Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births

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IMPORTANCE Birth defects affect approximately 1 in 33 children. Some birth defects are known to be strongly associated with childhood cancer (eg, trisomy 21 and acute leukemia). However, comprehensive evaluations of childhood cancer risk in those with birth defects have been limited in previous studies by insufficient sample sizes.

OBJECTIVES To identify specific birth defect–childhood cancer (BD-CC) associations and characterize cancer risk in children by increasing number of nonchromosomal birth defects.

DESIGN, SETTING, AND PARTICIPANTS This multistate, population-based registry linkage study pooled statewide data on births, birth defects, and cancer from Texas, Arkansas, Michigan, and North Carolina on 10 181 074 children born from January 1, 1992, to December 31, 2013. Children were followed up to 18 years of age for a diagnosis of cancer. Data were retrieved between September 26, 2016, and September 21, 2017, and data analysis was performed from September 2, 2017, to March 21, 2019.

EXPOSURES Birth defects diagnoses (chromosomal anomalies and nonchromosomal birth defects) recorded by statewide, population-based birth defects registries.

MAIN OUTCOMES AND MEASURES Cancer diagnosis before age 18 years, as recorded in state cancer registries. Cox regression models were used to generate hazard ratios (HRs) and 95% CIs to evaluate BD-CC associations and the association between number of nonchromosomal defects and cancer risk.

RESULTS Compared with children without any birth defects, children with chromosomal anomalies were 11.6 (95% CI, 10.4-12.9) times more likely to be diagnosed with cancer, whereas children with nonchromosomal birth defects were 2.5 (95% CI, 2.4-2.6) times more likely to be diagnosed with cancer before 18 years of age. An increasing number of nonchromosomal birth defects was associated with a corresponding increase in the risk of cancer. Children with 4 or more major birth defects were 5.9 (95% CI, 5.3-6.4) times more likely to be diagnosed with cancer compared with those without a birth defect. In the analysis of 72 specific BD-CC patterns, 40 HRs were statistically significant (adjusted $P < .05$) after accounting for multiple comparisons. Cancers most frequently associated with nonchromosomal defects were hepatoblastoma and neuroblastoma.

CONCLUSIONS AND RELEVANCE Several significant and novel associations were observed between specific birth defects and cancers. Among children with nonchromosomal birth defects, the number of major birth defects diagnosed was significantly and directly associated with cancer risk. These findings could inform clinical treatment for children with birth defects and may elucidate mechanisms that lead to these complex outcomes.

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Globally, more than 250 000 children are diagnosed with cancer annually,[1] and in the United States, cancer remains the leading cause of death by disease in persons younger than 20 years.[2] Being born with a birth defect is one of the strongest known risk factors for cancer in children.[3] For example, children with trisomy 21 have a 20-fold increased risk of acute lymphoblastic leukemia (ALL).[4,5] Whereas the association between chromosomal anomalies and cancer is recognized, a growing number of studies indicate that children with nonchromosomal birth defects may also be at increased risk of developing cancer.[4,6-14]

Despite the recognized association between birth defects and childhood cancers in general, the ability to identify associations between specific birth defects (eg, craniosynostosis) and specific cancer subtypes (eg, hepatoblastoma) has been limited in previous studies by insufficient sample size given the relative infrequency of these diagnoses.[4,7,9,14,15] In addition, findings from previous studies suggest there may be an association between the number of birth defects per child and cancer risk,[14-16] but larger populations are needed to better investigate the extent to which having multiple birth defects is associated with increased risk. The identification of birth defect–childhood cancer (BD-CC) patterns contributes to our understanding of potentially shared origins,[6,7] and the identification of previously unrecognized Mendelian disorders and may inform cancer surveillance or screening strategies for children with certain birth defects. To address this need, we established a diverse population-based birth cohort of more than 10 million births for January 1, 1992, to December 31, 2013, by pooling statewide data on births, birth defects, and cancer from Texas, Arkansas, Michigan, and North Carolina. We aimed to estimate cancer risk in children with chromosomal anomalies and nonchromosomal birth defects; identify novel and confirm previously reported BD-CC patterns; and evaluate whether cancer risk changes as the number of birth defects per child increases.

Key Points

Question What are the associations between specific birth defects and specific childhood cancers?

Findings In a large population-based registry study of more than 10 million children in 4 states, assessment of cancer risk among children with birth defects identified, 40 specific birth defect–childhood cancer associations were identified that were statistically significant, including several novel associations. Cancer risk increased with an increasing number of major nonchromosomal birth defects.

Meaning Children with nonchromosomal birth defects have an increased relative risk of cancer, although the absolute risk remains low at less than 1%.

