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CLINICAL STUDY – PATIENT STUDY

Is the incidence of brain tumors really increasing? A population-based analysis from a cancer registry

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Abstract Recently, an increasing incidence of brain tumors has been reported from multiple studies. Brain tumors diagnosed in the period 1985–2005 were identified through the Tuscan Cancer Registry, a population-based registry active since 1985 in the area of Florence and Prato. Age-standardized incidence rates and average annual percent change (APC) was calculated for the entire period from 1985 to 2005 for sex and behavior. A total of 4,417 brain tumors was registered, 1,900 (43%) in male and 2,517 (57%) in female patients. Malignant and benign tumor incidence rates were 8.3 and 4.1, respectively, among males and 6.4 and 7.2, respectively, among females. The age-adjusted annual incidence rate of all brain tumors was 13.9, with a statistically significant increasing rate throughout the period (APC: +3.2, CI 2.2–4.2). The annual incidence rate remained stable for malignant brain tumors but increased significantly for benign brain tumors (APC: +6.2, CI 4.5–7.9). In our population-based study, the incidence of brain tumors increased from 1985 to 2005 overall and for benign tumors, but not for malignant tumors. Part of the temporal variations may be attributed to improvement in diagnostic imaging techniques and, particularly for benign tumors, in changes in registration practice.

Keywords Brain tumor · Tumor incidence · Cancer registry · Population-based analysis

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Introduction

Brain tumors account for 1.7% of all new cancers [1] and similar rates have been reported from European and non-European populations [2, 3]. They represent a relatively uncommon group of neoplasms in terms of incidence, although they constitute a frequent form of cancer death, representing about 3.5% of the total cancer death rate [4].

Brain tumors constitute an heterogeneous group that includes morphologically malignant tumors as well as benign variants. Histological non-malignant tumors have an effect on survival because of their tendency to occupy space and tendency to undergo malignant transformation. Therefore, some authors consider it mandatory to include all tumors, malignant, borderline and benign, in registration of brain neoplasms [1]. Around 60% of pathological entities reported for CNS tumors are malignant in behavior although this percentage depends on the type of registration [1]. In fact, not all registries collect data on non-malignant tumors. Furthermore, anatomic, pathologic, and clinical features of brain tumors make it difficult to develop a correct classification of this heterogeneous group [5].

Recently, an increasing incidence of CNS tumors has been reported from multiple studies [1, 6]. However, part of this increase is probably not real but due to improvements in diagnostic techniques [1, 7].

Here, the incidence data on brain tumors from Tuscan cancer registry during the period 1985–2005 is presented and analyzed by age, sex and histology.

Materials and methods

Brain tumors diagnosed in the period 1985–2005 were identified through the Tuscan Cancer Registry, a

population-based registry active since 1985 in the area of Florence and Prato (inhabitants 1,150,000). The cancer registry receives copies of the patient records from hospitals, and these reports are collected into individual files for each tumor case by registrators of registry staff, under supervision of an epidemiologist and a pathologist. All the information concerning a single tumor is coded and entered into a computer. The registry receives documentation from hospitals as admission-discharge forms, ambulatories, pathology services, and from the regional mortality registry.

Cases are reported according to the International Classification of Diseases for oncology, second edition morphology codes (ICD-02) and the tenth revision topography codes (ICD-10). The spectrum of collected tumors comprises all malignant and non-malignant primary brain tumor types. Behavior is coded: 0 for benign tumors, 1 for low or uncertain malignant potential or borderline malignancy, 2 for in situ lesions, and 3 for malignant tumors.

Tumors at any of the following sites are collected: brain (C71.0–C71.9), meninges (C70.0–C70.9), spinal cord, cranial nerves and other part of CNS (C72.0–C72.9), pituitary and pineal glands (C75.0–C75.9). The data obtained are classified into diagnostic groups according to the WHO 2000 [8] classification on the basis of ICDO-2 morphology codes. CNS lymphomas and haemopoietic neoplasm were excluded.

