Original Article

Cancer Diagnostic Profile in Children With Structural Birth Defects: An Assessment in 15,000 Childhood Cancer Cases

Jeremy M. Schraw, PhD [1,2]; Tania A. Desrosiers, PhD[3]; Wendy N. Nembhard, PhD[4]; Peter H. Langlois, PhD[5]; Robert E. Meyer, PhD[6,7]; Mark A. Canfield, PhD[5]; Sonja A. Rasmussen, MD[8,9]; Tiffany M. Chambers, MS[2,10]; Logan G. Spector, PhD[11]; Sharon E. Plon, MD[10,12]; and Philip J. Lupo, PhD [1,2,10]

BACKGROUND: Birth defects are established risk factors for childhood cancer. Nonetheless, cancer epidemiology in children with birth defects is not well characterized. **METHODS:** Using data from population-based registries in 4 US states, this study compared children with cancer but no birth defects (n = 13,111) with children with cancer and 1 or more nonsyndromic birth defects (n = 1616). The objective was to evaluate cancer diagnostic characteristics, including tumor type, age at diagnosis, and stage at diagnosis. **RESULTS:** Compared with the general population of children with cancer, children with birth defects were diagnosed with more embryonal tumors (26.6% vs 18.7%; $q < 0.001$), including neuroblastoma (12.5% vs 8.2%; $q < 0.001$) and hepatoblastoma (5.0% vs 1.3%; $q < 0.001$), but fewer hematologic malignancies, including acute lymphoblastic leukemia (12.4% vs 24.4%; $q < 0.001$). In age-stratified analyses, differences in tumor type were evident among children younger than 1 year and children 1 to 4 years old, but they were attenuated among children 5 years of age or older. The age at diagnosis was younger in children with birth defects for most cancers, including leukemia, lymphoma, astrocytoma, medulloblastoma, ependymoma, embryonal tumors, and germ cell tumors (all $q < 0.05$). **CONCLUSIONS:** The results indicate possible etiologic heterogeneity in children with birth defects, have implications for future surveillance efforts, and raise the possibility of differential cancer ascertainment in children with birth defects. ***Cancer* 2020;0:1-10**. © *2020 American Cancer Society*.

LAY SUMMARY:

• Scientific studies suggest that children with birth defects are at increased risk for cancer. However, these studies have not been able to determine whether important tumor characteristics, such as the type of tumor diagnosed, the age at which the tumor is diagnosed, and the degree to which the tumor has spread at the time of diagnosis, are different for children with birth defects and children without birth defects.

• This study attempts to answer these important questions. By doing so, it may help scientists and physicians to understand the causes of cancer in children with birth defects and diagnose cancer at earlier stages when it is more treatable.

KEYWORDS: birth defects, cancer predisposition, childhood cancer, epidemiology.

INTRODUCTION

Congenital anomalies occur in as many as 3% of all livebirths in developed countries and are a leading cause of infant mortality.[1,2] The majority of children with congenital anomalies do not have a known chromosomal or genetic etiology,[3,4] and they may be referred to as having nonchromosomal structural birth defects. Studies by our group and others support associations between birth defects and childhood cancer.[5-12] In particular, birth defects appear to be strongly associated with germ cell tumors (GCTs), soft-tissue sarcomas, embryonal tumors, including neuroblastoma, hepatoblastoma, retinoblastoma, medulloblastoma, nephroblastoma (Wilms tumor), and atypical teratoid/rhabdoid tumors. Studies have also reported that associations are strongest among younger children (eg, those younger than 6 years).[6,8-10,12-14]

These studies provide compelling evidence that birth defects are associated with increased childhood cancer risk, but it remains largely unknown whether or how important diagnostic characteristics (ie, tumor type, Surveillance,

Corresponding Author: Philip J. Lupo, PhD, Baylor College of Medicine, 1 Baylor Plaza, MS: BCM622, Houston, TX 77030 (philip.lupo@bcm.edu).

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas; [2]Center for Epidemiology and Population Health, Baylor College of Medicine, Houston, Texas; [3]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina; [4]Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [5]Birth Defects Epidemiology and Surveillance Branch, Department of State Health Services, Austin, Texas; [6]Department of Maternal and Child Health, University of North Carolina, Chapel Hill, North Carolina; [7]State Center for Health Statistics, North Carolina Division of Public Health, Raleigh, North Carolina; [8]Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida; [9]Department of Epidemiology, University of Florida College of Medicine and College of Public Health and Health Professions, Gainesville, Florida; [10]Department of Pediatrics, Baylor College of Medicine, Houston, Texas; [11]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota; [12]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

We acknowledge the Texas Birth Defects Registry, the Texas Cancer Registry, the Texas Center for Health Statistics, the Texas Department of State Health Services, the Arkansas Reproductive Health Monitoring System, the Arkansas Cancer Registry, the Michigan Department of Health and Human Services, the North Carolina Central Cancer Registry, the North Carolina Birth Defects Monitoring Program, the North Carolina State Center for Health Statistics, and the North Carolina Division of Public Health.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32982, **Received:** October 18, 2019; **Revised:** April 27, 2020; **Accepted:** May 1, 2020, **Published online** Month 00, 2020 in Wiley Online Library (wileyonlinelibrary.com)

Epidemiology, and End Results [SEER] summary stage at diagnosis, and age at diagnosis) differ in children with birth defects in comparison with the general population of children with cancer. Such differences could reflect etiologic heterogeneity or differential surveillance in children with birth defects in comparison with the general population of children with cancer, and they may have implications for diagnosis, treatment, and prognosis. Thus, comprehensively characterizing cancer diagnostic characteristics in children with birth defects may generate hypotheses for etiologic research[15] and could inform surveillance efforts, such as those recently discussed by Malkin et al.[16] Our objective was to describe the distributions of tumor types, SEER stages at diagnosis, and ages at diagnosis in children and adolescents with nonchromosomal structural birth defects in comparison with children and adolescents without birth defects.

