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Trends in Pediatric Central Nervous System Tumor Incidence in the United States, 1998–2013

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Abstract

Background: Brain and other central nervous system (CNS) cancers are the leading cause of U.S. pediatric cancer mortality. Incidence trends can provide etiologic insight. We report trends in incidence rates of pediatric malignant CNS cancers and pilocytic astrocytoma (nonmalignant but historically registered) in the United States.

Methods: Age-standardized incidence rates and annual percent changes (APC) in rates during 1998 to 2013 were calculated for children aged 0 to 19, stratified by subtype, age, sex, and for gliomas, histology and location. We estimated the absolute change in number of cases diagnosed U.S.-wide during 2013 compared with the expected number of cases had 1998 rates remained stable.

Results: Rates of all pediatric malignant CNS cancer combined (n = 18,612) did not change [APC: 0.16; 95% confidence interval (CI): −0.21–0.53]. There were statistically significant changes in several subtypes; however, glioma incidence (n = 10,664) increased by 0.77% per year (95% CI: 0.29–1.26), embryonal cancer rates (n = 5,423) decreased by 0.88% per year (95% CI: −1.33 to −0.43), and pilocytic astrocytoma rates (n = 6,858) increased by 0.89% per year (95% CI: 0.21–1.58). Of the 1,171 malignant tumors and 450 pilocytic astrocytomas diagnosed in U.S. children in 2013, we estimated 120 excess gliomas, 94 excess pilocytic astrocytomas, and 72 fewer embryonal CNS tumors than would be expected had 1998 rates remained stable.

Conclusions: The gradual changes in incidence we observed for specific types of pediatric CNS cancers are likely due to a combination of changes in classification and diagnosis and true changes in CNS cancer.

Impact: Continued surveillance of pediatric CNS tumors should remain a priority, given their significant contribution to pediatric cancer–related deaths.

Introduction

Among U.S. children, cancer is the second leading cause of death. In 2018, it is expected over 10,000 children aged 0 to 14 will be diagnosed with cancer and that just over 1,100 will die from the disease (1). Central nervous system (CNS) tumors are the second leading cause of childhood cancer and as of 2016 became the leading cause of cancer-related death in children (2, 3). Although this was attributed to a decrease in mortality from leukemia, it is critical to determine whether incidence of CNS tumors in children is changing. Studies in the 1980s and 1990s reported increasing rates of childhood CNS tumors, which were largely attributed to the innovations in diagnosis, namely the increasing use of MRI (4–6).

The etiology of pediatric CNS tumors is largely unknown. Genetic predisposition syndromes, ionizing radiation (such as CT scans and radiotherapy), and high birth weight are known risk factors for pediatric CNS cancers, but account for a small percentage of cases (7, 8). Ionizing radiation is most strongly associated with the risk of nonmalignant brain tumors, namely meningiomas and schwannomas (9). Radiofrequency electromagnetic fields (RF-EMF) were classified as possibly carcinogenic by the International Agency for Research on Cancer (IARC) based on findings from some of the epidemiologic studies and experimental data (10). Because RF-EMF is radiation (albeit nonionizing) and because children are especially sensitive to cranial irradiation, there is concern that rising RF-EMF exposure will result in increasing incidence of pediatric CNS cancers (11–13). Careful surveillance of trends is, therefore, critical especially in children.

Reports on trends in pediatric CNS cancer in the post-MRI era have had mixed findings, typically reporting small increases or stable rates (6, 14–16). There are many histologic subtypes of pediatric CNS cancers with distinct biologies and potentially distinct time trends. Existing studies have generally reported trends for either all pediatric CNS cancers combined or a single subtype (17, 18). Reporting on all CNS cancers combined can mask important subtype-specific changes over time, whereas reporting on a single subtype alone may be misleading due to the heterogeneity of CNS cancers and potential shifts in diagnosis and reporting patterns from one subtype to another.

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We have aimed to take an approach that balances these two challenges and in so doing, to provide a comprehensive overview of recent (1998–2013) incidence rates and trends for the common histologic subtypes of pediatric malignant CNS tumors and pilocytic astrocytoma (the most common nonmalignant pediatric CNS tumor) using clinically relevant categorizations and stratifying by age, sex, and race/ethnicity.

Materials and Methods

Data were obtained from 29 cancer registries belonging to the North American Association of Central Cancer Registries (NAACCR). NAACCR harmonizes data for registries participating in the Centers for Disease Control and Prevention National Program of Cancer Registries (NPCR) and the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Our analyses were restricted from 1998 to 2013 and 29 registries receiving NAACCR certification for at least 14 of the 15 years studied. Certification indicates meeting NAACCR's standards for completeness, accuracy, and timeliness (19). The selected registries cover approximately 60% of the U.S. population. A listing of included registries is in the Supplementary Materials and Methods.

We included all malignant tumors and pilocytic astrocytomas diagnosed among persons aged 0–19 years and classified as CNS or miscellaneous intracranial or intraspinal neoplasms, according to the International Classification of Childhood Cancer, third edition (ICCC-3; ref. 20). This excludes germ cell tumors, neuroblastoma, and lymphomas of the CNS.

