Chapter 1

Epidemiology

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Abstract

More than 250 000 new cases of primary malignant brain tumors are diagnosed annually worldwide, 77% of which are gliomas. A small proportion of gliomas are caused by the inheritance of rare high-penetrance genetic variants or high-dose radiation. Since 2009, inherited genetic variants in 10 regions near eight different genes have been consistently associated with glioma risk via genome-wide association studies. Most of these variants increase glioma risk by 20–40%, but two have higher relative risks. One on chromosome 8 increases risk of IDH-mutated gliomas sixfold and another that affects TP53 function confers a 2.5-fold increased risk of glioma. Functions of some of the other risk variants are known or suspected, but future research will determine functions of other risk loci. Recent progress also has been made in defining subgroups of glioma based on acquired alterations within tumors. Allergy history has been consistently associated with reduced glioma risk, though the mechanisms have not yet been clarified. Future studies will need to be large enough so that environmental and constitutive genetic risk factors can be examined within molecularly defined, etiologically homogeneous subgroups.

DESCRIPTIVE EPIDEMIOLOGY¹

Glioma incidence by age and histologic subtype

Primary malignant brain tumors are the 17th most common cancer type worldwide, with more than 250 000 new cases diagnosed annually (Forman et al., 2013). Approximately 77% of these are gliomas, which include pilocytic astrocytoma (World Health Organization (WHO) grade I), diffuse astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), glioblastoma (WHO grade IV), oligodendroglioma (WHO grade II), anaplastic oligodendroglioma (WHO grade III), ependymomas (WHO grade II), anaplastic ependymoma (WHO grade III), and mixed gliomas (Louis et al., 2007). In the USA more than 19 000 new cases of glioma are diagnosed each year with an age-adjusted average annual incidence rate of 6.24 per 100 000 population (Ostrom et al., 2014b). Brain tumor incidence rates have increased over the past three decades, with improved reporting, increased use of diagnostic imaging, and changing attitudes toward diagnosis in the elderly suspected to account for much of this observed increase (Ohgaki and Kleihues, 2005). Although primary brain tumors are relatively rare compared with metastatic brain tumors or more common primary cancer sites such as lung, breast, prostate, and colorectal, they constitute an important source of morbidity and mortality. In children, brain tumors cause one-quarter of all cancer deaths (Ostrom et al., 2015a).

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¹Abbreviations used in the chapter are listed at the end of the chapter before the References section.
The histologic distribution of glioma is very different in adults versus that observed in children (Fig. 1.1). Pilocytic astrocytoma (WHO grade I), the most common glioma in children, accounts for 37% of all glioma diagnoses among those under age 20 (Fig. 1.1A). Glioblastoma (WHO grade IV), the most common glioma in adults, accounts for 67% of all adult glioma diagnoses (Fig. 1.1B) (Ostrom et al., 2014b).

The incidence rates of both pilocytic astrocytoma and ependymoma decrease throughout childhood and into adolescence (Fig. 1.2A). In adults, overall incidence of glioma dramatically increases with advancing age. However, the incidence of oligodendroglioma and ependymoma peaks in middle age and there is a decline in the incidence of glioblastoma among those 85 years and older (Fig. 1.2B) (Ostrom et al., 2014b). As with other cancers, the increased incidence of glioma with age could be due to the length of time required for malignant transformation, the necessity of many genetic alterations prior to the onset of clinical disease, and/or diminished immune surveillance.

Differences in glioma incidence by sex, ethnicity, and geographic location

Men have higher incidences rates of glioma, embryonal tumors, germ cell tumors, and primary central nervous system (CNS) lymphoma, whereas women have higher incidence rates of meningioma and pituitary tumors. The 1.3-fold increased risk of glioma in males versus females is among the most consistent findings in brain tumor epidemiology (Ostrom et al., 2014b, 2015a). Because of the consistency of this finding, even in pediatric populations, a comprehensive understanding of glioma etiology must account for this observation. However, this important epidemiologic observation remains unexplained.

Interpretations of ethnic and geographic variation in the occurrence of brain tumors are complicated by problems in ascertainment and reporting. Regions with the highest reported rates of primary malignant brain tumors (e.g., Northern Europe, US white population, and Israel: rates of 11–20 per 100,000 population) generally have better access to medical imaging than areas...
with the lowest rates (e.g., India and the Philippines: rates of 2–4 per 100,000 people) (Inskip et al., 1995). However, some of the variation suggests ethnic differences in inherited susceptibility and/or cultural or geographic differences in risk factors (Jacobs et al., 2012; Dubrow et al., 2013). Most notably, the rate of malignant brain tumors in Japan, an economically prosperous country, is less than half the rate in Northern Europe (Forman et al., 2013). Furthermore, in the USA, whites have higher rates of glioma than African Americans but lower rates of meningioma (Fig. 1.3) (Ostrom et al., 2014b). These observations would be difficult to attribute solely to differences in access to medical care or diagnostic practices.

The absolute variation in the occurrence of brain tumors between high-risk and low-risk areas is on the order of fourfold, compared with the 20-fold difference observed for lung cancer or the 150-fold difference observed for melanoma (Forman et al., 2013). Thus, for glioma, it seems unlikely that there are strong environmental risk factors associated with geography.

