

## The epidemiology of glioma in adults: a “state of the science” review

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Gliomas are the most common primary intracranial tumor, representing 81% of malignant brain tumors. Although relatively rare, they cause significant mortality and morbidity. Glioblastoma, the most common glioma histology (~45% of all gliomas), has a 5-year relative survival of ~5%. A small portion of these tumors are caused by Mendelian disorders, including neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome. Genomic analyses of glioma have also produced new evidence about risk and prognosis. Recently discovered biomarkers that indicate improved survival include O<sup>6</sup>-methylguanine-DNA methyltransferase methylation, isocitrate dehydrogenase mutation, and a glioma cytosine–phosphate–guanine island methylator phenotype. Genome-wide association studies have identified heritable risk alleles within 7 genes that are associated with increased risk of glioma. Many risk factors have been examined as potential contributors to glioma risk. Most significantly, these include an increase in risk by exposure to ionizing radiation and a decrease in risk by history of allergies or atopic disease(s). The potential influence of occupational exposures and cellular phones has also been examined, with inconclusive results. We provide a “state of the science” review of current research into causes and risk factors for gliomas in adults.

**Keywords:** brain tumors, epidemiology, genome-wide association studies, glioma, risk factors.

Gliomas are the most common primary malignant brain tumors in adults. They can occur anywhere in the central nervous system but primarily occur in the brain and arise in the glial tissue.<sup>1</sup> While these tumors are typically malignant, some types do not consistently behave in a malignant fashion. Gliomas are either astrocytic, oligodendrocytic, or a mix of these 2 cell types and are typically categorized according to the *International Classification of Diseases–Oncology*, version 3 (ICD-O-3) and World Health Organization (WHO) grade.<sup>2</sup> Gliomas can be WHO grades I–IV based on malignant behavior. The most commonly occurring histologic types of gliomas in adults include astrocytoma (grades I–IV), oligodendroglioma (grades II–III), and oligoastrocytoma (grades II–III). However, there is no consensus definition of gliomas as a larger class of histologies,<sup>1,3</sup> which can make comparisons between

studies challenging. This review primarily covers the recent (2002–2013) research on selected risk factors in the epidemiology of glioma in adults (ages ≥20 y), excluding ependymomas, which are extremely rare.

### Descriptive Epidemiology

#### *Incidence of Glioma*

Many different organizations track the incidence of gliomas. This can be done using data collected through government cancer surveillance (ie, statewide or countrywide cancer registries)<sup>1,3–7</sup> or through the use of health system records.<sup>8–10</sup> Incidence rates of glioma vary significantly by histologic type, age at

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diagnosis, gender, race, and country. The lack of consistent definition of glioma and various glioma histologic types as well as differences in data collection techniques may cause difficulty in comparing incidence rates from different sources. Overall age-adjusted incidence rates (adjusted to the national population of each respective study) for all gliomas (ICD-O-3 morphology codes 9380–9480) range from 4.67 to 5.73 per 100 000 persons.<sup>11,12</sup> Age-adjusted incidence of glioblastoma (ICD-O-3 morphology codes 9440–9442, WHO grade IV), the most common and most deadly glioma subtype in adults, ranges from 0.59 to 3.69 per 100 000 persons.<sup>1,4,6,8,10,12</sup> Table 1 provides an overview of age-adjusted incidence rates for additional glioma histologic types from population-based studies.

Anaplastic astrocytoma and glioblastoma increase in incidence with age, peaking in the 75–84 age group. Oligodendrogliomas and oligoastrocytomas are most common in the 35–44 age group. Older persons are less likely to have microscopically confirmed diagnoses of glioma, which may affect age-related incidence rates.<sup>13</sup> In general, gliomas are more common in men than women, with the exception of pilocytic astrocytoma, which occurs at similar rates in men and women (Supplementary Table 1).<sup>1,6,10,13</sup> In the United States, gliomas are more common in non-Hispanic whites than in blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives.<sup>1</sup>

Many analyses have examined the incidence rates of glioma to assess whether rates are increasing. The results of these have

**Table 1.** Age-adjusted incidence rates per 100 000 persons, by histology and country/region (all ages)

Histologic Type	Region (organization)	Years	Overall	
			Rate	95% CI
Pilocytic astrocytoma <i>ICD-O-3 morphology code 9421</i>	Austria <sup>9</sup> (ABTR)	2005	0.57	0.43–0.75
	Korea <sup>6</sup>	2005	0.18	
	US <sup>1</sup> (CBTRUS)	2006–2010	0.33	0.32–0.34
	Korea <sup>6</sup>	2005	0.23	
Anaplastic astrocytoma <i>ICD-O-3 morphology code 9401</i>	US <sup>1</sup> (CBTRUS)	2006–2010	0.56	0.55–0.58
	Austria <sup>9</sup> (ABTR)	2005	0.44	0.33–0.58
	Korea <sup>6</sup>	2005	0.13	
Glioblastoma <i>ICD-O-3 morphology codes 9440–9442</i>	US <sup>1</sup> (CBTRUS)	2006–2010	0.37	0.36–0.38
	Australia <sup>8 a</sup>	2000–2008	3.40	
	England <sup>153</sup>	1999–2003	2.05	
	Korea <sup>6</sup>	2005	0.59	
	US <sup>1</sup> (CBTRUS)	2006–2010	3.19	3.16–3.21
	Greece <sup>12</sup>	2005–2007	3.69	
Oligodendroglioma <i>ICD-O-3 morphology code 9450</i>	Austria <sup>9</sup> (ABTR)	2005	0.20	0.13–0.30
	England <sup>153</sup>	1999–2003	0.21	
	Korea <sup>6</sup>	2005	0.10	
	US <sup>1</sup> (CBTRUS)	2006–2010	0.27	0.26–0.28
Anaplastic oligodendroglioma <i>ICD-O-3 morphology codes 9451, 9460</i>	England <sup>153</sup>	1999–2003	0.09	
	Korea <sup>6</sup>	2005	0.06	
	US <sup>1</sup> (CBTRUS)	2006–2010	0.11	0.10–0.11
Oligoastrocytoma <i>ICD-O-3 morphology code 9382</i>	Austria <sup>9</sup> (ABTR)	2005	0.27	0.19–0.39
	England <sup>153</sup>	1999–2003	0.10	
	Korea <sup>6</sup>	2005	0.03	
	US <sup>1</sup> (CBTRUS)	2006–2010	0.20	0.20–0.21
Astrocytic tumors <i>ICD-O-3 morphology codes 9380–9382, 9384, 9400–9442</i>	Austria <sup>9 b</sup> (ABTR)	2005	5.33	4.93–5.75
	England <sup>153</sup>	1999–2003	3.48	
	Europe <sup>5</sup> (RARECARE)	1995–2002	4.80	
Oligodendroglial tumors	Austria <sup>9 c</sup> (ABTR)	2005	0.70	0.55–0.86
	Europe <sup>5 d</sup> (RARECARE)	1995–2002	0.40	
All glioma <sup>e</sup> <i>ICD-O-3 morphology codes 9380–9480</i>	Finland <sup>11</sup>	2000–2002	4.67	4.20–5.20
	Greece <sup>12</sup>	2005–2007	5.73	

Abbreviations: ABTR, Austrian Brain Tumor Registry; CBTRUS, Central Brain Tumor Registry of the United States; RARECARE, Surveillance of Rare Cancer in Europe (EU).

<sup>a</sup>Rate in person-years.

<sup>b</sup>ICD-O-3 morphology codes 9381,9384, 9400–9401 9410–9411, 9420–9421, 9424–9425, and 9440–9442.

<sup>c</sup>ICD-O-3 morphology codes 9382 and 9450–9451.

<sup>d</sup>ICD-O-3 morphology codes 9450–9451.

