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Original Article

Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000–2008): Findings of a multicenter Australian study

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Abstract

Background: The incidence of primary brain tumors by subtype is currently unknown in Australia. We report an analysis of incidence by tumor subtype in a retrospective multicenter study in the state of New South Wales (NSW) and the Australian Capital Territory (ACT), with a combined population of >7 million with >97% retention rate for medical care.

Methods: Data from histologically confirmed primary brain tumors diagnosed from January 2000 through December 2008 were weighted for patient outflow and data completeness, and age standardized and analyzed using joinpoint analysis.

Results: A significant increasing incidence in glioblastoma multiforme (GBM) was observed in the study period (annual percentage change [APC], 2.5; 95% confidence interval [CI], 0.4–4.6, $n = 2275$), particularly after 2006. In GBM patients in the ≥65-year group, a significantly increasing incidence for men and women combined (APC, 3.0; 95% CI, 0.5–5.6) and men only (APC, 2.9; 95% CI, 0.1–5.8) was seen. Rising trends in incidence were also seen for meningioma in the total male population (APC, 5.3; 95% CI, 2.6–8.1, $n = 515$) and males aged 20–64 years (APC, 6.3; 95% CI, 3.8–8.8). Significantly decreasing incidence trends were observed for Schwannoma for the total study population (APC, −3.5; 95% CI, −7.2 to −0.2, $n = 492$), significant in women (APC, −5.3; 95% CI, −9.9 to −0.5) but not men.

Conclusion: This collection is the most contemporary data on primary brain tumor incidence in Australia. Our registries may observe an increase in malignant tumors in the next few years that they are not detecting now due to late ascertainment. We recommend a direct, uniform, and centralized approach to monitoring primary brain tumor incidence by subtype, including the introduction of nonmalignant data collection.

Key Words: Australia, cancer, incidence, late ascertainment, primary brain tumor

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INTRODUCTION

Trends in the overall incidence of primary brain tumors have been widely reported as either increasing,[4,12,15,20] stable,[6,13] or decreasing.[13] A large Danish study[4] of 11,935 cases of adult glioma between 1943 and 1997 reported a 1.7-fold increase in the incidence from 2.2 to 3.7 cases per 100,000 person-years. Histological confirmation was found in almost all glioma cases in the last 20 years of that study. The authors also examined 4845 cases of adult meningioma during the same period and reported a 3.9-fold increase from 0.61 to 2.42 cases per 100,000 person-years. Surprisingly, the increasing incidence trend over time associated with glioma was seen to plateau after 1968, well before Denmark's introduction to computerized tomography (CT) in 1978 and magnetic resonance imaging (MRI) in 1985. On the other hand, the authors found that the incidence of meningioma continued to rise throughout the years studied, possibly related to a lower clinical threshold for imaging older patients. A second study of 18,630 cases of adult primary intracranial meningioma encompassed Denmark, Finland, Norway, and Sweden from 1968 through 1997.[18] Increasing trends were again noted in both males (1.4–1.9 cases per 100,000 person-years) and females (2.6–4.5 cases per 100,000 person-years). The authors suggested this was due to the widespread use of new imaging technologies.[18] The updated study however, covering the same region from 1974 to 2003 and almost 60,000 patients aged 20–79 years, showed increasing incidence rates for glioma and meningioma overall, but flattening of trends in the latest years 1998–2003.[8]

In the United States, Inskip *et al*.[13] analyzed almost 40,000 brain cancer cases over a 30-year period from 1977 to 2006 using the Surveillance, Epidemiology and End Results (SEER) database and reported stable, even decreasing, overall incidence rates in most age groups. During the earlier study period (1977–1991), large and statistically significant increases were demonstrated in persons aged <30 and ≥65 years. In the later study period (1991–2006), a stable incidence was reported across the board, with the exception of females aged 20–29 years who showed a significant increasing trend in frontal lobe malignancies (annual percentage change [APC], 4.27; 95% confidence interval [CI], 1.88–6.71). Interestingly, although incorporating brain *cancer* subtypes including metastatic disease but excluding meningioma and lymphoma (and thus not directly comparable to the current study), the authors highlight expected delay adjustment with an upward revision of incidence rates, so the observed increases may in fact be underestimates. This phenomenon termed "late ascertainment"[5] is common to many cancer registries and is associated with a data lag of 3–5 years that is also reflected in Australian registries.