### Incidence of molecular subgroups of glioma

Recent studies have focused on using molecular markers to help clarify glioma classification (Cancer Genome Atlas Research Network, 2008; Jiao et al., 2012; Liu et al., 2012; Brennan et al., 2013; Wiestler et al., 2013; Eckel-Passow et al., 2015; Mur et al., 2015; Spiegel-Kreinecker et al., 2015). For example, three acquired molecular alterations (IDH mutation, 1p19q co-deletion, and TERT promoter mutation) found in glioma tumor cells define five etiologically and clinically distinct groups of glioma patients that account for over 95% of grade II–IV gliomas (Eckel-Passow et al., 2015). Figure 1.4 shows the proportions of these molecular groups expected among incident infiltrating grade II–IV adult gliomas, estimated at the population level (Rice et al., 2015). Further work will help to establish the precise distribution and utility of these and other molecular classifications currently being considered.

### INHERITED RISK FACTORS FOR GLIOMA

Inherited genetic predisposition to glioma has long been suspected because of increased familial risk and the existence of glioma in rare familial cancer syndromes (Malmer et al., 2007). Below, we briefly review both the hereditary syndromes and the more common inherited variants associated with increased risk of glioma.

#### Hereditary cancer syndromes associated with glioma risk

Gliomas are thought to arise through the progressive accumulation of genetic and epigenetic alterations that permit cells to evade normal regulatory mechanisms and escape destruction by the immune system (Wrensch et al., 2005a; Schwartzbaum et al., 2006). Rare inherited genetic mutations conferring increased glioma risk within families have long been known (Table 1.1), but they explain only a small proportion of brain tumor incidence at the population level (Hemminki et al., 2009).

Li–Fraumeni syndrome, caused by a constitutive loss-of-function mutation in the TP53 gene, is the familial tumor syndrome most frequently associated with glioma. However, numerous other rare Mendelian disorders increase risk of glioma, including neurofibromatosis 1 and neurofibromatosis 2, tuberous sclerosis, Lynch syndrome, and melanoma-neural system tumor syndrome (Ostrom et al., 2015b).

A recent paper from the Gliogene Consortium demonstrated that rare loss-of-function mutations in the POT1 gene are associated with greatly increased risk of glioma in families (Bainbridge et al., 2015). This is the first monogenic cause of glioma to be discovered since CHK2 mutations were identified as an alternative
cause of Li–Fraumeni syndrome at the turn of the century (Bell et al., 1999). Interestingly, POT1 mutations seem to confer greater risk for oligodendroglioma than for astrocytoma. Of eight POT1 mutation carriers diagnosed with a glioma in the Gliogene study, six had oligodendrogial tumors (four oligodendroglioma and two mixed oligoastrocytoma) (Bainbridge et al., 2015). Other studies have shown that inherited mutations of POT1 also underlie some cases of familial melanoma (Robles-Espinoza et al., 2014; Shi et al., 2014). Three such families also contained individuals with an adult-onset malignant brain tumor (Robles-Espinoza et al., 2014), strongly supporting the findings of the Gliogene Consortium.

### Genome-wide association studies of glioma

Prior to the advent of genome-wide association studies (GWAS), attempts to identify specific common inherited variants associated with glioma did not yield consistent findings (Walsh et al., 2013). In a GWAS, individuals with the disease of interest and healthy controls are genotyped at hundreds of thousands of single-nucleotide polymorphisms (SNPs) to discover inherited variants which are significantly more common in those with disease than in those without. The glioma GWAS identified 10 independently significant SNP associations located in eight gene regions, including near TERC, TERT, EGFR, CCDC26, CDKN2B, PHLDB1, TP53, and RTEL1 (Table 1.2) (Shete et al., 2009; Wrensch et al., 2009; Sanson et al., 2011; Stacey et al., 2011; Walsh et al., 2014). These germline SNPs, that are more frequent in glioma cases than controls, also are called glioma risk loci, risk alleles, or risk variants. Although some of these risk loci are in or near genes or chromosomal regions not previously associated with glioma (i.e., TERC, TERT, RTEL1, involved in telomere maintenance and CCDC26, and PHLDB1, of unknown function), several of the glioma risk genes identified through GWAS have previously been identified in glioma tumor studies (i.e., TP53, CDKN2B, EGFR) and glioma-associated familial cancer syndromes (i.e., CDKN2B, TP53). Interestingly, the inherited risk variants are not within the exonic (protein-coding) portions of these genes. This suggests that inherited differences in gene regulation, not protein structure, confer glioma risk at these loci.

Four of these eight glioma risk regions identified by GWAS contain variants that appear to contribute to development of all glioma grades and histologies (TERT, RTEL1, EGFR, TP53) (Table 1.2) (Jenkins et al., 2011; Walsh et al., 2013; Rice et al., 2015). However, the other four regions contain variants associated with the development of certain glioma grades, histologies, or molecular subtypes (TERC, CDKN2B, PHLDB1, CCDC26) (Table 1.2) (Jenkins et al., 2011, 2012; Rice et al., 2013; Walsh et al., 2013). SNPs near CDKN2B on chromosome 9 increase risk of astrocytomas, regardless of grade, but