Available information includes year of diagnosis, age at diagnosis, sex and diagnostic confirmation. Diagnostic confirmation codes indicating "positive histology", "positive cytology no positive histology" and "positive microscopic confirmation, method not specified" were considered microscopically confirmed. Codes indicating "positive laboratory test/marker study", "direct visualization without microscopic confirmation", "radiography and other imaging techniques without microscopic confirmation", "clinical diagnosis only, unknown whether or not microscopically confirmed" were considered not microscopically confirmed.

Population-based incidence rates were calculated for brain tumors as a group as well as for individual tumor types. Incidence rates were age-standardized to the year 2000 European standard population. Average annual percent change (APC) was calculated for the entire period from 1985 to 2005 for sex and behavior. All the reported incidence rates are per 100,000 (person years).

Results

A total of 4,417 brain tumors was registered within the period from 1 January 1985 to 31 December 2005. Of these, 1,900 cases (43%) were diagnosed in male, and 2,517 cases (57%) in female patients. Benign and borderline brain tumors constituted 48% (2,123 cases) with incidence rates of 5.8 and 0.9, respectively; malignant brain tumors accounted for the remaining 52% (2,291 cases), with an incidence rate of 7.3.

By gender, the age-adjusted annual incidence rate among males was 8.3 for malignant (1,194 cases), 4.1 for benign (597 cases) and 0.9 for uncertain or borderline tumors (113 cases). Among females, the rate was 6.4 for malignant (1,097 cases), 7.2 for benign (1,293 cases), and 0.9 for uncertain or borderline tumors (121 cases) (Fig. 1).

The age-adjusted annual incidence rate of all brain tumor was 13.9, with an increasing rate from 1985 [10] to 2005 (14.3) and the increase was statistically significant (APC: +3.2, CI 2.2–4.2) (Fig. 2). The rate increased more in females (9.1 in 1985 and 14.8 in 2005, APC: +3.9, CI 2.9–5) than in males (10.9 in 1985 and 13.5 in 2005, APC: +2.3, CI 1.1–3.4) throughout the period.

Malignant brain tumors age-adjusted annual incidence rate remained stable (6.9 in 1985 and in 2005, APC: 0.6, CI −0.3–1.4) (Fig. 2). An increased incidence rate among females was revealed with a statistical significance (5.2 in 1985, 5.7 in 2005, APC: +1.3, CI +0.3, +2.3); among males trend was stable (8.6 in 1985, 8.9 in 2005, APC: 0, CI −1.2, +1.3). Benign brain tumors age-adjusted annual incidence rate significantly increased from 3.1 in 1985 to 6.1 to 2005 (APC: +6.2, CI 4.5–7.9) (Fig. 2). The increase was in both females (3.9 in 1985 and 7.8 in 2005, APC: 5.9, CI 4.2–7.6) and males (2.1 in 1985 and 4.3 in 2005, APC: +6.7, CI 4.7–8.7).

Among all brain tumors, 49% were histologically confirmed and this proportion decreases over time (50.4% in 1985–1994, 46.2% in 1995–2005). Specifically, 51% of malignant, 44% of benign and 31% of borderline brain tumors were histologically verified, while 38% were radiologically and 13% clinically diagnosed cases.

According to the WHO brain tumor classification system, tumors were grouped according to the evaluation of ICDO-2 morphology codes. If tumors not specified (40% of

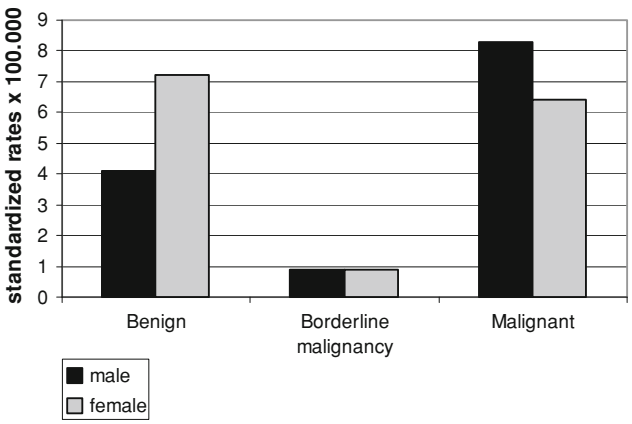

Fig. 1 Brain tumors standardized incidence rates (per 100,000) by gender and by behavior from 1985 to 2005

