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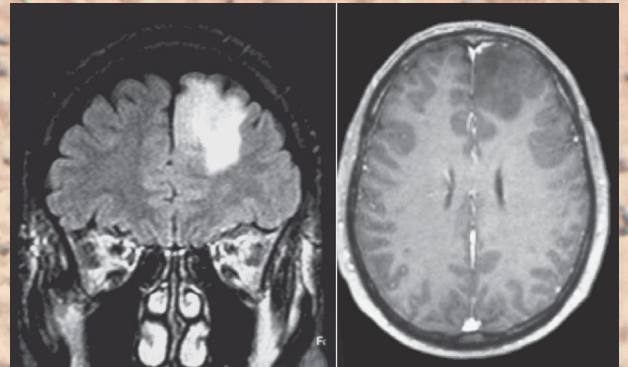
Epidemiology and Brain Tumours: Practical Usefulness

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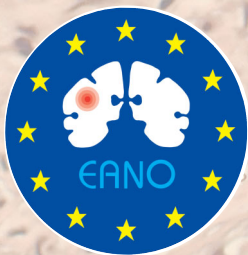
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Epidemiology and Brain Tumours: Practical Usefulness

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, ethnical 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.

Descriptive epidemiology further constitutes the basis for all risk factor research. With re-

gard to primary brain tumours, only few risk factors including certain germ-line mutations and exposure to ionizing radiation are known to date. Latest results from epidemiological studies focusing on the exposure to radiofrequency electromagnetic fields from mobile phones and their implications are addressed. However, not only environmental risk factor research but also the incorporation of molecular techniques in epidemiological study designs has considerably contributed to our present-day knowledge. Herein, the latest findings on genetic risk loci and tumour-specific sub- and risk groups are highlighted. Hence, the translation of all those

findings into clinical applicability is now a major aim and largely depends on the development of practical, robust, and widely accepted biomarkers, which will pave the way for individualized patient treatment. **Eur Assoc Neuro-Oncol Mag 2013; 3 (2): 56–60.**

Key words: brain tumour epidemiology, descriptive epidemiology, risk factor research, susceptibility loci, risk groups, ionizing radiation, non-ionizing radiation

■ 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 ethnical 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-

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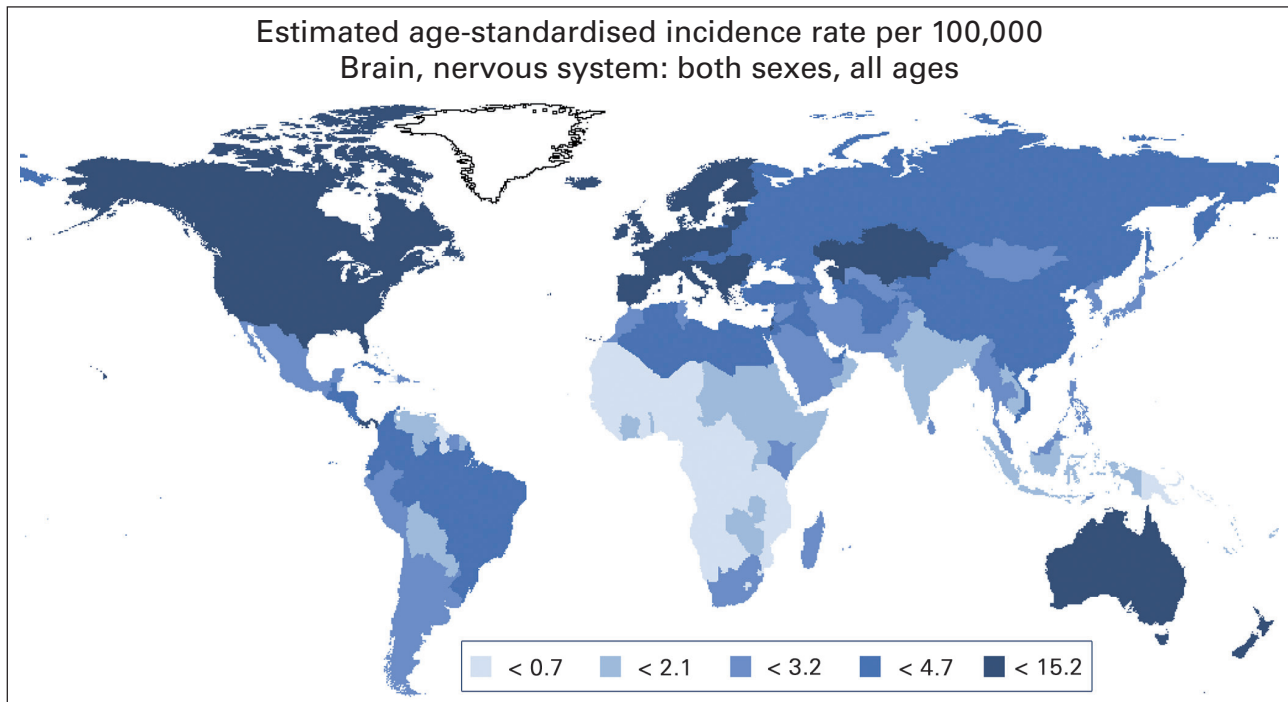


