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Maternal prenatal use of alcohol, tobacco, and illicit drugs and associations with childhood cancer subtypes

Courtney E. Wimberly[1,2], **Natalie B. Gulrajani**[3], **Jeffrey B. Russ**[4], **Daniel Landi**[2,4], **Joseph L. Wiemels**[5], **Lisa Towry**[6], **John K. Wiencke**[7], **Kyle M. Walsh**[1,2,3,4,8]

[1]Department of Neurosurgery, Duke University School of Medicine, Durham, NC, USA

[2]Preston Robert Tisch Brain Tumor Center, Duke University School of Medicine, Durham, NC, USA

[3]Children's Health and Discovery Institute, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

[4]Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

[5]Center for Genetic Epidemiology, Norris Comprehensive Cancer Center, and Department of Population and Public Health Sciences, University of Southern California, Los Angeles, CA, USA

[6]Alex's Lemonade Stand Foundation, Bala Cynwyd, PA, USA

[7]Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

[8]Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA

Abstract

Background: The association between childhood cancer risk and maternal prenatal substance use/abuse remains uncertain due to modest sample sizes and heterogeneous study designs.

Methods: We surveyed parents of children with cancer regarding maternal gestational use of tobacco, alcohol, and illicit drugs, using a Likert-type scale, and demographic, perinatal, and clinical variables. Multivariable log-Poisson regression assessed differences in frequency of prenatal substance use across fifteen childhood cancer subtypes, adjusting for birthweight, gestational age, and demographic factors.

Results: Respondents from 3145 unique families completed the survey (92% biological mothers). A minority reported gestational use of tobacco products (14%), illicit drugs including marijuana or cocaine (4%), or more than a moderate amount of alcohol (2%). Prenatal illicit drug use was associated with increased prevalence of intracranial embryonal tumors (prevalence ratio

Corresponding Author: Kyle M. Walsh, Kyle.Walsh@Duke.edu, Phone: 919-684-8732, Fax: 919-684-8787, DUMC Box 3050, Durham, NC 27710.

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[PR]=1.94, CI=1.05-3.58), including medulloblastoma (PR=1.82) and supratentorial primitive neuroectodermal tumors (PNETs; PR=2.66), and was also associated with retinoblastoma (PR=3.11; CI=1.20-8.08). Moderate to heavy alcohol consumption was strongly associated with elevated prevalence of non-Hodgkin lymphoma (PR=5.94; CI=1.84-19.21). Prenatal smoking was not associated with elevated prevalence of any childhood cancer subtype.

Conclusions: We identify novel associations between illicit drug use during pregnancy and increased prevalence of non-glioma central nervous system tumors, including medulloblastoma, supratentorial PNETs, and retinoblastoma. Gestational exposure to alcohol was positively associated with non-Hodgkin lymphoma.

Impact: While alcohol and tobacco use during pregnancy has declined, gestational cannabis use has risen. Investigating its impact on neurodevelopment and brain tumorigenesis is vital, with important implications for childhood cancer research and public health education.

Keywords

Cancer risk factors; epidemiology; substance use; prenatal exposure; neurodevelopment

INTRODUCTION

Childhood cancer represents a significant public health concern with rising incidence and marked disparities observed among various cancer subtypes and demographic groups. Recent strides in therapeutic approaches have contributed to improved survival rates,(1) yet the factors driving the increase in childhood cancer incidence, especially for certain subtypes, remain elusive. (2,3) Additionally, the varying rates of change in childhood cancer incidence across different racial and ethnic backgrounds suggest complex interactions between genetics, environment, and socioeconomic factors.(4)

While many genetic factors have been shown to augment childhood cancer risk in large genome-wide association studies (GWAS)(5,6), few modifiable risk factors have been established to-date. Such factors include fetal exposure to ionizing radiation(7), very high birthweight(8), in utero diethylstilbestrol exposure(9), congenital cytomegalovirus (CMV) infection(10,11), parental age(12,13), and maternal use of assisted reproductive technologies.(14,15) Notably, these risk factors all represent *in utero* exposures. It therefore seems likely that fetal development represents a critical window during which subtle environmental perturbations can alter cellular differentiation and development and exert substantial impacts on tumorigenesis.

Maternal substance use during pregnancy is a modifiable exposure which impacts fetal development and represents a potential childhood cancer risk factor. Although previous research has explored associations between maternal prenatal substance use and childhood cancer risk, most literature to date has focused on gestational exposure to tobacco and alcohol, with illicit drug use receiving less attention. There has been a longstanding recognition that *in utero* exposure to tobacco, alcohol, and illicit substances can impact fetal development, particularly neurodevelopment. For example, fetal alcohol exposure has been linked to a spectrum of brain disorders, ranging from gross structural changes to

more subtle developmental delays.(16) At a cellular level, it has been demonstrated that neurogenesis itself, particularly the generation and migration of inhibitory interneurons, can be disrupted by exposure to tobacco, alcohol, and illicit substances,(17) while rodent models of prenatal exposure to synthetic cannabinoids suggest that they can potently disrupt brain development and corticogenesis.(18) Although it remains to be elucidated exactly how teratogenic substances affect neurodevelopment at the level of specific neuronal subpopulations and developmental regulatory programs, it is becoming clear that progenitor cell populations are sensitive to perturbation by in utero exposure to maternal substance use.

Given its unclear contribution to the development of specific childhood cancer subtypes, and the potential for recall and self-report biases to impact results of retrospective studies, further investigation of maternal prenatal substance use – particularly illicit drug use – and its association with childhood cancer is warranted. Identifying additional, modifiable exposures that can reduce childhood cancer incidence is crucial to primary prevention and public health.

To examine the association of maternal substance use with subtype-specific childhood cancer risk, we performed a cross-sectional analysis of childhood cancer families from the Alex's Lemonade Stand Foundation's (ALSF) My Childhood Cancer: Survey Series cohort. Parents representing >3000 childhood cancer patients provided data on maternal prenatal tobacco, alcohol and illicit drug use, birthweight, and other demographic and gestational factors. Our study design attempts to minimize biases due to differential exposure misclassification (*e.g.*, recall bias) by examining whether prenatal maternal substance use is associated with specific childhood cancer subtypes, controlling for contributions from other perinatal factors, within a sample of families that were all impacted by a childhood cancer diagnosis.