Methods

Study Design and Participants

Three data linkages were performed in each state: (1) birth defects registry to birth certificates; (2) cancer registry to birth certificates; and (3) birth defects registry to corresponding cancer registry. Linkages yielded 4 study groups: (1) children without a birth defect or cancer; (2) children with a birth defect but without cancer; (3) children without a birth defect but with cancer; and (4) children with both a birth defect and cancer. This study was approved by following regulatory bodies: Baylor College of Medicine institutional review board (IRB); Texas Department of State Health Services IRB; North Carolina Division of Public Health IRB; University of North Carolina Chapel Hill IRB; Arkansas Department of Health Scientific Advisory Committee; University of Arkansas for Medical Sciences IRB; and Michigan Department of Health and Human Services IRB. A waiver of consent was granted by the IRBs of all participating institutions because the study used existing, deidentified public health data and recontact of participants to obtain informed consent would not be possible given the scope of the study.

Birth Certificate Data

The study included all recorded live births in Texas from January 1, 1999, to December 31, 2013 (n = 5 742 007); in Arkansas from January 1, 1995, to December 31, 2011 (n = 629 086); in Michigan from January 1, 1992, to December 31, 2011 (n = 2 570 403); and in North Carolina from January 1, 2003, to December 31, 2012 (n = 1 239 578). Differences in study years reflect availability of data from state-specific registries. Demographic data, including self-reported maternal race/ethnicity, were obtained from birth certificates. Data were retrieved between September 26, 2016, and September 21, 2017, and data analysis was performed from September 2, 2017, to March 21, 2019.

Birth Defects Ascertainment

Birth defects surveillance systems in Texas, Arkansas, and North Carolina employ active ascertainment methods to identify infants and pregnancies with birth defects; passive ascertainment methods are used in Michigan. These methods have been described previously.[4,17-21] Diagnoses were coded using the Centers for Disease Control and Prevention modification of the British Paediatric Association Classification of Diseases and the World Health Organization's *International Classification of Diseases, Ninth Revision, Clinical Modification*. Specific birth defects included in analyses were major birth defects[19,20] included as part of the National Birth Defects Prevention Network annual report[17] or the National Birth Defects Prevention Study.[19]

Childhood Cancer Ascertainment

Data on cancer site, morphologic features, behavior, and age at diagnosis were obtained from population-based cancer registries of the participating states. All these registries follow the standards of the National Program of Cancer Registries within the Centers for Disease Control and Prevention and are certified as to the completeness, timeliness, and quality of their data by the North American Association of Central Cancer Registries.[22]

The childhood cancer cases identified across the 4 states were coded into 12 major groups according to the *International Classification of Childhood Cancer*, third edition. The classification schema used is publicly available (https://seer.cancer.gov/iccc/iccc3_ext.html). Children diagnosed at younger than

18 years are included in the analysis. In the subset of 235 children with more than 1 cancer diagnosis, only the first primary cancer was considered.

Record Linkage

Individual records in the assembled birth cohort were linked across data sources using both deterministic and probabilistic linkage procedures by investigators from each participating state: Texas, M.A.C. and P.H.L.; Michigan, G.C.; North Carolina, T.A.D. and R.E.M.; and Arkansas, W.N.N. At least 95% of birth defect diagnoses and more than 75% of childhood cancer diagnoses across the cohort were matched to birth certificates.[4,21,23] Linked data were then deidentified and provided to the primary investigators (P.J.L., J.M.S., with assistance with data cleaning and processing), who systematically cleaned and coded the data across states for analysis.

Statistical Analysis

Summary statistics describing the number of births, birth defects, and cancer diagnoses were calculated overall and by state (eTable 1 in the Supplement). Subsequent analyses were conducted separately among children with nonchromosomal defects (ie, children with no syndromic diagnosis [514 140], chromosomal anomalies [21 861], or single-gene disorders if indicated [3566]), with each group compared with the reference group of 9 641 507 children without a birth defect.