### Table 1.1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Features</th>
<th>Associated histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>Neurofibromatosis 1</td>
<td>Dominant</td>
<td>Neurofibromas, schwannomas, café-au-lait macules</td>
<td>Astrocytoma, optic nerve glioma</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis 2</td>
<td>Dominant</td>
<td>Acoustic neuromas, meningiomas, neurofibromas</td>
<td>Spinal ependymoma</td>
</tr>
<tr>
<td>TSC1, TSC2</td>
<td>Tuberous sclerosis</td>
<td>Dominant</td>
<td>Multisystem nonmalignant tumors</td>
<td>Glioblastoma, astrocytoma</td>
</tr>
<tr>
<td>MSH2, MLH1, MSH6, PMS2</td>
<td>Lynch syndrome</td>
<td>Dominant</td>
<td>Gastrointestinal, endometrial, and other cancers</td>
<td>Glioblastoma, astrocytoma</td>
</tr>
<tr>
<td>TP53</td>
<td>Li–Fraumeni syndrome</td>
<td>Dominant</td>
<td>Numerous cancers, especially breast, brain, and soft-tissue sarcoma</td>
<td>Glioblastoma, astrocytoma, choroid plexus tumor</td>
</tr>
<tr>
<td>POT1</td>
<td>Melanoma-oligodendroglioma susceptibility syndrome</td>
<td>Dominant with reduced penetrance</td>
<td>Predisposition to melanoma and oligodendrogial tumors</td>
<td>Oligodendroglioma and mixed oligoastrocytoma</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Melanoma-neural system tumor syndrome</td>
<td>Dominant</td>
<td>Predisposition to melanoma and astrocytic tumors</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>IDH1/IDH2</td>
<td>Ollier disease/Maffucci syndrome</td>
<td>Postzygotic mosaicism/dominant with reduced penetrance</td>
<td>Intraosseous benign cartilaginous tumors, cancer predisposition</td>
<td>Glioma</td>
</tr>
</tbody>
</table>

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are not associated with risk of oligodendroglial tumors (Walsh et al., 2013). SNPs in PHLDB1 increase risk of IDH-mutated gliomas, regardless of grade or histology (Rice et al., 2013). SNPs in CCDC26 on chromosome 8q24 increase risk of IDH-mutated astrocytomas and also of oligodendroglial tumors, regardless of IDH mutation status (Jenkins et al., 2012).

This risk region on chromosome 8q24 is a striking example where GWAS initially identified variants that only modestly increase disease risk, but these variants were tagging or marking a much less common variant that confers a very high risk of specific glioma subtypes (Jenkins et al., 2012; Enciso-Mora et al., 2013). By sequencing the genomic region and conducting extensive validation genotyping, researchers showed that the G allele of SNP rs55705857 confers an approximately sixfold increased risk of IDH-mutated astrocytoma and oligodendroglial tumors (Jenkins et al., 2012). The mechanism by which rs55705857 confers risk of glioma is not understood. One possibility is that rs55705857 may be involved in long-range interactions with MYC, also located on 8q24.2, but this is still speculative (Tseng et al., 2014).

The sixfold increased risk of IDH-mutated glioma and oligodendroglioma associated with rs55705857 is the same magnitude of effect as that of BRCA1 mutations on breast cancer risk (Jenkins et al., 2012). However, glioma is sufficiently infrequent that the absolute risk, even with very high relative risk, remains small (about 6/1000 individuals) and insufficient to justify genetic screening (Rice et al., 2015). Because breast cancer is a much more common cancer, the lifetime risk for women who have inherited deleterious variants in BRCA1 increases to about 65/100 (Gail et al., 1989; Antoniou et al., 2003). Even so, BRCA1 testing is still only recommended for women who have an indication of inherited risk due to family history or early age at onset because screening the general population would identify many women as high-risk who will not develop breast cancer in their lifetime. Because glioma is much rarer than breast cancer, rs55705857 currently has little utility in genetic testing due to its low specificity. For glioma screening based on inherited risk variants to be feasible, one would need to identify a subgroup of people with substantially higher glioma risk than that of the general population.

<table>
<thead>
<tr>
<th>Gene (chromosome)</th>
<th>Lead single-nucleotide polymorphism (risk allele)</th>
<th>Risk allele frequency</th>
<th>Odds ratio</th>
<th>Hypothesized function</th>
<th>Associated histology/molecular subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERC (3q26.2)</td>
<td>rs1920116 (G)</td>
<td>0.71</td>
<td>1.27</td>
<td>Increased telomere length/ telomerase activity</td>
<td>Astrocytoma III–IV</td>
</tr>
<tr>
<td>TERT (5p15.33)</td>
<td>rs2736100 (C)</td>
<td>0.50</td>
<td>1.33</td>
<td>Increased telomere length/ telomerase activity</td>
<td>All glioma subtypes</td>
</tr>
<tr>
<td>EGFR (7p11.2)</td>
<td>rs2252586 (A)</td>
<td>0.28</td>
<td>1.15</td>
<td>Undetermined</td>
<td>Astrocytoma III–IV</td>
</tr>
<tr>
<td>EGFR (7p11.2)</td>
<td>rs1979158 (A)</td>
<td>0.81</td>
<td>1.22</td>
<td>Undetermined</td>
<td>Astrocytoma III–IV</td>
</tr>
<tr>
<td>CCDC26 (8q24.21)</td>
<td>rs55705857 (G)</td>
<td>0.07</td>
<td>6.10</td>
<td>Undetermined</td>
<td>Oligodendroglial tumors, IDH-mutated astrocytomas</td>
</tr>
<tr>
<td>CDKN2B (9p21.3)</td>
<td>rs1412829 (G)</td>
<td>0.41</td>
<td>1.43</td>
<td>Increased ANRIL expression</td>
<td>Astrocytoma II–IV</td>
</tr>
<tr>
<td>PHLDB1 (11q23.3)</td>
<td>rs498872 (A)</td>
<td>0.28</td>
<td>1.52</td>
<td>Undetermined</td>
<td>IDH-mutated glioma</td>
</tr>
<tr>
<td>TP53 (17p13.1)</td>
<td>rs78378222 (C)</td>
<td>0.01</td>
<td>2.65</td>
<td>Alteration of TP53 polyadenylation signal</td>
<td>All glioma subtypes</td>
</tr>
<tr>
<td>RTEL1 (20q13.33)</td>
<td>rs6010620 (G)</td>
<td>0.77</td>
<td>1.42</td>
<td>Alteration of RTEL1–PCNA interaction domain</td>
<td>All glioma subtypes</td>
</tr>
<tr>
<td>RTEL1 (20q13.33)</td>
<td>rs4809324 (C)</td>
<td>0.10</td>
<td>1.66</td>
<td>Increased telomere length/ telomerase activity</td>
<td>Astrocytoma III–IV</td>
</tr>
</tbody>
</table>
The recently defined molecular subgroups of glioma based on presence or absence of tumor TERT promoter mutation, IDH mutation, and/or 1p/19q co-deletion have distinct associations with the known glioma risk variants (Eckel-Passow et al., 2015). In addition to the previously discussed relationship between certain risk variants and IDH mutation, there is some evidence that variants near TERC and RTEL1 are more strongly associated with gliomas harboring somatic mutation of the TERT promoter (Eckel-Passow et al., 2015). Figure 1.5 summarizes our current understanding of the hypothesized pathways of adult glioma development based on inherited and acquired mutations (Rice et al., 2015). For some molecular subgroups, our understanding of the interplay between inherited variation and acquired tumor alterations is based on a relatively small number of patients. Therefore, further investigations will be needed to verify, refine, and expand our understanding of inherited variation in gliomagenesis.

