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Childhood Cancer in Children with Congenital Anomalies in Oklahoma, 1997-2009

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Abstract

Background—Data-linkage studies have reported an association between congenital anomalies and childhood cancer. However, few studies have focused on the differences in the effect of congenital anomalies on cancer as a function of attained age. We aimed to examine associations between anomalies and childhood cancer as a function of attained age among children born in Oklahoma.

Methods—Data were obtained from the Oklahoma State Department of Health from 1997-2009 (n=591,235). We linked Vital Statistics records for singleton deliveries to the Oklahoma Birth Defects Registry and the Oklahoma Central Cancer Registry using name and birth date. In order to assess the relation between anomalies and childhood cancer, we used Cox regression analysis allowing for a non-proportional hazards for anomalies as a function of age.

Results—There were 23,368 (4.0%) children with anomalies and 531 (0.1%) children with cancer. When considering 3-year age intervals, we detected an increased hazard of any childhood cancer in children with anomalies compared to those without anomalies before one year of age (HR: 14.1, 95% CI: 8.3, 23.7) and at three years of age (HR: 2.3, 95% CI: 1.6, 3.2). The increased hazard declined with increasing time since birth, with the effect diminished by six years of age.

Conclusions—Our results were consistent with previous studies indicating an increased rate of childhood cancer among children with anomalies at younger ages. Furthermore, our study added a methodological refinement of assessing the effect of anomalies as a function of attained age.

Keywords

neoplasms; children; infant; congenital abnormalities; proportional hazards models

Introduction

Although rare, childhood cancer is the number one cause of childhood mortality from disease in the US in children 5-14 years, accounting for 19% of deaths in children 5-9 years and 16% of deaths in children 10-14 years (Heron, 2013). Among the many potential risk factors under investigation regarding the etiology of childhood cancer is congenital anomalies. One theory regarding the common etiology of these health outcomes relates to Knudson's 2-hit hypothesis of cancer (Knudson, 2001). Children born with anomalies may have had the first genetic 'hit' from the anomaly, making it more likely for these children to develop cancer (Carozza et al., 2012). Although much work has been conducted regarding specific genetic conditions and risk of childhood cancer, little is known regarding the mechanism of the majority of childhood cancers. There is increasing evidence that some childhood cancers are initiated in utero. Narod et al. (1991) estimated that a small percentage (4.2%) of childhood cancers had an underlying genetic etiology, including heritable and non-heritable conditions. There is stronger evidence for chromosomal aberrations for certain types of cancer than others, primarily leukemia, although these aberrations are not present in all children with cancer (Buffler et al., 2005; Greaves, 2005; Greaves and Wiemels, 2003). It is unclear how congenital anomalies impact the risk of cancers in childhood aside from rare genetic conditions and syndromes, such as Down syndrome, ataxia telangiectasia, and Beckwith-Wiedemann syndrome, which account for a minority of childhood cancers (Clericuzio, 1999; Narod et al., 1991).

Of the 22 studies evaluating congenital anomalies and childhood cancer identified in our literature review, all reported a positive association, either overall or with specific anomalies and/or cancers (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008; Botto et al., 2013; Carozza et al., 2012; Dawson et al., 2015; Durmaz et al., 2011; Fisher et al., 2012; Mann et al., 1993; Mehes et al., 1985; Menegaux et al., 2005; Merks et al., 2008; Mertens et al., 1998; Mili et al., 1993a; Mili et al., 1993b; Narod et al., 1997; Nishi et al., 2000; Partap et al., 2011; Rankin et al., 2008; Savitz and Ananth, 1994; Windham et al., 1985; Zierhut et al., 2011). These studies included case-control, standardized morbidity ratio (SMR) studies, and cohort studies conducted through record linkage. However, few studies discussed differences in the effect of congenital anomalies on childhood cancer as a function of attained age, with only one evaluating the association for multiple age groups (Agha et al., 2005; Botto et al., 2013; Carozza et al., 2012; Dawson et al., 2015). Dawson et al. (2015) observed a higher hazard of cancer among those aged one to four years (hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 1.26, 2.48), but not among those from three months to one year or over the age of four with limited sample size per age group when excluding anomalies known to be associated with childhood cancer. While several other studies reported an increased rate of childhood cancer at earlier ages among those with congenital anomalies, the association was not investigated in detail, with the focus of the analyses on the overall association (Agha et al., 2005; Botto et al., 2013; Carozza et al., 2012). These differences may have important clinical implications for earlier diagnosis and treatment, especially for young children with congenital anomalies, and are therefore important to explore in more detail.