To optimize clinical relevance and ensure sufficient stability in rates, we aggregated specific histologies of malignant tumors according to a scheme like one previously used by the Central Brain Tumor Registry of the United States (CBTRUS; ref. 21), employing ICD-O-3 histology codes. NAACCR provided ICD-O-3 histology codes for the full span of our study, despite ICD-O-3's implementation in 2001, by converting earlier ICD-O-2 codes to ICD-O-3 with the express aim of minimizing the impact of the change on trends over time. The major groups included gliomas, embryonal tumors, and ependymal tumors. Gliomas were subclassified as low-grade, high-grade, or other; embryonal tumors were subclassified as medulloblastomas, primitive neuroectodermal tumors (PNET), or other. Glioma grade was determined on the basis of World Health Organization (WHO) histologic grade (22).

Our justification for this approach, rather than standard classification schemes for pediatric cancer (i.e., ICCC-3; ref. 23) or CNS cancer (i.e., the WHO Classification of Tumors of the CNS; ref. 22) and the details of our groupings can be found in the Supplementary Materials and Methods and Supplementary Table S1. Gliomas were stratified by location and histology according to the International Classification of Diseases for Oncology (third edition, ICD-O-3). Rates for pilocytic astrocytoma and glioma were stratified by method of diagnostic confirmation (microscopic vs. radiographic).

Up until 2000, pilocytic astrocytoma was registered as a malignant cancer (behavior code 3). In ICD-O-3, the code changed to borderline behavior (1, 24). Despite the change, U.S. registrars were instructed to continue to record the cancers as behavior code 3 for consistency (25). We included all cancers with a behavior code of 3 in our analyses, making pilocytic astrocytoma an exception.

Other nonmalignant brain tumors were excluded because they have only been continuously recorded since 2004, when cancer registries began routinely collecting these cases in response to the 2002 Benign Brain Tumor Cancer Registries Amendment Act, which recognized the disruption to normal function caused by these tumors and the importance of their surveillance. Quality and completeness of registration for nonmalignant tumors are likely to have increased since 2004 and, therefore, trends were not considered reliable.

Statistical analysis

Incidence rates were calculated using SEER*Stat (Version 8.3.4), age-standardized to the 2000 US standard population by 5-year age groups and expressed per million person-years. Analysis of trends was conducted using the JoinPoint regression program (Version 4.5.0.1). Joinpoint models a best-fit regression line through the observed data (26). The annual percent change (APC) has been reported as a summary measure without inflection points (or joinpoints) to provide an interpretable summary and prevent overinterpretation of potentially unstable estimates at the tails. Annual rates of each subtype by age are displayed graphically so readers can make interpretations based on the shape of the curves.

Age-standardized and age-specific (0–4, 5–9, 10–14, and 15–19 years) rates and trends were stratified by subtype (see above), sex, and race/ethnicity [Latino, non-Latino white (White), non-Latino black (Black), non-Latino other]. Narrower race/ethnicity categories recorded in registries (Asian/Pacific Islander and American Indian/Alaska Native) could not be used due to small numbers.

We compared the expected case counts in 2013 under the current trends to the counts expected had 1998 rates remained stable until 2013. We estimated this by applying 1998 and 2013 rates to age-specific 2013 U.S. census population counts. Joinpoint models produce fitted rates for each year along the best-fit regression line. Modeled rates from the Joinpoint models for 1998 and 2013, rather than the observed rates were used to reduce the effect of instability (noise) on the single-year rates.

The analysis was approved by the NAACCR Institutional Review Board.

Results

Between 1998 and 2013, 18,612 malignant CNS tumors and 6,856 pilocytic astrocytomas were diagnosed among children aged 0 to 19 in 29 U.S. cancer registries. Age-standardized incidence rates were 22.81 [95% confidence interval (CI): 22.49–23.14) and 8.41 (95% CI: 8.21–8.61) per million person-years, respectively (Table 1).

There was no significant change in incidence for all malignant CNS cancers combined (APC: 0.16; 95% CI: −0.21–0.53; Table 1). In stratified analyses, CNS cancer rates significantly decreased among Latinos (APC: −1.06; 95% CI: −1.61 to −0.52) and increased significantly among Whites (APC: 0.49; 95% CI: 0.07–0.92; Table 2).

Subtype-specific trends are illustrated in Fig. 1 and Tables 3 and 4. Gliomas accounted for 57% ($n = 10,664$) of all malignant CNS tumors. The incidence rate of glioma increased by 0.77% per year (95% CI: 0.29–1.26), equivalent to 120 excess cases U.S.-wide in 2013 compared with 1998 estimated rates. Increases appeared to be consistent across age, sex, and race/

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Table 1. Age-standardized[a] incidence rates (ASR) per million person-years and APC by subtype, age, sex, and race/ethnicity, 1998–2013

