Understanding racial disparities in pediatric malignant glioma management: A United States perspective.

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Background:

The diagnosis of malignant glioma confers a poor prognosis in the pediatric population. What remains to be understood is if racial disparities impact management and survival amongst this demographic. Correspondingly, the aim of this study was to determine if racial disparities in the management and survival of pediatric malignant glioma within the United States (US) existed and what their predictors would be.

Materials and Methods:

All pediatric malignant gliomas patients with known race status (White, Black, Other) in the US National Cancer Database (NCDB) between the years 2005-2016 were retrospectively reviewed. Demographic, socioeconomic and clinical data were then abstracted and analyzed by comparison and regression techniques.

Results:

A total of 1803 pediatric malignant glioma cases were identified, with 48% female and a median age of 8 years old. Brainstem locations were reported in the 48% of cases. Socioeconomically, there were statistical differences with respect to insurance status, yearly income, household education level and metropolitan residences between the racial groups (all $P<0.01$). With respect to treatment, there was only statistical difference in the proportion of patients treated with surgical resection (White 43% vs Black 34% vs Other 37%, $P=0.02$). There were no differences between race groups for radiation therapy ($P=0.73$) or chemotherapy ($P=0.12$). The odds of surgical resection were significantly less in the Black group compared to the White group (OR 0.69, $P<0.01$), although there was no difference in overall survival between the two groups in those treated with ($P=0.44$) or without ($P=0.27$) surgical resection. Primary predictors of surgical resection in the Black group were deep tumor location ($P<0.05$) and low yearly income ($P=0.02$).

Conclusions:

Racial disparities can exist amongst the management of pediatric malignant gliomas, however the impact on overall survival collectively remains to be seen. In this US perspective, we identified predictors of racial disparity in surgical treatment for this devastating diagnosis. There is a need to evaluate for hospital-dependent initiatives to ensure management is not sabotaged by racial inequality in the future as we continue to advance our treatment of pediatric malignant gliomas.

Population-based whole-genome sequencing with constrained gene analysis identifies predisposing germline variants in children with central nervous system tumors

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Abstract:

Background: The underlying cause of central nervous system (CNS) tumors in children is largely unknown. In this nationwide, prospective population-based study we investigate rare germline variants across known and putative CPS genes and genes exhibiting evolutionary intolerance of inactivating alterations in children with CNS tumors.

Methods: One hundred and twenty-eight children with CNS tumors underwent whole-genome sequencing of germline DNA. Single nucleotide and structural variants in 315 cancer related genes and 2,986 highly evolutionarily constrained genes were assessed. A systematic pedigree analysis covering 3,543 close relatives was performed.

Results: Thirteen patients harbored rare pathogenic variants in nine known CPS genes. The likelihood of carrying pathogenic variants in CPS genes was higher for patients with medulloblastoma than children with other tumors (OR 5.9, CI 1.6-21.2). Metasynchronous CNS tumors were observed exclusively in children harboring pathogenic CPS gene variants (n=2, p=0.01).

In general, known pCPS genes were shown to be significantly more constrained than both genes associated with risk of adult-onset malignancies ($p=5e^{-4}$) and all other genes ($p=5e^{-17}$). Forty-seven patients carried 66 loss-of-functions variants in 60 constrained genes, including eight variants in six known pCPS genes. A deletion in the extremely constrained *EHMT1* gene, formerly somatically linked with sonic hedgehog medulloblastoma, was found in a patient with this tumor.

Conclusions: ∽10% of pediatric CNS tumors can be attributed to rare variants in known CPS genes. Analysis of evolutionarily constrained genes may increase our understanding of pediatric cancer susceptibility.

A novel classification of pediatric CNS tumors for cancer registries using a clustering analysis

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Background:

To accurately evaluate the burden of pediatric central nervous system (CNS) tumors, estimate resources for cancer control, and monitor outcomes, a classification system that segregates tumors into clinically relevant groups is essential. The current classification of pediatric CNS tumors included in the third revision of the International Childhood Cancer Classification does not identify key clinical groups, such as low- and high-grade gliomas. To address this need, a novel classification was embarked upon using ICD-O-3 codes, CBTRUS grouping, incidence, survival, and treatment modalities as inputs.

Materials and Methods:

For each ICD-O-3 code with >50 new cases/year in CBTRUS from 2000 to 2016, 2 clinicians reached consensus defining the efficacy of three treatment modalities: surgical resection, radiotherapy, and chemotherapy. Then, patient level 5-year overall survival (OS) times were simulated based on total incidence and 5-year OS for each code. Subsequently, 5 factors were included as potential classifiers: tumor behavior, CBTRUS sub-group, and efficacy of the three treatment modalities. A "survival tree" was developed using recursive partitioning. Starting with the patient cohort (root), univariate cox proportional hazards model was used to identify statistically significant ($P < 0.05$) factors. The factors with the largest hazard ratio were selected manually to create child nodes. Within each child node, the partitioning process was repeated on remaining factors until no statistically significant factor remained.

Results:

This process yielded 17 clusters. Subsequently, these clusters were compiled into 4 main groups based on survival: low- (>90% OS), intermediate- (75-90% OS), high- (50-75% OS), and very high-risk (<50% OS) tumors. The 4 groups include 11 subgroups, including subgroups like "low-risk glial and glioneuronal tumors" that includes pilocytic astrocytoma or "high-risk neuroepithelial tumors" that includes anaplastic ganglioglioma. Further validation of the classification will be sought through three processes: a) using patient-level data from the CBTRUS registries; b) utilizing additional datasets that include pediatric CNS tumor survival from other countries or regions; and c) through a structured consensus process using multidisciplinary experts.

Conclusions:

This systematic method to develop a classification for pediatric CNS tumors is novel and incorporates not only morphology codes, but treatment and survival data. This classification would

allow for more relevant estimations of outcomes and better estimation of resource utilization for cancer control. Furthermore, this strategy could be replicated for other disease groups.

Prevalence of brain and central nervous system tumors in children and adolescents in the US, 2022

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Background:

Brain tumors are among the most common childhood and adolescent cancers, as well as the leading cause of death among solid childhood cancers. There are various methods to estimate the burden of brain tumors on the pediatric population, including years of potential life lost (YPLL), median survival, and complete prevalence. Complete prevalence is the measure of people alive with a disease at a specified time, theoretically capturing all previous diagnoses. Estimating complete prevalence poses many methodological issues due to the inherent "incompleteness" of modern population-based cancer registries. In this analysis, the prevalence of childhood and adolescent brain tumors is estimated by histology and sex for the year 2022.

