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Cancer Risk by Attained Age among Children with Birth Defects in Arkansas

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Abstract

Background: Few studies have evaluated associations between birth defects and risk of pediatric cancers by age of attainment. Therefore, we assessed the risk of cancer among children with and without birth defects by age at attainment.

Methods: We examined cancer risk in children ≤14 years with and without birth defects born between 1996 and 2011 by linking data from the Arkansas Reproductive Health Monitoring System, Arkansas Central Cancer Registry, and birth certificates. Age of attainment for cancer was calculated as person-years from birth to cancer diagnosis, death, or end of study period, whichever occurred first. Using Cox proportional hazards models, we evaluated associations by attained age groups (<1, 1-4, 5-9, and 10-14 years) between: (1) groups of birth defects (any, chromosomal, and non-chromosomal) and any cancer; (2) non-chromosomal birth defects by organ system and any cancer; and (3) non-chromosomal birth defects and subtypes of cancer.

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CRediT authorship contribution statement

Jenil Patel: Conceptualization, Investigation, Data curation, Formal analysis, Writing - original draft. **Jeremy M. Schraw:** Resources, Data curation, Validation, Writing - review & editing. **Philip J. Lupo:** Methodology, Funding acquisition, Investigation, Writing - review & editing. **Amir Mian:** Writing - review & editing. **Wendy N. Nembhard:** Supervision, Conceptualization, Funding acquisition, Methodology, Investigation, Writing - review & editing, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Results: In the cohort of 629,086 children, 23,341 (3.7%) children had birth defects and 1,037 (0.2%) children had cancer. For children with non-chromosomal birth defects, specifically cardiovascular and genitourinary, highest risk of any cancer was observed in first year of life (Hazard Ratio [HR] 18.5; 95% confidence interval [CI] 10.1-33.8). For children with chromosomal birth defects, increased cancer risk was observed among those 1-4 years-old (HR 20.0; 95% CI 8.3-48.4).

Conclusion: Overall, cancer risk among children with birth defects was highest among those <5 years-old. Our findings, consistent with previous studies, may inform surveillance strategies for children with birth defects.

Keywords

neoplasms; children; cancer; infants; birth defects; congenital abnormalities; anomalies; age of attainment; proportional hazards models; pediatric cancers

1. Introduction

In the United States (US), more than 15,000 children are diagnosed with cancer annually.[1,2] Few established risk factors are identified for pediatric cancer, including specific cancer predisposition syndromes (e. g., Li-Fraumeni syndrome). Recent studies have demonstrated that birth defects are one of the strongest risk factors for pediatric cancers.[3,4,5,6,7,8] Specific chromosomal birth defects are known to increase risk of specific pediatric cancers, for example, Down syndrome-acute leukemia and chromosome 13q14 deletion syndrome-retinoblastoma.[7,9,10,11,12,13] Additionally, there is strong evidence that non-chromosomal birth defects are associated with cancer in children.[13-17] In fact, both major non-chromosomal birth defects (e.g., non-syndromic critical congenital heart defects) and minor birth defects (e.g., rib anomalies) are associated with increased risk of cancer in children.[14,16,18] However, the etiology for most cases remains unknown.[19]

While most studies have shown associations of birth defects with childhood cancers, fewer have explored this association by attained age. There is some evidence that cancer risk in these children is particularly high in the very young.[7,13,20-22] For example, Dawson et al. observed 1.74 times higher risk for any cancer among children with birth defects by 4 years of age.[21] Additionally, in a recent study using data from Oklahoma, Janitz et al. demonstrated that children <1 year-old with birth defects had the highest risk of developing cancer compared to their contemporaries without birth defects.[22] Based on this evidence, our objective was to assess the risk of cancer among children with and without birth defects in Arkansas by age of attainment. We also explored associations based on birth defects by organ system and by subtypes of pediatric cancers.

2. Materials and Methods

2.1. Study Design and Participants

We conducted a retrospective cohort study using all live births in Arkansas between January 1, 1996 and December 31, 2011. We evaluated differences in cancer risk by birth defects

status, specifically the presence or absence of a chromosomal or non-chromosomal structural birth defect.