MATERIALS AND METHODS

Study Design

We performed a case-only analysis of children with cancer enrolled in the Genetic Overlap Between Anomalies and Cancer in Kids (GOBACK) registry linkage study. Detailed methodology for the GOBACK study has been published previously.[5] Briefly, investigators developed retrospective birth cohorts by linking individual-level information from birth certificates, birth defect registries, and cancer registries in Arkansas (1995-2011), Michigan (1992-2011), North Carolina (2003-2011), and Texas (1999-2013). De-identified data from each participating state were then pooled for analysis. This study was approved by the institutional review board of each participating institution and was performed in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived by the institutional review boards because this study used de-identified data collected by public health agencies.

Data Collection

All study participants included in this analysis were diagnosed with cancer before the age of 18 years. Children without cancer and children with cancer and a chromosomal or single-gene syndrome ascertained by the participating birth defect registries (trisomies 13, 18, and 21; 22q11.2 deletion syndrome; Turner syndrome; tuberous sclerosis complex; or neurofibromatosis) were excluded (n = 383). Information on each child's sex, gestational age at delivery, and plurality as well as maternal age, race/ethnicity, and education was obtained from birth certificates. Children were categorized as having no birth defect, 1 isolated major structural birth defect, or multiple major structural birth defects according to the number of diagnoses recorded by registries. Major structural birth defects were defined as those included in the case definitions used by the National Birth Defects Prevention Network (Supporting Table 1).[17] Population-based birth defect registries in Arkansas, North Carolina, and Texas recorded diagnoses with the Centers for Disease Control and Prevention–modified British Paediatric Association coding system; Michigan recorded diagnoses with the coding system of the *International Classification of Diseases, Ninth Revision, Clinical Modification*. All participating cancer registries recorded site, histology, and behavior codes per the *International Classification of Diseases for Oncology, Third Edition*. These were used to classify childhood cancer diagnoses per the *International Classification of Childhood Cancer, Third Edition* (*ICCC-3*) system except for intracranial and intraspinal GCTs, which were categorized as central nervous system (CNS) tumors. All other GCTs were classified as extracranial. Ewing sarcoma of bone included children in *ICCC-3* site group 8c; results were unchanged when all Ewing sarcoma family tumors (*ICCC-3* site groups 8c, 9d.1, and 9d.2) were evaluated collectively. Only cancers diagnosed at an age < 18 years were included, and in children diagnosed with more than 1 cancer (n = 230), only the first primary tumor was included in the study.

Statistical Analysis

Data analysis and visualization were performed in R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) with the gmodels and ggplot2 packages. Differences in the frequencies of tumor types and SEER stages at diagnosis by birth defect status were assessed with the chi-square test or Fisher exact test, as appropriate.[18,19] An analysis of tumor type was first performed in the entire cohort and subsequently after stratification by age at cancer diagnosis. To be consistent with our previous assessment, we divided children into those diagnosed at <1, 1 to 4, 5 to 9, and ≥10 years.[10] Medians and interquartile ranges were calculated for the age at diagnosis, and 2-sided Mann-Whitney U tests were used to assess differences by birth defect status. Because we previously had shown that cancer risk was greater in children with multiple major birth defects,[5] we also assessed potential differences in diagnostic characteristics between children with an isolated birth defect and children with multiple birth defects. To correct for multiple testing, we maintained a 5% false discovery rate in each analysis (tumor type, age

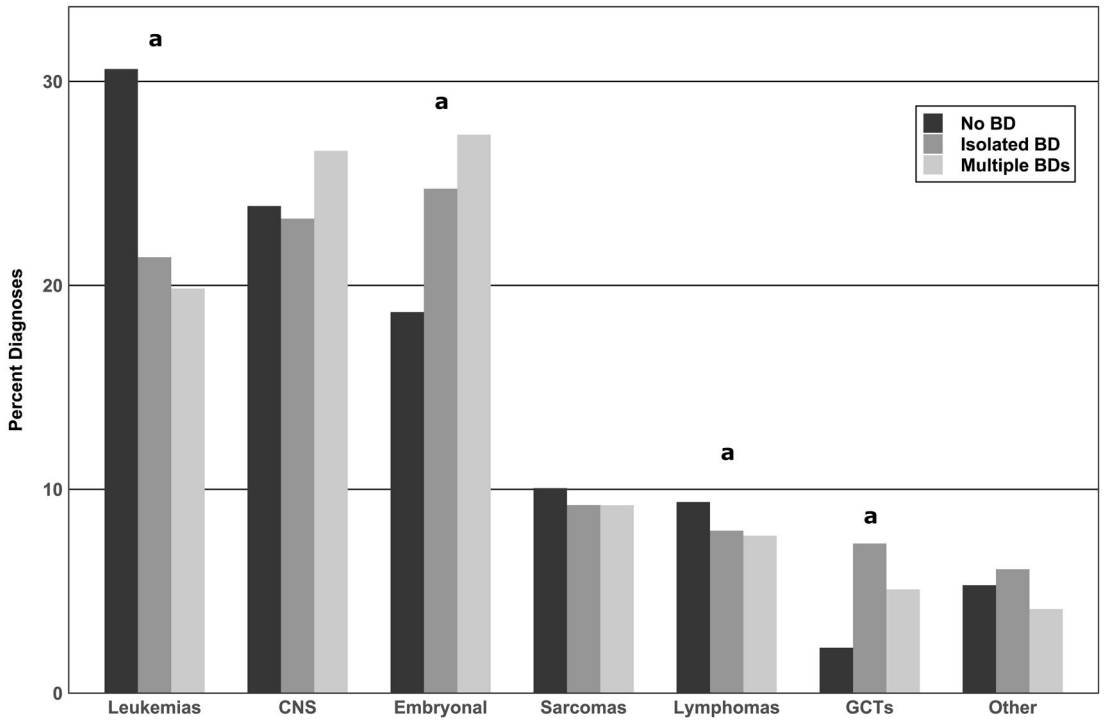

FIGURE 1. Distributions of cancer diagnoses by BD status. [a]There was a significant difference in the proportion of total cancer diagnoses between children with BDs and children without BDs ($q < 0.001$). No significant differences were observed when we compared children with an isolated BD and those with multiple major BDs. BD indicates birth defect; CNS, central nervous system; GCT, germ cell tumor.

