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Jeannette R. Wong-Siegel  
*Washington University School of Medicine in St. Louis*

Kimberly J. Johnson  
*Washington University in St. Louis*

Katie Gettinger  
*Washington University School of Medicine in St. Louis*

Nicole Cousins  
*Washington University School of Medicine in St. Louis*

Nicole McAmis  
*Washington University School of Medicine in St. Louis*

See next page for additional authors

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Congenital neurodevelopmental anomalies in pediatric and young adult cancer

Jeannette R. Wong-Siegel1 | Kimberly J. Johnson2 | Katie Gettigner1 | Nicole Cousins1,2 | Nicole McAmis1 | Ashley Zamarione1 | Todd E. Druley1

1 Division of Hematology and Oncology, Department of Pediatrics, Washington University School of Medicine, Saint Louis, Missouri
2 Brown School Masters of Public Health Program, Washington University in St. Louis, Saint Louis, Missouri

Correspondence
Todd E. Druley, MD, PhD, Division of Hematology and Oncology, Department of Pediatrics, Washington University School of Medicine, Campus Box 8510, Room 4302, 4515 McKinley Avenue, Saint Louis, MO 63110.
Email: druley_t@wustl.edu

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Congenital anomalies that are diagnosed in at least 120,000 US infants every year are the leading cause of infant death and contribute to disability and pediatric hospitalizations. Several large-scale epidemiologic studies have provided substantial evidence of an association between congenital anomalies and cancer risk in children, suggesting potential underlying cancer-predisposing conditions and the involvement of developmental genetic pathways. Electronic medical records from 1,107 pediatric, adolescent, and young adult oncology patients were reviewed. The observed number (O) of congenital anomalies among children with a specific pediatric cancer subtype was compared to the expected number (E) of anomalies based on the frequency of congenital anomalies in the entire study population. The O/E ratios were tested for significance using Fisher’s exact test. The Kaplan–Meier method was used to compare overall and neurological malignancy survival rates following tumor diagnosis. Thirteen percent of patients had a congenital anomaly diagnosis prior to their cancer diagnosis. When stratified by congenital anomaly subtype, there was an excess of neurological anomalies among children with central nervous system tumors (O/E = 1.56, 95%CI 1.13–2.09). Male pediatric cancer patients were more likely than females to have a congenital anomaly, particularly those <5 years of age (O/E 1.35, 95%CI 0.97–1.82). Our study provides additional insight into the association between specific congenital anomaly types and pediatric cancer development. Moreover, it may help to inform the development of new screening policies and support hypothesis-driven research investigating mechanisms underlying tumor predisposition in children with congenital anomalies.

KEYWORDS
birth defects, cancer, congenital, development, pediatrics, predisposition

1 | INTRODUCTION

The etiology of most childhood malignancies is poorly understood. Unlike adult cancers at the molecular level, pediatric cancers have a relative paucity of acquired somatic mutations (Chmielecki et al., 2017; Vogelstein, Papadopoulos, Velculescu, Zhou, & Kinzler, 2013), and these mutations, on their own, generally do not generate tumors that phenocopy pediatric cancer in animal models (Bueno et al., 2013; Bursen et al., 2010; Montes et al., 2011). This suggests additional germline genetic or epigenetic variation is required for tumor formation or malignant transformation. Recent reports have suggested that 8–30% of pediatric oncology patients have a cancer predisposition (Knapke, Nagarajan, Correll, Kent, & Burns, 2012; Zhang et al., 2015). It is well known that children with Down syndrome have an
increased risk for leukemia (Mili, Khoury, Flanders, & Greenberg, 1993; Mili, Lynch, Khoury, Flanders, & Edmonds, 1993; Miller, 1963; Nishi, Miyake, Takeda, & Hatae, 2000), while those diagnosed with Beckwith-Wiedemann syndrome are at an increased risk for developing embryonal tumors, especially Wilms tumors (DeBaun & Tucker, 1998; Riccardi, Sujansky, Smith, & Francke, 1978). In addition to known cancer predisposition syndromes, there is growing literature supporting an association between sporadic birth defects and pediatric malignancy.