<sup>e</sup>Ependymomas (ICD-O-3 morphology codes 9383, 9391–9394) are included in this calculation.

generally shown the incidence of glioma overall and glioma subtypes to be fairly stable over the time periods assessed.<sup>3,7,14,15</sup> An examination of the annual age-adjusted incidence in Nordic countries between 1979 and 2008 found no clear trend in glioma incidence rates during this period, though there was a slight increase in brain tumor incidence rates overall.<sup>7</sup> In an analysis of data from 12 Surveillance, Epidemiology, and End Results cancer registries between 1997 and 2008, no significant trend in incidence rates of all gliomas was found overall, although a slight decrease in incidence of low-grade glioma was observed.<sup>7,15</sup> An analysis of Israeli brain tumor incidence found a significantly decreasing trend in incidence rates of low-grade gliomas (ICD-O-3 morphology codes 9380–9480, WHO grade II) between 1980 and 2009.<sup>3</sup>

### Survival After Diagnosis With Glioma

The most conclusive prognostic factors for glioblastoma are extent of tumor resection, age at diagnosis, and Karnofsky performance status.<sup>16,17</sup> Survival also varies significantly by grade across all glioma subtypes. Many groups that track the incidence of glioma also track the proportion of persons who survive set periods of time after their diagnoses. Five-year relative survival proportions for glioma by histology from population-based studies are presented in Table 2 (see Supplementary Table 2 for 1-y and 10-y relative survival proportions). Pilocytic astrocytoma (grade I) has the highest relative survival.<sup>1,18</sup> Glioblastoma has the poorest overall survival, with only 0.05% to 4.7% of patients surviving 5 years past diagnosis. In general, gliomas with an oligodendroglial component have increased survival, as opposed to those with an astrocytic component.<sup>1,5,18–20</sup> Age is significantly associated with survival after diagnosis for all glioma, but the effect is most pronounced for glioblastoma.<sup>1</sup> Recently, it was shown in population-based parallel cohorts of diffuse low-grade gliomas that early surgical resection was associated with better overall survival than were biopsy and watchful waiting.<sup>21</sup>

The 22981/26981 trial by the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada demonstrated a survival benefit for glioblastoma patients who received concurrent temozolomide with postoperative radiation, with median survival of 14.6 months for those receiving concurrent therapy versus 12.1 months for those who received radiotherapy alone.<sup>22</sup> This treatment regimen, known colloquially as the Stupp protocol, was the result of this trial and was first presented in 2004. In the years since this trial was completed, it has been established as the standard of care for primary glioblastoma.<sup>23</sup> For various reasons—including tolerance of chemotherapy, access to chemotherapeutic agents, and overall performance status—not all persons with glioblastoma receive this regimen. This result was then confirmed in a large study of glioblastoma patients,<sup>17</sup> and several analyses found statistically significant trends in increasing survival for glioblastoma after this development, especially in those who received surgery followed by radiation.<sup>24–26</sup> There has been an increasing trend in survival from oligodendroglioma, which is also attributed to improvements in diagnosis and treatment.<sup>14</sup>

### Biomarkers and Molecular Pathology

Current WHO brain tumor classification relies on traditional methods using morphology to classify diffuse gliomas into histologic

categories and later to assign a grade based on presence of mitoses, vascular endothelial proliferation, and necrosis. Although this method provides considerable information regarding outcome, significant variation exists within given grades and histologies. Recent advances in molecular diagnostic techniques provide alternative methods for tumor classification using molecular abnormalities and signaling pathways involved in gliomagenesis. These molecular subtypes have distinct prognoses and treatment responses.<sup>27–31</sup> While there is significant correlation between traditional pathologic groupings and newer molecular subtypes, overlap is incomplete.

Glioblastoma was the first cancer to be systematically studied by The Cancer Genome Atlas Research Network, which revealed recurrent alterations in 3 core pathways: (i) retinoblastoma (*RB*) signaling (cyclin-dependent kinase inhibitor 2A/2C [*CDKN2A/CDKN2C*] deletion, *RB* mutation, cluster of differentiation 4/6 [*CD4/CD6*] amplification), (ii) tumor protein 53 (*TP53*) signaling (*CDKN2A* deletion, *TP53* mutation, mouse double minute 1/4 [*MDM1/MDM4*] amplification), and (iii) receptor tyrosine kinase signaling (phosphatase and tensin homolog/neurofibromin 1/phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [*PTEN/NF1/PIK3CA*] mutation, epidermal growth factor receptor/platelet derived growth factor receptor [*EGFR/PDGFR*] amplification).<sup>32</sup> Subsequent studies showed that glioblastomas can be subclassified according to gene expression profiles.<sup>29</sup> The majority of glioblastomas are categorized in the classical subtype, possessing hallmark *EGFR* alterations and focal homozygous deletion of *CDKN2A*. The mesenchymal subtype displays some similarity to classical glioblastomas but with frequent focal hemizygous deletions of *NF1*. The neural subtype is the most poorly defined, and there is evidence that the neural expression pattern may be partly attributable to contamination of non-malignant tissue.<sup>27</sup> The proneural subtype showed distinct amplification and mutation of *PDGFRA* and point mutations in isocitrate dehydrogenase 1/2 (*IDH1/IDH2*).<sup>27</sup> In fact, the most recent glioblastoma publication from The Cancer Genome Atlas showed that the only subgroup with improved survival was proneural tumors with *IDH1* mutations and hypermethylation across the genome.<sup>27</sup>

Concomitant loss of chromosomes 1p and 19q is one of the best studied molecular alterations in gliomas and is strongly associated with oligodendroglial morphology and improved survival.<sup>33</sup> In fact, the vast majority of these tumors with 1p/19q codeletion have *IDH* mutations and frequently carry gene mutations in the far upstream element binding protein 1 (*FUBP1*—on chromosome 1p) and capicua transcriptional repressor (*CIC*—on chromosome 19q).<sup>31,34,35</sup> These tumors rarely possess *EGFR* amplifications common to primary glioblastomas and also lack *TP53* and alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) mutations, which are common in secondary glioblastomas and lower-grade astrocytomas.<sup>31,36,37</sup>

Other established markers of favorable prognosis are mutations in *IDH1* and *IDH2*, present in 70%–80% of lower-grade gliomas and secondary glioblastomas and only a small proportion of primary glioblastomas (~5%–10%).<sup>38–40</sup> Subsequent studies have found a strong link between *IDH* mutations and a genome-wide glioma cytosine-phosphate-guanine island methylator phenotype (G-CIMP) across all glioma subtypes.<sup>30,41</sup> G-CIMP is more prevalent among lower-grade gliomas, is strongly associated with proneural glioblastomas, and has better patient

