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Original Article

Risk of malignant childhood germ cell tumors in relation to demographic, gestational, and perinatal characteristics

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ABSTRACT

Background: Childhood germ cell tumors (GCTs) are a rare assortment of neoplasms, with mostly unknown etiology, that are believed to originate very early in life. Few studies have examined risk factors by histologic subtype, despite evidence of different risk profiles.
Materials and methods: In this population-based case-control study, 451 childhood malignant GCT cases ages 0–5 years were identified from the California Cancer Registry. Differentiating between common histologic subtypes, we identified 181 yolk sac tumors, 216 teratomas, and 54 rarer subtypes. Cases were linked to their birth certificates and 271,381 controls, frequency matched by birth year, were randomly selected from California birthrolls to investigate the contributions of demographic, gestational, and pregnancy factors using unconditional logistic regression analysis.
Results: Compared to non-Hispanic whites, Asian/Pacific Islander children were at an increased risk for developing GCTs (odds ratio [OR] = 1.94; 95% confidence interval [CI] = 1.47, 2.56). Among pregnancy complications and procedures, yolk sac tumors were positively associated with the presence of fetopelvic disproportion (OR = 2.97; 95% CI = 1.55, 5.68), while teratomas were strongly associated with polyhydramnios or oligohydramnios (OR = 14.76; 95% CI = 7.21, 30.19) and the presence of an ear, face, or neck anomaly at birth (OR = 93.70; 95% CI = 42.14, 208.82).
Conclusions: Malignant yolk sac tumors and malignant teratomas exhibited distinct demographic and gestational characteristics; additionally, complications in pregnancy and labor may be brought on by specific histologic subtypes.

1. Introduction

Childhood germ cell tumors (GCTs) are an assorted group of malignant and benign neoplasms that vary with respect to their clinical presentation, histopathology, and biologic characteristics, but are all believed to originate from primordial germ cells [1,2]. In children under 5 years of age, the two most common GCT subtypes are teratomas and yolk sac tumors [3]. GCTs comprise 3.5% of all cancers in those younger than 15 years of age [4]; in the United States, the GCT rate for children ages 0–14 is approximately 6.0 per million [5], while in Europe the rate is estimated to be 4.8 per million [6]. GCTs are infrequently studied and their etiology is largely unknown.

Although epidemiologic studies of GCTs in children are rare, positive associations have been reported between cancer incidence and Asian/Pacific Islander race, abnormal fetal growth, birth defects, and congenital malformations, suggesting that early life exposures are important in their etiology [7–11]. Other studies have reported that exposures to traffic pollution, certain solvents, and residence in agriculturally intense areas have been associated with GCTs [12–14], while the role of breastfeeding, parental smoking, and exposure to female hormones or pesticides has been suggested [13,15–18]. Likely due to small sample sizes, few studies of younger cases differentiated by histological subtype [19–21], despite evidence for distinct etiologies and ages of diagnosis, as well as heterogeneous tumor DNA methylation signatures, suggesting differences in exposure windows and, possibly, causal mechanisms [3,19–22].

In this large, population-based case-control study of California children, we aimed to examine the association between demographic, gestational, and perinatal characteristics and the occurrence of malignant childhood GCTs. Additionally, we separately

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assessed two common histological subtypes in our study population of young children, i.e. yolk sac tumors and teratomas. Our analyses were limited to tumors that are malignant.

2. Population characteristics and methods

This report utilizes data from subjects enrolled in a large case-control study which ascertained cases of childhood cancer—diagnosed between 1988 and 2013—from the California Cancer Registry; all children were 5 years old or younger at the time of diagnosis [23]. Eligible cases had to be born in California and linkable to birth certificates. Using first and last names, date of birth, and social security number when available, we were able to link 89% of all cases to a California birth certificate in the parent study. We selected controls, for whom there was no record of a cancer diagnosis before age 6, randomly from California birth records and frequency matched them to cases by birth year. Approval for this study was received from the human subjects' protection boards at the University of California, Los Angeles and the California Health and Human Services Agency.

Cases of GCTs were identified via the International Classification of Childhood Cancer, Version 3 (ICCC-3), using codes 101–105 (n = 451). Histological subtypes of GCTs were defined according to the International Classification of Diseases for Oncology, Version 3 (ICD-O-3): yolk sac tumors (ICD-O-3 code 9071; n = 181) and malignant teratomas (ICD-O-3 codes 9080-9084 with malignant behavior code; n = 216) were most prominent in our population. There were 54 GCT cases coded as neither a teratoma nor a yolk sac tumor (mixed germ cell tumors, n = 26; germinomas, n = 16; other, n = 12).

Cases and controls were excluded from analyses if they were likely nonviable births (gestational age <20 weeks, n = 117; birth weight <500 g, n = 276; indeterminate sex, n = 3), or had missing values for neighborhood-level socioeconomic status (SES) (n = 388). Controls were additionally excluded if they died of other causes before the age of 6 (n = 577) or did not reside in California (n = 767). Our final analytic dataset consisted of 451 GCT cases and 271,381 controls.