Studying the age-specific association may identify a high-risk group from which to learn more about the potential etiology of both congenital anomalies and childhood cancer. Furthermore, understanding which specific congenital anomalies and cancers are related can generate hypotheses regarding specific genetic mutations and hereditary patterns of cancer (Agha et al., 2005). To evaluate whether the association between congenital anomalies and childhood cancer varied with age, we conducted a retrospective cohort study using data available from the Oklahoma State Department of Health (OSDH).

Methods

Study Subjects

Our cohort included all singleton births delivered in Oklahoma between January 1, 1997 and March 31, 2009 (n=591,235). Information on births, including covariates, was obtained from birth certificates at OSDH. Institutional Review Board approval was obtained from the University of Oklahoma Health Sciences Center and OSDH.

Congenital Anomalies

Children born between January 1, 1997 and March 31, 2009 with congenital anomalies (n=23,368) were identified by linking the birth certificate records with the Oklahoma Birth Defects Registry (OBDR). Inclusion diagnoses consisted of Centers for Disease Control British Pediatric Association codes listed in Table 1. OBDR is an active surveillance system that works with all birthing hospitals in Oklahoma to identify children with anomalies, which can be reported up to age six (at the time of this study), although the child must display signs/symptoms of an anomaly before the age of two. OBDR allowed for up to eight anomalies per child, with 37% of children included in the analysis having multiple anomalies.

We classified anomalies into the following categories established by National Birth Defects Prevention Network (2004): chromosomal, central nervous system (CNS), eye and ear (combined), cardiovascular, orofacial, gastrointestinal, genitourinary, musculoskeletal, and other (Table 1). We combined eye and ear anomalies since these were rare individually and were often reported together in the literature. We excluded children with an anomaly classified as a malignant neoplasm in OBDR from all analyses as these children did not remain at risk for developing childhood cancer at the beginning of the follow-up period (n=133).

Childhood Cancer

We identified children in the Oklahoma Central Cancer Registry (OCCR) who were born in Oklahoma and diagnosed with cancer between January 1, 1997 and March 31, 2009 (n=531). In this study, only children with histologically confirmed malignant tumors were included, with the exception of benign CNS tumors (2004-2009). Beginning in 2004, benign CNS tumors and CNS tumors of borderline histology were required to be included in cancer registries as certain types of benign tumors may progress to malignancy and it may be difficult to distinguish between benign and malignant tumors. Further, because of the confined nature of the CNS, these benign tumors may pose a significant risk of morbidity

and mortality (Davis et al. 1997). Age at cancer diagnosis was assigned by OCCR using dates of birth and cancer diagnosis and was analyzed in whole years.

We categorized childhood cancers to the International Classification of Childhood Cancers, Third edition, which is based on the International Classification of Diseases for Oncology, Third edition, using the primary site, histology, and behavior of the tumor specific to childhood cancers (Steliarova-Foucher et al., 2005). Thus, the childhood cancer categories evaluated in this study include leukemias, lymphomas, CNS tumors, neuroblastoma, retinoblastoma, renal tumors, hepatic tumors, malignant bone tumors, soft-tissue/other extraosseous sarcomas, germ-cell tumors, other malignant epithelial neoplasms/melanomas, and other/unspecified malignant neoplasms.

Database Linkage

We used Registry Plus™ Link Plus software v. 2.0 (CDC, Atlanta, GA), to link the birth records to the OBDR and OCCR datasets using both probabilistic and deterministic methods, allowing us to manually review all potential links identified by the software (National Program of Cancer Registries, 2012). Because a unique identifier was not available, we used the variables of first and last name, sex, and date of birth to link birth certificates to OBDR, resulting in 91% of children in OBDR linking to the birth certificates registry. We then linked this combined dataset to the OCCR, which resulted in a 77% linkage using the variables of first and last name and date of birth (sex was not provided). The OSDH has an ongoing linkage with death records, which we used to determine which children died during the follow-up period (January 1, 1997-March 31, 2009) and the year of death, if available. Because the linkage with death records was not complete at the time of this study, year of death was not available for 34% of the deceased subjects (n=1,637).

Statistical Analysis

To compare the differences among covariates between those with and without anomalies, we used a Chi-Square Test of Independence. We used a two-sample Wilcoxon Rank Sum Test to assess the difference in age at cancer diagnosis between children with and without anomalies, since age at diagnosis was not normally distributed when evaluated using the Shapiro-Wilk statistic ($p<0.0001$).