**Table 2.** Five-year relative survival by histologic type and country/region (all ages)

Histologic Type	Region (organization)	Years	5 y		
			Rate	95% CI	
Pilocytic astrocytoma <i>ICD-O-3 morphology code 9421</i>	US <sup>1</sup> (CBTRUS)	1995–2010	94.4	93.4–95.2	
	UK & Ireland <sup>18</sup> (EUROCARE)	1995–2002	80.6	68.4–88.6	
	Northern Europe <sup>18</sup> (EUROCARE)	1995–2002	81.9	68.4–90.3	
	Central Europe <sup>18</sup> (EUROCARE)	1995–2002	79.7	62.6–89.9	
	Eastern Europe <sup>18</sup> (EUROCARE)	1995–2002	57.3	33.5–75.8	
	Southern Europe <sup>18</sup> (EUROCARE)	1995–2002	97.3	74.7–100.0	
Astrocytoma, NOS <i>ICD-O-3 morphology codes 9440, 9410, 9420</i>	US <sup>1</sup>	1995–2010	47.3	45.8–48.7	
	Korea <sup>20</sup>	1994–2004	51.6		
	UK & Ireland <sup>18</sup> (EUROCARE)	1995–2002	39.0	34.7–43.3	
	Northern Europe <sup>18</sup> (EUROCARE)	1995–2002	49.4	42.7–55.8	
	Central Europe <sup>18</sup> (EUROCARE)	1995–2002	35.4	29.9–40.9	
	Eastern Europe <sup>18</sup> (EUROCARE)	1995–2002	28.0	22.5–33.8	
	Southern Europe <sup>18</sup> (EUROCARE)	1995–2002	42.6	33.9–51.1	
Anaplastic astrocytoma <i>ICD-O-3 morphology code 9401</i>	US <sup>1</sup>	1995–2010	26.5	24.8–28.2	
	Korea <sup>20</sup>	1994–2004	25.2		
	UK & Ireland <sup>18</sup> (EUROCARE)	1995–2002	17.6	13.5–22.2	
	Northern Europe <sup>18</sup> (EUROCARE)	1995–2002	10.8	7.8–14.4	
	Central Europe <sup>18</sup> (EUROCARE)	1995–2002	28.8	19.3–39.0	
	Eastern Europe <sup>18</sup> (EUROCARE)	1995–2002	11.7	7.1–17.4	
	Southern Europe <sup>18</sup> (EUROCARE)	1995–2002	18.1	11.8–25.4	
Glioblastoma <i>ICD-O-3 morphology codes 9440–9442</i>	US <sup>1</sup>	1995–2010	4.7	4.4–5.0	
	Korea <sup>20</sup>	1994–2004	8.9		
	US <sup>154</sup>	1997–2000	0.1		
	UK & Ireland <sup>18</sup> (EUROCARE)	1995–2002	2.2	1.6–2.9	
	Northern Europe <sup>18</sup> (EUROCARE)	1995–2002	1.9	1.2–2.9	
	Central Europe <sup>18</sup> (EUROCARE)	1995–2002	4.4	3.2–5.9	
	Eastern Europe <sup>18</sup> (EUROCARE)	1995–2002	2.2	1.0–4.4	
	Southern Europe <sup>18</sup> (EUROCARE)	1995–2002	2.8	1.8–4.3	
	Oligodendroglioma <i>ICD-O-3 morphology code 9450</i>	US <sup>1</sup> (CBTRUS)	1995–2010	79.1	77.4–80.7
		Korea <sup>20</sup>	1994–2004	73.5	
UK & Ireland <sup>18</sup> (EUROCARE)		1995–2002	65.8	57.5–73.0	
Northern Europe <sup>18</sup> (EUROCARE)		1995–2002	74.1	64.4–81.8	
Central Europe <sup>18</sup> (EUROCARE)		1995–2002	75.5	61.8–85.2	
Eastern Europe <sup>18</sup> (EUROCARE)		1995–2002	47.8	32.4–62.0	
Southern Europe <sup>18</sup> (EUROCARE)		1995–2002	63.8	51.4–74.1	
Anaplastic oligodendroglioma <i>ICD-O-3 morphology codes 9451, 9460</i>		US <sup>1</sup> (CBTRUS)	1995–2010	50.7	47.5–53.8
	Korea <sup>20</sup>	1994–2004	50.4		
	UK & Ireland <sup>18</sup> (EUROCARE)	1995–2002	35.5	24.4–46.9	
	Northern Europe <sup>18</sup> (EUROCARE)	1995–2002	35.1	21.2–49.5	
	Central Europe <sup>18</sup> (EUROCARE)	1995–2002	29.7	13.4–48.3	
	Eastern Europe <sup>18</sup> (EUROCARE)	1995–2002	6.1	1.3–16.6	
	Southern Europe <sup>18</sup> (EUROCARE)	1995–2002	33.3	14.7–53.6	
	Oligoastrocytoma <i>ICD-O-3 morphology code 9382</i>	US <sup>1</sup> (CBTRUS)	1995–2010	61.0	58.3–63.6
England & Wales <sup>19</sup>		1971–1995	39.0		
Astrocytic tumors <i>ICD-O-3 morphology codes 9380–9382, 9384, 9400–9442</i> <i>and site codes C71, C72.0, C72.8–C72.9</i>		England & Wales <sup>19</sup>	1971–1995	10.0	
		Europe <sup>5</sup> (RARECARE)	1995–2002	15.0	
		England & Wales <sup>19</sup>	1971–1995	39.6	
Oligodendroglial tumors <i>ICD-O-3 morphology codes 9450–9451, 9460</i> <i>and site codes C71, C72.0, C72.8–C72.9</i>	Europe <sup>5</sup> (RARECARE)	1995–2002	55.0		

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; EUROCARE, European Cancer Registry Based Study on Survival and Care of Cancer Patients; NOS, not otherwise specified; RARECARE, Surveillance of Rare Cancer in Europe (EU).

outcomes.<sup>30,41,42</sup> Methylation of the O<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) gene promoter is a positive prognostic factor for glioblastomas, especially in the setting of chemotherapy with alkylating agents (eg, temozolomide).<sup>43–45</sup> The impact of *MGMT* methylation on survival in patients with WHO grades II–III gliomas is less clear.<sup>46,47</sup> The significant overlap among 1p/19q codeletion, *IDH* mutation, G-CIMP phenotype, and *MGMT* methylation complicates assessment of the independent prognostic role of these alterations.

Recent studies indicate that gliomas can additionally be classified based on their telomere maintenance mechanisms.<sup>31,37,48</sup> Point mutations in the telomerase reverse transcriptase (*TERT*) gene promoter, leading to increased telomerase activity, are found in ~75% of oligodendrogliomas and primary glioblastomas.<sup>48,49</sup> Gliomas that do not carry *TERT* promoter mutations frequently harbor mutations of the telomere binding protein *ATRX*, activating the pathway of alternative lengthening of telomeres (*ALT*). Nearly 75% of WHO grades II–III astrocytomas and secondary glioblastomas activate this telomerase-independent telomere maintenance pathway.<sup>31,50</sup>

### Constitutive Genetic Risk Factors

A heritable genetic contribution to gliomagenesis was initially suggested by the increased incidence of these tumors in families with Mendelian cancer syndromes (see Table 3). Linkage studies conducted within families containing multiple affected members have had little success identifying high-penetrance glioma risk variants.<sup>51,52</sup> Although numerous familial cancer syndromes are associated with increased glioma risk, monogenic Mendelian disorders account for only a small proportion of adult glioma incidence at the population level.<sup>53</sup> Segregation analyses have found that a polygenic model best explains the incidence pattern of adult gliomas.<sup>54</sup> Results from genome-wide association

studies (GWASs) have supported this conclusion by identifying common genetic variation in 7 genes that increase glioma risk.<sup>53</sup>

The role of common heritable variants in conferring glioma risk has been investigated in case-control studies since the early 1990s. These early studies were candidate-gene analyses, assaying a limited set of genetic polymorphisms located in genes/pathways believed to be relevant to gliomagenesis (eg, DNA repair,<sup>55</sup> nonhomologous end-joining,<sup>56</sup> folate metabolism<sup>57</sup>). Robustly replicated glioma risk loci have not emerged from these candidate studies, and inconsistent associations are the norm. A recent study evaluating 60 previously reported glioma risk loci from 28 publications successfully replicated only those variants first identified by GWASs, despite the replication sample size being larger than that of each candidate-gene study.<sup>58</sup>

Five GWASs of glioma patients have been conducted to date, resulting in the identification of 8 independently significant germline DNA single nucleotide polymorphism (SNP) associations located in 7 genes (see Table 4).<sup>59–63</sup> Variants in 4 of the genes associated with glioma risk (*TERT*, regulator of telomere elongation helicase 1 [*RTEL1*], *EGFR*, and *TP53*) appear to contribute to development of all glioma grades and histologies, including oligodendroglial tumors.<sup>58,64</sup> Variants in the remaining 3 genes (*CDKN2B*; pleckstrin homology-like domain, family B, member 1 [*PHLDB1*]; and coiled-coil domain containing 26 [*CCDC26*]) contribute only to the development of specific grades, histologies, and molecular subtypes.<sup>58,64,65</sup> The first 2 GWASs of glioma detected genome-wide significant associations at *TERT*, *RTEL1*, and *CDKN2B*.<sup>59,60</sup> One study included only patients with high-grade tumors, primarily glioblastomas.<sup>59</sup> The other included patients with gliomas of all grades and histologies.<sup>60</sup> Only the latter study detected association signals within an intron of *CCDC26* (rs4295627 on 8q24.21) and *PHLDB1* (rs498872 on 11q23.3). These results suggest that the *CCDC26* and *PHLDB1* associations are driven by their effect on low-grade glioma risk. In the analysis by Shete et al.<sup>60</sup> rs4295627

