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Associations Between Birth Defects and Childhood and Adolescent Germ Cell Tumors According to Sex, Histologic Subtype, and Site

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Abstract

Background: Studies have reported increased rates of birth defects among children with germ cell tumors (GCTs). However, few studies have evaluated associations by sex, type of defect, or tumor characteristics.

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Methods: We evaluated birth defect-GCT associations among N=552 pediatric patients with GCTs enrolled in the Germ Cell Tumor Epidemiology Study and N=6,380 population-based controls without cancer from the Genetic Overlap Between Anomalies and Cancer in Kids Study. We estimated the odds ratio (OR) and 95% confidence interval (CI) of GCTs according to birth defects status using unconditional logistic regression. We considered all defects collectively, genetic and chromosomal syndromes, and non-syndromic defects. We stratified by sex, tumor histology (yolk sac tumor, teratoma, germinoma, mixed/other) and location (gonadal, extragonadal, intracranial).

Results: Birth defects and syndromic defects were more common among GCT cases than controls (6.9% vs. 4.0%, 2.7% vs. 0.2%, respectively, both p<0.001). In multivariable models, GCT risk was increased among children with birth defects (OR 1.7, CI 1.3–2.4) and syndromic defects (OR 10.4, CI 4.9–22.1). When stratifying by tumor characteristics, birth defects were associated with yolk sac (OR 2.7, CI 1.3–5.0) and mixed/other histologies (OR 2.1, CI 1.2–3.5), and both gonadal (OR 1.7, CI 1.0–2.7) and extragonadal (OR 3.8, CI 2.1–6.5) tumors. Non-syndromic defects specifically were not associated with GCTs. In sex-stratified analyses, associations were observed among males but not females.

Conclusions: Our data suggest that syndromic birth defects are at increased risk of pediatric GCTs in males, whereas children with non-syndromic defects are not at increased risk.

PRECIS:

We evaluated whether birth defects were associated with pediatric germ cell tumors, accounting for type of birth defect, tumor histology and location, and sex of the patient. We found that syndromic birth defects were associated with germ cell tumors in males, whereas there was no increased risk among females or children with non-syndromic birth defects.

PLAIN LANGUAGE SUMMARY: We investigated whether birth defects (like congenital heart disease or Down syndrome) are linked to childhood germ cell tumors (GCTs) – cancers that mainly develop in the ovaries or testes. We studied different types of birth defects (defects that were caused by chromosome changes like Down syndrome or Klinefelter syndrome, and defects that were not) and different types of GCTs. Only chromosome changes like Down syndrome or Klinefelter syndrome were linked to GCTs. Our study suggests that most children with birth defects are not at increased risk of germ cell tumors, because most birth defects are not caused by chromosome changes.

Keywords

germ cell tumors; childhood cancer; birth defects; cancer predisposition; epidemiology

INTRODUCTION

Childhood germ cell tumors (GCTs) are a heterogeneous group of tumors that originate *in utero*. It is believed that GCTs originate from the primordial germ cell, and that the tumor's histologic subtype reflects the cell's differentiation state at the time of tumor initiation[1, 2], a hypothesis which is supported by the loss of imprinting seen in some tumors but not others.[3] Tumors arising from undifferentiated germ cells are termed seminomatous and include testicular seminomas, ovarian dysgerminomas, and intracranial germinomas. In contrast,

nonseminomatous tumors are a histologically diverse group including choriocarcinomas, embryonal carcinomas, teratomas, and yolk sac tumors.[4] Mixed tumors present with features of more than one histology. Incidence varies by age, sex, and histologic subtype[5]: in both males and females, incidence is approximately 15 cases per million during infancy. Thereafter, incidence declines and remains low throughout mid-childhood, but increases during adolescence. In older children and adolescents, peak incidence rates are substantially greater among males (50 cases per million) than females (15 cases per million). In infants and young children, teratomas and yolk sac tumors predominate; embryonal carcinomas, teratomas, and mixed GCTs are most common in adolescent males while dysgerminomas and teratomas are most common in adolescent females.

