Epidemiology of Brain Cancer
Brian Alexander, MD, MPH

Outline
I. Definitions
II. Epidemiology
III. Descriptive epidemiology of brain cancer
IV. Risk factors associated with brain cancer
V. An epidemiologic investigation
VI. Conclusions

Definitions

Epidemiology of ‘Brain Cancer’

“Brain cancer” can be more specifically named ‘primary brain cancer’
- Much popular confusion of terms
Cancer of the brain, NOT in the brain
- 150,000-200,000 brain metastases annually
- 18,820 primary brain tumors in 2006
Even ‘primary brain cancer’ is too general for any useful purpose
- Diverse group of neoplasms arising from different cells in the CNS
- No environmental or genetic factor is associated with a proportional increase in all cancer subtypes

Primary brain tumors

Most brain tumors are named after the type of cell from which they develop
Gliomas are the most common type and arise from glial cells (astrocytes, oligodendrocytes, ependymal cells)
Other types of brain tumors include meningiomas, nerve sheath tumors, embryonal tumors (including medulloblastoma), pituitary tumors, and craniopharyngioma

Classification of Primary Brain Tumors

Histopathologic
- Identified by light microscopy with regards to original cell type
- Classified according to degree of differentiation based on standard features
Molecular
- Specific mutations
- Protein expression
- Gene expression clustering
Gliomas

Account for ~50% of all primary brain tumors

Arise from glial cells
- Astrocytes
- Oligodendrocytes
- Ependymal cells

Develop throughout the brain

Meningiomas

The meninges are the membranes covering the brain and spinal cord

Brain tumor treatment by type

<table>
<thead>
<tr>
<th>Pathologic type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Surgical resection</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Resection +/- focal radiation</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>Resection + focal radiation +/- chemotherapy</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Resection + focal chemoradiation + chemo</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Resection + CSI + focal RT + chemo</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Resection +/- focal radiation</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>Resection + chemotherapy</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Resection + radiation</td>
</tr>
</tbody>
</table>

Brain tumor outcomes by type

<table>
<thead>
<tr>
<th>Pathologic type</th>
<th>2 yr OS</th>
<th>Conditional survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>66%</td>
<td>73%</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>45%</td>
<td>68%</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>5%</td>
<td>36%</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>80%</td>
<td>83%</td>
</tr>
</tbody>
</table>

What is epidemiology?

“The study of the distribution and determinants of disease frequency”
- Descriptive epidemiology- establish patterns by linking frequency of disease occurrence to person, place and time
- Analytic epidemiology- determine causation by linkages to specific etiologic factors

Hippocrates examined the relationships between occurrence of disease and environmental factors
Finding and leveraging “natural experiments”
**Why is epidemiology important?**

To make inferences into the nature of disease by examining the characteristics at a population level.

To provide an empirical basis and foundation for public health and preventative interventions.

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**1854 Soho Cholera Epidemic**

August 31st, 1854- Cholera outbreak in Soho district of London.

John Snow - *On the Mode of Communication of Cholera, 1849*

John Snow and Reverend Henry Whitehead conducted neighborhood investigations in the district.

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**British Doctors Study**

October 1951- Richard Doll and Austin Bradford Hill began a prospective study at the behest of the MRC.

Wrote to all registered physicians in the UK.

- 34,449 responses from male physicians.

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**1854 Soho Cholera Epidemic**

Linked cases to the Broad Street Pump.

- Later linked pump to index case from a nearby cesspool.

Snow compared the cholera mortality rates of the subscribers of two large companies.

- Southwark and Vauxhall- 71/10,000.
- Lambeth Company- 5/10,000.

Evidence of cholera transmission by fecal contaminated water.

Information on disease as well as public health intervention.