We used Cox regression to calculate HR and 95% CIs for the association between anomalies and childhood cancer. Cancer-free survival time was calculated as time from birth to cancer diagnosis, death, or the end of the study period, whichever occurred first. For those children who died during the study follow-up, but were missing year of death, we calculated their cancer-free survival time from birth until cancer diagnosis or the end of the follow-up period, whichever came first. We assessed the HRs for children with any anomaly and any type of cancer, any anomaly and specific types of cancer, as well as specific anomalies and any cancer in separate models. Furthermore, we analyzed non-chromosomal anomalies separately from total anomalies. Analyses evaluating associations with specific cancer types compared children with each specific cancer type to all children without cancer (n=590,738). Similarly, analysis of specific anomalies compared children with each specific anomaly to all children without anomalies (n=567,867). This allowed us to use a consistent

comparison group when evaluating all categories of anomalies and cancer outcomes. Children with multiple anomalies were included in multiple categories of specific anomalies, as applicable.

Due to small numbers, we excluded several types of anomalies and specific cancers from analyses of specific anomalies and cancers, respectively, but included them in the overall analyses for any anomaly and any cancer. We excluded familial/congenital neoplasms, other fetal/placental anomalies, other and unspecified congenital anomalies, fetal alcohol syndrome, endocrine/metabolic disorders, integument, and congenital infections (<3% of children with anomalies in each category) when evaluating associations between specific anomalies and any type of cancer. Furthermore, we did not analyze neuroblastoma, retinoblastoma, renal tumors, malignant bone tumors, other malignant epithelial neoplasms/melanomas, or other/unspecified malignant neoplasms in the analysis of any type of anomaly with specific cancers ($n < 10$ for each cancer type). We also excluded hepatic tumors from our analysis of any non-chromosomal anomaly and specific cancer types ($n < 10$).

We evaluated the proportional hazards assumption for the Cox regression model by assessing 1) the relationship between the Schoenfeld residuals and the log of survival time and 2) by creating an interaction term between the variable of interest and the log of survival time. Assessment of the Schoenfeld residuals provided an overall indication of model fit and whether the proportional hazards assumption was met. The test for proportionality, using an interaction with the log of time, provided a statistical test to directly determine whether the assumption was met. If either assessment indicated the assumption was violated, we treated the variable as violating the proportional hazards assumption. If the assumption was violated for the primary exposure of congenital anomalies, we included an interaction with the log of time in the model. For all models that included an interaction with time, we reported the HRs for congenital anomalies across three-year intervals: <1 year, 3 years, 6 years, 9 years, and 12 years.

We detected no effect modification for the association between congenital anomalies and cancer by the selected variables of birthweight, maternal age, and gender, which were chosen based on indications from the literature (Agha et al., 2005; Savitz and Ananth, 1994).

We used a directed acyclic graph to guide the selection of potential confounders, which included gender, maternal age, prenatal care (information on prenatal vitamin use was not available), plurality (restricted to singletons), socioeconomic status (measured through maternal education), and family history of anomalies and cancer. However, we did not have information for all children regarding family history. In a quantitative assessment, we observed that none of the potential confounders changed the regression coefficient of congenital anomalies by more than 20% when controlled in the model of any congenital anomaly and any childhood cancer and models of any anomaly and specific cancers, thus, only crude models are presented for these analyses. With the exception of genitourinary (maternal education) and musculoskeletal (prenatal care) non-chromosomal anomalies, none of the potential confounders changed the estimate >20% for the assessment of specific anomalies and any childhood cancer.

We used an alpha of 0.05 to define statistical significance and SAS v.9.3 (Cary, NC) for all analyses.

Results

There were 23,368 (4%) children with anomalies and 567,867 (96%) children without anomalies included in the analysis (Table 2). There were 531 (0.1%) children with cancer, with 56 (11%) having anomalies and 475 (89%) without anomalies. Among children with anomalies, the most common anomalies were cardiovascular (30.2%) and musculoskeletal (29.2%). Although those with and without anomalies differed across all characteristics examined, children with anomalies had a notably lower percentage of females (41.3% v. 49.1%), higher percentage of first-born children (43.0% v. 40.5%), lower gestational age at birth (<37 weeks: 18.0% v. 7.9%), higher percent born with low birthweight (16.2% v. 6.0%), and a higher percentage that were deceased by the end of follow-up (5.3% v. 0.6%) compared to children without anomalies. The percentage of missing data for covariates was similar between those with and without anomalies.

