13 or its shared receptor with IL-4, IL-4RA, plays an independent role in allergic conditions and glioblastoma. Alternatively, some aspect of allergic conditions themselves might reduce glioblastoma or glioma risk. Each of the polymorphism-glioblastoma associations is in the opposite direction of a corresponding polymorphism-asthma association, consistent with previous findings that self-reported asthmatics and people who have allergic conditions are less likely to have glioblastoma than are people who do not report these conditions. This result addresses lingering doubts that associations between allergic conditions and glioblastoma merely are reporting artifacts resulting from recall bias or effects of the tumor on the immune system [101]. These results were confirmed weakly when data from three additional countries—approximately tripling the original number of cases and controls—were added; in addition, Schwartzbaum and colleagues [111] identified an association between the T-G haplotype of IL-4RA and glioblastoma risk. Moreover, their original finding of the association between the IL-13 C1112T SNP and glioblastoma subsequently was confirmed by Wiemels and colleagues [104] in a large case–control study of glioma (456 cases and 541 controls). Furthermore, Wiemels and colleagues [104] report that this same IL-13 SNP was associated inversely with IgE levels in controls ($P = .04$) and observed an association of borderline statistical significance between an IL-4RA haplotype and glioma (OR 1.49; 95% CI, 0.99–2.25). In spite of this molecular evidence of an association between allergic conditions and glioblastoma, further research is needed to evaluate the complete IL-4/IL-13 pathways to determine their potential function in glioblastoma development or progression.

A variety of viruses (papovaviruses, including simian virus 40 [SV40], JC virus, and BK virus; adenoviruses; retroviruses; the herpes viruses; and influenza) and parasitic infections (*Toxoplasma gondii*) also have been investigated in relation to gliomagenesis in experimental animals and limited epidemiologic studies. The potential risk from these agents generally has been addressed inadequately in epidemiologic studies, however [112,113]. With relative consistency, results from two case–control series suggest that prior clinical disease associated with VZV infection and anti-VZV IgG levels may be associated inversely with adult glioma risk [106–108]. It might be the specific nature of the immune system's response to antigens, and not exposure to the antigen per se, that is responsible for this inverse association with glioma [100–103].

With respect to SV40, between 1955 and 1963, an unknown proportion of all inactivated and live polio vaccines distributed was contaminated with SV40 [114]. In Germany, where children were followed over a 20-year period, those inoculated with the polio vaccine contaminated with SV40 had higher occurrences of glioblastoma, medulloblastoma, and some less common brain tumor types than children not given the contaminated vaccine [115]. In the United States, no difference in brain tumor risk was found for glioma or meningioma between the two groups of children [116], but one study reported that the incidence of ependymoma was 37% greater in the children receiving the contaminated vaccine [114]. Results pertaining to infections should be validated in studies in which serologic measurement of viral or bacterial exposure is ascertained before the development of brain tumors and in which there is serologic or symptom-based confirmation of infection.

Results pertaining to HLA–cell surface molecules that modulate immune responses, in part by presenting antigenic peptides to T-lymphocytes, also suggest the importance of immunologic responses in glioma development. Tang and colleagues [117] showed that glioblastoma is associated positively with the HLA genotype B*13 and the HLA haplotype B*07-Cw*07 ($P = .01$ and $P < .001$, respectively) and is associated inversely with the genotype Cw*01 ($P = .05$). If confirmed, these results could explain partially the increased glioblastoma incidence among whites, because B*07 and B*07-Cw*07 are more common among whites. Guerini and colleagues [118] compared a small group of patients who had glioma in Northern Italy with control organ donors from the same region and demonstrated a positive association between HLA DRB1*14 and the presence of symptomatic cerebral glioma (OR 2.48; 95% CI, 1.09–5.45). Facoetti and colleagues [119] found that HLA class I antigens were lost in approximately half of glioblastoma tumors but in only 20% of grade 2 astrocytoma tumors; selective HLA-A2 antigen loss was observed in approximately 80% of glioblastoma lesions and half of the grade 2 astrocytoma tumors; and HLA class I antigen loss was correlated significantly ($P < .025$) with tumor grade. Studies of HLA may contribute to understanding immune escape mechanisms used by glioma, because HLA antigens mediate interactions of tumor cells with the host immune response; further, HLA antigen defects in astrocytoma brain tumors may explain the poor clinical response rates observed in the majority of the T cell-based immunotherapy clinical trials [119].

Summary

Brain tumors seemed to have increase in incidence over the past 30 years, but the rise probably results mostly from use of new neuroimaging techniques. Treatments have not improved prognosis for the most rapidly fatal brain tumors. Established brain tumor risk factors (exposure to therapeutic ionizing radiation, rare mutations of penetrant genes, and familial history) explain only a small proportion of brain tumors, and only one of these

potentially is modifiable. It is likely that genetic and environmental characteristics play a role in familial aggregation of glioma, and these factors have not been identified. Among associations currently being investigated, those of interest include reproductive and menstrual factors for glioma and meningioma, cell phone use for glioma and acoustic neuroma, familial aggregation of meningioma, allergic conditions for glioma, and a variety of inherited polymorphisms potentially associated with glioma. Results from studies based on molecular biomarkers of immunologic factors (eg, antibodies and IgE), although sparse, are promising; future examination of these factors should take place in cohort studies or studies within large health systems with archived specimens to minimize the possibility of tumor growth and treatments affecting the factor of interest; further, to include a sufficient number of participants diagnosed with brain tumors, large studies will be needed. Current research on glioma and polymorphisms associated with allergic conditions and immunologic responses may aid in understanding the complex immunologic modulation of gliomagenesis. Focused a priori hypotheses will be needed for these studies and for studies involving genetic polymorphisms that, in conjunction with environmental carcinogens or behavioral factors, may increase brain tumor risk. In addition to these promising leads, new hypotheses should consider previous findings from well-established risk factors, such as gender, race, and ethnicity. New concepts in brain tumor etiology and clinical management are the goal of such research, with an aim at eradicating this devastating disease.

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