Epidemiology and Brain Tumours: Practical Usefulness

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Epidemiology and Brain Tumours: Practical Usefulness

Adelheid Wöhrer

Abstract: Primary brain tumours are rare tumours which occur across all ages and comprise a large spectrum of different entities. This review compiles population-based information on age distribution, gender predilection, ethnic disparities, geographic variations, and time trends in the incidence of primary brain tumours. Unlike clinical trials, which are prone to selection bias, population-based incidence and mortality data provide a comprehensive picture of the real-life scenario and are thus of high relevance to the neuro-oncology community.

Background and Descriptive Epidemiology

Primary brain tumours are rare tumours which occur across all ages. In children, however, they are especially frequent; in this age cohort, they constitute the second most common tumours following leukaemias and are the most common cause of cancer-related death [1, 2]. Primary brain tumours comprise a large spectrum of different tumour entities, each being associated with a distinct biological background and disease course [3]. Thus, the prognosis of the individual patient varies considerably by tumour type, age at diagnosis, and neurological impairment. Based on their biological behaviour, brain tumours are categorized into benign, intermediate, and malignant tumours [4]. Cancer registration is most often restricted to malignant brain tumours (ie, cancer), whereas benign and intermediate lesions are not routinely reported. However, due to the localization within the central nervous system (often in close proximity to eloquent areas) and the potential for malignant transformation, non-malignant tumours (approximately 50% of all brain tumours) considerably impact patient morbidity and mortality as well. Therefore, registration of all brain tumours – including non-malignant lesions – is of high relevance.

Incidence and Mortality

Reported overall incidence rates of primary brain tumours reach up to 20 per 100,000 person-years [5], the most common tumours in adults being meningiomas, glioblastomas, and pituitary adenomas [5, 6]. In children, however, the encountered spectrum of brain tumours differs substantially from that in adults due to a higher prevalence of embryonal tumours, eg medulloblastomas, pilocytic astrocytomas, and ependymomas [6, 7].

The overall impact of brain tumour-related deaths on Western populations in terms of premature mortality has been quantified as an average of 21.3 years of a potential life lost [8]. This adds to a substantial loss of productivity due to the high occurrence of brain tumours in younger “working-age” individuals [9] and considerable costs for supportive care for daily living activities. Alternately, the diagnosis of a brain tumour renders the affected patients often in difficult financial situations due to frequent job losses and high treatment expenses [10]. On the other hand, survival times are increasing due to innovations in diagnosis and therapy. Hence, tumour- and/or therapy-associated effects on the social and cognitive functioning of long-term survivors “quality-of-life” are becoming increasingly relevant [11].

Gender Predilection, Regional Variation, and Ethnical Disparities

Overall, primary brain tumours are more frequent in females than males (female incidence rate [IR] 22.25 per 100,000 person-years, male 18.8 per 100,000 person-years) [5]. While meningiomas are twice as common in females, gliomas, embryonal tumours, lymphomas, and germ cell tumours show a slight male predilection (m/f ratio approximately 1.4).

Interestingly, CBTRUS data from the United States indicate ethnic disparities with a lower overall incidence of brain tumours in American Indian or Alaska Natives (AIAN; IR 13.15 per 100,000 person-years) as well as the Asian and Pacific Islander (API) population in the United States (IR 12.98 per 100,000 person-years) compared with whites (“Caucasians”; IR 20.61 per 100,000 person-years) and Afro-Americans (IR 20.12 per 100,000 person-years) [5]. However, the observed rates for the majority of brain tumour entities are significantly higher in whites of European ancestry when compared with Afro-Americans, AIAN, and API ethnicities. The only exceptions are meningiomas and tumours of the pitui-
tary, which are significantly more common in Afro-Americans [5]. These ethnical disparities might in fact account for the observed regional variation in the world-wide incidence of malignant brain tumours, with higher incidence rates being reported from developed countries (Figure 1) [12]. Still, differences in diagnostic and case ascertainment procedures between individual countries might obscure the picture. However, a higher incidence of germ cell tumours had been advocated for East Asia [13, 14] but this has not been confirmed in a recently conducted joint study between Japan and the United States [15].

### Time Trends

With the increasing availability of MR imaging, the overall incidence of brain tumours virtually increased during the 1980s but has remained relatively stable ever since. However, epidemiological data have shown a continuous rise in primary CNS lymphomas in the immunocompetent population over the last decades, whereas the incidence seems to be decreasing in patients with AIDS since the introduction of highly active anti-retroviral therapies [16, 17]. Conflicting data exist for acoustic neurinomas, with some reporting an increase in incidence rates [18], which has not been confirmed by others [19].