Materials and Methods:

Incidence data from 2000-2018 by histology, sex, and single age at diagnosis for malignant and non-malignant brain tumors was obtained from the Central Brain Tumor Registry of the United States (CBTRUS) (2004-2018 for non-malignant tumors), a merged dataset of the National Program of Cancer Registries US Cancer Statistics (USCS) and National Cancer Institute's Surveillance, Epidemiology and End Results. Incidence data from 2001-2018 was obtained for International Classification of Childhood Cancer (ICCC)-defined histologies by sex, and single age at diagnosis from USCS. Incidence data by sex and single age and survival data for children ages 0-19 at time of diagnosis were obtained from SEER 9 for 1975-2018. Prevalent case counts were estimated by histology and behavior for the year at prevalence, 2022, using prevEst in R 4.0.

Results:

There were 41,965 prevalent brain tumor cases in children and adolescents ages 0-19 in 2022. The histologic group with the highest prevalence was gliomas, with 26,052 cases and a PR of 34.97. The next most prevalent histologic groups were embryonal tumors (3,789 cases) and tumors of the sellar region (3,636 cases). Prevalence of brain tumors was higher than any ICCC-defined histology, where leukemias, myeloproliferative & myelodysplastic diseases were the most prevalence non-brain cancer type (37,027 cases), followed by lymphomas and reticuloendothelial neoplasms (12,143 cases). Prevalence of most brain tumor histologies did not differ substantially by sex, with the exception of medulloblastoma (1,815 cases in males as compared to 1,056 cases in females), tumors of the pituitary (1,493 cases in females as compared to 750 cases in males), and germ cell tumors (539 cases in males as compared to 354 cases in females).

Conclusions:

Brain tumors have higher prevalence than any other cancer type in children and adolescents in the US. Childhood brain tumor survivors have unique needs due to both tumor and treatment effects, and prevalence estimates allow for estimation of the total population with these needs.

Incidence trends of childhood central nervous system tumors in Finland 1990–2017

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Background: Central nervous system (CNS) tumors are a leading cause of cancer-related morbidity and mortality in children. Higher incidence rates of CNS tumors have been reported in the Nordic countries than other European countries. As the etiology of CNS tumors is still largely unknown, monitoring changes in cancer incidence is critical for instigating hypothesis-based research on potential environmental risk factors and assessing the public health burden. Our aim is to characterize incidence rates and trends of pediatric CNS tumors in Finland over the last three decades.

Materials and Methods: Data on all benign and malignant incident CNS tumors diagnosed in children aged 0–14 years in 1990–2017 were extracted from the Finnish Cancer Registry and classified according to the 2016 WHO classification of CNS tumors. We included only first primary cancers. CNS lymphomas were excluded. We analyzed age-standardized incidence rates (ASR) for pediatric CNS tumors overall and by sex, age, tumor histology, grade and location using Poisson regression. In addition, we used joinpoint regression to evaluate changes in trends.

Results: Overall, 1117 pediatric CNS tumor cases were registered in Finland with a 1.2:1 male to female ratio. Tumors were most frequent in the age group 0-4 years (428 tumors). The predominant tumor location was the infratentorial area (42% of tumors), followed by the supratentorial brain (31%) and the spinal cord (6%). The average annual ASR was 4.3 per 100,000 person-years (95% CI 4.26, 4.34). The most common tumor type was pilocytic astrocytoma (30% of tumors), followed by medulloblastoma (10%) with incidence rates of 1.30 and 0.45 per 100,000 person-year, respectively. Overall, 96% of the tumors were histologically verified with benign tumors (grade I) comprising 48% of the tumors. The overall incidence of pediatric CNS tumors increased steadily by an annual percentage change (APC) of 0.8% (95% CI 0.2, 1.4). We observed no major changes

in incidence trends of tumor histology groups or tumor location groups. The ASR of benign tumors increased by an APC of 1.0 (95% CI 0.1, 2.0).

Conclusions: Utilizing the high-quality and completeness of data in the Finnish Cancer registry, we found that the incidence of pediatric CNS tumors in Finland has increased slightly but steadily from 1990 until 2017. Although variations in diagnostic and registration practices over time might have affected the rates, the trend may also reflect a true increase in incidence.

Central nervous system tumours in children in the European Cancer Information System (ECIS)

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Background:
Central nervous system (CNS) tumours are the most frequent solid tumours in childhood, accounting for around 15-20% of all paediatric malignancies.
Early detection and treatment improvements have increased their survival.
Computation and dissemination of reliable indicators to monitor childhood cancer burden is the goals of the European Cancer Information System (ECIS), developed and maintained by the European Commission's Joint Research Centre (JRC) and based on data from registries affiliated to the European Network of Cancer Registries (ENCR).
The current study focuses on childhood CNS tumours, analysing incidence indicators and reporting on data quality and variable completeness.

Materials and Methods:
Data were collected via the 2015 data call to European cancer registries (CRs), and come from both childhood-specifics and general registries contributing with an incidence period of at least 5 years. Childhood CRs were prioritised when their areas overlap with those of the general CRs.
The data call protocol included demographic variables, incidence date, tumour variables, follow-up, cause of death and treatment variables.
Tumours were coded according to the International Classification for Childhood Cancer.
Internal consistency and multiple primary tumours were checked through the JRC-ENCR Quality Check Software.
Number of new diagnosis, crude incidence rates, age-standardised incidence rates (ASR) and cumulative risk are some of the indicators available in the ECIS web application, detailed by diagnostic group and subgroup, CR and incidence period (https://ecis.jrc.ec.europa.eu/index.php). Moreover, the percentage (%) of tumours microscopically verified (MV) and the % of cases with unspecified morphology (UM) were calculated. The completeness of variables included in the protocol was analysed.

