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# Incidence of CNS tumors in Appalachian children

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## Abstract

**Objective—**Determine whether the risk of astrocytomas in Appalachian children is higher than the national average.

**Methods—**We compared the incidence of pediatric brain tumors in Appalachia versus non-Appalachia regions, covering years 2000–2011. The North American Association of Central Cancer Registries (NAACCR) collects population-based data from 55 cancer registries throughout United States and Canada. All invasive primary (i.e. non-metastatic tumors), with age at diagnosis 0–19 years old, were included. Nearly 27,000 and 2,200 central nervous system (CNS) tumors from non-Appalachia and Appalachia, respectively comprise the cohorts. Age-adjusted incidence rates of each main brain tumor subtype were compared.

**Results—**The incidence rate of pediatric CNS tumors was 8% higher in Appalachia, 3.31 [95% CI, 3.17–3.45] versus non–Appalachia, 3.06, [95% CI, 3.02–3.09] for the years 2001–2011, all rates are per 100,000 population. Astrocytomas accounted for the majority of this difference, with the rate being 16% higher in Appalachian children, 1.77, [95% CI, 1.67–1.87] versus non-Appalachian children, 1.52, [95% CI, 1.50–1.55]. Among astrocytomas, World Health Organization (WHO) grade I astrocytomas were 41% higher in Appalachia, 0.63 [95% CI, 0.56–0.70] versus non-Appalachia 0.44 [95% CI, 0.43–0.46] for the years 2004–2011.

**Conclusions and Relevance—**This is the first study to demonstrate that Appalachian children are at greater risk of CNS neoplasms, and that much of this difference is in WHO grade I astrocytomas, 41% more common. The cause of this increased incidence is unknown and we discuss the importance of this in relation to genetic and environmental findings in Appalachia.

### Keywords

Appalachia; pediatric; brain tumor; astrocytoma; pilocytic

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## INTRODUCTION

In the U.S., primary central nervous system (CNS) tumors are the most common pediatric solid tumors, with 4,620 estimated new cases in 2015.[1,2] Despite the increase in five year survival rates since the 1970s, there is still significant mortality and morbidity associated with these tumors in children.[3] Gliomas, tumors derived from neuroepithelial cells (astrocytes, oligodendrocytes, and ependymal cells), account for the majority of these primary CNS tumors.[2,3] World Health Organization (WHO) grading is used to group CNS tumors into histological subtypes based on the cell of origin. Grade is determined by evidence of mitosis, necrosis, and microvascular proliferation.[4] WHO grade I tumors are benign tumors and are generally curable by surgical excision, whereas most high-grade tumors recur and spread. However, even grade I tumors can be debilitating and lethal if growing in unresectable deep-seated regions of the brain.

Data from the Central Brain Tumor Registry of the United States (CBTRUS) show that the majority of gliomas in children are astrocytomas.[2,3] Pilocytic astrocytomas are the main subtype of WHO grade I tumors and comprise the majority of astrocytomas in children, with the posterior fossa being the most common site.[2–4] In contrast, supratentorial WHO grade IV glioblastomas account for the majority of gliomas in adults.[2] Furthermore, *IDH1*, *EGFR*, and *NF1* are the main driver genes in adult gliomas, whereas *BRAF* mutations and rearrangements are characteristic of most grade I pediatric gliomas.[5,6]

Certain risk factors have been established for adult gliomas. The Brain Tumor Epidemiology Consortium (BTEC) reports advanced age, Caucasian ethnicity, and male gender as the main inherent risk factors, with exposure to ionizing radiation as the main environmental risk factor.[7] Many familial cancer syndromes increase glioma risk including neurofibromatosis 1 (NF1), NF2, tuberous sclerosis 1 (TSC1), TSC2, Lynch Syndrome, and Li-Fraumeni syndrome.[5] Furthermore, recent research suggests that other factors may also increase the risk of gliomas in adults, including a history of childhood obesity and/or tall stature.[8,9] However, much less is known about pediatric glioma risk factors. Other than the well-known link between NF1 and pediatric gliomas, most cases are sporadic and not linked to known lifestyle, demographic, or geographic variables.

Our clinical practice at the Markey Cancer Center is a primary source of healthcare for the heart of Appalachia in Kentucky and our experience suggested that our rate of pediatric brain tumors may be disproportionately high, considering the size of our catchment area. According to the Appalachian Regional Commission (ARC), Appalachia comprises the region from southern New York to northern Mississippi that follows the Appalachian Mountains encompassing 428 counties and 13 states. Historically, Appalachia is a rural community heavily reliant on mining, agriculture, and heavy industry. Based on the Appalachian Community Cancer Network (AACN) report, the Appalachian region is known to have a high cancer burden, though specific studies focused on Appalachian children are lacking. We therefore decided to test our impression using tumor registry data and our results indicate that Appalachian children are indeed at increased risk for certain tumors of the CNS.

