

# A multicenter study of primary brain tumor incidence in Australia (2000–2008)

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There are conflicting reports from Europe and North America regarding trends in the incidence of primary brain tumor, whereas the incidence of primary brain tumors in Australia is currently unknown. We aimed to determine the incidence in Australia with age-, sex-, and benign-versus-malignant histology-specific analyses. A multicenter study was performed in the state of New South Wales (NSW) and the Australian Capital Territory (ACT), which has a combined population of >7 million with >97% rate of population retention for medical care. We retrospectively mined pathology databases servicing neurosurgical centers in NSW and ACT for histologically confirmed primary brain tumors diagnosed from January 2000 through December 2008. Data were weighted for patient outflow and data completeness. Incidence rates were age standardized and trends analyzed using joinpoint analysis. A weighted total of 7651 primary brain tumors were analyzed. The overall US-standardized incidence of primary brain tumors was 11.3 cases 100 000 person-years ( $\pm 0.13$ ; 95% confidence interval, 9.8–12.3) during the study period with no significant linear increase. A significant increase in primary malignant brain tumors from 2000 to 2008 was observed; this appears to be largely due to an increase in malignant tumor incidence in the  $\geq 65$ -year age group. This collection represents the most contemporary data on primary brain tumor incidence in Australia. Whether the observed increase in malignant primary brain tumors, particularly in persons aged  $\geq 65$  years, is due to improved detection, diagnosis, and care delivery or a true change in incidence remains undetermined.

We recommend a direct, uniform, and centralized approach to monitoring primary brain tumor incidence that can be independent of multiple interstate cancer registries.

**Keywords:** Australia, brain tumor, incidence, primary neoplasm.

In the 1970s and 1980s, an increased incidence of brain tumors was reported internationally and correlated with the emergence of imaging technologies, such as computed tomography (CT) and magnetic resonance imaging (MRI),<sup>1–3</sup> and wider clinical awareness of brain tumors.<sup>4</sup> In Australia, a small number of descriptive epidemiologic studies of primary central nervous system (CNS) tumors were published in series from Melbourne, Tasmania, and Adelaide<sup>5–8</sup> from the early 1990s. One Victorian study<sup>5</sup> of 4577 tumors reported age-standardized incidence rates of malignant CNS tumors of 5.0 cases per 100 000 males and 3.4 cases per 100 000 females but reported no significant trends during the period 1986–1988 regarding specific histological subtypes. The other Victorian study<sup>6</sup> analyzed 3575 cases of primary benign and malignant brain tumors over the period 1982–1990, with no clear trend in incidence. The Tasmanian study<sup>7</sup> analyzed 1752 cases from 2 registries during the period 1978–1992 and reported increasing age-standardized primary brain cancer incidence rates in males (from 16.3 to 26.2 cases per 100 000 person-years) and females (from 9.7 to 18.0 cases per 100 000 person-years) aged  $\geq 75$  years, most prominently in cases of glioblastoma multiforme (GBM). The Adelaide study<sup>8</sup> was a short study of a low sample population, showing an increased risk of glioma among women who reported working with cathode-ray tubes. During the early 1990s, when use of CT and MRI technology became widespread in Australia, no change in national brain cancer incidence

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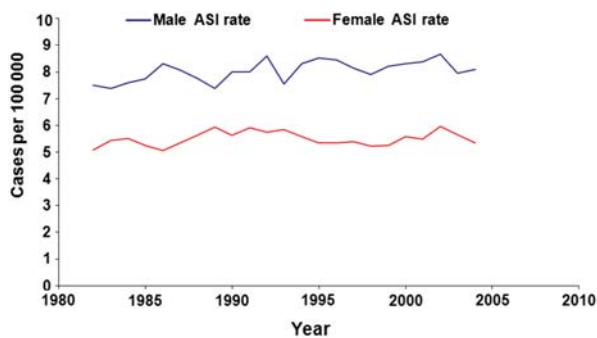