Diagnosed in at least 120,000 US babies each year, congenital anomalies are the leading cause of infant death and contribute to disability and pediatric hospitalizations (Centers for Disease Control and Prevention, 2008; Hoyert, Mathews, Menacker, Strobino, & Guyer, 2006; Mathews and MacDorman, 2012; Rosano, Botto, Botto, & Mastroiacovo, 2000; Yoon et al., 1997). Multiple linkage studies have reported a prevalence of 2–3% of children with congenital anomalies in the general population (Hoyert et al., 2006; Yoon et al., 1997). Several large-scale epidemiologic studies have provided substantial evidence of an association between congenital anomalies and cancer risk in children (Agha et al., 2005; Altmann, Halliday, & Giles, 1998; Bjorge, Cnattingius, Lie, Tretli, & Engeland, 2008; Botto et al., 2013; Carozza, Langlois, Miller, & Canfield, 2012; Hall, Ritz, Cockburn, Davidson, & Heck, 2017; Janitz et al., 2016; Mili, Khoury et al., 1993); Narod, Hawkins, Robertson, & Stiller, 1997; Rankin, Siff, Pearce, Parker, & Ward Platt, 2008; Rios et al., 2016; Windham, Bjerkedal, & Langmark, 1985). Studies have demonstrated significant associations specifically between neurological congenital anomalies and pediatric cancer (Altmann et al., 1998; Bjorge et al., 2008; Botto et al., 2013; Carozza et al., 2012; Narod et al., 1997), with some suggesting a specific link between neurological malformations and central nervous system tumors (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008; Narod et al., 1997).

While the reported relationships between congenital anomalies and cancer risk are variable, these associations suggest that some individuals with congenital anomalies may have underlying cancer-predisposing conditions. Further investigation into the associations between specific anomalies and tumor subtypes may refine our understanding of pediatric, adolescent, and young adult (AYA) cancer development. Therefore, we conducted a retrospective study, reviewing the electronic medical records for pediatric and AYA oncology patients seen at a large academic pediatric medical center to quantify associations between congenital anomalies and pediatric malignancies.

2 | MATERIALS AND METHODS

2.1 | Study cohort

The study population consisted of all pediatric and AYA (ages 0–23 years) oncology patients diagnosed from January 1, 2004 to December 31, 2014 at St. Louis Children’s Hospital with no selection for demographics, insurance provider or other criteria other than cancer with or without a congenital anomaly. Information ascertained from review of both in- and outside-hospital electronic medical records were included in the analysis. Patients diagnosed with chromosomal anomalies, cancer predisposition syndromes, or benign tumors were excluded based on genetic sequencing results, pathology reports, and physician notes documenting clinical criteria for diagnosis. In addition, patients diagnosed with a benign tumor according to the ICD-O-3 classification criteria (Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005) or who had less than one year of documented follow-up were excluded from the analysis. The Washington University in St. Louis Institutional Review Board approved this study.

Study data were collected and managed using REDCap electronic data capture tools (Harris et al., 2009). Pathology and radiologic reports were reviewed to confirm tumor diagnosis and histology for classification purposes. Site and morphology codes were assigned according to the International Classification of Diseases-Oncology, third edition (ICD-O-3). Tumors and subtypes, when sample sizes were large enough, were then classified according to the International Classification of Childhood Cancer, third edition (ICCC-3) (Steliarova-Foucher et al., 2005). Additional demographic characteristics were also recorded, including sex, race, age, treatment(s) received, length of follow-up, and other long-term outcomes related to the primary tumor diagnosis.

2.2 | Congenital anomaly ascertainment

Congenital anomalies were identified through text abstractions from physician letters, operative summaries, clinical notes, physician consults, and outside hospital records when available. A congenital anomaly was only included in this study if it occurred prior to and was not an associated functional symptom of the primary tumor diagnosis and the anomaly met at least one diagnostic code in the congenital anomalies chapter of the ninth revision of the International Classification of Diseases (ICD-9). Patients who were documented to have more than one congenital anomaly subtype were included in analysis for each subtype, but were only included once when calculating the overall prevalence of congenital anomalies in this study population.

All congenital anomaly indications were classified according to the standardized birth defects classification established by the National Birth Defects Prevention Network Appendix 3.1 “Birth Defects Descriptions for NBDPN Core, Recommended, and Extended Conditions” (https://www.nbdpn.org/docs/Appendix_3_1_BirthDefectsDescriptions2015_2016DEC14.pdf). Collaboration with the Division of Pediatric Neurology at Washington University in St. Louis also identified additional diagnoses to include as neurodevelopmental conditions, such as developmental delay, hydrocephalus, cerebral palsy, epilepsy and recurrent seizures, convulsions, and anomalies of skull and facial bones. These conditions were also reviewed for diagnosis prior to the primary tumor diagnosis, as well as excluding those diagnoses that were also presenting functional symptoms of the tumor itself (e.g., hydrocephalus secondary to mass effect from a brain tumor). In addition, classification of these conditions using ICD-9 billing codes was reviewed and established with the Division of Pediatric Neurology faculty prior to initiating electronic record
reviews. Based on sample size, neurological anomalies were further subclassified by developmental delay, movement disorder, and structural defects.

