Epidemiology of Glioma

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Estimated New US Cancer Cases 2017

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>23%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Brain & other nervous system 1.6%

Brain & other nervous system 1.2%

ACS, 2017
Estimated US Cancer Deaths 2017

Males 318,420

Lung & bronchus 27%
Colon & rectum 9%
Prostate 8%
Pancreas 7%
Liver & intrahepatic bile duct 6%
Leukemia 4%
Esophagus 4%
Urinary bladder 4%
Non-Hodgkin lymphoma 4%
Brain & other nervous system 3%
All other sites 24%

Females 282,500

Lung & bronchus 25%
Breast 14%
Colon & rectum 8%
Pancreas 7%
Ovary 5%
Uterine corpus 4%
Leukemia 4%
Liver & intrahepatic bile duct 3%
Non-Hodgkin lymphoma 3%
Brain & other nervous system 3%
All other sites 24%

ACS, 2017
Overall incidence of primary brain and CNS tumors is 22.6 per 100,000 population

Malignant: 7.2 per 100,000 population
Non-Malignant: 15.5 per 100,000 population
Gliomas are the most common type of malignant brain tumor

- Gliomas account for ~27% of all brain tumors, and ~80% of malignant tumors
- Glioma is a heterogeneous disease with multiple subtypes
- The most common glioma histology glioblastoma (GBM) (~56%)
  - Very poor outcomes
- Lower grade gliomas (LGG, or non-GBM) are the second most common type of glioma in adults (~30%)
Incidence of glioblastoma varies across the population

- Incidence of glioblastoma increases with age.  
  - Median age at diagnosis is 64.
- Incidence is higher in males as compared to females
- Globally:  
  - Incidence of glioma is highest in Northern Europe.
- United States:  
  - Incidence is highest in non-Hispanic whites
- Higher socioeconomic status has been associated with increased risk of glioblastoma (Porter et al., 2015)
Outcomes after diagnosis with glioblastoma are generally poor.
- Median survival: 12 months (Stupp et al., 2005)
- Five-year relative survival: ~5% (Thakkar et al., 2014; CBTRUS 2017)

Several factors predict improved survival:
- High Karnofsky Performance Score (KPS)
- Younger age at diagnosis
- Greater extent of surgical resection
- Biomarkers (MGMT promoter methylation, mutation of IDH1)
Incidence of glioblastoma has not changed substantially since the 1990s

- Incidence increases in the 1980s and 1990s are often attributed to increasing use of new imaging technologies.
- Since 1992, incidence of glioblastoma among adults has increased 0.4% per year in the US.
- These incidence patterns are similar to those observed in other countries.

Glioblastoma Incidence in the US (Ages 18+, 1973-2014)

- 1973-1978 APC=-7.3% (95% CI: -11.1%, -3.3%)
- 1978-1992 APC=2.7% (95% CI: 1.8%, 3.6%)
- 1992-2014 APC=0.4% (95% CI: 0.1%, 0.7%)

APC= Annual Percentage Change; 95% CI= 95% Confidence interval

SEER, 2017
Searching for a cause for glioma ... 

- Many environmental and genetic risk factors have been studied.

- No environmental risk factor accounting for a large number of glioma cases has been identified.
  - Validated environmental risk factors likely account for only a fraction of incident cases

- No genetic risk factors that explain a large proportion of inherited risk for glioma have been identified
  - Genetic factors are estimated to account for ~25% of glioma risk (Kinnersley et al., 2016)
  - A small proportion of gliomas are due to inherited syndromes
  - Genetic association studies have identified common genetic variants that explain ~27% of genetic risk for glioblastoma (Melin et al., 2017)
GENETIC GLIOMA RISK FACTORS
Inherited syndromes associated with glioma

Estimated that hereditary cancer syndromes account for ~1% of adult glioma cases

- Neurofibromatosis 1 (NF1)
- Neurofibromatosis 2 (NF2)
- Tuberous sclerosis (TSC1, TCS2)
- Lynch syndrome (MSH2, MLH1, MSH6, PMS2)
- Li-Fraumei syndrome (TP53)
- Melanoma-neural system tumor syndrome (p16/CDKN2A)
- Ollier disease/Maffucci syndrome (IDH1, IDH2)

Genetic association studies in ‘glioma families’

‘Familial’ glioma (2+ glioma cases within a family) accounts for ~5% of glioma cases

- Family-based studies have consistently demonstrated that first degree relatives of glioma patients have ~2x the glioma risk in comparison to the general population.
- Linkage studies in affected ‘glioma families’ have not identified high-penetrance risk variants that are able to be validated.
- Additional analyses of these families have found that most inherited mutations in glioma families are private.
Genome-wide association studies have identified 12 common genetic variants associated with sporadic glioblastoma risk.