**TELOMERE MAINTENANCE AND GLIOMA**

Recent studies of both inherited glioma risk variants and of acquired mutations found in glial tumors identify a substantial role for telomere maintenance in gliomagenesis. Below we briefly review telomere biology and the emerging role of telomeres in glioma development.

**Telomere biology and heritability of telomere length:**

Human telomeres, located at the ends of chromatids, are composed of tandem hexanucleotide DNA repeats (TTAGGG) and several associated telomere-binding proteins, including the shelterin complex (Griffith et al., 1999). The primary function of telomeres is to compensate for incomplete DNA replication at chromosome ends, caused by the eukaryotic “end replication...
Telomere length and risk of glioma

Two case-control studies have attempted to directly measure LTL and determine its association with glioma risk (Walcott et al., 2013; Wang et al., 2014). The first of these studies, with 101 glioma patients and 198 healthy controls, did not identify a significant association between glioma risk and LTL, but a larger study of 467 glioma patients and 467 controls showed that glioma patients had significantly longer LTL than control subjects (Wang et al., 2014). Individuals in the upper tertile of LTL had increased risk of glioma relative to individuals in the middle tertile (odds ratio, 3.5). Paradoxically, those in the lowest tertile of LTL also had increased risk of glioma compared to those with intermediate LTL.

As discussed above, GWAS have implicated SNPs near TERC, TERT, and RETL1 in gliomagenesis (Shete et al., 2009; Wrensch et al., 2009; Walsh et al., 2014). Interestingly, the top glioma risk alleles near TERC and TERT also are very significantly associated with longer LTL ($p = 5.5 \times 10^{-20}$ and $4.4 \times 10^{-19}$, respectively) (Walsh et al., 2014). Although these findings do not rule out the possibility that other genes in these two regions may underlie the genetic association with glioma, they strongly support the idea that inherited risk for glioma is, to some degree, mediated through longer telomere length. This is further supported by the family-based study, mentioned above, that recently identified POT1 mutations as a cause of glioma, since dysfunction of this shelterin complex protein was also associated with increased LTL in mutation carriers (Bainbridge et al., 2015).

Unlike those near TERC and TERT, glioma risk alleles near RETL1 are not consistently associated with LTL and suggest the presence of multiple causal alleles (Walsh et al., 2014). Although rs6010620 is associated with significantly shorter LTL ($p = 1.1 \times 10^{-7}$), rs4809324 is associated with a modest increase in LTL ($p = 0.039$) (Walsh et al., 2014). Thus, genetic variation near RETL1 may impact gliomagenesis through multiple mechanisms, not all of which are necessarily telomere-dependent. Another possibility is that the presence of longer versus shorter telomeres may have different relevance at different stages of the oncogenic process.

Telomere shortening and cancer

In cells requiring continuous renewal (e.g., germ and stem cells), telomere length is maintained by telomerase. Telomerase is inactive in most adult cells, but is often reactivated in cancer cells (Blackburn et al., 2006). The telomerase enzyme adds nucleotides to telomeres and is composed of a reverse transcriptase (encoded by TERT) and an RNA template (encoded by TERC) (Wang and Meier, 2004). Telomere maintenance in glioma occurs in at least two ways: through reactivation of telomerase or through a homologous recombination-based mechanism known as alternative lengthening of telomeres (ALT) (Chang et al., 2003; Heaphy et al., 2011b). How telomerase is reactivated in tumor cells was recently discovered when sequencing of germline DNA in melanoma-prone families identified two different activating mutations in the promoter of TERT (Horn et al., 2013). Somatic mutations at these same positions were identified in tumor DNA from sporadic melanoma cases (Huang et al., 2013). Soon after, targeted sequencing of the TERT promoter was carried out in a diverse set of human tumors (Killela et al., 2013). Mutations of the TERT promoter are observed in approximately 75% of glioblastomas and 20% of grade II and III astrocytomas and generate a novel GA-binding protein transcription factor-binding site that upregulates TERT mRNA expression (Bell et al., 2015). Strikingly, 75% of oligodendrogliomas also harbor TERT promoter mutations, despite otherwise being largely molecularly and clinically dissimilar from glioblastomas (Killela et al., 2013; Eckel-Passow et al., 2015).