Results:
47265 CNS malignant and non-malignant tumours (germ cell tumours excluded) in children (age group 0-19) from 111 CRs in 32 countries were considered, accounting for 18% of all childhood tumours.
Malignant tumours represented 75% of CNS tumours, 20% of uncertain behaviour tumours and 5% of benign. The majority of the cases (99%) qualified as first tumours while 624 occurred as second primary tumours. Astrocytoma was the most frequent CNS tumour (39%).
%MV was 80% (higher than 70% in 77% of CRs). %UM accounted for 14% of tumours (lower than 15% in 52% of CRs)

ASRs presented a huge variability among CRs. ASR in the period 2010-2013 corresponded to 41 per million children (aged 0-14) in Hungary and 35 in Switzerland. ASRs in 2010-2013 corresponded to 41 and 21 per million children (aged 0-19) in Modena and Naples respectively.
Grade was missing in 84% of CNS tumours, vital status in 7% and cause of death in 61%.
Surgery variable was missing in 64% of tumours and bone marrow transplantation variable in 94%.

Conclusions:
Incidence indicators available in the ECIS web application quantify the share of CNS tumours burden in children and basis for research. Contribution in ECIS by National French, German and Romanian CRs and other regional childhood CRs is essential to achieve a registration coverage of nearly 95% in the European Union. Timeliness of ECIS indicators is of utmost importance to provide an up-to-date overview of childhood cancer burden in the EU and Europe.

Epidemiology of childhood brain tumors in France: preliminary results of a nationwide study

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Background: Primary central nervous system tumors (PCNST) among children (0-19 years) represent a heterogeneous group of pathologic entities that remain a real challenge to deal with. We present an exhaustive record of histologically-proven pediatric PCNST in France.

Materials and Methods: Patients were identified through the French Brain Tumor Database, a national database that includes, in a prospective manner, all histologically-confirmed cases of PCNST in France. Patients (0-19 years old), with histologically-confirmed PCNST diagnosed between 2006 and 2015 were included. Number of cases, incidence rates, gender distribution, type of surgery (resection/biopsy) and number of cryopreserved samples were provided for each histological subtype (included rare subtypes).

Results: 6692 cases of newly diagnosed and histologically confirmed PCNST (males/females: 3692/3000) have been recorded over ten years. Main histological results included 4864 tumors of neuroepithelial tissue (72.68%) [2830 gliomas (42.29%), 819 neuronal and mixed neuronal-glial tumors (12.24%), 1005 embryonal tumors (15.02%), 210 others (3.14%)], 746 tumors of the

meninges (11.15%) [140 meningiomas (2.09%), 551 mesenchymal tumors (8.23%), 55 others (0.82%)], 251 tumors of cranial and paraspinal nerves (3.75%), 223 germ cell tumors (3.33%), 284 craniopharyngiomas (4.24%), and 324 all others (4.84%).

The overall crude incidence rate (CR) was 4.334 per 100,000 person-years. The CR in the 0-4 years old population was 4.418 per 100,000 person-years, 4.184 per 100,000 person-years in the 0-14 years old and 4.789 per 100,000 person-years in the 15-19 years old. Age-standardized incidence rates will be detailed in the presentation. Moreover, the specific characteristics of the 0-4 and 15-19 years groups, according to histological subtypes and sex predominance, will be also detailed. For example, anaplastic ependymomas accounted for 101/171 (59.06%) of all ependymoma cases in the 0-4 years population, and for 16/99 (16.16%) of all ependymoma cases in the 15-19 years population. Embryonal tumors accounted for 422/1715 (24.61%) of all PCNST in the 0-4 years population, and for 100/1835 (5.45%) of all PCNST in the 15-19 years population. Among mesenchymal tumors, lipomas accounted for 98 cases in the 0-4 years population, and for 10 cases in the 15-19 years population.

Discussion: Changes in histological classifications over time have led to bias in the comparison of incidence rates according to the time periods. One of the solutions to minimize this bias could be to record not only the international code but also the precise title of each tumor subtype. One of the advantages of our study is to have collected not only the international coding system, but also the precise name of each tumor subtype. Even if our study refers to the 2007 WHO classification, our results will make it possible to better compare epidemiological studies that will be made with the 2016 and/or 2021 WHO classification.

Conclusions: To the best of our knowledge, this is the biggest French report of all histologically-confirmed cases of PCNST diagnosed in children and adolescents. All histological subtypes are detailed with their frequency and distribution. This may have major epidemiological, clinical and research implications.

Spatial Clustering of Pediatric Brain Tumors in Texas, USA

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Background: Brain tumors are the leading cause of cancer-related mortality and morbidity in children and adolescents. Thus, preventing the onset of pediatric brain tumors is the best-case scenario; however, few known risk factors have been identified. Given the rarity of these tumors, geospatially mapping these cases may provide insight into socio-environmental factors that may increase risk.

Materials and Methods: The Texas Cancer Registry is one of the largest statewide, population-based cancer registries in the U.S. In Texas, 5,199 primary brain tumors were diagnosed among patients ≤19 years old from 1995 to 2017. Residential address at diagnosis was geocoded. Using the 2000 U.S. Census, we summed the number of pediatric brain tumors in each block group (BG) in Texas. A BG contains 600 to 3,000 people. Incidence of pediatric brain tumors was calculated using total population ≤19 years old in each BG. To evaluate whether incidence of pediatric brain tumors had any meaningful geographic patterns, we performed hot spot analysis in ArcGIS pro using the Getis-Ord Gi* cluster analysis method. Getis Ord Gi* compares the BG's neighborhood incidence to the state and identifies statistically significant spatial clusters of low (cold spots) or high (hot spots) incidence. The *contiguity edges only* option was used to conceptualize spatial relationships among the BGs that form a neighborhood.

Results: After removing BGs with ≤10 people below age 20 years, 14,392 BGs remained for analysis. The median incidence of pediatric brain tumors within a BG in Texas during the study period was 43.3 cases per 1,000,000. The global spatial autocorrelation test (Global Moran's I) indicated significant but moderate spatial clustering of pediatric brain tumors across the entire state ($I= 0.035$; $p<0.001$). There was a high degree of local spatial clustering of pediatric brain tumors in Texas, with 194 BGs (1.3%) being in a hot spot cluster. Majority (88.1%) of the hot spots were located inside metropolitan areas, outside of the Texas-Mexico Border region. We plan to further refine our analysis to reduce the temporal incongruency between date of diagnosis and census data, which may improve the precision of our findings. We also plan to repeat the analyses for the three major tumor types: astrocytoma, medulloblastoma, and ependymoma.

Conclusions: In Texas, we found a non-random distribution of high incidence of pediatric brain tumors clustered by BG. It is also notable that most of the hot spots were observed in the most populous metropolitan areas. Future work may assess characteristics unique to these hot spots to identify potentially modifiable risk factors for these tumors.