2.3 Statistical analysis

Bivariate analyses comparing basic demographic factors between patients comprising the pediatric and AYA cancer cohort with and without a congenital anomaly, as well as any differences among the different anomaly and tumor subtypes, were calculated using $\chi^2$ or Fisher’s exact test when sample sizes were less than 5. Additional comparisons were made based on age at diagnosis and gender. The follow-up time was measured from the age at primary tumor diagnosis until the date of last clinic visit, death, or until December 31, 2015, which provided at least one year of follow-up for each patient in the study. Loss of follow-up was noted for those patients who were last seen in a clinic visit but were subsequently deceased with no recorded date of death on file or who chose to pursue further medical management at another institution.

To determine whether there was an excess of congenital anomalies among a particular pediatric or AYA cancer subtype, the observed number of congenital anomalies among patients with cancer subtype was compared to the expected frequency of the anomalies among children in the entire study population, based on previously described methods (Narod et al., 1997). The observed-to-expected (O/E) ratios were tested for significance using the Fisher exact test (http://www.openepi.com/SMR/SMR.htm) (Soe & Sullivan, 2006). Comparisons were made by primary tumor diagnosis, congenital anomaly subtype, gender, and age at diagnosis.

Sensitivity analyses were conducted using patients diagnosed with leukemias as the reference group for calculation of the expected number of congenital anomalies among patients with a specific cancer subtype. Our rationale for using leukemia cases as an alternative comparison group is because leukemias are primarily associated with Down syndrome (Botto et al., 2013; Dawson, Charles, Bower, de Klerk, & Milne, 2015; Harris et al., 2009; Hoyert et al., 2006; Miller, 1963; Shu et al., 1988). Therefore, we made the assumption that the frequency of congenital anomalies observed in our leukemia patient sub-population (after excluding Down syndrome leukemia cases) may provide a more accurate estimate of the prevalence of congenital anomalies observed in the general population (after applying the same exclusions we applied in this study).

3 RESULTS

Distinct ICD-9 codes were selected to identify children with various congenital anomalies that were diagnosed prior to a cancer diagnosis. Of 1,107 pediatric and AYA oncology patients, 141 (13%) were identified with a congenital anomaly prior to their primary tumor diagnosis (Table 1). Due to a small sample size, gastrointestinal and genitourinary anomalies were collapsed together (Table 2). In addition, there were seven patients who were diagnosed with more than one congenital anomaly. While more males than females had a congenital anomaly prior to their primary tumor diagnosis, the distribution of sex, race, age at primary tumor diagnosis, primary tumor subtype, follow-up, and vital status were not significantly different between pediatric and AYA oncology patients with and without a congenital anomaly.

### Table 1 Descriptive characteristics of 1,107 oncology patients diagnosed January 1, 2004 to December 31, 2014

| Characteristic | Total number of patients (N = 1107) | Patients with a congenital anomaly (N = 141) |
|---------------|-------------------------------------|---------------------------------------------|
| Sex           |                                     |                                             |
| Male          | 638 (58)                            | 88 (14)                                     |
| Female        | 469 (42)                            | 53 (11)                                     |
| Race          |                                     |                                             |
| White         | 915 (83)                            | 119 (13)                                    |
| Black         | 138 (12)                            | 16 (12)                                     |
| Other         | 42 (4)                              | 3 (7)                                       |
| Unknown       | 12 (1)                              | 3 (25)                                      |
| Age at primary cancer diagnosis (y) |                      |                                             |
| <5            | 353 (32)                            | 53 (15)                                     |
| 5–9           | 247 (22)                            | 26 (11)                                     |
| 10–14         | 285 (26)                            | 32 (11)                                     |
| 15+           | 222 (20)                            | 30 (14)                                     |
| Primary cancer diagnosis |                          |                                             |
| Leukemia      | 270 (24)                            | 32 (12)                                     |
| Lymphoma      | 109 (10)                            | 10 (9)                                      |
| Central nervous system | 367 (33)                          | 53 (14)                                    |
| Peripheral nervous system | 70 (6) | 11 (16) |
| Renal         | 45 (4)                              | 7 (16)                                      |
| Bone          | 65 (6)                              | 2 (3)                                       |
| Soft tissue sarcoma | 79 (7)                           | 13 (16)                                    |
| Germ cell     | 46 (4)                              | 6 (13)                                      |
| Other         | 56 (5)                              | 7 (13)                                      |
| Follow-up (y) |                                     |                                             |
| <5            | 606 (55)                            | 79 (13)                                     |
| 5–9           | 453 (41)                            | 53 (12)                                     |
| 10+           | 48 (4)                              | 9 (19)                                      |
| Vital status  |                                     |                                             |
| Alive         | 957 (86)                            | 127 (13)                                    |
| Deceased      | 106 (10)                            | 6 (6)                                       |
| Lost to follow-up | 44 (4)                           | 8 (18)                                      |