Owing to concern that the proportional hazards assumption might be violated,[7] we evaluated Cox, Weibull, and log logistic regression models for time-to-event analyses. Because there were no differences across models (eTable 2 and eTable 3 in the Supplement), we computed Cox regression models to generate hazard ratios (HRs) and 95% CIs for each BD-CC combination to be consistent with previous assessments.[4,9,15] To comply with state data-suppression rules, measures of association were only computed when there were 5 or more cases of a BD-CC combination (resulting in 600 pairwise associations; eTable 4 in the Supplement). We also computed models for risk of any cancer, any malignant hematologic neoplasm, any central nervous system (CNS) tumor, and any non-CNS solid tumor according to the number of major nonchromosomal defects present. Person-years were calculated as time from birth to death, cancer diagnosis, or end of the study period in those alive without cancer (December 31, 2011, in Arkansas and Michigan; December 31, 2012, in North Carolina; and December 31, 2013, in Texas). Covariates evaluated in all models included maternal age, child sex, state of birth, and maternal race/ethnicity.[24] In addition, models for hepatoblastoma, Wilms tumor, and ALL were adjusted for birth weight because of the well-established associations of these cancers compared with others (ie, risk for ALL and Wilms tumor risk increase in parallel with birth weight, whereas hepatoblastoma risk decreases as birth weight increases).[25-27] Finally, models including ventricular septal defects, atrial septal defects, or patent ductus arteriosus were adjusted for birth weight and gestational age in sensitivity analyses because of the known associations of preterm birth with these cardiac phenotypes.[19]

We focused our reporting of specific BD-CC associations on those that were statistically significant after accounting for multiple comparisons. To identify these, we computed Bonferroni-Holm adjusted *P* values for birth defect variables in the subset of models from eTable 4 in the Supplement, which reported HRs for a specific cancer (N = 72 BD-CC associations) to fix the family-wise error rate at $\alpha = .05$. Statistical analyses were performed in R version 3.3.3 using the *survival*, *ggplot2*, and *survminer* packages (The R Foundation for Statistical Computing). Associations between specific birth defects and specific childhood cancers were deemed statistically significant if their *P* value was below the critical value established by the Bonferroni-Holm multiple testing correction procedure. All *P* values were 2-sided.

Results

The numbers of births, diagnoses of birth defects, diagnoses of cancer, and diagnoses of both a birth defect and cancer (ie, co-occurring diagnoses) are presented in **Table 1**. Median length of follow-up was 8.5 years among children without birth defects and 8.1 years among children with birth defects. Overall, more than 530 000 children were diagnosed with at least 1 birth defect in our assessment. Compared with children without birth defects, those with chromosomal anomalies were 11.6 (95% CI, 10.4-12.9) times more likely to be diagnosed with any cancer in childhood or adolescence (**Table 2**). All chromosomal anomalies (ie, trisomy 13, 18, 21, and Turner syndrome) and all single-gene disorders with specific diagnostic codes included in these birth defects registries (ie, neurofibromatosis and tuberous sclerosis) were associated with an increased risk of cancer. In addition, after excluding those 2 groups (ie, those with any chromosomal anomalies or single-gene disorders), children with nonchromosomal birth defects were 2.5 (95% CI, 2.4-2.6) times more likely to be diagnosed with cancer (Table 2). All final models were adjusted for

Table 1. Distribution of Births, Birth Defects, and Cancer by State

Characteristic	No. (%)				
	Texas	Arkansas	Michigan	North Carolina	Total
Birth years	1999-2013	1995-2011	1992-2011	2003-2012	1992-2013
Births[a]	5 742 007 (56.4)	629 086 (6.2)	2 570 403 (25.2)	1 239 578 (12.2)	10 181 074
Birth defects[b]	251 516 (4.4)	23 341 (3.7)	224 026 (8.7)	40 684 (3.3)	539 567
Age cutoff for birth defects diagnoses, y	1	2	2	1	NA
Cancer[c]	8649 (0.2)	1037 (0.2)	4099 (0.2)	1325 (0.1)	15 110
Co-occurring birth defect and cancer, No.[d]	917	75	1012	119	2123

Abbreviation: NA, not applicable.

[a] Percentage of total births in the assembled study cohort.

[b] Number and percentage of children in the cohort diagnosed with any chromosomal anomaly, single-gene disorder, or nonchromosomal birth defect.

[c] Percentage of total births within state.

[d] Co-occurring birth defect and cancer.

maternal age, child sex, and state of birth, because additional variables (ie, maternal race/ethnicity and plurality) did not influence BD-CC associations (eTable 5 in the Supplement). We further stratified our results by race/ethnicity and observed similar associations across all groups (eTable 6 in the Supplement). Nonchromosomal defects most strongly associated with cancer diagnosis included biliary atresia and spina bifida (Table 2; eTable 7 in the Supplement). The risk of specific cancers among children with any chromosomal anomaly and among children with any nonchromosomal birth defect is presented in eTable 8 in the Supplement.