Gliomas that do not maintain telomere length through activation of telomerase frequently activate the ALT pathway via mutation of either ATRX or DAXX (Heaphy et al., 2011a). More than half of all adult grade II and III astrocytomas have mutations in ATRX, and this proportion is even higher when limited to IDH-mutated astrocytoma (Heaphy et al., 2011b; Kannan et al., 2012). DAXX mutations are primarily limited to pediatric gliomas (Heaphy et al., 2011b).
A growing body of epidemiologic and tumor genomic research has identified an important role for telomere maintenance in glioma predisposition, initiation, and prognosis. Though further research is necessary, several points seem clear: (1) inherited variants in or near telomere-related genes (TERC, TERT, RTEL1, POT1) are associated with glioma risk; (2) mutations affecting telomere maintenance pathways (TERT promoter, ATRX, DAXX) are among the most recurrent acquired somatic events observed in gliomas; and (3) these inherited variants and acquired somatic mutations primarily cause lengthening, not shortening, of telomeres. However, as noted above, the importance of longer versus shorter telomeres may vary during the oncogenic process.

ENVIRONMENTAL AND DEVELOPMENTAL RISK FACTORS

Below we briefly review nongenetic risk factors that have been studied for gliomas, which are summarized in Table 1.3.

Allergies, infections, and immunologic risk factors

Numerous studies have shown that allergic conditions, including asthma, hayfever, eczema, and food allergies, are less frequently reported by glioma cases than controls, suggesting that these conditions reduce glioma risk (Schoemaker et al., 2006; Wigertz et al., 2007; Scheurer et al., 2008; Berg-Beckhoff et al., 2009; I’yasova et al., 2009; Wiemels et al., 2009; McCarthy et al., 2011).

A formal meta-analysis concluded that allergies reduce glioma risk by nearly 40% (Linós et al., 2007). The association between increased allergies and reduced brain tumor risk was recently validated using prospectively collected data from US veterans, minimizing the potential for recall bias (Cahoon et al., 2014). Further support for this inverse association has been contributed by five studies showing that glioma patients have lower levels of an atopy biomarker, immunoglobulin E (IgE) (Wiemels et al., 2007, 2009; Calboli et al., 2011; Schlehofer et al., 2011; Schwartzbaum et al., 2012).

Although mechanisms governing the potential anti-glioma effects of allergy have not been identified, they may arise from the anti-inflammatory effects of interleukin-4 (IL-4) and IL-13 cytokines involved in allergic and autoimmune disease, or from increased tumor immunosurveillance in those with allergies and autoimmune disease (Dunn et al., 2002; Dinarello, 2003). It is also possible that the inverse association results from immune suppression by the preclinical tumor, but validation in prospective data sources makes this explanation less likely (Cahoon et al., 2014).

Reduced glioma risk has also been attributed to a reported history of varicella-zoster virus (VZV) infections (i.e., chickenpox and shingles) and positive IgG to VZV (Wrensch et al., 1997b, 2001, 2005b). With relative consistency, results suggest that history of chickenpox or shingles and anti-VZV IgG levels are inversely associated with adult glioma risk (Wrensch et al., 1997b, 2001, 2005b). Given the ubiquity of VZV exposure, it may be the specific nature of a person’s VZV-associated immune response, and not exposure to the virus itself, that is responsible for this inverse association with glioma (Wiemels et al., 2011). Strong anti-VZV reactions in highly allergic individuals may be a biomarker of effective CNS immunosurveillance (Lee et al., 2014).

At present, there is no strong epidemiologic evidence suggesting that human cytomegalovirus (HCMV) plays a role in the development of glioma. However, HCMV nucleic acids and proteins are found in the tumors of some glioblastoma patients, and HCMV DNA has also been found in the peripheral blood of glioblastoma patients (Poltermann et al., 2006). However, others report that antibody positivity to HCMV in glioma patients is not different from that in controls or the general population (Wrensch et al., 2005b; Poltermann et al., 2006). The presence of HCMV gene products in blood or tumor tissue may result from reactivation of infection or from infected tumor cells shedding viral DNA (Mitchell

Table 1.3

<table>
<thead>
<tr>
<th>Nongenetic risk factors studied as possible glioma risk factors</th>
<th>Establishment of risk factors</th>
<th>Association (magnitude and direction)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Established risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose radiation</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Male vs. female gender</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>White vs. African American ethnicity</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Increasing age</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>Probable risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergies/asthma</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Elevated IgE</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Chickenpox/antivaricella-zoster virus IgG</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td><strong>Probably not risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic radiation</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Head injury</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Residential power lines/electromagnetic fields</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Cell phone use</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>

+++ strong risk factor, relative risk >3; + risk factor >1; – risk factor <1; × no consistent associations.
et al., 2008). Renewed interest in HCMV may spark new epidemiologic studies, and these studies should consider the potential importance of low-level infection, which will require stringent technical conditions to quantify. Papovaviruses, including simian virus 40, JC and BK viruses, adenoviruses, retroviruses, herpes and influenza viruses, and parasitic infections (e.g., *Toxoplasma gondii*), have also been investigated in relation to gliomagenesis in experimental animal models and in limited epidemiologic studies (Ohgaki and Kleihues, 2005; Ostrom et al., 2014a). Like HCMV, the potential risk from these agents has not been adequately addressed in epidemiologic studies (Wrensch et al., 2005a; Schwartzbaum et al., 2006).