at diagnosis, and stage at diagnosis) via the Benjamini-Hochberg method.[20] Statistical significance was defined as a false discovery rate–adjusted q value <0.05. To comply with data suppression rules, exact counts were suppressed for cells with fewer than 5 observations.

RESULTS

Cancer Diagnostic Profile by Birth Defect Status

Cancer was diagnosed in 13,111 children without birth defects and in 1616 children with birth defects, of whom 477 were diagnosed with an isolated major birth defect and 1139 were diagnosed with 2 or more major birth defects. Differences in tumor type by birth defect status were evident (Fig. 1 and Table 1). Birth defect status was associated with the frequency of diagnosis for 9 of the 28 tumor types evaluated (all $q < 0.05$). Specifically, medulloblastoma, neuroblastoma, hepatoblastoma, and extracranial GCTs were more frequent in children with birth defects in comparison with children without them. Collectively, embryonal tumors (defined per the method of Tulla et al[21]) and intracranial or extracranial GCTs accounted for 40.1% of all cancers diagnosed in children with a birth defect and 27.3% in children without a birth defect ($q < 0.001$). In contrast, acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma were more frequent in children without birth defects. No differences were observed when we compared children with multiple birth defects and children with an isolated birth defect except for a lower frequency of retinoblastoma.

Birth defect status was associated with the age at diagnosis for 18 of the 28 tumor types evaluated (Table 2). Specifically, when comparing children with birth defects and children with no birth defects, we observed a younger median age at cancer diagnosis for ALL, acute myeloid leukemia, astrocytoma, medulloblastoma, ependymoma, primitive neuroectodermal tumors, all evaluated subtypes of non-CNS embryonal tumors, extracranial GCTs, other or unspecified soft-tissue sarcomas, and other or unspecified malignant neoplasms (all $q < 0.05$). Compared with children with an isolated major birth defect, children with multiple birth defects were diagnosed at an even younger median age for leukemia, CNS tumors, neuroblastoma, and sarcomas.

Birth defect status was associated with the SEER stage at diagnosis among children with CNS tumors,

TABLE 1. Cancer Diagnoses by Birth Defect Status

	No Birth Defect (n = 13,111), No. (%)	Isolated Birth Defect (n = 477), No. (%)	Multiple Birth Defects (n = 1139), No. (%)	q^a	q^b
Leukemia	4013 (30.61)	102 (21.38)	226 (19.84)	<0.001	0.58
ALL	3194 (24.36)	70 (14.68)	131 (11.50)	<0.001	0.22
AML	464 (3.54)	17 (3.56)	50 (4.39)	0.41	0.55
Lymphoma	1229 (9.37)	38 (7.97)	88 (7.73)	0.12	0.92
HL	329 (2.51)	—	16 (1.40)	0.002	0.30
NHL	415 (3.17)	11 (2.31)	37 (3.25)	0.75	0.45
Burkitt lymphoma	142 (1.08)	7 (1.47)	10 (0.88)	0.94	0.45
CNS tumors	3132 (23.89)	111 (23.27)	303 (26.6)	0.29	0.31
Astrocytoma	1153 (8.79)	36 (7.55)	113 (9.92)	0.66	0.29
Medulloblastoma	353 (2.69)	15 (3.14)	48 (4.21)	0.03	0.45
Ependymoma	251 (1.91)	5 (1.05)	19 (1.67)	0.42	0.46
PNET	95 (0.72)	—	11 (0.97)	0.75	0.53
Intracranial GCTs	87 (0.66)	—	16 (1.40)	0.08	0.62
Teratoma	35 (0.27)	—	10 (0.88)	0.03	0.65
Germinoma	36 (0.27)	—	5 (0.44)	0.50	0.99
Non-CNS embryonal tumors	2450 (18.69)	118 (24.74)	312 (27.39)	<0.001	0.44
Neuroblastoma	1070 (8.16)	51 (10.69)	151 (13.26)	<0.001	0.31
Retinoblastoma	452 (3.45)	23 (4.82)	24 (2.11)	0.44	0.02
Nephroblastoma	734 (5.60)	28 (5.87)	70 (6.15)	0.55	0.89
Hepatoblastoma	169 (1.29)	15 (3.14)	66 (5.79)	<0.001	0.09
Sarcomas	1318 (10.05)	44 (9.22)	105 (9.22)	0.45	0.99
Ewing sarcoma of bone	117 (0.89)	—	—	0.07	0.10
Osteosarcoma	167 (1.27)	—	8 (0.70)	0.09	0.83
Embryonal RMS	221 (1.69)	—	15 (1.32)	0.33	0.73
Alveolar RMS	78 (0.59)	—	—	0.41	0.33
Other sarcoma	685 (5.22)	29 (6.08)	76 (6.67)	0.10	0.11
Extracranial GCTs	292 (2.23)	35 (7.34)	58 (5.09)	<0.001	0.21
Other	694 (5.29)	29 (6.08)	47 (4.13)	0.45	0.23

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; GCT, germ cell tumor; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PNET, primitive neuroectodermal tumor; RMS, rhabdomyosarcoma.