**Table 3.** Monogenic Mendelian disorders associated with increased risk of glioma<sup>53</sup>

Gene (chromosome location)	Disorder/Syndrome	Mode of Inheritance	Phenotypic Features	Associated Gliomas
<i>NF1</i> (17q11.2)	Neurofibromatosis 1	Dominant	Neurofibromas, schwannomas, café-au-lait macules	Astrocytoma, optic nerve glioma
<i>NF2</i> (22q12.2)	Neurofibromatosis 2	Dominant	Acoustic neuromas, meningiomas, neurofibromas, eye lesions	Ependymoma
<i>TSC1,TSC2</i> (9q34.14,16p13.3)	Tuberous sclerosis	Dominant	Development of multisystem nonmalignant tumors	Giant cell astrocytoma
<i>MSH2,MLH1, MSH6,PMS2</i>	Lynch syndrome	Dominant	Predisposition to gastrointestinal, endometrial, and other cancers	Glioblastoma, other gliomas
<i>TP53</i> (17p13.1)	Li–Fraumeni syndrome	Dominant	Predisposition to numerous cancers, especially breast, brain, and soft-tissue sarcoma	Glioblastoma, other gliomas
<i>p16/CDKN2A</i> (9p21.3)	Melanoma-neural system tumor syndrome	Dominant	Predisposition to malignant melanoma and malignant brain tumors	Glioma
<i>IDH1/IDH2</i> (2q33.3/15q26.1)	Ollier disease/Maffucci syndrome	Acquired postzygotic mosaicism; dominant with reduced penetrance	Development of intraosseous benign cartilaginous tumors, cancer predisposition	Glioma

Abbreviations: *MLH1*, mutL homolog 1; *MSH2/MSH6*, mutS homolog 2/6; *NF1/NF2*, neurofibromin 1/2; *PMS2*, postmeiotic segregation increased 2; *TSC1/TSC2*, tuberous sclerosis 1/2.

**Table 4.** Heritable variants associated with glioma risk from GWASs

Candidate Gene (chromosome location)	Gene Function	SNP-Risk Allele	Odds Ratio	Risk Allele Frequency (controls)	Associated Glioma Subtype	Studies Detected (y)	Other Associations
<i>TERT</i> (5p15.33)	Maintains telomere ends	rs2736100-C	1.35	0.50	All glioma subtypes	Shete et al. (2009), <sup>60</sup> Wrensch et al. (2009), <sup>59</sup> Chen et al. (2011), <sup>71</sup> Sanson et al. (2011), <sup>61</sup> Rajaraman et al. (2012) <sup>63</sup>	Increases risk of cancer at other sites, including lung, testis, pancreas, and colon <sup>72</sup>
<i>EGFR</i> (7p11.2)	Produces transmembrane receptor	rs2252586-A	1.20	0.28	All glioma subtypes	Jenkins et al. (2011), <sup>64</sup> Sanson et al. (2011), <sup>61</sup> Rajaraman et al. (2012), <sup>63</sup> Walsh et al. (2013) <sup>58</sup>	
<i>EGFR</i> (7p11.2)	Produces transmembrane receptor	rs11979158-A	1.25	0.83	All glioma subtypes	Jenkins et al. (2011), <sup>64</sup> Sanson et al. (2011), <sup>61</sup> Rajaraman et al. (2012), <sup>63</sup> Walsh et al. (2013) <sup>58</sup>	
<i>CCDC26</i> (8q24.21)	Modulates cell differentiation and death	rs55705857-G	5.00	0.05	Oligodendroglial tumors/IDH-mutant astrocytic tumors	Shete et al. (2009), <sup>60</sup> Jenkins et al. (2011), <sup>64</sup> Jenkins et al. (2012), <sup>66</sup> Rajaraman et al. (2012), <sup>63</sup> Enciso-Mora et al. (2013) <sup>67</sup>	
<i>CDKN2B</i> (9p21.3)	Encodes cyclin-dependent kinase inhibitor	rs1412829-G	1.35	0.41	Astrocytic tumors, WHO grades II–IV	Shete et al. (2009), <sup>60</sup> Wrensch et al. (2009), <sup>59</sup> Rajaraman et al. (2012) <sup>63</sup>	
<i>PHLDB1</i> (11q23.3)	Produces protein	rs498872-A	1.50	0.32	IDH-mutant gliomas	Shete et al. (2009), <sup>60</sup> Rajaraman et al. (2012), <sup>63</sup> Rice et al. (2013) <sup>68</sup>	
<i>TP53</i> (17p13.1)	Encodes tumor suppressor protein	rs78378222-C	2.70	0.01	All glioma subtypes	Rice et al. (2011), <sup>62</sup> Egan et al. (2012), <sup>70</sup> Enciso-Mora et al. (2013) <sup>69</sup>	Increases risk of several Li–Fraumeni tumors, including basal cell carcinoma, prostate cancer, glioblastoma, and colorectal adenoma <sup>62</sup>
<i>RTEL1</i> (20q13.33)	Maintains stability and elongation of telomeres	rs6010620-A	1.40	0.75	All glioma subtypes	Shete et al. (2009), <sup>60</sup> Wrensch et al. (2009), <sup>59</sup> Chen et al. (2011), <sup>71</sup> Rajaraman et al. (2012) <sup>63</sup>	

Abbreviations: SNP, Single Nucleotide Polymorphism; RAF, Risk Allele Frequency; TERT, Telomerase Reverse Transcriptase; EGFR, Epidermal Growth Factor Receptor; CCDC26, Coiled-Coil Domain Containing 26; CDKN2B, Cyclin-Dependent Kinase Inhibitor 2B; PHLDB1, Pleckstrin Homology-Like Domain, Family B, Member 1; TP53, Tumor Protein P53; RTEL1, Regulator of Telomere Elongation Helicase.

in *CCDC26* was the most strongly associated locus in terms of both odds ratio and *P*-value, indicating that the magnitude of this subtype-specific association had to be much larger than the glioma associations at *TERT*, *RTEL1*, or *CDKN2B*.

A follow-up study clarified this issue by revealing that rs4295627 in *CCDC26* is associated with WHO grades II–III astrocytomas, but not glioblastoma. Furthermore, the risk allele was strongly associated with oligodendroglial tumors regardless of tumor grade, with the strongest effect observed for 1p/19q codeleted oligodendrogliomas and mixed oligoastrocytomas.<sup>64</sup> Subsequently, DNA samples from individuals with oligodendroglial tumors were pooled and subjected to long-range deep sequencing. The most strongly associated SNP in these fine-mapping analyses was rs55705857 in *CCDC26*, which had a minor allele frequency <5% in control subjects and conferred a 5-fold increased risk for development of *IDH*-mutated astrocytic tumors (independent of grade) and oligodendroglial tumors (independent of *IDH* mutation status).<sup>66</sup> Although the prevalence of glioma is lower than that of breast cancer, the relative risk associated with rs55705857 is comparable in magnitude to that observed for *BRCA1* (breast cancer 1) mutations and breast cancer risk. The rs55705857 association has since been replicated in an independent set.<sup>67</sup>

Similar to the discovery of an association between *CCDC26* SNPs and glioma risk, the association between *PHLDB1* variation (rs498872) and glioma risk is limited to *IDH*-mutated gliomas, regardless of tumor grade or histology.<sup>68</sup> The rs498872-A allele is associated with increased risk of *IDH*-mutated glioma, but not with any *IDH* wild-type glioma.

