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Epidemiology of Glioma

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1. Introduction

Gliomas constitute a broad class of neuroectodermal tumours believed to originate from sustentacular neuroglial cells (Kleihues and Cavenee 2000). Astrocytomas form the largest group of gliomas (>75%) and glioblastoma multiforme (GBM) is the most common type of astrocytoma (CBTRUS 2011). Gliomas that share histologic characteristics with ependymal or oligodendrocyte cells are named ependymomas and oligodendrogliomas, but may not necessarily originate from the aforementioned cell types (Kleihues and Cavenee 2000). Mixed gliomas include those which consist of more than one glia cell type. For example, oligodendroglial glioblastoma multiforme (as defined by some neuropathologists) are GBM tumours with an oligodendroglioma component and generally have a significantly worse clinical outcome than GBM tumours overall (Louis et al 2007). Another mixed glioma is oligoastrocytoma, which contains both oligodendrocyte and astrocyte cells.

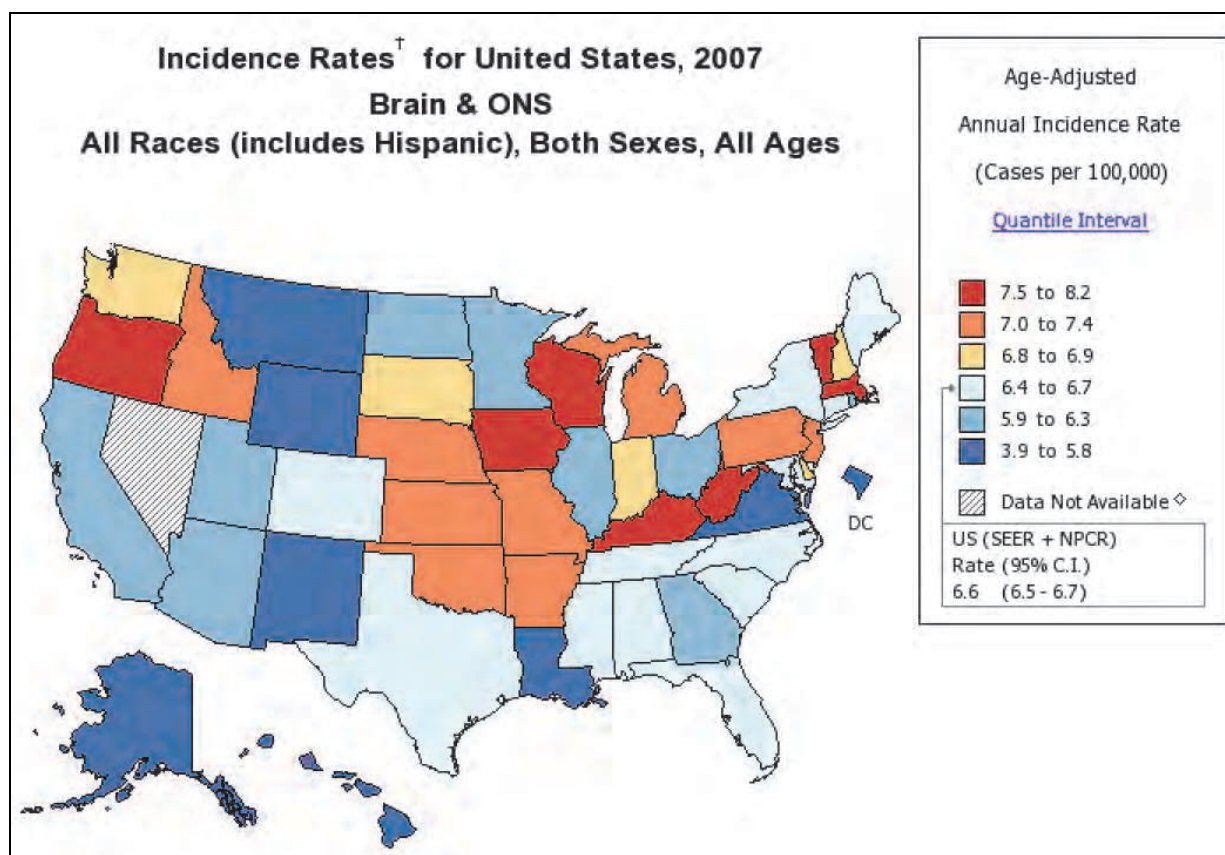
The Third Edition of the International Classification of Diseases for oncology (ICD-O-3) is widely used to categorize gliomas by histology (e.g., malignant glioma=9380, ependymoma NOS=9391, astrocytoma=9430, glioblastoma NOS=9440, oligodendroglioma NOS=9450) (Fritz et al 2000). Furthermore, tumours are grouped by site in the ICD-O-3 system using C-codes (e.g., cerebrum=C71.0, frontal lobe=C71.1, temporal lobe=C71.2, parietal lobe=C71.3, occipital lobe=C71.4, ventricle=C71.5, cerebellum=C71.6, spinal cord=C72.0). The World Health Organization (WHO) also has developed a classification index which grades gliomas by disease prognosis (I=best to IV=worst) (Kleihues et al 1993). Recent additions to the “WHO Classification of Tumours” include Grade I - angiocentric gliomas (predominantly occurring in children and young adults in the fronto-parietal cortex, temporal lobe, and hippocampal region), and Grade II - pilomyxoid astrocytoma (typically occurring in infants and children in the hypothalamic/chiasmatic region) (Louis et al 2007). Additionally, WHO has recognized a divergent pattern of gliomas named small cell glioblastoma characterized by EGFR amplification, p16INK4a homozygous deletion, PTEN mutations, and LOH 10q (Louis et al 2007).

2. Incidence and death rates

Gliomas comprise more than 80% of brain tumours (CBTRUS 2011), therefore, descriptive epidemiology about gliomas often is framed in the broader context of brain tumours as a whole.