We observed that as the number of major nonchromosomal birth defects per child increased, the risk of cancer also increased, with markedly greater risks among children with 2 or more major birth defects (**Figure 1**). This was true for any childhood cancer (Figure 1A) or when separately analyzed for hematologic cancers (Figure 1B), CNS tumors (Figure 1C), or non-CNS tumors (Figure 1D) (*P* for trend < .001 for each). Overall, children with 4 or more major birth defects were 5.9 (95% CI, 5.3-6.4) times more likely to be diagnosed with cancer than children without a birth defect. By evaluating the associations between specific cancer types and groups of birth defects, we made certain observations (**Figure 2**). For example, bone tumors were not associated with birth defects. In addition, some cancers, such as ALL, were associated with a few categories of birth defects, whereas others, such as germ cell tumors, were associated with defects in multiple organ systems.

Forty of the 72 BD-CC associations remained statistically significant after Bonferroni-Holm correction and adjustment for maternal age, child sex, state, and birth weight (**Table 3** includes the top 25 associations, and eTable 9 in the Supplement includes all statistically significant associations). There were 5 specific associations between chromosomal anomalies or single-gene disorders and childhood cancers (Table 3): hepatoblastoma among children with trisomy 18; ALL and acute myeloid leukemia among children with trisomy 21; and astrocytoma and nonrhabdomyosarcoma soft-tissue sarcoma among children with neurofibromatosis. Thirty-five of the BD-CC associations included nonchromosomal defects. For example, children with several forms of nonchromosomal congenital heart disease had an increased risk of hepatoblastoma and neuroblastoma. These associations remained consistent and statistically significant when also adjusting for gestational age in models that included congenital heart disease phenotypes associated with preterm birth (data not shown). Hydrocephaly and obstructive genitourinary defects were each associated with risk of multiple cancers. Notably, hydrocephaly (a CNS congenital anomaly) was associated with 2 CNS tumors, astrocytoma and ependymoma. To address the potential of hydrocephaly secondary to cancers diagnosed within the first year of life, we restricted analyses to children diagnosed with hydrocephaly when younger than 1 year and with their tumor at older than 1 year; these associations remained statistically significant (eTable 10 in the Supplement).

Table 2. Hazard Ratios and 95% CIs for Diagnosis of Any Cancer Among Children With Selected Chromosomal Anomalies, Single-Gene Disorders, and Nonchromosomal Birth Defects

Birth Defect	Co-occurring Cases, No.	HR (95% CI)[a]
Chromosomal Anomalies		
Any chromosomal anomalies	337	11.6 (10.4-12.9)
Trisomy 13	7	6.1 (2.9-12.8)
Trisomy 18	9	5.2 (2.7-10.0)
Trisomy 21	264	14.7 (13.0-16.7)
Turner syndrome	6	5.1 (2.3-11.3)
Single-gene disorders		
Tuberous sclerosis	10	2.3 (1.2-4.3)
Neurofibromatosis	38	54.1 (39.3-74.4)
Nonchromosomal Birth Defects		
Any nonchromosomal birth defect	1738	2.5 (2.4-2.6)
Congenital anomalies of the central nervous system	229	4.9 (4.3-5.5)
Spina bifida without anencephaly	30	6.6 (4.6-9.4)
Hydrocephaly without spina bifida	77	6.9 (5.5-8.6)
Microcephaly	32	3.0 (2.1-4.2)
Holoprosencephaly	18	4.2 (2.7-6.7)
Congenital anomalies of the eye	115	4.2 (3.5-5.0)
Anopthalmia or micropthalmia	12	4.9 (2.8-8.5)
Congenital cataract	12	4.2 (2.4-7.4)
Congenital anomalies of the respiratory system	250	2.9 (2.6-3.3)
Choanal atresia	11	6.3 (3.5-11.3)
Congenital anomalies of the heart and circulatory system	443	2.4 (2.2-2.6)
Right ventricular outflow tract defects	43	3.1 (2.3-4.1)
Pulmonary valve atresia and stenosis	42	3.2 (2.4-4.3)
Congenital anomalies of the digestive system	217	3.2 (2.8-3.7)
Hirschsprung disease	10	3.6 (2.0-6.7)
Biliary atresia	18	14.0 (8.8-22.2)
Congenital anomalies of the genitourinary system	350	2.3 (2.0-2.5)
Renal agenesis and hypoplasia	24	3.5 (2.3-5.2)
Obstructive genitourinary defects	122	2.9 (2.4-3.5)
Hypospadias	46	1.5 (1.1-1.9)
Congenital anomalies of the musculoskeletal system	389	2.1 (1.9-2.3)
Limb-reduction deformities	19	3.3 (2.1-5.1)
Upper-limb reduction deformities	13	3.4 (2.0-5.9)
Lower-limb reduction deformities	8	4.0 (2.0-8.0)
Omphalocele	8	6.0 (3.0-12.0)
Congenital anomalies of the integument[b]	90	3.9 (3.2-4.8)

Abbreviation: HR, hazard ratio.