aOther cancers include tumors of the thyroid, endocrine glands, liver, nasopharyngeal cavity, and skin.

bLength of follow-up calculated from date of primary tumor diagnosis to earliest occurrence of date of last follow-up, death, or end of study (December 31, 2015).

cPercent of patients with a congenital anomaly among total number of patients within the same demographic subgroup.
TABLE 2  
Distribution of congenital anomalies by subtype and ICD-9 code for 141 patients

| Classification                              | N  | Multiple* |
|---------------------------------------------|----|-----------|
| Neurological anomalies                      | 3  |           |
| Developmental delay                         |    |           |
| 315.0-315.9: Specific developmental delays  | 17 |           |
| 783.0-783.9: Lack of normal physiologic development | 10 |           |
| Movement disorders                          |    |           |
| 331.4: Obstructive hydrocephalus            | 1  |           |
| 343.0-343.9: Cerebral palsy                 | 5  |           |
| 345.0-345.9: Epilepsy and recurrent seizures| 21 |           |
| 779.0: Convulsions in newborn               | 1  |           |
| 780.3: Convulsions                         | 10 |           |
| Structural defects                          |    |           |
| 348.4: Arnold–Chiari malformation           | 3  |           |
| 741.0–741.9: Spina bifida                   | 3  |           |
| 742.0–742.9: Other congenital anomalies of the CNS | 3  |    |
| Cardiovascular anomalies                    | 4  |           |
| 745.0–745.9: Bulb is cordis/cardiac septal closure anomaly | 8  |   |
| 746.0–746.9: Other congenital anomaly of the heart | 12 |   |
| 747.0–747.9: Other congenital anomaly of the circulatory system | | |
| Gastrointestinal/genitourinary anomalies    | 4  |           |
| 750.0–750.9: Other congenital anomaly of upper alimentary | 8  |   |
| 751.0–751.9: Other congenital anomaly of digestive system | 6  |   |
| 752.0–752.9: Congenital anomaly of genital organs | 5  |   |
| 753.0–753.9: Congenital anomaly of urinary system | 3  |   |
| Musculoskeletal anomalies                   | 3  |           |
| 754.0–754.9: Certain congenital musculoskeletal deformities | 4  |   |
| 755.0–755.9: Other congenital anomalies of limbs | 4  |   |
| 756.0–756.9: Other congenital musculoskeletal anomalies | 6  |   |
| 658.8: Amniotic bands                       | 1  |           |
| Other anomalies                             | 2  |           |
| 743.0–743.9: Congenital anomaly of eye      | 2  |           |
| 749.0–749.9: Cleft palate and cleft lip     | 4  |           |
| 759.0–759.9: Other/unspecified congenital anomaly | 5  |   |

ICD-9, international classification of diseases; ninth revision; N, number of patients with each congenital anomaly diagnosis code.

*A total of 7 patients had more than one congenital anomaly diagnosis.

Among pediatric cancer patients who were identified as having a congenital anomaly there was a higher percentage of central nervous system (CNS), peripheral nervous system (PNS), renal, and soft tissue tumor (STS) diagnoses than in patients who were not identified as having a congenital anomaly.