Figure 1. World-wide incidence of malignant brain tumour types. Source: [Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>, accessed on 29/01/2013]. The world-wide distribution of age-standardized incidence rates of malignant brain tumours shows higher rates of disease occurrence in developed countries.

tary, which are significantly more common in Afro-Americans [5]. These ethnic 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 occur-

rence 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-

Table 1. Genetic brain tumour syndromes [3].

Syndrome	Gene	Locus	Brain tumour
Cowden syndrome/Lhermitte-Duclos syndrome	PTEN	10q23	Dysplastic gangliocytoma of the cerebellum
Li-Fraumeni syndrome	TP53	17p13	Astrocytoma, PNET
Naevoid basal cell carcinoma syndrome/ Gorlin syndrome	PTCH	9q31	Medulloblastoma
Neurofibromatosis I	NF1	17q11	Neurofibroma, MPNST, optic and other gliomas
Neurofibromatosis II	NF2	22q12	Bilateral vestibular schwannoma, meningioma, ependymoma, and others
Rhabdoid tumour predisposition syndrome	SMARCB1/INI1	22q11.2	ATRT
Von-Hippel-Lindau syndrome	VHL	3p25	Hemangioblastoma
Tuberous sclerosis	TSC1 TSC2	9p34 16p13	SEGA, cortical tubers
Turcot syndrome	APC hMLH1 hPSM2	5q21 3p21 7p22	Medulloblastoma, glioblastoma
Familial meningioma	SUFU	10q24.32	Multiple meningiomas [31]

PNET: primitive neuroectodermal tumour; MPNST: malignant peripheral nerve sheath tumour; ATRT: atypical teratoid/rhabdoid tumour; SEGA: subependymal giant cell astrocytoma

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

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

PDGFRA: platelet-derived growth factor receptor- α ; EGFR: epidermal growth factor receptor; WNT: wingless int; SHH: sonic hedgehog; PNET: primitive neuroectodermal tumour

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). First CEFALO results did not demonstrate an exposure-response relationship in children and adolescents [30].

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-penetrance 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 metabonomics. 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 methyl-transferase (MGMT) promoter methylation status in glioblastoma [44], as well as MYCC/MYCN amplification and markers for WNT activation in medulloblastoma [45, 46]. While some of those markers are screened for in the setting of clinical trials (eg, MGMT, 1p19q, MYCC/MYCN amplification) serving as patient stratification factors, even less markers have already translated into routine clinical use, where they provide prognostic and/or predictive information on the individual patient (IDH1 mutational analysis and assessment

of combined 1p19q loss) [47]. With regard to the various biomarkers, clinical and analytical test performances remain an important issue [48] and there is a need for a widely accepted consensus among neuropathologists and neuro-oncologists on the levels of evidence and clinical utility of the various biomarkers.

Conclusion and Implications for Clinical Use

Brain tumour epidemiology provides basic information on the burden and force of the disease in the communities. It further allows for continuous monitoring of time trends in the incidence and survival at the population level. In contrast to clinical trials, which are prone to selection bias, population-based data provide a comprehensive picture of the real-life scenario, and are thus of high relevance to treating clinicians.

The majority of brain tumours are sporadic lesions. Rare genetic syndromes and prior exposure to ionizing radiation are the only established risk factors to date and account for < 10 % of all brain tumours. Latest risk factor research has focused on the exposure to radiofrequency electromagnetic fields from mobile phones. Despite conflicting study results the IARC has recently classified radiofrequency electromagnetic fields as possibly carcinogenic to humans, thereby indicating that additional studies focusing on long-term and heavy use are warranted. Whether this carcinogenic classification results in concrete legislative acts to protect public health remains to be shown. However, not only environmental risk factor research but also molecular epidemiology have considerably added knowledge. With the incorporation of molecular techniques into epidemiological study designs several low-penetrance susceptibility loci for glioma risk have been identified, which provide first insights into disease causation but await validation in larger cohorts focusing on specific glioma types. Likewise, rapid advances in genetic and transcriptome-based molecular research have provided information on the underlying biology of the most common malignant brain tumours and led to the identification of prognostically relevant sub- and risk groups. Hence, the translation of all those findings into clinical applicability now largely depends on the development of practical, robust, and widely accepted subgroup-specific biomarkers, which will pave the way for individualized patient treatment.

Conflict of Interest

None.

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