MATERIALS AND METHODS

Study Population

We partnered with ALSF to conduct a series of open, internet-based longitudinal surveys of families affected by childhood cancer. From 2011 to 2022, the ALSF My Childhood Cancer (MCC): Survey Series explored families' experiences and attitudes from diagnosis, throughout treatment and follow-up care, and after bereavement (when applicable).(19) The English-language survey was publicly hosted on the Alex's Lemonade Stand Foundation webpage and advertised through Facebook, Twitter, and ALSF's childhood cancer-specific listserv. Parents were eligible to complete the survey if they had a child (living or deceased) who was diagnosed with cancer prior to the child's eighteenth birthday.

Parents navigated to the MCC survey and completed a registration form with contact and basic demographic information, then were contacted by email to complete future surveys – including the diagnosis survey. Parents could complete the surveys in one sitting or return to them at a later time, within 30 days of survey initiation. A total of 3145 families participated in the MCC survey series. In this cross-sectional study, we examined responses to the ALSF MCC diagnosis survey completed between January 2012 and April 2019, limiting to one parental respondent per family. When more than one parent from the same

family completed the survey, we included the biological mother's report (when available) in analyses. Otherwise, we included the first survey to have been completed.

Survey Instruments

Childhood cancer type and patient/parental demographics were collected at MCC: Survey Series registration. In the diagnosis survey (Supplementary Materials and Methods), participants were asked "How often did [child]'s biological mother do any of the following during pregnancy with [child]?" Responses were recorded on a 1-7 Likert-type scale, where 1 corresponded to "not at all" and 7 corresponded to "often." Respondents were asked about a variety of prenatal activities, including: "*smoked tobacco products*", "*used illegal drugs (i.e., marijuana, cocaine, etc.)*", and "*drank alcoholic beverages*". Responses to each substance type were collapsed into binary indicators (1/0) for analysis. For prenatal tobacco and illicit drug use, responses ≥2 were considered positive indicators of using either substance (coded as 1/yes). For prenatal alcohol, responses ≥5 were considered heavy use during pregnancy (coded as 1/yes). Those who responded "not sure" were excluded. Respondent race was collected as "American Indian/Alaska Native," "Asian," "Black/African American," "white/Caucasian," and "Other." Respondent ethnicity was collected as "Hispanic or Latino (of any race)" and "not Hispanic or Latino." For analysis, respondent race/ethnicity was collapsed into a binary indicator (0/1) for "non-Hispanic white" vs. "other." Respondents (94% U.S.-based) recorded child's birthweight in categories to the nearest pound, which were collapsed into a three-level ordinal variable with categories "low birthweight" (3 pounds or less, 4-5 pounds), "normal birthweight" (6-9 pounds), and "high birthweight" (10-11 pounds, 12 pounds or more). Respondents reported the child's birth order as "oldest child," "youngest child," "neither youngest nor oldest child," or "only child." Household income was recorded in the following bins: <$20,000; $20,000-$49,999; $50,000-$74,999; $75,000-$99,999; $100,000-$149,999; ≥$150,000. For analysis, household income was collapsed into a three-level ordinal variable with levels "<$50,000," "$50,000-$99,999," and "≥$100,000." Child's birth year was collapsed into the following bins and modeled as an ordinal variable: "Before 1990," "1990-1994," "1995-1999," 2000-2004, "2005-2009," "2010 and later."

Dependent variables were each of 15 specific childhood cancer subtype compared to all other subtypes collapsed, including: Hodgkin lymphoma, non-Hodgkin lymphoma, germ cell tumor, Kidney/Wilms' tumor, hepatoblastoma/liver cancer, neuroblastoma, retinoblastoma, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), ependymoma, astrocytoma (including: astrocytoma/anaplastic astrocytoma, juvenile pilocytic astrocytoma, diffuse intrinsic pontine glioma (DIPG), glioblastoma), and embryonal tumors of the CNS (including: atypical teratoid/rhabdoid tumor (AT/RT), supratentorial primitive neuroectodermal tumors (PNETs), medulloblastoma, and pineoblastoma). We also included an "all sarcoma" group, which combined the subcategories of rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma, and included other soft tissue sarcomas (*i.e.*, alveolar soft part sarcoma, angiosarcoma, clear cell sarcoma of the kidney, dermatofibrosarcoma protuberans, desmoplastic (small) round cell tumor, epithelioid sarcoma, infantile fibrosarcoma, intimal sarcoma, peripheral nerve sheath tumor, mesenchymal chondrosarcoma, spindle cell sarcoma, synovial sarcoma,

undifferentiated sarcomas, and unspecified paraspinal sarcoma). A small proportion of children (1.1%) had diagnoses that did not fit into any of these categories and were classified as “other” cancers (thyroid, Langerhans cell histiocytosis, pleuropulmonary blastoma, adrenocortical carcinoma, ectomesenchymoma).

Statistical Analyses

Independent variables of interest in this analysis included maternal prenatal tobacco, illicit drug, and alcohol use. Univariate associations between independent and dependent variables were assessed using Fisher’s exact tests. Respondent household income at diagnosis, whether the respondent was the child’s biological mother, child’s birth order, child’s birth year, and respondent non-Hispanic white race/ethnicity were included in multivariable models as potential confounders. Birth year was included because the prevalence of gestational smoking and drinking has trended down over the last three decades, while the prevalence of illicit drug use, particularly cannabis, has increased. Because our study is cross-sectional in nature, we adjusted for birth year to control for potential period effects. Child’s gestational age and birthweight were also included in multivariable models. Although these may not be confounders and could instead act as mediators on a potential pathway connecting maternal substance use to childhood cancer risk, we aimed to detect the direct effect of maternal substance use on childhood cancer and our modeling reflects that analytic choice. For multivariable analyses, log-Poisson models with robust variance were used to assess the direct effects in association analyses of prenatal tobacco, illicit drug, and alcohol use of childhood cancer, adjusting for potential confounders and gestational age and birthweight. Regression coefficients were exponentiated to prevalence ratios (PR) for reporting. Missing data rates for modeled covariates were low (5% or less for all covariates). If data were missing for a modeled covariate, that individual was excluded from the model. For all statistical tests, alpha <0.05 was used to determine statistical significance. Stata version 18.0 (StataCorp, College Station, TX) was used for data analysis.