Children with any anomaly and cancer had a younger median age at cancer diagnosis (1 year) than children without anomalies (3 years) ($p<0.0001$), which was consistent among children with non-chromosomal anomalies. When examining this comparison across specific cancer types, there was a younger median age at cancer diagnosis for soft tissue sarcomas (<1 year v. 2 years, $p=0.04$) for children with anomalies compared to without anomalies, with marginal differences for leukemia (2 years v. 3 years, $p=0.07$), CNS tumors (3 years v. 4 years, $p=0.05$), and germ cell tumors (<1 year v. 1 year, $p=0.06$). The observed age differences were similar when limiting the cancer-specific analyses to non-chromosomal anomalies; however, there was no difference among children with leukemia.

Any Congenital Anomaly with any Childhood Cancer and Specific Cancers

Overall, we detected an association with any congenital anomaly and any childhood cancer that differed with attained age, as indicated by violation of the proportional hazards assumption. We observed a significantly elevated hazard of any childhood cancer in children with anomalies compared to those without anomalies within the first year of life (HR: 14.1, 95% CI: 8.3, 23.7) (Table 3). The increased hazard of any cancer associated with anomalies declined with increasing age (HR for three years of age: 2.3, 95% CI: 1.6, 3.2), with no effect observed by six years of age. When evaluating specific cancer categories, we observed similar results for associations with CNS tumors, with a non-significant increase through 11 years of age (HR: 1.1, 95% CI: 0.3, 3.9). Children with anomalies had an overall higher hazard of leukemia, lymphoma, hepatic tumors, soft tissue sarcomas, and germ cell tumors. When limiting analyses to children with non-chromosomal anomalies, the results were similar with the exception of leukemia, which was no longer associated with congenital anomalies (Table 4).

Specific Congenital Anomalies with any Childhood Cancer

In our assessment of specific anomalies and any childhood cancer, we observed results similar to the overall association (Table 5). Among the anomaly types with an effect that

changed as age increased, there was a strong hazard of cancer under one year of age which decreased with increasing age. There was no association with childhood cancer among children with orofacial anomalies. When excluding chromosomal anomalies, the results were similar, but attenuated (Table 6). Of note, CNS, eye/ear, and musculoskeletal (after adjustment for prenatal care) anomalies did not differ as a function of attained age and were no longer associated with cancer after excluding chromosomal anomalies. Genitourinary anomalies were also no longer associated with childhood cancer after adjustment for maternal education.

Discussion

We observed an increased hazard of childhood cancer among children with congenital anomalies compared to children without anomalies, primarily before age six years. Dawson et al. (2015) also observed an increased HR among children between three months and four years of age (HR: 1.74, 95% CI: 1.28, 2.37), which was limited to anomalies and cancers not known to be associated, and was closer to the null than the HR we observed. The presence of any anomaly was associated with all specific cancer types. When excluding chromosomal anomalies, the association with leukemia was no longer significant and the HR was attenuated. When examining specific anomalies with any cancer, all anomaly types except orofacial anomalies were associated significantly with cancer. While several studies evaluated the association with orofacial anomalies (Bjorge et al., 2008; Botto et al., 2013; Dawson et al., 2015; Fisher et al., 2012; Menegaux et al., 2005; Mertens et al., 1998; Narod et al., 1997), only Carozza et al. (2012) observed an elevated rate of childhood cancer among children with oral clefts (IRR: 2.69, 95% CI: 1.34, 4.82). After excluding chromosomal anomalies, only cardiovascular and gastrointestinal anomalies were significantly associated with cancer, although the HRs for each anomaly type were elevated. Among children with non-chromosomal cardiovascular anomalies and cancer (n=14), atrial septal defect (n=10) and leukemia and lymphoma (n=8) were the most common anomaly and cancer types, respectively. However, only six children had both a nonchromosomal gastrointestinal anomaly and cancer, thus, we were unable to identify any patterns. These observations emphasize the importance of chromosomal anomalies in the association with childhood cancer, particularly in the association with leukemia. This was expected due to the known association between Down syndrome, a chromosomal anomaly, and leukemia (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008; Botto et al., 2013; Marshall et al., 2014; Mertens et al., 1998; Mili et al., 1993a; Mili et al., 1993b; Nishi et al., 2000; Rankin et al., 2008; Windham et al., 1985). Other studies reported significantly elevated incidence rate ratios (IRR) of cancer between 1.6 and 3.1, standardized morbidity ratios (SMR) of 1.7-2.2, and odds ratios of 2.1-4.5 in children with anomalies compared to those without anomalies (Agha et al., 2005; Altmann et al., 1998; Bjorge et al., 2008; Botto et al., 2013; Carozza et al., 2012; Fisher et al., 2012; Menegaux et al., 2005; Mili et al., 1993a; Mili et al., 1993b; Rankin et al., 2008; Savitz and Ananth, 1994; Windham et al., 1985). Of those assessing chromosomal anomalies separately, the IRRs for cancer were stronger, ranging from 12 to 17, but with generally wide confidence intervals (Altmann et al., 1998; Carozza et al., 2012; Fisher et al., 2012; Windham et al., 1985). In two studies that focused on non-chromosomal anomalies, the incidence rate of cancer was approximately two times higher in children with