# METHODS

## Descriptive Epidemiology

A cancer incidence data set was extracted from the standard 1995–2011 North American Association of Central Cancer Registries (NAACCR) Cancer Incidence of North America (CINA) analytic file to compare the incidence of CNS neoplasms in Appalachia and non-Appalachia (www.seer.cancer.gov, SEER*Stat Database: NAACCR Incidence - CiNA Analytic File, 1995–2011, for NHIAv2 Origin, Custom File With County, North American Association of Central Cancer Registries). The study dataset includes U.S. registry data in 55 North American Association of Central Cancer Registries (NAACCR) for years 2000–2011. Nine out the 55 registries did not have all data available for years 2000–2011 because data were either not collected or did not meet the registry data fitness for use by NAACCR (http://www.naaccr.org/Research/CINADeluxe.aspx). The following key variables were extracted and utilized: year of diagnosis; age at diagnosis; race; sex; registry; state at diagnosis; county at diagnosis; ICD-O-3 behavior code; ICD-O-3 histology code; WHO grade; diagnostic confirmation; reporting source; International Classification of Childhood Cancer (ICCC) site recode[10,11] and collaborative staging (CS) information.

The data analysis included only cases with age at diagnosis 0–19 years old in years 2000–2011. All invasive CNS primary tumors were included. Cases captured from death certificate or autopsy only were excluded. The WHO grade related analysis was limited to year 2004–2011 as the WHO grade for CNS tumor was captured in the CS site Specific factor 1 starting year 2004. Currently, the Appalachian region includes 428 counties/independent cities defined by the Appalachian Region Commission in thirteen states (http://www.arc.gov/counties), extending more than 1,000 miles from southern New York to northeastern Mississippi. The non-Appalachia region in this study includes the rest of regions covered in the 46 registries' data.

## Statistical Analysis

Age-adjusted rates of CNS neoplasms and their subtypes from 2000–2011 were calculated based on the U.S. 2000 standard population and compared between Appalachian and non-Appalachian regions. A Tiwari's approach was used to calculate 95% confidence intervals and perform rate ratio tests to determine statistical significances.[12] Age-adjusted rates for astrocytomas by WHO grade, race, Appalachian status and age were also calculated and compared. Distribution of astrocytomas by WHO grade was also examined to identify any changes over time. All statistical tests were two-sided with a targeted significance at 0.05. To control the family-wise error rate due to multiple comparisons, the statistics significances were determined based on the Holm-Bonferroni method.

# RESULTS

Our initial evaluation of primary CNS neoplasms (2000–2011) for children 0–19 years of age, categorized into Appalachia and non-Appalachia, found a significant increase in incidence and were 8% higher in Appalachia compared to non-Appalachia, 3.31[95% CI, 3.17–3.45] vs. 3.06 [95% CI, 3.02–3.09, Rate Ratio (RR) 1.08, P<0.001]. We then

determined which subtypes of CNS neoplasms were different between Appalachia and non-Appalachia children (Table 1). Ependymomas and other choroid plexus tumors were significantly lower in Appalachia, 0.21 [95% CI, 0.17–0.25] vs. 0.27 [95% CI, 0.25–0.28, RR 0.78, P=0.004]. Astrocytomas accounted for the majority of the difference seen in Appalachia, as the incidence of astrocytomas was almost 50% of all total cases and 16% higher in Appalachia than in Non-Appalachia, 1.77 [95% CI, 1.67–1.87] vs. 1.52 [95% CI, 1.50–1.55, RR 1.16, P<0.001]. Other gliomas excluding astrocytomas were 18% higher in Appalachia compared to non-Appalachia, 0.63 [95% CI, 0.57–0.69] vs. 0.53 [95% CI, 0.52–0.55, RR 1.18, P=0.002].

Since astrocytomas accounted for the majority of the difference, we then examined the incidence of different WHO grade astrocytomas in Appalachia and non-Appalachia (Table 2) from 2004–2011. While the rate of unclassified astrocytomas was higher in Appalachia, WHO grade I astrocytomas accounted for a majority of the overall increase. Of the different grades, only grade I astrocytomas were higher in Appalachia. The incidence of grade I astrocytomas was 41% higher in Appalachia, 0.63 [95% CI, 0.56–0.70] vs. 0.44 [95% CI, 0.43–0.46, RR 1.41, P<0.001]. Therefore, our results demonstrate that only primary CNS neoplasms were increased in Appalachia, and that grade I astrocytomas account for the majority of this difference. This held even in the stratified analysis by race/ethnicity, focusing only on non-Hispanic white children. Furthermore, within the Appalachian pediatric population, all age ranges showed similar degrees of increased risk for grade I astrocytomas (Table 3).