There have been few epidemiologic studies of childhood GCTs, and, apart from Klinefelter syndrome, gonadal dysgenesis, and disorders of sex development, few risk factors have been identified.[6] Differences in incidence rates have been reported by race and ethnicity, and there are reports of increased cancer incidence in relatives of children with GCTs, particularly cases with intracranial tumors.[2, 7] A Children's Cancer Group study reported that maternal exposure to chemicals/solvents or plastic/resin fumes was associated with increased odds of GCTs.[8] Large for gestational age and preterm birth appear more common among GCT cases, although there is concern for reverse causation.[2, 8] Parental demographic factors have also been evaluated, though studies have found conflicting results with respect to mother's age, education, and parity; parental alcohol and tobacco consumption do not appear to be risk factors for GCT in the offspring.[2, 8–10]

Birth defects, which are defined as structural or functional anomalies present at birth and are diagnosed in approximately 6% of livebirths globally,[11] are among the strongest and most consistent risk factors for cancer in children.[12, 13 11] Like GCTs, birth defects may result from *in utero* insults that disrupt cell differentiation or migration. This similarity suggests the possibility of shared etiologies, which may be reflected in birth defect-GCT associations. Indeed, Klinefelter, Turner, and Down syndromes have each been associated with pediatric GCTs.[1, 14, 15] Prior work suggests that cryptorchidism is associated with testicular GCT[16, 17], but less is known regarding other "non-syndromic" defects, which lack known chromosomal or genetic etiologies and constitute ≥85% of birth defect diagnoses. Some studies have reported associations[2, 15, 18–23] between GCTs and birth defects whereas others found none.[8, 9, 24] In our previous population-based assessment of >10 million births, non-syndromic defects in all major organ systems were associated with increased risk of pediatric GCTs, with greater than five-fold increases in the adjusted hazard ratio (HR) of GCT diagnosis observed for a number of birth defects phenotypes, including cardiac septal defects, clubfoot, and craniosynostosis.[12] Similarly, a report from the Children's Oncology Group (COG) described a two-fold increased risk of GCTs among male but not female children with birth defects, and observed that associations with specific birth defects varied for gonadal and extragonadal tumors, based on 278 cases.[16]

While there is evidence that associations between birth defects and GCTs vary by sex, histologic subtype, and anatomical location[2, 16], few studies have stratified on these factors[2, 8, 14, 16] and most have been performed in small samples (<100 cases with GCTs).[15, 18, 20, 21, 23–28] We sought to address these limitations through a comprehensive assessment of the

associations between birth defects and pediatric GCTs in a large study population, in which we could account for potential differences by sex, tumor histology, tumor location, and type of birth defect. Our aim is to elucidate associations between birth defects and specific GCT subtypes, which could inform future studies of GCT etiology and may assist in identifying children at risk for these tumors.

METHODS

Study Population

We performed a case-control study of pediatric GCTs using data from two existing studies of childhood cancer. Children with GCTs ("cases") were identified from among families enrolled on the Germ Cell Tumor Epidemiology (GaMETES) Study, which recruited families of children diagnosed with malignant primary GCTs between January 1, 2008 and December 31, 2015 through the COG Childhood Cancer Research Network. Additional eligibility criteria included age <20 years at diagnosis and at least one parent who was able to complete the study questionnaire in English or Spanish. Children without cancer ("controls") were selected from the Genetic Overlap Between Anomalies and Cancer in Kids (GOBACK) Registry Linkage Cohort, a population-based study of cancer risk in children with birth defects that includes linked data from birth defects registries, cancer registries, and vital records in Arkansas, Massachusetts, Michigan, North Carolina, Oklahoma, South Carolina, and Texas.

Cases—The case group has been described in detail previously.[29] Of the 866 study participants, questionnaire data (described below) was available for 638. We excluded: cases diagnosed ≤3 months of age (N=54) as some birth defects in this group (e.g., congenital hip dislocation, patent ductus arteriosus) may be consequences of prematurity or tumors that developed *in utero*; cases with missing birth defect descriptions (N=17); and cases with cryptorchidism (N=15), as information on cryptorchidism was not available among all controls. Therefore, 552 cases with GCTs were ultimately included in our analyses. There was no overlap between this group and those included in the previous report from the COG.[16] Diagnosis was confirmed using pathology reports obtained from the treating institution. Cases with germinoma (histologic codes 9060–9065), teratoma (9080–9084), embryonal carcinoma (9070, 9072), yolk sac tumor (9071), choriocarcinoma (9100, 9103, 9104), mixed histologic features (9085, 9101, 9102, 9105), or unknown histology were eligible. Due to the rarity of embryonal carcinoma (N=14 cases) and choriocarcinoma (N=3 cases), we included these in the 'mixed/other' category in analyses stratified by histology.