### Analytical Epidemiology

#### Environmental Risk Factors

##### Ionizing Radiation

To date, exposure to moderate-to-high doses of ionizing radiation is the only established environmental risk factor for the development of brain tumours [20]. Especially the occurrence of secondary neoplasms such as meningiomas, gliomas, and sarcomas subsequent to therapeutic irradiation of a primary lesion represents a severe and potentially fatal complication. The ALL-Berlin-Frankfurt-Münster study, for instance, found a 19-fold increased risk for brain neoplasms in previously treated patients compared with the general population [21]. The cumulative risk for having developed a brain tumour at 15 years after treatment was 3.5 % (95-% confidence interval [CI]: 1.5–5.5 %) if therapy included cranial irradiation, but was substantially lower (1.2 %; 95-% CI: 0.2–2.3 %) if cranial irradiation was omitted [21]. Overall, the association between brain tumours and ionizing radiation seems stronger for meningioma than for glioma [20].

**Radiation Exposure from X-Ray Investigations Including CT Scans**

In addition to cranial irradiation, a large retrospective study found also a positive association for CT scans, which were performed in individuals under the age of 22 years (excess relative risk 0.023; 95-% CI: 0.010–0.049; p < 0.0001) [22]. The relative risk of brain tumours after a cumulative dose of 50–74 mGy was 2.82 (95-% CI: 1.33–6.03), thus almost tripled. The authors concluded that radiation doses from CT scans should be kept as low as possible and alternative procedures should be considered [22]. Of note, a major limitation of the study constitutes its retrospective design covering a large time period (1985–2002) without accounting for the various technical improvements that had meanwhile resulted in considerable dose reductions [23].

Likewise, dental X-rays, which were performed in the past, when radiation exposure was still greater, appear to be associated with a slightly to moderately increased risk for the devel-
opment of meningiomas with odds ratios varying according to patient age and used technique from 1.4–1.9 [24].

Non-Ionizing Radiation
Over the last decade, exposure to low-frequency, non-ionizing electromagnetic fields via mobile phones has been critically discussed as a potential risk factor for brain tumours such as gliomas, meningiomas, and acoustic neurinomas [25]. The so far conducted case-control studies found inconsistent results, which were in part due to different study designs, small sample sizes, recall bias of mobile phone use, and lack of information on long-term use. The largest studies, so far, include the Interphone and Hardell studies [26–29]. A meta-analysis on both studies found a significantly increased risk for temporal lobe gliomas (most exposed part of the brain) with an odds ratio of 1.71 (95-% CI: 1.04–2.81) in the > 10-year latency group. Ipsilateral mobile phone use > 1640 h in total gave an odds ratio of 2.29 (95-% CI: 1.56–3.37) [25]. With regard to acoustic neurinomas, ipsilateral mobile phone use in the latency group > 10 years resulted in an odds ratio of 1.81 (95-% CI: 0.73–4.45). For ipsilateral cumulative use > 1640 h an odds ratio of 2.55 (95-% CI: 1.50–4.40) was found [25].

Based on a comprehensive literature search with special consideration given to the 2 studies mentioned above, the IARC has recently classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (press release No 208, 31-05-2011). However, whether the IARC carcinogenic classification has any impact on policy makers and results in concrete legislative acts to protect public health remains to be shown [25]. Furthermore, there are concerns that mobile phone use might differentially impact developing brains of children and adolescents. This is currently the topic of 2 large case-control studies: CEFALO and MOBI-KIDS (www.mbkids.net).

Table 1. Genetic brain tumour syndromes [3].

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Locus</th>
<th>Brain tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden syndrome/Lhermitte-Duclos syndrome</td>
<td>PTEN</td>
<td>10q23</td>
<td>Dysplastic gangliocytoma of the cerebellum</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>17p13</td>
<td>Astrocytoma, PNET</td>
</tr>
<tr>
<td>Naevus basal cell carcinoma syndrome/ Gorlin syndrome</td>
<td>PTCH</td>
<td>9q32</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>Neurofibromatosis I</td>
<td>NF1</td>
<td>17q11</td>
<td>Neurofibroma, MPNST, optic and other gliomas</td>
</tr>
<tr>
<td>Neurofibromatosis II</td>
<td>NF2</td>
<td>22q12</td>
<td>Bilateral vestibular schwannoma, meningioma, ependymoma, and others</td>
</tr>
<tr>
<td>Rhabdoid tumour predisposition syndrome</td>
<td>SMARCB1/INI1</td>
<td>22q11.2</td>
<td>ATRT</td>
</tr>
<tr>
<td>Von-Hippel-Lindau syndrome</td>
<td>VHL</td>
<td>3p25</td>
<td>Hemangioblastoma</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1</td>
<td>9p34</td>
<td>SEGA, cortical tubers</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC2</td>
<td>16p13</td>
<td></td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>APC</td>
<td>5q21</td>
<td>Medulloblastoma, glioblastoma</td>
</tr>
<tr>
<td></td>
<td>MSH2</td>
<td>3p21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hMLH1</td>
<td>7p22</td>
<td></td>
</tr>
<tr>
<td>Familial meningioma</td>
<td>SUFU</td>
<td>10q24.32</td>
<td>Multiple meningiomas [31]</td>
</tr>
</tbody>
</table>