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**Table V.—Standardized Death Rates Per Year Per 1,000 Men Aged 35 Years or More, in Relation to the Most Recent Amount Smoked**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Deaths</th>
<th>Non-Smokers</th>
<th>All Smokers</th>
<th>Men Smoking a Daily Average of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Men</td>
<td>All Smokers</td>
<td>1-14 g.</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>541</td>
<td>0.81</td>
<td>0.47</td>
<td>0.86</td>
</tr>
<tr>
<td>Other cancers</td>
<td>125</td>
<td>2.01</td>
<td>2.01</td>
<td>2.01</td>
</tr>
<tr>
<td>Other respiratory diseases</td>
<td>548</td>
<td>6.02</td>
<td>6.02</td>
<td>6.02</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>175</td>
<td>7.79</td>
<td>7.79</td>
<td>7.79</td>
</tr>
<tr>
<td>All causes</td>
<td>1,714</td>
<td>13.25</td>
<td>13.25</td>
<td>13.25</td>
</tr>
</tbody>
</table>

*That is, at November 1, 1951, for those smoking at that time and at the date of giving up for those who had given up at November 1, 1951.*
Difficulties with Epidemiology of Primary Brain Tumors

Relatively rare
Problems of classification
- Diversity of subtypes
- Difficulties of standardization
Changing methods of ascertainment
- Technology
Exposure assessment
- Diagnostic sensitivity bias
Heterogeneous cancer
- Different tumor types are usually grouped together
- May miss associations with subtypes

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Descriptive epidemiology

Trends in incidence and mortality by different variables
- Time
- Gender
- Race
- Geography

Incidence

22,070 new cases of malignant brain tumors in 2009
- 12,920 deaths
Time trends
- Average annual percentage increase 1.1%
(CBTRUS data)

True increase

Fig. 3. Logarithm regression analyses from 15 U.S. state cancer registries identifying sharp changes in incidence over time.
Conclusions: Temporal trends

What do the temporal trends tell us about brain tumors?
- Probably nothing

Gender and Race

Slight male predominance for malignant brain tumors
- 7.4 vs. 5.0/100,000 person-years
White>black
- 7.8 vs. 3.5/100,000 person-years
For meningioma, there is a female predominance
- 8.1 vs. 3.6/100,000 person-years
- Association with progesterone receptor

Geography

US exhibits geographic differences in incidence
- Hawaii: 4.52/100,000 person years
- North Dakota: 8.84/100,000 person years
Highest rates are in industrialized nations
Migrant studies show that migrants adopt rates of host country

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Genetic syndromes

Neurofibromatosis
- NF-1 and NF-2
Von Hippel-Lindau syndrome
- VHL
Li-Fraumeni syndrome
- TP53
Turcot’s syndrome
- APC
Basal cell nevus syndrome (Gorlin syndrome)
- PTCH
Familial glioma

Genetic variants- GWAS

Two groups using GWA approaches identified novel glioma susceptibility genes
UK/US study: 521,318 SNP genotypes in 1,878 cases and 3,670 controls for discovery with candidates replicated in 3 independent sets
- 5 loci- TERT, CDKN2A/CDKN2B, RTEL1, PHLD1, CCDC26
UCSF/TCGA/Mayo: 275,895 variants in 692 cases and 3,992 controls with candidates replicated in an independent set
- 2 loci- RTEL1 and CDKN2B
Occupational studies

Assume a common exposure
- Job classification as a proxy for actual exposure

Issues with detection bias
- Access to health care

Jobs studied for association to brain tumors
- White collar professionals, electrical workers, oil refinery workers, farmers, chemical industry

Some correlations reported, but none could be linked to a specific exposure

Vinyl chloride

Oil refinery and petrochemical workers

Agricultural exposures (pesticides, herbicides, fungicides)
- Farming as an occupation and residence on a farm have been associated with increased risk of brain tumors
- Meta-analysis of 33 studies
  - RR = 1.3 (95% CI = 1.1 to 1.6) among farmers
  - Not clear that one chemical is responsible for these associations

Radiation

Ionizing radiation
- Medical therapy
- Atomic bomb survivors

Electromagnetic fields
- Study in 1979 showing correlation using wiring configuration as surrogate for EMF