Early mortality in children diagnosed with CNS-tumors in Denmark and Sweden: the role of social background in a setting with universal health care

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Background: A growing body of research has demonstrated social inequalities in survival from childhood cancer, including tumors of the central nervous system (CNS). In fact, one study found a particular pronounced association between lower parental education and poorer survival after a CNS-tumor. Survival inequalities between socioeconomic groups have been observed also in high-income countries, including the Nordic countries, where universal health care is offered.

The mechanisms behind these associations, however, remain poorly understood, but differences in adherence to treatment has been one suggested pathway. However, this pathway may be more important for cancer types for which much of the treatment is given in the child's home, as for acute lymphoid leukemia, than for cancer types primarily treated in hospitals. Moreover, there are indications that the differences in survival between children of different social backgrounds start already within the first year after diagnosis, or even within the first month as indicated by a previous study from the U.S. Social differences occurring this early in the disease course are unlikely to be related to treatment adherence but are more likely to have other explanations.

It is, however, unclear if social inequalities are already seen for early mortality in settings with universal health care. Thus, we aimed at investigating the association between parental social factors and early mortality in children diagnosed with CNS-tumors in a register-based cohort study combining data from Denmark and Sweden. Moreover, we sought to assess whether potential associations with early mortality differed from corresponding associations for later mortality.

Materials and Methods: All children diagnosed with cancer at ages 0-19 years, during 1991-2014, were identified from the Danish and Swedish national cancer registers. From national administrative registers we collected information on parental social characteristics before the child's cancer diagnosis. We estimated odds ratios (OR) and 95% confidence intervals (CI) of early mortality (i.e. death within three months after cancer diagnosis) by parental education, income, employment, cohabitation and country of birth using logistic regression models, adjusting for country, sex, age at diagnosis, and time period of diagnosis. We also estimated ORs and 95% CI of the outcome later mortality (i.e. deaths occurring one to five years after cancer diagnosis).

Results: Among the 3,383 children diagnosed with a CNS-tumor, 117 (3.5%) died within three months after cancer diagnosis. Early mortality was higher among the disadvantaged groups, with the most pronounced associations observed for lower parental education, lower paternal income, maternal unemployment and single parents. The adjusted ORs of early mortality, comparing children of parents with lower education to children of parents with higher education was 1.84 (95% CI 1.10-3.09) and 1.79 (95% CI 1.05-3.06) for mothers and fathers respectively. No similarly elevated odds were observed for these associations with later mortality.

Conclusions: This population-based study revealed inequalities in early mortality from childhood CNS tumors by social background, also in countries with universal health care. Social differences occurring early in the disease course, rather than later, might indicate differences in the timing of diagnosis.

Mortality after a brain tumor diagnosis in children with cancer-linked birth defects: a Swedish register-based study of 40 years

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Background: Childhood brain tumor survival has tangibly improved over the past decades owning to effective multidisciplinary treatment and care. However, how children with birth defects—one of the factors most consistently associated with childhood cancer—fare after a brain tumor diagnosis is less clear. Evaluating brain tumor outcomes and survival in these malformations could help guide clinical practice and decision-making. As such, we aimed to assess survival after a brain tumor diagnosis in children with distinct groups of cancer-linked birth defects, to determine whether they might also influence the brain tumor prognosis.

Materials and Methods: This register-based nationwide cohort was conducted in Sweden, spanning the years 1970–2015. The National Cancer Register was used to identify the child population of Sweden with a brain tumor diagnosis (n=2,370). Diagnoses of CHD (n=32), Down syndrome (n<5), and neurocutaneous syndromes (n=72) in this population were retrieved from the National Medical Birth Register, Patient Register, and Cause of Death Register, while recorded deaths were retrieved from the Cause of Death Register. The effect of the syndromes under study on 5-year survival after a brain tumor diagnosis was evaluated using Cox proportional hazards regression models.

Results: We observed an increased 5-year mortality after a brain tumor diagnosis among children with CHD (HR 1.6, 95% CI 0.9–3.0), or Down syndrome (HR 5.1, 95% CI 1.2–21.3). Neurocutaneous syndromes overall, on the other hand, were associated with a markedly decreased 5-year mortality (HR 0.3, 95% CI 0.1–0.7), which also held true for neurofibromatosis type 1 (HR 0.2, 95% CI 0.1–0.9). Among children with a neurocutaneous syndrome, brain tumors were more commonly benign (79.2% versus 63.8% in children without a neurocutaneous syndrome) and predominantly belonged to low-grade astrocytomas (67.7% versus 34.4%) and, to a lesser extent, optic nerve gliomas (9.7% versus 1.3%). Finally, fewer relapses after a brain tumor diagnosis were reported in children with a neurocutaneous syndrome (18.5% versus 31.3%).

Conclusions: Even though CHD and Down syndrome are not customarily linked to childhood brain tumors, children with these syndromes fared worse after a brain tumor diagnosis compared to their syndrome-free counterparts. Children with neurocutaneous syndromes, however, experienced favorable five-year survival, likely due to the less aggressive brain tumor types observed in the context of these syndromes. While small numbers might have rendered some of these findings amenable to chance, understanding brain tumor outcomes in children with cancer-linked syndromes is important in the wake of improved survival for these syndromes and childhood brain tumors both.

Presence of antibodies to Varicella-Zoster virus and three other herpesviruses and survival in adults with glioma

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Background: Both self-reported and serological measures of Varicella-Zoster virus (VZV) have been consistently inversely associated with glioma risk, but the association with survival for glioma patients has not been investigated. There is growing evidence from clinical trials that some antiviral medications may offer potential avenues to improve glioma treatment. In this study we analyzed overall survival in relation to glioma patient antibody seropositivity to 4 common viral infections, including VZV, measured post-diagnosis.

Materials and Methods: We utilized immunoglobulin G (IgG) antibody seropositivity measurements to VZV, CMV, HSV, and EBV collected from 1377 patients with newly enrolled in the UCSF Adult Glioma Study (AGS) between 1991 and 2010, spanning 4 subject recruitment series. Blood was obtained a median of 3 months after the diagnostic surgery. Subject follow-up for survival is ongoing. The associations of glioma patient IgG levels with overall survival were estimated using Cox models adjusted for age, sex, self-reported ancestry, and current dexamethasone usage at time of blood draw. As the AGS is a decades-long study, results were also analyzed by recruitment series and then meta-analyzed to account for time-dependent treatment effects.