Some rows are nonmutually exclusive (eg, the leukemia and ALL rows and the CNS and astrocytoma rows); therefore, column sums exceed the total numbers given in the headers.

[a]Comparing children with birth defects and children without any birth defects with the chi-square test or the Fisher exact test if the expected cell counts were <5. *q* values <0.05 indicate statistical significance at a 5% false discovery rate.

[b]Comparing children with an isolated major birth defect and children with multiple major birth defects with the chi-square test or the Fisher exact test if the expected cell counts were <5. *q* values <0.05 indicate statistical significance at a 5% false discovery rate.

non-CNS embryonal tumors, and sarcomas (Fig. 2 and Supporting Table 2). Specifically, CNS tumors and sarcomas were less often reported as localized or in situ but were more often reported as unknown in the 2 categories of children with birth defects. Children with birth defects who were diagnosed with embryonal tumors more often had their tumor stage reported as localized or in situ. When analyses were restricted to children with an isolated birth defect versus multiple birth defects, stage was significantly different only for sarcomas, for which it was more often reported as unknown in children with multiple birth defects (58.7% vs 36.6% in children with an isolated birth defect; $q = 0.03$). We did not analyze individual tumor types because of the limited sample size.

Cancer Diagnostic Profile by Age and Birth Defect Status

Age-stratified analyses were performed to compare cancer diagnostic characteristics by birth defect status separately among children aged <1, 1 to 4, 5 to 9, and ≥10 years at cancer diagnosis (Fig. 3 and Supporting Table 3). Because of the sample size and because we observed few significant differences in the distributions of tumor types in children with an isolated birth defect versus multiple birth defects, these groups were combined for this analysis. ALL and retinoblastoma were less common in infants with a birth defect, whereas GCTs and hepatoblastoma were more common. Indeed, 13.4% of all cancers diagnosed in infants with a birth defect were GCTs, whereas 6.5% were in those without birth defects ($q < 0.001$). In children aged 1 to 4 years, birth defects were associated with more frequent diagnosis of medulloblastoma, hepatoblastoma, and extracranial GCTs but less frequent diagnosis of leukemia. In infants and children aged 1 to 4 years, birth defects were associated with more frequent diagnosis of hepatoblastoma but less frequent diagnosis of retinoblastoma and ALL. In children aged 5 to 9 years, other or unspecified soft-tissue sarcomas constituted a larger proportion of cancer diagnoses for children with birth defects, and in

TABLE 2. Median Age at First Cancer Diagnosis by Birth Defect Status

	No Birth Defect, Median (IQR), y	Isolated Birth Defect, Median (IQR), y	Multiple Birth Defects, Median (IQR), y	q^a	q^b
Leukemia	3.6 (4.0)	3.5 (4.1)	2.0 (4.1)	<0.001	0.001
ALL	3.7 (3.6)	3.5 (4.0)	3.0 (3.1)	0.03	0.44
AML	3.0 (7.0)	2.0 (4.5)	0.5 (0.5)	<0.001	0.03
Lymphoma	7.0 (8.1)	3.9 (5.6)	6.0 (8.8)	0.002	0.18
HL	11.9 (7.0)	11.8 (1.2)	11.9 (6.1)	0.75	0.94
NHL	7.0 (6.9)	6.3 (5.9)	6.0 (6.0)	0.08	0.80
Burkitt lymphoma	5.3 (5.2)	5.0 (4.3)	6.4 (4.8)	0.51	0.29
CNS tumors	5.0 (6.0)	4.0 (5.7)	2.1 (5.5)	<0.001	0.03
Astrocytoma	4.9 (5.4)	4.4 (5.2)	3.0 (5.0)	<0.001	0.25
Medulloblastoma	4.9 (5.6)	4.8 (3.5)	3.0 (4.0)	<0.001	0.09
Ependymoma	3.2 (4.6)	1.3 (0.4)	1.0 (4.0)	0.02	0.87
PNET	3.0 (4.0)	1.0 (0.4)	1.0 (2.3)	0.03	0.87
Intracranial GCTs	7.3 (9.0)	1.0 (3.9)	3.3 (13.8)	0.31	0.45
Teratoma	1.8 (5.0)	0.3 (0.2)	0.3 (3.5)	0.15	0.23
Germinoma	9.2 (4.9)	7.1 (5.5)	15.0 (2.0)	0.27	0.33
Non-CNS embryonal tumors	1.8 (2.3)	0.7 (1.8)	0.7 (2.0)	<0.001	0.12
Neuroblastoma	1.4 (2.5)	0.5 (1.2)	0.1 (1.0)	<0.001	0.03
Retinoblastoma	1.0 (1.5)	0.6 (0.6)	0.5 (0.2)	<0.001	0.09
Nephroblastoma	3.0 (2.6)	1.4 (2.5)	1.5 (3.0)	<0.001	0.60
Hepatoblastoma	1.6 (2.0)	1.1 (1.8)	1.0 (0.9)	0.02	0.39
Sarcomas	6.0 (8.6)	6.6 (7.0)	2.2 (5.5)	<0.001	0.004
Ewing sarcoma of bone	9.5 (6.4)	6.9 (1.9)	9.2 (0.0)	0.39	0.26
Osteosarcoma	10.1 (5.4)	13.0 (2.0)	8.0 (7.6)	0.51	0.29
Embryonal RMS	3.3 (3.7)	4.1 (3.5)	2.0 (3.2)	0.12	0.37
Alveolar RMS	4.0 (6.3)	5.0 (6.0)	3.5 (1.5)	0.74	0.45
Other sarcoma	5.0 (8.8)	7.0 (8.8)	1.2 (4.8)	<0.001	0.05
Extracranial GCTs	2.1 (10.4)	0.5 (1.2)	0.5 (0.7)	<0.001	0.30
Other	10.5 (10.7)	6.0 (9.9)	5.0 (11.0)	<0.001	0.39

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; GCT, germ cell tumor; HL, Hodgkin lymphoma; IQR, interquartile range; NHL, non-Hodgkin lymphoma; PNET, primitive neuroectodermal tumor; RMS, rhabdomyosarcoma.