California birth certificates provided information on parental demographics, gestational factors, and maternal reproductive and medical history. Information regarding complications in pregnancy and/or delivery, maternal comorbidities, clinical procedures conducted in the perinatal period, and abnormal conditions of the child were also obtained from birth certificates. Gestational age (≤37, 38–42, and ≥43 weeks) was estimated from the date of last menses; if the length was improbably long (>45 weeks) it was defined as missing. Size for gestational age was created using the method proposed by Alexander et al., as previously described [24]; size was defined as "small" if birth weight was less than the 10th percentile and "large" if birth weight was greater than the 90th percentile within gestational week, sex, and race [25]. Variables pertaining to education, prenatal care visits, and prenatal care payment were only available for births after 1988. SES was examined through several measures: maternal and paternal educational attainment (≤8 years, 9–11, 12, 13–15, and ≥16 years); source of payment for prenatal care (private insurance [including

Table 1
Demographic factors in relation to germ cell tumors, stratified by histological type.

Characteristic	Controls (n = 271,381)		All cases (n = 451)		Yolk sac tumors (n = 181)		Teratomas (n = 216)	
	Controls (%)		Cases (%)	Crude OR (95% CI)[a]	Cases (%)	Crude OR (95% CI)[a]	Cases (%)	Crude OR (95% CI)[a]
Mother's age (years)								
≤19	28,722	(10.6)	53 (11.8)	1.18 (0.87, 1.59)	27 (14.9)	1.58 (1.02, 2.43)	25 (11.6)	1.10 (0.71, 1.69)
20–29	140,747	(51.9)	221 (49.0)	Referent	84 (46.4)	Referent	112 (51.9)	Referent
30–34	63,166	(23.3)	107 (23.7)	1.08 (0.85, 1.36)	42 (23.2)	1.12 (0.77, 1.62)	47 (21.8)	0.93 (0.66, 1.31)
≥35	38,696	(14.3)	70 (15.5)	1.14 (0.87, 1.50)	28 (15.5)	1.23 (0.80, 1.87)	32 (14.8)	1.02 (0.69, 1.52)
Missing	50		0		0		0	
Mother's race/ethnicity and birth place								
White non-Hispanic	94,876	(35.2)	143 (31.7)	Referent	54 (30.0)	Referent	67 (31.2)	Referent
Hispanic, US born	43,796	(16.2)	62 (13.7)	0.93 (0.69, 1.26)	23 (12.8)	0.95 (0.58, 1.55)	34 (15.9)	1.08 (0.71, 1.64)
Hispanic, foreign born	80,640	(29.9)	194 (43.0)	1.08 (0.85, 1.37)	63 (35.0)	1.40 (0.97, 2.01)	56 (26.2)	0.97 (0.68, 1.39)
Black	18,112	(6.7)	24 (5.3)	0.88 (0.57, 1.35)	3 (1.7)	0.29 (0.09, 0.93)	17 (7.9)	1.33 (0.78, 2.26)
Asian/Pacific Islander	26,502	(9.8)	78 (17.3)	1.94 (1.47, 2.56)	33 (18.3)	2.23 (1.44, 3.44)	36 (16.8)	1.90 (1.27, 2.86)
Other	5977	(2.2)	12 (2.7)	0.99 (0.50, 1.94)	4 (2.2)	1.22 (0.44, 3.39)	4 (1.9)	0.92 (0.34, 2.54)
Missing	1478		3		1		2	
Mother's birth place								
Mexico	68,331	(25.2)	120 (26.6)	1.16 (0.93, 1.44)	60 (33.1)	1.72 (1.23, 2.41)	48 (22.2)	0.89 (0.64, 1.25)
US	153,542	(56.6)	232 (51.4)	Referent	79 (43.6)	Referent	120 (55.6)	Referent
Other foreign	49,235	(18.1)	99 (22.0)	1.33 (1.05, 1.68)	42 (23.2)	1.68 (1.15, 2.43)	48 (22.2)	1.24 (0.89, 1.74)
Missing	273		0		0		0	
Father's age (years)								
≤19	10,401	(4.1)	13 (3.1)	0.76 (0.43, 1.33)	7 (4.7)	1.08 (0.50, 2.35)	5 (2.5)	0.56 (0.23, 1.38)
20–29	112,156	(44.2)	185 (43.9)	Referent	70 (41.7)	Referent	96 (47.8)	Referent
30–34	64,974	(25.6)	105 (24.9)	0.98 (0.77, 1.24)	43 (25.6)	1.06 (0.73, 1.56)	48 (23.9)	0.86 (0.61, 1.21)
≥35	65,971	(26.0)	118 (28.0)	1.08 (0.85, 1.36)	48 (28.6)	1.18 (0.81, 1.70)	52 (25.9)	0.91 (0.65, 1.27)
Missing	17,879		30		13		15	
Father's race/ethnicity								
White non-Hispanic	83,123	(32.9)	121 (26.8)	Referent	41 (24.2)	Referent	62 (31.0)	Referent
Hispanic of any race	118,157	(46.8)	184 (40.8)	1.07 (0.85, 1.35)	84 (49.4)	1.51 (1.03, 2.21)	83 (41.5)	0.92 (0.66, 1.29)
Black	18,219	(7.2)	19 (4.2)	0.72 (0.44, 1.16)	3 (1.8)	0.34 (0.10, 1.08)	14 (7.0)	1.03 (0.58, 1.84)
Asian/Pacific Islander	20,453	(8.1)	64 (14.2)	2.15 (1.59, 2.92)	27 (15.9)	2.74 (1.68, 4.45)	30 (15.0)	1.95 (1.26, 3.01)
Other	12,624	(5.0)	63 (14.0)	1.58 (1.05, 2.38)	15 (8.8)	2.55 (1.40, 4.63)	11 (5.5)	1.14 (0.60, 2.17)
Missing	18,805		34		11		16	

[a] Odds ratios adjusted for the matching variable, birth year.