Information on child's sex (male, female), birthweight, and gestational age at birth (<38, 38–40, >40 weeks), as well as the mother's age at delivery (<20, 20–24, 25–29, 30–34, ≥35 years), educational attainment (no high school diploma, high school diploma, post-high school), self-described race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian/Alaska Native, or other), and ethnicity (Hispanic/Latino or not) were also collected.

Birth defects ascertainment among cases—Parents were asked whether they had ever been told by a doctor that their child had a birth defect, and if so, to provide a

written description of the birth defect and state the age at which it was diagnosed. Parents of boys were also asked if the child was born with cryptorchidism, hydrocele, atrophic testes, hypospadias, varicocele, orchitis, and/or groin hernias. In addition, array genotyping was performed to identify males with Klinefelter syndrome.[14] Study team members coded responses using International Classification of Disease, 9th revision (ICD-9) codes. For this analysis, we considered birth defects to be those conditions captured by ICD-9 codes 740.0–759.9. We excluded birth defects first recognized after the child's cancer diagnosis, to limit bias from the incidental discovery of birth defects caused by increased medical scrutiny in children undergoing treatment for cancer.

Controls—Controls (ten per case) were children in the GOBACK Registry Linkage Cohort from North Carolina (birth years 2003–2011), Oklahoma (birth years 1997–2012), and Texas (birth years 1999–2012) without a diagnosis of cancer (N=6,372).[12] These states were chosen due to the comparability of the practices and coding systems (six-digit Centers for Disease Control and Prevention-modified British Paediatric Association [CDC-BPA] codes) between their birth defects registries. Children were considered to have no history of cancer if their birth certificate could not be linked to a record of a malignant primary tumor in their state's population-based cancer registry by their eighteenth birthday. Controls were frequency matched to cases on sex and maternal race/ethnicity. Information on birthweight, gestational age, as well as maternal age, education, and race/ethnicity were obtained from birth certificates.

Birth defects ascertainment among controls—In each state, birth certificates were linked to data from birth defects surveillance systems to obtain information on birth defects diagnoses, which were coded using CDC-BPA six-digit codes, an extension of the ICD-9 coding system. All participating registries are population-based, active surveillance systems that collect information on all phenotypes considered as birth defects among cases and perform regular validation studies to verify data quality and timeliness.[30]

Statistical Analysis

We categorized birthweight as low (<2,500g), normal (2,500–3,999g), or high (≥4,000g). We first evaluated all birth defects (ICD-9/CDC-BPA codes 740–759) collectively, then separately evaluated non-syndromic defects and genetic/chromosomal syndromes. We further classified non-syndromic defects by organ system (central nervous system, cardiorespiratory, digestive, genitourinary, or musculoskeletal).

We summarized demographic characteristics and birth defects prevalence according to case-control status, tumor histology, and tumor location using counts and percentages. We tested for significant differences between cases and controls using X^2 or Fisher's exact tests, and computed logistic regression models to estimate the odds ratio (OR) and 95% confidence interval (95% CI) of GCT diagnosis according to birth defects status, adjusting for sex and maternal education. We computed models for all birth defects and all GCTs collectively, and when there were ≥5 exposed cases, we also evaluated non-syndromic and syndromic defects specifically; stratified by GCT histology (germinoma, teratoma, yolk sac tumor,

mixed/other) and location (gonadal, extragonadal); and repeated analyses separately among males and females.

To address the possibility of exposure misclassification, and based on the prevalence of birth defects in studies where this was ascertained using orthogonal methods[12, 26, 27], we performed probabilistic bias analyses using the 'episensr' R package (v1.1.0).[31, 32] We variously assumed 50%, 60%, and 70% sensitivity and 80% specificity for classification of birth defects status among cases, and 95% sensitivity and specificity for classification of birth defects status among controls (as the participating registries are believed to capture essentially all birth defects cases in their catchment areas and perform extensive quality checks to correct potential false positives).[30]

Ethical Approvals and Reporting Guidelines

This study was approved by the Baylor College of Medicine Institutional Review Board (IRB) and conducted in accordance with the principles of the Declaration of Helsinki. The GaMETES Study was approved by the University of Minnesota IRB. Informed consent was obtained from cases ≥18 years of age, or parents of cases <18 years of age; assent was obtained from cases 8–17 years of age. The GOBACK Registry Linkage Study was approved by the IRBs of Baylor College of Medicine, the University of North Carolina at Chapel Hill, the University of Oklahoma Health Sciences Center, and the relevant ethical and regulatory bodies of participating agencies. The requirement for written informed consent was waived as the study involved secondary analysis of de-identified data collected for public health surveillance. To protect privacy and confidentiality and comply with the requirements of some participating IRBs, exact counts are suppressed throughout the text and tables when there are five or fewer controls in a group.