2.2. Birth Defects Ascertainment

Children with structural birth defects were identified from the Arkansas Reproductive Health Monitoring System (ARHMS), one of the oldest active birth defects surveillance systems in the US,[23] that maintains statewide active surveillance of approximately 40,000 births every year. An abstraction team, comprised of specially-trained professionals in health information management, reviews medical records in all hospitals that provide obstetrical or pediatric care, as well as some pediatric specialty-care clinics and prenatal diagnosis centers.[23] ARHMS includes more than 60 major and minor birth defects and uses six-digit British Pediatric Association extension of the International Classification of Diseases, Ninth Edition Clinical Modification (ICD-9-CM) coding system, as modified by the National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention (CDC/NCBDDD) and by ARHMS. Eligibility for inclusion in ARHMS is as follows: live births with an initial diagnosis of a birth defect up to 2 years of age, stillbirths of ≥20 weeks' gestation, early fetal loss, as well as elective terminations at any gestational age. Only livebirths were included in this study. Additionally, this assessment was focused on major birth defects, which would limit the likelihood of incidental findings due to a cancer diagnosis early in life.[17]

To be included in ARHMS, a child must have a birth defect diagnosed by two years of age and must be ascertained before the child's fifth birthday. A total of 23,342 children with birth defects were identified. Of these, 942 children had chromosomal birth defects such as trisomy 13, Down syndrome, trisomy 18, Turner syndrome, or 22q11.2 Deletion syndrome.

2.3. Birth Certificate Data

The Health Statistics Branch of the Arkansas Department of Health (ADH) collects data on all births and mortality in the state.[24] For this study, all 605,745 unaffected livebirths between 1996 and 2011 were identified from birth certificates. Demographic information obtained from birth certificate data included: infant sex (male/female), plurality (singleton, twin, triplet, other), maternal age at delivery (<20, 20-29, 30-39, and ≥40 years), completed weeks of gestational age (<28, 28-31, 32-36 and ≥37 weeks), birth weight (<400, 400-1499, 1500-2499 and ≥2500 g), maternal education (≤8, 9-12, 12-16 and >16 years) and maternal race (White, Black, Asian or Pacific Islanders and other or unknown).

2.4. Cancer Ascertainment

Cancer status was obtained for all children from the Arkansas Central Cancer Registry (ACCR), which is a population-based registry with statewide cancer cases.[25] Data on children from January 1, 1996 to December 31, 2011 were obtained from the ACCR and included primary cancer site, morphologic features, behavior, and age at diagnosis (years). The registry follows the standards of the National Program of Cancer Registries within the CDC and is certified as to the completeness, timeliness, and quality of their data by the North American Association of Central Cancer Registries.[25] The pediatric cancer cases identified for this study were classified according to the International Classification

of Childhood Cancer, third edition schema (https://seer.cancer.gov/iccc/iccc3_ext.html). Because of small numbers of cancer cases for this study, we grouped the pediatric cancers into five main categories: (1) hematologic (any leukemia/lymphoma); (2) central nervous system (CNS) tumors; (3) non-CNS embryonal tumors (any peripheral nervous system tumor, retinoblastoma, any renal or hepatic tumor); (4) sarcomas (any bone or soft tissue sarcoma); and (4) germ cell tumors.

2.5. Record Linkage

ARHMS data were linked to birth certificate data and then all birth certificate data were linked to ACCR data by the ADH using both deterministic and probabilistic linkage procedures. The linkage cohort identified 629,086 children with and without birth defects from years 1996 to 2011.

2.6. Statistical Analysis

Age of attainment for cancer was calculated in person-years as time from birth to cancer diagnosis, death (for infants <2 years), or end of the study period, whichever occurred first. Analyses were restricted to 14 years-old or younger to represent those cancers diagnosed in childhood. A total of 629,086 children with and without birth defects were included in the analysis.

Continuous and categorical variables were evaluated by t-test and Fisher's exact test, respectively, to determine statistical significance. We calculated cancer incidence as number of new cases during the study period to obtain percentages of children diagnosed with cancer among those with each birth defect. Using Cox proportional hazards models, we calculated hazard ratios (HRs) and 95% confidence intervals (CI) for risk of any cancer in children with any birth defect, children with chromosomal birth defects, and children with non-chromosomal birth defects. Considering the rarity of birth defects and pediatric cancers, we set a threshold of at least 3 co-occurring birth defect-cancer cases for all models in order to report HRs and 95% CIs.