[a]From Kruskal-Wallis tests comparing children with birth defects and children without any major birth defects. *q* values <0.05 indicate statistical significance at a 5% false discovery rate.

[b]From Kruskal-Wallis tests comparing children with an isolated birth defect and children with multiple major birth defects. *q* values <0.05 indicate statistical significance at a 5% false discovery rate.

children aged ≥10 years, intracranial GCTs were more frequent.

DISCUSSION

Epidemiological studies provide strong evidence of an association between birth defects and childhood cancer.[5-10] However, these assessments have not comprehensively described diagnostic characteristics, such as tumor type, age at diagnosis, and stage at diagnosis, in children with birth defects. It remains largely unknown whether and how these important clinical features, which may reflect etiologic heterogeneity or differential diagnostic practices and affect treatment and prognosis, differ from the general population of children with cancer. To address these questions, we analyzed data from approximately 15,000 childhood cancer cases from a large, multistate birth cohort of more than 10 million births, and we observed several striking differences in cancer diagnostic characteristics by birth defect status. More embryonal tumors and GCTs but fewer leukemias were diagnosed in children with birth defects. With few exceptions, we found that the distributions of tumor types were not markedly different between children with an isolated birth defect and children with multiple birth defects, although our prior work suggests that both the relative cancer risk and the absolute cancer risk are greater in children with multiple birth defects.[5]

Most epidemiological studies have examined the relative risk of cancer in children with birth defects in comparison with children without birth defects, and these report consistent associations between birth defects and embryonal, germ cell, and soft-tissue tumors, with mixed results for leukemia and lymphoma.[5,10,11,22] Fewer have presented data on the distribution of cancer diagnoses in children with birth defects. Collins et al[23] reported a lower relative frequency of leukemia in children with congenital heart disease in comparison with children without it (28% vs 36%) and a higher relative frequency of neuroblastoma (9.0% vs 6.7%). Wong-Siegel et al[13] reported larger proportions of central and peripheral nervous system tumors, soft-tissue sarcomas, and renal tumors in pediatric cancer patients with birth

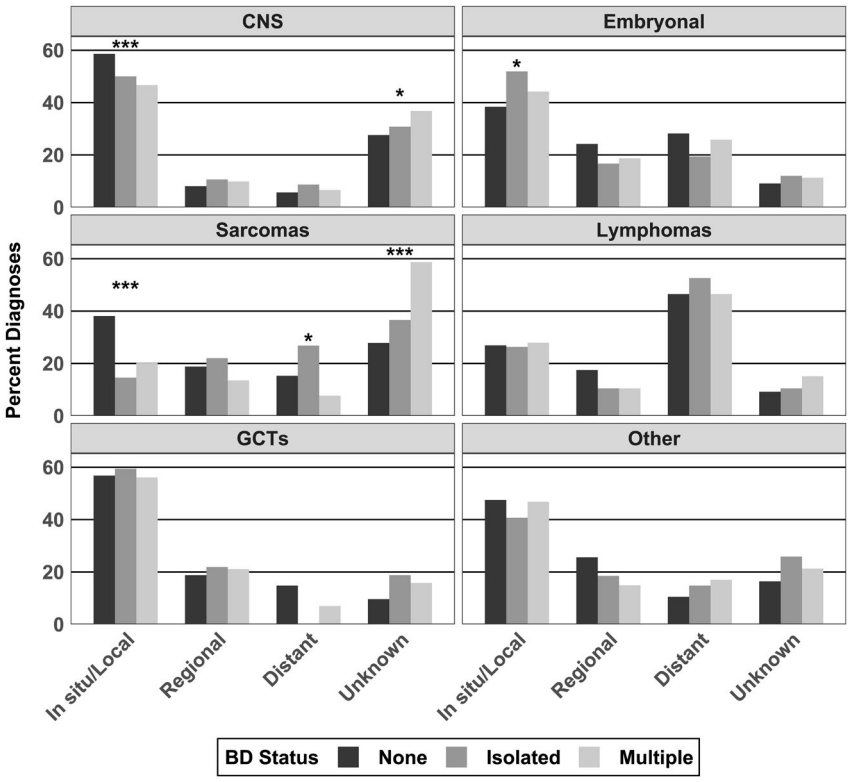

FIGURE 2. Surveillance, Epidemiology, and End Results summary stage for first cancer diagnosis by BD status. *$q < 0.05$; ***$q < 0.001$. BD indicates birth defect; CNS, central nervous system; GCT, germ cell tumor.

defects in comparison with those without birth defects. Agha et al[12] also reported that CNS tumors were more frequent in children with birth defects in comparison with those without birth defects, whereas lymphoma was less frequent, although these differences were not statistically significant. In contrast to our study and others, this group reported that leukemia constituted a larger percentage of cancer diagnoses in children with a birth defect.

The majority of the cancers evaluated were diagnosed at a younger median age among children with a birth defect versus children without a birth defect, and in age-stratified analyses, the most pronounced differences in tumor type were observed in children younger than 5 years. These findings are consistent with reports showing that the excess cancer risk associated with birth defects is greatest in young children.[6,8-10,12-14] A study of adolescents and young adults aged 15 to 25 years reported an elevated risk only for non-Hodgkin lymphoma in those with a nonchromosomal birth defect in comparison with those without a birth defect.[24] We did not observe a difference in the proportion of lymphoma diagnoses in children aged ≥10 years by birth defect status but did report a small increase in the proportion of intracranial GCTs. Collectively, these data suggest that cancer diagnostic characteristics in older children and adolescents with birth defects are similar to those of the general population without birth defects, although small distinctions may persist.