2.1 Incidence

Overall, brain tumors are relatively rare events. Only 1 in 165 men and women will be diagnosed with cancer of the brain and other nervous system tumours in their lifetime (Altekruse et al 2010). The incidence rate (IR) per 100,000 person-years (100KP-Y) for malignant adult brain tumours ranges from 5.4 (95%CI =4.7-6.1) for the state of Hawaii to 12 (95%CI=12-13) for Wisconsin. IRs by state among children 0-19 years are less variable, ranging from 2 to 4. While geographic differences in IRs might suggest an environmental etiology for brain tumours, ecologic comparisons often do not account for variations in quality of reporting, diagnostic practices, and access/utilization to health care. States falling into the highest quantile for both age-adjusted incidence and death rates (DR) per 100KP-Y include Kentucky (IR=7.9, 95%CI=7.0-8.7; DR=4.9, 95%CI=4.3-5.6), Iowa (IR=7.6, 95%CI=6.7-8.6; DR=5.4, 95%CI=4.6-6.2), and Oregon (IR=7.5, 95%CI=6.7-8.4; DR=5.2, 95%CI=4.5-5.9) (Figures 1 and 2) (NCI State Cancer Profiles 2011). A noticeable cluster of states (depicted in red) with the highest death rates is located along the northern portion of the U.S. from Oregon to Iowa (Figure 2).

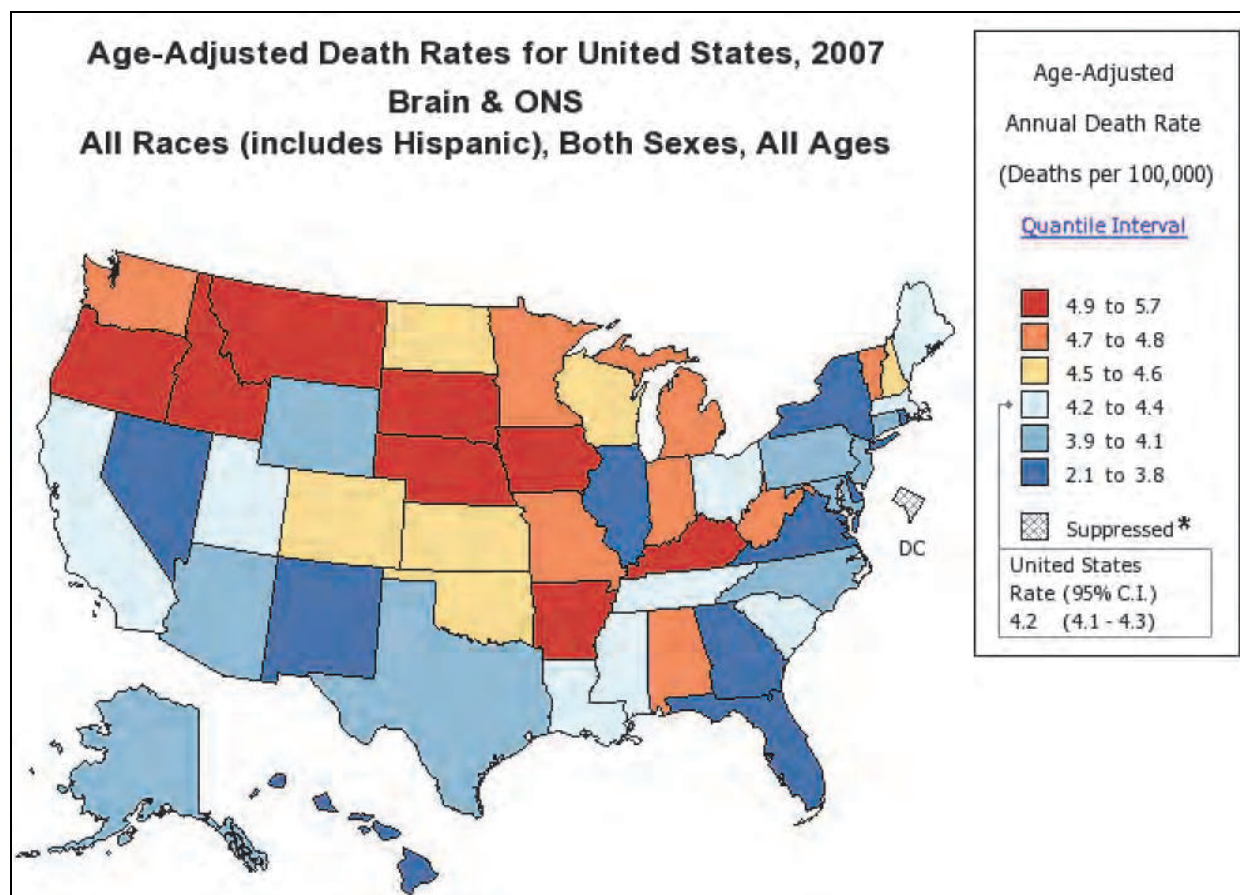


†Age-adjusted (2000 U.S. standard population) cases per 100,000 population per year.
 ◇Data not available for Nevada.

Fig. 1. Incidence rates (NCI State Cancer Profiles 2011).

Gliomas IRs vary by histology, race, and sex. **Histology.** For example, the age-adjusted rate per 100KP-Y for glioblastoma is 3.19 (95% CI=3.16-3.23) compared with less than 0.2 for anaplastic oligodendroglioma (IR=0.12, 95%CI=0.11-0.13) and protoplasmic/fibrillary astrocytoma (IR=0.11, 95%CI=0.10-0.11) (CBTRUS 2011). **Race.** Whites consistently have

higher IR rates than blacks by histologic group (e.g., IR=3.55, 95%CI=3.52-3.59 vs. 1.64, 95%CI=1.57-1.72 for glioblastoma; IR=0.47, 95%CI=0.45-0.48 vs. 0.19, 95%CI=0.17-0.22 for anaplastic astrocytoma; IR=0.29, 95%CI=0.27-0.30 vs. 0.17, 95%CI=0.15-0.19 for ependymoma/anaplastic ependymoma) (CBTRUS 2011). **Sex.** Similarly, men consistently have higher age-adjusted IRs than women by histology (e.g., IR=3.99, 95%CI=3.94-4.04 vs. IR=2.53, 95%CI=2.49-2.57 for glioblastoma; IR=0.48, 95%CI=0.46-0.50 vs. 0.35, 95%CI=0.33-0.36 for anaplastic astrocytoma; and IR=0.27, 95%CI=0.26-0.29 vs. IR=0.25, 95%CI=0.24-0.27 for ependymoma/anaplastic ependymoma), although the latter difference is not statistically significant (CBTRUS 2011). Interestingly, the female prevalence rate (PR) for primary brain tumours per 100KP-Y (PR=264.8) is higher than males (PR=158.7), perhaps attributable to survival bias among women (Porter et al 2010).



