Etiology of Brain Tumors

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Overview

• What is Epidemiology?
• What causes brain tumors?
• Epidemiology approach
• Risk factors by tumor subtypes
• Comment on Ongoing/Future Studies
What is Epidemiology?

• The study of the distribution and determinants of disease and health in human populations.
• Descriptive
• Analytic
  – What causes disease?
  – When we find causes, can we prevent disease?
This suggests that important environmental determinants are widely distributed or that constitutional factors also play a major role, Inskip 1995.
What Causes Brain Tumours?

- Inherited conditions
- Nutrition
- Immune factors
- Occupational/Chemical factors
- Ionizing Radiation
- Non-Ionizing Radiation
Inherited Syndromes

- Inherited predisposition in about 5% of cases
- Known germline mutations
- Li-Fraumeni Syndrome (p53 Syndrome)
- Tuberous Sclerosis (Bourneville’s Disease)
- Neurofibromatosis I (von Recklinghausen’s Disease; Peripheral Neurofibromatosis)
- Neurofibromatosis II (Bilateral Acoustic Neurofibromatosis; Central Neurofibromatosis)
- Neviod Basal Cell Carcinoma Syndrome (Gorlin)
- Hereditary Nonpolyposis Colorectal Carcinoma Syndrome (Turcot Syndrome; Lynch Cancer Family Syndrome)
- Familial Adenomatous Polyposis (Adenomatous Polyposis Coli; Turcot Syndrome; Gardner Syndrome)
- von Hippel-Lindau Disease
- Multiple Endocrine Neoplasia Type I (Wermer Syndrome)
- Cowden’s Disease (Kowden’s Syndrome; Multiple Hamartoma Syndrome)
Nutrition

• Maternal consumption (childhood tumours)
  – Risk
    • Cured meats (N-nitroso compounds)
  – Protective
    • yellow orange vegetables
    • OR=0.5 in children < 5yrs and 3 trimesters multivitamin use

• Adults
  – Protective
    • yellow orange vegetables.
    • coffee and tea consumption
Allergies

• Allergies reduce glioma risk by nearly 40 percent
  – 50,000 people and 3,400 glioma patients.
  – When duration and timing assessed the results are inconsistent.

• Biomarkers of allergies
  – Allergy and inflammation genes seem to be involved in glioma development and progression
  – Cohort – risk inversely related to allergic sensitization (IgE before disease) for glioma but not meningioma or schwannoma. Stronger in women than men. (2011)
  – Studies ongoing
Occupational/Chemical Factors

- Occupational titles studied for years with inconsistent results
- Pesticides
  - Conflicting results
- Solvents
  - Inconclusive
- EMF
  - Evidence considered inadequate to classify
Proven and Possible Animal Neurocarcinogens

• Alkylating N-Nitrosamides (4 nitrosourea derivatives)
• Ethynitrosoureas (14 compounds)
• PAHs
• Fluorenylacetamides (25 compounds)
• Acrylamide, Acrylonitrile, Bromoethane, Chloroethane, C.I. Direct Blue 15, 3,3' -dimethyloxybenzidine dihydrochloride, 3-3' dimethylbenzidine dihydrochloride, Diphenhydramine hydrochloride, Ethyl hydrazine, Ethylene oxide, Furosemide, Glycidol, 1,H-Benzotriazole, Isoprene, Propylene imine, Propane sultone

Compiled from Sampson and Bigner 1998, Sills et. al. 1999.
## Chemical-specific scores from environmental questions (300 Cases/Controls)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>OR*</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-butadiene (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.9</td>
<td>0.4 – 1.8</td>
</tr>
<tr>
<td>1,3-butadiene (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.5</td>
<td>0.2 – 1.1</td>
</tr>
<tr>
<td>Acrylamide (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.9</td>
<td>0.4 – 1.9</td>
</tr>
<tr>
<td>Acrylamide (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.9</td>
<td>0.4 – 2.0</td>
</tr>
<tr>
<td>PAHs (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>1.0</td>
<td>0.5 – 1.9</td>
</tr>
<tr>
<td>PAHs (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.6</td>
<td>0.3 – 1.3</td>
</tr>
<tr>
<td>NOCs (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.8</td>
<td>0.4 – 1.6</td>
</tr>
<tr>
<td>NOCs (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.6</td>
<td>0.3 – 1.2</td>
</tr>
<tr>
<td>Acrylonitrile (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>1.2</td>
<td>0.6 – 2.4</td>
</tr>
<tr>
<td>Acrylonitrile (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.8</td>
<td>0.4 – 1.8</td>
</tr>
<tr>
<td>Ethylene oxide (2(^{\text{nd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.9</td>
<td>0.4 – 1.9</td>
</tr>
<tr>
<td>Ethylene oxide (3(^{\text{rd}}) tertile vs. 1(^{\text{st}}) tertile)</td>
<td>0.7</td>
<td>0.3 – 1.5</td>
</tr>
</tbody>
</table>
Do Chemicals in our Environment Cause Brain Tumors?