Fig. 1. Incidence data calculated by the Australian Institute of Health and Welfare (AIHW) for “Malignant neoplasm of brain” (*International Classification of Diseases, 10<sup>th</sup> Revision, C71*) over the period 1982–2004.<sup>9</sup> The incidence represented in the graph above is age standardized using 2001 Australian census data as the standard population. According to the AIHW graph, little change in the brain tumor incidence has been seen in Australia over 22 years, despite changes in reporting, classification, and population demographics during this time.

was observed by the Australian Institute of Health and Welfare (AIHW).<sup>9</sup> In fact, a decrease was observed, particularly for females. Despite changes in brain tumor pathology classification that occurred during the AIHW report canvassing period of 1982–2004,<sup>10</sup> again no significant trends were demonstrated in the AIHW data (Fig. 1).

A number of reports regarding primary brain tumor incidence are derived from North American<sup>3,11–14</sup> and European<sup>2,4</sup> sources. One of the most comprehensive is the 2007–2008 Statistical Report of the Central Brain Tumor Registry of the United States (CBTRUS)<sup>14</sup> which provides a primary CNS tumor age-adjusted incidence of 18.2 cases per 100 000 people in 2004. According to the 2002–2003 Statistical Report of CBTRUS,<sup>12</sup> the incidence was 13.4 cases per 100 000 people in 1995. Given that CBTRUS reports CNS tumor incidence age-adjusted to the 2000 US standard population and that the period of these reports is well embedded in the MRI era in the United States, the observed increase in incidence of ~36% in <1 decade is not likely to be adequately explained by an “aging population” or by “better diagnosis.” However, the change may in part be due to variations in methodologies used by sources contributing to the CBTRUS database and to delayed tumor reporting or “late ascertainment”<sup>15</sup> from its 15–19 cooperating state registries.

Given the limited data regarding the primary brain tumor incidence from Australasian sources, our goal was to determine the incidence in Australia with age-, sex-, and benign versus malignant histology-specific analyses and trends.

## Materials and Methods

### Database

A retrospective multicenter analysis was performed from January 2009 through August 2010 of all 13 pathology

databases servicing the 24 neurosurgical centers, including all major teaching hospitals, in the ACT and NSW recording tumors diagnosed during the period from 2000 through 2008. The population of NSW and ACT increased from 6.8 to 7.3 million people from 2000 to 2008. Ethics approval was granted by the NSW Cancer Institute for the collection of de-identified data from all nominated centers (see Acknowledgements). Databases were queried based on the Systematized Nomenclature of Medicine, *International Classification of Diseases, 10<sup>th</sup> Edition* (ICD-10), or text diagnoses using either specifically written search programs or pre-existing database search engines by a nominated data collector at the site. The use of fully identifiable data at the site allowed for control of repeated presentations to that institution prior to de-identification. Data were initially collected for the years 1994–2008, with complete data from all centers available from mid-1999.

### 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. Systemic lymphoma and metastatic, extracerebral, and germ cell tumors ( $n = 1800$ ) were excluded from the analysis. Tumors in patients from overseas or other Australian states and territories were also excluded from the analysis ( $n = 450$ ). Discrepancies in data completeness were followed up with the collecting institution, and if further specific searches did not yield more complete data, the records were excluded from the analysis ( $n = 50$ ). A large number of re-entrant and recurrence data were excluded ( $n = 2450$ ), the majority (56%) of which came from the conglomeration of 4 databases at the 1 center. The analysis included pituitary, craniopharyngeal duct, and pineal tumors; hemangioma; hemangiopericytoma; primary central nervous system lymphoma; and cranial nerve tumors (Supplemental Appendix 1).