Results: These 1377 glioma patients had median survival of 2.1 years. VZV antibody seropositivity was associated with improved survival outcomes in glioma patients (Hazard ratio, HR=0.67, 95% Confidence Interval 0.52-0.86, p=0.002), with a grade-IV glioma specific association (HR=0.59, 0.44-0.80, p=0.0007). Antibody seropositivity to three other common viruses (CMV, EBV, HSV) were not associated with overall survival for glioma patients (p=0.826, p=0.382, p=0.469, respectively). In a meta-analysis across AGS series, VZV seropositivity remained significant (meta-HR=0.63, 0.45-0.89, p=0.007), while associations with seropositivity to the other viruses remained null. There was no evidence of between-series heterogeneity ($p<0.05$).

Conclusions: This is the first study, to our knowledge, to associate VZV seropositivity with survival among glioma patients. The association was exclusive to VZV, and not present for three other common viruses studied, potentially suggesting VZV-specific glioma immune interaction. Our results controlled for dexamethasone usage, a known immunosuppressor. IgG seropositivity measurements were taken post-glioma diagnosis, therefore further study is needed to determine the direction of causation, and if anti-VZV treatment, such as VZV vaccination, might be beneficial in glioma prognosis.

Breastfeeding and Risk of Childhood Brain Tumors: An International Pooled Analysis

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Background: Childhood brain tumors (CBT) have overtaken leukemia as the leading cause of cancer mortality in young people. There is evidence that allergic conditions and infectious exposures are associated with CBT, but studies have reported mixed findings regarding breastfeeding, which influences the developing immune system and may protect against childhood leukemia. Our objective was to determine whether breastfeeding is associated with reduced risk of CBT.

Materials and Methods: We pooled data from ten studies in the Childhood Cancer & Leukemia International Consortium. Nine used case-control designs whereas one used a registry linkage design. Studies were performed in Canada, France, Germany, Greece, New Zealand, the United Kingdom, and the United States of America between 1974 and 2019. We evaluated associations between ever breastfeeding and breastfeeding ≥6 months with CBT collectively, and astrocytoma, medulloblastoma/primitive neuroectodermal tumor (PNET), and ependymoma specifically. We computed unconditional logistic regression models in the pooled dataset, adjusting for study, sex, mode of delivery, birthweight, age at diagnosis, and maternal age, education, and race/ethnicity, and confirmed our results by random effects meta-analysis.

Results: The present study included 2,701 cases with CBT (N=1,279 cases of astrocytoma, N=709 cases of medulloblastoma/PNET, and N=265 cases of ependymoma) and 8,268 controls. Breastfeeding prevalence was 59.4% among controls and 58.8% among cases. Neither ever breastfeeding nor breastfeeding ≥6 months were associated with CBT or the evaluated subtypes in pooled or meta-analyses.

Conclusions: In this large international pooled analysis, we found no evidence that breastfeeding was associated with reduced risk of CBT collectively or with astrocytoma, medulloblastoma/PNET, or ependymoma specifically. Although breastfeeding should be encouraged as the optimal means of providing nutrition to neonates, additional research will be necessary to identify modifiable risk factors for CBT and facilitate prevention efforts.

Trends in Primary Brain Tumors by Malignant and Non-Malignant Status from National Program of Cancer Registries, 2004-2017

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Background: Despite advances in cancer diagnosis and clinical care, survival rates for many primary brain and other central nervous system (CNS) histologies remain poor. This study performs a comprehensive update to date survival analysis on primary brain and CNS tumors.

Materials and Methods: Survival differences by time-period of diagnosis were determined using the National Program of Cancer Registries Survival Analytic file for primary brain and CNS tumors overall, and by the 5 most common histologies within age groups (for diagnosis years 2004-2017. Survival was compared for time periods: 2004-2007, 2008-2012 and 2013-2017. Kaplan-Meier and age-stratified multivariable Cox proportional hazards models were constructed to evaluate survival differences. Models were adjusted for sex, race/ethnicity, extent of surgery and radiation. Malignant and non-malignant tumors were assessed separately

Results: Aside from Hemangioma in ages 40+ years, no notable changes in survival were observed across time periods for non-malignant tumors. Significant survival improvements were observed for younger patients (0-14 years) with embryonal tumors and ependymal tumors. Significant improvements in survival were also observed in ages 15-39 years for anaplastic astrocytoma and for patients >40 years diagnosed with an anaplastic astrocytoma or glioblastoma. Patients >40 years diagnosed in 2013-2017 with a primary malignant CNS tumor had a significant survival improvement compared to those diagnosed in 2004-2007. When compared to 2004-2007, there were improvements in survival in 2008-2012 and 2013-2017 in all age groups.

Conclusions: Overall survival for malignant brain and other CNS tumors in 2013-2017 improved slightly compared to earlier years for all age groups. Survival trends are essential to identify population-level effects of diagnostic and treatment improvements.

Survival Experience and Prevalence of Central Nervous System (CNS) Tumour by Sex in Canada -- a report from The Brain Tumour Registry of Canada Surveillance Research Collaboration Group

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Background: Established in 2016, the Brain Tumour Registry of Canada Surveillance Research Collaboration aims to address the gap in knowledge on CNS tumours within the Canadian setting. Using recent death-linked Canadian Cancer Registry (CCR) data, we present detailed survival and prevalence information for all primary CNS tumours (excluding Quebec).

Material and methods: Patients diagnosed with primary CNS tumours during 2010-2017 were included. Vital status was obtained through linkage by Statistics Canada to the Canadian Vital Statistics Death Database and the T1 personal income tax returns file with a cut-off date of December 31, 2017. For prevalence, January 1, 2018 was used as the index date with the last CNS tumour diagnosis of a patient contributing towards prevalence estimates. For net survival, the Pohar-Perme method of estimation through the period approach was used including the first CNS tumour diagnosis in a patient under 100 years of age. International Classification of Diseases for Oncology (3rd edition) site/histology codes were grouped into 25 histological categories, irrespective of tumour behaviour, according to the schema developed by the United States Central Brain Tumour Registry.