	Malignant CNS cancer			Pilocytic astrocytoma		
	n (%)	ASR (95% CI)	APC (95% CI)	*n* (%)	ASR (95% CI)	APC (95% CI)
Total	18,612 (100)	22.81 (22.49–23.14)	0.16 (−0.21–0.53)	6,856 (100)	8.41 (8.21–8.61)	0.89 (0.21–1.58)
Age, years						
0–4	6,307 (33.9)	32.11 (31.32–32.91)	0.35 (−0.35–1.06)	1,949 (28.4)	9.93 (9.49–10.38)	1.06 (−0.12–2.26)
5–9	4,969 (26.7)	24.77 (24.09–25.47)	−0.02 (−0.70–0.66)	1,903 (27.8)	9.49 (9.06–9.92)	0.45 (−0.77–1.69)
10–14	3,884 (20.9)	18.61 (18.03–19.2)	0.13 (−0.56–0.83)	1,769 (25.8)	8.47 (8.08–8.88)	0.76 (−0.16–1.70)
15–19	3,452 (18.5)	16.20 (15.67–16.75)	0.15 (−0.66–0.97)	1,235 (18.0)	5.80 (5.48–6.13)	1.54 (0.42–2.67)
Sex						
Male	10,242 (55.0)	24.52 (24.04–25.00)	0.06 (−0.46–0.57)	3,533 (51.5)	8.46 (8.18–8.74)	1.22 (0.44–2.01)
Female	8,370 (45.0)	21.03 (20.58–21.48)	0.30 (−0.26–0.86)	3,323 (48.5)	8.35 (8.07–8.64)	0.54 (−0.31–1.40)
Ethnicity/race[b]						
Latino	3,330 (17.9)	19.04 (18.40–19.70)	−1.06 (−1.61 to −0.52)	1,056 (15.4)	6.08 (5.72–6.46)	0.33 (−0.74–1.42)
White	12,018 (64.6)	25.58 (25.12–26.04)	0.49 (0.07–0.92)	4,697 (68.5)	9.95 (9.67–10.24)	1.13 (0.38–1.89)
Black	2,139 (11.5)	18.17 (17.41–18.96)	0.65 (−0.28–1.60)	716 (10.4)	6.08 (5.64–6.54)	2.72 (0.56–4.94)
Other	884 (4.7)	16.54 (15.47–17.67)	1.08 (−0.38–2.57)	261 (3.8)	4.89 (4.31–5.52)	0.32 (−1.32–1.99)
Unknown	241 (1.3)			126 (1.8)		

[a]Age-standardized to the 2000 U.S. standard population by 5-year age groups and expressed per million person-years.
[b]Race/ethnicity categories are mutually exclusive. Unknown race/ethnicity cancers do not have incidence rates or trends given a lack of denominator (population size) estimate for this group.

ethnicity, groups other than Latinos though only reached statistical significance among 10- to 14-year-olds (APC: 1.09; 95% CI:0.30–1.89), females (APC: 1.00; 95% CI: 0.30–1.71), and Whites (APC: 1.31; 95% CI: 0.64–1.98). As shown in Fig. 1 and Table 4, low-grade gliomas (12.9% of gliomas) decreased significantly (APC: −2.85; 95% CI: −4.23 to −1.46), whereas rates of high-grade (21.3%) and other (65.8%) increased (APC_{other}: 1.25; 95% CI: 0.68–1.83; $APC_{high\ grade}$: 1.55; 95% CI: 0.18–2.95).

Forty-three percent ($n = 4,589$) of gliomas were coded "glioma, malignant," without specific classification and are, therefore, categorized as "other" rather than "low" or "high grade" (Table 4). Of these, 72% ($n = 3,323$) were in the brain stem or optic nerve, where biopsies and surgery are rarely performed. Overall, the incidence of "glioma, malignant" increased 3.13% per year (95% CI: 2.19–4.08), but the increase appears to have been driven primarily by glioma of the optic nerve (APC: 3.92; 95% CI: 1.76–6.13). Of the specific glioma histologies, significant increases were observed for glioblastoma (APC: 3.01; 95% CI: 0.97–5.08) and pleomorphic xanthoastrocytoma (APC: 3.45; 95% CI: 0.99–6.98). Significant decreases were observed for astrocytoma NOS (not-otherwise-specified APC: −2.40; 95% CI: −3.38 to −1.42), oligodendroglioma NOS (APC: −5.16, 95% CI: −6.58 to −3.71), and fibrillary astrocytoma (APC: −4.13; 95% CI: −7.17 to −1.00; Table 4; Supplementary Fig. S1).

Embryonal cancers accounted for 29% ($n = 5,423$) of all malignant CNS tumors with incidence rates decreasing significantly (APC: −0.88; 95% CI: −1.33 to −0.43; Table 2) between 1998 and 2013, equivalent to 72 fewer cases in 2013, compared with expected rates based on 1998 rates. The decreasing trend was consistent by sex, but was not observed for 0- to 4-year-olds (APC: 0.14; 95% CI: −1.03 to 1.33). Rates of medulloblastoma, the most common embryonal tumor, remained stable (APC: 0.05; 95% CI: −0.79 to 0.69; Fig. 1; Table 3), whereas the rates of PNETs decreased significantly (APC: −5.67; 95% CI: −6.54 to −4.80) and rates of other embryonal tumors [which include atypical teratoid/rhabdoid tumors (ATRT)] increased significantly (APC: 6.99; 95% CI: 1.49–12.77).

Ten percent of all malignant CNS tumors were ependymal ($n = 1,881$); incidence rates remained stable (APC: 0.63; 95% CI: −0.89–2.16) with no significant trends observed in any demographic group (Table 2). Other malignant CNS cancers (3.4%, $n = 644$) decreased significantly (APC: −2.79; 95% CI: −5.01 to −0.51) and consistently across all strata.