An absence of any overall trend in the incidence of brain cancers in both males and females in the population of England during 1998–2007 was recently reported.[7] This stable incidence trend, along with the leveling off of incidence trends in four Nordic countries during 1974-2003, has led some authors to conclude that mobile phones result in no significant increased risk of brain tumors.[8] However, given an expected delay between long-term near-field electromagnetic radiation exposure and tumor detection, the European study[8] was criticized for stopping case ascertainment in 2003,[11] and for not presenting results stratified by anatomic site.[10] In this regard, our recently published Australian study[9] reported a significant increase in the malignant tumor incidence most evident from 2006 onward, although at that time, analyses of incidence pertaining to tumor subtypes were not available. Further, the English study[7] that reported no change in the overall incidence did report results stratified by anatomic site and found significantly increased rates of tumors of the temporal lobe in both men and women, and increased rates in frontal lobe tumors in men only. Such changes may not be due to chance occurrence.[19] Regardless of risk association,[11,14,16] these data reflect an ongoing need for incidence trend monitoring of both malignant and nonmalignant tumors.

Given the limited data regarding primary brain tumor incidence from Australasian sources, our goal was to develop an understanding of the Australian incidence with age-, sex-, and pathology-specific analyses and trends. The three pathological subtypes analyzed in this paper, namely glioblastoma multiforme, meningioma, and Schwannoma, are consistent with previous publications,[11,13,16] including INTERPHONE.[14] Further, because Australia lags behind the United States and Europe by several years in terms of the proliferation of imaging technology and mobile phone use, we feel that now is an optimal time to begin data collection and pave the way for future association studies.

MATERIALS AND METHODS

A full account of our methods has been published recently.[9]

Database

A retrospective multicenter analysis was performed from January 2009 through July 2010 of all 13 pathology databases servicing the 24 neurosurgical centers, including all major teaching hospitals, in the Australian Capital Territory (ACT) and New South Wales (NSW) recording brain tumors diagnosed during 2000–2008. The population of NSW and ACT increased from 6.8 to 7.3 million between 2000 and 2008. Databases were queried with control for repeated presentations to and tumor recurrence in individual institutions. Data were initially

collected for years 1994–2008, with complete data from all centers available from mid-1999.[9]

Inclusion and exclusion criteria

Approximately 12,000 records were analyzed for the period of diagnosis (2000–2008), with exclusion of records based on diagnosis, topography, and completeness, yielding a total of 7251 records for final analysis. All tumors were microscopically confirmed at a single pathology department but no independent review was performed as this was beyond the scope of the current study. Systemic lymphoma, and metastatic, extracerebral, and germ cell tumors were excluded from the analysis (not presented but discussed in our previous paper[9]), as were tumors in patients from overseas or other Australian states and territories. The analysis included pituitary, craniopharyngeal duct, and pineal tumors, and hemangioma, hemangiopericytoma, primary central nervous system (CNS) lymphoma, and cranial nerve tumors.[9]

Coding and grading

International Classification of Diseases, 10th Edition (ICD-10), and Systematized Nomenclature of Medicine (SNOMED) classification systems were used to code all records according to 2004 guidelines of the Centers for Disease Control and Prevention.[3] Tumors were graded according to the 2007 World Health Organization (WHO) Classification of Tumors publication.[21] The initial but not any representing diagnosis of each patient was used for our analysis.[9]

Standardization and statistical analysis

The ACT and NSW populations were used to benefit from the relatively low outward migration rate. Cross-border flows were estimated at 3.2% using 2008 Australian Hospital Statistics data for public and private hospitals[1] and an overall weighting for patient outflow, inflow, and data completeness of 5% was used. Incidence rates were age-adjusted using the direct method and were standardized to the 2001 Australian Standard and 2006 Australian Census population in 5-year age groupings. Incidence rates were also standardized to the 2000 US Standard Population and 2000 World Standard Population using the direct method of analysis. Unless otherwise specified, the reporting of incidence rates has been limited to US standardized rates for ease of comparison with the existing literature. Log-linear Poisson regression was used to statistically compare trends over time.[9,12,17] Trends were expressed as annual percentage change over the 9-year period, with corresponding two-sided 95% CIs using up to two joinpoints with log-linear modeling for average annual percentage change calculation (AAPC). Trends were also analyzed in the same fashion over the period 2001–2006. Joinpoint regression software, version 3.3.1, was used to identify any sharp changes in the incidence as described elsewhere.[9]