anomalies compared to those without anomalies (Botto et al., 2013; Fisher et al., 2012). These IRRs/SMRs estimated the average incidence rates over time and did not account for age dependence in the data, which was observed in our analysis.

According to Marshall et al. (2014) several cancers have pre-clinical and/or clinical evidence of a prenatal origin (neuroblastoma, medulloblastoma, retinoblastoma, B-cell acute lymphoblastic leukemia, transient myeloproliferative disorder, and myeloid leukemia-Down syndrome). Although the underlying mechanisms for the association between congenital anomalies and childhood cancer are unknown for the majority of cancers and anomalies, there is increasing evidence of initial genetic changes in utero that may lead to development of childhood cancer, particularly at an early age. Additionally, Narod et al. (1997) suggested that mutations of some developmental genes in utero may increase the risk of childhood cancer, but have no impact on cancer in adults. Childhood cancer due to heritable conditions is rare, but somatic mutations may increase a child's risk for both anomalies and childhood cancer. Mutations that occur early in embryogenesis may affect multiple tissues, thus increasing the risk for anomalies and/or cancer of organs in childhood, which may explain the association between nonchromosomal anomalies and solid tumor cancers (Narod et al., 1997).

Few studies have discussed differences in the effect of congenital anomalies on childhood cancer as a function of attained age (Agha et al., 2005; Botto et al., 2013; Carozza et al., 2012; Dawson et al., 2015). Our study reinforced the importance of evaluating the proportional hazards assumption and reporting the HRs by attained age. Agha et al. (2005) hypothesized that differential mortality among children with certain anomalies, primarily chromosomal and multiple anomalies, may have reduced the IRR of cancer after one year of age as these children did not have the opportunity to develop cancer. As treatment and survival improve for severe and life-threatening anomalies over time, it will be important to assess how the relationship with cancer changes in older children (Agha et al., 2005). Botto et al. (2013) observed that the hazard of cancer for children with chromosomal anomalies continued to differ from children without anomalies through age 14, which may support the theory of differential mortality in Agha et al. (2005).

The trend of a higher hazard of cancer in children <1 year of age, which decreased with increasing age, was similar for all anomaly types except orofacial which did not change as a function of attained age. We also observed that children with chromosomal, orofacial, genitourinary, and musculoskeletal anomalies had a younger age at death than children without anomalies (data not shown). These children may not have had the opportunity to develop cancer due to differential mortality, which may underestimate the true association. An alternative theory is in accordance with Knudson's two-hit hypothesis (Knudson, 2001). A congenital anomaly may contribute to an earlier age at cancer diagnosis than in children without anomalies, whose first 'hit' would have potentially occurred later in development (Carozza et al., 2012). Recently, epigenetic alterations have been proposed in the etiology of congenital anomalies and cancer, providing an important link between genetics and environmental exposures that may occur early in development (Hobbs et al., 2014; Moore, 2009). A primary example relates to Beckwith–Wiedemann syndrome, which is an imprinting disorder characterized by overgrowth and may include abdominal wall defects in

addition to other anomalies (Soejima and Higashimoto, 2013). Through multiple types of genetic alterations, these children have a 5-25% increased risk for embryonal tumors such as Wilms tumor (Hitchins, 2015; Soejima and Higashimoto, 2013). Epigenetic patterns are being explored for other types of childhood cancer, including acute lymphoblastic leukemia, (Lee et al., 2015) and may contribute to the understanding of non-syndromic anomalies (Hobbs et al., 2014). As this growing field expands, future studies should consider incorporating these advanced methods for evaluating relationships between anomalies and childhood cancer.