Health Maintenance Organizations and Blue Cross-Blue Shield] and other payment methods [government aid programs, worker's compensation, Title V, and self-pay]), which we previously observed to be a reasonable proxy for family income [26]; and a multifactorial neighborhood SES index which utilized principal components analysis to develop a single, five-level SES measure from seven census-tract level SES indicators, including mean educational attainment, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value [27].

Multivariable logistic regression was used to evaluate the relationship between GCTs, demographic factors, gestational factors, and complications related to pregnancy or labor. Pregnancy and labor complications or procedures are reported in our tables if there were at least five exposed cases. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) in unadjusted analyses of demographic factors that only controlled for the matching factor, birth year. In adjusted analyses of SES and gestational factors, we additionally controlled for maternal age (≤19, 20–29, 30–34, and ≥35 years old) and a combined maternal race/ethnicity and birthplace variable (non-Hispanic White, Hispanic [US born], Hispanic [foreign born], black, Asian/Pacific Islander, and other). Effect estimates for paternal education were adjusted for paternal age (≤19, 20–29, 30–34, and ≥35 years old) and paternal race/ethnicity (non-Hispanic White, Hispanic of any race, black, Asian/Pacific Islander, and other). For analyses related to pregnancy/labor complications and birth anomalies, a two-level maternal race variable was created (white vs. non-white) for adjustment purposes. Other demographic variables were left out of final regression models because they did not change effect estimates by 10% or more, including paternal age, paternal race/ethnicity, and maternal birthplace (US, Mexico, or other foreign). California birth certificates do not collect data on paternal birthplace. Approximately 1.7% of birth certificates did not have a father listed. For all analyses, we excluded any individuals with missing data points for the variables of interest. We additionally conducted sensitivity analyses of gestational factors and pregnancy or labor complications stratified by child's sex, as some previous studies have either controlled for sex or found differences between boys and girls [17,20,21]. We also ran analyses stratifying SES measures by race. In order to check whether preterm birth, gestational age, and Cesarean section were a consequence of the teratoma being diagnosed *in utero*, we conducted sensitivity analyses where we examined associations after excluding cases diagnosed within 5 days of birth.

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

In our population, mean ages at diagnosis were 14.8 months for all GCTs, 19.7 months for yolk sac tumors, and 8.2 months for teratomas.

GCT cases were more common among children born to parents from Asian/Pacific Islander backgrounds and foreign-born Hispanic mothers (Table 1). Elevated effect estimates for Asian/Pacific Islander race were observed across histologic subtypes, and yolk sac tumors were more common among children born to Hispanic fathers. Mothers of young age at birth (≤19) were also at increased risk of having a child who developed a yolk sac tumor. Teratomas were most commonly diagnosed in families with mothers and fathers who had completed high school, while yolk sac tumors were more common among children of parents with less than 8 years of formal education (Table 2). Furthermore, our neighborhood-level SES index showed a U-shaped relationship with yolk sac tumors.

Table 2
Socioeconomic status indicators in relation to germ cell tumors, stratified by histological type.