**Ionizing radiation**

Sources of exposure to ionizing radiation include therapeutic and diagnostic medical procedures, occupation, atmospheric testing of nuclear weapons, and proximity to atomic bomb explosions. Survivors of the bombing of Hiroshima have higher incidence rates of glioma, schwannoma, and pituitary tumors, although there is no increased risk for brain tumors in survivors who were exposed *in utero* (Preston-Martin, 1996). The once, but no longer, common use of ionizing radiation to treat tinea capitis and skin hemangioma in infants and children has been associated with a threefold relative risk of gliomas (Braganza et al., 2012). Furthermore, second primary brain tumors occur more frequently than expected in patients previously treated for brain tumors with radiation therapy. The standardized incidence ratio for second CNS tumors in brain tumor patients treated by surgery alone is 2.0 (95% confidence interval (CI), 1.2–3.2) versus 5.1 (95% CI, 2.5–9.4) for patients treated by radiotherapy with or without surgery or chemotherapy, or both (Salminen et al., 1999). However, these results may be influenced by the fact that people with higher-grade tumors are more likely to both receive radiation therapy and have multiple primary cancers, possibly due to an underlying genetic predisposition.

Results from case-control studies of exposure to ionizing radiation and glioma risk may vary due to under-reporting of exposure, imprecise estimates of age at first exposure, or a low prevalence of exposure to high doses of ionizing radiation. The consistent and strong results from prospective studies of people exposed to ionizing radiation provide unquantifiable evidence of a linear dose–response between ionizing radiation exposure and glioma incidence. Future studies should consider the potential for interaction between ionizing radiation and both age at exposure and genetic variation that may mediate susceptibility. Despite the known association between ionizing radiation and brain tumor risk, therapeutic doses of ionizing radiation contribute to the development of only a small proportion of brain tumors because exposure to therapeutic levels of ionizing radiation is rare.

Elucidating a possible role of more common radiation exposures, such as that resulting from dental radiographs, requires reliable assessment of exposure. Evidence thus far does not support a role for diagnostic radiation in causing glioma, but the evidence is stronger for meningioma and acoustic neuroma (Claus et al., 2012; Han et al., 2012). Because radiation dosage has decreased dramatically since the time period during which patients in these studies received X-rays, the public health impact of dental X-rays on brain tumor incidence is likely declining (Claus et al., 2012).

**Nonionizing radiation**

Neither a large population-based study of adult glioma in the San Francisco Bay Area nor other epidemiologic studies of adult brain tumors support the hypothesis that residential power lines increase the risk of brain tumors (Wrensch et al., 1999). A limitation with studies of electromagnetic field exposures and adult brain tumors is that the pertinent exposure period and the mechanisms through which electromagnetic fields might contribute to brain tumor risk are unknown.

Mobile phone technology was introduced in the 1980s and the vast majority of people in the USA now use these phones. Public concern over the potential health effects of mobile phones has prompted studies focused on exposure to radiofrequency fields and brain tumor risk. In 2011, the Monograph Program of the International Agency for Research on Cancer (IARC) on the evaluation of carcinogenic risks to humans classified radiofrequency fields as a possible carcinogen (IARC group 2B). This means that there “could be some risk” of carcinogenicity and that “additional research into the long-term effects of mobile phone use is warranted.” Recent epidemiologic studies reporting on glioma risk in relation to mobile phone use in adults have demonstrated generally null results (Ostrom et al., 2014a). Time trends of age-standardized brain tumor incidence rates are an important tool to examine the possible associations between mobile phone use and brain tumor risk. The increase in prevalence of mobile phone use has been extremely rapid worldwide. However, brain tumor incidence rates have remained generally stable (Little et al., 2012).

The UK Million Women study examined brain tumor risk in relation to duration and level of mobile phone usage in a prospective manner (Benson et al., 2013). Glioma risk was not significantly different for daily users compared with never-users in the UK study. Current
evidence published since the IARC monograph in 2011 does not support an association between mobile phone use and brain tumor risk in adults. Although brain cancer incidence has not increased with the marked increase in mobile phone use, the latency period of some types of brain tumors may be extremely long. Thus, the potential association between cellular phone use and brain tumor risk deserves continued monitoring as data on long-term heavy users of cellular phones are accrued.

Other investigated but inconclusive factors

Numerous dietary, experiential, and environmental factors studied in relation to glioma risk have shown inconsistent associations, with one or more studies finding a positive association and others observing no association. Such factors include head injury and trauma (Hochberg et al., 1984; Preston-Martin et al., 1998; Hu et al., 1998; Inskip et al., 1998; Baldwin and Preston-Martin, 2004), a history of seizures (Hochberg et al., 1984; Wrensch et al., 1997a), dietary calcium intake (Hu et al., 1999; Tedeschi-Blok et al., 2001), dietary intake of N-nitroso compounds (Preston-Martin and Henderson, 1984; Lee et al., 1997; Schwartzbaum et al., 1999; Chen et al., 2002), dietary antioxidant intake (Lee et al., 1997; Hu et al., 1999; Schwartzbaum et al., 1999; Chen et al., 2002), dietary maternal intake of N-nitroso compounds (for pediatric glioma) (Baldwin and Preston-Martin, 2004), dietary maternal and early-life intake of antioxidants (for pediatric glioma) (Baldwin and Preston-Martin, 2004), tobacco smoking (Lee et al., 1997), and alcohol consumption (Wrensch et al., 2005a). A history of head trauma is a difficult exposure to assess in glioma epidemiology because brain tumors may be incidentally found following imaging at the time of trauma. A large prospective cohort study of incident intracranial tumors after hospitalization for head injuries was conducted in Denmark, but observed no increased risk of glioma during an average of 8 years of follow-up (Inskip et al., 1998). Similarly, a history of seizures may actually be representative of an early subclinical brain tumor, making it difficult to establish the temporality of any glioma–seizure relationship.