One limitation with linking large databases was that all birth defect and cancer records did not link to birth certificates, resulting in potential under-ascertainment of both anomalies and cancer. The lack of a complete linkage could be due to multiple factors, including last name changes or children moving in or out of state. Our analysis indicated that children with poorer health outcomes, such as low birthweight and small size for gestational age, and cardiovascular anomalies were less likely to link to a birth record (data not shown). It is possible that some of these children died in the perinatal period, but had differing classifications of live or stillbirth status between OBDR and the birth certificate dataset. In our evaluation of under-ascertainment of cancer, we observed no differences among those with cancer who did and did not link to birth records regarding type of cancer, year of birth, year of diagnosis or age at diagnosis (data not shown). If children who truly had anomalies and cancer were under-ascertained for the analysis, this could result in an underestimate of the true association. To address the high percentage of children who were deceased and missing year of death, we compared our model, which assumed complete follow-up for those missing dates of death, to a model excluding these observations. Both models resulted in similar HRs. This indicated that even though we may have overestimated the person time for those with missing year of death, there was little effect on the HR.

Our data were collected from a population-based registry and included all births in Oklahoma between 1997 and 2009. All diagnosis and treatment facilities, except federal, Indian Health Services and tribal facilities, are required to report cancers to the OCCR. The majority of children with cancer, especially those under 18 years of age, are treated at one of two facilities in Oklahoma. Some children receive cancer treatment outside of Oklahoma, but the OCCR works with other state cancer registries to collect information through data exchange, resulting in few Oklahoma residents with cancer unaccounted for in the OCCR. However, despite the study being population-based, there were only 56 children with both anomalies and cancer in our study due to the rarity of both health events in children. The small sample size prohibited us from exploring associations between specific anomalies and specific cancer types and limited the statistical power to detect more modest associations. Future studies would benefit from pooling data from multiple states to better understand the impact of specific anomalies as a function of attained age on specific cancers.

In conclusion, our results were consistent with previous studies assessing congenital anomalies and childhood cancer. However, our study added the methodological improvement of assessing the effect of anomalies as a function of attained age, which provided a more precise understanding that the rate of cancer increased at earlier ages for children with anomalies and was similar to that in children without anomalies at older ages.

A possible implication of these observations is the need for enhanced surveillance for childhood cancer at a younger age in children with anomalies, primarily under six years of age depending on the anomaly type. Our findings of an overall pattern of increased rates of cancer among young children with anomalies may serve to enhance awareness of potential susceptibility. However, translation of these findings into secondary prevention efforts would require larger studies to elucidate specific anomalies that may increase risk of certain cancers and to discern age-related patterns for specific anomaly/cancer associations. Future directions include confirming a lack of association between anomalies and cancer in older children and determining if cancer survival differs among childhood cancer patients with and without anomalies.

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Table 1

Distribution of Congenital Anomaly Categories among Children with Anomalies (n=23,368) in Oklahoma, 1997-2009^a

Congenital Anomaly Category	Centers for Disease Control British Pediatric Association Codes	N	%
Chromosomal	758000-758999	1259	5.4
Central Nervous System	740000-742999, 331890-331899, 335000-335099, 352600-352699	2143	9.2
Eye/Ear	743000-743999, 362700-362799, 363200-363299, 744000-744999, 744000-744059, 744090-744099	1319	5.6
Cardiovascular	745000-747889, 747900-747999, 425300-425399, 426700-426799, 427810-427999, 453000-453099, 457800-457899	7059	30.2
Orofacial	748000-749299, 744800-744899, 744900-744999	1997	8.5
Gastrointestinal	750000-751999, 524000-524199, 553000-553999	3736	16.0
Genitourinary	752000-753999	4124	17.7
Musculoskeletal	754000-756999, 658000-658999	6825	29.2
Other ^b	214000-214999, 216000-216999, 228020-228199, 229800-229899, 237700-237729, 238000-238089, 239200, 253200, 253800, 255200, 255800, 257800, 277000-277999, 279110-279119, 634920, 648300, 653700, 635820, 655400, 655500, 656400, 757000-757999, 759000-759999, 760710-760799, 771000-771299, 774000-774499	1915	8.2

^aSum exceeds total subjects due to multiple anomalies per child.

^bOther: familial/congenital neoplasm, other fetal/placental anomalies, other and unspecified congenital anomalies, fetal alcohol syndrome, endocrine/metabolic disorders, integument, and congenital infections.