The association with the SNP rs78378222 located in the 3' untranslated region of *TP53*<sup>62</sup> has been validated for oligodendroglioma and mixed oligoastrocytoma histologies.<sup>69,70</sup> This risk allele is relatively rare (~1% in European-ancestry controls). It confers a 3-fold increased risk for glioma, and unlike other known glioma risk loci, its functional contribution to gliomagenesis has been resolved. The risk allele of rs78378222 changes the polyadenylation signal of *TP53*, leading to impaired 3'-end processing of *TP53* mRNA.<sup>62</sup> Because inherited *TP53* mutations cause Li-Fraumeni syndrome, and somatic *TP53* mutation is frequently observed in gliomas, a direct impact of the rs78378222 variant on gliomagenesis seems probable.

Significant glioma-risk SNPs have been identified in 2 telomerase-related genes, *TERT* and *RTEL1*, among both European-ancestry and East Asian populations.<sup>71</sup> The inherited *TERT* SNP most strongly associated with glioma risk, rs2736100, is located in the first intron of the gene.<sup>59–61</sup> This risk allele is associated with astrocytic and oligodendroglial tumors, regardless of grade or *IDH* mutation status, and has been associated with increased risk for cancer at other sites.<sup>72</sup> The strongest glioma-risk SNP in *RTEL1*, rs6010620, is associated with all glioma grades and histologies, though it is not associated with other cancer types. The glioma-risk alleles in *TERT* and *RTEL1* are associated with significantly older ages at diagnosis among patients with glioma,<sup>73</sup> supporting the hypothesis that telomerase-based mechanisms of gliomagenesis are distinct pathways with characteristic differences in clinical presentation.

### Epidemiologic Risk Factors

Many risk factors have been examined as potential contributors to glioma risk. Most significantly, these include a decrease in risk by

history of allergies or atopic disease(s) and an increase in risk by exposure to ionizing radiation. The potential influence of nonionizing radiation (eg, cellular phones) and occupational exposures has also been examined, with inconclusive results. A summary and update are provided below for each of these factors.

### Allergies

Epidemiologic studies of large and diverse groups of cases and controls<sup>74–81</sup> consistently suggest that allergic conditions, including asthma, hay fever, eczema, and food allergies, reduce glioma risk. See Table 5 for an overview of recent studies examining the relationship between allergic conditions and glioma risk. Results from a meta-analysis<sup>82</sup> reveal that allergies reduce glioma risk by nearly 40%. However, findings pertaining to associations between allergy duration and timing and glioma risk are inconsistent. One analysis found that glioma risk decreases with increasing number of allergy types (eg, seasonal, medication, pet, food), age at allergy diagnosis, and increased time since allergy diagnosis.<sup>76</sup> Other studies have found that the decrease in glioma risk provided by these conditions was strengthened by current or recent diagnosis.<sup>79,81</sup> The relation between allergy and glioma risk may not be consistent across histologic types of glioma. A pooled assessment of 7 case-control studies suggests that oligodendroglioma and anaplastic oligodendroglioma risks were significantly reduced among participants with a history of asthma alone or in combination with a history of allergies, but not as a result of a history of allergies alone.<sup>83</sup>

Recent epidemiologic results concerning the potential role of antihistamine use and glioma are also inconsistent.<sup>76,77,84,85</sup> While numerous analyses have demonstrated an increase in glioma risk with antihistamine use, some have found this effect only in those with previous history of allergy or asthma diagnosis.<sup>77,84</sup> Expanded analyses show that regular use of antihistamines increased glioma risk for only WHO grade III tumors, regardless of asthma or allergy history.<sup>85</sup> Results from another analysis<sup>76</sup> suggest an inverse association between antihistamine use and high-grade glioma risk (WHO grades III–IV), but only among those with no medically diagnosed allergy.

Five studies have shown that glioma patients have lower levels of a biomarker of allergy, immunoglobulin E (IgE).<sup>80,86–89</sup> While the use of prediagnostic serum IgE levels addresses the problem of differential recall among those reporting histories of allergy, IgE levels may be influenced by the preclinical tumor.<sup>80</sup> However, SNPs are clearly not affected by a developing tumor. Investigators therefore evaluated germline SNPs that play a role in IgE production or allergy (eg, interleukin 13 [*IL13*], *IL4*, and *IL4* receptor-alpha [*IL4Ra*]) to determine whether they were associated with glioma risk.<sup>86,89–93</sup> Results of these studies of *IL13*<sup>86,90,94</sup> and *IL4Ra*<sup>86,91–93</sup> SNPs are conflicting. In a meta-analysis that included 7 case-control studies, Sun et al.<sup>94</sup> found that rs20541 [*IL13*] but not rs1801275 [*IL-4Ra*]<sup>94</sup> may be a genetic indicator of glioma risk.

There is also mixed evidence for interaction between known glioma risk SNPs and self-reported history of allergy. In a recent validation study of 60 SNPs previously associated with glioma risk or from selected candidate-gene studies,<sup>59–62</sup> none was associated with allergy-related genes.<sup>58</sup> A large case-control study found evidence for modification of the association between asthma history and glioma risk by rs498872 (*PHLDB1*) genotype (greater protection from asthma with increasing number of risk

**Table 5.** A summary of selected recent (2002–2013) case-control and cohort studies exploring environmental exposures and risk of glioma

Study (y)	Population	Tumor Type	Exposure Type	Ratio [Measure] (95% CI)
<i>Allergies, Atopic Disease, and Antihistamine Use</i>				
Linos et al. (2007) <sup>82</sup>	53 223 persons (3450 cases) (meta-analysis) [Sweden, US, Australia, Canada, France, Germany]	Glioma	History of atopic disease (ie, asthma, eczema, hay fever, or allergy)	0.61 [OR] (0.55–0.67)
Wigertz et al. (2007) <sup>81</sup>	1527 cases and 3309 frequency-matched population-based controls [Denmark, Norway, Finland, Sweden, UK]	Glioma	Physician diagnosis of any of asthma, hay fever, eczema, or other type of allergy	0.70 [OR] (0.61–0.80)
Scheurer et al. (2008) <sup>77</sup>	325 cases and 600 frequency-matched controls [US]	Glioma	Antihistamine use (>10 y)	3.5 [OR] (1.56–8.14)
Schoemaker et al. (2010) <sup>155</sup>	1863 cases and 4073 frequency-matched population-based controls [Denmark, Sweden, Finland, UK]	Glioma	History of asthma diagnosis and RA of rs498872 (PHLDB1)	0 RA: 1.33 [OR] (0.77–1.67) 1 RA: 0.56 [OR] (0.36–0.86) 2 RA: 0.67 [OR] (0.28–1.60)
			History of any allergy and RA of rs4977756 (CDKN2B)	0 RA: 0.57 [OR] (0.42–0.78) 1 RA: 0.62 [OR] (0.49–0.80) 2 RA: 0.94 [OR] (0.66–1.34)
			History of any allergy and RA of rs6010620 (RTEL1)	0 RA: 1.05 [OR] (0.48–2.33) 1 RA: 0.83 [OR] (0.61–1.14) 2 RA: 0.56 [OR] (0.45–1.69)
Schlehofer et al. (2011) <sup>88</sup>	Prediagnosis samples from 275 cases and 963 controls (nested within cohort study) [Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK]	Glioma	IgE concentration of at least 0.35 kilo	0.73 [OR] (0.51–1.06)
Calboli et al. (2011) <sup>87</sup>	Prospective samples from 169 cases and 520 controls [US]	Glioma	Borderline elevated total IgE levels (25–100 kU/L)	0.63 [OR] (0.42–0.93)
			elevated IgE (>100 kU/L)	0.98 [OR] (0.61–1.56)
Lachance et al. (2011) <sup>95</sup>	855 cases and 1160 controls [US]	WHO grades III and IV glioma	History of allergies	0.62 [OR] (0.51–0.76)
			History of allergy and RA of rs4295627 (CCDC26)	0 RA: 0.61 [OR] (0.48–0.79) >0 RA: 0.64 [OR] (0.45–0.90)
			History of allergy and RA of rs4977756 (CDKN2B)	0 RA: 0.40 [OR] (0.28–0.58) >0 RA: 0.76 [OR] (0.59–0.97)
			History of allergy and RA of rs4809324 (RTEL1)	0 RA: 0.68 [OR] (0.54–0.86) >0 RA: 0.44 [OR] (0.29–0.68)
McCarthy et al. (2011) <sup>76</sup>	419 cases and 612 hospital-based controls [US]	Glioma	Reported allergy	LGG: 0.44 [OR] (0.25–0.76) HGG: 0.66 [OR] (0.49–0.87)
			Ever use of antihistamine	LGG: 0.78 [OR] (0.46–1.33) HGG: 0.75 [OR] (0.57–0.99)
McCarthy et al. (2011) <sup>83</sup>	Pooled 7 case-control studies, 617 total cases (329 O, 146 AO, 142 OA) and 1260 controls [US, Denmark, Sweden]	Oligodendroglioma	History of allergies and/or asthma	AO: 0.6 [OR] (0.4–0.9)
			History of asthma	O: 0.5 [OR] (0.3–0.9) AO: 0.3 [OR] (0.1–0.9)