RESULTS

Relative to GCT cases excluded due to missing questionnaire data, those with complete data were less likely to be diagnosed with gonadal tumors (46.1% vs. 55.0%, p=0.04) and more likely to have a mother who identified as non-Hispanic white (42.6% vs. 69.9%, p<0.001). There were no differences with respect to sex, age at diagnosis, tumor histology, or maternal age at delivery. Table 1 shows demographic characteristics by case-control status, as well as the distributions of tumor histologic subtypes and locations among cases. Cases and controls differed with respect to birthweight and gestational age; mothers of cases tended to be older and to have greater education levels at the time of delivery than mothers of controls (all p<0.05). Among cases, mixed/other tumors were the most common histologic subtype (31.3%), and the site of most tumors was gonadal (50.4%). We present demographic information according to tumor histology in Supplemental Table S1 and tumor location in Supplemental Table S2.

Relative to controls, cases were more often diagnosed with birth defects (6.9% vs. 4.0%; p<0.001) and syndromic defects (2.7% vs. 0.2%; p<0.001) (Table 2). Prevalence of non-syndromic defects was similar between cases and controls. Among GCT cases, the most common syndrome diagnoses were Klinefelter syndrome (N=8) and Down syndrome (N=2). A list of the birth defects reported in cases with GCTs is provided in Supplemental Table

S3, and information regarding birth defects among cases according to tumor histology and location is provided in Supplemental Table S4 and Supplemental Table S5. In multivariable logistic regression models (Table 3), we found increased odds of GCTs among children with any birth defect (OR 1.7, 95% CI 1.3–2.4) or syndromic birth defects (OR 10.4, 95% CI 4.9–22.1), but not non-syndromic defects (OR 1.1, 95% CI 0.7–1.6). When stratifying by tumor histology, birth defects were associated with yolk sac tumors (OR 2.7, 95% CI 1.3–5.0) and mixed/other tumors (OR 2.7, 95% CI 1.2–3.5), but not germinomas; few GCT cases with teratomas had co-occurring defects. When stratifying by tumor location, odds of gonadal (OR 1.7, 95% CI 1.0–2.7) and extragonadal tumors (OR 3.8, 95% CI 2.1–6.5) were increased, whereas few cases with intracranial GCTs were diagnosed with co-occurring defects. We observed strong associations (ORs >5) of syndromic birth defects with tumors of mixed/other histology, and both gonadal and extragonadal tumors. Non-syndromic defects were not associated with GCTs.

Males with syndromic defects were at increased risk of extragonadal tumors and tumors with mixed/other histology, whereas non-syndromic defects were not associated with GCTs in this group and no birth defect-GCT associations were evident among females. In a sensitivity analysis excluding children with Klinefelter syndrome (eight cases and ≤5 controls), associations between syndromic defects and GCTs among males were attenuated, but odds of any (OR 9.9, 95% CI 2.1–37.3), extragonadal (OR 22.7, 95% CI 4.6–86.7), and gonadal tumors (OR 9.4, 95% CI 2.0–35.2) remained elevated.

Misclassification bias-corrected ORs and 95% CIs for the association of any birth defect with GCTs ranged from 2.18 (0.81–5.83) given 70% sensitivity and 80% specificity in the case group to 8.13 (1.17–56.31) assuming 50% sensitivity and 80% specificity in the case group.

DISCUSSION

Using data from a large cohort of pediatric GCT cases from the GaMETES Study and controls from the GOBACK Registry Linkage Cohort12, we sought to evaluate the associations between birth defects and GCTs. Birth defects were reported in a larger proportion of cases than controls, and in multivariable models were associated with GCTs overall, tumors with yolk sac or mixed/other histology, and tumors at both gonadal and extragonadal (but not intracranial) sites. These associations appeared to be driven by syndromic defects in males.