Table 2

Distribution of demographic, maternal, and birth characteristics and cancer status by congenital anomaly status in Oklahoma, 1997-2009

Characteristic	All Congenital Anomalies (n=23,368)		No Congenital Anomalies (n=567,867)		p-value
	N	%	N	%	
Female (v. males)	9650	41.3	278619	49.1	<0.0001
Race/Ethnicity					<0.0001
White non-Hispanic	16170	69.2	380972	67.1	
African American non-Hispanic	1960	8.4	53643	9.5	
American Indian non-Hispanic	2599	11.1	59815	10.5	
Asian non-Hispanic	350	1.5	11730	2.1	
Hispanic	2289	9.8	61707	10.9	
Mother's Age at Child's Birth					<0.0001
<20 years	3489	14.9	84695	14.9	
20-34 years	17584	75.3	437211	77.0	
35 years	2284	9.8	45518	8.0	
Unknown	11	0.1	443	0.1	
Mother's Education					<0.0001
Less than High School	5458	23.4	129890	22.9	
High School	8788	37.6	208280	36.7	
More than High School	8856	37.9	224315	39.5	
Unknown	266	1.1	5382	1.0	
Prenatal Care					<0.0001
Presence	21322	91.2	524676	92.4	
Absence	333	1.4	6817	1.2	
Unknown	1713	7.3	36374	6.4	
Number of Previous Births					<0.0001
0	10041	43.0	229754	40.5	
1	6988	29.9	178917	31.5	
2	3928	16.8	98408	17.3	
3	2411	10.3	60786	10.7	
Unknown	0	0.0	5 ^a	0.0	
Gestational Age at Birth					<0.0001
<37 weeks	4200	18.0	45037	7.9	
37-39 weeks	12110	51.8	304809	53.7	
40 weeks	6280	26.9	199787	35.2	
Unknown	778	3.3	18234	3.2	
Birthweight (grams)					<0.0001
High Birthweight (≥ 4000)	1691	7.2	47872	8.4	
Normal Birthweight (2500-<4000)	17807	76.2	485003	85.4	
Low Birthweight (<2500)	3781	16.2	33767	6.0	
Unknown	89	0.4	1225	0.2	

Characteristic	All Congenital Anomalies (n=23,368)		No Congenital Anomalies (n=567,867)		p-value
	N	%	N	%	
Deceased (v. Alive) at End of Follow-Up	1249	5.3	3540	0.6	<0.0001
Cancer (v. No Cancer)	56	0.2	475	0.1	<0.0001

^a Sample size less than or equal to 5 is suppressed due to confidentiality.

Table 3

Unadjusted association between any congenital anomaly and childhood cancer, overall and by type of cancer, Oklahoma, 1997-2009^a

	All Childhood Cancer ^b	Leukemia	Lymphoma	Central Nervous System Tumors ^b	Hepatic Tumors	Soft Tissue Sarcomas	Germ Cell Tumors
N with Cancer	531	212	40	102	10	31	17
N with Anomalies	56	18	5 ^c	11	5 ^c	5 ^c	6
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall	3.0 (2.2, 3.9)	2.3 (1.4, 3.8)	2.8 (1.0, 7.9)	3.1 (1.6, 5.7)	25.0 (7.2, 86.2)	3.7 (1.3, 10.6)	13.6 (5.0, 36.7)
<1 year	14.1 (8.3, 23.7)			17.9 (3.5, 91.5)			
3 years	2.3 (1.6, 3.2)			3.6 (1.9, 6.8)			
6 years	1.1 (0.7, 1.9)			1.9 (0.8, 4.5)			
9 years	0.8 (0.4, 1.4)			1.3 (0.4, 4.0)			
12 years	0.6 (0.3, 1.1)			1.0 (0.3, 3.8)			

^aChildhood cancers classified per the International Classification of Childhood Cancers, Third Edition.

^bProportional hazards assumption not met, thus a continuous time interaction model was used. Overall HR (95% CI) presented for comparison purposes.

^cSample size less than or equal to 5 is suppressed due to confidentiality.

Unadjusted association between any non-chromosomal congenital anomalies and childhood cancer, overall and by type of cancer, Oklahoma, 1997-2009.^a

Table 4

	Any Childhood Cancer ^b	Leukemia	Lymphoma	Central Nervous System Tumors ^b	Hepatic Tumors	Soft Tissue Sarcomas	Germ Cell Tumors
N with Cancer	519	204	40	101	9	31	17
N with Anomalies	44	10	5 ^c	10	5 ^c	5 ^c	6
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall	2.5 (1.8, 3.3)	1.4 (0.7, 2.6)	3.0 (1.1, 8.4)	2.9 (1.5, 5.6)	N/A	3.9 (1.4, 11.2)	14.3 (5.3, 38.7)
<1 year	10.7 (6.0, 19.1)			25.0 (4.8, 130.0)			
3 years	2.0 (1.4, 2.9)			3.4 (1.7, 6.7)			
6 years	1.0 (0.6, 1.8)			1.6 (0.6, 4.1)			
9 years	0.7 (0.4, 1.4)			1.0 (0.3, 3.4)			
12 years	0.5 (0.3, 1.2)			0.7 (0.2, 3.1)			

^aChildhood cancers classified per the International Classification of Childhood Cancers, Third Edition.