For our subgroup analyses involving groups of non-chromosomal birth defects by organ system, we divided the birth defects by those of the nervous system, heart and circulatory system, digestive tract, genitourinary system, and musculoskeletal system. We did not have enough cases (n>3) to analyze birth defects of the eye, ear, face and neck, or respiratory system so we excluded these groups from the analysis. We also estimated the HR and 95% CI for all non-chromosomal birth defects and subtypes of cancer (hematologic malignancies, CNS tumors, embryonal tumors, sarcomas, and germ cell tumors). For each Cox proportional hazards model, we evaluated the proportional hazards assumption by 1) including the interaction with log survival time; and 2) using Schoenfeld and scaled Schoenfeld residuals. If either method indicated violation of proportionality assumption, we reported HRs over the following time intervals: <1 years, 1-4 years, 5-9 years, and 10-14 years. We analyzed: (1) main groups of birth defects (all, chromosomal and non-chromosomal) and any cancer; (2) subgroups of non-chromosomal birth defects by organ systems and any cancer; and (3) subgroups of non-chromosomal birth defects and subtypes

of cancer. We did not have sufficient numbers to perform stratified analyses of chromosomal birth defects and cancer subtypes.

Based on prior research, we assessed confounding using the statistical change-in-estimate technique for the covariates: plurality, maternal age, gestational age, birth weight, maternal education, and maternal race.[15,17,20,26,27] None of these variables changed the regression coefficients for the association of any birth defect and any cancer by more than 10%. Therefore, only unadjusted models were presented for this analysis. All analyses were performed using Stata v15 (StataCorp, College Station, TX).

The research was conducted in accordance with the prevailing ethical principles. The research protocol was approved by the Office of Research Integrity and Compliance, Institutional Review Board (IRB) at the University of Arkansas for Medical Science and the Arkansas Department of Health, Scientific Advisory Committee.

3. Results

Maternal demographic and perinatal characteristics of the study sample with and without birth defects are presented in Table 1. In our population, 23,341 of 629,086 (3.7%) children were diagnosed with birth defects and 1,037 (0.2%) children were diagnosed with cancer. Among children with birth defects, children with cancer were more likely to weigh >=2500 g at birth (100% vs. 79.3%). Among children without birth defects, there were significant differences found in infant sex, gestational age, maternal education and race. Without the presence of birth defects, children with cancer were more likely to be male (54.1% vs. 45.9%), born ≥ 41 weeks gestational age (9.5% vs 7.1%), have maternal education > high-school (39.6% vs. 37.7%), and have maternal race as White (82.5% vs. 76.4%).

3.1. Cancer Risk in Children with Chromosomal and Non-Chromosomal Birth Defects

Attained age associations were reported only when there was a violation indicated in proportional hazards assumption of the overall association model (for all ages). We found positive associations for any cancer among children with any birth defect, any chromosomal defect, and any non-chromosomal defect (Table 2). In particular, highest risk for cancer was noted in children <1 year-old for non-chromosomal birth defects (HR 18.5; 95% CI 10.1-33.8). Among children with chromosomal birth defects, notable risk for cancer was observed among those 1-4 years-old (HR 20.0; 95% CI 8.3-48.4). We were unable to evaluate cancer risk for <1 year age group for chromosomal birth defects due to limited sample size. The risk of cancer in children with birth defects was attenuated for older compared to younger ages. Among children 5-9 years-old, those with chromosomal birth defects were 5.9 times more likely (95% CI 1.5-23.8) to develop cancer compared to those without birth defects. Finally, although statistically not significant, there was an increased risk of cancer among those 10-14 years-old with non-chromosomal birth defects (HR 1.3; 95% CI 0.7-2.4) when compared to children without a birth defect.