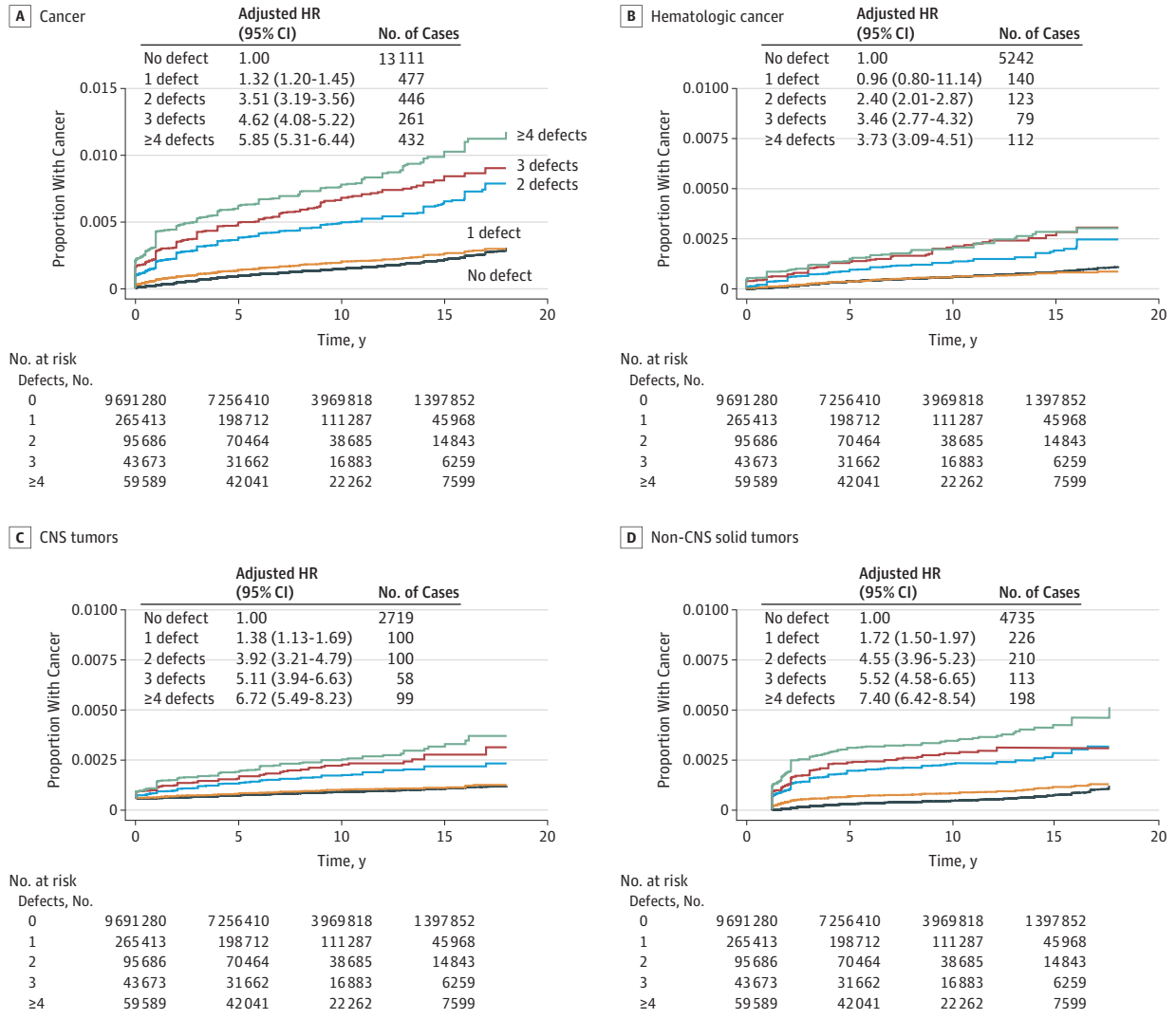
[a] All HRs are adjusted for maternal age, child sex, and state of birth.