Multiple population-based assessments in which birth defects status was ascertained prospectively by population-based registries have reported an excess of birth defects among children and adolescents with GCTs. A study conducted in Victoria, Australia, reported an OR of 8.9 (95% CI 2.6–30.3) for gonadal and germ cell tumors among children with a birth defect[20]. U.S. studies reported incidence rate ratios (IRRs) of GCTs among children with birth defects of 5.2 (2.7–9.4) in Texas[27] and 4.1 (95% CI 1.3–12.8) in Utah, Arizona, and Iowa.[15] A California study reported an adjusted HR of non-central nervous system (CNS) GCTs among children with non-chromosomal birth defects of 3.0 (95% CI 1.5–6.1)[22] and in our own assessment of >10M U.S. livebirths, HRs ranged from 5.0 (95% CI 3.3–7.4) for

musculoskeletal defects to 13.1 (95% CI 8.1–21.3) for CNS defects.[12] In the present study, which relied on retrospective maternal report of birth defects status among cases, syndromic defects were consistently associated with increased risk of GCTs among males. This finding is unsurprising given that Klinefelter syndrome, which affects males exclusively, was the most common syndrome diagnosis (N=8 cases) and is linked to increased incidence of pediatric GCTs.[14] We found little evidence of increased GCT risk among children with non-syndromic defects, which is in agreement with an earlier report from the COG, performed in a non-overlapping series of cases, in which mothers retrospectively reported birth defect diagnoses via telephone interview. The authors of that study found few associations with birth defects other than for cryptorchidism.[16]

When evaluating associations by site and histology, we observed increased odds of yolk sac tumors and mixed/other tumors but not germinomas or teratomas, and of gonadal and extragonadal but not intracranial GCTs in children with birth defects. In contrast, a study of 415 children diagnosed with GCTs at <5 years of age in the California Cancer Registry reported that teratomas were strongly associated with birth defects overall (OR 15.4, 95% CI 9.5–25.2) and ear, face, or neck anomalies specifically (OR 93.7, 95% CI 45.1–105.0).[2] We observed no excess of any specific category of non-syndromic defects among cases. As many children with syndromes have co-occurring structural defects, associations between structural defects and GCTs will likely appear stronger when children with syndromes are included; this could explain the null findings in our study since we excluded syndromic cases in our analyses of structural birth defects by organ system.

Few sex-stratified assessments are available for comparison. In reviewing death certificates from U.S. children with teratomas, Fraumeni observed genitourinary defects in 3/72 females and 3/19 males with sacrococcygeal teratomas[33], a pattern later recapitulated in a second study of death certificates performed in Great Britain.[18] A prospective Norwegian study utilizing data from population-based registers was also suggestive of increased risk of GCTs among males with birth defects, including non-significantly increased risk of testicular tumors (OR 1.4, 95% CI 0.7–2.9).[9] Johnson et al. reported a 2.5-fold (95% CI 1.3–4.9) increased risk of GCTs among males with birth defects but no increased risk among females[16], similar to the pattern we observed. The authors of that study also reported increased risk of seminomas in males with cryptorchidism, which we were unable to assess as information on cryptorchidism diagnosis was not available in controls.

Evidence suggests pediatric GCTs arise from the primordial germ cell (PGC). Approximately two weeks after fertilization, specification of the pluripotent PGC occurs and an elaborately orchestrated process of proliferation and migration to the gonadal ridge begins. This process is under complex genetic and epigenetic control, and, when perturbed, may result in GCT formation.[4, 29, 34, 35] While the exact mechanisms of association between birth defects and GCTs are unknown, it is probable that they have shared genetic or environmental causes, whereby the same insults lead to congenital malformations and improper specification, differentiation, or migration of the PGC. Among males with Klinefelter syndrome, it has been suggested that the increased risk of GCTs may relate to changes in the expression of genes escaping X chromosome inactivation.[14] We also report two cases of GCTs among children with Down syndrome. We and others have described

DNA methylation changes in children with Down syndrome, including at CpGs associated with potentially relevant pathways such as chemokine receptor activity.[36–38] In contrast, the etiologies of non-syndromic birth defects are poorly understood and likely multifactorial, with both genetic and environmental factors implicated. Certain genes, for example *CXCR4* and *CXCL2*[4, 39–41], which have been implicated both in the development of GCTs and congenital heart disease, regulate both PGC migration and organogenesis. Genetic or epigenetic alterations in such genes could result in the co-occurrence of non-syndromic birth defects and GCTs and explain the reported association of congenital heart disease with GCTs. [12, 16]