In addition to small study sample sizes, possible explanations for the inconsistent findings of many exposures include invalid or imprecise measurements of exposure due to self-report or proxy exposure assessments, unfocused hypotheses resulting from studies of large numbers of exposures without a specific rationale, inability to assess inherited variation as a genetic modifier of risk, and unaccounted-for protective environmental exposures or conditions (e.g., allergy). The levels generally encountered for some examined exposures (e.g., chemical compounds) are often too low to have a measurable impact on brain tumor risk. Continued progress in understanding risk factors is dependent on the construction of large-scale studies with better assessment of exposure, along with analysis of genetic factors that modify the effects of such exposure. Additionally, because recent molecular subgroups of glioma have distinct associations with inherited risk variants, different molecular subtypes may have different environmental or developmental risk factors.

PATIENT SURVIVAL FOLLOWING DIAGNOSIS

Associations with age, tumor subtype, and treatment

Survival time for glioma patients varies greatly by histologic type and age at diagnosis, as shown in Figure 1.6. For each age group, relative 2-year survival is lowest for patients with glioblastoma. Within histologic types, survival time generally decreases with increasing patient age (Ostrom et al., 2014b). The mechanisms for the strong, consistent inverse association between age at diagnosis and patient survival are poorly understood. In the case of glioma, this association is at least partially attributable to the frequency with which prognostically relevant somatic mutations are observed in patients of different ages, the most relevant of which is likely IDH (Parsons et al., 2008). Patients with IDH-mutated tumors have a significantly younger age of onset than patients with IDH-normal tumors.

With the exception of glioblastoma, lack of consistency in specifying grade and histology has complicated classifying glioma patients into prognostically homogeneous groups. However, recent evidence suggests that incorporating just three tumor markers may serve this purpose. Using TERT promoter mutation, IDH mutation, and lp/1q co-deletion to define five molecular subgroups of glioma, among adult patients diagnosed with glioblastoma, survival was associated with tumor molecular group independently of age, grade, and histology (Eckel-Passow et al., 2015). Although these results require additional validation in study designs that can control for other possible confounding factors, in the near future these molecular groups may be incorporated with histology in the pathologic diagnosis of glioma. It is anticipated that this will permit more precisely targeted clinical management for these patients, both in terms of selecting therapy and in testing new therapies in appropriately stratified clinical trials.

New glioma treatments are urgently needed. The addition of the chemotherapeutic agent temozolomide has improved the median survival time for glioblastoma patients by only ~2.5 months (Cohen et al., 2005; Dubrow et al., 2013). Among adult patients diagnosed
with a glioblastoma between 1995 and 2011, only 14.8% were living 2 years after diagnosis (Ostrom et al., 2014b). Five years after diagnosis, this number fell to 5.0%. Although the prognosis is poor for most patients with malignant brain tumors, 2-year survival rates increased from 28.6% in 1975 to 38.2% in 2004. The largest improvements in survival occurred in patients younger than 65 years in whom glial tumors other than anaplastic astrocytoma and glioblastoma were diagnosed (Ostrom et al., 2014b). This may not be attributable to improvements in treatment, but rather to improvements in detection. Imaging technology that permits earlier identification of tumors would appear to extend survival time by shifting the date of diagnosis earlier, not by shifting the date of death later (i.e., lead time bias).

**Prognostic markers**

The following have been consistently associated with improved glioma prognosis: younger age, higher Karnofsky performance scale score (although this is an intermediate endpoint), greater extent of resection and capacity for complete resection, lower degree of necrosis, less enhancement on preoperative magnetic resonance imaging studies, decreased volume of residual disease, smaller preoperative and postoperative tumor size, and tumor location (infiltration of the splenium, basal ganglia, thalamus, or midbrain is associated with poorer survival) (Lacroix et al., 2001; Jeremic et al., 2003; Lutterbach et al., 2003; Chang and Barker, 2005; Yan et al., 2009; Christensen et al., 2011). In addition to these patient and tumor characteristics, a number of prognostic biomarkers have been identified, some of which have been incorporated into the molecular subgroups previously discussed (Eckel-Passow et al., 2015).

A recent study identified a heritable genetic variant in *SSBP2* that was associated with improved survival among similarly treated glioblastoma patients (Xiao et al., 2012). Additionally, the rs55705857 variant on 8q24 is associated with longer progression-free survival in oligodendrogliaoma patients receiving radiation and chemotherapy (Cairncross et al., 2014). Further studies are examining inherited variation in relation to survival after glioma diagnosis.

Most recent efforts to identify prognostic factors have focused on tumor molecular markers and serologic factors. Glioblastoma was the first cancer systematically analyzed by The Cancer Genome Atlas (Cancer Genome Atlas Research Network, 2008). Subsequent studies suggested that glioblastomas could be grouped into four subtypes according to gene expression profiles (Verhaak et al., 2010). The majority of glioblastomas are categorized in the classic subtype, possessing...
hallmark EGFR amplifications. The mesenchymal subtype displays some similarity to classical glioblastomas, but with frequent hemizygous deletion of NF1. The neural subtype is the most poorly defined and may be partly attributable to sample contamination by nonmalignant tissue (Brennan et al., 2013). The proneural subtype showed distinct amplification and mutation of PDGFRA and point mutations in IDH1/IDH2 (Brennan et al., 2013). Patients with proneural subtype tumors usually have IDH mutations and hypermethylation across the genome, and experience improved survival compared with patients in other expression groups (Brennan et al., 2013).