Incidence rates of pilocytic astrocytoma increased by 0.89% per year (95% CI: 0.21–1.58), equivalent to 94 excess cases. In stratified analyses, rates increased across age, sex, and racial/ethnic groups; however, statistically significant increases were limited to 15- to 19-year-olds (APC: 1.54; 95% CI: 0.42–2.67), males (APC: 1.22; 95% CI: 0.44–2.01), non-Latino whites (APC: 1.13; 95% CI: 0.38–1.89), and non-Latino blacks (APC: 2.72; 95% CI: 0.56–4.94).

Exploratory analyses showed an increasing proportion of gliomas, and to a much lesser extent pilocytic astrocytomas, which were confirmed radiographically rather than microscopically (Supplementary Fig. S2). Beginning around 2006 and until 2013, there was a modest increase in the rate of radiographically confirmed pilocytic astrocytoma. For gliomas, the incidence of radiographically confirmed cases increased between 1998 and 2004 and then stabilized. The rate of microscopically confirmed malignant gliomas decreased modestly and steadily over the entire study period.

Discussion

In this large, population-based study covering 60% of the U.S. population, we did not observe a statistically significant change in the incidence rates of all malignant CNS cancers combined between 1998 and 2013. We observed a statistically significant increase in the incidence rate of glioma (0.77% per year) and of pilocytic astrocytoma (0.89% per year) and a statistically significant decrease in incidence of embryonal cancer (−0.88% per year). We estimated that there were 120 excess cases of glioma, 72 fewer embryonal cancers, and 94 excess cases of pilocytic astrocytoma diagnosed U.S.-wide in 2013 compared with the expected had 1998 rates remained stable.

Childhood CNS tumor incidence trends in the United States have rarely been reported with the granularity presented here, making comparisons of our findings with others challenging. Consistent with our results, however, CBTRUS (using 52 NAACCR registries) reported a borderline significant increase of 0.6% per

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Table 2. ASRs[a] of pediatric malignant brain and CNS cancers per million person-years and APC by subtype, age, sex, and race/ethnicity, 1998–2013

	n (%)	ASR (95% CI)	APC (95% CI)
Gliomas			
Total	10,664 (100)	13.05 (12.81–13.31)	0.77 (0.29–1.26)
Age, years			
0–4	2,906 (27.3)	14.80 (14.26–15.34)	0.55 (−0.08–1.18)
5–9	2,919 (27.4)	14.55 (14.03–15.09)	0.73 (−0.40–1.87)
10–14	2,471 (23.2)	11.84 (11.37–12.31)	1.09 (0.30–1.89)
15–19	2,368 (22.3)	11.12 (10.67–11.57)	0.75 (−0.31–1.83)
Sex			
Male	5,638 (52.9)	13.47 (13.12–13.82)	0.57 (−0.08–1.23)
Female	5,026 (47.1)	12.62 (12.27–12.97)	1.00 (0.30–1.71)
Ethnicity/race[b]			
Latino	1,712 (16.1)	9.94 (9.47–10.42)	−0.44 (−1.70–0.84)
White	7,057 (66.2)	14.94 (14.59–15.29)	1.31 (0.64–1.98)
Black	1,251 (11.7)	10.61 (10.03–11.21)	0.94 (−0.15–2.03)
Other	473 (4.4)	8.86 (8.08–9.70)	1.08 (−0.68–2.87)
Unknown	171 (1.6)		
Embryonal			
Total	5,423 (100)	6.67 (6.49–6.85)	−0.88 (−1.33 to −0.43)
Age, years			
0–4	2,250 (41.5)	11.45 (10.99–11.94)	0.14 (−1.03–1.33)
5–9	1,560 (28.8)	7.78 (7.40–8.17)	−1.11 (−2.08 to −0.12)
10–14	968 (17.8)	4.64 (4.35–4.94)	−2.13 (−3.80 to −0.42)
15–19	645 (11.9)	3.03 (2.80–3.27)	−1.98 (−4.02–0.10)
Sex			
Male	3,218 (59.3)	7.74 (7.47–8.01)	−0.86 (−1.36 to −0.36)
Female	2,205 (40.7)	5.55 (5.32–5.79)	−0.88 (−1.96–0.21)
Ethnicity/race[b]			
Latino	1,104 (20.4)	6.21 (5.85–6.59)	−2.55 (−3.54 to −1.56)
White	3,402 (62.7)	7.31 (7.07–7.56)	−0.66 (−1.33–0.01)
Black	590 (10.9)	5.03 (4.64–5.46)	0.30 (−0.66–1.27)
Other	280 (5.2)	5.24 (4.65–5.89)	0.03 (−2.40–2.52)
Unknown	47 (0.9)		
Ependymal			
Total	1,881 (100)	2.30 (2.20–2.41)	0.63 (−0.89–2.16)
Age, years			
0–4	839 (44.6)	4.27 (3.99–4.57)	0.97 (−1.18–3.18)
5–9	393 (20.9)	1.96 (1.77–2.16)	−0.15 (−2.51–2.27)
10–14	328 (17.4)	1.57 (1.41–1.75)	−0.26 (−3.05–2.61)
15–19	321 (17.1)	1.51 (1.35–1.68)	1.89 (−1.53–5.43)
Sex			
Male	1,034 (55.0)	2.47 (2.32–2.63)	1.16 (−0.54–2.89)
Female	847 (45.0)	2.13 (1.99–2.27)	−0.01 (−1.78–1.79)
Ethnicity/race[b]			
Latino	399 (21.2)	2.26 (2.04–2.49)	1.32 (−1.09–3.79)
White	1,158 (61.6)	2.47 (2.33–2.62)	0.25 (−1.48–2.01)
Black	211 (11.2)	1.80 (1.56–2.06)	1.11 (−3.16–5.56)
Other	101 (5.4)	1.88 (1.53–2.28)	4.05 (−0.23–8.52)
Unknown	12 (0.6)		
Other			
Total	644 (100)	0.79 (0.73–0.85)	−2.79 (−5.01 to −0.51)
Age, years			
0–4	312 (48.4)	1.59 (1.42–1.77)	−2.00 (−4.28–0.35)
5–9	97 (15.1)	0.48 (0.39–0.59)	−4.07 (−8.45–0.53)
10–14	117 (18.2)	0.56 (0.46–0.67)	−1.65 (−5.65–2.52)
15–19	118 (18.3)	0.55 (0.46–0.66)	−4.50 (−9.01–0.23)
Sex			
Male	352 (54.7)	0.84 (0.75–0.93)	−3.27 (−5.69 to −0.8)
Female	292 (45.3)	0.73 (0.65–0.82)	−2.16 (−5.07–0.84)
Ethnicity/race[b]			
Latino	115 (17.9)	0.63 (0.52–0.76)	−4.32 (−8.77–0.34)
White	401 (62.3)	0.86 (0.78–0.95)	−3.16 (−6.22–0.01)
Black	87 (13.5)	0.74 (0.59–0.91)	−1.65 (−5.61–2.48)
Other	30 (4.7)	0.56 (0.38–0.79)	
Unknown	11 (1.7)		

