Advances in Brain Tumor Research: Leveraging BIG data for BIG discoveries

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Estimated New US Cancer Cases 2016

- **Males**: 841,390
- **Females**: 843,820

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</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>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</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><strong>All other sites</strong></td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.*
Top US cancer deaths

Males: Lung (27%), prostate (8%), colorectal (8%)
Females: Lung (26%), breast (14%), colorectal (8%)
BTs account for 1-2% of all cancers

![Graph showing age-adjusted incidence rate per 100,000 for BTs by age group and malignancy status.

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-Malignant</th>
<th>Malignant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-14)</td>
<td>1.64</td>
<td>3.73</td>
<td>5.37</td>
</tr>
<tr>
<td>Children (0-19)</td>
<td>2.15</td>
<td>3.42</td>
<td>5.57</td>
</tr>
<tr>
<td>Adults (20+)</td>
<td>19.82</td>
<td>8.76</td>
<td>28.58</td>
</tr>
<tr>
<td>All Ages</td>
<td>14.75</td>
<td>7.23</td>
<td>21.98</td>
</tr>
</tbody>
</table>

a. Rates per 100,000 and age-adjusted to the 2000 United States standard population.
### Most Common Primary Brain and CNS Tumors by Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Most Common Histology</th>
<th>Second Most Common Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Histology</strong></td>
<td><strong>Rate</strong> (95% CI)</td>
</tr>
<tr>
<td>0-4</td>
<td>Embryonal Tumors</td>
<td>1.24 (1.17-1.31)</td>
</tr>
<tr>
<td>5-9</td>
<td>Pilocytic Astrocytoma</td>
<td>1.01 (0.95-1.07)</td>
</tr>
<tr>
<td>10-14</td>
<td>Pilocytic Astrocytoma</td>
<td>0.86 (0.81-0.92)</td>
</tr>
<tr>
<td>15-19</td>
<td>Tumors of the Pituitary</td>
<td>1.66 (1.58-1.73)</td>
</tr>
<tr>
<td>20-34</td>
<td>Tumors of the Pituitary</td>
<td>3.16 (3.10-3.23)</td>
</tr>
<tr>
<td>35-44</td>
<td>Meningioma</td>
<td>4.82 (4.72-4.91)</td>
</tr>
<tr>
<td>45-54</td>
<td>Meningioma</td>
<td>9.02 (8.89-9.14)</td>
</tr>
<tr>
<td>55-64</td>
<td>Meningioma</td>
<td>14.77 (14.59-14.95)</td>
</tr>
<tr>
<td>65-74</td>
<td>Meningioma</td>
<td>25.96 (25.66-26.27)</td>
</tr>
<tr>
<td>75-84</td>
<td>Meningioma</td>
<td>38.70 (38.22-39.18)</td>
</tr>
<tr>
<td>85+</td>
<td>Meningioma</td>
<td>51.31 (50.47-52.16)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>Meningioma</td>
<td>7.86 (7.81-7.90)</td>
</tr>
</tbody>
</table>
Childhood brain tumors are the most common cancer in children 0-14.

The most common types of brain tumors in children are gliomas (52.9%) and embryonal tumors (15.0%).

Incidence of brain tumors is highest among infants < 1 year old.
- Brain tumors are the third common cancer in AYA 15-39.
- The most common types of brain tumors in AYA are tumors of the pituitary (29.9%) and meningioma (15.9%).
- Incidence of brain tumors is highest among adolescents 15-19 and mortality is highest among this same age group.
In adults, there were decreases in incidence of colon, breast, lung, and prostate cancer, as well as malignant brain tumors.

In adolescents (15-19), there were increases in incidence of malignant and non-malignant brain-tumors.

In children (0-14), there were increases in incidence of acute lymphocytic leukemia, non-Hodgkin lymphoma, and malignant brain tumors.
• MANY environmental and genetic risk factors have been studied.

• No risk factor accounting for a large number of brain tumors has been identified.
  – Ionizing Radiation to the head
    • Israeli studies -- ~4 fold increased risk of meningioma; ~2 fold increased risk of gliomas
    • Childhood cancer survivor studies
  – Allergies, immune response
    • Decreased risk of brain tumor
Unproven causes of brain tumors

Glioma
- Head trauma
- Dietary nitrate consumption
- Filtered cigarette smoking
- Diagnostic ionizing radiation

Childhood brain tumors
- Active or passive maternal tobacco smoking
- Residential electromagnetic field exposures
- Exposure to air pollutants
- Maternal cosmetic use