Radiofrequency radiation
- Cell phones

Israeli Tinea Capitis Study

10,834 patients treated with radiation for tinea capitis between 1948-1960

Mean 1.5 Gy exposure to the brain surface

Increased relative risk for:
- Meningioma 9.5 (n=19)
- Glioma 2.6 (n=7)
- Nerve sheath tumors 18.8 (n=25)

Dose-response relationship found with RR approaching 20 for exposure to 2.5 Gy

Environment/Genetic Interaction

Even though radiation was associated with increased risk of meningioma, overall risk was low

Follow-up familial study suggested genetic interaction with radiation exposure risk

Lifespan Study

Lifespan Study
- 93,000 survivors from Hiroshima and Nagasaki and 27,000 controls

Of 80,160 subjects in the study, 32 estimated tumors related to radiation exposure, 20 schwannoma
Childhood Cancer Survivor Study

14,300 five year survivors
Meningioma developed in 66 patients (0.46%)
  • Median time to diagnosis: 17 years
  • Radiation exposure odds ratio: 9.9
Glioma in 40 patients (0.27%)
  • Median time to diagnosis: 9 years
  • Radiation exposure odds ratio: 6.8
Linear dose-response relationship

Tobacco

2004 Surgeon General’s Report
No causal relationship between smoking cigarettes and adult brain cancer in men and women

Alcohol

Most studies do not support a positive association (9 case-control studies null or inverse; 2 positive)

Dietary hypothesis

Exposure to N-nitroso compounds (NOC) increases the risk of glioma
Exposure to nutrients and phytochemicals, including antioxidants, lowers the risk of glioma by reducing the endogenous formation NOC

N-nitroso compounds

Potent neurocarcinogens in experimental studies that can induce glioma formation in rats
Exogenous sources
  • Tobacco smoke, cosmetics, others...
  • Foods with nitrite and nitrates
    - Cured/processed meats, vegetables, alcohol; drinking water
Endogenous sources: nitrosation
dietary precursors \[\rightarrow\] nitrous acid \[\rightarrow\] NOC \[\rightarrow\] brain
Inhibition of Nitrosation

Inhibition of nitrosation

\[
\text{dietary precursors} \xrightarrow{\text{(nitrate, nitrite)}} \text{nitrous acid} \xrightarrow{\text{NOC}} \text{nitric oxide + H}_2\text{O}
\]

Sources of nitrogen scavengers and antioxidants

- Ascorbic acid (vitamin C)
- α-tocopherol (vitamin E)
- Polyphenols

Fruits and vegetables
- Phenolic acids, flavonoids in beer hops
- Resveratrol in wine
- Phenolic acids in coffee
- Flavonoids in tea

Observational studies: meat

Meta-analysis of 9 case-control studies

RR of 1.48 (95% CI = 1.20-1.83) for adult glioma for high vs. low cured meat intake of all types

Huncharek et al., 2003

Observational studies: vitamins

Vitamins C and E

- 4 out of 6 studies reported inverse associations for vitamin E intake
- findings less consistent for vitamin C intake
- potential for interaction with meat intake

RF exposure - Cell phone use

No linkage has been found to link cell phone use and the development of brain tumors

Many studies have investigated a link

- 2 large US case-control studies
- Danish cohort study

ABC News, January 19, 2006

Cell Phones Don’t Cause Brain Tumors

- Latest study contradicts earlier research, which had suggested a link

c|net News, March 31, 2006

Study: Long-term cell use raises brain tumor risk

- Contradicting conclusions of other researchers, Swedish study cites link between brain tumors, extensive cell phone use.
TIME Magazine

CELL PHONES
Turns out they don’t cause cancer after all, according to a new Danish study.