*Counts suppressed since fewer than 16 cases reported in specific area-sex-race category.

Fig. 2. Death rates (NCI State Cancer Profiles 2011).

A higher male (IR=37) to female (IR=2.6) pattern also is observed internationally (Parkin et al 2005), although U.S. rates are higher in both men (IR=7.7, 95%CI=7.5-7.8) and women (IR=5.6., 95%CI=5.5-5.7) compared with international rates (NCI State Cancer Profiles 2011). Less developed countries tend to report lower rates (e.g., Africa, Pacific Islands; IR=3.0 per 100KP-Y for males and 2.1 for females) than more developed countries (e.g., Australia, New Zealand, Europe, North America; IR=5.8 per 100KP-Y for men and 4.1 for females), possibly reflecting less access to modern medical facilities (Parkin et al 2005, CBTRUS 2011). In contrast, the standardized (age, sex, site, year at diagnosis) IR for brain tumours in Japan, a

country well known for accessible MR-imaging, is relatively low (2.5 per 100KP-Y person-years) (Matsuda et al 2011). Similarly low rates have been observed in Korea (Lee et al 2010).

2.2 Death rates and survival

The annual number of brain tumour deaths at last count (2007) in the U.S. was $n=7,315$ for men and 5,919 for women. Age-adjusted rates steadily increased from 1975 to 1991, likely due to advances in neuroimaging, but have decreased linearly thereafter, with recent values on par with 1975 rates (Figure 3) (NCI State Cancer Profiles 2011). Overall DRs are higher among men (DR=5.1, 95%CI=5.0-5.2) than women (DR=3.5, 95%CI=3.4-3.6), however the difference is not statistically significant as was seen for IRs. The lowest DR for men and women combined was observed for the State of Hawaii (DR=2.1, 95%CI=1.4-3.0), which implemented almost complete universal health care coverage in 1994 under the Med-QUEST programme (Hawaii Department of Human Services 2011). However, Hawaii also has the largest non Caucasian population of any state (i.e., 72.8% Asian/Pacific Islander), a factor associated with lower brain tumour incidence and death rates (NCI State Cancer Profiles 2011).

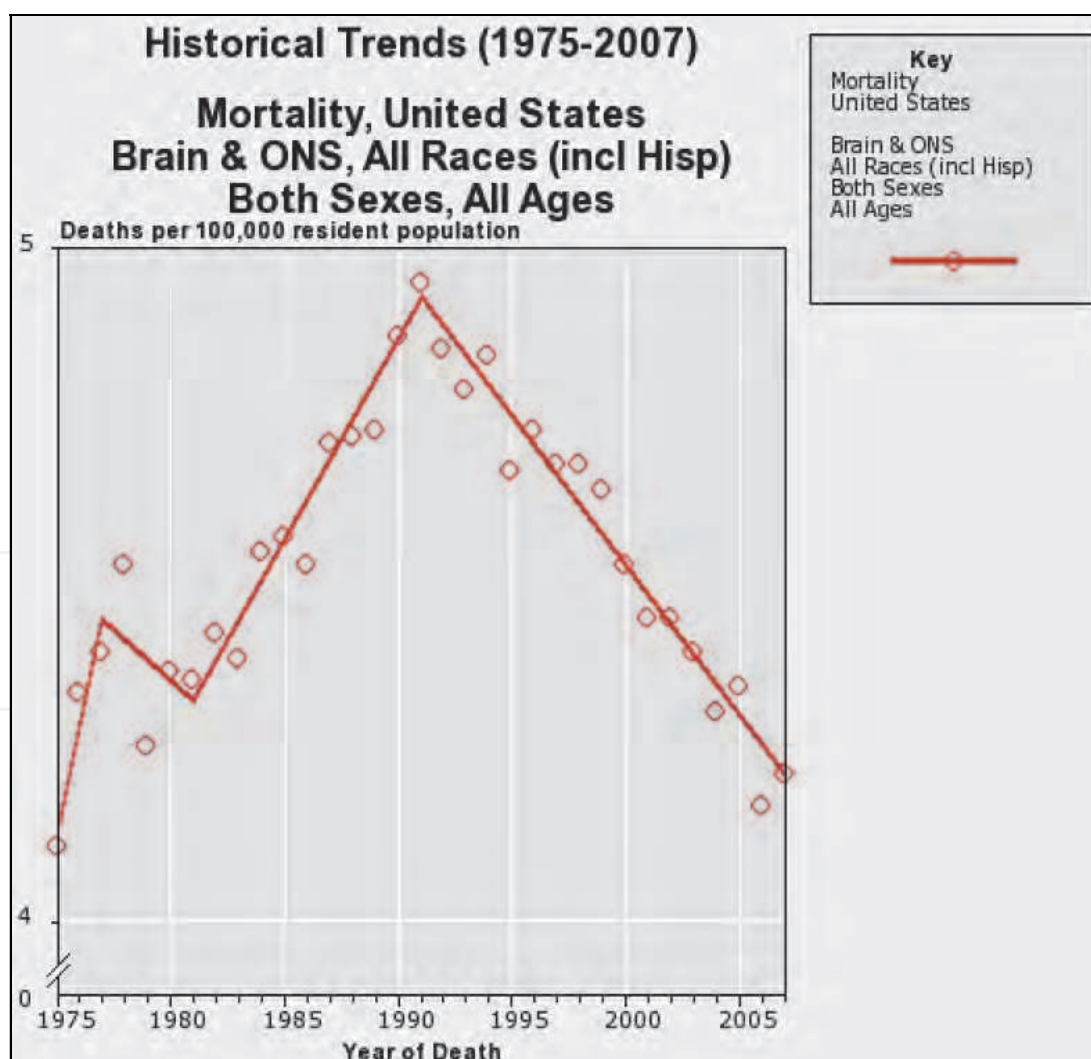


Fig. 3. Mortality trends (NCI State Cancer Profiles 2011).