RESULTS

Incidence by pathology

The most frequently encountered histology was a malignant tumor, glioblastoma multiforme (GBM; 30%, n = 2275) followed by a predominantly nonmalignant tumor, meningioma (24%, n = 1865). Pituitary tumors and Schwannoma accounted for 13% (n = 960) and 6% (n = 492) of all tumors, respectively. The primary malignant tumor incidence was found to have increased by approximately 35% between 2000 and 2008 (APC, 3.9; 95% CI, 2.4–5.4) with most of this increase occurring after 2006 [Figure 1a–c].[9]

Glioblastoma

A weighted total of 2275 GBM (n = 2197, 96.5%), gliosarcoma (n = 62, 2.7%), and giant cell glioblastoma (n = 17, 0.7%) were collected during 2000–2008, with a 1.6:1 male:female predominance. A significant increase in the incidence of all GBM from 3.22 to 3.96 cases per 100,000 person-years was observed in the study period of years 2000–2008 (APC, 2.5; 95% CI, 0.4–4.6; Figure 1a). During the same period, in patients in the ≥65-year group, the incidence rates increased from 10.30 to 14.42 cases per 100,000 person-years (APC, 3.0; 95% CI, 0.5–5.6) for both men and women combined [Figure 2]. This significant increase held for men (13.55–18.71 cases per 100,000 person-year; APC, 2.9; 95% CI, 0.1–5.8) but not for women (7.77–10.92 cases per 100,000 person-year; APC, 3.2; 95% CI, −2.9 to 9.6; Table 1; Figure 2).

Meningioma

A weighted total of 1865 meningiomas were collected during 2000–2008, with a 2.6:1 female:male predominance. Of these tumors, 92% were WHO Grade I, 7% WHO II, and 1% WHO III. From 2000 to 2008, a significantly increasing incidence trend in meningioma in men, both for total male population (APC, 5.3; 95% CI, 2.6–8.1, n = 515) and in males aged 20–64 years (APC, 6.3; 95% CI, 3.8–8.8), was observed [Table 1; Figures 1b and 3]. Incidence rates ranged from 1.1 to 1.8 cases per 100,000 person-years during 2000–2008 for all meningioma cases, and 1.2 to 2.0 cases per 100,000 person-years for men aged 20–64 years.

Nerve sheath tumors

A weighted total of 492 nerve sheath tumors were used in the analysis, with a 1.1:1 female:male ratio. The current collection did not include extra-cerebral nerve sheath tumors, so the majority (76%) were labeled acoustic neuroma/vestibular Schwannoma, 12% were labelled as cerebellar, and 12% as cerebral not otherwise specified (NOS). A significantly decreasing trend was observed in all Schwannoma cases for the period of 2000–2008 (APC, −3.5; 95% CI, −7.2 to −0.2), that was significantly present in women (APC, −5.3; 95% CI, −9.9 to −0.5) but