We also investigated the relatively high counts of astrocytomas with unknown grading. We evaluated time trends for astrocytomas combining all ages 0–19 years and evaluated the distribution of astrocytomas in 2004–2006, 2007–2009, and 2010–2011 using the entire NAACCR database combining Appalachia and non-Appalachia (Table 4). This demonstrated that unknown grade has decreased over time, especially in recent years as it comprised 50.8% and 56.1% for non-Appalachia and Appalachia in 2004–2006, but only 26.0% and 20.1% in 2010–2011, with a concomitant increase in the proportion of graded tumors. Furthermore, time-trend analysis indicated that grade I astrocytomas, as percentage of all astrocytomas, was higher in Appalachia compared to non-Appalachia over all three time periods: 2004–2006 (29.5% vs. 21.9%, p-value=0.001), 2007–2009 (33.2% vs. 29.9%, p-value=0.212), and 2010–2011 (44.4% vs. 37.1%, p-value=0.026). This more recent improvement in grading confirmed that the elevated risk of grade I pediatric astrocytomas was not merely the result of Appalachia-specific misclassifications.

## DISCUSSION

Our data indicate that Appalachian children are at significantly increased risk of low-grade brain tumors. One possible reason is that certain genetic risk factors may be more prevalent in Appalachia, which is relatively homogenous and enriched for Scotch-Irish ancestry. Although Kentucky is known for an increased risk for Lynch syndrome with the American Founder Mutation of MSH2[13], neither germline cancer predisposition syndromes, such as neurofibromatosis 1, which increase the risk of pilocytic astrocytomas, nor genes known to

increase the risk of pediatric astrocytomas such as *BRAF,* rearrangements RTEL1 have been identified in Appalachia.[14–17]

Environmental factors may also contribute to the increased risk of brain tumor development in Appalachia. The role of carcinogens in the etiology of brain tumors is controversial, but limited studies do demonstrate factors that are prevalent in Appalachia that includes smoking and pollution. Two studies identified an increased risk of brain tumors in the offspring of mothers having *in utero* exposures. Brooks *et al.* demonstrated that, in a Swedish prospective study, maternal smoking was associated with an increased risk of their children having a brain tumor, with a hazard ratio of 1.24; astrocytoma was the most common histology.[18] Appalachia is known for having higher cancer incidence rates than the rest of the US in both tobacco related and non-related cancers.[19,20] The SEARCH International Brain Tumor Study by Mueller *et al.* reported that reliance on well water during pregnancy, which increased systemic nitrite levels, was associated with a fivefold increased risk of astrocytoma in their children.[21] Well water use is Appalachia is also significantly higher than the national average.[22] Finally, carcinogens that are derived from coal mines are present at very high levels in Appalachia and have been linked to brain tumors in adults.[23] It is possible that these carcinogens may also predispose toward childhood brain tumors.

Relative to the national population, Appalachia has a higher white population and a substantially smaller population of blacks, 4% in Appalachia vs 13% nationally.[20] Since blacks have a lower incidence of brain tumors, including astrocytomas,[2,3] it raised the possibility of race/ethnicity as a confounding variable in this study. But even when restricting analysis to just whites, Appalachian children retained a statistically significant higher incidence of grade I astrocytomas (Table 1).

Geographic variation in cancer incidence is well established; however, pediatric tumors generally have demonstrated less regional variation than adult cancers.[24,25] This includes brain tumors, although prior analyses for pediatric brain tumors combined all types.[2,3,25] The magnitude of increased risk of astrocytomas in Appalachian children is in line with studies of radiation exposure from CT scans,[26,27] but less than the risk reported in atomic bomb survivors and the Israeli tinea capitis cohort exposed to radiation to the scalp.[28]

Our analysis demonstrated a high percentage of unknown grade of astrocytomas (Table 4). This has been previously reported, and may in part reflect the contribution of pediatric brainstem gliomas, which represents 15–20% of childhood brain tumors. This includes low-grade focal brainstem gliomas and high-grade diffuse intrinsic pontine gliomas. Such tumors are generally considered inoperable and a clinical/radiologic diagnosis is often accepted without the need for pathologic confirmation, although there is growing acceptance on the risk of surgical biopsy for the benefit of genetic tumor analysis.[29] We evaluated recent time trends for the distribution of astrocytomas, on the premise that more recent years might indicate a greater emphasis on grading gliomas according to WHO criteria—a temporal variation in the application of a diagnosis. Indeed, we found a significant decrease in the “unknown grade” group with a concomitant increase in all four grades, I-IV. Nevertheless, grade I astrocytomas remained disproportionately high in Appalachia across time intervals,

suggesting that some sort of temporary Appalachian-specific misclassification was not the cause for the higher incidence.