Results: Overall, 37575 persons were living with a CNS tumour in Canada on Jan 1, 2018 with 7360 having malignant diagnoses (4170 males and 3190 females) and 30215 having a nonmaligant diagnoses (12185 males and 18385 females). Female prevalent counts outnumbered males in malignant meningioma (70 vs. 55) and four non-malignant histology types including meningioma (8610 vs. 3635), tumours of cranial and spinal nerves (2030 vs. 1960), mesenchymal tumours (80 vs. 70) and the "unclassified tumours or not classified by CBTRUS" group (3615 vs. 2480). No sex difference in rare histology types is observed when the histology specific prevalence counts were lower than 100.
The survival experience of CNS tumours are in general similar between sexes when stratified by behaviour for most histology groups. The median survival for males and females respectively are 8.3 and 7.8 months for glioblastoma, 14.2 and 11.4 months for malignant glioma NOS, and more than 8 years for all but one non-malignant histology group. Females have better 5-year net survival rates than males among patients with malignant meningioma (0.60, 95%CI 0.49-0.69 vs. 0.44, 95%CI 0.32-0.55), non-malignant meningioma (0.87, 95%CI 0.86-0.88 vs. 0.81 95%CI 0.79-0.84), non-malignant ependymal tumours (0.97, 95%CI0.85-0.99 vs. 0.89 95%CI 0.79-0.95), and non-malignant unclassified tumours (0.66, 95%CI 0.63-0.69 vs. 0.59, 95%CI 0.55-0.62). In contrast, males have better 5-year net survival rates than females among patients with pilocytic astrocytoma (0.92, 95%CI 0.83-0.96 vs. 0.85, 95%CI 0.72-0.92), non-malignant neuronal and mixed neuronal-glial tumours (0.92, 95%CI 0.85-0.96 vs. 0.85, 95%CI 0.76-0.91).

Conclusion: We report the most comprehensive and up-to-date data on primary CNS tumour survival experience among Canadians. An estimated 37575 individuals are living with a CNS tumour diagnosed within last 8 years complementing previous estimates that an average of 5941 new cases are diagnosed each year. The overall 5-year net survival rate varies widely by tumour subtype.

Facility volume and survival among individuals diagnosed with malignant central nervous system tumors

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Background: Prior research has indicated that the volume of central nervous system (CNS) tumor patients seen by a facility is associated with patient outcomes. However, most prior studies have only examined short-term survival. In the current study, we examined whether facility CNS tumor patient volume is associated with survival overall and by CNS tumor subtype.

Materials and Methods: We obtained data from the National Cancer Database (NCDB) including all individuals diagnosed with CNS tumors from 2004 to 2016. All analyses were stratified by age group (0-14, 15-39, 40-64, and ≥65). We used Kaplan-Meier curves, Cox Proportional Hazards (PH) regression, and restricted mean survival time (RMST) analyses to examine associations between survival and facility volume quartile (Q) by age group. Models were adjusted for age, race/ethnicity, zip-code level income and education, insurance, sex, and CNS tumor subtype. We used robust standard errors to account for the clustering of patients within facilities.

Results: A total of 130,830 malignant first primary CNS tumor cases (0 to 14: n=9719, 15 to 39: n=20,324, 40 to 64: n=55,306, ≥65: n=45,481) were included in analyses. There was a consistently reduced hazard rate of death for individuals reported by Q4 vs. Q1 facilities in each age group ($HR_{0\text{-}14}$=0.82 95% CI 0.68-0.98, $HR_{15\text{-}39}$=0.88 95% CI 0.79-0.98, $HR_{40\text{-}64}$=0.82 95% CI 0.76-0.88, $HR_{\geq 65}$=0.79, 95% CI 0.74-0.86). Similarly, there was a consistently longer survival times within 5 years for Q4 vs. Q1 facilities ($RMST_{0\text{-}14}$=1.87 months, 95% confidence interval (CI) 0.75-2.99; $RMST_{15\text{-}39}$=1.05, 95% CI 0.29-1.81; $RMST_{40\text{-}64}$=3.17, 95% CI 2.72-3.62; $HR_{\geq 65}$=2.97, 95% CI 2.56-3.38). Associations were modified by cancer type (likelihood ratio test $p<0.01$) for all age groups with significant inverse associations between the hazard rate of death and facility CNS tumor patient volume for other glioma (all age groups), glioblastoma and anaplastic astrocytoma (40-64 and ≥65), and astrocytoma not otherwise specified (40-64 and ≥65).

Conclusions: These results suggest facility-level factors influence CNS tumor survival with longer patient survival for those reported by higher volume facilities. Identifying these factors will be critical to designing strategies that eliminate disparities in CNS tumor survival by facility volume.

Midline versus Hemispheric Pediatric High-Grade Gliomas; first-line treatment and survival characteristics in the Netherlands during the period 2003-2017 - a population-based study

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Background: Pediatric high-grade gliomas (pHGG) are among the most devastating childhood cancers. Due to their limited treatment options and tumor biology, pHGG located in the midline are considered to have worse survival outcomes compared to hemispheric pHGG. In this study we investigated differences in, and factors associated with, survival for midline and hemispheric pHGG.

Materials and Methods: Detailed population-based clinical data were gathered by trained registrars for all children (<18 years) diagnosed with a pHGG (including radiologically diagnosed brainstem tumors) in the Netherlands for the period 2003-2017. Tumors were grouped into midline and hemispheric tumors based on the clinical data and pathology reports. Differences in clinical characteristics were tested by Chi-squared, Fisher exact or Mann-Whitney-Wilcoxon test. Median survival time was determined by Kaplan-Meier method. Survival differences and associations were tested with Cox Proportional-Hazards Models.