Continued



Table 5. Continued

Study (y)	Population	Tumor Type	Exposure Type	Ratio [Measure] (95% CI)
Scheurer et al. (2011) <sup>85</sup>	534 controls and 1339 cases [US]	Glioma	History of allergy/asthma	GBM: 0.46 [OR] (0.36–0.58) Grade III: 0.43 [OR] (0.30–0.62) Grade II: 0.68 [OR] (0.46–0.99)
			Antihistamine use (>10 y) (no history of allergies/asthma)	GBM: 0.51 [OR] (0.16–1.59) Grade III: 2.94 [OR] (1.04–8.34) Grade II: 1.30 [OR] (0.27–6.14)
			Antihistamine use (>10 y) (history of allergies/asthma)	GBM: 1.24 [OR] (0.76–2.01) Grade III: 2.34 [OR] (1.20–4.57) Grade II: 1.33 [OR] (0.63–2.79)
Schwartzbaum et al. (2012) <sup>89</sup>	Samples collected prior to diagnosis within a larger cohort [Sweden]	Glioma	Prediagnostic total IgE level of at least 100 kUA/L Total IgE level of at least 100 kUA/L >20 y prediagnosis	0.75 [OR] (0.56–0.99) 0.54 [OR] (0.30–0.99)
Amirian et al. (2013) <sup>84</sup>	362 cases and 462 controls [US]	Glioma	Antihistamine use and positive allergy/asthma history	4.19 [OR] (2.06–8.51)
<i>Ionizing Radiation</i>				
Sadetzki et al. (2005) <sup>102</sup>	10 834 individuals who were treated for tinea capitis with X rays with matched population and sibling controls [Israel]	Malignant brain tumors	Mean estimated radiation dose to the brain of 1.5 Gy	1.98 [ERR/Gy] (0.73–4.6)
Neglia et al. (2006) <sup>104</sup>	14 361 childhood cancer survivors [US]	Glioma	Therapeutic radiation	0.33 [ERR] (0.07–1.71)
Preston et al. (2007) <sup>103</sup>	Atomic bomb survivors with nervous system tumors diagnosed between 1985 and 1995 [Japan]	Glioma	Atomic bomb	0.56 [ERR] (-0.2–2.0)
Taylor et al. (2010) <sup>105</sup>	17 980 childhood cancer survivors [UK]	Glioma	Therapeutic radiation	0.08 [ERR/Gy] (0.07–1.17) 10.8 [SIR] (8.5–13.6)
Davis et al. (2011) <sup>106</sup>	205 cases and 333 matched friend controls [US]	Glioma	≥3 CT scans	1.97 [OR] (0.92–4.23)
Pearce et al. (2012) <sup>109</sup>	175 000 children [UK]	Glioma	CT scans	0.019 [ERR/mGy] (0.00–0.07)
Mathews et al. (2013) <sup>110</sup>	680 000 people exposed to CT scans in childhood or adolescence [Australia]	All malignant brain tumors	CT scans	1.75 [IRR] (1.35–2.25)
<i>Cellular Phones</i>				
Frei et al. (2011) <sup>113</sup>	3.21 million persons >30 y old born after 1925 (358 403 subscribers before 1995; 3664 cases) [Denmark]	Glioma	>10 y of subscription	Men: 1.0 [RR] (0.8–1.3) Women: 1.0 [RR] (0.6–2.0)
Benson et al. (2013) <sup>114</sup>	791 710 women aged 50–64 y [UK]	Glioma	>10 y of use ≥daily use	0.8 [RR] 0.5–1.1 0.8 [RR] (0.6–1.1)
Hardell et al. (2013) <sup>115</sup>	593 cases diagnosed 2007–2009, and 1368 controls [Sweden]	All malignant brain tumors	Any use of mobile phone >2376 h call time	1.6 [OR] (1.0–2.7) 2.8 [OR] (1.6–4.8)
<i>Occupational Chemical Exposure</i>				
Carreon et al. (2005) <sup>156</sup>	341 female cases and 528 controls [US]	Glioma	Exposure to carbamate herbicides	3.0 [OR] (0.9–9.5)
Provost et al. (2007) <sup>151</sup>	105 cases and 210 individually matched controls [France]	Glioma	Any exposure to pesticides Fourth quartile of pesticide exposure	1.74 [OR] (0.81–2.66) 3.21 [OR] (1.13–9.11)

Samanic et al. (2008) <sup>147</sup>	261 male cases and 350 hospital-based controls [US]	Glioma	Exposure to insecticides	1.0 [OR] (0.7–1.5)
Yiin et al. (2012) <sup>157</sup>	798 cases and 1175 population-based controls [US]	Glioma	Exposure to pesticides	0.9 [OR] (0.6–1.3)
Ruder et al. (2013) <sup>152</sup>	798 cases and 1175 population-based controls [US]	Glioma	Farm use of phenoxy pesticide	0.96 [OR] (0.93–0.99)
Navas-Acién et al. (2002) <sup>139</sup>	All men gainfully employed in 1970 were followed 19 y (1971–1989) [Sweden]	Glioma	Any nonfarm pesticide use	0.72 [OR] (0.52–0.99)
			Any home pesticide use	0.79 [OR] (0.66–0.93)
			Exposure to any chlorinated solvent	0.86 [OR] (0.68–1.08)
			Possible/probable exposure to lead and >0.20 $\mu$ T of workday exposure to ELF	3.91 [RR] (1.26–12.15)
			Possible/probable exposure to solvents and >0.20 $\mu$ T of workday exposure to ELF	1.55 [RR] (1.14–2.12)
Röösli et al. (2007) <sup>122</sup>	20 141 railway workers [Switzerland]	All brain cancer deaths	Cumulative exposure (per 10 $\mu$ T-y)	0.94 (HR) (0.88–1.01)
Coble et al. (2009) <sup>130</sup>	489 cases and 799 controls [US]	Glioma	Cumulative exposure >45 milligauss-y average ELF $\geq$ 3.0 mG (men with glioblastoma only)	0.8 [OR] (0.5–1.2) 1.7 [OR] (0.9–3.2)
Baldi et al. (2011) <sup>131</sup>	105 cases and 442 controls [France]	Glioma	Ever occupational ELF	1.20 [OR] (0.66–2.17)
Koeman et al. (2014) <sup>129</sup>	120 852 men and women aged 55–69 y in 1986 [Netherlands]	Astrocytic glioma	Ever high occupational ELF exposure (men)	0.77 [HR] (0.34–1.71)
Turner et al. (2014) <sup>138</sup>	2054 glioma cases and 5601 controls	Glioma	Cumulative exposure >90th percentile, 1–4 y time window	1.85 [OR] (1.50–2.28)

Abbreviations: AO, anaplastic oligodendroglioma (WHO grade III); ERR, excess relative risk; GBM, glioblastoma multiforme; HGG, high-grade glioma (grade III or IV); HR, hazard ratio; IRR, incidence rate ratio; LGG, low-grade glioma (grade I or II); O, oligodendroglioma (grade II); OA, oligoastrocytoma (mixed glioma); OR, odds ratio; RA, risk allele; RR, relative risk; SIR, Standard Incidence Ratio.

alleles) and the effect of any allergy by rs4977756 (*CDKN2B*) and rs6010620 (*RTEL1*) genotypes (lesser and greater protective effects, respectively). These results were supported by the results of a case-control study that found that the inverse relationship between allergy history and glioma risk was stronger among those without the 9p21.3 risk allele (allele G, rs4977756 [*CDKN2B*]).<sup>95</sup> A recent study found an interaction between a reported history of allergy and the presence of *Varicella zoster* antibodies in blood samples collected prior to diagnosis.<sup>96</sup> This study again suggests the importance of immune function in gliomagenesis and/or tumor progression.