Because GaMETES did not enroll a non-cancer control series, we identified an external comparison group of children without cancer from an existing registry linkage cohort. A potential limitation to this approach is that birth defects status was ascertained differently in cases (parental report) and controls (population-based birth defects registries); both methods have potential drawbacks. While diagnoses recorded in population-based birth defects registries are verified by trained staff members and based on multiple data sources (e.g. birth, procedure, and hospital discharge or death records), these registries typically accept only diagnoses made in the first one to two years of life, and information on minor defects or neuropsychological phenotypes is often unavailable. Conversely, while parent report may not provide the same level of accuracy or completeness, it may be superior for identifying birth defects diagnosed later in childhood or for identifying children with other potentially relevant developmental phenotypes. Unfortunately, we are unaware of literature assessing the accuracy and completeness of parental report of birth defects status or whether this varies by child's age or other factors. Empirically, the proportion of GCT cases with a birth defect in the present study (8%) was less than that reported by Carozza (22%)[27], Lupo (20%)[12], or Merks (18%).[26] In the former two studies, information on birth defects status was obtained by review of records from birthing hospitals, pediatric genetics clinics, and other facilities, whereas in the latter it was based on a body surface examination performed by a specially trained pediatrician. These results suggest the possibility that birth defects may have been underreported among cases in the present study, and, therefore, we performed probabilistic bias analyses under a range of assumptions. Results suggested that, in the event birth defects were substantially underreported among cases, our results would be biased towards the null. However, the strongest associations we observed in the present study were for syndromic defects, and we hypothesize that these would not be subject to the same bias given that array genotyping of cases was performed.

The present study's strengths include its large sample size and consideration of sex, tumor histology, and tumor location. Our study highlights heterogeneity among birth defect-GCT associations according to these factors that may be important for future etiologic investigations. Our study also has certain limitations. COG data are not population-based and demographic factors such as sex, age, and race/ethnicity were associated with likelihood of enrollment on COG studies, including GaMETES[42], which may limit the generalizability of our findings. Perhaps for this reason, mothers of GCT cases had markedly greater educational attainment than mothers of controls. Although we adjusted for maternal education in our models, we cannot exclude the possibility of selection bias (since maternal education may have been related to participation in a research study) or information bias

(since maternal education may have been related to recall and reporting of birth defects and other potentially relevant exposures).

CONCLUSIONS

Multiple population-based studies suggest increased GCT risk among children with birth defects, but few provide estimates according to sex or tumor characteristics. Our findings indicate that syndromic birth defects are associated with pediatric GCTs among males but not females. Although our data do not suggest an association between non-syndromic birth defects and pediatric GCTs, additional studies are needed to confirm this finding, as there is potential for bias. In addition, estimation of the absolute risk for GCTs in children with birth defects may facilitate risk prediction and screening efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA ACCESSIBILITY STATEMENT:

Restrictions apply to the availability of these data, which were used under license for this study. Data from the GaMETES Study are available upon application to the corresponding author. Data from the GOBACK Registry Linkage Study are available upon application to the Texas Department of State Health Services, North Carolina Division of Public Health, and the Oklahoma State Department of Health.

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Table 1:

Demographic and maternal characteristics of germ cell tumor cases and controls.

	Controls		Germ Cell Tumor Cases	
	N	%	N	%
Sex				
Male	3,262	51.2	286	51.8
Female	3,110	48.8	266	48.2
Birthweight (g)				
<2,500	458	7.2	43	7.8
2,500–3,999	5,103	80.1	441	79.9
≥4,000	447	7.0	58	10.5
Gestational age at birth (wks)				
<38	1,239	19.4	82	14.9
38–40	4,663	73.2	375	67.9
>40	419	6.6	92	16.7
Maternal race/ethnicity				
Non-Hispanic White	4,324	67.9	371	67.2
Non-Hispanic Black	260	4.1	24	4.3
Hispanic	938	14.7	84	15.2
Asian/Pacific Islander	350	5.5	33	6.0
Other	500	7.8	43	7.2
Maternal age (yrs)				
<20	808	12.7	37	6.7
20–24	1,696	26.6	95	17.2
35–29	1,766	27.7	150	27.2
30–34	1,357	21.3	184	33.3
≥35	741	11.6	84	15.2
Maternal education				
Less than high school	1,977	31.0	28	5.1
High school	1,500	23.5	81	14.7
Greater than high school	2,426	38.1	441	79.9
Tumor histology				
Germinoma	-	-	160	29.0
Teratoma	-	-	100	18.1
Yolk sac tumor	-	-	105	19.0
Mixed/other	-	-	173	31.3
Missing or unknown	-	-	14	2.5
Tumor site				
Gonadal	-	-	278	50.4
Extragonadal	-	-	109	19.7