- We don’t know
- We cannot conclude that there is no association because
- We lack high quality human evidence and
- There are known animal neurocarcinogens and
- too many human associations suggested in the occupational literature to ignore.
- Need research on biomarkers for animal neurocarcinogens so they can be tested in humans.
Ionizing Radiation
(High exposure levels)

- **Israel Tinea Capitus Cohort**
  - Acoustic neuromas RR=18, Gliomas RR=2, Meningioma RR=9
  - Linear dose response
  - Risks greater in children than adults

- **Nasopharyngeal radium implants (children)**
  - RR=30.9 for brain tumors

- **Childhood Cancer Survivor Studies – radiation therapy**
  - US and UK
  - Meningioma (17 years) and glioma (9 years)
Diagnostic Radiation?

• CT scans
  – Effective dose from a single CT scan between 2 and 15 mSv.
  – Lowest dose for which there is good evidence of increased cancer risk is about 10 – 50 mSv.
  – Individual risk of developing a radiation cancer from a single procedure is extremely small
  – Cumulative effects are being evaluated.
Benefits and Risks

• Limit CT scans - medically necessary
• Risk to repeated low dose exposures may be relevant in radiosensitive subgroups.
• Children are sensitive to radiation and are a group of special concern.
  – Two cohort studies to date suggest increase risk of cancer, but not brain cancer
Non-Ionizing Radiation

• Mobile Phones
  – IARC(2011) classified RF fields as a possible carcinogen based on increased risk of glioma and vestibular schwannoma in heavy mobile phone users.
  – 5 new studies
    • 2 cohort studies – no association
    • 1 case-control – increase risk after 10 years use.
    • 2 surveillance studies have not shown increases in brain tumours concurrent with increases in use of cell phones.
Epidemiology Approach
How do We Study Cause?

Common Study Designs

• Case-Control studies
  – Recruit patients and individuals with similar characteristics without disease (controls)
  – Focus on prior history (medical, lifestyle, environment)
  – Estimate relative risks (ie: 2-fold history among those with disease compared to controls)

• Cohort studies
  – Identify group with common experience and follow to disease occurrence.
  – Large samples needed for uncommon diseases
Evaluation of Results

• How large is the risk?
• Does risk increase as exposure increases?
• Does exposure proceed disease?
• Does removing exposure reduce disease?
• Are results consistent with scientific knowledge (animal and human)
Risk Factors by Tumor Subtype

• Based on Human Data
• Categorized into established, probable or not probable risk factors
• Categorized by strength of association
  – +++ Relative Risk > 3 (strong risk)
  – +1 < Relative Risk < 3 (moderate risk)
  – -0.3< Relative Risk < 1 (protective)
Established Risk Factors – Gliomas

- High –dose radiation
  - Low doses need further study (dx exposures)
- Hereditary Syndromes
- Gender
- Ethnicity
- Increasing age
- Epilepsy, seizures, convulsions
  - Early symptom?

+++ RR>3
+ 1<RR<3
Probable Risk Factors – Gliomas

- Family Hx of Brain tumors  
- Mutagen sensitivity  
- Allergies/Asthma/elevated IgE  
- Chickenpox/anti-VZV IgG

+ 1 <RR<3  
- 0.3<RR<1
Probably Not Risk Factors

- Residential power frequency
- EMF
- Cellular phone use
- Prior cancers
- Filtered cigarette smoking
- Alcohol consumption
Too Few Studies to Assess

- Dietary intake
- Exogenous hormones
- Constitutive Polymorphisms
  - GSTs and CYP2E1
  - DNA repair: ERCC1, ERCC2, MGMT, XRCC7
  - Immune function: IL4R*, IL13* (asthma risk)
    HLA B*13, b*07-Cw*07
  - Others
Meningiomas

• Established Risk Factors
  – High-dose radiation +++
  – Hereditary syndromes +++
  – Gender +
  – Exogenous hormones +
• Probable: Family Hx +
• Probably not: head injury, cellular phone use, allergies/atopy
• Too few studies: endogenous hormones, constitutive polymorphisms

+++ RR>3
+1 <RR<3
Acoustic Neuromas

• **Established**
  – Ionizing Radiation

• **Probable**
  – Noise (2 studies)
Comment on Ongoing/Future studies
Why Don’t We Know More?

• Studies involve large populations with and without disease
• Studies require databases (like cancer registries) to be accurate and available for researchers to identify patients
• Studies usually require supplemental information from patients or their families
• When feasible, expensive to conduct
• Exposure assessment crude
Are we underestimating the role of the environment in gene-environment interaction research? (P Vineis Int J Epidemiol 2004)

The common genotyping methods allow little error in classification. On the contrary, sensitivity in environmental exposure assessment is often lower than 70% and specificity even lower... allowing for substantial error.

Relative Risks of 1.5 may be missed
What do We Know?

• Incidence patterns suggest causes vary by histology
• Environmental causes likely widely dispersed
• Risk factor profiles are emerging
• Prevention is in the distant future
  – improving QOL/survival are paramount
• Improving data infrastructures to facilitate these types of studies is key to progress
• Biomarkers of exposure are needed
• Multidisciplinary teams are critical
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