### Coding and Grading

ICD-10 and SNOMED classification systems were used to code all records at the central site by a limited number of professional coders to maximize consistency of coding. Reporting and coding rules were followed according to the 2004 guidelines of the Centers for Disease Control and Prevention,<sup>16</sup> with the important exception that pilocytic astrocytoma was coded as a benign rather than a malignant tumor. Tumors were graded according to the 2007 World Health Organization (WHO) Classification of Tumors publication<sup>17</sup> and assigned topography according to the Surveillance, Epidemiology, and End Results (SEER) program coding advice.<sup>18</sup> The initial—but not any re-presenting—diagnosis of each patient was used for our analysis. If 2 separate entries for the same patient differed in tumor grade, the higher grade of tumor was

used, provided that the entries occurred within 8 weeks of each other. If the time difference in entries was greater than this period, the initial diagnosis and grade were used.

### Population Selection and Standardization

The ACT and NSW populations were used to benefit from the relatively low outward migration rate. Cross-border flows were estimated using 2008 Australian Hospital Statistics data for public and private hospitals<sup>19</sup> and an overall weighting for patient outflow, inflow, and data completeness of 5% was used. Population data were obtained from the Australian Bureau of Statistics Census 2006. 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, reporting of incidence rates has been limited to US-standardized rates for ease of comparison with existing literature.

### Statistical Analysis

Descriptive information was tabulated for total numbers of tumors by age group, sex, and histology in both Microsoft Excel, version 2007, and SPSS software, version 17.0. Log-linear Poisson regression in which the logarithmic incidence rate (dependent variable) was calculated as an exponential function over time (independent variable) and in which the data were assumed to have a Poisson distribution was used to statistically compare trends over time.<sup>11,20</sup> Trends were expressed as annual percentage change (APC) over the 9-year period, with corresponding 2-sided 95% confidence intervals (CIs) using up to 2 joinpoints with log-linear modeling for average annual percentage change calculation (AAPC). Joinpoint Regression software, version 3.3.1, was obtained from the ACT Cancer Registry and was used to identify any sharp changes in the incidence during the time period studied. Joinpoints correspond to the point in time of a change in trend in which several different lines come to a juncture. The software fits the simplest joinpoint model that the data will allow using a series of permutation tests<sup>11</sup> using the Monte Carlo Permutation method for significance testing.<sup>20</sup> Incidence rates are expressed as mean  $\pm$  standard deviation.

## Results

### Description of the Data

The final weighted data set included 7651 primary brain tumors, with a total of 698–935 tumors per year from 2000–2008. Persons aged 0–19 years represented

**Table 1.** Frequency and percentage of total of nonspecific (NOS) codes

Morphology	Frequency, no.	Percentage
Astrocytoma high-grade, NOS	74	1.0
Astrocytoma low-grade, NOS	82	1.1
Glioma high-grade, NOS	62	0.8
Glioma low-grade, NOS	11	0.2

~6% of all tumors, whereas the majority (63%) of tumors were represented in persons aged 20–64 years, with the remaining 30% represented by persons  $\geq$ 65 years. Relatively equal proportions of tumors were represented among male and female patients (49% and 51%, respectively). Fifty-eight percent of tumors were benign (WHO grade I or II), whereas 42% were malignant (WHO grade III or IV), with minimal (cumulative 3.1%) representation in the data of nonspecific codes (Table 1). Elderly adults (age,  $\geq$ 65 years) recorded the largest proportion of malignant tumors (52%), whereas children (age, 0–19 years) and adults (age, 20–65 years) demonstrated a preponderance of benign tumors, with only 34% and 38% being malignant, respectively (Fig. 2A).