Unspecified for all brain tumor types
- Residential electromagnetic field exposures (many more positive than negative findings with “high” exposure occupations, but no consistent dose-response)
- Agricultural worker exposures
- Industrial Formaldehyde exposures
- Alcohol consumption
- Cell phone use
- Common drugs-fertility, oral contraceptives, sleeping pills, pain meds, headache meds, antihistamines

Wrensch et al, Neuro-oncology 2002
Strategies for finding genes that cause disease

**FAMILIES**  
Linkage Studies

- Simple Inheritance
- Single Gene
- Rare Variants
- ~600 Short Tandem Repeat Markers

**POPULATIONS**  
Association Studies (GWAS)

- 40% T, 60% C → Cases
- 15% T, 85% C → Controls

- Complex Inheritance
- Multiple Genes
- Common Variants
- 300,000 - 1,000,000 SNPs

Phenotype Measure
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Type of Pediatric BT</th>
<th>Gene</th>
<th>Chromosomal Location</th>
<th>Overall Incidence Pediatric BT incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>Neurofibroma/sarc Optic nerve glioma Astrocytoma</td>
<td>NF1</td>
<td>17q11</td>
<td>1:4000 4-45%</td>
</tr>
<tr>
<td>NF2</td>
<td>Schwannoma Meningioma Glioma Ependymoma</td>
<td>NF2</td>
<td>22q12</td>
<td>1:40,000 Unknown</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>Giant cell astrocytoma</td>
<td>TSC1</td>
<td>9q34</td>
<td>1:5000 6-14%</td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td>Hemangioblastoma</td>
<td>VHL</td>
<td>3p25</td>
<td>1:45,500 2%</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinoblastoma Pineoblastoma Malignant glioma</td>
<td>RB1</td>
<td>13q14</td>
<td>1:20,000 Very rare</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>Malignant glioma</td>
<td>TP53</td>
<td>17p13</td>
<td>Rare 2nd most common</td>
</tr>
<tr>
<td>Turcots</td>
<td>Medulloblastoma Glioma</td>
<td>APC</td>
<td>5q21</td>
<td>Very rare Very rare</td>
</tr>
<tr>
<td>Nevoid basal cell carcinoma</td>
<td>Medulloblastoma</td>
<td>PTCH</td>
<td>9q22.3</td>
<td>1:57,000 Unknown</td>
</tr>
</tbody>
</table>

Adapted from Kleihues et al, 2000; Melean et al, 2004
Gene mapping in families for BTs

GLIOGENE studies (ABTA supported)
- Families with 2 or more gliomas
- Most gliomas occurred in clusters of 2

Shete, et al.
- Linkage search identifies susceptibility region on chromosome 17

Sun, et al.
- Narrowed chromosome 17 linkage peak identified in Shete, et al., using a new model-based approach
Shete et al peak

Sun et al peak

Chromosome 17

Sun et al., 2012
Protection of telomeres 1 gene (POT1) and familial melanoma and familial glioma

POT1 loss-of-function variants predispose to familial melanoma


Brief Communication
Germline Mutations in Shelterin Complex Genes Are Associated With Familial Glioma


Neuro-Oncology

Neuro-Oncology 16(10), 1333–1340, 2014
doi:10.1093/neuonc/neu052
Advance Access date 9 April 2014

Germline rearrangements in families with strong family history of glioma and malignant melanoma, colon, and breast cancer

Gliogene International Case-Control (GICC) Study

- Largest glioma GWAS to date
- Validation of previously discovered risk factor (4 previous glioma GWAS studied)
- Discovery of new rare variants that may increase glioma risk
Prognostic Factors for BTs

- Karnofsky Performance Score (KPS)
- Age at diagnosis
- Extent of surgical resection
- Histological Type of Tumor
- Biomarkers??
Genetics and Prognosis: Methylation of MGMT

- Hypermethylation at MGMT – responsive to alkylating agents (i.e. Temozolomide)

- More responsive to both chemo and radiation if methylated

  Hegi et al., NEJM 2005
Genetics and Prognosis: Oligos and 1p/19q loss

- Concurrent loss of 1p and 19q
  - 50-70% of grade III anaplastic oligos

Van den Bent et al, Cancer 2003
IDH1/2 mutations – survival advantage!

A Glioblastoma
- IDH wild-type
- IDH mutated

B Anaplastic Astrocytoma
- IDH mutated
- IDH wild-type

Probability of Survival (%) vs Months

P=0.002
P<0.001
What have we learned about gliomas from The Cancer Genome Atlas (TCGA)?
TCGA: “No Platform Left Behind”

25* forms of cancer

- glioblastoma multiforme (brain)
- squamous carcinoma (lung)
- serous cystadenocarcinoma (ovarian)

Etc. Etc. Etc.