^bProportional Hazards assumption not met, thus a continuous time interaction model was used. Overall HR (95% CI) presented for comparison purposes.

^cSample size less than or equal to 5 is suppressed due to confidentiality.

Table 5

Unadjusted association between specific congenital anomalies and any childhood cancer, Oklahoma, 1997-2009.^a

	Chromosomal ^b	Central Nervous System ^b	Eye/Ear ^b	Cardiovascular ^b	Orofacial	Gastrointestinal ^b	Genitourinary ^b	Musculoskeletal ^b
N with anomalies	1259	2143	1319	7059	1997	3736	4124	6825
N with cancer	487	480	479	499	479	482	483	482
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall	11.9 (6.7, 12.2)	3.0 (1.2, 7.2)	3.6 (1.4, 9.7)	4.4 (2.9, 6.6)	2.5 (0.9, 6.6)	2.4 (1.4, 5.1)	2.5 (1.3, 5.1)	1.2 (0.6, 2.6)
<1 year	84.7 (33.8, 211.9)	18.8 (4.6, 77.8)	27.9 (6.1, 127.0)	22.5 (11.0, 46.1)		21.1 (7.0, 63.2)	15.6 (5.0, 48.6)	5.3 (1.4, 20.5)
3 years	7.3 (3.2, 16.6)	2.0 (0.6, 6.5)	2.2 (0.5, 9.1)	3.2 (1.9, 5.4)		1.1 (0.3, 3.8)	1.6 (0.6, 4.3)	1.0 (0.4, 2.5)
6 years	2.9 (0.8, 9.6)	0.8 (0.1, 4.9)	0.8 (0.1, 6.8)	1.5 (0.7, 3.2)		0.3 (0.1, 2.2)	0.7 (0.2, 2.9)	0.6 (0.2, 2.0)
9 years	1.6 (0.4, 7.1)	0.5 (0.1, 4.3)	0.4 (0.0, 5.9)	0.9 (0.4, 2.5)		0.2 (0.0, 1.6)	0.4 (0.1, 2.4)	0.4 (0.1, 1.9)
12 years	1.1 (0.2, 5.9)	0.3 (0.0, 4.0)	0.3 (0.0, 5.4)	0.7 (0.2, 2.1)		0.1 (0.0, 1.3)	0.3 (0.0, 2.1)	0.3 (0.0, 1.8)

^aClassification of congenital anomalies by Centers for Disease Control British Pediatric Association (CDC BPA) codes.

^bProportional hazards assumption not met, thus a continuous time interaction model was used. Overall HR (95% CI) presented for comparison purposes.

Association between specific congenital anomalies and any childhood cancer, excluding those with chromosomal anomalies, Oklahoma, 1997-2009.^a

Table 6

	Central Nervous System ^b	Eye/Ear	Cardiovascular ^b	Orofacial	Gastrointestinal ^b	Genitourinary ^{b,c}	Musculoskeletal ^d
N with Anomalies	1998	1179	6369	1887	3552	3932	6575
N with Cancer	478	477	489	479	481	480	481
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall	1.9 (0.6, 5.9)	2.0 (0.5, 8.1)	2.8 (1.7, 4.8)	2.6 (1.0, 6.9)	2.2 (1.0, 4.9)	1.7 (0.7, 4.0)	1.3 (0.6, 2.8)
<1 year			11.1 (4.2, 29.4)		18.5 (5.7, 60.2)	3.6 (0.5, 26.4)	
3 years			2.4 (1.3, 4.4)		1.0 (0.3, 3.8)	1.2 (0.4, 3.6)	
6 years			1.3 (0.5, 3.2)		0.3 (0.0, 2.4)	0.8 (0.2, 3.8)	
9 years			0.9 (0.3, 2.8)		0.2 (0.0, 1.8)	0.7 (0.1, 4.5)	
12 years			0.7 (0.2, 2.6)		0.1 (0.0, 1.5)	0.6 (0.1, 5.1)	

^aClassification of congenital anomalies by Centers for Disease Control British Pediatric Association (CDC BPA) codes.

^bProportional hazards assumption not met, thus a continuous time interaction model was used. Overall HR (95% CI) presented for comparison purposes.

^cAdjusted for maternal education.

^dAdjusted for prenatal care.