[b] Includes Centers for Disease Control and Prevention modification of the British Paediatric Association Classification of Diseases codes in the 757.0 to 757.9 range, or corresponding World Health Organization *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Discussion

In this population-based cohort of more than 10 million births across 4 racially and ethnically diverse US states, we observed that children with chromosomal anomalies, as well as

Figure 1. Risk of Selected Cancers According to Number of Major Birth Defects in Children Without Chromosomal Anomalies or Single-Gene Syndromes



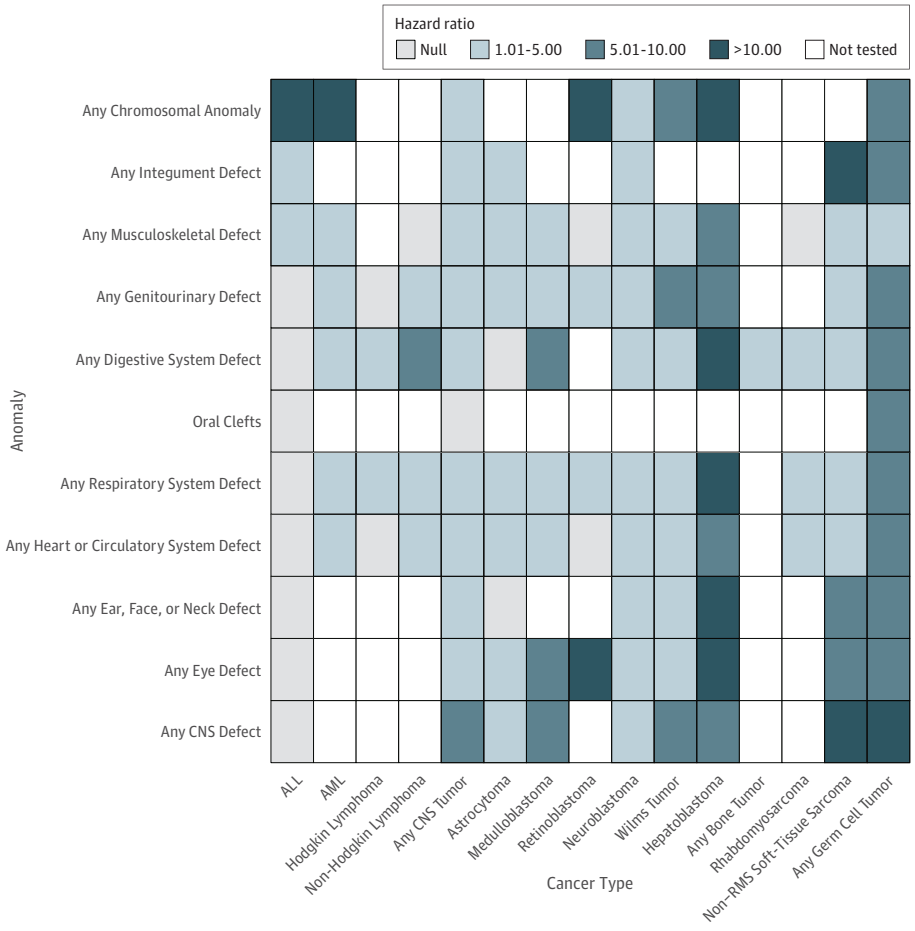
Panels show cumulative incidence and hazard ratios from Cox proportional hazard models (tables, inset) for risk of (A) any cancer, (B) any hematologic cancer, (C) any central nervous system (CNS) tumor, and (D) any non-CNS solid tumor. All hazard ratios are adjusted for maternal age, child sex, and state of birth. HR indicates hazard ratio.

children with nonchromosomal birth defects, were more likely to be diagnosed with cancer than unaffected children. Notably, some of these associations were for cancers that are not typically considered part of cancer predisposition syndromes (eg, germ cell tumors; Figure 2), which could inform clinical review among these patients. Based on our findings and the overall prevalence of birth defects, approximately 9.2% of childhood cancers could be attributed to these conditions. However, the overall absolute risk of cancer in children with any birth defect is less than 1%. These estimates of absolute risk are much lower than for those with known single-gene cancer predisposition syndromes (eg, 15% cancer risk in *TP53*-associated Li-Fraumeni syndrome), because the genetic factors underlying birth defects are heterogenous.

Cancer Risk in Children With Chromosomal Anomalies

Our large study population allowed us to estimate the magnitude of risks between several chromosomal anomalies and childhood cancer with better precision. For example, although there have been case reports of hepatoblastoma[28-30] and Wilms tumor[31] among children with trisomy 18, we were able to provide what is to our knowledge the first population-based estimate of the association between trisomy 18 and hepatoblastoma (HR, 79.1; 95% CI, 27.7-226.2). In addition, although the association between trisomy 18 and Wilms tumor was not included in Table 3 owing to the number of co-occurring cases (ie, <5), there was also an association (HR, 51.2; 95% CI, 16.2-161.9) similar to hepatoblastoma. The absolute risk of cancer in children with chromosomal anomalies was highest for

Figure 2. Relative Risk of Selected Cancers for Children With Birth Defects, Grouped by Organ System



All associations except those identified as null or not tested were significant at $P < .05$ (97 of 165 potential comparisons).
AML indicates acute myeloid leukemia; CNS, central nervous system; RMS, rhabdomyosarcoma.