[a]Age-standardized to the 2000 U.S. standard population by 5-year age groups and expressed per million person-years.
[b]Race/ethnicity categories are mutually exclusive. Unknown race/ethnicity cancers do not have incidence rates or trends given a lack of denominator (population size) estimate for this group.

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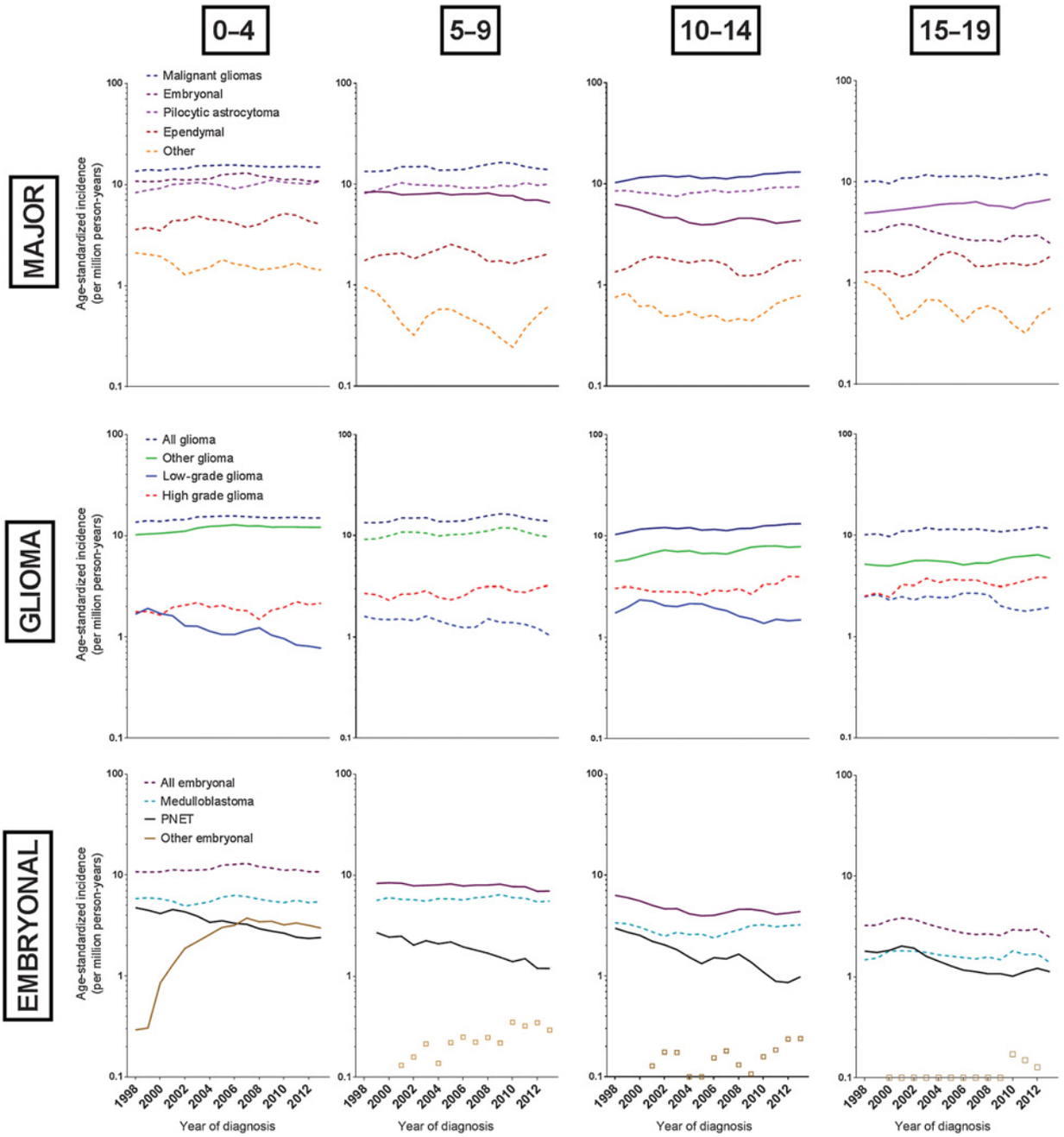