Overall, there was a deficiency of congenital anomalies in children diagnosed with bone tumors (O/E 0.24, 95%CI 0.04–0.80) (Figure 1). Excesses of congenital anomalies were noted for pediatric cancer patients diagnosed with CNS, PNS, renal, and STS tumors. Analyses conducted by congenital anomaly subtype indicated a significantly increased excess of neurological anomaly (O/E 1.54 95%CI 1.09–2.11) in patients with CNS tumors. There was also an excess of neurological anomalies in patients with PNS and soft tissue tumors and of cardiovascular anomalies in children diagnosed with leukemias (O/E 1.90 95%CI 1.03–3.24). No significant associations were noted for GI/GU, musculoskeletal, or other anomalies but notably there were positive associations for leukemias and renal tumors and all three anomaly subtypes.

Additional stratification by CNS tumor and neurological anomaly subtype was conducted to evaluate whether the observed association was driven by one or more specific subtypes. There was a deficiency of neurological anomalies in astrocytoma and ependymoma cases with positive associations noted for embryonal tumors, gliomas, and other CNS tumors (Table 3). In addition, there was an excess of embryonal and other tumors associated with developmental delay, gliomas, and other tumors with structural defects and with movement disorders. Further analyses by specific anomaly diagnoses could not be conducted due to limited sample size. Among the leukemia subtypes, 9 of the 12 cardiovascular anomalies were diagnosed in patients who had post-transplant lymphoproliferative disease (PTLD) secondary to prolonged immunosuppression (data not shown). Sensitivity analyses excluding all PTLD cases from the leukemia population resulted in a non-significant inverse association between leukemia and cardiovascular anomalies (O/E 0.92, 95%CI 0.23–2.49).

Additional subgroup analyses stratified by sex for congenital anomaly subtype and age at diagnosis were conducted. Overall, there was a trend towards a slight excess of congenital anomalies among males (O/E 1.09, 95%CI 0.88–1.33) but not females (O/E 0.89, 95%CI 0.67–1.15). When stratified by congenital anomaly subtype, there was a consistent excess of congenital anomalies among males for neurological (O/E 1.18, 95%CI 0.88–1.55), cardiovascular (O/E 1.12, 95%CI 0.66–1.78), gastrointestinal/genitourinary (O/E 1.51, 95%CI 0.91–2.36), and other anomalies (O/E 1.45, 95%CI 0.68–2.76). A non-significant excess of musculoskeletal anomalies was observed among females (O/E 1.56, 95%CI 0.76–2.85). When stratified by age at diagnosis, there was an overall excess of patients <5 years of age with any congenital anomaly (O/E 1.18, 95%CI 0.89–1.53, data not shown). Male patients <5 years of age with any congenital anomaly and diagnosed with their primary tumor were more common than females at the same age (O/E 1.35 95%CI 0.97–1.82) (Table 4).

Sensitivity analyses conducted using the leukemia patient subpopulation to calculate expected congenital anomaly numbers were consistent with the results previously reported above (Table 5).
Notably, there were stronger associations between neurological anomalies CNS tumors (O/E 2.54, 95% CI: 1.80–3.47), PNS tumors (O/E 3.21, 95% CI: 1.57–5.90), and STS (O/E 2.67, 95% CI: 1.24–5.06). In addition, there was a consistent excess of neurological anomalies regardless of primary tumor diagnosis by sex, with a slightly higher burden among males (O/E 1.93, 95% CI: 1.44–2.55) compared to females (O/E 1.50, 95% CI: 1.01–2.15).

Despite small sample sizes, using the Kaplan–Meier method to calculate survival by congenital anomaly indication was also noted to be slightly better for oncology patients diagnosed with a congenital anomaly compared to those without (at 10 years: 86.9% vs. 81.0%, respectively; p<0.20). In addition, survival was similar for patients with a neurological malignancy when stratified by congenital anomaly indication (at 10 years: 79.9% vs. 81.9%, respectively; p<0.89). No other significant differences in survival were noted when stratified by tumor or anomaly subtype (data not shown).

4 | DISCUSSION

Increased risks for subsequent CNS, neuroblastoma, germ cell, and rhabdomyosarcoma tumors among children with congenital anomalies have been previously reported, as well as specific risks for those with a neurological, circulatory, genitourinary, digestive, and musculoskeletal abnormality (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008; Botto et al., 2013; Carozza et al., 2012; Fisher et al., 2012; Narod et al., 1997; Rios et al., 2016). However, few studies have provided specific anomaly/tumor subtype comparisons (Baptiste et al., 1989; Birch et al., 1990; Durmaz et al., 2011; Gold et al., 1994; Hall et al., 2017; Johnson, Annegers, Frankowski, Spitz, & Buffler, 1987; Rankin et al., 2008; Sun, Overvad, & Olsen, 2014). Here, we observed an excess of neurological anomalies among patients diagnosed with CNS tumors and provided additional information on relationships between the congenital anomaly and primary tumor type. Increased cancer risks were observed for specific conditions in previous studies, including spina bifida, hydrocephalus, and congenital malformations of the spinal cord (Agha et al., 2005; Fisher et al., 2012; Narod et al., 1997). We found eight patients with spina bifida, hydrocephalus, and Arnold–Chiari malformations in our cohort, but there was not statistically significant evidence for enrichment.