Melin et al., 2017
VALIDATED GLIOMA RISK FACTORS
Ionizing radiation exposure

- Therapeutic radiation exposure to the head has consistently been associated with increased risk of brain tumor
  - Israeli Tinea Capitus cohort (Sadetzki, et al 2005)
  - Childhood cancer survivors cohorts (Neglia, et al. 2006)
- Glioma risk after therapeutic radiation exposure is inversely associated with age at exposure
- Mixed or minimal evidence
  - Atomic bomb studies
  - Diagnostic radiation (e.g. CT scans, x-rays)
Allergies and atopic disease

• History of allergies and atopic conditions has consistently been associated with decreased risk of glioma.
  – Respiratory allergies
  – Asthma
  – Eczema
• Effect is consistent for both glioblastoma and lower grade glioma
• This inverse association has been consistent across multiple studies
UNPROVEN GLIOMA RISK FACTORS
Cellular phones (non-ionizing radiation)

- Most studies have not observed increased odds of glioma for having ever been a regular cellular phone user.
- Small increases in odds have been observed in users with the highest total use
  - INTERPHONE, 2010; Cardis et al., 2011
- Cohort studies have shown null association between cellular phone use and glioma
  - Benson et al., 2015; Frei et al., 2011
- Time trends analyses from multiple countries have shown no significant increases in incidence that would be expected given estimated risk ratios from case-control studies
  - de Vocht et al., 2011; Deltour et al., 2012; Little et al., 2012; Chapman et al., 2016
Electromagnetic fields

- Many studies have attempted to assess the association between occupational exposure to electromagnetic fields and risk of brain tumors.
- EMF exposure can be difficult to accurately measure.
  - Many studies construct job exposure matrices (JEMs) based on job title and length of employment.
- Results of previous case-control studies have been mixed.
  - In the INTEROCC consortium, increased odds were observed only in individuals with most recent exposure (Turner, el al. 2014).

<table>
<thead>
<tr>
<th>Glioma</th>
<th>Exposure metric</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cumulative exposure (μT-years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.11</td>
<td>475</td>
<td>1,334</td>
<td>1.00 (ref.)</td>
<td></td>
</tr>
<tr>
<td>2.11–3.40</td>
<td>454</td>
<td>1,327</td>
<td>1.00 (0.85–1.16)</td>
<td></td>
</tr>
<tr>
<td>3.40–5.00</td>
<td>441</td>
<td>1,344</td>
<td>0.93 (0.78–1.11)</td>
<td></td>
</tr>
<tr>
<td>5.00–7.50</td>
<td>370</td>
<td>808</td>
<td>1.07 (0.88–1.31)</td>
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</tr>
<tr>
<td>7.50+</td>
<td>199</td>
<td>540</td>
<td>0.80 (0.63–1.00)</td>
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</tbody>
</table>

|        | Average exposure (μT) |       |          |             |
| <0.11  | 423            | 1,268 | 1.00 (ref.) |
| 0.11–0.13 | 398          | 1,273 | 0.98 (0.82–1.13) |
| 0.13–0.17 | 561          | 1,411 | 1.04 (0.89–1.22) |
| 0.17–0.24 | 330          | 856 | 0.95 (0.80–1.14) |
| 0.24+   | 237            | 545   | 1.00 (0.82–1.23) |

|        | Maximum exposed job (μT) |       |          |             |
| <0.13  | 453             | 1,370 | 1.00 (ref.) |
| 0.13–0.17 | 458          | 1,290 | 0.92 (0.79–1.08) |
| 0.17–0.23 | 430          | 1,202 | 0.85 (0.73–1.00) |
| 0.23–0.62 | 382          | 947   | 0.92 (0.78–1.09) |
| 0.62+   | 216            | 544   | 0.80 (0.65–0.98) |

|        | Exposure duration (y) |       |          |             |
| <5     | 1,333          | 3,849 | 1.00 (ref.) |
| 5–15   | 295            | 805   | 0.90 (0.77–1.05) |
| 15–25  | 142            | 371   | 0.94 (0.76–1.16) |
| 25+    | 169            | 328   | 1.22 (0.99–1.51) |

Turner et al., (2014)
Other explored sources of occupational exposures

• Mixed or minimal evidence
  – Farming associated with increased risk of glioma (Ruder et al., 2009)
  – Insecticides associated with increased risk of glioma (Louis et al., 2017)
  – Pesticides associated with increased risk of glioma (Yiin et al., 2012)
  – Military radiation exposure associated with increased risk of glioma, with increased effect in soldiers of higher rank (Grayson, 1996)
  – Rubber processing (Straif et al., 2000)

• No evidence
  – Metals and welding fumes (Parent et al., 2017)
  – Solvents (Benke et al., 2017)
  – Jet engine manufacturing (Marsh et al., 2013)
Viruses

- Viruses are known to cause brain tumors in experimental animals, but most have been minimally evaluated in glioma
- Prior infection with varicella zoster virus (chicken pox) has been repeatedly associated with decreased odds of glioma
  - Amirian et al., (2016)
- Limited and mixed evidence exists for other viral exposures, including:
  - Influenza
  - SV40
  - JC
  - BK

Wrensch et al., Neuro-oncology 2002
Other unproven environmental risk factors for glioma

- Air pollution
- Reproductive factors (e.g. parity, age at menarche, age at menopause)
- Exogenous hormone exposure (e.g. hormone replacement therapy, oral contraceptives)
- Prior cancer history
- Head trauma
- History of seizures
- *Toxoplasma gondii*
- Alcohol consumption
- Tobacco use

- Dietary nitrate consumption
- Vitamin use
- Cosmetics and hair dyes
- Sleeping pills
- Pain meds – Aspirin, NSAIDS
- Antihistamines

*Wrensch et al., Neuro-oncology 2002; Ostrom et al., 2014*
Limitations of case-control data for assessing glioma risk factors

- Many exposures that have been linked to glioma are difficult to measure, particularly when exposures are less recent
  - EMF exposure, total cell phone use
- Several studies of potential glioma risk factors conducted using case-control study designs have produced results not replicable in cohort studies (Johansen et al., 2017)
  - Ionizing radiation, sex hormone exposure
- It is likely that recall bias has inhibiting our ability to assess the relationship between
THANK YOU!
Key References

Key References, continued