Figure 1.

Age-specific incidence rates of brain/CNS cancers per million person-years by subtype and age at diagnosis, 3-year moving average, 1998–2013. From left to right, the columns of graphs show incidence rates for children ages 0–4, 5–9, 10–14, and 15–19 years. From top to bottom, the rows of graphs show incidence rates for all major subtypes, glioma subtypes, and embryonal cancer subtypes. Solid lines indicate significant trends. Lines omitted when there were too few cases for a trend analysis. Color legend: dark blue, malignant glioma; purple, embryonal cancer; fuchsia, pilocytic astrocytoma; orange, other; green, other glioma; red, high-grade glioma; royal blue, low-grade glioma; teal, medulloblastoma; black, PNET; brown, other embryonal.

year for all malignant CNS tumors among 0- to 14-year-olds between 2000 and 2014 and of 1% per year among 15- to 19-year-olds from 2000 to 2008 (14, 27). Between 2000 and 2014, they estimated an increase in gliomas among 0-to 14-year-olds of 1.5% per year (14). The Centers for Disease Control and Prevention (using 47 NAACCR registries) reported a decrease in embryonal tumors from 2000 to 2010 of 0.6% per year, also consistent with our results (27). The compatible findings within the United

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Table 3. ASR and APC for brain and CNS cancers by subtype and age at diagnosis, 1998–2013

Cancer types	*n*	ASR (95% CI)	APC (95% CI)
All ages			
Glioma	10,664	13.05 (12.81–13.31)	0.77 (0.29–1.26)
Low-grade glioma	1,374	1.67 (1.58–1.76)	−2.85 (−4.23 to −1.46)
High-grade glioma	2,274	2.77 (2.66–2.89)	1.55 (0.18–2.95)
Other glioma	7,016	8.61 (8.41–8.82)	1.25 (0.68–1.83)
Embryonal	5,423	6.67 (6.49–6.85)	−0.88 (−1.33 to −0.43)
Medulloblastoma	3,201	3.95 (3.81–4.09)	−0.05 (−0.79–0.69)
PNET	1,678	2.05 (1.96–2.16)	−5.67 (−6.54 to −4.8)
Other embryonal	544	0.67 (0.61–0.73)	6.99 (1.49–12.77)
0–4 Years			
Glioma	2,906	14.8 (14.26–15.34)	0.55 (−0.08–1.18)
Low-grade glioma	234	1.19 (1.04–1.35)	−5.75 (−8.57 to −2.84)
High-grade glioma	376	1.91 (1.72–2.12)	0.66 (−1.53–2.9)
Other glioma	2,296	11.69 (11.22–12.18)	1.2 (0.41–2)
Embryonal	2,250	11.45 (10.99–11.94)	0.14 (−1.03–1.33)
Medulloblastoma	1,096	5.58 (5.26–5.92)	−0.27 (−1.57 to 1.06)
PNET	679	3.46 (3.2–3.73)	−5.33 (−7.29 to −3.33)
Other embryonal	475	2.42 (2.2–2.64)	6.93 (1.25–12.93)
5–9 Years			
Glioma	2,919	14.55 (14.03–15.09)	0.73 (−0.4–1.87)
Low-grade glioma	271	1.35 (1.19–1.52)	−1.67 (−4.96 to 1.74)
High-grade glioma	556	2.77 (2.55–3.01)	1.7 (−0.63–4.08)
Other glioma	2,092	10.43 (9.99–10.88)	0.84 (−0.38–2.07)
Embryonal	1,560	7.78 (7.4–8.17)	−1.11 (−2.08 to −0.12)
Medulloblastoma	1,161	5.79 (5.46–6.13)	−0.05 (−1.19–1.11)
PNET	362	1.8 (1.62–2)	−5.39 (−8 to −2.71)
Other embryonal	37	0.18 (0.13–0.25)	
10–14 Years			
Glioma	2,471	11.84 (11.37–12.31)	1.09 (0.3–1.89)
Low-grade glioma	379	1.82 (1.64–2.01)	−2.93 (−5.2 to −0.59)
High-grade glioma	638	3.06 (2.82–3.3)	1.78 (−0.46–4.08)
Other glioma	1,454	6.97 (6.61–7.33)	1.86 (0.86–2.86)
Embryonal	968	4.64 (4.35–4.94)	−2.13 (−3.8 to −0.42)
Medulloblastoma	602	2.88 (2.66–3.12)	0.51 (−1.39–2.45)
PNET	344	1.65 (1.48–1.83)	−7.51 (−10.04 to −4.9)
Other embryonal	22	0.11 (0.07–0.16)	
15–19 Years			
Glioma	2,368	11.12 (10.67–11.57)	0.75 (−0.31–1.83)
Low-grade glioma	490	2.3 (2.1–2.51)	−2.19 (−4.52–0.2)
High-grade glioma	704	3.3 (3.07–3.56)	1.72 (−0.42–3.9)
Other glioma	1,174	5.51 (5.2–5.84)	1.4 (0.09–2.73)
Embryonal	645	3.03 (2.8–3.27)	−1.98 (−4.02–0.1)
Medulloblastoma	342	1.61 (1.44–1.78)	−0.12 (−2.3–2.1)
PNET ther embryonal[a]	293	1.38 (1.22–1.54)	−4.48 (−7.32 to −1.55)