To further evaluate the role of allergy and inflammation-related genes, a case-control study compared 911 immune function genes in germline DNA from 2 large independent studies (1056 glioblastoma cases and 2384 controls).<sup>97</sup> The authors found an association in both datasets with *CD25*, a gene on the surface of immune suppressive regulatory T cells that are expressed at lower-than-average levels in people with allergy and may be involved in immune suppression that characterizes glioblastoma development and progression. Pathway correlation analysis was also conducted on the large independent case-control studies described above, which found evidence for the role of cytokine signaling pathway in gliomagenesis ( $P = .003$ ). Cytokines are immune-regulatory proteins involved in both allergy and glioma development and progression.<sup>98</sup>

Moving from germline DNA to the mRNA transcriptome, an analysis studied expression of 919 allergy and inflammation-related genes and their association with an indicator of tumor aggressiveness (*CD133* expression) in 142 glioblastoma tissue samples.<sup>99</sup> They found that 69% of these genes were negatively correlated with *CD133* expression ( $r = -0.40$ ). That is, the more aggressive the tumor, the lower the expression of the majority of allergy- and inflammation-related genes. At the same time evidence supported that tumor-associated macrophages—alternatively activated immune cells that constitute ~30% of tumor cells and are involved in the development of tumor microenvironment—enhance tumor development.<sup>100</sup>

### ***Ionizing Radiation***

An association with high-dose ionizing radiation and all brain tumors has been observed in A-bomb studies, nuclear-test fallout data, therapeutic radiation for cancer and benign conditions, and occupational and environmental studies.<sup>101</sup> Information is somewhat limited at the level of the specific histologic type of tumor, as shown in Table 5, particularly for low to moderate dose settings.

That different parts of the brain may vary in their radiosensitivity was established in studies of the Israeli tinea capitis cohort (with mean dose of 1.5 Gy and 40 years of follow-up), where a doubling of risk was observed for gliomas and higher risks were apparent for meningiomas and acoustic neuromas. Follow-up of this cohort demonstrated a linear dose-response association for all primary malignant tumors.<sup>102</sup>

Data from the atomic bomb survivors replicated glioma-specific risks consistent with a linear dose response at moderate doses.<sup>103</sup> Two studies of cancer survivors who had received relatively high dose radiation treatments for a primary cancer had increased odds of gliomas.<sup>104,105</sup>

The dose levels associated with CT scans are in this range of concern (the range of effective doses from a single CT scan is

estimated to be between 2 and 15 mSv). While the individual risk of developing iatrogenic cancer from a single diagnostic procedure is extremely small, the cumulative effects of these exposures are being evaluated, given that 30% of patients undergo repeat CT scans, sometimes in the same doctor visit.

Epidemiology studies of diagnostic radiation exposures have provided inconsistent results with respect to overall brain tumor risk.<sup>106</sup> Two case-control studies of adults have demonstrated increased risks specific to gliomas,<sup>106,107</sup> most recently after 3 or more cumulative CT scan exposures to the head only in cases with a family history of cancer.<sup>106</sup> In contrast, dramatic increases in per capita effective doses in the last 2 decades are of concern, as medical radiation now makes up half of the per capita radiation exposure. A consensus of radiation experts has concluded that the lowest acute dose of X or gamma radiation for which there is good evidence of increased cancer risks is ~10–50 mSv.<sup>108</sup>

Two recent cohort studies of children experiencing CT scans in Britain<sup>109</sup> and Australia<sup>110</sup> have suggested increases in cancer, including brain cancer, in young adults after childhood exposures to CT scans (maximum follow-up time ~20 y for both studies). While almost 60% of the CT scans were of the brain, and the elevated risks observed for other solid tumor sites appeared to be dose dependent, these data were not consistent with an increasing risk per unit dose for tumors of the brain. As such, the data relating to brain tumors and specifically to gliomas from diagnostic exposures to CT scans are emerging but inconclusive at this time.

It is curious that an association between high-dose ionizing radiation and brain tumors for identified forms and doses of exposure is considered established in the brain tumor epidemiology literature,<sup>101</sup> and yet this conclusion is not generally accepted in the radiation science literature. This may stem from several factors: the long-held belief that the brain is a highly differentiated organ with low mitotic activity, making it radioresistant<sup>111</sup>; the potential for biases in the case-control evidence available on these rare tumors; the limited number of cohort studies providing experience across a range of exposure doses; or the lack of quantitative histology-specific risk estimates for brain tumors. While the evidence for an association between exposures to high levels of ionizing radiation and all brain tumors is persuasive, the site-specific data for glioma need clarification and quantification.

### ***Nonionizing Radiation: Cellular Phones***

Cellular phone technology was introduced in the 1980s but became popular in the mid-1990s worldwide, and currently the vast majority of people use cellular phones. The brain is the organ that absorbs the most radiofrequency fields when the cellular phone is held to the head. Due to public health concerns that cell phone use could be a possible emerging risk factor, the association between risk of development of glioma and cellular phone use has been investigated extensively. 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), based mainly on epidemiologic findings of an increased risk of glioma and vestibular schwannoma in heavy cellular phone users.<sup>112</sup>

Recently 6 epidemiologic studies reporting on glioma risk in relation to cellular phone use in adults have been published: 3

incidence time trends studies, 2 large cohorts (Danish and UK), and 1 case-control study (see Table 5 for results of cohort and case-control studies). Analyses of time trends of age-standardized incidence rates of glioma in high-quality registration data are an important tool to examine the possible association of cellular phone use and glioma risk. Cellular phone use has reached over 100 subscriptions per 100 inhabitants since 2005 in the Nordic countries, and the increase in prevalence of cellular phone use has been extremely rapid worldwide. If the rates remain stable, this sets minimum latency periods and upper boundaries on the magnitude of risk compatible with these observations. The incidence rates of glioma were stable in Denmark, Finland, Norway, and Sweden<sup>7</sup> among the 40–59 age group, with annual percent change (APC) in rates of 0.1% (95% CI: –0.2% to –0.3%) in men and 0.0% (95% CI: –0.2% to –0.2%) in women over the period 1979–2008,<sup>7</sup> and in the USA with APC of 0.0% (95% CI: –0.3% to –0.3%) over the period 1992–2008.<sup>15</sup> No sudden increases were noted through 2008 in these countries<sup>7,15</sup> and through 2009 in Israel.<sup>3</sup> While they supported the absence of an association, the Nordic and American studies also showed that glioma incidence time trends were not compatible with the magnitude of risks reported in case-control studies by Hardell and colleagues.<sup>115</sup> These descriptive epidemiologic studies were informative for periods of up to 15 years after start of use but were limited in their ability to draw conclusions for very small segments of the users.