	Controls		Germ Cell Tumor Cases	
	N	%	N	%
Intracranial	-	-	165	29.9

Column percentages may not sum to 100% due to missing values.

Table 2:

Birth defects prevalence among cases and controls.

	Controls		Germ Cell Tumor Cases		
	N	%	N	%	p[1]
Any birth defect	255	4.0	38	6.9	<0.001
Non-syndromic	241	3.8	23	4.2	0.7
Syndromic	14	0.2	15	2.7	<0.001
Non-syndromic defects [2]					
Central nervous system	24	0.4	<5	-	-
Eye, ear, face, or neck	44	0.7	5	0.9	0.6
Cardiorespiratory	84	1.3	5	0.9	0.5
Digestive	31	0.5	<5	-	-
Genitourinary	80	1.3	11	2.0	0.2
Musculoskeletal	124	1.9	<5	-	-

1. By Chi-square or Fisher's exact test.

2. Categories are non-mutually exclusive.

Table 3:

Odds Ratio and 95% Confidence Interval of Pediatric Germ Cell Tumors According to Birth Defect Status.

	Any birth defect		Non-syndromic		Syndromic	
	All subjects					
	N	OR (95% CI)	N	OR (95% CI)[1]	N	OR (95% CI)[1]
Any GCT	38	1.7 (1.3–2.4)	23	1.1 (0.7–1.6)	15	10.4 (4.9–22.1)
Tumor histology						
Germinoma	7	1.1 (0.5–2.2)	<5	-	<5	-
Yolk sac tumor	11	2.7 (1.3–5.0)	8	1.9 (0.8–3.9)	<5	-
Mixed/other	15	2.1 (1.2–3.5)	9	1.3 (0.6–2.5)	6	12.0 (4.1–13.1)
Tumor site						
Gonadal	19	1.7 (1.0–2.7)	14	1.3 (0.7–2.2)	5	7.3 (2.3–19.5)
Extragonadal	15	3.8 (2.1–6.5)	5	1.2 (0.4–2.8)	10	40.0 (16.1–94.3)
	Males					
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Any GCT	27	1.9 (1.2–2.9)	14	1.0 (0.5–1.7)	13	15.5 (6.3–40.0)
Tumor histology						
Germinoma	5	1.0 (0.4–2.3)	<5	-	<5	-
Yolk sac tumor	7	3.3 (1.3–7.7)	<5	-	<5	-
Mixed/other	10	2.2 (1.1–4.0)	5	1.3 (0.6–2.8)	5	13.7 (4.0–44.3)
Tumor site						
Gonadal	15	2.2 (1.1–3.9)	10	1.7 (0.8–3.3)	<5	-
Extragonadal	12	5.8 (2.8–11.3)	<5	-	10	78.5 (28.1–225.0)
	Females					
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Any GCT	11	1.3 (0.7–2.3)	9	1.1 (0.5–2.2)	<5	-
Tumor histology						
Germinoma	<5	-	<5	-	<5	-

		Any birth defect		Non-syndromic		Syndromic	
		All subjects					
		N	OR (95% CI)	N	OR (95% CI)[1]	N	OR (95% CI)[1]
	Yolk sac tumor	<5	-	<5	-	<5	-
	Mixed/other	<5	-	<5	-	<5	-
Tumor site							
	Gonadal	6	1.2 (0.5–2.5)	<5	-	<5	-
	Extragonadal	<5	-	<5	-	<5	-

Abbreviations: CI=confidence interval; GCT=germ cell tumor; OR=odds ratio.

1. Adjusted for maternal education. Models computed among all subjects are adjusted for sex.