### Incidence Trends

This study found an overall US-standardized incidence rate for primary brain tumors of 11.3 cases per 100 000 person-years ( $\pm$  0.13; 95% CI, 9.8–12.3 cases per 100 000 person-years during the study period, with no significant linear increase observed (Fig. 2B). An overall crude rate of 11.8 cases per 100 000 person-years (range, 10.1–12.7 cases per 100 000 person-years) was calculated for the study period. Rates were slightly higher among males but more variable in females (11.7  $\pm$  0.26 cases per 100 000 person-years [95% CI, 10.0–12.6 cases per 100 000 person-years] and 11.4  $\pm$  0.25 cases per 100 000 person-years [95% CI, 10.0–13.0 cases per 100 000 person-years, respectively), but again with no obvious linear increase and well below latest reported US rates (Fig. 2C). No significant trends were demonstrated for benign tumors when analyzed by sex and age groupings. Of note, an overall significant increase in primary malignant brain tumors was observed over the study period from 2000 to 2008 (APC, 3.9; 95% CI, 2.4–5.4) (Fig. 3A), particularly since 2004 (overall AAPC, 3.9; 95% CI, 2.6–5.2). Of note, data since 2004 have not yet been published by the AIHW, and only preliminary data from the NSW Cancer Registry are available (see below). This overall increasing trend in malignant tumors was consistent for both males (APC, 2.3; 95% CI, 0.4–4.2) and females (APC, 2.3; 95% CI, 0.3–4.3)—again, particularly since 2004 (AAPC for males, 2.3 [95% CI, 0.7–3.9]; AAPC for females, 2.3 [95% CI, 0.6–4.0]) (Fig. 3B). Driving this increase is the increase in malignant tumors in the  $\geq$ 65-year age group (APC, 1.54; 95% CI, 0.1–3.0) (Fig. 3C), with no significant difference by sex (Table 2).

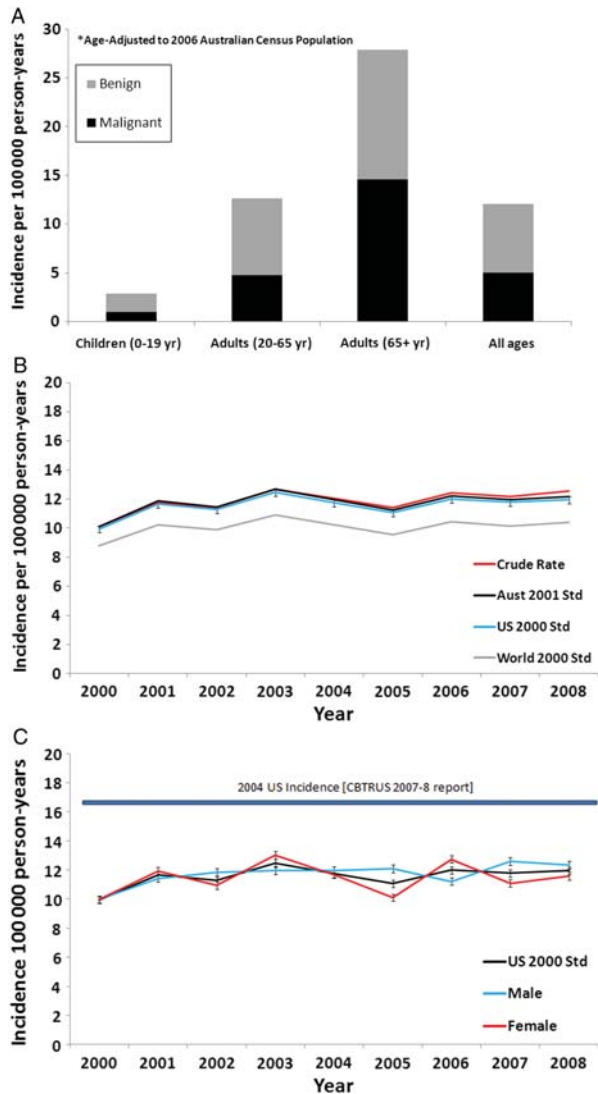


Fig. 2. (A) Average annual age-adjusted incidences of primary brain tumors, by age and proportionally by behavior. Data have been age-adjusted to 2006 Australian Census data. Benign, World Health Organization (WHO) grade I and II tumors; malignant, WHO grade III and IV. (B) Incidences of all primary brain tumors, by calendar year, from the Australian Capital Territory (ACT) and New South Wales (NSW) populations. Rates are age standardized to the 2001 Australian Standard, the 2000 US standard, and 2000 World standard populations. To avoid congestion, confidence intervals are displayed for the US-standardized trend only. (C) US-standardized incidence rates, by sex, of all primary brain tumors from the ACT and NSW populations by calendar year. Confidence intervals are displayed. The latest (2008) Central Brain Tumor Registry of the United States incidence of 18.2 cases per 100 000 person-years is shown.<sup>14</sup>

