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Neuroepidemiology

Descriptive epidemiology and risk factors of primary central nervous system tumors: Current knowledge

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ABSTRACT

Although comparisons are difficult due to differences in methodologies, the annual incidence rates of central nervous system (CNS) tumors range from 8.5 to 21.4/100,000 population according to cancer registries, with a predominance of neuroepithelial tumors in men and meningiomas in women. An increase in the incidence of CNS tumors has been observed during the past decades in several countries. It has been suggested that this trend could be due to aging of the population, and improvements in diagnostic imaging and healthcare access, but these factors do not explain differences in incidence by gender and histological subtypes. Several etiological hypotheses related to intrinsic (sociodemographic, anthropometric, hormonal, immunological, genetic) and exogenous (ionizing radiation, electromagnetic fields, diet, infections, pesticides, drugs) risk factors have led to analytical epidemiological studies to establish relationships with CNS tumors. The only established environmental risk factor for CNS tumors is ionizing radiation exposure. However, for other risk factors, studies have been inconsistent and inconclusive due to systematic differences in study design and difficulties in accurately measuring exposures. Thus, the etiology of CNS tumors is complex and may involve several genetic and/or environmental factors that may act differently according to histological subtype.

1. Introduction

Central nervous system (CNS) tumors represent a complex heterogeneous group of pathological entities with different histological, clinical and prognostic statuses. The main histological subtypes are neuroepithelial tumors, meningiomas and neurinomas, and our knowledge of their epidemiology is based on mortality statistics and population-based cancer registries. While mortality statistics are exhaustive for

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lethal tumors, registries compile data for all tumors, including those of lesser lethality. Registries started collecting data on CNS tumors relatively late compared with other cancer sites because of specific difficulties in recording benign tumors, which account for half of all CNS tumors.

In the United States (US), a pilot study [the Surveillance, Epidemiology, and End Results (SEER) Program] compiled all CNS tumors diagnosed between 1984 and 1989 in four states (Connecticut, Massachusetts, Missouri and Utah) concurrently with general cancer registries, and was expanded to 11 states in 1992. However, it is only since 2004 that every state has been required to collect data on all CNS tumors, including benign ones (Central Brain Tumor Registry of the United States [CBTRUS]) [1].

In France, a registry of CNS tumors was implemented in Gironde in 1999 to add to data provided by a network of general cancer registries called FRANCIM [2,3]. This network has created a common database that brings together all cancer data from 13 'general' registries that collect data from all tumor sites, including the CNS, and 12 'specific' registries that are devoted to specific sites or populations, some dating back to 1975 [4]. A clinical French Brain Tumor Database (FBTD) was also implemented in 2004 to prospectively record all primary CNS tumor cases nationwide for which histological diagnoses were available, although the medical data were not individually reviewed to ensure that all the diagnoses were eligible [5]. Objectives of the FBTD were to perform epidemiological studies, implement clinical and basic research protocols, and standardize the healthcare of patients affected by primary CNS tumors.

Only a few countries, such as the United Kingdom (UK) [6], Austria [7] and Japan [8], have established surveillance of CNS tumors, making reliable data of their occurrence in time worldwide only partial and limited. Yet, despite the limitations and heterogeneity of registration procedures across cancer registries, the available data show an increase in the incidence of CNS tumors in recent decades, especially in the elderly. Although the incidence has recently tended to level off in some countries, such as the US [9], no such stabilization has been observed in other countries [3,10]. These temporal and geographical variations have led to several etiological hypotheses, related to intrinsic and exogenous risk factors, which have been investigated in epidemiological studies. Ionizing radiation, electromagnetic fields and pesticides are the risk factors that have received the most attention. However, apart from ionizing radiation, findings regarding other intrinsic and environmental risk factors remain unresolved. Several case-control studies have been conducted to explore the relationship between risk factors and brain tumors, especially neuroepithelial tumors. The present review examines the available data on the descriptive epidemiology of CNS tumors and their potential risk factors.

2. Descriptive epidemiology

This is an important tool for healthcare system actors. However, neurosurgeons, neuro-oncologists, epidemiologists, clinicians and politicians may have different opinions and interpretations of such health-related statistics.

2.1. *Incidence data*

Incidence (the number of new cases in a given population, usually per 100,000 inhabitants and per year) is the basic parameter used to describe the burden of CNS tumors in populations. Data on the prevalence of CNS tumors are rare [11,12]. Table 1 describes the annual incidence rates of primary CNS tumors according to population-based registries. Wide geographical variations have been observed, with incidence rates ranging from 8.5/100,000 in Estonia to 21.4/100,000 in the US. The incidence was 19.4/100,000 in the French department of Gironde, a higher rate than in most other studies. Meningioma was the most common brain tumor reported to the CBTRUS before glioma (7.6 vs 6.5/100,000), whereas the opposite pattern was observed for other registries, which may be expected as it was the first cancer registry to include benign tumors. However, caution is needed in comparisons of incidence rates, as real geographical differences, most probably due to intrinsic and environmental risk factors, cannot be excluded. Case-ascertainment methodology, histological classification, completeness, analysis periods and the standard population used for age adjustment of rates also vary across cancer registries, making it challenging to compare statistics. In addition, registries differ as to when they began to include reports of benign brain tumors. Final confirmation of CNS tumors can also vary by histological type and by region, while some tumors, such as meningioma and acoustic neuroma, are not microscopically confirmed but by radiography. Nevertheless, across registries, the standard approach is to include both brain and other CNS tumors in all statistics. Thus, all comparative statistics must be cautiously interpreted.

The incidence of tumors from the Gironde CNS Tumor Registry was presented in more detail, by histological subtype and gender, during the 2000–2012 period for a total of 3648 tumors (10% of medullary tumors) [13]. Neuroepithelial tumors (including 63% of glioblastoma) were the most frequent histological subtype in adults, and represented 41% of all tumors, ahead of meningeal tumors (36%), tumors of the cranial and spinal nerves (12%), lymphomas (3%) and other tumors (8%). These results were consistent with the FBTD, which included 43,929 histologically confirmed cases during 2004–2009 [14]. As expected, the CNS Tumor Registry included more tumors of the meninges than did the FBTD (36 vs 32%, respectively), which did not register tumors without histological confirmation.

Before 30 years of age, the incidence of neuroepithelial tumors is about 3/100,000, including childhood neuroepithelial tumors, mainly represented by astrocytoma (especially pilocytic), embryonal medulloblastoma and ependymoma. The incidence reaches 5/100,000 at age 50 years and sharply increases, exceeding 20/100,000 at age 70 before declining slightly in the extremely older age groups. The incidence of meningioma is lower before 30 years of age ($<$ 1/100,000), but rapidly increases, particularly in women, to exceed 10/100,000 after age 50 and 20/100,000 after age 80.

The incidence of CNS tumors is generally higher in women (21.8/100,000) than in men (18.4/100,000), but the gender pattern differs according to histological subtype. Neuroepithelial tumors are more frequent in men (9.7/100,000 vs 7.0/100,000