Survival rates for the majority of malignant gliomas remain disappointingly low, despite decades of advances in surgical, radiation, and chemical therapies, in contrast to improvements in many other cancers. GBMs, for example, typically present as highly aggressive, difficult to treat tumours without clinical, radiologic, or morphologic forewarning of a less virulent precursor tumour (Kanu et al 2009; Ostrom and Barnholtz-Sloan 2011). Secondary GBMs account for only about 10% of all GBMs, based on the presence of IDH1/2 mutations (Ohgaki and Kleihues 2011). The infiltrating nature of these tumours makes treatment difficult. Other obstacles to effective treatment and improved survival include multi-drug resistance, radioresistance, an impermeable blood-brain barrier, a lack of preclinical models, and a rudimentary understanding of neurooncogenetics (Kanu et al 2009).

The relative survival percentages (RSP) for gliomas compared with the general U.S. population vary tremendously by histology and age at diagnosis. For example, the majority of patients diagnosed between age 0-14 years with pilocytic astrocytoma (RSP=97.3%), oligodendroglioma (RSP=95.3), protoplasmic & fibrillary astrocytoma (RSP=84.3%), and mixed glioma (RSP=75.6%) will live beyond 5 years, compared with anaplastic astrocytoma (RSP=32.0%) and glioblastoma (RSP=20.9%) (CBTRUS 2011). In contrast, 5-year relative RSPs are considerably lower across histologic types for those diagnosed between age 45-54 (e.g., RSP=82.4% for pilocytic astrocytoma; RSP=76.8% for oligodendroglioma; RSP=51.1% for mixed glioma; RSP=39.5% for protoplasmic & fibrillary astrocytoma; RSP=28.6% for anaplastic astrocytoma; and RSP=5.6% for glioblastoma). Only 0.8% of patients diagnosed between age 55-64 will be alive after 10 years.

5-Year Relative Survival (whites) by Year of Diagnosis

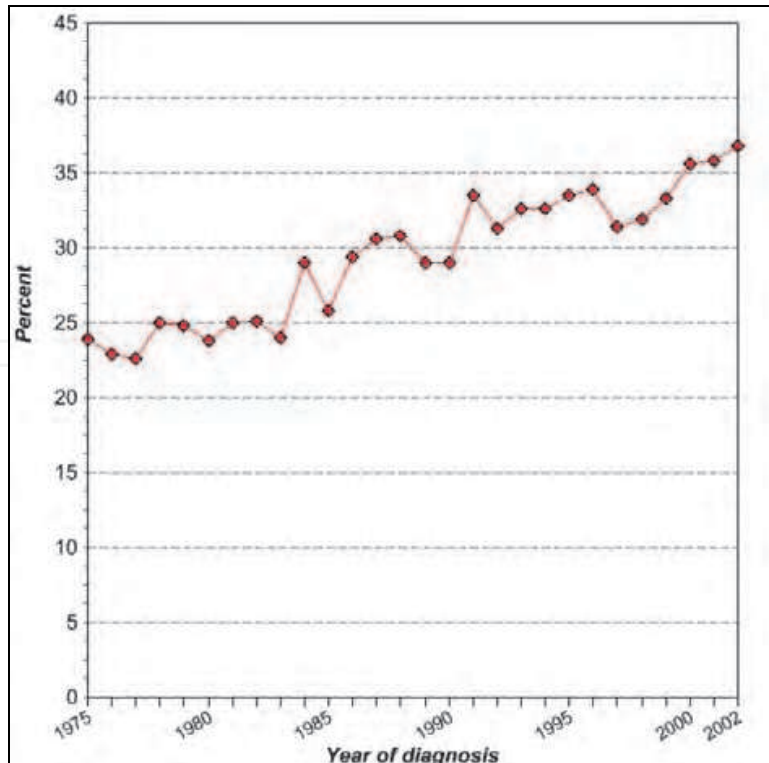


Fig. 4. Survival percent (whites) for cancers of the brain and other nervous system tumours (NCI-SEER 2011).

RSPs also vary by race and sex. Black women (44%) have the highest 5-year RSPs for cancers of the brain and other nervous system tumours, when compared with white women (36.5%), black men (34.8%), and white men (32.6%) (Altekruse et al 2010). When examined by year of diagnosis from 1975 to 2002, whites (Figure 4) consistently have lower 5-year RSPs than blacks independent of sex (Figure 5) (NCI-SEER 2011).

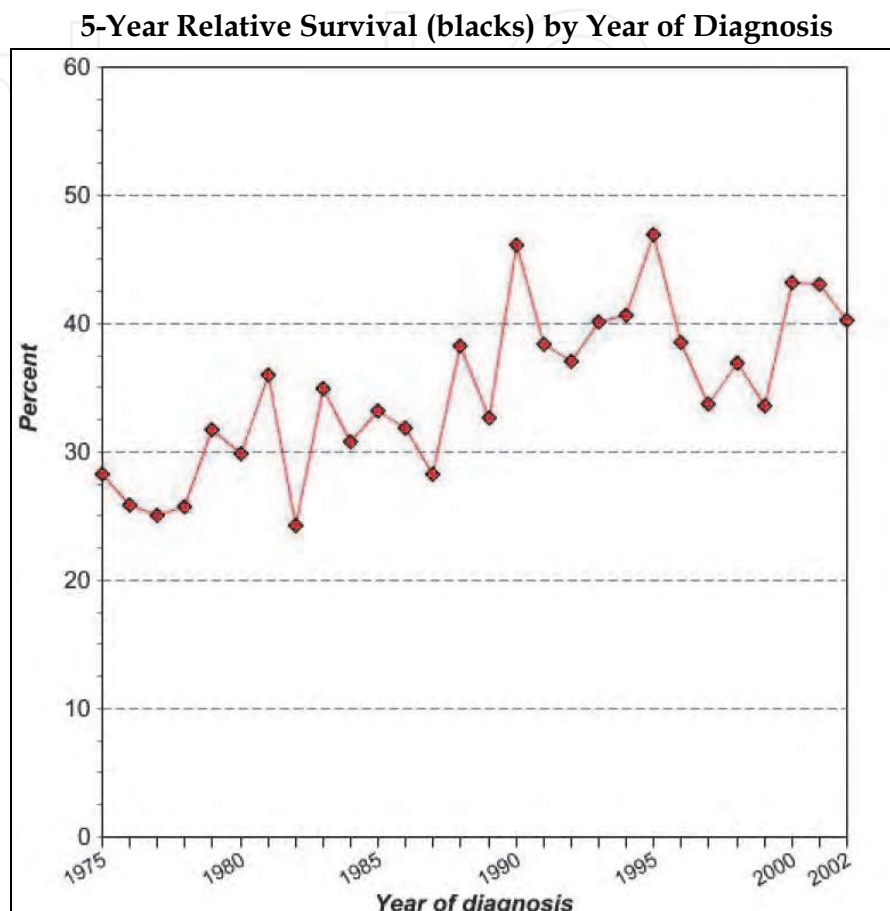


Fig. 5. Survival percent (blacks) for cancers of the brain and other nervous system tumours (NCI-SEER 2011).