Prior studies have also highlighted an increased risk of tumor development when diagnosed with multiple anomalies (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008). We found that 5% (7) of our patients had more than one congenital anomaly, but we did not
find evidence for an enrichment of children or adolescents with multiple congenital anomalies amongst our cancer patients. A recent data-linkage study also reported a significantly increased rate of childhood cancer among children with anomalies at younger ages (Janitz et al., 2016). Here, we demonstrated an excess of congenital anomalies among patients diagnosed with their primary tumor <5 years of age, with most of this excess attributable to the male subgroup.

Certain congenital anomalies already have established associations with neurological malignancies. For example, Neurofibromatosis type 1 increases a patient's risk for optic gliomas, malignant peripheral nerve sheath tumors, and other gliomas (Korf, 2000). Previous studies have reported associations between CNS tumors and congenital anomalies, but there were not enough cases to evaluate associations between specific histologic subtypes or congenital anomaly condition (Botto et al., 2013; Jones et al., 1995). Here, despite our small sample size, we observed a non-significant, but consistent, excess for gliomas with neurological structural defects and movement disorders and for embryonal tumors with developmental delay. While the subgroups have small numbers that can make these results unstable, Table 3 shows that each subgroup had a similar relative effect size and that the overall association is not being driven by one subgroup. In addition, these subgroup results for gliomas and embryonal tumors are consistent with associations to birth defects previously reported (Bailey et al., 2017; Mallol-Mesnard et al., 2008; Partap, MacLean, Von Behren, Reynolds, & Fisher, 2011). Further collaboration and development of larger pediatric cohorts is warranted in order to attain the necessary power to discern the absolute and relative risk of neurological tumor development with the congenital neurocognitive anomalies listed here.

We also observed evidence of an excess of congenital anomalies among male cancer patients, especially in males diagnosed with their primary tumor <5 years of age. A male excess was observed in a retrospective study of birth defects, but this was driven by hypospadias and not observed among neurological anomalies (Botto et al., 2013). There were a limited number of sex-specific congenital anomalies in our study, and therefore sex-specific analyses conducted in previous studies could not be replicated with our study population. A previous study by Fisher et al. (2012) found no significant differences in sex regardless of congenital anomaly or tumor indication, but a Canadian linkage study reported a significant excess of male cancer patients among children with a congenital abnormality compared to those without (57% vs. 51%, p < 0.001) (Agha et al., 2005). An overall excess of males diagnosed with childhood cancers has also been previously reported, with male gender cited as a potential risk factor for development of brain tumors in a pediatric population.

### Table 3: Comparison of observed to expected frequencies for neurological tumor and neurological anomaly subtype

| CNS tumor subtype | All neurological anomalies | Developmental delay | Structural defects | Movement disorders |
|-------------------|---------------------------|---------------------|-------------------|-------------------|
|                   | O  | E  | O/E (95%CI) | O  | E  | O/E (95%CI) | O  | E  | O/E (95%CI) | O  | E  | O/E (95%CI) |
| Astrocytoma       | 8  | 13.5 | 0.59 (0.28–1.13) | 2  | 3.6 | 0.56 (0.09–1.84) | 0  | 0.7 | –          | 6  | 8.8  | 0.68 (0.28–1.42) |
| Embryonal         | 7  | 5.4  | 1.30 (0.57–2.56) | 3  | 1.4 | 2.14 (0.55–5.83) | 0  | 0.2 | –          | 4  | 3.4  | 1.18 (0.37–2.84) |
| Ependymoma        | 2  | 3.6  | 0.56 (0.09–1.84) | 1  | 1.0 | 1.00 (0.05–4.93) | 0  | 0.2 | –          | 1  | 2.3  | 0.43 (0.02–2.14) |
| Glioma            | 6  | 4.0  | 1.50 (0.61–3.12) | 0  | 0.9 | –          | 1  | 0.2 | 5.00 (0.25–24.67) | 5  | 2.6  | 1.92 (0.70–4.26) |
| Other             | 13 | 7.7  | 1.69 (0.94–2.82) | 4  | 1.9 | 2.11 (0.67–5.08) | 1  | 0.3 | 3.33 (0.17–16.44) | 8  | 4.8  | 1.67 (0.77–3.17) |

