Cancer Epidemiology 46 (2017) 42–49

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Original Article

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

Clinton Hall[a], Beate Ritz[a], Myles Cockburn[b], Tom B. Davidson[c], Julia E. Heck[a,*]

[a] Department of Epidemiology, Fielding School of Public Health, University of California, CA, USA
[b] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[c] Division of Pediatric Hematology/Oncology, Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

ARTICLE INFO

*Article history:*
Received 29 September 2016
Received in revised form 10 November 2016
Accepted 2 December 2016
Available online 23 December 2016

*Keywords:*
Germ cell tumor
Yolk sac tumor
Teratoma
Childhood
Cancer
Congenital malformation
Race
Perinatal
Risk factor
Epidemiology

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

* Corresponding author at: Department of Epidemiology, UCLA School of Public Health, 650 Charles E. Young Drive, Box 951772, Los Angeles, CA 90095-1772, USA.
*E-mail address:* jeheck@ucla.edu (J.E. Heck).

http://dx.doi.org/10.1016/j.canep.2016.12.002
1877-7821/

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.