Among adults, other factors associated with poorer survival include tumour site (frontal, cerebellum, multilobular), and socioeconomic status (less affluent individuals have lower survival rates) (Tseng et al 2006). The latter suggests that socioeconomic inequalities play an important role in glioma outcome, perhaps due to chronic comorbidities, inadequate access and utilization of health care, and longer wait times after surgery for adjuvant therapies (Tseng et al 2006).

While population-based relative survival statistics paint a dismal prognostic picture for certain glioma types, conditional survival rates suggest a more favorable long term outcome for patients who have already survived for a specified amount of time after diagnosis (Table 1) (Porter et al 2011). For Example, a GBM patient has a 70.4% (95%CI=55.6-81.2) relative probability of living 10 years beyond their diagnosis date if they have already survived 5 years. In comparison, the 10-year unconditional probability for GBM is less than 3% (not shown in Table).

Histologic Category	Survival upon 2 years (95%CI)	Survival upon 5 years (95%CI)
Anaplastic astrocytoma	45.4 (38.2-52.3)	73.6 (62.7-81.8)
Anaplastic oligodendroglioma	53.7 (37.8-67.2)	75.6 (51.2-89.0)
Diffuse astrocytoma	53.6 (42.9-63.2)	73.7 (59.6-83.6)
Glioblastoma multiforme	26.2 (20.6-32.1)	70.4 (55.6-81.2)
Hemangioblastoma/hemangioma	93.9 (80.5-98.2)	97.6 (69.3-99.8)
Oligodendroglioma	68.6 (63.1-73.5)	78.5 (72.5-83.3)
Pilocytic astrocytoma	95.9 (92.6-97.8)	99.2 (91.6-99.9)

Table 1. Relative probability of a patient living 10 years beyond their diagnosis date if they have already survived 2 and 5 years.

3. Risk factors

The key epidemiologic determinants of glioma risk include advancing age, male sex, and Caucasian race (Bondy and Wrensch 1996). Few environmental or lifestyle exposures, except for ionising radiation, have been found to be consistently associated with glioma risk. Suspected risk factors include lifestyle behaviors (e.g., smoking, alcohol consumption, coffee drinking), infectious agents (e.g., polyomaviruses, cytomegaloviruses, influenza, varicella zoster, *Toxoplasma gondii*), diet/vitamins (e.g., nitrosamine compounds, vitamin C, vitamin D₃), beauty products (e.g., hair dyes and lighteners, hair waving and straightening chemicals), industrial exposures (e.g., rubber manufacturing, petroleum products), mobile phones, electromagnetic fields, allergies/immunity, agricultural/farm animal exposures, handedness, birth weight/height, and various genetic polymorphisms. While the list is long, methodologic biases are believed to account for the bulk of observed associations. A comprehensive review of factors hypothesized to play a role in the etiology of brain tumors is beyond the intent of the current work and the reader is referred to several recent reviews on the topic (Ostrom and Barnholtz-Sloan 2011; Ohgaki 2009; Fisher et al 2007; Schwartzbaum et al 2006; Ohgaki and Kleihues 2005; Wrensch et al 2002). Rather, the aim of this section is to address the etiology of gliomas in the context of recent publications and current scientific debate on the topic.

3.1 Mobile phones

Mobile (cellular) phones initially appeared on the market in the late 1970's in Japan and soon thereafter were sold in Europe and the U.S. (Bellis 2011). The first commercial wireless call originating in the U.S. occurred on 13 October 1983 (Green 2008).

However, the widespread and frequent use of mobile phones on an affordable scale was not achieved until the earlier 2000's when unlimited usage service contracts became a viable

option to “pay by the minute” billing plans. By the end of 2010 there were approximately 303 million mobile phone subscribers in the U.S., representing 9 times the number in 1995 (CTIA 2011). The World Health Organization estimates 4.6 billion subscribers globally in 2010 (WHO 2011).

The main challenge of epidemiologic studies on mobile phone risk has been the lack of long term, frequent use exposure data (NRPB 2003), especially among users who may be genetically predisposed to brain tumours (Wrensch et al 2009; Shete et al 2009). Population stratification and gene-environment interactions may mask the risk of mobile phone use in insufficiently powered studies. Compounding the situation, the average latency period for many cancers is measured in decades, sometimes as long as 50-60 years, and similarly long intervals may apply to brain tumours (Challis 2007). The flat or declining brain tumour incidence trends observed in the population during the same time period of increasing mobile phone use would seem incongruent if mobile phones are a significant cause of brain tumours (Inskip et al 2010). However, competing risks could explain the effect if brain tumours are caused by more than one factor.

The majority of epidemiologic studies to date generally do not support a causative association between mobile phone use and brain tumours (Ahlbom et al 2009). However, methodologic concerns point to a cumulative underestimation of risk (Kundi 2010). Downward bias may have affected studies that excluded deceased and terminally ill patients, if mobile phone use presumably increases the case fatality rate vis-à-vis enhanced tumor progression. Pre-diagnostic effects of brain tumours may have reduced cell phone use and differentially resulted in lower risk estimates, since referents would not have been affected (NRPB 2003). The use of interviews rather than mailed questionnaire data collection (where it is possible to verify mobile phone use by checking billing records) may have decreased risk estimates due to non-differential exposure misclassification from relying on proxy information. Furthermore, participants tend to underestimate the prevalence of mobile phone use by up to 15% compared with non-participants, leading to a differential reduction in risk estimates for mobile phone use, since participation rates among cases typically are higher than referents by 10-15% (Vrijheid et al 2009; The INTERPHONE Study Group 2010). Risk estimates below unity for brain tumours have been reported in several analyses of mobile phone use (The INTERPHONE Study Group 2010; Inskip et al 2001; Johansen et al 2001; Muscat et al 2000; Hepworth et al 2006). A biologic basis for the results, particularly reports of decreased risk for contralateral use, is ambiguous. In many cases, the inverse associations likely are explained by the aforementioned factors that bias risk estimates in the downward direction. On the other hand, studies in which the participants' status was blinded at interview tended to yield positive risk estimates compared with those who were not blinded (Myung et al 2008).