### Table 4: Comparison of observed to expected frequencies by gender for congenital anomalies and age at primary tumor diagnosis

| Age at diagnosis (y) | Male | Female |
|----------------------|------|--------|
|                      | O    | E      | O/E (95%CI) | O    | E      | O/E (95%CI) |
| Any congenital anomaly | 88   | 81.0 | 1.09 (0.88–1.33) | 53   | 59.6 | 0.89 (0.67–1.15) |
| Neurological         | 47   | 39.9 | 1.18 (0.88–1.55) | 27   | 29.6 | 0.91 (0.61–1.31) |
| Cardiovascular       | 16   | 14.3 | 1.12 (0.66–1.78) | 12   | 10.8 | 1.11 (0.60–1.89) |
| Gastrointestinal/genitourinary | 17   | 11.3 | 1.51 (0.91–2.36) | 5    | 8.4  | 0.60 (0.22–1.32) |
| Musculoskeletal      | 6    | 7.6  | 0.79 (0.32–1.64) | 9    | 5.8  | 1.56 (0.76–2.85) |
| Other                | 8    | 5.5  | 1.45 (0.68–2.76) | 3    | 4.1  | 0.72 (0.19–1.99) |

**O.** observed frequency; **E.** expected frequency calculated with the prevalence rate of the anomaly in the entire study population; **95%CI.** 95% confidence interval.
| Sex                 | Any congenital anomaly | Neurological | Cardiovascular | Gastrointestinal/genitourinary | Musculoskeletal | Other |
|---------------------|------------------------|--------------|----------------|--------------------------------|----------------|-------|
|                     | O/E 95%CI              | O/E 95%CI    | O/E 95%CI      | O/E 95%CI                      | O/E 95%CI      | O/E 95%CI       |
| Male                | 88/76 1.16 (0.94-1.43) | 47/24 1.93 (1.44-2.55) | 16/25 0.64 (0.38-1.02) | 17/15 1.16 (0.70-1.81) | 6/8 0.73 (0.30-1.52) | 8/8 0.97 (0.45-1.83) |
| Female              | 53/56 0.95 (0.72-1.24) | 27/18 1.50 (1.01-2.15) | 12/19 0.64 (0.35-1.09) | 5/11 0.46 (0.17-1.02) | 9/6 1.43 (0.70-2.62) | 3/6 0.48 (0.12-1.32) |
| Primary cancer subtype |                       |              |                |                                |                |       |
| Lymphoma            | 10/13 0.78 (0.39-1.38) | 3/4 0.71 (0.18-1.94) | 4/5 0.89 (0.28-2.14) | 1/3 0.38 (0.02-1.90) | 1/2 0.67 (0.03-3.29) | 1/2 0.67 (0.03-3.29) |
| Central nervous system | 53/43 1.22 (0.92-1.58) | 36/14 2.54 (1.80-3.47) | 5/14 0.36 (0.13-0.79) | 6/8 0.72 (0.29-1.50) | 5/5 1.06 (0.39-2.36) | 2/5 0.43 (0.07-1.41) |
| Peripheral nervous system | 11/8 1.33 (0.70-2.30) | 9/3 3.21 (1.57-5.90) | 1/3 0.38 (0.02-1.90) | 0/2 - | 0/1 - | 1/1 1.11 (0.06-5.48) |
| Renal               | 7/5 1.32 (0.58-2.61) | 3/2 1.76 (0.45-4.80) | 1/2 0.59 (0.03-2.90) | 1/1 1.00 (0.05-4.93) | 1/1 1.67 (0.08-8.22) | 2/1 3.33 (0.56-11.01) |
| Bone                | 2/8 0.26 (0.04-0.86) | 0/3 - | 0/3 - | 2/2 1.18 (0.20-3.89) | 0/1 - | 0/1 - |
| Soft tissue sarcoma | 13/9 1.38 (0.77-2.31) | 8/3 2.67 (1.24-5.06) | 1/3 0.34 (0.02-1.70) | 2/2 1.11 (0.19-3.67) | 2/1 2.00 (0.34-6.61) | 0/1 - |
| Germ cell           | 6/6 1.09 (0.44-2.27) | 1/2 0.59 (0.03-2.90) | 1/2 0.56 (0.03-2.74) | 1/1 0.91 (0.05-4.48) | 2/1 3.33 (0.56-11.01) | 1/1 1.67 (0.08-8.22) |
| Other               | 7/7 1.06 (0.46-2.10) | 3/2 1.43 (0.36-3.89) | 3/2 1.30 (0.33-3.55) | 2/1 1.54 (0.26-5.08) | 0/1 - | 0/1 - |