Inskip et al. NEJM 2001

Muscat et al. JAMA 2000

Danish study

Danish study- Results

RF/cell phone conclusions

No data supporting a connection of cell phone use and brain tumors
No clear mechanism that would lead to brain tumor development

Caveats
- Short follow-up in comparison with possible latency period
- Regular users defined conservatively

Table 3. Odds Ratios for Brain Cancer by Amount and Duration of Handheld Cellular Telephone Use

<table>
<thead>
<tr>
<th>Latency, y</th>
<th>Person-years</th>
<th>Obs</th>
<th>Exp</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>109318</td>
<td>58</td>
<td>56.9</td>
<td>1.06 (0.67 to 1.63)</td>
</tr>
<tr>
<td>1</td>
<td>105621</td>
<td>266</td>
<td>265.3</td>
<td>1.03 (0.91 to 1.17)</td>
</tr>
<tr>
<td>5-9</td>
<td>132841</td>
<td>235</td>
<td>244.1</td>
<td>0.96 (0.84 to 1.10)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>169195</td>
<td>28</td>
<td>42.5</td>
<td>0.66 (0.44 to 0.99)</td>
</tr>
</tbody>
</table>

420,095 cellular telephone subscribers in Denmark from 1982-1995
Researchers linked name and address to personal identification numbers, then to Danish Cancer Registry

No data supporting a connection of cell phone use and brain tumors
No clear mechanism that would lead to brain tumor development

Caveats
- Short follow-up in comparison with possible latency period
- Regular users defined conservatively
Head injuries

Anecdotal evidence back to descriptions by Harvey Cushing
Conflicting data of association with meningioma
  • Case-control
  • Relationship to birth order or trauma
Recall bias
Potential confounding by ionizing radiation in cases with serious or repetitive head trauma

Noise exposure (acoustic trauma)

Acoustic neuroma (nerve sheath tumor of the VIII/auditory cranial nerve) associated with acoustic trauma
OR = 2.2 for 10 or more years of noise exposure (determined by job exposure)
OR = 13.2 for 20 years duration
Acoustic trauma causes tissue destruction and repair
Preston-Martin, Br J Cancer 1990

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Nonoccupational risk indicators of glioblastoma in adults
Hocberg et al. Journal of Neuro-oncology 1990

Case-control study of 160 patients with WHO grade III-IV astrocytoma
Questionnaire administered to patients and controls matched for age, sex and place of residents
Questions designed to assess past exposures
  • "Considerably large amount"

An epidemiologic investigation
The allergy story

Table 2: Association between glioblastomas and inferred dimensions of lifestyle and of medical history

<table>
<thead>
<tr>
<th></th>
<th>No of cases (N = 160)</th>
<th>No of control (N = 117)</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish, home-cooked</td>
<td>26</td>
<td>26</td>
<td>0.9</td>
<td>0.5 - 1.6</td>
</tr>
<tr>
<td>Fish, fried</td>
<td>8</td>
<td>3</td>
<td>0.6</td>
<td>0.3 - 1.0</td>
</tr>
<tr>
<td>Regular consumption of</td>
<td>7</td>
<td>12</td>
<td>1.0</td>
<td>0.6 - 1.8</td>
</tr>
<tr>
<td>Beer</td>
<td>87</td>
<td>66</td>
<td>0.7</td>
<td>0.4 - 1.2</td>
</tr>
<tr>
<td>Coffee 1-5 cups</td>
<td>70</td>
<td>78</td>
<td>1.1</td>
<td>0.6 - 2.2</td>
</tr>
<tr>
<td>Coffee 6+ cups</td>
<td>39</td>
<td>38</td>
<td>0.9</td>
<td>0.5 - 1.8</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>44</td>
<td>47</td>
<td>1.0</td>
<td>0.6 - 2.0</td>
</tr>
<tr>
<td>&gt;30 pack years</td>
<td>15</td>
<td>15</td>
<td>1.0</td>
<td>0.6 - 2.0</td>
</tr>
<tr>
<td>Regular use of</td>
<td>27</td>
<td>24</td>
<td>0.8</td>
<td>0.5 - 1.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>39</td>
<td>32</td>
<td>1.1</td>
<td>0.6 - 2.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
<td>79</td>
<td>1.1</td>
<td>0.6 - 2.0</td>
</tr>
<tr>
<td>Oral complications (one</td>
<td>27</td>
<td>24</td>
<td>0.9</td>
<td>0.4 - 1.9</td>
</tr>
<tr>
<td>each)</td>
<td>84</td>
<td>83</td>
<td>1.1</td>
<td>0.7 - 2.0</td>
</tr>
<tr>
<td>Scars or lesions</td>
<td>8</td>
<td>4</td>
<td>1.6</td>
<td>0.5 - 5.1</td>
</tr>
<tr>
<td>Headache or dizziness</td>
<td>12</td>
<td>47</td>
<td>0.5</td>
<td>0.3 - 1.0</td>
</tr>
<tr>
<td>Oral health history</td>
<td>49</td>
<td>45</td>
<td>1.0</td>
<td>0.6 - 1.6</td>
</tr>
<tr>
<td>Home blood pressure</td>
<td>13</td>
<td>14</td>
<td>0.8</td>
<td>0.4 - 2.3</td>
</tr>
</tbody>
</table>
Further studies