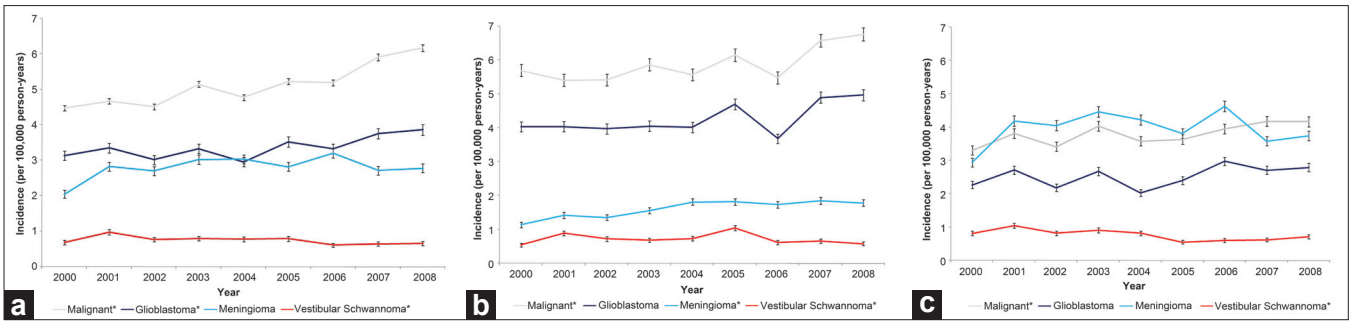

Figure 1: US standardized brain tumor incidence rates by major histological groupings by calendar year in the Australian Capital Territory and New South Wales populations for the (a) total population, (b) male population, and (c) female population. Confidence intervals are displayed. Asterisk denotes significance

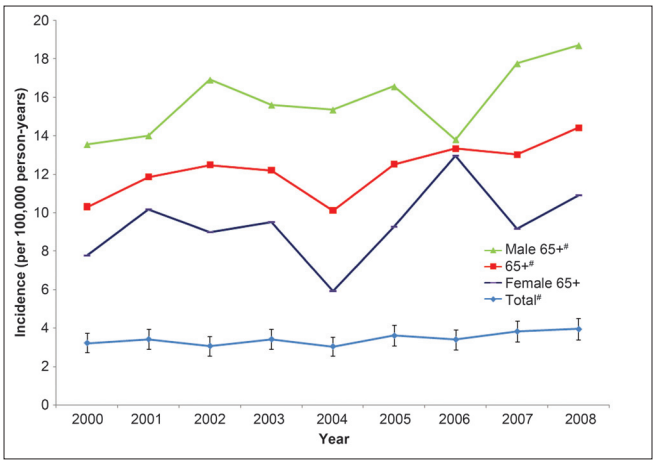

Figure 2: US standardized brain tumor incidence rates for glioblastoma multiforme by calendar year in the Australian Capital Territory and New South Wales populations for the total population, total population aged 65 years and above, and male population aged 65 years and above. Confidence intervals are displayed. All three trends show a significant (*) increase using joinpoint analysis

Table 1: Overall incidence rate trends, by annual percentage change, for primary brain tumors in the Australian Capital Territory and New South Wales populations

Subgroup**	No. of cases	APC	(95% CI)
Glioblastoma multiforme			
All persons	2275	2.5*	0.4, 4.6
Women	885	2.2	−1.5, 6.0
Men	1390	2.6	−0.1, 5.4
Persons aged ≥65 years			
All	1027	3.0*	0.5, 5.6
Women	438	3.2	−2.9, 9.6
Men	589	2.9*	0.1, 5.8
Meningioma			
All persons	1865	1.9	−1.6, 5.5
Women	1350	0.6	−3.6, 5.0
Men	515	5.3*	2.6, 8.1
Persons aged 20–64 years			
All persons	1227	1.9	−0.9, 4.9
Women	936	0.5	−3.2, 4.4
Men	291	6.3*	3.8, 8.8
Schwannoma			
All persons	491	−3.5*	−7.2, −0.2
Women	258	−5.3*	−9.9, −0.5
Men	233	−1.0	−7.9, 6.3

CI indicates confidence intervals, *Significance of the APC. Note that APC values are statistically significant from the value 0, **All models use exponential Poisson regressions and were adjusted for age groups, APC: Annual percentage change

not in men (APC, −1.0; 95% CI, −7.9 to −6.3; Table 1; Figures 1a–c and 4). Part of our dataset on nonmalignant tumors included the collection of nonhistologically confirmed data from the largest stereotactic radiosurgery (SRS) center in the region. Even upon the exclusion of the SRS data, analysis for both meningioma and nerve sheath tumors in the period 2000–2008 maintained the significant trends described above (data not shown).

DISCUSSION

The key finding of this two-part study[9] is a significant increase in primary malignant brain tumors, particularly GBM, occurring over the time period 2000–2008, especially evident after 2006.