3.2. Cancer Risk in Children with Non-Chromosomal Birth Defects in Specific Organ Systems

For non-chromosomal birth defects by organ systems, risk was highest within the first year of life for all evaluated subgroups of non-chromosomal birth defects: 1) heart and circulatory system (HR 11.5; 95% CI 4.2-31.5) and 2) genitourinary system (HR 18.1; 95% CI 5.7-57.3). For children 1-4 years-old, HRs ranged from 3.4 (95% CI 1.2-9.0) for genitourinary defects to 7.7 (95% CI 2.5-24.0) for digestive system defects (Table 3). While no significant associations were observed among children ≥5 years-old, our numbers were relatively small. Among children with birth defects at ages 10-14, we did observe non-significant elevated odds for those with genitourinary defects (HR 2.8; 95% CI 0.7-11.3) and musculoskeletal defects (HR 1.1; 95% CI 0.2-8.1), compared to children without birth defects, however the sample size were <3 cancer cases for these associations.

3.3. Risk of Subtypes of Cancer among Children with Non-Chromosomal Birth Defects

We explored the associations between any non-chromosomal birth defect and subtypes of cancer by age-of-attainment. Similar to earlier findings, the highest risk was observed in the first year of life for embryonal tumors (HR 22.7; 95% CI 10.2-50.2) (Table 4). For those 1-4 years-old, the risk estimates ranged from 1.4 (95% CI: 0.4-4.3) for hematologic malignancies to 15.8 (95% CI: 3.5-71.2) for germ cell tumors. While no embryonal or germ cell tumors were observed among children with birth defects aged 5-9, increased risk was observed for sarcomas (HR 3.9; 95% CI 1.4–11.0). Elevated non-significant estimates were observed for embryonal (HR 7.3; 95% CI 0.7-80.1) and germ cell tumors (HR 6.1; 95% CI 0.5-67.1) for children with birth defects aged 10-14 years, however the sample size were <3 co-occurring birth defect-cancer cases for these associations.

4. Discussion

In the present analysis of cancer risk by age of attainment among children with birth defects in Arkansas, we observed the strongest associations among the youngest children. Particularly, we observed greater risk of cancer up to five years of age among children with chromosomal birth defects. Among children with non-chromosomal birth defects, higher risk for cancer was noted primarily during the first year of life. For specific non-chromosomal birth defects and any cancer, we observed significantly higher cancer risk for infants with defects of the cardiovascular, gastrointestinal, and musculoskeletal systems. Among cancer subtypes, we observed a similar pattern of greater risk in the first year of life among children with birth defects, particularly for embryonal cancers. We also noted an increased risk for embryonal and germ cell tumors in older children (≥10 years) with non-chromosomal birth defects, although these results are limited by sample size and should be interpreted with caution.

Our study findings are consistent with other studies that have explored associations between birth defects (chromosomal and non-chromosomal) and pediatric cancers. However, except for a recent study in Oklahoma by Janitz et al., [16] majority of these studies did not report findings by attained age groups; these studies reported greater risk for cancer among children with birth defects at younger ages.[7,13,20,21] For example, Botto et al. reported

the highest hazard for cancer in the first three to five years of age among children with non-chromosomal birth defects.[20] Agha et al. reported nearly six-times higher risk among infants with any birth defect (relative risk 5.8; 95% CI 3.7-9.1).[7] Additionally, Dawson et al. showed doubled risk of developing cancer among children born with a birth defect, especially in the first four years of life.[21]

After exploring overall associations for both chromosomal and non-chromosomal birth defects with pediatric cancers, we focused our further analyses on non-chromosomal birth defects by organ systems and subtypes of cancers. A growing number of studies have evaluated the association between non-chromosomal birth defects and childhood cancer, though not always specific to analysis by certain age groups.[13-17] Similar to these studies, our study confirms the strong association between cardiovascular defects and neoplasms in early childhood, especially during first year of life.[28,29] After excluding children with chromosomal birth defects or leukemia, Fisher and colleagues found more than a three-fold risk of cancer in children with CHDs.[15] Two other studies have shown a 28%-45% increased cancer risk among children with CHDs.[28,30] Our findings on positive associations between pediatric cancers and gastrointestinal defects are consistent with a previous study by Fisher and colleagues, in which a statistically significant association (HR 2.44) was observed between birth defects of the digestive system and pediatric cancers.[15]