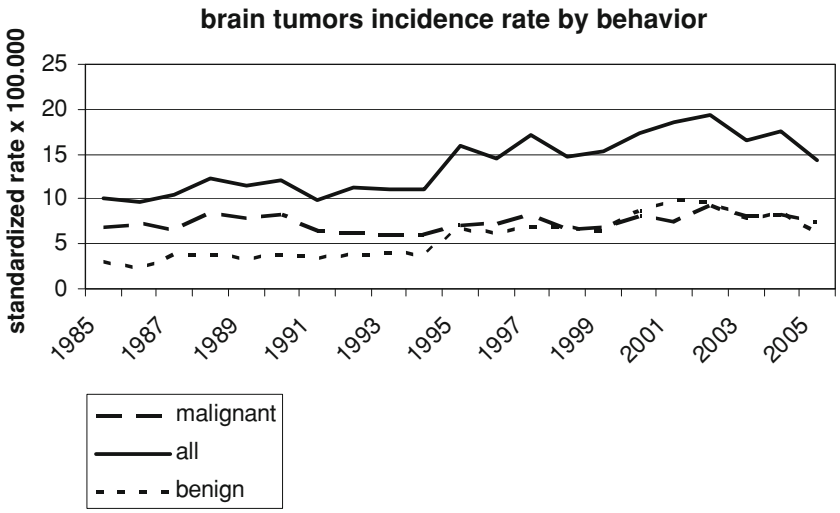

Fig. 2 Trends in age standardized incidence rates (per 100,000) of brain tumors according to behavior

all tumors) were excluded, neuroepithelial tumor constituted the largest group of primary brain tumors (1,267, 28.7%), followed by tumors of the meninges (1,258, 28.5%) (Table 1). Among the neuroepithelial tumors, astrocytic tumors accounted for 25.3% of all primary tumors (incidence rate 3.8), followed by oligodendroglial tumors (1.3%, incidence rate 0.2); among astrocytic tumors, glioblastomas accounted for 14.8% of all primary tumors (incidence rate 2.1).

By gender, meningiomas were more frequent in females, while gliomas were more common among males (Table 1).

The age-specific annual incidence rate of brain tumor was low in childhood (4.0, 5–9 years of age), adolescence (4.1, 10–14 years of age and 3.9, 15–19 years of age) and young adulthood (4.0, 20–24 years of age, 4.1, 25–29 years of age). Then incidence rates increased (6.2, 30–34 years of age, 8.3, 35–39 years of age) reached a peak in the age group 75–79 years (48.8), decrease in advanced age (38.5, 85 + years of age) (Fig. 3). Age specific incidence showed similar rates until 60 years of age for malignant and benign tumors, then incidence rates increased more for malignant than for benign tumors (60–64 age group: incidence rate 13.6 for benign, 18.1 for malignant).

Age distribution of benign tumors was similar over time, although an higher incidence rate in the 2001–2005 than in 1985–1989 period was showed, particularly for older age group (70–74 age group: benign tumor incidence rate 10.3 in 1985–1989, 25.7 in 2001–2005).

Among children and adolescents groups, which comprise 188 cases (4.2%) of all brain tumors registered, the age-specific incidence rate was highest in very young children (5.6, 0–≤5 years of age).

The most common tumor in this age cohort (0–18 years of age) was pilocystic astrocytoma followed by medulloblastoma, while among adults, the most common histologic types were meningiomas, astrocytomas and glioblastomas.

Table 1 Standardized incidence rates (per 100,000) of brain tumors according to WHO classification from 1985 to 2005

	Male		Female		Total	
WHO histology grouping	*n*	Rate	*n*	Rate	*n*	Rate
Tumors of neuroepithelial tissue						
Astrocytic	608	4.4	512	3.3	1,120	3.8
Oligodendroglial	27	0.2	32	0.2	59	0.2
Ependymal	22	0.2	21	0.2	43	0.2
Choroid plexus	0.0	0.0	1	0.0	1	0.0
Neuronal and mixed neuronal-glial	6	0.1	5	0.0	11	0.1
Pineal	0.0	0.0	1	0.0	1	0.0
Embryonal	20	0.2	12	0.1	32	0.2
Tumors of cranial and spinal nerves	58	0.5	58	0.5	116	0.5
Tumors of the meninges						
Meningothelial cells	356	2.3	873	4.9	1,229	3.7
Mesenchymal, non meningothelial	17	0.1	12	0.1	29	0.1
Germ cell tumors	1	0.0	0	0.0	1	0.0
Tumors of the sellar region	1	0.0	2	0.0	3	0.0
Unclassified tumors	784	5.2	988	5.1	1,772	5.2
Total	1,900	13.3	2,517	14.4	4,417	13.9