[a]Fewer than 16 cells, trends and rates ommitted.

States are not surprising given the shared data sources. By restricting to only high-quality registries, we decreased the likelihood of data quality influencing our findings. By including more narrowly defined histologic subgroups, we have shown diverging patterns in subtype-specific incidence rates underlying a higher level, average trend. Our results are consistent with recent trends in Europe showing, for example, increasing incidence of pilocytic astrocytoma and ATRT and decreasing incidence of PNET and embryonal cancers overall (28, 29).

The trends we report are likely to be the result of a combination of changing classification, reporting, diagnosis, and true changes in CNS cancer incidence. We observed increasing incidence rates of radiographically confirmed diagnoses of malignant glioma and pilocytic astrocytoma. We hypothesize there are at least three ways for shifting patterns in method of confirmation to influence incidence trends: (i) as imaging becomes more powerful and accessible, an increasing share of diagnoses have been made through imaging rather than biopsy leading to more general diagnosis categories; (ii) not previously detectable cancers are now being detected radiographically; and (iii) more frequent surveillance of patients with tumor predisposition syndromes and diagnoses by radiologists have led to increased reporting to registries by radiologists. The latter two factors could lead to the appearance of increasing incidence in the absence of a true increase in CNS cancer. A detailed analysis of subtype-specific trends in mortality and survival over the same period has not been conducted to our knowledge but may provide insight into whether detection of potentially indolent cancers is contributing to the observed trends.

In addition to changes in method of detection, some subtype trends are likely explained by the increasing availability and understanding of molecular pathology. For example, we found that "other" embryonal tumors (mostly ATRT) increased by 6.99% per year and PNET incidence decreased 5.67% per year. Up until the late 1990s, PNET and ATRT were difficult to distinguish based on clinical and pathologic features and

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Table 4. ASR per million person-years and APC of glioma by topography and histology, 1998–2013

	n	ASR (95% CI)	APC (95% CI)
Topography			
Brain stem	2,658	3.28 (3.16–3.41)	0.89 (0.20–1.58)
Optic nerve	1,392	1.72 (1.63–1.81)	3.92 (1.76–6.13)
Temporal lobe	1,263	1.53 (1.45–1.62)	0.01 (−0.88–0.91)
Cerebrum	1,129	1.38 (1.3–1.47)	0.74 (−0.69–2.18)
Frontal lobe	1,069	1.29 (1.22–1.37)	2.58 (0.82–4.37)
Brain, NOS	779	0.95 (0.89–1.02)	−1.4 (−3.18–0.41)
Cerebellum, NOS	530	0.65 (0.59–0.71)	0.7 (−1.97–3.45)
Parietal lobe	503	0.61 (0.56–0.67)	−2.59 (−4.71 to −0.43)
Overlapping lesions	487	0.59 (0.54–0.65)	−1.2 (−3.07–0.71)
Other	854	1.04 (0.97–1.12)	−0.38 (−1.82–1.09)
Histology			
Low-grade gliomas (major histologies)			
Oligodendroglioma, NOS	580	0.42 (0.65–0.76)	−5.16 (−6.58 to −3.71)
Fibrillary astrocytoma	398	0.93 (0.44–0.54)	−4.13 (−7.17 to −1.00)
Pleomorphic xanthoastrocytoma	347	0.70 (0.38–0.47)	3.45 (0.99–5.98)
High-grade gliomas (major histologies)			
Astrocytoma, anaplastic	761	1.38 (0.86–1.00)	0.72 (−1.12–2.59)
Other gliomas (major histologies)			
Glioma, malignant	4,589	5.65 (5.49–5.82)	3.13 (2.19–4.08)
Astrocytoma, NOS	2,096	2.56 (2.45–2.67)	−2.4 (−3.38 to −1.42)
All other glioma histologies combined			
Other	762	1.41 (0.86–0.99)	−1.97 (−4.64–0.78)

Abbreviation: NOS, not otherwise specified.

most tumors were classified as PNET. Since then, increasing recognition of the distinct genetic signature of ATRT has increased the frequency of its diagnosis (30, 31). Similarly, tumors previously identified as astrocytoma NOS, which after molecular testing show H3F3A mutations, are now being diagnosed and classified as glioma NOS based on evolving understanding of the etiology and prognosis of cancers displaying these mutations (22, 32). This is reflected in our findings; astrocytoma NOS incidence decreased by 2.4% per year and glioma NOS incidence increased by 3.13% per year.

