Birth Defects are Associated with Pediatric Germ Cell Tumors Among Males but not Females

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BACKGROUND

Germ cell tumors (**GCTs**) are a heterogeneous group of tumors that arise from primordial germ cells. GCTs are rare in young children, but account for 15% of cancers in adolescents and young adults. Major histologic groups include teratomas, yolk sac tumors, seminomas/dysgerminomas, and mixed GCTs. GCTs may occur in a variety of anatomical locations.

Birth defects are structural or functional anomalies present at birth; they are diagnosed in 3% of U.S. livebirths.

Birth defects may be associated with GCTs, but:
- Many studies did not stratify by tumor histology or location
- Many studies did not evaluate a broad range of defects

PURPOSE

To comprehensively evaluate associations between birth defects and GCTs by type of defect, tumor histologic subtype, and tumor location.

METHODS

Cases were <20 years of age and diagnosed with malignant GCTs at Children's Oncology Group institutions between 07/2008-12/2015. Birth defects were ascertained via parental questionnaire.

We selected 10 controls per case, matched on sex and maternal race/ethnicity, from birth certificates in TX, NC, and OK. Birth defects were ascertained via linkage to population-based birth defects surveillance systems in each state.

We classified birth defects as syndromic (due to chromosomal or genetic syndromes) or non-syndromic. Non-syndromic defects were further categorized by organ system.

We compared the prevalence of birth defects between cases and controls using X^2 tests, and computed logistic regression models to estimate the odds ratio (**OR**) and 95% confidence interval (**CI**) of GCTs according to birth defects status. Models were adjusted for maternal age, and adjusted for or stratified on sex.

TABLE 1. CASE AND CONTROL DEMOGRAPHICS, N (%)

	CONTROLS	CASES
Male	3,262 (51.2)	286 (51.8)
Birthweight (g)		
<2,500	458 (7.6)	43 (7.9)
2,500-3,999	5,103 (84.9)	441 (81.4)
≥4,000	447 (7.4)	58 (10.7)
Gestational age (wks)		
<38	1,239 (19.6)	82 (14.9)
38-40	4,663 (73.8)	375 (68.3)
>40	419 (6.6)	92 (16.8)
Maternal race/ethnicity		
White	4,324 (67.9)	371 (67.2)
Black	260 (4.1)	24 (4.3)
Hispanic	938 (14.7)	84 (15.2)
Other/unknown	850 (13.3)	73 (13.2)
Maternal age (yrs)		
<20	808 (12.7)	37 (6.7)
20-24	1,696 (26.6)	95 (17.3)
25-29	1,766 (27.7)	150 (27.3)
30-34	1,357 (21.3)	184 (33.5)
≥35	741 (11.6)	84 (15.3)
Maternal education		
< High school	1,977 (33.5)	28 (5.1)
High school	1,500 (25.4)	81 (14.7)
> High school	2,426 (41.1)	441 (80.2)

FIGURE 1. OR AND 95% CI OF GCT SUBTYPES ACCORDING TO BIRTH DEFECTS STATUS.

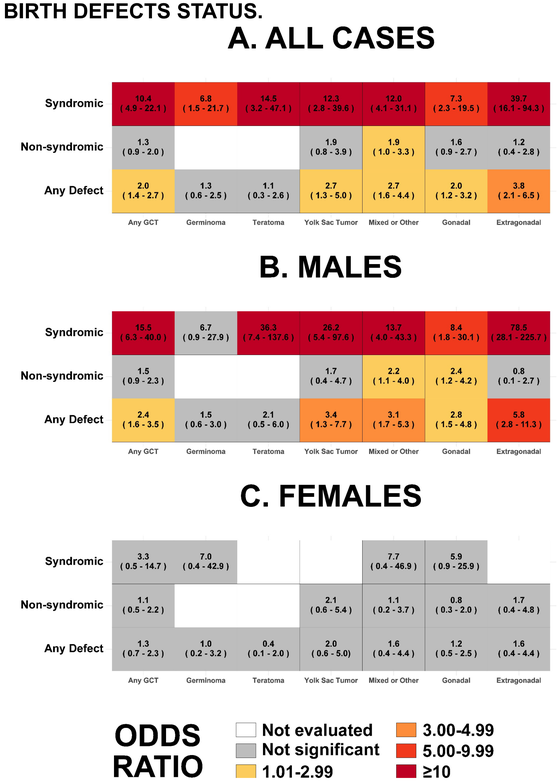

TABLE 2. BIRTH DEFECTS PREVALENCE AMONG CASES AND CONTROLS, N (%)

	CONTROLS	CASES	P-VALUE
Any birth defect	255 (4.0)	44 (8.0)	<0.001
Syndromic birth defects	14 (0.2)	15 (2.7)	<0.001
Non-syndromic birth defects	241 (3.8)	29 (5.3)	0.10
Central nervous system	24 (0.4)	1 (0.2)	0.70
Eye, ear, face, or neck	44 (0.7)	5 (0.9)	0.60
Cardiorespiratory	84 (1.3)	5 (0.9)	0.50
Digestive	31 (0.5)	1 (0.2)	0.50
Genitourinary	80 (1.3)	11 (2.0)	0.20
Musculoskeletal	124 (1.9)	10 (1.8)	0.90

RESULTS

Greater proportions of cases than controls were high birthweight or >40 weeks gestation at birth. Mothers of cases were more often ≥35 years of age and more often had post-high school education **(Table 1)**.

Cases were more likely than controls to be diagnosed with any birth defect or a syndromic birth defect. There were no significant differences between cases and controls with respect to categories of non-syndromic defects **(Table 2)**.

Among all cases combined, birth defects were associated with GCTs overall, tumors with yolk sac or mixed histology, and gonadal as well as extragonadal tumors. These associations were primarily driven by syndromic defects, which were strongly associated (OR>5) with all GCT subtypes. Non-syndromic defects were associated with mixed GCTs **(Fig. 1A)**.

Non-syndromic defects were associated with a two-fold increased risk of tumors with mixed GCTs and gonadal tumors among males **(Fig. 1B)**.

We did not observe associations between birth defects and GCTs among females **(Fig. 1C)**.

In an analysis of specific birth defect categories, elevated point estimates were observed among children with genitourinary defects for yolk sac tumors (OR 3.4, CI 1.0-8.6), gonadal tumors (OR 2.2, CI 0.9-4.5), and extragonadal tumors (OR 2.2, CI 0.5-6.0).

CONCLUSION

Our results suggest that non-syndromic birth defects, particularly genitourinary defects, are associated with pediatric GCTs. Associations were strongest for tumors with mixed or yolk sac histology, and appear to be specific to males. The apparent effect modification by sex may be attributable to differences in the distribution of tumor type by sex, and, for syndromic defects, an increased risk of testicular GCTs among males with Klinefelter syndrome.