ALL among those with trisomy 21 (0.9%; eTable 11 in the Supplement).

Cancer Risk in Children With Nonchromosomal Birth Defects

We observed that an increasing number of major nonchromosomal birth defects were associated with an increasing risk of developing cancer independent of the category of cancer (hematologic cancers, CNS tumors, and non-CNS solid tumors). The risk increased particularly among those with 2 or more birth defects, although the absolute risk of developing cancer remains less than 1% in children with 4 or more major birth defects, because childhood cancer is a rare outcome (eTable 12 in the Supplement). The patterns of children with multiple birth defects and cancer identified through this study indicate the possibility of undiagnosed or as-yet-unrecognized cancer predisposition syndromes.[13]

Because of our sample size, we were able to conduct novel analyses of specific BD-CC associations, overcoming a limitation of previous registry linkage studies.[4,6,7,15] The cancers most frequently associated with nonchromosomal defects were hepatoblastoma and neuroblastoma. This finding is consistent with previous hypotheses that embryonal tumors could be associated with developmental disruptions rather than with carcinogenic exposures, thereby sharing pathophysiologic features with birth defects.[8,15] To our knowledge, few studies to date have evaluated shared pathways between these birth defects and embryonal tumors, and only a few syndromes associated with birth defects (eg, Beckwith-Wiedemann syndrome) are known to be associated with an increased risk of certain embryonal tumors (eg, hepatoblastoma).[27,28]

Hepatoblastoma has been reported in other studies of cancer risk among children with birth defects.[9,13,15] In a combined report by the Children's Oncology Group and the Utah Population Database, genitourinary defects were associated with hepatoblastoma.[28] This association was also reported in an independent study using data from Washington State.[14] In these studies,[14,28] congenital heart disease overall was also associated with hepatoblastoma, consistent with our findings that 4 different cardiac phenotypes were associated with hepatoblastoma risk. As noted, the mechanisms underlying these associations are unclear; however, these patterns could represent previously unidentified developmental disorders.[8,14,28]

Four of the 6 specific birth defect–neuroblastoma associations involved cardiac phenotypes. Although associations between congenital heart disease and neuroblastoma have been previously reported,[8,32] results have been equivocal.[33] This could

Table 3. Hazard Ratios and 95% CIs for the Top 25 Statistically Significant Specific Birth Defect–Specific Childhood Cancer Associations

Birth Defect[a]	Cancer[b]	Co-occurring, No.	HR (95% CI)
Chromosomal Anomalies and Single-Gene Disorders			
Trisomy 21	Acute lymphoblastic leukemia	116	27.8 (22.8-33.8)
Trisomy 21	Acute myeloid leukemia	85	124.8 (97.6-159.6)
Trisomy 18	Hepatoblastoma	5	79.1 (27.7-226.2)
Neurofibromatosis	Astrocytoma	18	301.5 (189.1-480.8)
Neurofibromatosis	Non-rhabdomyosarcoma soft tissue sarcomas	8	241.1 (119.8-484.9)
Nonchromosomal Birth Defects			
Congenital anomalies of the nervous system			
Spina bifida without anencephaly	Non-rhabdomyosarcoma soft tissue sarcomas	16	75.6 (46.0-124.3)
Hydrocephaly without spina bifida	Astrocytoma	9	8.5 (4.2-17.0)
Hydrocephaly without spina bifida	Ependymoma	5	23.6 (9.7-57.3)
Hydrocephaly without spina bifida	Epithelial neoplasms	6	12.1 (5.4-27.0)
Congenital anomalies of the heart and circulatory system			
Left ventricular outflow tract defects	Neuroblastoma	6	7.8 (3.5-17.3)
Pulmonary valve atresia and stenosis	Hepatoblastoma	5	22.6 (9.1-55.7)
Ventricular septal defect	Hepatoblastoma	15	10.6 (5.8-19.2)
Atrial septal defect	Hepatoblastoma	21	8.1 (4.8-13. 7)
Atrial septal defect	Neuroblastoma	33	3.6 (2.6-5.1)
Patent ductus arteriosus	Hepatoblastoma	12	12.2 (6.6-22.8)
Patent ductus arteriosus	Neuroblastoma	19	3.9 (2.5-6.2)
Congenital anomalies of the digestive system			
Pyloric stenosis	Medulloblastoma	5	6.4 (2.7-15.6)
Biliary atresia	Non-Hodgkin lymphoma	7	164.2 (77.8-346.8)
Congenital anomalies of the genitourinary system			
Renal agenesis and hypoplasia	Wilms tumor	7	20.2 (9.0-45.1)
Obstructive genitourinary defects	Extracranial germ cell tumors	9	34.9 (17.5-69.6)
Obstructive genitourinary defects	Hepatoblastoma	10	8.8 (4.3-18.3)
Obstructive genitourinary defects	Neuroblastoma	17	4.6 (2.8-7.4)
Obstructive genitourinary defects	Non-rhabdomyosarcoma soft-tissue sarcomas	11	6.1 (3.3-11.0)
Congenital anomalies of the musculoskeletal system			
Congenital hip dislocation	Extracranial germ cell tumors	6	51.2 (22.3-117.8)
Craniosynostosis	Hepatoblastoma	8	9.7 (4.3-22.2)