To address the possibility that subtype trends reflect classification shifts rather than true net changes, we reported trends in broader, aggregated groups that are less subject to classification patterns. Even trends in the aggregated groups, however, can be subject to practice changes, if, for example, new technology identifies cancers that would not have previously been reported. In the future, large biobanking efforts such as the Children's Brain Tumor Tissue Consortium (33), may allow for the retrospective classification of tumors using uniform standards that reflect our present day understanding of etiology. For this to contribute to trends research, however, accurate estimates of the size of the population contributing to the consortium would be needed as rate denominators.

Aside from classification and diagnosis, changes in risk factor prevalence could have contributed to changing incidence of pediatric CNS tumors. Ionizing radiation is the strongest known modifiable risk factor for pediatric CNS tumors (7). The dose–response relationship is strongest for meningiomas, which are nonmalignant and excluded from this analysis, but a significant association has also been found with gliomas (9). Steeply increasing use of CT scans could contribute to increasing incidence of gliomas among children aged 5 and older (younger children would have insufficient latency; ref. 34). Recent guidelines to identify pediatric patients at emergency departments who may not benefit from CT (35), and the increasing adoption of the "as low as reasonably achievable (ALARA)" principle for balancing dose with image quality, may decrease current and future dose from pediatric CT scans (36). Given the uncertain association between RF-EMF and malignant CNS tumors (37), it is unclear if and to what extent increases in exposure contribute to the glioma trends.

High birth weight is associated equally with increased risk of gliomas, astrocytomas, and embryonal tumors (5% increase in risk per 500-g increase; ref. 38). However, it is unlikely that high birth weight is driving increases in glioma and astrocytoma, given the U.S. prevalence of high birth weight has decreased over recent decades (39). Cancer predisposition syndromes, such as neurofibromatosis type 1 and 2, Li-Fraumeni syndrome, and Cowden syndrome are estimated to account for approximately 9% of all pediatric CNS cancers (40, 41) and prevalence of these inherited syndromes occurs over generations, making them unlikely drivers of the observed trends over the 15 years of this study. As brain tumor etiology is poorly understood, changes in another unknown exposure could have contributed to the changes in CNS tumor incidence we observed. Further research on the causes of pediatric brain tumors is merited.

The primary strength of this work is the coverage, size, and quality of the registries. Despite being the leading cause of childhood cancer–related death (2), pediatric CNS cancers are rare. The 29 geographically dispersed registries yielded sufficient cases to estimate recent trends by narrow subtype, age, sex, and race/ethnicity. The contributing registries have high completeness and standards that minimize misclassification and missingness (42, 43). Unlike previous studies (14, 27, 44, 45), we restricted to registries that received NAACCR certification to ensure the highest data quality. This is especially critical for CNS cancers, given the rarity of these tumors, the diversity of subtypes, and the varying classification systems.

The data does have inherent limitations. First, as has been outlined, trends in classification, diagnosis, or reporting could be mistaken for true trends in underlying rates. In light of this, we have shown results for all subtypes at specific and aggregated

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levels, and been cautious in our interpretation. Second, the collection of demographic variables, both in cancer registries (numerators) and in the census (denominators), can impact the estimation of rates and trends in subpopulations defined by these variables. For example, NAACCR introduced a Latino identification algorithm in 2003. Prior to that, each registry used its own approach (46). In addition, the 2010 census used different methods than the 2000 census to assign race/ethnicity to those reporting "some other race" or multiple races (47). The decreasing incidence rates of all malignant CNS cancers and gliomas among Latinos were not observed in the other race/ethnic groups and should be interpreted cautiously, given the changes in race/ethnicity classification in the registry and the census and distinct Latino migration patterns (48, 49).

In sum, we present recent trends in pediatric CNS tumor incidence rates in the United States, overall and stratified by subtype, age, sex, and race/ethnicity. Our data demonstrated that the overall incidence rate of malignant CNS tumors has not changed significantly between 1998 and 2013. We observed increasing rates of glioma and pilocytic astrocytoma and decreasing rates of embryonal cancer. Absolute increases were small (equivalent to 94 excess pilocytic astrocytoma and 120 excess glioma cases in a year) and partially offset by decreases in embryonal cancers (72 cases). Continued surveillance of pediatric CNS tumors should remain a priority, given their significant contribution to pediatric cancer–related deaths. The development and promotion of a historically compatible, clinically relevant, and widely accepted classification scheme for pediatric CNS tumors would improve the feasibility, comparability, and usefulness of trends analyses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D.R. Withrow, A.B. de Gonzalez, M.S. Shiels
Development of methodology: D.R. Withrow, A.B. de Gonzalez, M.S. Shiels
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.S. Shiels
Analysis and interpretation of data (e.-g., statistical analysis, biostatistics, computational analysis): D.R. Withrow, A.B. de Gonzalez, C.J.K. Lam, K.E. Warren, M.S. Shiels
Writing, review, and/or revision of the manuscript: D.R. Withrow, A.B. de Gonzalez, C.J.K. Lam, K.E. Warren, M.S. Shiels
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.R. Withrow
Study supervision: D.R. Withrow, M.S. Shiels

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Cancer Epidemiology, Biomarkers & Prevention

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Trends in Pediatric Central Nervous System Tumor Incidence in the United States, 1998–2013

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