### Discussion

An overall increase in age-adjusted incidence rates of primary malignant brain tumors was observed in the ACT and NSW during the period 2000–2008, particularly among persons aged  $\geq 65$  years. One hundred

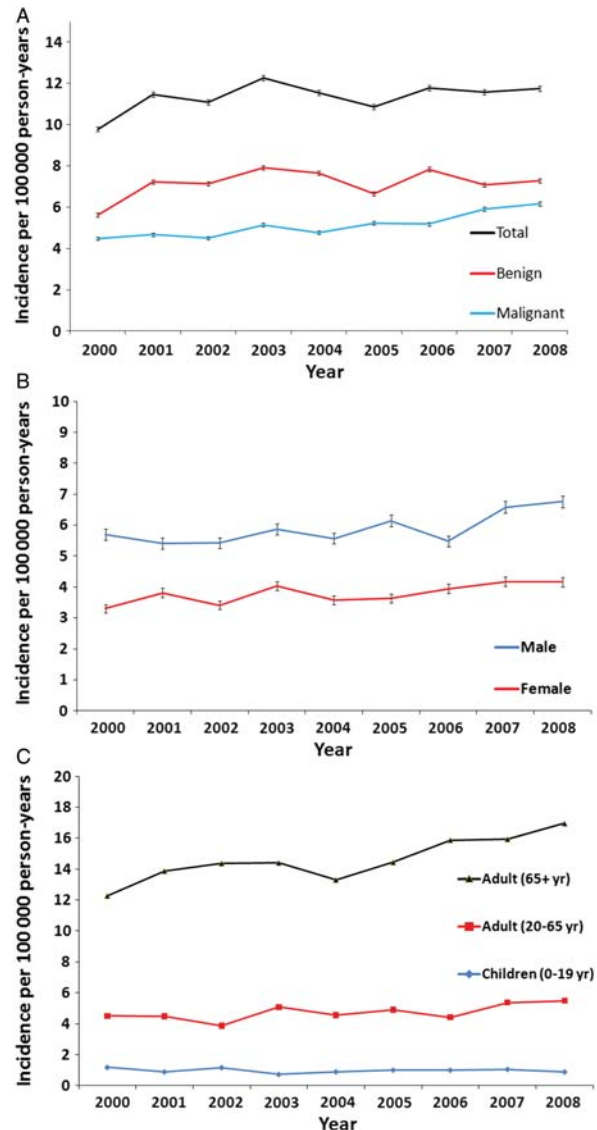


Fig. 3. (A) US-standardized brain tumor incidence rates by WHO grade, by calendar year, from the Australian Capital Territory (ACT) and New South Wales (NSW) populations. Confidence intervals are displayed. Benign, World Health Organization (WHO) grades I and II; malignant, WHO grades III and IV. (B) US-standardized malignant brain tumor incidence rates, by sex and calendar year, from the ACT and NSW populations. (C) Malignant brain tumor incidence rates, by age grouping and calendar year, from the ACT and NSW populations.

percent of tumors were histologically confirmed, with data collected from 13 pathology units (ie, directly from the source of histological diagnosis), servicing an area of  $>7$ -million persons with minimal outward migration for health services. Similar increases in the primary brain tumor incidence in the elderly population have been reported elsewhere around the world,<sup>2,21</sup> but to our knowledge, no comparable study has been conducted in Australasia.