Data Availability

De-identified, individual-level data are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Duke University Institutional Review Board (Pro00100771) and did not require informed consent.

RESULTS

Between January 2012 and April 2019, parents from 3145 unique families (69% of 4536 registered families) completed the diagnosis survey. Median time from diagnosis to survey completion was 3 years (IQR=1-7 years) and did not differ across cancer subtypes. Respondents were largely the biologic mother (92%) and identified as non-Hispanic white. The greatest proportion (41%) of respondents had an annual household income of $50,000-$99,999 prior to their child’s cancer diagnosis. The majority of children were male, weighed 6-9 pounds at birth and were born at term. 412 respondents (13%) reported maternal tobacco

smoking during pregnancy, 13 (<1%) reported heavy alcohol use, and 78 (3%) reported illicit drug use during pregnancy (Table 1). A comparison of demographic characteristics between respondents who reported any prenatal substance use vs. those reporting no substance use appears in Supplementary Table S1.

Univariate relationships between cancer subtype and maternal use of tobacco, alcohol, and illicit drugs were tested (Supplementary Table S2), comparing each specific cancer subtype to all other subtypes grouped together. Ever smoking tobacco during pregnancy was inversely associated with rhabdomyosarcoma (P=0.007) and neuroblastoma (P=0.038), and positively associated with NHL (P=0.037). Ever using illicit drugs during pregnancy was positively associated with childhood CNS embryonal tumors (P=0.008), retinoblastoma (P=0.043), and inversely associated with ALL (P=0.016). Moderate to heavy prenatal alcohol use showed a strong positive association with NHL (P=0.001). We also explored the combined effect of tobacco and moderate-to-heavy alcohol use (vs. no use). While many effect estimates were unable to be calculated due to zero cell counts, we observed a very strong association between NHL with smoking and drinking combined (P=<0.001) (Supplementary Table S2).

We separately assessed associations for childhood cancer subtype with prenatal tobacco, illicit drug, and alcohol use using multivariable models (Figure 1). Ever smoking tobacco during pregnancy was associated with decreased prevalence of rhabdomyosarcoma (PR=0.48; CI=0.24-0.93; P=0.030) and “all sarcomas” (PR=0.60; CI=0.43-0.85; $P=3.5x10^{-3}$) (Table 2). For neuroblastoma, the magnitude of effect from univariate analyses was attenuated and did not reach statistical significance (PR=0.77; CI=0.56-1.04; P=0.09). The association between tobacco use during pregnancy and NHL from univariate analyses was also attenuated and did not reach statistical significance (PR=1.50; CI=0.91-2.46; P=0.11).

In multivariable models, the positive association between illicit drug use during pregnancy and retinoblastoma in offspring persisted, reaching statistical significance (PR=3.11; CI=1.20-8.08; P=0.02). The association between illicit drug use during pregnancy and CNS embryonal tumors in offspring was comparable to results from univariate analysis and remained statistically significant (PR=1.94; CI=1.05-3.58; P=0.04) (Table 2). We attempted to further investigate potential heterogeneity in the association between illicit drug use and CNS embryonal tumors within strata of medulloblastoma, AT/RT, and supratentorial PNETs. (20) Prenatal illicit drug use was associated with similar increases in medulloblastoma (PR=1.82; CI=0.90-3.69; P=0.10) and supratentorial PNETs (PR=2.66; CI=0.42-16.94; P=0.30), though neither reached statistical significance due to reduced sample size. Due to the low number of patients with an AT/RT diagnosis and positive history of substance use in our study population, the models investigating AT/RT failed to converge. While the small number of respondents reporting moderate-to-heavy alcohol use limited our ability to assess associations in multivariable models, the association between heavy alcohol use during pregnancy and development of NHL persisted in multivariable models (PR=5.94; CI=1.84-19.21; $P=2.91x10^{-3}$).

We performed the same multivariable analyses in the subset of survey respondents who were biological mothers. Effect measures remained generally consistent. However, confidence intervals for associations between illicit drug use and CNS embryonal tumors and retinoblastoma crossed the null. Because effect estimates remained consistent, we suspected that these changes were likely attributable to the reduced sample size and resultantly wider confidence limits. Association results from analyses restricted to biological mother respondents appear in Supplementary Table S3.

DISCUSSION

We observed associations between illicit drug use during pregnancy and elevated occurrence of embryonal tumors of the CNS, including medulloblastoma and supratentorial PNETs, as well as retinoblastoma. Moderate to heavy prenatal alcohol use was also associated with NHL. We also observed inverse associations between prenatal tobacco use and childhood sarcoma, particularly rhabdomyosarcoma, in analyses adjusting for birthweight and gestational term.

Tobacco use during pregnancy has been identified as a potential risk factor for childhood cancers, particularly hematologic malignancies.(21–27) However, more recent work suggests these associations may be subtype-specific.(28) Further, prior associations between maternal prenatal smoking and childhood cancer risk may suffer from reverse confounding if studies did not carefully control for birthweight, as smoking reduces birthweight and higher birthweight has been consistently associated with increased risk of many pediatric malignancies. To our knowledge, no studies to date have reported a protective effect of tobacco use on childhood sarcoma risk. Sarcoma risk has been associated not only with birthweight but also with longitudinal growth patterns throughout childhood and adolescence.(29) While we adjusted for birthweight in our analyses, if maternal smoking had subsequent impacts on childhood and adolescent growth rates or timing of pubertal growth spurts, this could potentially mediate the protective association observed in our analyses.

Existing literature on the epidemiology of smoking most often measures cigarettes per day or pack-years. However, incorporating data across studies with different measures is fraught and frequently resorts to use of a simple ever vs. never smoker grouping. Studies of illicit substance use frequently adhere to similar data analysis procedures that have been informed by the many decades of epidemiologic research on tobacco use. Regarding timing, studies of tobacco use most often focus on second and third trimester use, which represent continued use after the mother is aware of her pregnancy. Epigenetic analysis of the effects of maternal smoking on newborn DNA methylation have begun to incorporate gestational timing of cigarette consumption into models and suggest that first trimester use followed by tobacco cessation in the second and third trimester still leads to detectable differences in the newborn methylome.(30) Our study did not collect data on first, second, and third trimester use and future research will be needed to study this more comprehensively.