The best-established marker of favorable prognosis in glioma patients is mutation of either IDH1 or IDH2, present in 70–80% of lower-grade gliomas and glioblastomas preceded by a lower-grade glioma (referred to as secondary glioblastoma) (Yang et al., 2009; Ogaki and Kleihues, 2013). Subsequent studies have found a strong link between IDH mutation and a genome-wide glioma cytosine–phosphate–guanine island methylator phenotype (G-CIMP) (Noushmehr et al., 2010; Mur et al., 2013). G-CIMP is more prevalent among lower-grade gliomas, is strongly associated with the proneural expression pattern, and has better patient outcomes (Wick et al., 2009; Noushmehr et al., 2010; Christensen et al., 2011; Brennan et al., 2013). Methylation of the MGMT gene promoter is a positive prognostic factor for glioblastomas, especially in the setting of chemotheraphy with alkylating agents such as temozolomide (Esteller et al., 2000; Hegi et al., 2005; Chen et al., 2013). The impact of MGMT methylation on survival in patients with grades II–III gliomas remains unresolved (Sadones et al., 2009; van den Bent et al., 2011).

Concomitant loss of chromosomes 1p and 19q is strongly associated with oligodendrogialtumour morphology and improved patient survival (Smith et al., 2000). The vast majority of tumors with lp/19q co-deletion have IDH mutations, and frequently carry gene mutations in FUBP1 (on chromosome lp) and CIC (on chromosome 19q) (Labussiere et al., 2010). These tumors rarely possess the EGFR amplifications common in primary glioblastomas or the TP53 and ATRX mutations common in secondary glioblastomas and lower-grade astrocytomas (Jiao et al., 2012; Kanno et al., 2012; Liu et al., 2012). The significant overlap among lp/19q co-deletion, IDH mutation, G-CIMP phenotype, and MGMT methylation makes assessing the independent prognostic role of these alterations difficult. Recent studies also indicate that the telomere-lengthening mechanism of gliomas (telomerase-based vs. ALT) may correlate with patient prognosis, but further research is needed to characterize these relationships (Jiao et al., 2012; Liu et al., 2012; Killela et al., 2013).

Amplification of IL-6, a cytokine that may promote glioblastoma, has been associated with decreased glioblastoma survival (Tchirkov et al., 2007). Higher circulating levels of CCL22, a macrophage-derived T-cell trafficking chemokine, is associated with longer survival time in patients with glioblastoma (Zhou et al., 2015). Analyses of atopy, IgE, and additional cytokines in relation to glioma prognosis may help us better understand the complex nature of the immunologic response to gliomagenesis, including secreted tumor-specific factors and host immune responses. Such investigations may also have important implications for glioma immunotherapy. An additional link between brain tumors and the immune system is the need for malignant cells to evade immunosurveillance, presumably using mechanisms similar to those of foreign tissue growth. Future studies should also include the examination of T-cell activities such as that of regulatory T cells, which have been associated with tissue graft acceptance, as well as brain tumor prognosis (Fecci et al., 2006; Yong et al., 2007).

CONCLUSIONS

Over the past 7 years, our knowledge of glioma risk and development has been fundamentally transformed by three sets of discoveries: (1) common inherited variation increases risk of glioma (Shete et al., 2009; Wrensch et al., 2009; Sanson et al., 2011; Stacey et al., 2011; Walsh et al., 2014); (2) many gliomas contain acquired mutations in IDH1 or IDH2 and these tumors are fundamentally different from gliomas lacking these mutations (Parsons et al., 2008); and (3) many gliomas contain acquired TERT promoter mutations which also appear to be driver mutations in a large proportion of gliomas (Killela et al., 2013). Inherited genetic variants in eight different gene regions have been consistently associated with glioma risk via GWAS, including those in/near TERC, TERT, EGFR, CCDC26, CDKN2B, PHLD1, TP53, and RTEL1. Another recent study performed whole-exome sequencing in glioma patients from high-risk families, identifying POT1 mutations as a rare cause of glioma (Bainbridge et al., 2015). These findings of inherited and acquired alterations underlying gliomagenesis provide a solid foundation for future epidemiologic research.

Few strong environmental risk factors have been identified for glioma, although ionizing radiation is consistently associated with increased brain tumor risk. Additionally, a personal history of allergies/atopy has been consistently associated with reduced glioma risk. We now have the molecular tools to classify glioma into more homogeneous subgroups with respect to etiology, which will help overcome some of the shortcomings of
previous studies of environmental risk factors for glioma. Future studies will need to be large enough so that environmental and constitutive genetic risk factors can be examined within etiologic subgroups, as defined by tumor genetic profiles. When these issues are addressed, the potential interaction between inherited genetic variants, somatic alterations in glial tumors, and environmental exposures can be comprehensively evaluated.

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GENE ABBREVIATIONS USED

ACYP2, acylphosphatase 2, muscle type; ATRX, alpha thalassemia/mental retardation syndrome X-linked; CCDC26, coiled-coil domain containing 26; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDKN2B, cyclin-dependent kinase inhibitor 2B; CTC1, CTS telomere maintenance complex component 1; DAXX, death-domain-associated protein; EGFR, epidermal growth factor receptor; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; MGMT, methylated-DNA–protein-cysteine methyltransferase; NAF1, nuclear assembly factor 1 ribonucleoprotein; NF1, neurofibromin 1; OBFC1, oligonucleotide/oligosaccharide-binding fold containing 1; PDGFRA, platelet-derived growth factor receptor, alpha polypeptide; PHLD1, pleckstrin homology-like domain, family B, member 1; POT1, protection of telomeres 1; RTEL1, regulator of telomere elongation helicase 1; TERC, telomerase RNA component; TERT, telomerase reverse transcriptase; TP53, tumor protein p53; ZNF208, zinc finger protein 208.

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