For comparison purposes, local cancer registry data were obtained from yearly cancer incidence reports

**Table 2.** Overall incidence rate trends, by annual percentage change (APC), for primary brain tumors from the Australian Capital Territory and New South Wales populations<sup>a</sup>

Subgroup	No. of cases	APC	(95% CI)
All persons			
Brain tumors	7651	1.2	(-0.6 to 3.0)
Benign tumors	4445	1.7	(-1.4 to 4.9)
Malignant tumors	3206	3.9 <sup>b</sup>	(2.4-5.4)
Malignant tumors			
Males	1907	2.3 <sup>b</sup>	(0.4-4.2)
Females	1299	2.3 <sup>b</sup>	(0.3-4.3)
Persons aged $\geq 65$ years			
Malignant tumors	1223	1.54 <sup>b</sup>	(0.1-3.0)
Men	693	2.6	(-2.7 to 8.2)
Women	530	0.6	(-2.1 to 3.4)

CI indicates confidence intervals.

<sup>a</sup>All models use exponential Poisson regression and were adjusted for age group.

<sup>b</sup>Denotes significance of the APC. Note that APC values are statistically significant from the value 0.

from November, 2006 to December, 2009,<sup>22-27</sup> with numbers prior to 2004 for the ACT being average annual numbers. Case numbers were adjusted for percentage of histological verification (mean, ~85%) on the basis of published rates to aid comparison. Overall raw numbers from the current study are less than the combined ACT and NSW Cancer Registry numbers, particularly in the earlier years of the study period (Fig. 4). The difference in raw numbers between the 2 sets may reflect a different definition of “malignant” brain tumors. More notable, however, is an upward trend in raw tumor numbers seen in both data sets, but most marked in our study, particularly in the latest years of 2007 and 2008. This observed increase in malignant tumors noted by us is curious, considering that no such reports have been issued by the Australian cancer registries. Possible explanations for the discrepancy in raw numbers between our data set and those of the registries include differences in diagnostic and histological definitions and data lag time or “late ascertainment” by the NSW Cancer Registry.<sup>15</sup>

### Definition of Diagnosis

Cancer registries and previous independent studies have included nonoperative brain tumor diagnoses as well as tumors diagnosed at autopsy.<sup>2,14</sup> Although this approach yields large sample sizes, our study aimed to provide a greater acuity in assessment of histological subtypes that is lost upon inclusion of tumors diagnosed solely on the basis of imaging technology, conservative (ie, non-operative) treatment, or clinical decision-making. Of importance, pathology data represent the primary point of diagnosis, and provide the most up to date information on histology, topography, and time of diagnosis—a definition more consistent with the European Network of Cancer Registries.<sup>28</sup> Our study involved the histological