The association between alcohol use and childhood cancer risk is less well-studied and has focused mostly on low-to-moderate prenatal alcohol consumption. Data from the registry-

based, case-control ESCALE study in France have not revealed associations between alcohol consumption and either childhood primary CNS tumors or childhood leukemias.(31–33) Gestational exposure to alcohol is associated with various adverse effects on fetal development, but its direct link to the increased risk of NHL in offspring observed in our sample is not established. The specific causes of NHL are not fully understood, and it is generally thought to result from a combination of genetic predisposition and environmental factors, such as infections and exposure to certain chemicals or radiation. While alcohol can weaken the immune system, which may theoretically increase susceptibility to infections linked to NHL, there is limited direct evidence connecting gestational alcohol exposure to NHL risk in offspring.

While the present study did not ask respondents to specify which illicit drugs were used in the prenatal period, marijuana is the most commonly used illicit substance during pregnancy.(34) Exogenous cannabinoids are capable of crossing the placental barrier and may interfere with normal neurodevelopment in the fetal brain.(34) Fetal exposure to marijuana has been associated with altered neurodevelopmental traits that persist into adolescence and adulthood, including schizophrenia, ADHD, and autism, although the contribution of socioeconomic factors and genetic confounding require further evaluation.(35–37) Murine studies of *in utero* cannabinoid exposure have also identified widespread changes in the epigenomic landscape of neural cells in offspring, including DNA methylation changes, histone H3 modifications, and altered DNA occupancy of RNA polymerase II.(38)

The molecular biology of childhood brain tumor formation reflects perturbations in pathways governing normal neuronal and embryonal development, with cerebellar tumors mirroring conserved fetal transcriptional programs and populated by tumor-initiating cells that resemble multipotent neural lineage-specific precursors.(39,40) Correspondingly, hallmark germline and somatic mutations driving the formation of embryonal tumors such as AT/RT, medulloblastoma, and pineoblastoma frequently disrupt master regulators of transcriptional and translational control, including the SWI/SNF chromatin remodeling complex (*e.g.*, *SMARCB1*), the pre-mRNA spliceosome (*e.g.*, U1 small nuclear RNA), and the translational Elongator complex (*e.g.*, *ELP1*).(41–43) DNA methylation and contemporary molecular registry studies have elucidated miRNA biogenesis defects, functional RB1 loss, and MYC activity as driving and shared factors in tumors with PNET histology, including pineoblastoma and retinoblastoma, as well as some types of medulloblastoma.(44) *In utero* exposure to cannabinoids and other exogenous compounds may similarly perturb heavily conserved patterns of embryonic development and thereby initiate pediatric cancer formation.

A strength of our analysis is the large sample size, including 3145 children diagnosed with cancer before their 18th birthday. Rather than investigate all hematologic malignancies jointly, which is typically dominated by the contributions of ALL, this enabled us to separately evaluate the contributions of prenatal substance use in ALL (N=921), AML (N=148), Hodgkin lymphoma (N=121), and NHL (N=62) and to identify a novel potential relationship between prenatal alcohol exposure and development of NHL. We were also able to stratify CNS tumors into three subgroups (astrocytoma, ependymoma, embryonal CNS tumors) and to examine associations with maternal illicit drug use within strata of

medulloblastoma and supratentorial PNET. The ability to investigate gestational exposure to illicit substances is often limited by the relatively low prevalence of the exposure (3% in our data) and by unreliable self-report, which is particularly pernicious when case and control parents differentially misreport behaviors as sensitive as gestational drug use. Because we employed a cross-sectional survey design in which all parental respondents had a child diagnosed with cancer, the effect of such recall bias is likely to be non-differential across cancer subtypes. However, effect sizes may be attenuated when a factor is associated with multiple cancer subtypes due to the inclusion of children with cancer among the comparator group.

Our study has several limitations, including that survey participants were a self-selected population of caregivers who independently navigated to the ALSF MCC survey portal. Therefore, the participants in our study population do not represent a random sample of childhood cancer caregivers. Additionally, MCC survey respondents are primarily non-Hispanic white and biologic mothers, and household income was not adjusted for inflation over time. Therefore, results may not be broadly generalizable. However, the distribution of household incomes in our sample aligns reasonably well with that of the U.S. population, and the preponderance of biologic mothers within our respondent pool is a strength in the specific context of studying maternal substance use during pregnancy. Parents of children diagnosed with cancer at older ages, such as osteosarcoma, may less accurately recall perinatal exposures from many years earlier, although we adjusted for time between birth and survey completion and this did not meaningfully alter results. Additionally, mothers who used alcohol or illicit drugs during pregnancy may also less accurately recall other gestational factors that were included as covariates in our analyses. However, we did observe a significant association between maternal substance use and lower birthweight, as would be expected. Finally, prenatal tobacco, alcohol, and illicit drug use information, as well as birthweight and gestational age, were self-reported (by the birth mother in 92% of families), but could not be independently validated. The survey did not capture the timing of the exposure (*e.g.*, first, second, third trimester), nor did it capture which illicit drugs were used. Therefore, we cannot address potential heterogeneity across exposure windows or across types of illicit drug use.