To investigate whether the younger age at cancer diagnosis in children with a birth defect could be due to differential medical care or increased cancer surveillance, we evaluated potential differences in the SEER stage at diagnosis by birth defect status. Specifically, we hypothesized that if differences in age at cancer diagnosis were the result of increased surveillance among children with birth defects, their cancers would more frequently be reported as localized or in situ in comparison with children without birth defects. We did not observe consistent evidence that children with a birth defect were more often diagnosed with localized or in situ tumors. Cancer surveillance is not routinely recommended for children with nonchromosomal structural birth defects, and a younger age at diagnosis was noted for cancers that are not considered amenable to surveillance, such as ALL and acute myeloid leukemia. These data suggest that differential medical

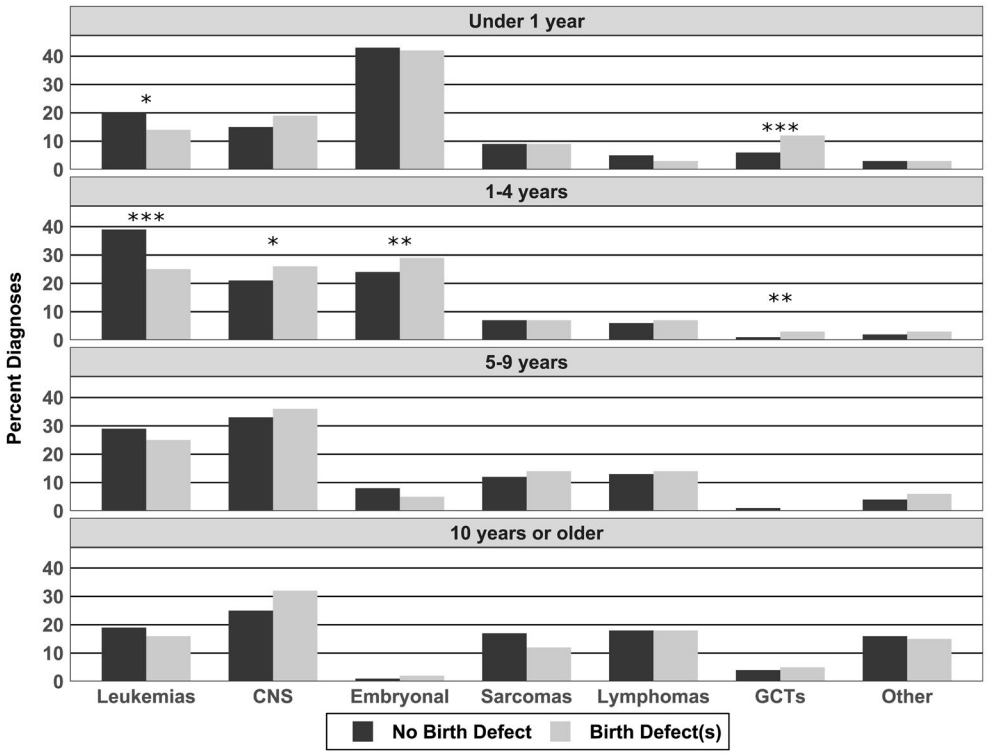

FIGURE 3. Age-stratified distributions of cancer diagnoses in children and adolescents according to birth defect status. *q < 0.05; **q < 0.005; ***q < 0.001. CNS indicates central nervous system; GCT, germ cell tumor.

care or screening in children with birth defects does not fully explain their younger age at cancer diagnosis.

The basis for the observed associations between birth defect status and SEER stage at diagnosis is unclear. Stage may be reported as unknown in instances when diagnostic tests are not performed because of contraindicating medical conditions or when the patient dies before diagnostic workup can be completed.[25] Children with congenital heart disease, the most common category of structural birth defects, are at increased risk for hospital-acquired infections and complications from anesthesia or surgery in comparison with the general pediatric population.[26-28] These concerns may discourage physicians from performing tests that are invasive or require general anesthesia. Differences in the clinical management or natural history of cancer between children with birth defects and children without birth defects may also affect these results. For example, biopsy and surgical resection are performed less frequently for brain tumor patients with neurofibromatosis type 1 than for children with sporadic brain tumors,[29,30] and Down syndrome is associated with an increased risk of mortality during the early phases of chemotherapy in children with ALL.[31,32] Further investigations are warranted to determine whether children with birth defects receive differential cancer diagnostic workup or treatment. Likewise, with the exception of children with Down syndrome and leukemia, the survival of children with cancer and birth defects has not been investigated.

It has been hypothesized that childhood cancers, particularly embryonal tumors and GCTs, could result from aberrant genetic or epigenetic control of fetal development and thus share a common etiology with birth defects.[6,33] Our observation that these tumors represent larger proportions of cancers in children with birth defects supports this hypothesis, as do other lines of evidence. For example, variants in *BRCA1* and *BRCA2* have recently been linked with nonsyndromic cleft lip and/or palate,[34] and sonic hedgehog (Shh) signaling, a critical regulator of CNS development, is used to define a molecular subtype of medulloblastoma.[35,36] Some studies report that maternal exposures that are associated with an increased risk of birth defects, such as in vitro fertilization, are also associated with small increases in the risk of some childhood cancers, such as hepatoblastoma.[37,38] However, a recent meta-analysis of 14 cohort studies

found no increased risk of cancer among children conceived with assisted reproductive technology or in vitro fertilization.[39] It is, therefore, possible that certain birth defect–cancer associations may be explained by exposures that are both teratogenic and carcinogenic, although this is unproven. Finally, it is well established that perinatal characteristics, particularly birthweight, differ between children with birth defects and children without birth defects. The lower mean birthweight of children with birth defects could explain the observed association with hepatoblastoma[40] as well as the lack of association with ALL.[41] Case-case designs such as this can be useful for understanding disease etiology,[15,42] but the current analysis is not intended to identify genetic and environmental exposures that may underlie birth defect–cancer associations, and further research is necessary in this area.