Results: In total, 272 pHGG patients (midline n=217, 80%, hemispheric n=55, 20%) were diagnosed during 2003-2017. Midline and hemispheric pHGG differed significantly in sex (midline: females 53% versus hemispheric: females 35%, p=0.02) and age (midline: median 7 years versus hemispheric: median 11 years, p<0.001). Significant differences were found for first-line neurosurgical intervention (41% of midline versus 98% of hemispheric pHGG patients, p<0.001) and systemic therapy (32% of midline versus 71% of hemispheric pHGG patients p<0.001). Notably, 20% of midline patients received temozolomide compared to 62% of hemispheric pHGG patients (p<0.001). No significant difference was found for first-line radiotherapy. However, total cumulative dose and number of fractions differed significantly between midline (median 45 Gy and 17 fractions) and hemispheric pHGG (median 59.4 Gy and 30 fractions, both p<0.001), reflecting hypofractionation regimens in midline pHGG in the Netherlands. Median survival for midline pHGG (9 months) differed significantly from hemispheric pHGG (14 months, p=0.01).
When interrogating midline pHGG, median survival for females (8.8 months) was worse compared to males (9.7 months, p=0.045). Females had significant longer symptom duration (42 days) before their first contact with an oncologist compared to males (37 days, p<0.001). In addition, first-line dexamethasone use was higher in females (70%) than in males (55%, p=0.035). The risk of dying was significantly higher among females compared to males (HR1.33 (95%CI 1.01-1.77)). This significance disappeared after adjustment for symptom duration, neurosurgery, radiotherapy, systemic therapy and dexamethasone, and only dexamethasone remained significantly associated (HR 1.68 (95%CI 1.2-2.35)) with poorer survival, while radiotherapy showed a borderline significance for better survival (HR 0.68 (95%CI 0.46-1)).

Conclusions: Midline pHGG had significantly lower survival outcome compared to hemispheric pHGG. Female midline pHGG patients had even a poorer survival outcome than their male counterparts. It is unclear why survival for both midline and hemispheric pHGG in this retrospective population-based study is substantially inferior to international published data. Underlying reasons may be found in differences in treatment characteristics, data type (hospital/trial-based versus population-based data) or incompleteness of non-microscopically verified cases. Gender survival differences for midline pHGG disappeared when adjusting for first-line treatment, and only dexamethasone remained significantly associated with survival. If the use of dexamethasone is related to a more severe disease presentation at diagnosis is subject to further research.

Pooled Analysis of Meningioma Risk Following Treatment for Childhood Cancer

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Background: Childhood cancer survivors who received cranial radiotherapy are at high risk of developing subsequent meningiomas; however, the magnitude of the radiation-related risk, possible effects of chemotherapy, and modifiers of the dose-response relationships are not well characterized.

Materials and Methods: We conducted a pooled analysis of four matched case-control studies from Europe and North America with estimates of radiation dose in gray (Gy) to the subsequent tumor location in cases and comparable locations in controls. The pooled odds ratios (ORs), excess odds ratios (EORs) and associated 95% confidence intervals (CIs) were estimated using multivariable conditional logistic regression.

Results: The pooled data included 273 meningioma cases and 738 controls after a median follow-up of 22 years. Odds of meningioma increased with increasing radiation dose (EOR/Gy=1.44, 95% Confidence Interval [CI]:0.62-3.61) and there was no evidence of departure from linearity (p>0.50). Participants who received exposures of 24 Gy or more had more than 30-fold higher odds of meningioma compared to unexposed childhood cancer survivors (OR=33.7, 95%CI: 14.1-80.3). The radiation dose-response association showed lower risk among patients treated after age 10 years than before age 10 (EOR/Gy=0.57, 95%CI: 0.18-1.91 vs 2.20, 95%CI: 0.87-6.31, p=0.03), but there was no clear trend in the radiation dose-response by age at treatment among patients under age 10 (p-trend=0.41). A non-significantly lower EOR/Gy was observed for survivors of CNS tumors and leukemia than among survivors of other first cancers (p=0.15) and results remained unchanged with age at exposure also included in the model as effect modifier (p=0.23). There was no evidence for a difference in the EOR/Gy with sex (p=0.34), calendar year of follow-up (p-trend=0.46), attained age (p-trend=0.50). There was a non-significant increase in the EOR/Gy with time since exposure (p=0.11) and radiation-related risk remained significantly elevated 30 years after exposure (EOR/Gy=3.76, 95%CI: 0.77-29.15). After controlling for radiation dose and type of first cancer (CNS, leukemia and other), we found an increased risk of meningioma after any methotrexate (OR=3.43, 95% CI:1.56-7.57), but no evidence of a dose-response relationship or interaction with radiation dose (p>0.11).

Conclusions: This pooled study shows that the meninges are highly sensitive to radiation, with notably higher risks for children irradiated before age 10. Radiation-related risks remain elevated for decades following exposures underscoring the need for long-term follow-up of childhood cancer survivors who received cranial irradiation.

Novel specific susceptibility loci identified for pediatric and adult ependymoma in first histology-specific genome-wide association study

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Background: Despite extensive research, a small proportion of the variants contributing to the genetic architecture of brain tumors have been reported. The published genome-wide association studies (GWAS) have been largely performed on pooled histological subtypes of glioma and most of these studies have been conducted primarily for adult tumors. Therefore, we aimed to perform the first GWAS specifically for ependymoma to identify the genetic variants associated with the risk of these tumors and to investigate the similarities/differences between the genetic architectures of adult and pediatric ependymomas.

Materials and Methods: Germline SNP-array data of ependymoma cases were obtained from eight studies or biobanks across the United States and Europe. Controls were randomly selected with the ratio of 10:1 from two of those studies and a separate publicly available database. Additionally, germline whole genome sequencing data on cases and controls from St Jude Cloud were utilized. In total, 397 pediatric cases and 228 adult cases and 4321 controls were included. The same quality control procedures were applied to all studies. Data were imputed based on the Haplotype Reference Consortium (r1.1) using EAGLE (v2.4). The association between genetic variants and ependymoma risk was investigated using logistic regression as well as GMMAT, which is a mixed model and uses random effects to account for population structure and relatedness. The results were adjusted for sex, ancestry, and principal components. Meta-analyses were performed based on GMMAT and logistic regression. PAINTOR was used to identify the plausible causal variants, and eQTL and gene enrichment analyses were performed.

Results: We identified eight independent significant SNPs which were specifically associated with pediatric ependymoma risk, of which six SNPs were plausible causal. The significant variants were located on 6p21.32 (*HLA-DQA*), 6p21.33 (*BX927178/CR759828*), 7p21.3 (*UMAD1*), 11p12 (*LRRC4C*), 11q24.2 (*KRT18P59*), and 21q11.2 (*LOC112268283/FEM1AP1*). The 17 identified independent significant SNPs associated with risk of adult ependymoma were located on 2q33.1 (*ALS2CR12*), 4p16.1 (*SORCS2*), 6p11.2, 6p21.33 (*XXbac-BPG248L24.13*), 7q31.32, 8p23.1 (*LOC157273*), 8q24.3 (*PLEC*), 10p13 (*PTER*), 11q23.3 (*GRIK4*), 19q13.11 (*CEP89*), and 22q11.1 (*XKR3*), of which ten variants were plausible causal. One intronic variant associated with susceptibility of both pediatric and adult ependymomas was detected; rs68160486 (*CCDC85A*, 2p16.1 $P_{\text{Pediatric}}=3.41\text{x}10^{-8}$, $P_{\text{Adult}}=1.75\text{x}10^{-9}$).