Abbreviations: BD-CC, birth defect-childhood cancer; HR, hazard ratio.

[a] All BD-CC associations are significant after Bonferroni-Holm correction at a family-wise error rate of α = .05.

[b] All models are adjusted for maternal age, child sex, and state of birth. Models for acute lymphoblastic leukemia, Wilms tumor, and hepatoblastoma are also adjusted for birth weight.

be owing to heterogeneity among individual congenital heart disease phenotypes and the different origins (and potential cancer associations) therein.[34] The association between congenital heart disease and neuroblastoma is biologically plausible because neural crest–derived cells are essential in cardiac development,[34] and neuroblastoma originates from embryonal neural crest–derived cells.[33] Neural crest cells play an important role in the septation of the outflow tract of the heart,[35] which is consistent with the associations we observed specifically between ventricular outflow tract defects and neuroblastoma.

Another novel finding of our study was the observation of increased cancer risk in children with craniosynostosis. Previous population-based studies have not reported increased cancer risk in children with craniosynostosis,[4,6,7,9,12,13] possibly owing to its low birth prevalence (6.3 per 10 000 live births).[18] In the study by Botto et al,[36] there was a nonsignificantly increased risk of any cancer among children with craniosynostosis. Craniosynostosis is not a characteristic birth defect in common cancer predisposition syndromes other than rare *RECQL4*-associated disorders. There are some case reports suggesting associations between craniosynostosis and hepatoblastoma,[37] Wilms tumor,[38] medulloblastoma,[39] and neuroblastoma.[40] Notably, fibroblast growth factor receptor (*FGFR*) genes have been implicated in the development of craniosynostosis[41] and it is suspected that they play a role in some childhood cancers.[41,42] If validated, our findings may implicate genes related to craniofacial development in cancer risk.[43]

Finally, the association observed between biliary atresia and non-Hodgkin lymphoma may be attributable to liver transplant, immunosuppressive therapy, and subsequent lymphoma risk,[44] underscoring the potential role of nongenetic exposures in certain BD-CC associations.

Limitations

Several limitations must be considered. Although procedures for cancer registries are consistent across states, there is less uniformity in birth defect surveillance procedures.[17] To address differences by case ascertainment methodology (active vs passive), we evaluated the risk of specific cancers for children with birth defects in Texas (active) and Michigan (passive) separately and found consistent associations across these states (eTable 13 in the Supplement). Another potential concern is that during the diagnostic evaluation of children with cancer, birth defects may also be identified. To address this, we evaluated the associations restricted to children diagnosed with a birth defect at younger than 1 year and with cancer at older than 1 year in Texas and North Carolina (states only ascertaining birth defects through the first year of life). Twelve of the 13 BD-CC associations with 5 or more co-occurring diagnoses remained statistically significant, suggesting that ascertainment bias in children with cancer does not fully explain the observed associations (eTable 14 in the Supplement). Owing to limitations in linkage procedures, children who migrated away from their state of birth would be lost to follow-up; therefore, data from these children would not be appropriately censored or identified if they subsequently were diagnosed with cancer. However, data from our group suggest that there is nondifferential migration based on the presence or absence of a birth defect,[45] which limits the possibility of differential misclassification.

Conclusions

Using a large and diverse population-based cohort, our results demonstrate precise estimates of cancer risk in children with chromosomal anomalies and nonchromosomal birth defects and observed that cancer risk increased with the number of birth defects reported per child. We described several novel BD-CC associations, including craniosynostosis and hepatoblastoma; pyloric stenosis and medulloblastoma; and several different cardiac phenotypes and neuroblastoma. The BD-CC patterns observed in our study may represent novel cancer predisposition syndromes. If further validated, our results may inform cancer surveillance protocols for early tumor detection in children with specific birth defects. Future studies should evaluate the molecular features of children with co-occurring birth defects and cancers to further elucidate the mechanisms that lead to these complex outcomes.

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