Multiple data types

- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic report/images
- Tissue anatomic site
- Surgical history
- Gene expression/RNA sequence
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence
- RPPA (protein)
- Subset for Mass Spec

Biospecimen Core Resource with more than 150 Tissue Source Sites

6 Cancer Genomic Characterization Centers

3 Genome Sequencing Centers

7 Genome Data Analysis Centers

Data Coordinating Center
Cancer is a disease of the genome

• If we precisely characterize the cancer genome can we cure cancer??
  – Drivers
  – Passengers
  – Rapid evolution
    • Development of treatment resistance
    • Clonal evolution
  – Other components of biological process -- complex signaling
Mutational Landscape of Cancers

TCGA, 2014
Ohio Brain Tumor Study (OBTS) Statistics

- **Accrual began at:**
  - 9/07 University Hospitals Seidman Cancer Center
  - 7/08 University of Cincinnati
  - 9/08 Cleveland Clinic
  - 11/09 The James

- **Pre-treatment blood samples on ~75%**
- **Pre-treatment snap-frozen tumor tissue on ~60%**
- **Pre-treatment FFPE tumor tissue on ~80%**
- **Questionnaire on ~60%**
- **Biorepository has over 5000 tumor specimens related to these patients**

- **64% MALIGNANT 690 TOTAL**
- **36% NON MALIGNANT TOTAL 379**

- **WORKING TOTAL = 1075**
  - 6 with pending histology

- **Glioblastoma** 36%
- **Malignant Meningioma** 5%
- **Meningioma** 19%
- **Vestibular Schwannoma** 6%
- **Pituitary Adenoma** 8%
- **Other Non-Malignant** 2%
- **Pending** 0%
- **Other Malignant** 1%
- **All Other Glioma** 23%
LGG subtypes -- TCGA

Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network

Alterations
- CIC, FUBP1, NOTCH1
- PIK3CA, PTBP1, TERT, IDH1/2
- TP53, ATRX
- MYC, CCND2, IDH1/2
- PTEN, NF1, CDKN2A
- EGFR, MDM4, TERT

Clinical
- LGG: frequent
- GBM: rare
- LGG: rare
- GBM: frequent

TCGA, NEJM, 2015
Further glioma subtyping - TCGA

Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma

Michael Giovannetti, 1,2,11 * Sarah A. Sambetti, 1,2,11 Fatima A. Tajbakhsh, 1,2,11 Kuan E. Tung, 1,2,11 Brian M. Zeleznikier, 1,2,11 Simon C. Lee, 1,2,11 Maxime Trail, 1,2,11 Nazan Kazaz, 1,2,11 Arnaud Descombes, 1,2,11 Antoine Becq, 1,2,11 Audrey V. Chlouverakis, 1,2,11 Joelle Pouille, 1,2,11 Éric Uy, 1,2,11 Vincent J. Gauthier, 1,2,11 Sarah M. Ferguson, 1,2,11 Jean-François Côté, 1,2,11 Claire J. Emsley, 1,2,11 Emily S. H. Tam, 1,2,11 Emerit Alain, 1,2,11ong Xu, 1,2,11 Michael A. Krzyzanski, 1,2,11 Mark R. Hryniuk, 1,2,11 Joseph A. Lachance, 1,2,11 Anthony M. Miller, 1,2,11 Andrew D. W. Clark, 1,2,11 Alice J. D'Amours, 1,2,11 Michael H. Golomb, 1,2,11 David A. O'Reilly, 1,2,11 David A. Brown, 1,2,11 Nathan S. Su, 1,2,11 Ling J. S. Leung, 1,2,11 John R. C. Kean, 1,2,11 John C. R. McArthur, 1,2,11 Jean-A. Duchesne, 1,2,11 Anthony G. Prideaux, 1,2,11 Julian R. Shaw, 1,2,11 Michael V. H. Sharpe, 1,2,11 Peter M. Luu, 1,2,11 David H. Golub, 1,2,11 TCGA Research Network, Murtuza Hossaini, 1,2,11 Antoine Becq, 1,2,11 and Paul B. Jones, 1,2,11

Ceccerelli et al, Cell 2016
Medulloblastoma subtypes

Northcott et al, 2012
Brain Tumor web resources

• Central Brain Tumor Registry of the United States – www.cbtrus.org

• Surveillance, Epidemiology and End Results Program (SEER) – http://seer.cancer.gov/statistics/summaries.html

• American Cancer Society Facts and Figures -- http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2013/index

• The Cancer Genome Atlas (TCGA) -- http://cancergenome.nih.gov/