While is possible that some respondents categorized “illicit drugs” differently from others, the survey did provide examples and included marijuana in that list *(“i.e., marijuana, cocaine, etc.”)*. Over the past two decades, the use of cannabis by pregnant women increased from 3.4% to 7% in a large, representative survey of American women. Those reporting using cannabis during the first trimester increased from 6% to 12% in that time, corresponding with ongoing state-level legalization of personal cannabis use in the U.S.(45) Our results support new efforts focused on both media literacy and science literacy targeted toward women who use cannabis frequently, particularly to those who are pregnant or may become pregnant in the near future.(46)

Prenatal substance use, regardless of socioeconomic status, has significant implications for maternal and fetal health. While it is crucial to emphasize that recreational drug use is not restricted to those living in poverty, the impact of socioeconomic factors on prenatal substance use cannot be ignored. First, individuals from lower socioeconomic

backgrounds may face additional stressors such as financial instability and limited access to healthcare.(47) These stressors can potentially drive some individuals to cope through substance use, including during pregnancy.(48) Consequently, prenatal substance use in disadvantaged populations may be exacerbated by these external pressures. Conversely, substance use during pregnancy can also affect socioeconomic status. Women who use drugs while pregnant may face challenges in accessing prenatal care, maintaining employment, or providing a stable environment for their child, potentially perpetuating a cycle of disadvantage.(49)

This study provides valuable insights into potential associations between maternal prenatal substance use and childhood cancer, expanding the focus beyond traditional factors to include illicit drug use and moderate-to-heavy alcohol use. We observed intriguing connections between illicit drug use during pregnancy and the occurrence of specific childhood cancers, including embryonal tumors of the CNS and retinoblastoma, but no association with astrocytoma despite its larger sample size. Moreover, our findings suggest a potential link between moderate-to-heavy prenatal alcohol use and NHL Although the limitations of our research warrant cautious interpretation of results, particularly regarding the precision with which effect sizes could be estimated, the robustness of our methodology, minimization of differential recall bias, and the specificity of our associations within developmentally-related neuronal malignancies contribute to a growing body of evidence highlighting how maternal substance use during pregnancy might impact both neurogenesis and childhood cancer development. As we continue to unravel the intricate molecular and developmental mechanisms underlying these associations, our study underscores the need for further laboratory research, targeted educational efforts, and potential public health interventions aimed at enhancing the well-being of women of childbearing age and their children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia

ALSF	Alex's Lemonade Stand Foundation
AT/RT	Atypical teratoid/rhabdoid tumor
CMV	Cytomegalovirus
CNS	Central nervous system
DIPG	Diffuse intrinsic pontine glioma
GWAS	Genome-wide association studies
JPA	Juvenile pilocytic astrocytoma
MCC	My Childhood Cancer
NHL	non-Hodgkin lymphoma
PNET	Primitive neuroectodermal tumor

REFERENCES

1. Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. Cancer. 2014;120:2497–506. [PubMed: 24853691]
2. Giddings BM, Whitehead TP, Metayer C, Miller MD. Childhood leukemia incidence in California: High and rising in the Hispanic population. Cancer. 2016;122:2867–75. [PubMed: 27351365]
3. Wright E, Amankwah EK, Winesett SP, Tuite GF, Jallo G, Carey C, et al. Incidentally found brain tumors in the pediatric population: a case series and proposed treatment algorithm. J Neurooncol. 2019;141:355–61. [PubMed: 30411179]
4. Muskens IS, Feng Q, Francis SS, Walsh KM, Mckean-Cowdin R, Gauderman WJ, et al. Pediatric glioma and medulloblastoma risk and population demographics: a Poisson regression analysis. Neurooncol Adv. 2020;2:vdaa089. [PubMed: 32864610]
5. Wiemels JL, Walsh KM, de Smith AJ, Metayer C, Gonseth S, Hansen HM, et al. GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. Nat Commun. 2018;9:286. [PubMed: 29348612]
6. Foss-Skiftesvik J, Li S, Rosenbaum A, Hagen CM, Stoltze UK, Ljungqvist S, et al. Multi-ancestry genome-wide association study of 4069 children with glioma identifies 9p21.3 risk locus. Neuro-Oncology. 2023;noad042.
7. Harvey EB, Boice JD, Honeyman M, Flannery JT. Prenatal x-ray exposure and childhood cancer in twins. N Engl J Med. 1985;312:541–5. [PubMed: 3969117]
8. O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. Int J Epidemiol. 2015;44:153–68. [PubMed: 25626438]
9. Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect. 2000;108 Suppl 3:573–94. [PubMed: 10852857]
10. Wiemels JL, Talbäck M, Francis S, Feychting M. Early Infection with Cytomegalovirus and Risk of Childhood Hematologic Malignancies. Cancer Epidemiol Biomarkers Prev. 2019;28:1024–7. [PubMed: 30996022]
11. Francis SS, Wallace AD, Wendt GA, Li L, Liu F, Riley LW, et al. In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia. Blood. 2017;129:1680–4. [PubMed: 27979823]
12. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental Age and Risk of Childhood Cancer: A Pooled Analysis. Epidemiology. 2009;20:475–83. [PubMed: 19373093]

13. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. Cancer Epidemiology. 2017;49:202–15. [PubMed: 28715709]
14. Gulrajani NB, Montes S, McGough D, Wimberly CE, Khattab A, Semmes EC, et al. Assisted reproductive technology and association with childhood cancer subtypes. Cancer Med. 2022;12:3410–8. [PubMed: 35929579]
15. Wang T, Chen L, Yang T, Wang L, Zhao L, Zhang S, et al. Cancer risk among children conceived by fertility treatment. Int J Cancer. 2019;144:3001–13. [PubMed: 30548591]
16. Wozniak JR, Riley EP, Charness ME. Diagnosis, epidemiology, assessment, pathophysiology, and management of fetal alcohol spectrum disorders. Lancet Neurol. 2019;18:760–70. [PubMed: 31160204]
17. Ansen-Wilson LJ, Lipinski RJ. Gene-environment interactions in cortical interneuron development and dysfunction: A review of preclinical studies. NeuroToxicology. 2017;58:120–9. [PubMed: 27932026]
18. Gilbert MT, Sulik KK, Fish EW, Baker LK, Dehart DB, Parnell SE. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicology and Teratology. 2016;58:15–22. [PubMed: 26708672]
19. Wimberly CE, Towry L, Caudill C, Johnston EE, Walsh KM. Impacts of COVID-19 on caregivers of childhood cancer survivors. Pediatr Blood Cancer [Internet]. 2021 [cited 2021 Apr 26];68. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7995053/
20. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23:1231–51. [PubMed: 34185076]
21. Mucci LA, Granath F, Cnattingius S. Maternal Smoking and Childhood Leukemia and Lymphoma Risk among 1,440,542 Swedish Children. Cancer Epidemiology, Biomarkers & Prevention. 2004;13:1528–33.
22. Müller-Schulte E, Kurlemann G, Harder A. Tobacco, alcohol and illicit drugs during pregnancy and risk of neuroblastoma: systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103:F467–73. [PubMed: 29162685]
23. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault G. Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. Cancer Causes Control. 2008;19:283–95. [PubMed: 18283545]
24. Brooks DR, Mucci LA, Hatch EE, Cnattingius S. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. Cancer Causes Control. 2004;15:997–1005. [PubMed: 15801484]
25. Auger N, Goudie C, Low N, Healy-Profitós J, Lo E, Luu TM. Maternal use of illicit drugs, tobacco or alcohol and the risk of childhood cancer before 6 years of age. Drug and Alcohol Dependence. 2019;200:133–8. [PubMed: 31129483]
26. Bluhm EC, Daniels J, Pollock BH, Olshan AF. Maternal Use of Recreational Drugs and Neuroblastoma in Offspring: A Report from the Children's Oncology Group (United States). Cancer Causes Control. 2006;17:663–9. [PubMed: 16633913]
27. Kwan ML, Metayer C, Crouse V, Buffler PA. Maternal Illness and Drug/Medication Use during the Period Surrounding Pregnancy and Risk of Childhood Leukemia among Offspring. American Journal of Epidemiology. 2007;165:27–35. [PubMed: 17035343]
28. de Smith AJ, Kaur M, Gonseth S, Endicott A, Selvin S, Zhang L, et al. Correlates of Prenatal and Early-Life Tobacco Smoke Exposure and Frequency of Common Gene Deletions in Childhood Acute Lymphoblastic Leukemia. Cancer Research. 2017;77:1674–83. [PubMed: 28202519]
29. Diessner BJ, Spector LG. Birthweight and site of osteosarcoma development. Pediatric Blood & Cancer. 2017;64:e26443.
30. Monasso GS, Jaddoe VWV, de Jongste JC, Duijts L, Felix JF. Timing- and Dose-Specific Associations of Prenatal Smoke Exposure With Newborn DNA Methylation. Nicotine & Tobacco Research. 2020;22:1917–22. [PubMed: 32330269]

31. Rudant J, Menegaux F, Leverger G, Baruchel A, Lambilliotte A, Bertrand Y, et al. Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). Cancer Causes Control. 2008;19:1277–90. [PubMed: 18618277]
32. Bailey HD, Lacour B, Guerrini-Rousseau L, Bertozzi A-I, Leblond P, Faure-Conter C, et al. Parental smoking, maternal alcohol, coffee and tea consumption and the risk of childhood brain tumours: the ESTELLE and ESCALE studies (SFCE, France). Cancer Causes Control. 2017;28:719–32. [PubMed: 28477209]
33. Plichart M, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE). Eur J Cancer Prev. 2008;17:376–83. [PubMed: 18562965]
34. Thompson R, DeJong K, Lo J. Marijuana Use in Pregnancy: A Review. Obstet Gynecol Surv. 2019;74:415–28. [PubMed: 31343707]
35. Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician. 2020;66:98–103. [PubMed: 32060189]
36. Baranger DAA, Paul SE, Colbert SMC, Karcher NR, Johnson EC, Hatoum AS, et al. Association of Mental Health Burden With Prenatal Cannabis Exposure From Childhood to Early Adolescence: Longitudinal Findings From the Adolescent Brain Cognitive Development (ABCD) Study. JAMA Pediatr [Internet]. 2022 [cited 2022 Sep 30]; Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2795863
37. Corsi DJ, Donelle J, Sucha E, Hawken S, Hsu H, El-Chaâr D, et al. Maternal cannabis use in pregnancy and child neurodevelopmental outcomes. Nat Med. Nature Publishing Group; 2020;26:1536–40.
38. Smith A, Kaufman F, Sandy MS, Cardenas A. Cannabis Exposure During Critical Windows of Development: Epigenetic and Molecular Pathways Implicated in Neuropsychiatric Disease. Curr Envir Health Rpt. 2020;7:325–42.
39. Vladoiu MC, El-Hamamy I, Donovan LK, Farooq H, Holgado BL, Sundaravadanam Y, et al. Childhood cerebellar tumours mirror conserved fetal transcriptional programs. Nature. Nature Publishing Group; 2019;572:67–73. [PubMed: 31043743]
40. Hovestadt V, Smith KS, Bihannic L, Filbin MG, Shaw ML, Baumgartner A, et al. Resolving medulloblastoma cellular architecture by single-cell genomics. Nature. Nature Publishing Group; 2019;572:74–9. [PubMed: 31341285]
41. Muskens IS, Zhang C, de Smith AJ, Biegel JA, Walsh KM, Wiemels JL. Germline genetic landscape of pediatric central nervous system tumors. Neuro Oncol. Oxford Academic; 2019;21:1376–88.
42. Suzuki H, Kumar SA, Shuai S, Diaz-Navarro A, Gutierrez-Fernandez A, De Antonellis P, et al. Recurrent noncoding U1 snRNA mutations drive cryptic splicing in SHH medulloblastoma. Nature. Nature Publishing Group; 2019;574:707–11. [PubMed: 31664194]
43. Waszak SM, Robinson GW, Gudenas BL, Smith KS, Forget A, Kojic M, et al. Germline Elongator mutations in Sonic Hedgehog medulloblastoma. Nature. Nature Publishing Group; 2020;580:396–401. [PubMed: 32296180]
44. Li BK, Vasiljevic A, Dufour C, Yao F, Ho BL, Lu M, et al. Pineoblastoma segregates into molecular sub-groups with distinct clinicopathologic features: A Rare Brain Tumor Consortium registry study. Acta Neuropathol. 2020;139:223–41. [PubMed: 31820118]
45. Volkow ND, Han B, Compton WM, McCance-Katz EF. Self-reported Medical and Nonmedical Cannabis Use Among Pregnant Women in the United States. JAMA. 2019;322:167. [PubMed: 31211824]
46. Willoughby JF, Hust SJT, Couto L, Kang S, Pingel B, Li J, et al. Examining science and media literacy health communication messages to reduce intentions to use cannabis while pregnant. Psychology of Addictive Behaviors [Internet]. US: American Psychological Association; 20230420 [cited 2023 Jun 8]; Available from: https://psycnet.apa.org/fulltext/2023-65877-001.pdf
47. Caballo B, Dey S, Prabhu P, Seal B, Chu P, Kim L. The Effects of Socioeconomic Status on the Quality and Accessibility of Healthcare Services. Zenodo; 2021 [cited 2023 Nov 8]; Available from: https://zenodo.org/record/4740684

48. Woods SM, Melville JL, Guo Y, Fan M-Y, Gavin A. Psychosocial Stress during Pregnancy. Am J Obstet Gynecol. 2010;202:61.e1–61.e7.