Although the use of population-based cancer registries is essential to obtaining generalizable epidemiologic information on tumor incidence, these sources have limitations, including potential differences in the data quality and reporting across registries, and lack of centralized pathologic review. Variation on the quality of registry data impacting differently between Appalachian and non-Appalachian population that may have produced the differences in our data is a possibility although unlikely. It is important that variables in diagnosing a tumor as “glioma” versus the more specific “astrocytoma” cannot be directly addressed in registry data. Our analysis must therefore be considered with these caveats.

It must also be noted that Appalachia is not a homogenous region. Risk factors and potential environmental exposures as well as levels of poverty and educational attainment which are closely tied to cancer incidence vary within the region classified as Appalachia.[19] Therefore, findings from our investigation should take this into account and provide limitations for future investigations.

In summary, we report for the first time that Appalachian children are at increased risk of low-grade astrocytomas. A large scale epidemiological study focusing on the environment and molecular genetics would therefore represent an important contribution to the field and advance our understanding of why pediatric gliomas occur.

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**Table 1**

Age-adjusted incidence rates and rate ratios of CNS neoplasms in Appalachian and non-Appalachian children, 2000–2011.

| Types of CNS | Non-Appalachia | | | Appalachia | | | Rate Ratio | P-value | Significance* |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate | (95% CI) | N | Rate | (95% CI) | | | |
| CNS Neoplasms | *26,960* | *3.06* | *(3.02–3.09)* | *2,197* | *3,31* | *(3.17–3.45)* | *1.08* | *<0.001* | S |
| Ependymomas and choroid plexus tumor | 2,347 | 0.27 | (0.25-.028) | 137 | 0.21 | (0.17–0.25) | 0.78 | 0.004 | S |
| *Astrocytomas* | *13,431* | *1.52* | *(1.50–1.55)* | *1,170* | *1.77* | *(1.67–1.87)* | *1.16* | *<0.001* | S |
| Intracranial and intraspinal embryonal tumors | 5,584 | 0.63 | (0.62–0.65) | 401 | 0.61 | (0.55–0.68) | 0.97 | 0.529 | NS |
| *Other Gliomas* | *4,685* | *0.53* | *(0.52–0.55)* | *414* | *0.63* | *(0.57–0.69)* | *1.18* | *0.002* | S |
| Other specified intracranial/intraspinal | 541 | 0.06 | (0.06–0.07) | 39 | 0.06 | (0.04–0.08) | 0.97 | 0.889 | NS |
| Unspecified intracranial/intraspinal | 372 | 0.04 | (0.04–0.05) | 26 | 0.04 | (0.03–0.06) | 0.93 | 0.830 | NS |

Rates per 100,000; CI = confidence interval;

*Significance is based on Holm-Bonferroni approach; NS = not significant; S = significant.

**Table 2**

Age-adjusted incidence rates and rate ratios of astrocytomas, classified by WHO grad.e and race in Appalachian and non-Appalachian children, 2004–2011.