Glioblastoma

The recent published incidence rates (2004–2006) from the Central Brain Tumor Registry of the United States (CBTRUS) for GBM (3.17 ± 0.04 per 100,000 person-years)[2] are similar to rates from the present study averaged over the period (~3.4 ± 0.51 per 100,000 person-years). Incidence rates and trends over the period 2000–2008 from our study are also similar to the Danish results discussed above.[4] Further, when our data were analyzed using multiple joinpoints in the time period 2001–2006, that is, the years for which there are corresponding published Australian cancer registry data, no significant increase was seen (data not presented). Our findings are therefore also consistent with the most up-

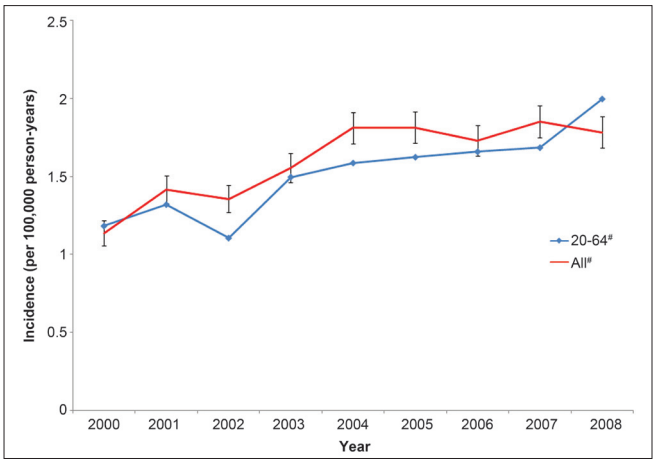

Figure 3: US standardized brain tumor incidence rates for meningioma for the total male population and male population aged 20–64 years by calendar year from the Australian Capital Territory and New South Wales populations. Confidence intervals are displayed. Both trends show a significant (*) increase using joinpoint analysis

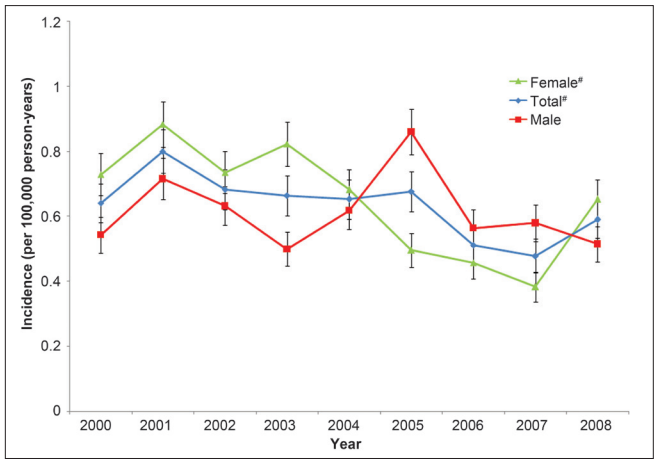

Figure 4: US standardized brain tumor incidence rates, by sex, of Schwannoma in the Australian Capital Territory and New South Wales populations, by calendar year. Confidence intervals are displayed. Asterisk denotes significance

to-date data on malignant tumors from our local cancer registries, except that the increasing trend we report herein is largely due to the higher brain cancer incidence observed in the years 2007 and 2008, data that may not have as yet been received and/or analyzed by Australian registries. Our relatively early access to these data via the direct analysis of local pathology databases has been discussed in the first part of this study.[9]

Meningioma

Significant trends were observed for meningioma in the period 2000–2008, particularly in men. These trends held significance when nonhistologically confirmed tumors from the region's largest SRS center were excluded (data not presented). The 2010 CBTRUS report for data for the period 2004–2006 quotes the incidence of male meningioma as 3.76 (95% CI, 3.70–3.83) cases per 100,000 person-years.[2] This rate is higher than US standardized rates from the present study. A trend analysis using the same database (CBTRUS) over the years 1985–1999 reported an increase in the overall meningioma incidence (AAPC, 1.5),[12] but no significant trends by gender. Incidence rates from the current study are thus more akin to observed rates and increasing trends for meningioma in Europe during the approximate period 1970–2000 described above.