49. Stone R Pregnant women and substance use: fear, stigma, and barriers to care. Health & Justice. 2015;3:2.

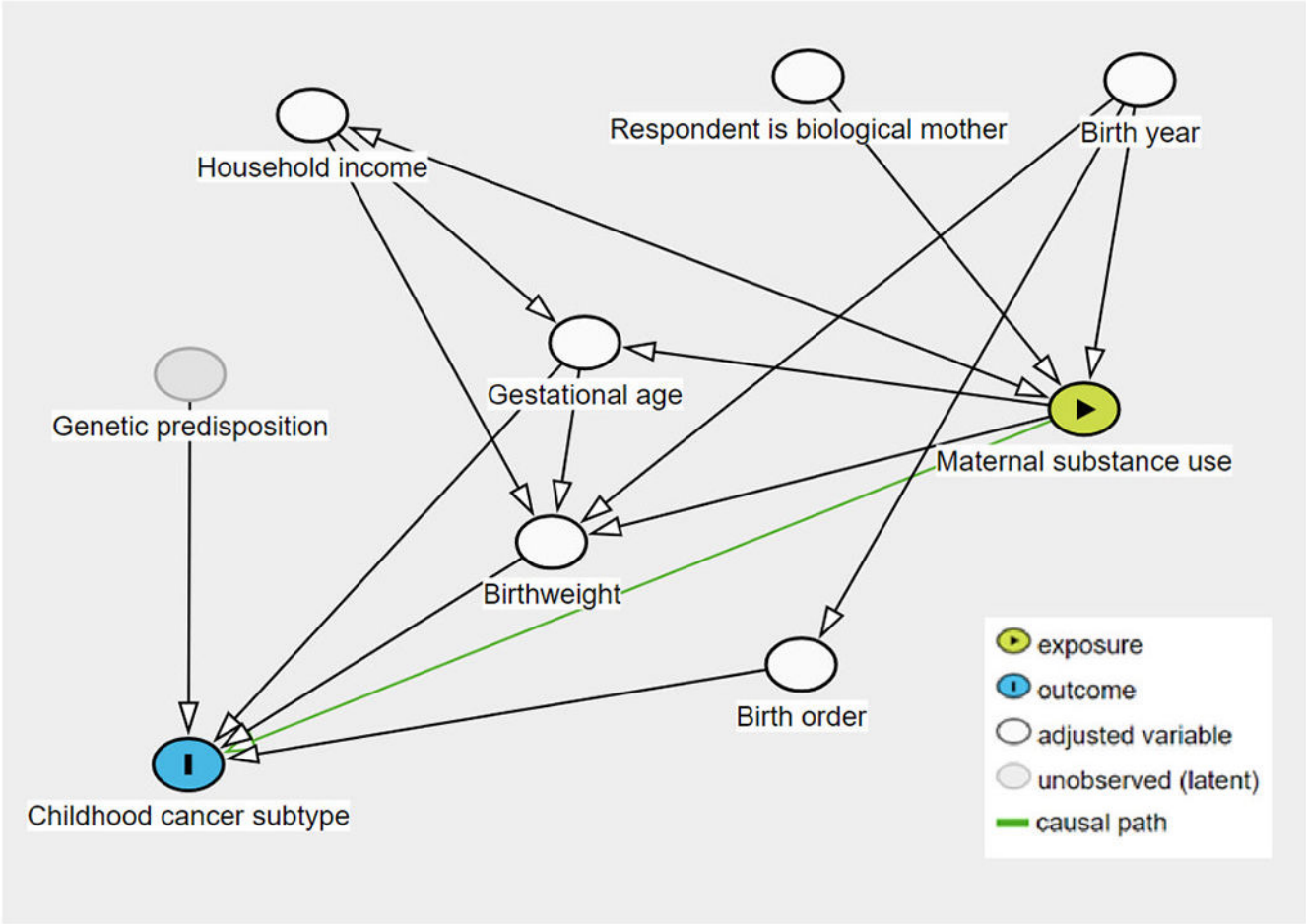

FIGURE 1. Directed acyclic graph (DAG) of primary regression analysis investigating the relationship between maternal substance use during pregnancy (tobacco smoking, moderate to heavy alcohol consumption, illicit drug use) and childhood cancer subtype.

Variables in the model include potential confounders (birth year, household income, child's birth order, respondent status as biological mother) and potential mediators that were controlled for in the analysis (birthweight, gestational age) in order to evaluate the direct effect of the primary exposure of interest (maternal substance use) on childhood cancer subtypes. (Image generated with dagitty)

TABLE 1.