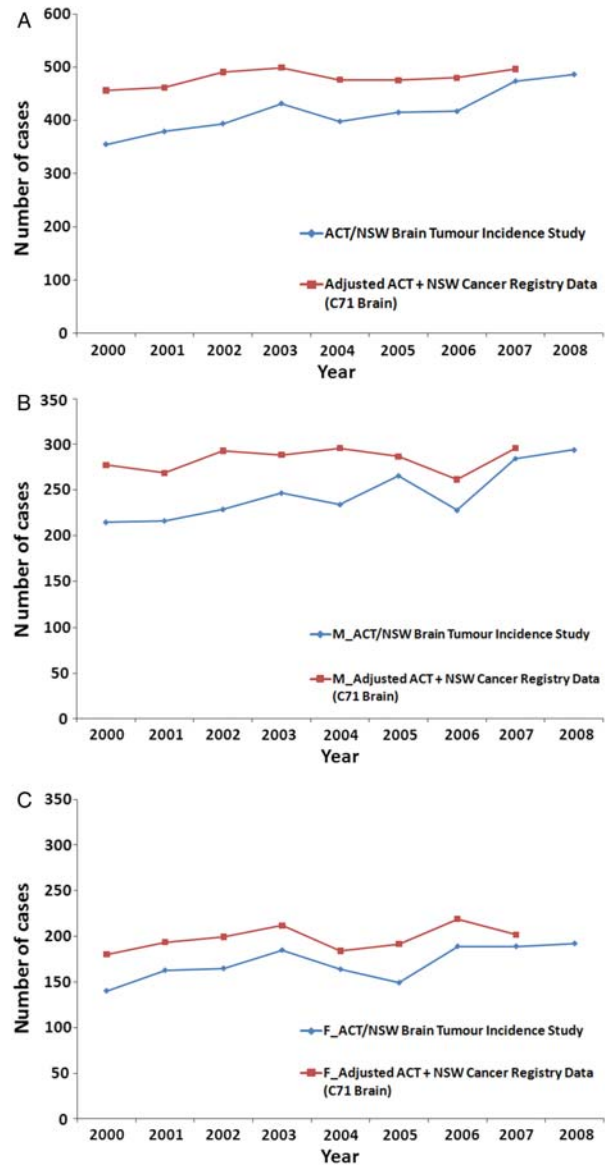


Fig. 4. Comparison of case numbers for malignant brain tumors, Australian Capital Territory (ACT) and New South Wales (NSW), 2000–2008, by sex [(A) total; (B) male; (C) female] between the current study and the combined data from the NSW Central Cancer Registry (CCR)<sup>22-25</sup> and the ACT Cancer Registry.<sup>26,27</sup> Case numbers have been adjusted according to published histological verification rates per year and by sex (mean, ~85%) to aid comparison. The Australian Institute of Health and Welfare mentioned previously is the Australian Government body monitoring brain tumor data collection across the whole nation, whereas the aforementioned sources are state based. For comparison purposes, we have included all World Health Organization grade II tumors with/3 (malignant) behavior per current collection practices of Australian registries, despite the ambiguity this creates in definition of tumors as benign/nonmalignant.

confirmation of every tumor. Other sources have argued that the timing of diagnosis should be based on the date of first *clinical* diagnosis.<sup>14</sup> This approach is

justified for tumors that are either inoperable or slow growing and thus allows capture of tumors with a “wait-and-watch” approach. Logistically, however, this was beyond the scope of the current study but would be an interesting approach to adopt in the future as an additional component of primary brain tumor incidence. Our local Australian cancer registries quote 85% histological confirmation, and a 15% addition in tumor numbers would no doubt enhance the current study.

#### Late Ascertainment

As previously noted by Clegg et al.,<sup>15</sup> delayed reporting may lead to downwardly biased incidence trends. The study of 9 cancer registries involved in the SEER program over a 17-year period highlighted the importance of “late ascertainment” by comparing reported initial (after a standard 2-year delay) and final incidence rates. They found significant differences between these rates and estimated a reporting lag time of  $\geq 4$  years. This delay likely applies to our own Australian cancer registries, owing to the sheer bulk of processing required to publish incidence rates from multiple different sources. We believe that we have minimized the occurrence of this bias in our study by referring directly to the data sources themselves—namely, all relevant pathology units assessing primary brain tumor specimens in the chosen geographical area. Our results may thus be reconciled with increasing rates in later years that have perhaps not yet been captured by registry methods.