Characteristic	Controls (n = 273,519)		All cases (n = 451)		Yolk sac tumors (n = 181)		Teratomas (n = 216)	
	Controls (%)		Cases (%)	Crude OR (95% CI)	Cases (%)	Crude OR (95% CI)	Cases (%)	Crude OR (95% CI)
Mother's education (years)[a,b]								
8 or less years	29,450	(12.6)	58 (14.6)	1.17 (0.82, 1.67)	37 (24.5)	2.22 (1.31, 3.77)	16 (8.0)	0.55 (0.30, 0.98)
9 to 11 years	43,018	(18.5)	72 (18.1)	0.97 (0.71, 1.33)	28 (18.5)	1.11 (0.66, 1.87)	33 (16.6)	0.74 (0.48, 1.15)
12 years	66,075	(28.4)	116 (29.2)	Referent	36 (23.8)	Referent	70 (35.2)	Referent
13 to 15 years	47,387	(20.3)	77 (19.4)	0.91 (0.68, 1.22)	29 (19.2)	1.12 (0.68, 1.84)	42 (21.1)	0.84 (0.57, 1.24)
16 or more years	47,147	(20.2)	74 (18.6)	0.79 (0.58, 1.09)	21 (13.9)	0.67 (0.38, 1.21)	38 (19.1)	0.75 (0.49, 1.16)
Missing	14,318		31		16		10	
Father's education (years)[b,c]								
8 or less years	30,017	(13.8)	51 (13.9)	0.98 (0.69, 1.39)	32 (22.7)	1.65 (0.98, 2.72)	14 (7.8)	0.48 (0.26, 0.88)
9 to 11 years	33,526	(15.4)	49 (13.4)	0.82 (0.58, 1.17)	23 (16.3)	1.06 (0.62, 1.82)	21 (11.7)	0.63 (0.37, 1.06)
12 years	65,961	(30.3)	116 (31.6)	Referent	41 (29.1)	Referent	65 (36.1)	Referent
13 to 15 years	39,402	(18.1)	64 (17.4)	0.93 (0.70, 1.28)	17 (12.1)	0.78 (0.44, 1.40)	36 (20.0)	0.89 (0.58, 1.38)
16 or more years	48,528	(22.3)	87 (23.7)	0.97 (0.70, 1.35)	28 (19.9)	0.75 (0.42, 1.34)	44 (24.4)	0.99 (0.64, 1.52)
Missing	29,961		61		26		29	
Source of payment for prenatal care[a,b]								
Private/HMO/BCBS	117,219	(49.9)	210 (51.6)	Referent	75 (48.1)	Referent	108 (53.2)	Referent
MediCal/Govt/self-pay	117,589	(50.1)	197 (48.4)	0.91 (0.73, 1.15)	81 (51.9)	0.97 (0.67, 1.39)	95 (46.8)	0.85 (0.63, 1.17)
Missing	12,587		21		11		6	
Neighborhood-level SES index[a,b]								
Low	68,022	(25.1)	105 (23.2)	1.02 (0.76, 1.35)	44 (24.3)	1.20 (0.75, 1.93)	47 (21.8)	0.86 (0.57, 1.30)
Medium-low	66,039	(24.3)	121 (26.8)	1.19 (0.91, 1.56)	48 (26.5)	1.39 (0.89, 2.19)	64 (29.6)	1.17 (0.81, 1.71)
Medium	59,933	(22.1)	92 (20.4)	Referent	31 (17.1)	Referent	49 (22.7)	Referent
Medium-high	42,884	(15.8)	68 (15.1)	0.98 (0.71, 1.34)	28 (15.5)	1.22 (0.73, 2.05)	29 (13.4)	07. (0.49, 1.24)
High	34,503	(12.7)	65 (14.4)	1.16 (0.84, 1.61)	30 (16.6)	1.67 (1.00, 2.81)	27 (12.5)	0.92 (0.57, 1.49)

[a] Odds ratios adjusted for birth year, maternal age, and maternal race/ethnicity/birth place.
[b] Data for this variable is only available for births after 1988.
[c] Odds ratios adjusted for birth year, paternal age and paternal race/ethnicity.

In sensitivity analyses, results for SES differed by race among yolk sac tumors (Supplementary Table 1). For Asian/Pacific Islanders, there was a generally negative association between SES and yolk sac tumors; children born to mothers and fathers with less than 8 years of formal education were at an increased risk, while those born to parents with more than 16 years of formal

Table 3
Child and gestational factors in relation to germ cell tumors, stratified by histological type.