Table 2. Molecular-genetic subtypes of common brain tumours as revealed by integrated genomic analysis

<table>
<thead>
<tr>
<th>Brain tumour</th>
<th>Molecular subtypes</th>
<th>Prognostic impact</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>IDH1 mutation/G-CIMP+ hypermethylation</td>
<td>Improved outcome</td>
<td>Sturm et al, 2012 [34]</td>
</tr>
<tr>
<td></td>
<td>H3F3A G34 mutation</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H3F3A K27 mutation</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesenchymal expression</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proneural expression (PDGFRA amplification)</td>
<td>Improved outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Classical expression EGFR amplification</td>
<td>Improved outcome</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>WNT/wingless</td>
<td>Improved outcome</td>
<td>Northcott et al, 2011 [36]</td>
</tr>
<tr>
<td></td>
<td>SHH Group 3</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 4</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior fossa ependymomas</td>
<td>Poor outcome</td>
<td>Witt et al, 2011 [37]</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td>CNS PNET</td>
<td>Group 1 (primitive neural)</td>
<td>Poor outcome</td>
<td>Picard et al, 2012 [38]</td>
</tr>
<tr>
<td></td>
<td>Group 2 (oligoneural)</td>
<td>Poor outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3 (mesenchymal lineage)</td>
<td>Poor outcome</td>
<td></td>
</tr>
</tbody>
</table>

PDGFRA: platelet-derived growth factor receptor-α; EGFR: epidermal growth factor receptor; WNT: wingless int; SHH: sonic hedgehog; PNET: primitive neuroectodermal tumour
Clinical Implications of Brain Tumour Epidemiology

Genetic Risk Factors
Genetic Tumour Syndromes
Genetic predisposition to primary brain tumours is well-known in the setting of rare tumour syndromes (Table 1). They involve tumour suppressor genes and are inherited in an autosomally dominant trait. However, the vast majority of brain tumours (> 90 %) occurs outside the setting of an established germ-line mutation [3].

Susceptibility Loci
Genome-wide association studies have recently identified 7 susceptibility variants for gliomas, which are associated with moderate increases or decreases in risk (odds ratios from 0.6–1.2) [32, 33]. While variants at 7p11.2 (EGFR both loci) affect all glioma subtypes, 20q13.33 (RTEL1), 5p15.33 (TERT), and 9p21.3 (CDKN2B) differentially impact the risk for glioblastoma, 8q24.21 (CCDC26) for oligodendroglioma, and 11q23.3 (PHLDB1) for low-grade glioma [32]. These data show that common low-penetration susceptibility alleles are associated with the development of glioma and provide insights into disease causation [33]. Still, larger studies focusing on specific tumour subtypes or -groups are required to identify additional susceptibility loci and validate the proposed ones for glioma risk.

Molecular Epidemiology
Molecular epidemiology is a relatively new concept integrating the rapid advances in the fields of genomics, transcriptomics, proteomics, and metabolomics. With regard to brain tumour research, the integration of these high-throughput molecular techniques has significantly increased our understanding of the underlying genetic mechanisms of the most common brain tumours such as glioblastoma or medulloblastoma. Within traditional tumour entities further genetic subtypes have been identified, which differ not only in terms of cells of origin and involved genetic pathways, but also in their clinical outcomes and differential responses to therapy [34, 35]. Genetic brain tumour subtypes are listed in Table 2. Still, sophisticated molecular-genetic techniques are not widely available, cost-intensive, and not generally applicable to individual patients. Hence, the translation of such findings into clinical applicability now largely depends on the development of practical and robust subgroup-specific biomarkers and therapies [39].

Despite the huge number of proposed biomarkers for brain tumours, only single candidate biomarkers, which provide prognostic and/or predictive information, have translated into clinical use so far. The most prominent examples of tissue-based biomarkers include isocitrate dehydrogenase (IDH) 1 and 2 mutations in diffuse gliomas [40, 41], combined 1p19q loss in oligodendroglioma [42, 43], O6-methylguanine methyltransferase (MGMT) promoter methylation status in glioblastoma [44], as well as MYCC/MYCN amplification and 2 mutations in diffuse gliomas [40, 41], combined 1p19q loss in glioblastoma [42], 8q24.21 (CCDC26) for oligodendroglioma, and 11q23.3 (PHLDB1) for low-grade glioma [32]. These data show that common low-penetration susceptibility alleles are associated with the development of glioma and provide insights into disease causation [33]. Still, larger studies focusing on specific tumour subtypes or -groups are required to identify additional susceptibility loci and validate the proposed ones for glioma risk.

References:
Clinical Implications of Brain Tumour Epidemiology


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