The use of data from a large, population-based birth cohort is a key strength of the current study. We have performed a comprehensive assessment of cancer diagnostic characteristics in children with birth defects by linking records from birth certificates, birth defect registries, and cancer registries for more than 10 million livebirths in 4 racially, ethnically, and geographically diverse US states. Because all participating registries are population-based, ascertainment of both birth defects and cancers during the study period should be nearly complete. In addition, both birth defects and cancer diagnoses were systematically recorded by trained registry staff using standardized coding systems, and this ensured complete, consistent, and high-quality data. Our large sample size permitted us not only to compare cancer diagnostic characteristics by birth defect status but also to describe the relationship of birth defect status with major childhood cancer types separately among children with an isolated birth defect versus children with multiple birth defects and within several age strata, and this has not been possible in previous investigations.

Our study also has potential limitations. Residential migration into or out of our study area is not measured. For example, our study sample does not capture cancer diagnoses among children who were born in our study area but moved out of state before their diagnosis. The potential impact of this limitation on our findings is difficult to assess and would require national registries to measure, and these resources currently do not exist. Birth defect registries do not systematically record minor birth defect diagnoses (eg, café au lait spots or skin tags); therefore, we were unable to investigate whether the cancer diagnostic profile differs in children with these conditions. Similarly, some cancer-associated syndromes such as WAGR syndrome and Beckwith-Wiedemann syndrome are not systematically recorded by registries, and affected children could not be identified. We were unable to evaluate the sources of information used to determine cancer stage, which may be informative in determining whether cancer diagnostic workup or survival differs among children with birth defects versus those without birth defects. We had a modest multiple testing burden in comparison with many epidemiological studies (eg, genome-wide or epigenome-wide association studies) and corrected for this by using the Benjamini-Hochberg procedure. However, the possibility of chance findings cannot be excluded.

These data suggest that children with nonchromosomal structural birth defects have a unique cancer diagnostic profile, including more frequent diagnoses of non-CNS embryonal tumors and GCTs, and a younger age at diagnosis in comparison with children without birth defects. Differences in tumor types were most apparent in infants and young children and were largely absent after 10 years of age. Children with a birth defect were not more likely to have localized or in situ tumors at diagnosis, and this suggests that increased surveillance does not fully explain the observed differences; however, they were more likely to have the stage reported as unknown in comparison with children without birth defects. It is possible that the latter finding reflects differences in cancer diagnostic practices or survival in children with birth defects. By providing a comprehensive overview of cancer diagnostic characteristics in children with birth defects, who represent approximately 3% of all livebirths in the United States, we hope to guide future research into childhood cancer etiology and surveillance. Specifically, by describing the distributions of tumor types and ages at cancer diagnosis in this population for the first time, this study may guide the identification of risk factors for childhood cancer. Similarly, this knowledge may help to suggest appropriate screening modalities and the ages at which children with birth defects might be surveilled. Our findings also raise the possibility of differential cancer diagnosis or survival in children with birth defects, topics that are almost wholly uninvestigated.

FUNDING SUPPORT

This study was funded by Alex's Lemonade Stand Foundation (Epidemiology Grant), the Cancer Prevention and Research Institute of Texas (RP140258, RP170071, and RP160097), and the National Cancer Institute (3P30CA125123-0851).

CONFLICT OF INTEREST DISCLOSURES

Wendy N. Nembhard reports grants from the Centers for Disease Control and Prevention, the March of Dimes, and the National Institutes of Health

outside the submitted work. Sharon E. Plon reports nonfinancial support from Baylor Genetics Laboratories outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jeremy M. Schraw: Conceptualization, data curation, formal analysis, methodology, visualization, writing–original draft, and writing–review and editing. **Tania A. Desrosiers:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Wendy N. Nembhard:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Peter H. Langlois:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Robert E. Meyer:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Mark A. Canfield:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Sonja A. Rasmussen:** Conceptualization, methodology, writing–original draft, and writing–review and editing. **Tiffany M. Chambers:** Data curation, writing–original draft, and writing–review and editing. **Logan G. Spector:** Methodology, supervision, visualization, writing–original draft, and writing–review and editing. **Sharon E. Plon:** Conceptualization, funding acquisition, writing–original draft, and writing–review and editing. **Philip J. Lupo:** Conceptualization, funding acquisition, methodology, supervision, writing–original draft, and writing–review and editing.