O, observed frequency; E, expected frequency calculated from prevalence rate of the anomaly in the leukemia patient study population; 95%CI, 95% confidence interval. O/E ratios were not generated when the observed frequency: 0. Bolded text indicates $p < 0.05$. 

TABLE 5  Sensitivity analysis of observed-to-expected prevalence ratios for congenital anomalies by gender and primary tumor using the expected frequencies generated from the leukemia patient study population.
surveillance of children with a pediatric cancer predisposition is such interventions. Current international consensus for longitudinal neurosurgical and radiation oncology expertise for CNS tumors incidence of leukemia is higher than CNS tumors in the general population of this study, though the number of CNS tumor cases was higher than leukemia cases in the same population. Studies have also reported conflicting associations of head circumference with childhood cancer development of mesenchymal glioblastoma (Sun, Overvad et al., 2014). Interestingly, male, but not female, astrocytes with increased density (Good et al., 2001; Matsumoto & Arai, 1986; Witelson, Glezer, 2006; Greenough, Carter, Steerman, & DeVoogd, 1977) and neuronal apoptosis (Sun, Warrington, & Rubin, 2012). In addition to gross differences in the male and female brain (McCarthy et al., 2009; Wilson and Davies, 2007), model organism and neuroimaging research has suggested sex differences in synaptic patterns (Ciofi, Leroy, & Tramu, 2006; Greenough, Carter, Steerman, & DeVoogd, 1977) and neuronal density (Good et al., 2001; Matsumoto & Arai, 1986; Witelson, Glezer, & Kigar, 1995). Interestingly, male, but not female, astrocytes with complete loss of NF1 and p53 had greater inactivation of the retinoblastoma (RB) tumor suppressor gene, resulting in greater risk for development of mesenchymal glioblastoma (Sun, Overvad et al., 2014). These data will refine future studies investigating shared biological processes among neurological anomaly development, sex differentiation, and oncogenesis.

There are several limitations to this study. Most notably, we did not have a control group of children without pediatric cancer to calculate the expected number of congenital anomalies. Furthermore, the number of CNS tumor cases was higher than leukemia cases in this cohort, which could be a reflection of referral patterns since the incidence of leukemia is higher than CNS tumors in the general population. This finding is likely due to the requirement for neurosurgical and radiation oncology expertise for CNS tumors whereas leukemia therapy is largely outpatient without a need for such interventions. Current international consensus for longitudinal surveillance of children with a pediatric cancer predisposition is targeted to conditions that provide a ≥1% risk of cancer. Future clinical studies must focus on calculating the absolute and relative risk of cancer in these subgroups of children with specific congenital anomalies. Translational research will revolve around putative common mechanisms driving aberrant neurocognitive development and early childhood CNS tumorigenesis. It is reasonable to think that such studies would also add important mechanistic insights into the same tumors in children without congenital anomalies. It is encouraging that outcomes for children with and without congenital anomalies are generally good (≥80% OS) and similar, at least at this single institution. This suggests that therapies designed against the tumorigenic mechanisms in patients with congenital anomalies are likely to prove efficacious in those without.

In conclusion, this study expands previous associations between congenital anomalies and pediatric cancer by integrating neurocognitive deficits and movement disorders as well as new insights into age, gender, and tumor type differences in children with congenital anomalies and cancer. While sample sizes were small, limiting statistical significance in most groups, there were many associations that could be interrogated in larger datasets to more precisely identify potential subgroups of children that may benefit from increased surveillance in specialty clinics. For future translational research, investigations into common mechanisms altering normal development as well as predisposition to tumorigenesis (e.g., RAS, MAPK, Jumanji family of histone modifiers) in patient-specific inducible pluripotent stem cells or other in vivo models could reveal much about the links between developmental biology and pediatric cancer.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Todd E. Druley http://orcid.org/0000-0002-3245-7561

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