Nerve sheath tumors

Female nerve sheath tumors in the 2010 CBTRUS publication quote an incidence rate of 1.60 (95% CI, 1.57–1.64) cases per 100,000 person-years.[2] Although these rates are higher than US standardized rates for vestibular Schwannoma in the present study, CBTRUS data also include both malignant and nonmalignant nerve sheath tumors in the quoted rate. A study examining vestibular Schwannoma data from two sources (CBTRUS 1995–1999, and the Los Angeles County Cancer Surveillance Program 1995–1998) found average annual incidence rates of 0.55 (95% CI, 0.51–0.58) and 0.80 (95% CI, 0.66–0.94) cases per 100,000 person-years, respectively, in females.[22] The incidence for nerve sheath tumors was approximately 1.07 cases per 100,000 person-years for both sources in the same study. These rates are more in keeping with the present study.

A recent study from Denmark presenting 2283 cases of vestibular Schwannoma over a 42-year study period reported an increasing incidence from 0.31 to 2.28 tumors per 100,000 person-years between 1976 and 2004, and stabilizing at 1.94 tumors per 100,000 person-years in 2008.[23] The study is unique in that all cases of vestibular Schwannoma in Denmark are referred to a single center for treatment, and the data have been prospectively entered into a database since 1976. Increased clinical awareness and technological advances in MRI technology seem to have accounted for the increase in the incidence, and the 2008 rate is considered by those authors as a true incidence. Our rates of vestibular Schwannoma are considerably less than those reported in Denmark, and show a decreasing trend. This may be due in part to changing clinical practice in the treatment of vestibular Schwannoma toward nonoperative (SRS) management.

Strengths and limitations of this study

We are primarily concerned with histologically confirmed primary intracerebral tumors and our collection excludes tumors diagnosed solely based on clinical, imaging, and post-mortem examination. Our study has a relatively high rate of histological specificity, with a low rate of nonspecific codes used,[9] and we believe this strength

will allow more precise and timely trend analysis through sourcing of brain tumor incidence data at the point of definitive diagnosis, namely, the pathology department. We also consider it a methodological strength that a different definition of "malignant" tumors has been used in the present study when compared to established Australian practice. Our definition is based on WHO Grade III and IV tumors and excludes lymphoma, metastatic disease, germ cell and extracerebral tumors, whereas Australian registries include WHO Grade II tumors of uncertain/borderline behavior among others in their definition.[9,24-27] Defining brain tumors in terms of the WHO Classification of CNS tumors allows the use of the most contemporary and widely used classification system in the international literature, and thus a more optimal comparison of rates within and between countries.

The limitations of our study have been described in our preceding publication.[9] Briefly, the main limitations we encountered involved the uncertainty regarding the completeness of case capture rates due to lack of standardization, lack of independent pathological review of diagnoses, lack of multiple sources of notification, the presence of cross-talk between databases, and lack of control for re-entry of data from the one patient visiting multiple different institutions in the study area (an uncommon situation anecdotally). Although we have attempted to validate our incidence rates through direct comparison of malignant rates with our gold standard in Australia (i.e., the cancer registries), we acknowledge that there is no such comparator for nonmalignant tumors in Australia. This implies a cautious approach when interpreting our published nonmalignant tumor rates but at the same time provides the first Australian insight into their "ball-park" incidence rates.

CONCLUSION

The current study represents the most contemporary collection of primary brain tumors in Australia and underpins the importance of continued monitoring. We observed significant increases in incidence rates for GBM, particularly after 2006, and meningioma with overall incidence rates comparable to recent US and European data. Incidence trends for Schwannoma, in contrast to the European experience, were observed to be significantly decreasing, but were akin to overall Schwannoma incidence rates from the United States. We are unaware of any recent peer-reviewed publications reporting a significant increase in primary brain tumor incidence, including GBM, during surveillance years as recent as those reported in the present study, which distinctively analyzes primary brain tumor incidence data as recent as December 2008. We support a direct, uniform, and centralized approach to monitoring primary brain tumor incidence by histopathological subtype, including the introduction of nonmalignant data collection.

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