Characteristic	Controls (n = 271,381)	All cases (n = 451)		Yolk sac tumors (n = 181)		Teratomas (n = 216)	
	Controls (%)	Cases (%)	Adjusted OR (95% CI)[a]	Cases (%)	Adjusted OR (95% CI)[a]	Cases (%)	Adjusted OR (95% CI)[a]
Child's sex							
Male	138,573 (51.1)	256 (56.8)	1.25 (1.04, 1.51)	132 (72.9)	2.56 (1.84, 3.55)	95 (44.0)	0.75 (0.57, 0.98)
Female	132,808 (48.9)	195 (43.2)	Referent	49 (27.1)	Referent	121 (56.0)	Referent
Child's birth weight (g)							
≤2499 g	16,584 (6.2)	41 (9.1)	1.58 (1.14, 2.18)	6 (3.3)	0.56 (0.25, 1.26)	32 (14.8)	2.68 (1.82, 3.91)
2500–3999 g	226,640 (83.6)	361 (80.0)	Referent	154 (85.1)	Referent	164 (75.9)	Referent
≥4000 g	27,914 (10.3)	49 (10.9)	1.16 (0.86, 1.57)	21 (11.6)	1.18 (0.74, 1.86)	20 (9.3)	1.06 (0.66, 1.69)
Missing	243	0		0		0	
Child's birth weight (g) among cases diagnosed>5 days after birth[c]							
≤2499 g	16,584 (6.2)	16 (4.4)	0.73 (0.44, 1.21)	6 (3.3)	0.56 (0.25, 1.26)	8 (6.1)	0.98 (0.48, 2.01)
2500–3999 g	226,640 (83.6)	206 (85.0)	Referent	154 (85.1)	Referent	112 (85.5)	Referent
≥4000 g	27,914 (10.3)	38 (10.6)	1.07 (0.76, 1.50)	21 (11.6)	1.18 (0.74, 1.86)	11 (8.4)	0.87 (0.46, 1.61)
Missing	243	0		0		0	
Gestational age (weeks)							
≤37 wks (Preterm)	26,828 (10.4)	86 (20.1)	2.23 (1.76, 2.83)	21 (12.1)	1.22 (0.77, 1.94)	58 (28.6)	3.59 (2.63, 4.90)
38–42 wks (Term)	221,930 (85.8)	325 (75.9)	Referent	145 (83.8)	Referent	136 (67.0)	Referent
≥43 wks (Post-Term)	9835 (3.8)	17 (4.0)	1.22 (0.75, 2.00)	7 (4.1)	1.11 (0.52, 2.37)	9 (4.4)	1.54 (0.78, 3.04)
Missing	12,788	23		8		13	
Gestational age (weeks) among cases diagnosed >5 days after birth[c]							
≤37 wks (Preterm)	26,828 (10.4)	40 (11.6)	1.16 (0.83, 1.62)	21 (12.1)	1.22 (0.77, 1.94)	13 (10.4)	1.02 (0.57, 1.81)
38–42 wks (Term)	221,930 (85.8)	291 (84.6)	Referent	145 (83.8)	Referent	107 (85.6)	Referent
≥43 wks (Post-Term)	9835 (3.8)	12 (3.8)	1.05 (0.60, 1.83)	7 (4.1)	1.11 (0.52, 2.37)	5 (4.0)	1.10 (0.45, 2.69)
Missing	12,788	16		8		6	
Size for gestational age							
Small	27,241 (10.4)	36 (10.4)	0.77 (0.55, 1.09)	19 (10.9)	1.06 (0.65, 1.71)	13 (6.3)	0.57 (0.32, 0.99)
Normal	204,669 (78.0)	352 (80.9)	Referent	136 (78.2)	Referent	173 (83.2)	Referent
Large	30,472 (11.6)	47 (10.8)	0.89 (0.65, 1.21)	19 (10.9)	0.94 (0.58, 1.52)	22 (10.6)	0.86 (0.55, 1.34)
Missing	8999	16		7		8	
Number of prenatal care visits[b]							
≤5	13,595 (5.9)	32 (8.0)	1.48 (1.01, 2.16)	8 (5.2)	0.69 (0.33, 1.44)	23 (11.6)	2.75 (1.71, 4.44)
06-Oct	71,320 (30.7)	136 (34.1)	1.18 (0.95, 1.49)	47 (30.3)	0.81 (0.57, 1.16)	75 (37.9)	1.68 (1.22, 2.33)
Nov-15	122,784 (52.9)	195 (48.9)	Referent	94 (60.6)	Referent	75 (37.9)	Referent
16+	24,237 (10.4)	36 (9.0)	0.95 (0.67, 1.36)	6 (3.9)	0.34 (0.15, 0.78)	25 (12.6)	1.70 (1.08, 2.68)
Missing	15,459	29		12		11	
Multiple birth							
Single	264,274 (97.4)	446 (98.9)	Referent	180 (99.4)	Referent	212 (98.1)	Referent
Multiple	7107 (2.6)	5 (1.1)	0.42 (0.18, 1.02)	1 (0.5)	0.22 (0.03, 1.58)	4 (1.9)	0.71 (0.26, 1.91)
Parity							
0	106,705 (39.3)	166 (36.8)	Referent	61 (33.7)	Referent	96 (44.4)	Referent
1	84,875 (31.3)	157 (34.8)	1.24 (0.99, 1.55)	60 (33.1)	1.37 (0.94, 1.99)	70 (32.4)	0.94 (0.68, 1.27)
2 or more	79,612 (29.4)	128 (28.4)	1.11 (0.86, 1.43)	60 (33.1)	1.57 (1.06, 2.34)	50 (23.1)	0.72 (0.50, 1.04)
Missing	189	0		0		0	
Method of delivery							
Vaginal	202,697 (74.7)	297 (65.9)	Referent	138 (76.2)	Referent	120 (55.6)	Referent
Cesarean	68,507 (25.3)	154 (34.1)	1.58 (1.30, 1.93)	43 (23.8)	0.98 (0.69, 1.38)	96 (44.4)	2.48 (1.88, 3.26)
Missing	177	0		0		0	
Method of delivery among cases diagnosed >5 days after birth[c]							
Vaginal	202,697 (74.7)	277 (76.9)	Referent	138 (76.2)	Referent	101 (77.1)	Referent
Cesarean	68,507 (25.3)	83 (23.1)	0.90 (0.70, 1.15)	43 (23.8)	0.98 (0.69, 1.38)	30 (22.9)	0.89 (0.59, 1.34)
Missing	177	0		0		0	
History of miscarriages							
None	224,223 (82.7)	379 (84.0)	Referent	153 (84.5)	Referent	182 (84.3)	Referent
1	34,291 (12.6)	53 (11.8)	0.94 (0.71, 1.26)	21 (11.6)	0.97 (0.61, 1.53)	24 (11.1)	0.89 (0.58, 1.36)
2 or more	12,592 (4.6)	19 (4.2)	0.93 (0.58, 1.48)	7 (3.86)	0.91 (0.43, 1.97)	10 (4.6)	1.01 (0.53, 1.92)

[a] Odds ratios adjusted for birth year, maternal age, and maternal race/ethnicity/birth place.
[b] Data for this variable is only available for births after 1988.
[c] Analysis excludes cancers diagnosed within 5 days of birth (all germ cell tumors, n = 360; yolk sac tumors, n = 181; teratomas, n = 131).

education were at a decreased risk. Among non-Hispanic whites, the relationship with the neighborhood-level SES index was U-shaped for yolk sac tumors. Across races, individual-level SES measures exhibited no association with yolk sac tumors. We also conducted sensitivity analyses by sex for gestational characteristics and pregnancy or labor complications (Supplementary Table 2), which revealed some differences in likelihood of fetopelvic disposition and Cesarean section between boys and girls.