We also observed increased risk for sarcomas from ages 5-9 (HR 3.9; 95% CI 1.4-11.0). This is consistent with a previous study in Canada that found higher incidence rates for soft tissue sarcoma (1.2 vs. 0.6/100,000 person-years).[7] A recent study of pooled data from four US states (TX, MI, NC, and AR) showed associations between spina bifida and different forms of sarcomas (non-RMS soft tissue sarcoma).[17] Furthermore, our findings on non-chromosomal birth defects and CNS tumors were consistent with previous literature; a population-based study of 5.2 million children in Norway and Sweden found high standardized incidence ratios (SIR) for brain/nervous system cancers in children with birth defects (SIR 2.5-Norway; 1.3-Sweden).[31] However, we highlight the highest risk during 1 to 4 years-old (HR 10.3, 95% CI 5.4-19.5).[31]

To our knowledge, only the study by Janitz et al. included age-of-attainment analyses of non-chromosomal birth defects, as ours.[16] Of note, our results for non-chromosomal birth defects and pediatric cancer across age groups are consistent with this study. For example, similar to our results, cancer risk among children with birth defects was highest before age six years. Also consistent with our findings concerning the associations of non-chromosomal birth defects grouped by organ system and any cancer, they observed greatly increased cancer risk in the first year of life for infants with cardiovascular (HR 22.5; 95% CI 11.0-46.1), gastrointestinal (HR 21.1; 95% CI 7.0-63.2) or genitourinary defects (HR 15.6; 95% CI 5.0-48.6). In their analysis of cancer subtypes among infants with any non-chromosomal defect, they reported increased risk only for all cancers combined and CNS tumors (HR 25.0; 95% CI 4.8-130.0), whereas we also observed increased risk for hematologic malignancies, embryonal tumors, and germ cell tumors. These differences may be due to limited number of cancer cases in both studies or by differences in the underlying population.

The mechanisms for the association between birth defects and risk of pediatric cancers are largely unknown. One hypothesis by Narod et al. suggested that somatic alterations during earlier phases of embryogenesis can affect multiple developing tissues and thus increase the risk of both birth defects and cancer in the affected child.[5,22] This could be particularly important for malignancies that occur early in life. That said, other mechanisms including novel cancer predisposition syndromes or unidentified environmental risk factors that lead to both phenotypes. Finally, from a developmental perspective, birth defects and cancer may share common etiological pathways in some children, and this may explain the stronger association in early childhood.[32]

Our study has several strengths. First, we utilized valid and reliable population based registry-linked data.[33] Registry data can reduce the biases associated with clinical or interview-based studies,[14,34] and provide the most accurate assessment of cancer occurrence in the general population.[33] Hence we consider this as a robust data source for our study. Another strength of our study is the use of age-stratified modelling to explore age-specific birth defect-cancer associations.

Our study must also be considered in light of certain limitations. Although we were able to evaluate cancer and birth defects in a large population-based sample, our co-occurring case counts were small, which limited the assessment of less common phenotypes, as well as relatively modest associations as seen in older age groups. A second limitation is possible loss to follow up for children with birth defects who relocated to another state after birth. However, a previous study has shown that the migration of these children is non-differential in nature based on presence or absence of birth defect.[35]

Another potential issue to consider is that children diagnosed with cancer earlier in life (e.g., <2 years of age) may have received greater diagnostic scrutiny and could have received a birth defect diagnosis as a consequence of the cancer diagnosis. We limited the potential for this by focusing our assessment on major birth defects that are commonly ascertained regardless of cancer diagnosis. Additionally, other assessments have evaluated the impact of this potential bias by excluding children diagnosed with cancer at early ages, and in sensitivity analyses, these exclusions did not impact the observed birth defect-cancer associations.[17] Conversely, it has been hypothesized that children with birth defects are also likely to get an earlier diagnosis of cancer due to more robust disease surveillance. In another recent paper, authors investigated stage at cancer diagnosis by birth defects status and did not observe earlier diagnoses of cancer among children with birth defects.[36] Based on these findings, we propose that differential diagnostic scrutiny or disease surveillance does not substantially impact our findings.

In conclusion, this study adds to the growing body of evidence that children with non-syndromic birth defects have a higher risk of cancer compared to children without birth defects. Additionally, we have demonstrated that these associations are much stronger for young children with birth defects. While the mechanisms underlying these associations are not clear and likely to be different according to a specific birth defect-cancer pattern, it is hoped that our study can inform future cancer surveillance strategies among younger children living with birth defects.