Discussion

The age-adjusted annual incidence rate of all brain tumor was 13.9 and a statistically significant increasing rate was apparent from 1985 to 2005.

Recently, an incident rate for primary brain tumors of 18.7 per 100,000 person years has been reported by the Central Brain Tumor Registry of the United States (CBTRUS) and prevalence rates of 209.00 per 100,000 in 2004 and 221.8 per 100,000 in 2010 were estimated [2, 9,

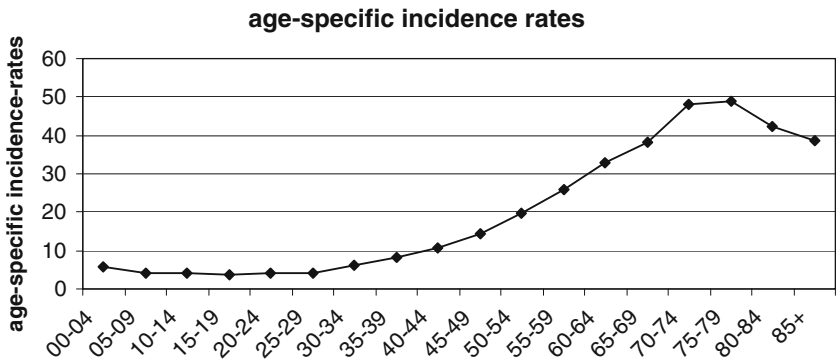

Fig. 3 Age-specific incidence rates (per 100,000) of brain tumors from 1985 to 2005

10]. Using national cancer registration data, Arora et al. [1, 3] recently reported an overall age-standardized incidence rate in England of 9.13 in the period 1999–2003, while the Austrian National Cancer Registry found an age-adjusted incidence rate of 18.1 per 100,000 in 2005.

Differences may reflect variations in reporting. Under-reporting of benign tumors has been suggested by some authors, and differences in definitions, lack of complete case definition, differential use of diagnostic techniques and possible differences in neuropathology practice have been reported to affect the comparability of data among registries [11]. In most countries, brain tumor registration is restricted to malignant tumors and only a few countries report incidence rates fn benign and borderline brain tumors [3]. However, evaluation of benignity in brain tumors depends on tumor location and morphology other than behavior [11]. In the literature, the percentage of benign tumors generally ranges from 25.4 to 54.4% [10, 11]. In the present study, 48% of all collected tumors had non-malignant behavior.

Our analysis showed that benign brain tumors were more frequent in females as compared with males. These results are concordant with those from a population-based study on 1,688 primary brain tumors which confirmed the female predominance, mainly due to the amount of meningiomas [3]. A recent analysis from CBTRUS also reported that the overall incidence rate is higher in females than in males [10.]

In agreement with data available in the literature, in the present study, age-specific incidence rates were low in childhood, increased in adulthood until the age group 75–79 years, then declined [11]. As recently reported in the literature, the age-specific incidence rates in childhood are highest in the very young (0–5 years of age) [3]. An analysis from CBTRUS reported that 9% of all tumors were diagnosed at ages less than 20 years with an incidence rate of 3.8 per 100,000 [11]. A recent study on data from England's national cancer registration system from 1995 through 2003 reported age-standardized rates of 3.56, 3.26 and 14.57 per 100,000 for 0–14, 15–24 and 25–84 years age groups, respectively [12]. In an analysis from Japan between 1989 and 2008, annual incidence rates were found of 28.5, 40.9 and 38.4 per million for the 0–4, 5–9 and 10–14 years age groups, respectively [13].