REFERENCES

1. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief*. 2018;328:1-8.
2. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88:1008-1016.
3. Carmichael SL. Birth defects epidemiology. *Eur J Med Genet*. 2014;57:355-358.
4. Kirby RS. The prevalence of selected major birth defects in the United States. *Semin Perinatol*. 2017;41:338-344.
5. Lupo PJ, Schraw JM, Desrosiers TA, et al. Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. *JAMA Oncol*. 2019;5:1150-1158.
6. Botto LD, Flood T, Little J, et al. Cancer risk in children and adolescents with birth defects: a population-based cohort study. *PLoS One*. 2013;8:e69077.
7. Fisher PG, Reynolds P, Von Behren J, Carmichael SL, Rasmussen SA, Shaw GM. Cancer in children with nonchromosomal birth defects. *J Pediatr*. 2012;160:978-983.
8. Bjorge T, Cnattingius S, Lie RT, Tretli S, Engeland A. Cancer risk in children with birth defects and in their families: a population based cohort study of 5.2 million children from Norway and Sweden. *Cancer Epidemiol Biomarkers Prev*. 2008;17:500-506.
9. Janitz AE, Neas BR, Campbell JE, et al. Childhood cancer in children with congenital anomalies in Oklahoma, 1997 to 2009. *Birth Defects Res A Clin Mol Teratol*. 2016;106:633-642.
10. Norwood MS, Lupo PJ, Chow EJ, et al. Childhood cancer risk in those with chromosomal and non-chromosomal congenital anomalies in Washington State: 1984-2013. *PLoS One*. 2017;12:e0179006.
11. Johnson KJ, Lee JM, Ahsan K, et al. Pediatric cancer risk in association with birth defects: a systematic review. *PLoS One*. 2017;12:e0181246.
12. Agha MM, Williams JI, Marrett L, To T, Zipursky A, Dodds L. Congenital abnormalities and childhood cancer. *Cancer*. 2005;103:1939-1948.
13. Wong-Siegel JR, Johnson KJ, Gettinger K, et al. Congenital neurodevelopmental anomalies in pediatric and young adult cancer. *Am J Med Genet A*. 2017;173:2670-2679.
14. Windham GC, Bjerkedal T, Langmark F. A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967-1980. *Am J Epidemiol*. 1985;121:49-56.
15. Martinez ME, Cruz GI, Brewster AM, Bondy ML, Thompson PA. What can we learn about disease etiology from case-case analyses? Lessons from breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2710-2714.
16. Malkin D, Nichols KE, Schiffman JD, Plon SE, Brodeur GM. The future of surveillance in the context of cancer predisposition: through the murky looking glass. *Clin Cancer Res*. 2017;23:e133-e137.
17. Canfield MA, Honein MA, Yuskiv N, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. *Birth Defects Res A Clin Mol Teratol*. 2006;76:747-756.
18. Clarkson DB, Fan YA, Joe H. A remark on algorithm 643: FEXACT: an algorithm for performing Fisher's exact test in r × c contingency tables. *ACM Trans Math Softw*. 1993;19:484-488.
19. Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in r × c contingency tables. *J Am Stat Assoc*. 1983;78:427-434.
20. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57:289-300.
21. Tulla M, Berthold F, Graf N, et al. Incidence, trends, and survival of children with embryonal tumors. *Pediatrics*. 2015;136:e623-e632.
22. Del Risco Kollerud R, Blaasaas KG, Claussen B, et al. Family history of cancer and the risk of childhood solid tumours: a Norwegian nationwide register-based cohort study. *Br J Cancer*. 2018;118:905-912.
23. Collins RT II, Von Behren J, Yang W, et al. Congenital heart disease complexity and childhood cancer risk. *Birth Defects Res*. 2018;110:1314-1321.
24. Von Behren J, Fisher PG, Carmichael SL, Shaw GM, Reynolds P. An investigation of connections between birth defects and cancers arising in adolescence and very young adulthood. *J Pediatr*. 2017;185:237-240.
25. Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, eds. SEER Summary Staging Manual—2000: Codes and Coding Instructions. National Cancer Institute; 2001.
26. White MC, Peyton JM. Anaesthetic management of children with congenital heart disease for non-cardiac surgery. *Contin Educ Anaesth Crit Care Pain*. 2011;12:17-22.
27. Przybylski R, Hedequist DJ, Nasr VG, et al. Adverse perioperative events in children with complex congenital heart disease undergoing operative scoliosis repair in the contemporary era. *Pediatr Cardiol*. 2019;40:1468-1475.
28. Geskey JM, Cyran SE. Managing the morbidity associated with respiratory viral infections in children with congenital heart disease. *Int J Pediatr*. 2012;2012:646780-646780.
29. Packer RJ, Iavarone A, Jones DTW, et al. Implications of new understandings of gliomas in children and adults with NF1: report of a consensus conference. *Neuro Oncol*. Published online February 14, 2020. doi:10.1093/neuonc/noaa036
30. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol*. 2017;19:750-761.
31. Buitenkamp TD, Izraeli S, Zimmermann M, et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood*. 2014;123:70-77.
32. Pennella CL, Rossi JG, Baialardo EM, et al. Acute lymphoblastic leukemia in children with Down syndrome: comparative analysis versus patients without Down syndrome. *Arch Argent Pediatr*. 2018;116:e500-e507.
33. Maguire LH, Thomas AR, Goldstein AM. Tumors of the neural crest: common themes in development and cancer. *Dev Dyn*. 2015;244:311-322.
34. Rodriguez N, Maili L, Chiquet BT, Blanton SH, Hecht JT, Letra A. BRCA1 and BRCA2 gene variants and nonsyndromic cleft lip/palate. *Birth Defects Res*. 2018;110:1043-1048.
35. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012;123:465-472.
36. De Luca A, Cerrato V, Fuca E, Parmigiani E, Buffo A, Leto K. Sonic hedgehog patterning during cerebellar development. *Cell Mol Life Sci*. 2016;73:291-303.
37. Spector LG, Brown MB, Wantman E, et al. Association of in vitro fertilization with childhood cancer in the United States. *JAMA Pediatr*. 2019;173:e190392.
38. Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies and the risk of birth defects. *N Engl J Med*. 2012;366:1803-1813.

39. Gilboa D, Koren G, Barer Y, et al. Assisted reproductive technology and the risk of pediatric cancer: a population based study and a systematic review and meta analysis. *Cancer Epidemiol*. 2019;63:101613.
40. Spector LG, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer*. 2012;59:776-779.
41. Milne E, Greenop KR, Metayer C, et al. Fetal growth and childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium (CLIC). *Int J Cancer*. 2013;133:2968-2979.
42. Prentice RL, Vollmer WM, Kalbfleisch JD. On the use of case series to identify disease risk factors. *Biometrics*. 1984;40:445-458.