Two large recent studies have reported increased risks for mobile phone use, especially among heavy users. A multicentric study (13 countries) with 2708 glioma cases and matched referents (age within 5 years, sex, and region of residence within each study centre) observed a 1.40 odds ratio (OR) [95% confidence interval (CI)=1.03-1.89] for glioma among those in the highest mobile phone exposure category (cumulative call time \geq 1640 hours) compared with the lowest category (never a regular user) (The INTERPHONE Study Group 2010). A subset analysis of the concordance between tumour and preferred side of phone use similarly showed an increased estimated risk among those in the highest decile of cumulative call time (OR=1.55, 95%CI=1.24-1.99). Risk estimates were not reduced for the contralateral side, suggesting against potential reporting bias (Kundi et al 2009). A linear

dose response pattern (i.e., consistently increasing risk estimates with dose) is a feature of many but not all known carcinogens and conveys greater weight for a causative association. An upward trend across deciles of cumulative call time was not observed in the above study.

However, in a second recently-conducted study of $n=1251$ malignant brain tumours ($n=1148$ gliomas) and $n=1267$ referents (aged 20-80 years at diagnosis), adjusted estimated risk (age, sex, socioeconomic index, and year of diagnosis) increased with cumulative hours (h) of mobile phone use (none, OR=1.0; 1-100 h, OR=1.2, 95%CI=0.98-1.4; 1001-2000 h, OR=1.5, 95%CI=1.1-2.1; >2000 h, OR=2.5, 95%CI=1.8-3.5) (Hardell et al 2011). Similarly, estimated risk (in the category with >74 hours cumulative use) increased with latency time [years (y) since first use of a cell phone until diagnosis] (none, OR=1.0; >1-5 y, OR=1.0, 95%CI=0.7-1.4; >5-10 y, OR=1.2, 95%CI=0.9-1.6; >10 y, OR=2.7, 95%CI=2.0-3.8), although the linear effect was less pronounced than for cumulative hours of exposure. A key advantage of this study was the use of a mailed questionnaire, which allowed participants to verify responses by checking telephone bills (Kundi 2010). Recall bias could have increased risk estimates in positive studies if more cases than referents believed mobile phone use to be the cause of their brain tumour (Sage and Carpenter 2009; Hepworth et al 2006).

Studies of mobile phone use have been difficult to compare and interpret due to methodologic differences and the paucity of rigorous design. Background levels of electromagnetic radiation (e.g., power lines, fluorescent lights, computer monitors, televisions, and mobile phone base stations) may have confounded studies that did not account for such effects. A recent case-referent study conducted in Japan found a dose-response pattern for increasing exposure to power-frequency magnetic fields (MF) measured in a child's bedroom and brain tumours (<0.1 μT , OR=1.0; 0.1 to <0.2 μT , OR=0.74, 95%CI=0.17-3.18; 0.2 to <0.4 μT , OR=1.58, 95%CI=0.25-9.83; ≥ 0.4 μT , OR=10.9, 95%CI=1.05-113). The OR reported for bedroom MF levels above 0.3 μT , as opposed to above 0.4 μT , was 16 (95%CI=1.85-153). Mobile phones emit both radiofrequency and extremely-low frequency electromagnetic fields (Sage et al 2007). The level of near-field electromagnetic radiation typically emitted on a continuous basis by smart mobile phones ranges from 0.5-0.1 μT (spikes up to 93.5 μT have been recorded during send/receive mode operations), which is above the highest exposure category reported in the Japanese study (Sage et al 2007; Stevenson 2011). Measurements could have been influenced by near-field interference (Silva 2007; Jaffa and Herz 2007), however readings were generally consistent with other independent sources (Sage and Johansson 2007). A large pooled analysis of low-frequency MFs and childhood brain tumors did not observe a dose-response relationship (Kheifets et al 2010). However, inconsistent/imprecise exposure measurements and low participation rates (40%-80%) across studies may have biased results. Furthermore, the actual exposure levels in brain tissue may not necessarily reflect the levels radiated by the mobile phone due to anatomic details and variations in tissue conductivity/permittivity (Kouveliotis et al 2006; Kuster and Balzano 1992).

In March 2010, the Mobile Telecommunications and Health Research Programme (MTHR) initiated funding of a prospective cohort study that will follow approximately 250,000 mobile phone users across 5 European countries for up to 30 years (MTHR 2011; Stewart 2000). While MTHR concludes that short term (less than 10 years) exposure to mobile phone signals does not appear to be associated with an increase in brain and nervous system tumours, they emphasize that there remains "significant uncertainties that can only be resolved by monitoring the health of a large cohort of phone users over a long period of

time (MTHR 2011).” Furthermore, the reactions of children to mobile phone emissions may be different and/or stronger than those of adults (as is the case for other environmental exposures such as lead, tobacco smoke, ultraviolet radiation, and ionising radiation) and very little research has been conducted so far to determine whether this is the case (MTHR 2011). No studies on mobile phone use and risk of brain tumours have been planned for the U.S. that are comparable in size and detail to the COSMOS.

The thermal radiation emitted during average mobile phone use is low and generally is not believed to cause direct DNA damage or any other significant deleterious biologic effects on the brain (Wainwright 2000; Johansen et al 2001; Sage and Carpenter 2009; NRPB 2003). However, questions remain regarding the non-thermal effects of non-ionising radiation from mobile phones. Using positron emission tomography (PET), a National Institutes of Health study of 47 participants demonstrated a 7% increase in brain glucose uptake (a measure of metabolic activity) in response to mobile phone signals, supposedly independent of any thermal effects (Volkow et al 2011). The increases in regional glucose metabolism induced by the mobile phone signals were similar in magnitude to those reported after suprathreshold transcranial magnetic stimulation of the sensorimotor cortex. The authors hypothesize that the non-thermal effects on neuronal activity may be mediated by changes in cell membrane permeability, calcium efflux, cell excitability, and/or neurotransmitter release. A significant change in cell proliferation in response to radiofrequency MFs, independent of thermal activity, has been reported in a cell culture experiment involving transformed human epithelial amnion cells (Velizarov et al 1999). Effects demonstrated in other studies include up-regulation of apoptosis genes, induction of reactive oxygen species, changes in protein conformation, the creation of stress proteins, and immune system disturbances (Zhao et al 2007; Sage and Carpenter 2009; NRPB 2003; Valentini et al 2007; Ruediger 2009). Caution is advised when interpreting these effects since numerous contradictory results are present in the literature.