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Table 1

Demographic, maternal, and birth characteristics for children by cancer and birth defects status in Arkansas, 1996-2011 (N = 629,086)

	Without Birth Defect (N= 605,745)			Birth Defect (N = 23,341)		
	No Cancer N= 604,783	Cancer N = 962	p-value[a]	No Cancer N = 23,266	Cancer N = 75	p-value[a]
	N (%)	N (%)		N (%)	N (%)	
Gender						
Female	296964 (49.1)	442 (45.9)	0.05	9447 (40.6)	33 (44.0)	0.56
Male	307819 (50.9)	520 (54.1)		13819 (59.4)	42 (56.0)	
Plurality						
Singleton	587664 (97.2)	942 (97.9)	0.31	21475 (92.3)	69 (92.0)	0.95
Twin	16517 (2.7)	19 (1.9)		1056 (4.5)	4 (5.3)	
Triplet/Multiple	568 (0.1)	1 (0.1)		30 (0.1)	0 (0.0)	
Unknown	34 (0.0)	0 (0.0)		705 (3.0)	2 (2.7)	
Maternal age at birth						
< 20 years	96573 (16.0)	148 (15.4)	0.19	3447 (14.8)	11 (14.7)	0.18
20-29 years	366796 (60.1)	577 (60.0)		12895 (55.4)	35 (46.7)	
30-39 years	133838 (22.1)	232 (24.1)		5187 (22.3)	23 (30.7)	
>40 years	7330 (1.2)	5 (0.5)		403 (1.7)	3 (4.0)	
Unknown	246 (0.0)	0 (0.0)		1334 (5.7)	3 (4.0)	
Gestational age						
<28 weeks	3449 (0.6)	2 (0.2)	0.01	789 (3.4)	2 (2.7)	0.56
28-31 weeks	5707 (0.9)	14 (1.5)		914 (3.9)	1 (1.3)	
32-36 weeks	52429 (8.7)	68 (7.1)		3665 (15.6)	16 (21.3)	
37-40 weeks	496320 (82.1)	781 (81.2)		14557 (62.6)	43 (57.3)	
≥41 weeks	42635 (7.1)	91 (9.5)		1800 (7.7)	8 (10.67)	
Unknown	4243 (0.7)	6 (0.6)		1541 (6.6)	5 (6.7)	
Birth weight						
<400g	475 (0.1)	0 (0.0)	0.13	15 (0.1)	0 (0.0)	<0.001
400-1499g	8028 (1.3)	12 (1.3)		1684 (7.2)	0 (0.0)	
1500-2499g	42087 (7.0)	49 (5.1)		3108 (13.4)	0 (0.0)	
≤2500 g	554193 (91.6)	901 (93.7)		18459 (79.3)	75 (100.0)	
Maternal education						
< High School	130032 (21.5)	186 (19.3)	0.04	4591 (19.7)	15 (20.0)	0.60
High School Diploma	240778 (39.8)	392 (40.8)		8665 (37.2)	33 (44.0)	
> High School	228186 (37.7)	381 (39.6)		8026 (34.5)	23 (30.7)	
Unknown	5787 (1.0)	3 (0.3)		1984 (8.5)	4 (5.3)	
Maternal Race						
White	462258 (76.4)	794 (82.5)	<0.001	16713 (71.8)	57 (76.0)	0.83
Black	117528 (19.4)	145 (15.1)		4420 (19.0)	12 (16.0)	

	Without Birth Defect (N= 605,745)			Birth Defect (N = 23,341)		
	No Cancer N= 604,783	Cancer N = 962	p-value[a]	No Cancer N = 23,266	Cancer N = 75	p-value[a]
	N (%)	N (%)		N (%)	N (%)	
Asian	8566 (1.4)	7 (0.7)		216 (0.9)	1 (1.3)	
Other	16431 (2.7)	16 (1.7)		1917 (8.3)	5 (6.7)	

[a] p values are from Fisher's exact test.

Table 2

Cox regression models assessing association between type of birth defect and any cancer by age of attainment, Arkansas, 1996-2011.