In brain tumor diagnosis, histology remains the gold standard. However, in our study, only 49% of all brain tumors were histologically confirmed; the analysis through 1985–2005 showed a decrease in this proportion. In the literature, the percentage of 60–80% histologically verified brain tumors have been reported [3, 9–11]. In the Tuscan Cancer Registry, the proportion of microscopic verification is nearly 80%, but for some tumor sites such as the brain the proportion is lower, according to reports from the Italian Network of Cancer Registries (52% of microscopic confirmed for brain tumors), since clinical diagnostic practice is oriented toward other non-invasive techniques in the absence of surgery [14]. Microscopic confirmation was higher among malignant than benign tumors, which are more frequently radiologically diagnosed and not surgically removed [3].

According to the literature, if we exclude neoplasms not specified, neuroepithelial tumors constituted the largest group of primary tumors, followed by meningiomas [3]. Comparable trends were reported in the literature [5], although some authors suggested that meningiomas that are not treated surgically and lack histological confirmation could be underreported [15]. In CBTRUS analysis, meningiomas were the most frequently reported histologically, followed by glioblastomas and astrocytomas [11].

By gender, neuroepithelial tumors were more frequent in male and meningiomas in female patients, as recently reported in the literature [3, 11]. By age, pilocytic astrocytoma followed by medulloblastomas was the most represented tumor in the age group 0–18 years, while in the older patients, meningiomas, astrocytomas and glioblastomas were the most frequent diagnosed tumors, according to recent reports [3, 16].

An increase in brain tumors incidence has been reported, especially among the elderly, by numerous authors [1, 17], and it has been debated whether this increase is due to a

true increase in incidence, caused by an unidentified risk factor, or whether it reflects improved diagnostic techniques [4, 7, 17].

Incidence rates for brain and CNS cancer have increased in the Nordic countries in the last few decades, ranging from 10–12 per 100,000 among men and between 11 and 13 per 100,000 among women [4]. On the other hand, it has recently been reported that the incidence of gliomas and meningiomas did not increase between 1974 and 2003 in four Scandinavian countries [18]. Similar trends in brain tumor incidence have been found in Canada and France, where the increase leveled off around 2000 [19]. Recently, a decrease in brain tumor incidence has been reported in some countries [4]. In our population-based study, the overall incidence of brain tumors from 1985 to 2005 has increased, and the increment is statistically significant for benign tumors.

Part of the increase in incidence may be explained by increasing use of neuroimaging techniques. In fact, the improvement in registration of benign tumors and in diagnostic methods have been suggested to be the cause of this increase [1, 7, 18], although some authors hypothesize a real increase for some types of brain tumors [17]. The incidence decrease recently observed in Sweden has been attributed to a reduced autopsy intensity among the elderly, an underreporting, or an age-specific differential in the use of new imaging techniques [4]. Data on tumors of the nervous system from surveillance, epidemiology and end results (SEER) program of the National Cancer Institute have reported a statistically significant decreasing trend from 1992 to 2007 [20]; interestingly, during the period of this analysis, cell phone use has become common [20]. However, mixed findings have been reported from multiple studies on mobile phone use and risk of brain tumors, without a clear indication of an increased risk of cancer [21]. Lack of detection, misdiagnosis, and incomplete registration are suggested to influence different and sometimes unexpected effects, such as the recently found protective effect of regular use of mobile phones [21]. Incidence is influenced by registration practice, by the greater diagnostic specificity with a consequent shift in registered categories, and by the underreporting of tumors, particularly for unbiopsied neoplasms [1, 4]. Moreover, interpretation of the temporal variations of brain tumors is problematic because the group of brain tumors comprises different histological subtypes with varying prognoses.

The overall incidence of brain tumor increased mainly for benign tumors, and we think that the increase can be attributed in most part to improvements in diagnostic techniques and changes in registration practice. However, further observations are needed to evaluate the real trend of brain tumor incidence: descriptive patterns of brain tumor incidence can be monitored through analyses of high quality cancer registries [22], by comparing results from different registries, and by detecting changes suggestive of possible etiologic modifications. Registration practices are not always the same and different results perhaps depend on different types of registry (specific or general): thus, a collaboration between neurosurgeons, pathologists, neurologists, oncologists and epidemiologists is needed to record and analyze the real epidemiology of primary brain tumors.

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