Demographic characteristics of survey respondents and their child diagnosed with cancer

	Number of respondents (N=3145)	Percentage of study population[a]
Respondent biological mother	2905	92
Respondent non-Hispanic white	2812	89
Household income at diagnosis		
<$50,000	941	30
$50,000-$99,999	1277	41
$100,000+	765	24
Missing	162	5
Maternal prenatal tobacco use		
Yes	412	13
No	2692	86
Missing	41	1
Maternal prenatal alcohol use		
Yes	13	<1
No	3084	98
Missing	48	2
Maternal prenatal illicit drug use		
Yes	78	3
No	3020	96
Missing	47	1
Child sex		
Male	1723	55
Female	1421	45
Missing	1	<1
Child age at diagnosis		
0-2 years	1024	33
3-5 years	813	26
6-9 years	545	17
10+ years	763	24
Child gestational term		
Full term	2773	88
Premature	351	11
Missing	21	1
Child birthweight		
Low birthweight (≤5 pounds)	249	8
Normal birthweight (6-9 pounds)	2719	87

	Number of respondents (N=3145)	Percentage of study population[a]
High birthweight (10+ pounds)	157	5
Missing	20	<1
Child birth order		
Youngest child	1279	23
Only child	730	23
Oldest child	708	41
Neither oldest nor youngest child	399	13
Missing	29	<1
Child cancer subtype [b]		
Acute lymphoblastic leukemia (ALL)	921	29
Neuroblastoma	428	14
All sarcomas[c]	416	13
Astrocytoma[d]	234	7
CNS embryonal[e]	212	7
Wilms tumor	184	6
Rhabdomyosarcoma	158	5
Acute myeloid leukemia (AML)	148	5
Non-Hodgkin lymphoma (NHL)	121	4
Ewing sarcoma	114	4
Osteosarcoma	95	3
Hodgkin lymphoma	62	2
Ependymoma	61	2
Hepatoblastoma	61	2
Germ cell tumor	56	2
Retinoblastoma	55	2
Other[f]	39	1

[a] Percentages may total to >100% due to rounding

[b] Due to the inclusion of the “All sarcomas” category, proportions in this section will sum to >100%, and frequencies will sum to >3145

[c] Includes subtypes rhabdomyosarcoma, osteosarcoma, Ewing Sarcoma and 48 other soft tissue sarcomas with analytic groups too small for analysis, including 1 alveolar soft part sarcoma, 1 angiosarcoma, 8 clear cell sarcoma of the kidney, 1 dermatofibrosarcoma protuberans, 10 desmoplastic round cell tumor, 2 epithelioid sarcoma, 1 encapsulated extra-skeletal sarcoma, 4 infantile fibrosarcoma, 1 intimal sarcoma, 4 peripheral nerve sheath tumor, 1 mesenchymal chondrosarcoma, 1 spindle cell sarcoma, 2 synovial sarcoma, 10 undifferentiated sarcomas, and 1 unspecified paraspinal sarcoma.

[d] Including diffuse intrinsic pontine glioma (DIPG; N=62), glioblastoma (N=32), juvenile pilocytic astrocytoma (N=25), and other diffuse astrocytoma (N=115)

[e] Including atypical teratoid/rhabdoid tumor (AT/RT; N=17), medulloblastoma (N=170), supratentorial primitive neuroectodermal tumors (PNETs; N=24), and pineoblastoma (N=1)

[f] Includes cancer subtypes too few for analysis, including: thyroid, Langerhans cell histiocytosis, pleuropulmonary blastoma, adrenocortical carcinoma, and ectomesenchymoma

TABLE 2.

Relationships between maternal gestational substance use and childhood cancer subtype[a]

Cancer Type	Tobacco use (PR[b]; 95% CI)	P-value	Illicit drug use (PR[b]; 95% CI)	P-value
ALL[d] (N[c]=829)	1.00 (0.84-1.19)	1.00	**0.58 (0.34-0.97)**	**0.040**
Neuroblastoma (N[c]=395)	0.77 (0.56-1.04)	0.09	0.55 (0.23-1.28)	0.16
All sarcomas (N[c]=381)	**0.60 (0.43-0.85)**	**3.52×10^{-3}**	1.36 (0.82-2.25)	0.23
Astrocytoma[e] (N[c]=212)	1.02 (0.69-1.49)	0.93	1.21 (0.56-2.62)	0.62
CNS embyronal[f] (N[c]=192)	1.19 (0.82-1.73)	0.35	**1.94 (1.05-3.58)**	**0.035**
Wilms' tumor (N[c]=175)	1.26 (0.85-1.88)	0.24	1.21 (0.51-2.86)	0.66
Rhabdomyosarcoma (N[c]=145)	**0.48 (0.24-0.93)**	**0.030**	1.25 (0.47-3.29)	0.66
AML[g] (N[c]=136)	1.46 (0.95-2.25)	0.08	0.64 (0.16-2.55)	0.52
Ewing sarcoma (N[c]=105)	0.64 (0.33-1.25)	0.19	1.98 (0.81-4.83)	0.13
Non-Hodgkin lymphoma (N[c]=106)	1.50 (0.91-2.46)	0.11	1.58 (0.59-4.21)	0.36
Osteosarcoma (N[c]=87)	0.76 (0.40-1.46)	0.41	0.97 (0.25-3.74)	0.97
Hodgkin lymphoma (N[c]=60)	1.12 (0.56-2.26)	0.75	-	-
Ependymoma (N[c]=59)	1.51 (0.78-2.91)	0.22	1.37 (0.33-5.77)	0.67
Hepatoblastoma (N[c]=57)	1.09 (0.54-2.20)	0.81	1.25 (0.31-5.07)	0.75
Germ cell tumor (N[c]=53)	1.32 (0.62-2.81)	0.47	1.52 (0.43-5.35)	0.51
Retinoblastoma (N[c]=51)	0.64 (0.25-1.62)	0.35	**3.11 (1.20-8.08)**	**0.020**

[a] Multivariable, log-Poisson model with robust variance, controlling for: whether respondent is biological mother, household income at diagnosis (ordinal; 3-level), child's birthweight, child's gestational age, child's birth year (ordinal; 6-level), child's birth order (ordinal; 4-level), and respondent non-Hispanic white race/ethnicity

[b] Prevalence ratios by subtype, comparing the listed cancer subtype to all other childhood cancer patients in the study. Therefore, it should it noted that the reference group changes slightly for each subtype comparison.

[c] Minimum number of cases included in model for prenatal tobacco, alcohol, or illicit drug use. For some exposures, sample size may be slightly larger due to more complete covariate data.

[d] Acute lymphoblastic leukemia

[e] Includes diffuse intrinsic pontine glioma (DIPG), glioblastoma, juvenile pilocytic astrocytoma, and other diffuse astrocytoma, as described in Table 1.

[f] Includes atypical teratoid/rhabdoid tumor (AT/RT), medulloblastoma, supratentorial primitive neuroectodermal tumors (PNETs), and pineoblastoma, as described in Table 1.

[g] Acute myeloid leukemia