	Any birth defect (n = 23,341)[a, b]		**Any chromosomal (n= 942)[a, b]**		**Any non-chromosomal (n = 22,399)[a, b]**	
N with Cancer	**75**		**10**		**65**	
	n	**HR (95% CI)**	**n**	**HR(95% CI)**	**n**	**HR(95% CI)**
Overall	75	**2.3 (1.7 – 3.1)**	10	**8.1 (3.9 – 17.0)**	65	**2.1 (1.5 – 2.8)**
<1 year	13	**18.1 (10.2 – 32.4)**	<3	-	12	**18.5 (10.1 – 33.8)**
1 to 4 years	33	**6.5 (4.5 – 9.2)**	5	**20.0 (8.3 – 48.4)**	28	**5.7 (3.9 – 8.4)**
5 to 9 years	14	**1.8 (1.0 – 3.1)**	<3	-	12	1.6 (0.9 – 2.8)
10 to 14 years	15	1.4 (0.8 – 2.5)	<3	-	13	1.3 (0.7 – 2.4)

[a] Proportional Hazards Assumption for overall association model was violated.

[b] Interaction with log of survival time included in the overall model.

Table 3

Cox proportional hazard regression models assessing unadjusted association between subgroups of non-chromosomal birth defects by organ systems and any cancer by age of attainment, Arkansas, 1996-2011 (n = 65 cancer cases).

	Central Nervous System[a, b]		**Cardiovascular**[a, b]		**Gastrointestinal**[a, b]		**Genitourinary**[a, b]		**Musculoskeletal**[a, b]	
N with birth defects	**1,318**		**6,872**		**1,817**		**3,775**		**2,645**	
N with cancer	4		19		5		10		5	
Age	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**
Overall	4	2.6 (0.9 – 7.5)	19	**2.2 (1.3 – 3.6)**	5	2.1 (0.8 – 5.6)	10	**2.1 (1.1 – 4.1)**	5	1.6 (0.6 – 4.1)
<1 year	<3	-	4	**11.5 (4.2 – 31.5)**	<3	-	3	**18.1 (5.7 – 57.3)**	<3	-
1-4 y	<3	-	9	**5.4 (2.8 – 10.4)**	3	**7.7 (2.5 – 24.0)**	4	**3.4 (1.2 – 9.0)**	<3	-
5-9 y	<3	-	3	1.0 (0.3 – 3.2)	<3	-	<3	-	<3	-
10-14 y	<3	-	3	0.9 (0.2 – 3.7)	<3	-	<3	-	<3	-

[a] Proportional Hazards Assumption for overall association model was violated.

[b] Interaction with log of survival time included in the overall model.

Table 4

Cox proportional hazard regression models to assessing unadjusted associations between any non-chromosomal birth defect and subtypes of cancer by age of attainment, Arkansas, 1996-2011 (N = 62 cancer cases).

		Hematologic Malignancies[a, b]		Central Nervous System Tumors[a, b]		Embryonal Tumors[a, b]		Sarcomas[a, b]		Germ Cell Tumors[a, b]
N with birth defects	**371**		**259**		**189**		**132**		**35**	
N with cancer	15		16		17		9		5	
	n	**HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR (95% CI)**	**N**	**HR (95% CI)**
Overall	15	1.0 (0.4 – 2.9)	16	**4.2 (1.9 – 9.5)**	17	**2.4 (1.5 – 4.1)**	9	1.5 (0.4 – 5.0)	5	**5.4 (2.0 – 14.6)**
<1 year	<3	-	<3	-	7	**22.7 (10.2 – 50.2)**	0	-	<3	-
1-4 y	3	1.4 (0.4 – 4.3)	11	**10.3 (5.4 – 19.5)**	9	**8.2 (4.1 – 16.4)**	3	**8.6 (2.6 – 28.4)**	<3	-
5-9y	5	1.8 (0.7 – 4.5)	<3	-	<3	-	4	**3.9 (1.4 – 11.0)**	<3	-
10-14y	5	1.4 (0.5 – 3.9)	3	1.0 (0.3 –3.3)	<3	-	<3	-	<3	-

[a] Proportional Hazards Assumption for overall association model was violated.

[b] Interaction with log of survival time included in the overall model.