In our study population, more girls presented with teratomas and more boys were diagnosed with yolk sac tumors (Table 3). Low birth weight and preterm children were at an increased risk of developing teratomas, but not yolk sac tumors; however, after removing teratomas diagnosed within 5 days of birth, the associations with low birth weight and preterm birth became null (OR = 0.98, 95% CI = 0.49, 2.01 and OR = 1.02, 95% CI = 0.57, 1.81, respectively). Among teratoma cases, an increased risk was observed in mothers who had 5 or fewer, 5–10, and 16 or more prenatal care visits, compared to mothers who had between 11 and 15 prenatal care visits. Mothers with two or more previous births were more common among yolk sac tumor cases. Having a Cesarean section was associated with an increased risk for all GCTs, but when stratifying by subtype, the observed association was due to an increased risk among teratoma cases; this association disappeared after excluding teratoma cases diagnosed within 5 days of birth (OR = 0.89; 95% CI = 0.59, 1.34).

We observed some positive associations between GCTs and pregnancy complications, labor complications, and birth anomalies (Table 4). Conditions associated with an increased risk in GCTs were the presence of fetopelvic disproportion and polyhydramnios or oligohydramnios, with the former driven by yolk sac tumors and the latter by teratomas. We checked the site of yolk sac tumor cases with fetopelvic disproportion, and none of those cases had a tumor in the brain. We also observed an association between teratomas and premature rupture of membranes. Procedures associated with an increased risk of teratomas were admission to the neonatal intensive care unit (NICU), transfer to another facility within 24 h of delivery, and receiving assisted ventilation for less than 30 min after birth. The strongest risk factor for GCTs in this population was the presence of an ear, face, or neck anomaly at birth, though the presence of any congenital anomaly was also predictive of GCT diagnosis overall. All congenital anomalies appeared mainly in teratoma cases.

4. Discussion

Our findings illustrate that children diagnosed with malignant teratomas and yolk sac tumors are distinct with respect to some demographic factors; we also observed some associations with poorer birth outcomes and pregnancy complications. The distribution of cases by sex in this age group is similar to what is reported nationally [28]. Both teratomas and yolk sac tumors were more common among children of Asian/Pacific Islander descent, and yolk sac tumors were also seen more often among the children of foreign-born Hispanic mothers, as previously reported [29]. As a consequence, they were associated with risk factors more common in these demographic groups in California, including greater parity and less than 8 years of formal education, characteristics more common among foreign-born Hispanic parents, as well as fetopelvic disproportion, more commonly found in Asian mothers in California. Yet, associations between these factors and cancer

Table 4
Pregnancy complications, labor complications, and birth abnormalities in relation to germ cell tumors, stratified by histological type.