| WHO Grade | Non-Appalachia | | | Appalachia | | | Rate Ratio | P-value | Significance * |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate | (95% CI) | N | Rate | (95% CI) | | | |
| Total | 9948 | 1.53 | (1.50 1.56) | 908 | 1.81 | (1.69 1.93) | 1.18 | <0.0001 | S |
| **All** | | | | | | | | | |
| Grade I | 2,873 | 0.44 | (0.43 – 0.46) | 315 | 0.63 | (0.56 – 0.70) | 1.41 | <0.001 | S |
| Grade II | 1,039 | 0.16 | (0.15 – 0.17) | 79 | 0.16 | (0.12 – 0.19) | 0.98 | 0.912 | NS |
| Grade III | 518 | 0.08 | (0.07 – 0.09) | 34 | 0.07 | (0.05 – 0.09) | 0.85 | 0.389 | NS |
| Grade IV | 745 | 0.12 | (0.11 – 0.12) | 71 | 0.14 | (0.11 – 0.18) | 1.22 | 0.134 | NS |
| Undefined | 659 | 0.10 | (0.09 – 0.11) | 38 | 0.08 | (0.05 – 0.11) | 0.75 | 0.086 | NS |
| Unknown | 4,114 | 0.64 | (0.62 – 0.66) | 371 | 0.74 | (0.67 – 0.82) | 1.17 | 0.005 | S |
| **Non-Hispanic White** | | | | | | | | | |
| Grade I | 1,861 | 0.54 | (0.52 – 0.57) | 272 | 0.67 | (0.60 – 0.76) | 1.25 | 0.001 | S |
| Grade II | 661 | 0.19 | (0.18 – 0.21) | 74 | 0.18 | (0.14 – 0.23) | 0.96 | 0.800 | NS |
| Grade III | 326 | 0.09 | (0.08 – 0.10) | 31 | 0.08 | (0.05 – 0.11) | 0.82 | 0.344 | NS |
| Grade IV | 429 | 0.12 | (0.11 – 0.14) | 46 | 0.11 | (0.08 – 0.15) | 0.92 | 0.656 | NS |
| Undefined | 374 | 0.11 | (0.10 – 0.12) | 33 | 0.08 | (0.06 – 0.12) | 0.76 | 0.154 | NS |
| Unknown | 2,653 | 0.77 | (0.74 – 0.80) | 321 | 0.81 | (0.72 – 0.90) | 1.04 | 0.517 | NS |

Rates per 100,000; CI = confidence interval;

*Significance is based on Holm-Bonferroni approach; NS = not significant; S = significant.

**Table 3**

Age specific incidence rates and rate ratios of grade I astrocytomas, classified by age group in Appalachian and non-Appalachian children, 2004–2011.

| Age Group | Non-Appalachia | | | Appalachia | | | Rate Ratio | P-value | Significance* |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate | (95% CI) | N | Rate | (95% CI) | | | |
| 0–4 Years | 751 | 0.47 | (0.44 – 0.51) | 72 | 0.61 | (0.48 – 0.77) | 1.64 | 0.053 | NS |
| 5–9 Years | 799 | 0.51 | (0.48 – 0.55) | 89 | 0.73 | (0.59 – 0.90) | 1.43 | 0.002 | S |
| 10–14 Years | 753 | 0.46 | (0.43 – 0.49) | 89 | 0.69 | (0.56 – 0.85) | 1.51 | 0.001 | S |
| 15–19 Years | 570 | 0.33 | (0.31 – 0.36) | 65 | 0.47 | (0.06 – 0.60) | 1.41 | 0.015 | S |

Rates per 100,000; CI = confidence interval;

*Significance is based on Holm-Bonferroni approach; NS = not significant; S = significant.

**Table 4**

Distribution of WHO Grade by Year of Diagnosis for Astrocytomas, 2004–2011

| WHO Grade | Total | | | | 2004–06 | | | | 2007–09 | | | | 2010–11 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NAP | | AP | | NAP | | AP | | NAP | | AP | | NAP | | AP | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Grade I | 2,873 | 28.9 | 315 | 34.7 | 785 | 21.9 | 102 | 29.5 | 1,143 | 29.9 | 109 | 33.2 | 945 | 37.1 | 104 | 44.4 |
| Grade II | 1,039 | 10.4 | 79 | 8.7 | 311 | 8.7 | 20 | 5.8 | 407 | 10.7 | 32 | 9.8 | 321 | 12.6 | 27 | 11.5 |
| Grade III | 518 | 5.2 | 34 | 3.7 | 147 | 4.1 | 11 | 3.2 | 195 | 5.1 | 16 | 4.9 | 176 | 6.9 | 7 | 3.0 |
| Grade IV | 745 | 7.5 | 71 | 7.8 | 229 | 6.4 | 18 | 5.2 | 276 | 7.2 | 34 | 10.4 | 240 | 9.4 | 19 | 8.1 |
| N/A | 659 | 6.6 | 38 | 4.2 | 291 | 8.1 | 1 | 0.3 | 164 | 4.3 | 7 | 2.1 | 204 | 8.0 | 30 | 12.8 |
| Unknown | 4,114 | 41.4 | 371 | 40.9 | 1,819 | 50.8 | 194 | 56.1 | 1,633 | 42.8 | 130 | 39.6 | 662 | 26.0 | 47 | 20.1 |
| Total | 9,948 | 100.0 | 908 | 100.0 | 3,582 | 100.0 | 346 | 100.0 | 3,818 | 100.0 | 328 | 100.0 | 2,548 | 100.0 | 234 | 100.0 |