The likelihood that mobile phone use has no impact on the brain is small. Yet, the exact biophysical/biologic mechanism(s), if any, underlying mobile phone effects on neuronal cells, especially in the context of cancer, remains to be confirmed. Additional research is needed to determine if mobile phone use specifically increases brain tumor risk, either independently or in combination with other potential risk factors. Until then, limiting exposure to potentially vulnerable populations (e.g., fetus, children) would seem to be prudent precautionary public health policy, especially given the unknown latency for the development of brain cancer (Kundi et al 2009; Sage and Carpenter 2009). Radiofrequency MF absorption rates are estimated to be two times higher in children than adults, due to the lower thickness of pinna, skin and skull of younger children (Wiert et al 2008). Accordingly, risk may be greater among individuals who use a mobile phone at younger ages, yet few studies have addressed this potential risk group as they age into adulthood. Based on an increased risk for glioma, the WHO/International Agency for Research on Cancer (IARC) has formally classified radiofrequency electromagnetic fields, such as those emitted by wireless communication devices, as “possibly carcinogenic to humans (Group 2B) (WHO/IARC 2011).”

3.2 Atopic diseases and farm exposures

Several (Berg-Berkhoff et al 2009; Wigertz et al 2007; Schwartzbaum et al 2003; Hochberg et al 1990; Schlehofer et al 1992; Schlehofer et al 1999; Ryan et al 1992; Brenner et al 2002; Linos et al 2007; Wang and Diepgen 2005; Carrozzi and Viegi 2005) **but not all** (Hagströmer et al

2005; Turner et al 2005; Siegmund et al 2008; Eriksson et al 2005; Cicuttini et al 1997) epidemiologic studies of atopic diseases (e.g., asthma, allergies) have been negatively associated with glioma risk. The protective association has been suggested to reflect increased immune surveillance, although the exact biologic mechanism is unknown (Linos et al 2007; Carrozzi and Viegi 2005). Alterations of the immunological system can enhance the inflammatory response and promote tumor development (Carrozzi and Viegi 2005). The reduced association with allergies also may be due to reverse causality (i.e., immunosuppression induced by the tumor) (Wigertz et al 2007). Glioma patients are known to have an impaired immune system (Dix et al 1999). Interestingly, therapeutic immunity to intracranial tumors has been induced in the laboratory by peripheral immunization with interleukin-4 (IL-4) transduced glioma cells [Okada et al 2001; Benedetti et al 1998].

Farmers have been found to have an increased risk for brain cancer in some studies (Kristensen et al 1996; Reif et al 1989; Wingren et al 1992; Ahlbom et al 1986; Musicco et al 1982; Musicco et al 1988; Brownson et al 1990; Heineman et al 1995), although they generally are healthier than the population-at-large (Kristensen et al 1996; Bråbäck 2002; Population and Public Health Branch (PPHB) 1995; Blair et al 2005; Ronco et al 1992), live longer (Alavanja 1996), and die less frequently from cancer overall (Blair et al 1993). Being raised on a farm (Alfven et al 2006; Ege et al 2007; Riedler et al 2001; Braun-Fahrlander et al 1999; Riedler et al 2000; von Ehrenstein et al 2000; Kilpelainen et al 2000; Klintberg et al 2001; Ernst and Cormier 2000; Remes et al 2003; Leynaert et al 2001; Gassner-Bachmann and Wüthrich 2000; Vercelli 2008) or in a rural area (Godfrey 1975) has been shown to protect against asthma, hay fever, and atopic sensitization. Farm children are exposed to higher concentrations of airborne allergens, but paradoxically become sensitized less frequently and manifest a weaker sensitization response than non-farm controls (Gassner-Bachmann and Wüthrich 2000). The protective effect may be due to a form of "tolerance" that conceivably develops early in life, following repeated exposure to high levels of allergens (e.g., organic dusts, fungi, and endotoxins). Component lipopolysaccharides have been shown to excite Th1 responses and suppress the development of immunoglobulin-E (IgE)-antibodies (Klintberg et al 2001; Bråbäck 2002).

Specific determinants of asthma and atopy in the farm setting remain largely unknown. Any relationship with glioma risk likely is complex and must be interpreted in light of substantial heterogeneity in the protective ability of farming environments and differences in farming practices, especially with respect to microbial exposures (Alfven et al 2006; Ege et al 2007; Vercelli 2008). By self-selection, those who manifest allergies may choose a career path other than farming (i.e., healthy worker effect) (Bråbäck 2002). Farmers represent a diverse group (e.g., dairy, field crop, hog, beef cattle, poultry, fish, marijuana, cotton, and organic), and brain cancer risk, or lack thereof, for farmers could reflect differences in activities and the type, magnitude, and seasonality of exposures. In one report, marijuana smoking was associated with glioma risk, but the study did not specifically examine marijuana farming (Efird et al 2004). Farmers and their families have greater contact with seasonal elements. Season of birth has been associated with adult (Brenner et al 2004; Koch et al 2006; Mainio et al 2006; Efird 2009) and childhood brain tumours (Makino et al 2011; McNally et al 2002; Heuch et al 1998; Yamakawa et al 1979; Hoffman et al 2007; Halperin et al 2004), but the period of greatest risk has varied between studies.

Differences in the definition and the lack of objective measures of atopy should be considered when interpreting the above studies (Wang and Diepgen 2005; Schoemaker et al 2006). Furthermore, there is no definitive trend toward a decreasing risk for glioma with

younger ages at onset of the allergic condition, arguing against an immunologic cause for glioma (Schoemaker et al 2006). Paradoxically, increased risk for glioma has been observed in patients with AIDS-related immuno-suppression (Goedert et al 1998; Frisch et al 2001; Grulich et al 1999), but not in those with iatrogenic immuno-suppression (Schiff 2004). Many farm chemicals are classified as probable or likely human carcinogens by the US Environmental Protection Agency (EPA) (e.g., acephate, dichlorvos, dimethoate, lindane, parathion, phosmet, and tetrachlorvinphos) and these agents acting alone or in parallel with decreased atopic sensitization conceivably may increase glioma risk (US Environmental Protection Agency 2003).