#### Unknown Individual Subtype Trends

Finally, we suggest suboptimal coverage and reporting of specific histological subtypes by current surveillance methods. Unlike the United States, there is no mandatory collection of benign brain tumor data in Australia, although we have attempted to collect both benign and malignant primary brain tumor data in a timely fashion. We have been unable to access the raw data of our local registries, but their public reports quote malignant brain tumor rates in terms of *International Classification of Diseases, Oncology 3*, C71 topography and morphology classifications. A number of reports discuss tumors not necessarily considered to be malignant brain tumors, such as low-grade astrocytoma, oligodendroglioma, and ependymoma.<sup>22–25</sup> Furthermore, the latest report from the NSW Cancer Registry included melanoma, germ cell, embryonal, and soft-tissue tumors in its analysis.<sup>22</sup> This creates ambiguity in the comparison of rates. Finally, an unknown proportion of “unspecified” tumors are used for determination of the incidence by the cancer registries. Although this is an unavoidable consequence of their collection methods, it is a limitation we have endeavored to minimize through direct collection of histological diagnoses (100% in our study’s database versus an average of 85% in our local cancer registry databases), as evidenced by a  $\sim 3\%$  rate of nonspecific histological diagnoses in our study (Table 1).

#### Limitations

The main limitations of the current study are the unavailability of identifiable data throughout the entire analysis and uncertainties regarding complete case capture rates. Control for re-presentations of 1 patient to multiple different institutions was difficult in the current study because of the use of multiple separate databases with limited cross-communication. Ethics approval for data matching of identifiable data was sought but not granted due to staff shortages. We attempted to minimize this error, however, by controlling for repeated presentations to the one institution. Retrospective database mining inherently introduces an element of uncertainty in data quality that was compounded in the current study by the use of multiple different database systems and search methods. Issues around adequate coding of diagnoses, database technology, and diligence of data collectors contribute to this issue. The use of dedicated data collectors employed by the local pathology units and multiple site visits helped minimize this uncertainty. In view of the limitations presented, we need to be cautious in our approach to interpretation of the observed increase in primary malignant brain tumors. Additional examination of histological subtypes is currently being performed and the authors do not suggest an association with reported risk factors in the literature. However, because the observed increase in incidence is confined to malignant tumors among persons aged  $\geq 65$  years, we question whether an association between greater diagnostic capability/delivery of care<sup>10</sup> and tumor incidence is at play in the years 2000–2008 in Australia.

Australia is  $\sim 1$  decade behind the United States and Europe in terms of the implementation of certain imaging technologies, with the introduction of CT and MRI imaging occurring in the late 1980s to mid-1990s in the ACT and NSW. Some authors suggest that the latest reported increases in incidence from the United States and Europe are not adequately explained by advances in imaging technology or a lower clinical threshold for scanning. We believe that monitoring of these trends in Australia over the next 10–15 years presents an ideal opportunity to discover potential associated risk factors in brain tumor development through the establishment of a central nationwide brain tumor registry that examines both benign and malignant tumors in a timely fashion. Exclusion of benign tumors produces a tendency to underestimate incidence and an undervaluing of the importance of benign brain tumors, some of which can progress histologically to cancer. This raises issues of feasibility and whether such a collection should be combined with existing brain tumor registries or established as separate entity, similar to the recent experience of the Austrian Brain Tumor Registry.<sup>29</sup>

#### Conclusions

To our knowledge, this collection constitutes the most contemporary data on primary brain tumor incidence

in the Australasian region. Data were 100% histologically confirmed and were mined directly at the coal-face of brain tumor diagnosis from a relatively large and overall medically self-contained Australian subpopulation, minimizing the effect of late ascertainment of data and providing greater diagnostic specificity. It is unclear at this time whether the observed increase in malignant primary brain tumors, particularly among persons aged  $\geq 65$  years, is due to improved detection, diagnosis, and delivery of care or to a true change in incidence. Australian Cancer Registry data have an average lag time of 4 years from collection to reporting, an experience shared by CBTRUS.<sup>12-14</sup> Given the current importance of identifying risk factors for specific brain tumors,<sup>30</sup> which we recognize is beyond the scope of a cancer registry, we believe that at an international level, our study supports consideration of the establishment of a centralized registry for each nation that (1) directly receives histologically confirmed primary brain tumor data from all relevant pathology units, and (2) analyzes and reports data according to an international agreement regarding the precise definition of primary benign versus malignant histological subtypes suitable for collection.

## Supplementary Material

Supplementary material containing an appendix to this paper is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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