The Danish cohort of early private subscribers of cellular phones is a record-linkage study on the entire Danish population older than 30, with follow-up for cancer incidence until 2007.<sup>113</sup> All individuals who subscribed to private cellular phone service in their names, irrespective of occupational or private use, between the introduction of cellular phones and 1995 were traced and their dates of subscription obtained from records. Glioma risk in relation to duration of subscription was then examined. The UK Million Women study was a prospective cohort study in which risk in relation to duration and level of cellular phone use was examined.<sup>114</sup> Glioma risk was the same among those with >10 years of cellular phone use as in the comparison group in both cohorts, and the risk of glioma was not significantly lower for daily users of cellular phones compared with never-users in the UK study.<sup>116</sup> A case-control study conducted by Hardell and colleagues<sup>115</sup> found that odds ratios were markedly elevated in all categories of use. The publication of the study, however, reported risks incompatible with the incidence time trends, lacked methodological detail, and had no validation of the self-reported questionnaire data against cellular phone subscription records.

The evidence published since the IARC monograph in 2011 does not support an association between cellular phone use and the risk of glioma in adults. However, if an association exists—given that its latency period is unknown and the information on long-term heavy users of cellular phones is limited—this association between exposure and disease deserves continued monitoring.

### **Nonionizing Radiation: Extremely Low Frequency Magnetic Fields**

A possible association between occupational exposure to extremely low frequency magnetic fields (ELFs) and brain tumors/gliomas has been examined over several decades (see Table 5

for an overview of recent studies). There are studies of specific occupational groups, comparing rates of incident or fatal gliomas with those in the general population,<sup>117–119</sup> as well as occupational cohort studies with measured and/or modeled ELF exposure estimates, or ELF estimated through job exposure matrices (JEMs).<sup>120–122</sup> General population studies based on self-reported ELF, or ELF estimated through expert assessment, specific measurements, JEMs, or some combination thereof have also been performed.<sup>123–126</sup>

Previous studies were typically limited by small study sizes, a lack of occupational history data, and the inability to consider separate histologic subtypes of brain tumors. Although some positive associations have been observed, the IARC in 2002 concluded that the evidence was inadequate to classify ELF as a carcinogen for brain tumors.<sup>127</sup> A meta-analysis reported a significant positive association between occupational ELF and brain tumors overall among 48 previous studies published from 1993 to 2007. However, findings were limited, as there was no exposure–response relationship.<sup>128</sup> Results from more recent studies of glioma have been mixed.

Rööslä et al.<sup>122</sup> followed 20 141 Swiss railway workers for 30 years and found no differences in risk of brain tumors with levels of cumulative ELF. Koeman et al.<sup>129</sup> in the Netherlands Cohort Study, found no clear association between ever-occupational ELF exposure, duration of exposure, or cumulative exposure and brain cancer risk overall.

Coble et al.<sup>130</sup> examined the association between occupational ELF—as estimated using a JEM and specific job modules to gather more detailed information on electrical occupations—and glioma risk in a US hospital-based case-control study. No association was observed between indicators of maximum exposed job, duration, lifetime average, or cumulative exposure for either glioma or glioblastoma overall, although there was a positive association observed between average ELF  $\geq 3.0$  mG and glioblastoma in men.<sup>130</sup> There was no clear association observed between occupational ELF exposure and glioma risk in a population-based case-control study in Gironde, France.<sup>131</sup>

Although little is known about potential biological mechanisms through which ELF may play a role in risk of glioma development, it is thought that it would likely act in cancer promotion/progression.<sup>127,132,133</sup> Results from previous studies that examined ELF in different time windows of exposure were mixed; however, some observed stronger positive associations with ELF exposure.<sup>120,123,126,134–137</sup> Most recently, findings from the large-scale INTEROCC study, including 2054 glioma cases and 5601 controls, revealed no association with lifetime cumulative occupational ELF exposure, but positive associations were described within the most recent exposure time window, 1–4 years prior to the date of diagnosis/reference date (Table 5).<sup>138</sup> ELF exposure may also act as a cocarcinogen with other exposures, hence further investigation may be warranted.<sup>139</sup>

### **Occupational Chemical Exposures**

Possible associations between occupational titles and/or exposures and brain tumors have been studied for years, with inconsistent findings (see Table 5 for an overview of recent studies). Previous studies have inconsistently observed an increased risk of glioma in the following occupations: physician, firefighter, chemical and other industrial workers,<sup>140</sup> and military

personnel.<sup>141,142</sup> However, in contrast to previous studies,<sup>58,142–144</sup> there was no association between farming and glioma risk in the Upper Midwest Health Study (UMHS) conducted between 1995 and 1998.<sup>145</sup> The difference in findings might be explained by differences in the study populations: UMHS included nonurban controls with farming as their longest job, whereas De Roos's study<sup>143</sup> included only controls with at least 5 years of farm experience. In both the UMHS and a Canadian study, being an engineer, an architect, or a surveyor was associated with an increased risk of glioma.<sup>145,146</sup> The Canadian study found an increased risk of glioma among teachers,<sup>146</sup> whereas UMHS did not observe such an association.<sup>145</sup>

In 2001, a case-control study in Iowa observed a significantly increased risk of glioma for women associated with employment in the agricultural and apparel/textile industries, electrical and electronic equipment, department stores, and other retail industries. Employment as a salesperson, record clerk, waitress, or farmer was also associated with a significantly increased glioma risk.<sup>142</sup> In contrast, a decreased risk of glioma was reported among forestry workers, fishermen, and seamen in a study including 5 Nordic countries.<sup>141</sup>

Researchers have also examined the association between occupational exposures and risk of glioma. In the UMHS, study researchers developed, a priori, a list of 21 exposures of interest identified from the literature. These exposures ranged from pesticides (farmers, pesticide applicators) to lead (gas station attendants, plumbers) to polychlorinated biphenyls (electrical workers, construction workers) to *N*-nitroso compounds (rubber manufacturing workers). Of these 21 exposures, 2 (exposure to raw meat and possible exposure to nonionizing radiation) were associated with an elevated risk of glioma.<sup>145</sup> In both the UMHS and De Roos' study, an elevated risk of glioma was observed for butchers and meat cutters.<sup>143,145</sup>

### Pesticides

The UMHS included 228 cases and 417 controls who reported applying farm pesticides. There was no positive association observed between cumulative years of use of any farm pesticide (insecticide, herbicide, or fungicide) and risk of glioma.<sup>64</sup> Although use of phenoxy pesticides was associated with a decreased risk of glioma, the association disappeared after excluding proxy respondents. The lack of association between glioma risk and pesticide use was also observed in other studies in the US and Europe<sup>139,147–149</sup>; 2 French studies,<sup>150,151</sup> however, reported a positive association between risk of glioma and pesticide use.

### Solvents

More recently, analyses of the UMHS observed decreased glioma risk associated with exposure to chlorinated solvents, including cumulative exposure (parts per million/y)<sup>152</sup> both overall and for women only. However, a high number of proxy respondents and possible poor recall among cases could have influenced these results. The authors also investigated possible gene-environment interactions through blood samples genotyped for glutathione-S-transferases P1, M3, and T1 (*GSTP1*, *GSTM3*, and *GSTT1*). Subjects with functional GST genes who had been exposed to solvents were not at increased risk of glioma, suggesting that exposure to neither chlorinated solvents nor the cytotoxic

metabolites of chlorinated solvents is a major risk factor for glioma.<sup>152</sup>

### The Future of the Epidemiology of Gliomas

Significant progress has been made in identifying potential risk factors for gliomas, including several heritable genetic factors, allergic/atopic disease, and ionizing radiation exposures. Numerous other exposures have been studied with inconsistent results. The significant progress in understanding glioma heterogeneity afforded by modern "omic" technologies and accumulating data is revealing a relatively small number of etiologically similar glioma subtypes that can be characterized by tumor biomarkers. This should greatly enhance the ability to discover risk factors for these subtypes that have been obscured due to glioma etiologic heterogeneity. These omic approaches have also revealed biomarkers important for prognosis and treatment response. Allergy and atopic conditions have been shown to mediate glioma risk, and the specific roles of immune function genes in gliomagenesis and/or tumor progression warrant further investigation. Numerous other exposures are continuing to be examined, including cell phone occupational exposures and ELF. Continued analysis of multicenter studies, as well as other fully clinically annotated datasets of omic data, will potentially lead to further understanding of the interactions of genes and environment in the development of glioma.

### Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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