3.3 Infectious agents

Polyomaviruses have been detected in the cancerous brain tissue of some patients diagnosed with gliomas (Rollison et al 2003). Polyomaviruses manifest a strong tropism for glial cells in vivo, possibly due to the interaction of glial transcription factors such as Tst-1/Ict6/SCIP with viral promoter sequences (Vasilyera et al 2004). The inoculation of immunologic immature neonate mice with human polyomavirus has been shown to readily cause tumor formation at multiple sites including the brain; older mice do not develop tumors in response to polyoma virus either in the laboratory or by natural infection (Nagashima et al 1984; Zu Rhein and Varakis 1979; London et al 1978; London et al 1983, Sanders 1977; Nagashima et al 1984; Zu Rhein and Varakis, 1979). Similarly, owl and squirrel monkeys injected (intracerebral, subcutaneous, or intravenous) with human JC polyomavirus have developed astrocytomas and glioblastomas (London et al 1978; London et al 1983). Recently, two new members of the *Polyomaviridae* family, *Karolinska Institutet Virus* (KIPyV) and *Washington University virus* (WUPyV), have been detected in samples from children with lower respiratory tract disease (Foulongne et al 2008).

Paradoxically, animals are not a permissive host for human JC virus replication, even though integrated JC viral DNA has been identified in the tumors of animals induced with the virus (White et al. 2005; Miller et al, 1984). Though monkeys themselves are not affected, simian virus (SV)-40 (extracted from monkey kidneys) gives cancer to hamsters (Rosenfeld 1962). Human adenovirus type 12 and Rous sarcoma virus are examples of other neuro-oncogenic viruses capable of causing gliomas under laboratory conditions (Zimmerman 1975). Yet, adenovirus in the worst case only causes respiratory disease in humans (Rosenfeld 1962). Some tumor viruses must be injected in animals on the first day of life to be effective, although they may not cause cancer until years later (Bailar and Gurian 1964).

Analogous to human and simian polyomaviruses causing brain tumours in non-permissive rodents, animal polyomaviruses conceivably may cause brain tumours in humans, yet little is understood about the latter topic. Polyomavirus are ubiquitous among animals (e.g., cattle, birds, rodents,) (Ashok and Atwood 2006). For example, mouse polyomaviruses (*Mus musculus*) are capable of inducing a wide array of mesenchymal and epithelial cell type cancers in mice (Dawe et al 1987). Exposure to farm animals has been associated in some studies with childhood brain tumours (Efird et al 2003; Bunin et al 1994) but not adult brain tumors (Ménégoz et al 2002).

Epidemiologic evidence in support of a viral/pathogenic etiology for brain tumors remains controversial. In adults, *Toxoplasma gondii* infection has been associated with an increased prevalence of astrocytomas (Schuman et al 1967), while decreased glioma risk has been associated with a history of infections/colds (Schlehofer et al 1999), and chicken pox

(Wrensch et al 2005; Wrensch et al 2001). On the other hand, increased risk for childhood brain tumors has been associated with a history of chicken pox (Bithell et al 1973), influenza (Dickinson et al 2002; Linos et al 1998), measles (Dickinson et al 2002), general viral infections (Fear et al 2001; Linet et al 1996), and neonatal urinary tract infections (Linet et al 1996). A 7.5-fold OR (95% CI=1.3-44.9) for low grade astrocytoma has been observed for neonatal urinary tract infections (Linet et al 1996).

A recent cohort study of 20,132 workers in poultry slaughtering and processing plants, a group with high potential exposures to avian leukosis/sarcoma, reticuloendotheliosis, and Marek's disease viruses, were observed to have a significant excess of brain cancer, compared with the U.S. population (standardized mortality ratio=1.7, 95% CI=1.1-2.4). Although the aforementioned poultry viruses are well established carcinogens in their natural species, it is not known if they cause cancer in humans (Johnson et al 2000).

An infectious etiology for brain tumors is complicated by many factors (Naumova 2006). The same infectious agent may present a different pattern of incidence depending on the host location. A peak evident in the general population may not behave uniformly within certain subpopulations. Temperature, humidity, precipitation, and indoor air quality are among the mitigating factors that may affect the survival and transmissibility of a pathogen. Other factors include poor nutrition, population density, travel, hygiene practices, cultural practices in food consumption/preparation, changes in herd immunity, or evolution of the infectious agent over time. Furthermore, seasonal variation in immune function may increase host susceptibility to infections at certain times of the year (Melnikov et al 1987; Carandente et al 1988).

4. Discussion

The vast majority of glioma cases are idiopathic in origin. Demographic differences in incidence by race, sex, and country suggests that genetics, hormones, and environmental risk factors may play a role in some gliomas. However, study bias (e.g., participation, information, survival), variations in health care access/utilization, residual confounding, and other yet-to-be realized influences may explain the differences in glioma incidence. Complicating matters, the etiology of glioma may be multifactor in nature. That is, several factors operating in unison may cumulatively increase/decrease risk or mask the effect of individual factors when examined in isolation. Additionally, gene-environment and gene-gene interactions may modify underlying risk. Future epidemiologic studies will benefit by improved measures of environmental exposures, more precise statistical methods for detecting interaction effects, and larger multicentre collaborations aimed at better understanding the impact of population stratification.

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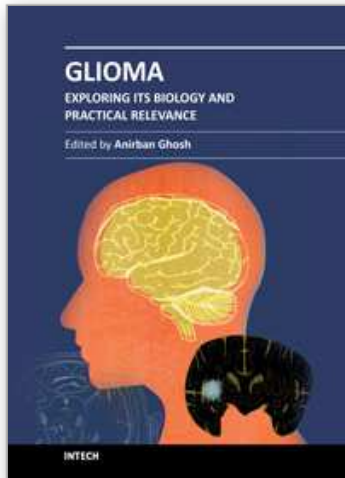
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The title 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

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