Since that first publication, the association between atopy and brain tumors has been investigated in at least three cohort studies and 8 case control studies. A meta-analysis of these studies by Linos et al. was published in JNCI in 2007.

Relative risk of the association between allergy and glioma

Relative risk of the association between allergy and meningioma

Biomarkers in epidemiologic studies

IgE is the class of immunoglobulin associated with atopic disease.

Allergy sufferers have elevated levels of antigen specific IgE.

IgE might have utility as a surrogate for exposure measurement.

Atopy also associated with T_{H}2 related cytokines such as IL-4 and IL-13.

Reduced Immunoglobulin E and Allergy among Adults with Glioma Compared with Controls

Wiemels et al. Cancer Research 2004

Case(n=228)-Control(n=289) study of newly diagnosed glioma patients in San Francisco.

Total, respiratory-specific and food-specific IgE levels were assessed in serum samples.

Reduced Immunoglobulin E and Allergy among Adults with Glioma Compared with Controls

Wiemels et al. Cancer Research 2004
Biological mechanism

Immune regulation in the CNS appears to be more humoral in nature than cell-mediated.

Perhaps to minimize damage to the tissue architecture of the CNS (from the inflammatory nature of a cell-mediated assault).

Adapted from: Elenkov IJ, Chrousos GP. Ann NY Acad Sci 2002; 966:290-303

Biological mechanism (cont’d)

Hyper-reactive state of the immune system may result in increased immune surveillance.

Glioma patients are often characterized by a broad depression of T-cell function.

Malignant rat cell glioma can be eradicated with the retroviral-mediated delivery of the IL-4 gene into brain tumors.

Eradication of Rat Malignant Gliomas by Retroviral-mediated, in Vivo Delivery of the Interleukin 4 Gene

Benedetti et al. Cancer Research 1999

Rats were coinjected with 1:1 mixture glioblastoma cells and retroviral producer cells secreting various levels of IL-4.

Control rats- All died in one month

Low secretors- 27% survival

Intermediate secretors- 56% survivors
Summary - Risk factors

Non-modifiable
- Age
- Sex
- Race
- Hereditary syndromes
- Family history of brain tumors
- Gene variants

Environmental
- Ionizing radiation
- Occupational?
- Head trauma?
- Non-ionizing radiation?
- Diet?
- Allergies?

Summary

Primary brain cancer occurs as neoplastic transformation of normal brain cells.
Primary brain cancer is a heterogeneous group which has implications from risk factors to outcomes and treatment.
Epidemiology defines the distribution of diseases in populations and strives to uncover causative relationships.
Epidemiologic studies in brain cancer have uncovered several non-modifiable risk factors, one environmental factor (radiation) and several other possibilities.