Characteristic	Controls (n = 273,519) Controls (%)	All cases (n = 451)		Yolk sac tumors (n = 181)		Teratomas (n = 216)	
		Cases (%)	Crude OR (95% CI)[a]	Cases (%)	Crude OR (95% CI)[a]	Cases (%)	Crude OR (95% CI)[a]
Data available for births 1983–2005							
Breech or abnormal presentation	6575 (3.0)	12 (3.4)	1.14 (0.64, 2.02)	2 (1.4)	–	8 (4.6)	1.58 (0.78, 3.23)
Fetal distress	6821 (3.1)	11 (3.1)	0.99 (0.54, 1.81)	5 (3.5)	1.11 (0.46, 2.72)	5 (2.9)	0.94 (0.38, 2.28)
Fetopelvic disproportion	5322 (2.4)	19 (5.4)	2.28 (1.43, 3.64)	10 (7.1)	2.97 (1.55, 5.68)	7 (4.0)	1.74 (0.82, 3.73)
Data available for births 1989–2005							
Amniocentesis	4283 (2.3)	11 (3.5)	1.55 (0.84, 2.84)	2 (1.7)	–	8 (5.0)	2.20 (1.07, 4.50)
Assisted ventilation required for <30 minutes	665 (0.4)	9 (2.9)	8.36 (4.29, 16.30)	1 (0.9)	–	8 (5.0)	14.76 (7.21, 30.19)
Polyhydramnios or oligohydramnios	1040 (0.6)	13 (4.2)	7.74 (4.43, 13.53)	2 (1.7)	–	10 (6.3)	11.89 (6.25, 22.63)
Data available for births 1989+							
Induction of labor	24,233 (10.2)	37 (9.1)	0.88 (0.63, 1.25)	14 (8.9)	0.92 (0.53, 1.60)	16 (7.9)	0.74 (0.43, 1.25)
Stimulation of labor	26,103 (11.0)	41 (10.0)	0.90 (0.65, 1.25)	21 (13.4)	1.23 (0.77, 1.97)	15 (7.4)	0.67 (0.40, 1.14)
Prolonged labor (>20 h)	1876 (0.8)	6 (1.5)	1.59 (0.66, 3.85)	3 (1.9)	–	3 (1.5)	–
Neonatal intensive care unit (NICU) admission	8175 (3.4)	46 (11.3)	3.71 (2.72, 5.06)	2 (1.3)	–	40 (19.7)	7.41 (5.22, 10.53)
Transfer to another facility within 24 h of delivery	1384 (0.6)	19 (4.7)	8.11 (5.04, 13.06)	3 (1.9)	–	15 (7.4)	13.17 (7.63, 22.75)
Moderate/Heavy meconium staining of amniotic fluid	9689 (4.1)	13 (3.2)	0.77 (0.44, 1.34)	5 (3.2)	0.76 (0.31, 1.86)	6 (3.0)	0.72 (0.32, 1.61)
Premature rupture of membranes (>12 h)	4541 (1.9)	13 (3.2)	1.72 (0.99, 2.99)	3 (1.9)	–	8 (3.9)	2.14 (1.05, 4.34)
Data available for births 1991+							
Any congenital anomaly	1527 (0.7)	23 (6.1)	9.12 (5.92, 14.05)	2 (1.4)	–	19 (10.1)	15.43 (9.46, 25.18)
Presence of ear/face/neck anomaly at birth	72 (0.03)	7 (2.0)	47.92 (21.86, 105.04)	0 (0.0)	–	7 (3.8)	93.70 (42.14, 208.32)
Data available for births 2006+							
Antibiotics received by the mother during labor	5410 (10.2)	13 (13.5)	1.30 (0.71, 2.40)	3 (7.5)	–	9 (20.9)	2.14 (0.98, 4.66)
Epidural or spinal anesthesia during labor	23,982 (45.2)	49 (51.0)	1.21 (0.80, 1.83)	18 (45.0)	0.97 (0.51, 1.85)	26 (60.5)	1.78 (0.95, 3.35)
Infection with Group B streptococcus	3352 (6.3)	8 (8.3)	1.22 (0.56, 2.65)	3 (7.5)	–	4 (9.3)	–

[a] Odds ratios adjusted for birth year and maternal race (white v. non-white).

risk still remained after adjusting for maternal race/ethnicity and age, perhaps due to residual confounding. Fetopelvic disproportion is also related to high maternal body mass index [30], which we were not able to examine because California birth certificates did not record this during most of the study period; and high birthweight, but there were few cases in our population with birthweights >4000 g.

There was a distinct pattern of gestational characteristics for teratomas, including lower or higher number of prenatal care visits and greater risk of low birthweight, preterm birth, and Cesarean delivery. Previous studies have associated GCTs (all types grouped together and ages <16) with preterm birth, low as well as high birthweight, and with both low and high parity [11,13,31]. However, the observed associations between teratoma risk, low birth weight, preterm birth, and Cesarean delivery are likely explained by reverse causation. After removing teratoma cases diagnosed within 5 days of birth, associations with all three factors became null; it is likely that the teratoma was the reason for early or Cesarean delivery in our population, as cases are increasingly diagnosed *in utero* [32]. The U-shaped relationship between the number of prenatal visits and teratomas can perhaps be explained by two competing factors related to higher risk pregnancies; first, the larger numbers of foreign-born and lower-income parents likely explains the relationship with fewer prenatal care visits; also *in utero* teratoma diagnosis could result in higher numbers of prenatal visits among those cases. When tumors are diagnosed via obstetric ultrasound, Cesarean delivery may be recommended to prevent tumor rupture [33]. However, we did not have a variable indicating the reason for Cesarean delivery in our population. Several pregnancy and labor complications and procedures at birth were associated with both major tumor types, but effect estimates were higher for teratomas. Both polyhydramnios and oligohydramnios, previously reported to be more common in sacrococcygeal teratomas [34], are related to preterm labor, other birth defects, and the need for assisted ventilation at birth [33].

A small number of previous epidemiologic studies of GCTs in young children that distinguished between subtypes reported differences in risk factors: prenatal vitamin supplementation was protective against teratomas (OR = 0.60; 95% CI = 0.20, 0.90), but not yolk sac tumors (OR = 1.10; 95% CI = 0.50, 2.30) [20]; our group previously reported teratoma risk (OR = 1.26; 95% CI = 1.12, 1.41), but not yolk sac tumor risk (OR = 0.92; 95% CI = 0.68, 1.24), to increase with traffic pollution exposure in the perinatal period [19]. Another group reported a similar, but weaker, pattern when examining associations between pesticide exposure in fathers, teratoma risk (OR = 1.10; 95% CI = 0.60, 2.10), and yolk sac tumor risk (OR = 0.90; 95% CI = 0.50, 1.40) [21]. The distinct risk factor patterns suggest different etiologies for these subtypes.