Conclusions: The genetic architectures of adult and pediatric ependymomas appear to largely differ from one another. We identified novel variants for these tumors that have not been previously reported for GWAS of combined glioma subtypes. This analysis highlights the need to conduct additional GWAS of more refined glioma subtypes, perhaps even utilizing newer data on molecularly defined subtypes that are emerging in updated pathological classification schemes.

Functional consequence of low grade glioma risk SNP in modified HEK293T cells.

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Background:

Genome-wide association studies (GWAS) have contributed to our understanding of glioma susceptibility. To date, 25 risk loci for development of any of the glioma subtypes are known. However, GWAS studies reveal little about the molecular processes that lead to increased risk, this is especially the case for non-coding single nucleotide polymorphisms (SNP). A particular SNP, *rs11706832*, residing in the second intron of *LRIG1*, has been shown to increase the susceptibility for *IDH1* mutated low grade gliomas (LGG). Leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) has been shown to be important in cancer development, acting as a negative regulator of epidermal growth factor receptor (EGFR), however the mechanism of this particular risk SNP, and its potential effect on *LRIG1*, is not known.

Materials and Methods:

Using CRISPR-CAS9, *rs11706832* was edited in HEK293T cells. Four HEK293T clones with the risk allele were compared to four clones with the non-risk allele, with regards to gene expression of *LRIG1* using RT-qPCR, global gene expression with RNA-seq, and the abundance of a small set of metabolites using gas chromatography-mass spectrometry (GC-MS).

Results:

The experiment did not reveal any effect of the SNP on the expression levels of *LRIG1*. The neighboring gene SLC25A26 show a low, non-significant, over expression for the risk allele. Global gene expression analysis revealed an upregulation of several mitochondrial genes, and by applying a gene enrichment analysis of 74 differentially expressed genes, a significant enrichment of type I interferon response genes was seen, where many genes in this program was downregulated in cells carrying the risk allele C. Using gene count data of IDH1 mutated LGGs from the cancer genome atlas (TCGA), a similar under expression of type I interferon genes was associated with the risk allele

Conclusions:

The SNP does not show to affect expression or alternative splicing in *LRIG1*, but a weak non-significant overexpression for *SLC25A26*. Cell lines with risk SNP show an under expression of type I interferon response program, which is also seen in TCGA.

Long-term medical and functional outcomes of ependymoma survivors: a population-based, matched cohort study

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Background:
Ependymoma is the third most common pediatric central nervous system tumour. Treatment approaches are intensive and may include surgery, radiation, and chemotherapy. There are no longitudinal population-based cohort studies evaluating the long-term medical and functional outcomes of survivors of childhood ependymoma.
Materials and Methods:
Using a provincial pediatric cancer registry, all five-year ependymoma survivors diagnosed between 1987-2015 in Ontario, Canada were identified and matched to cancer-free population controls based on age, sex, and geographical location. Cases were followed from the index date (5 years from latest of diagnosis, or relapse/subsequent malignancy prior to age 18 years) until December 31, 2020 or censorship (death, or relapse/ new cancer after age 18 years). Clinical data were linked to administrative health databases to estimate the cumulative incidences and cause-specific hazard ratios (HR) of mortality, hospitalizations, strokes, hearing loss requiring a hearing aid, receipt of homecare services, and subsequent malignant neoplasms (SMNs) between cohorts, accounting for matching and competing risks.
Results:
Of 166 ependymoma diagnoses in the study period, 70 (42.2%) were excluded, most commonly due to early death prior to the index date. Ninety-six cases [61.5% female; median diagnostic age: 7 years, interquartile range (IQR) 2-11; median attained age: 22 years, IQR 15-30] were matched to 480 controls. Twenty-five cases (26.1%) received craniospinal irradiation. The 10-year survival probability after the index date was 92.8% in cases and 99.6% in controls (HR 9.3, 95% CI 2.3-45.2, p=0.002). Compared to controls, cases were at higher risk of hospitalization (HR 3.2, 95% CI 2.2-4.6, p<0.0001), stroke (HR 33.3, 95% CI 5.7-629.1, p<0.0001), and receiving homecare services (HR 4.1, 95% CI 2.5-6.5, p<0.0001). Cases were at high risk of hospitalizations, strokes, hearing loss, and SMNs, with cumulative incidences of 64.7% (95% CI 46.6-78.0), 9.7% (95% CI 3.4-19.9), 13.5% (95% CI 5.3-25.5), and 12.8% (95% CI 4.7-24.9) at 20-years post index date, respectively.
Conclusions:
As survival of pediatric ependymoma improves, establishing the burden of late morbidity is critical. Dedicated screening programs for late sensory and neurovascular sequelae are warranted, as are interventions during and following treatment to mitigate the risk of developing such complications.

Localized variation in ancestral admixture identifies pilocytic astrocytoma risk loci among Latino children

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Background:

Pilocytic astrocytoma (PA) is the most common pediatric brain tumor. PA has at least a 50% higher incidence in populations of European ancestry compared to other ancestral groups, which may be due in part to genetic differences.

Materials and Methods:

We first compared the global proportions of European, African, and Amerindian ancestries in 301 PA cases and 1185 controls of self-identified Latino ethnicity from the California Biobank. We then conducted admixture mapping analysis to assess PA risk with local ancestry.

Results:

We found PA cases had a significantly higher proportion of global European ancestry than controls (case median = 0.55, control median = 0.51, P value = $3.5x10^{-3}$). Admixture mapping identified 13 SNPs in the 6q14.3 region (*SNX14)* contributing to risk, as well as three other peaks approaching significance on chromosomes 7, 10 and 13. Downstream fine mapping in these regions revealed several SNPs potentially contributing to childhood PA risk.

Conclusions:
There is a significant difference in genomic ancestry associated with Latino PA risk and several genomic loci potentially mediating this risk.