The pattern we observed with regards to race/ethnicity is similar to that seen in the United States as a whole, as GCT rates nationally are higher among Asian (8.6 per million) than White (6.6 per million), Hispanic (6.5 per million) or Black children (4.7 per million) [35]. In our study, the majority of case mothers who identified themselves as Asian/Pacific Islander were born abroad (85.9%). Of these mothers, 15 were born in the Philippines (20.3%), 12 in Vietnam (16.2%), and 10 in China (13.5%), and an additional 24 Asian/Pacific Islander cases (32.4%) had an unspecified maternal birth place. GCT rates in children ages <5 are elevated in several East Asian countries, including China (Tianjin cancer registry; 9.6 per million); Japan (9.6 per million), Korea (Seoul; 11.4 per million) but not in South or Southeast Asian nations including the Philippines (Manila/Rizal; 5.7 per million), Thailand (3.0 per million), or Vietnam (Hanoi; 5.6 per million) [36]. However, a number of cancer registries in Asia cover small areas and cancer rates may fluctuate greatly due to small numbers.

The relation between yolk sac tumors and SES differed by race and most associations were null or inconsistent. Few studies have reported on the relationship between GCTs and SES with adjustment for important confounding factors such as parental age and race/ethnicity. Consistent with our results, an increased risk with lower levels of maternal education was previously reported in a population-based study of four Scandinavian countries [31]. In contrast, a pooled population-based analysis of five US states, which included California births from 1988 to 1997, did not find an association with maternal education [37]. A nationwide US study also suggested a lower risk of GCTs in higher-poverty areas, but poverty metrics were on the county-level, making results difficult to compare to our individual or census-tract level measures [38]. The small number of studies, and the varying measures of socioeconomic status used, suggest a need for more research in this area.

Although small numbers limited our ability to estimate odds ratios for yolk sac tumors and several complications listed on birth certificates, there were few conditions or procedures with a higher prevalence in yolk sac tumor cases compared with controls. A number of population-based studies have established that children with GCTs are more likely to have birth defects [39,40]. Children with teratomas had a strongly increased risk of having any congenital anomaly, particularly anomalies of the ear, face, or neck. Cleft palate, branchial cyst, and facial hemangiomata have been previously reported in teratoma cases [41,42]. After the exclusion of ear, face, or neck anomalies, teratoma cases still had a strongly elevated risk of anomalies at other sites (OR = 10.72; 95% CI = 5.65, 20.35), which is consistent with the literature, as cardiac, musculoskeletal, gastrointestinal, genitourinary, and central nervous system anomalies have also been reported [41,42]. Common etiologic factors may play a role in predisposing children to teratomas and other congenital anomalies.

Our study was not likely to be affected by recall bias or selective participation. However, because birth certificates must be registered with the state of California within 10 days of birth, congenital anomalies diagnosed after that time could not be included. A population-based study in the UK estimated that 6.4% of GCT cases had a co-occurring congenital anomaly [40], a percentage that is very close to the 6.1% observed in our study—suggesting that, for most cases, the birth certificate did capture the presence of an anomaly. Nonetheless, it is difficult to assess the true prevalence of anomalies and their relationship to cancer risk because the presence of an anomaly increases the likelihood of miscarriage, fetal death or stillbirth, and planned pregnancy termination.

While birth certificate data collection is prospective in nature, our data may be subject to differential misclassification if medical personnel disproportionately reported pregnancy, labor, or other complications by case status. In our population, 107 GCT cases (23.7%) were diagnosed within 10 days of birth, of which 97 were teratomas; consequently, this may have influenced medical personnel reporting. Information on birth certificates is known to have differing levels of reliability and validity [43–46], and factors related to pregnancy complications tend to have high specificity (>95%) but low sensitivity [44,46]. Gestational factors and demographic characteristics generally have better validity; in California, sensitivity for most racial-ethnic classifications is estimated to be 94%–99% [43,47].

The present report provides additional evidence on the influence of birthweight and gestational age on GCTs, but our data suggests that these associations are likely products of reverse causation, as any associations dissipated after removing cases diagnosed within 5 days of birth. However, histologically-driven differences in risk factors may still exist; our data shows that certain pregnancy complications are more common among yolk sac tumor cases, like fetopelvic disproportion, while others, such as

the presence of an ear, face, or neck anomaly at birth, are more common among malignant teratoma cases. Our study also confirms that Asian/Pacific Islander race and congenital malformations are risk factors for GCTs.

Conflicts of interest

None.

Author contributions

Clinton Hall: Contributions include design of study, analysis and interpretation of study data, drafting and revision of manuscript, and final publication review.

Dr. Beate Ritz: Contributions include conception and design of study, acquisition of data, revision of manuscript, and final publication review.

Dr. Myles Cockburn: Contributions include conception and design of study, acquisition of data, revision of manuscript, and final publication review.

Dr. Tom Davidson: Contributions include interpretation of data, revision of manuscript, and final publication review.

Dr. Julia E. Heck: Contributions include conception and design of study, acquisition of data, interpretation of data, drafting and revision of manuscript, and final publication review.

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Appendix A. Supplementary data

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