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ORIGINAL PAPER

Family history of cancer and malignant germ cell tumors in children: A report from the Children's Oncology Group

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Abstract Family history of testicular cancer is an established risk factor for adult testicular germ cell tumors (GCT). We evaluated the association between family history of cancer and pediatric GCT in a Children's Oncology Group case–control study that included 274 GCT cases (195 female and 79 male) diagnosed <age 15 years and 418 controls frequency matched to cases on sex and age. Family history data were collected through telephone interviews with biological mothers and fathers and unconditional logistic regression was used to evaluate associations with GCT adjusting for potential confounders. A family history of cancer with onset <age 40 years was associated with a reduced risk of GCT among female cases (Odds Ratio (OR) = 0.50, 95% Confidence Interval (CI) 0.28–0.89) and an increased risk among male cases (OR = 2.56, 95% CI 1.02–6.44). Male cases were more likely to report family history of melanoma compared with male controls (OR = 4.65, 95% CI 1.40–15.4). There was an inverse association between family history of ovarian or uterine cancers and GCT in girls (OR = 0.46, 95% CI 0.22–0.96). These sex and cancer site specific associations should be confirmed in additional studies as they may provide clues to the etiology of pediatric GCT.

Keywords Germ cell tumor · Family history · Children

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Introduction

Pediatric malignant germ cell tumors (GCTs) comprise a rare and heterogeneous group of neoplasms representing approximately 3% of childhood cancers. The SEER age-adjusted incidence of malignant GCTs for 2001–2005 was 5.9 per million children under the age of 15 years, with an increase in incidence of 1.2% per year between 1975–2005 in the United States [1]. Marked differences exist in the pathology of these tumors by sex and histologic type [2]. Potential risk factors that have been evaluated for pediatric GCT include parental demographic characteristics, in utero exposure to hormones and pesticides, maternal reproductive history, parental smoking, occupation, and alcohol consumption, and congenital abnormalities [3–11]; however, none has emerged as a consistent risk factor.

Further elucidation of the etiology of GCT in boys may come from results of studies of adult testicular cancer, 95% of which are GCTs [12]. Studies of adult ovarian cancer are less applicable as <5% are GCTs [13, 14]. Family history of testicular cancer is one of the few well-established risk factors for adult testicular GCT [15], with evidence that the relative risk is much higher in brothers than in fathers of testicular GCT patients [16–19]. Analyses of family history of other cancers in individuals with testicular GCT have produced less consistent results [3, 19–26].

Since the majority of adult testicular cancers are GCTs, it is reasonable to hypothesize that the relationship between

family history and risk of GCT may also exist in pediatric GCT in boys. Previous studies of family history of cancer in children with malignant GCTs are limited in number, with only three previous studies reporting associations between family history of cancer and pediatric GCT [4–6]. No clear associations between risk of GCT and family history of cancer emerged, although the small number of cases ($n = 41$, 73, and 105) included in these studies limits the ability to draw definitive conclusions.

The Children's Oncology Group (COG) has conducted the largest case–control study of pediatric GCT to date. In this analysis, we evaluated the association between family history of cancer and pediatric malignant GCT.

Materials and methods

Study population

The details of case and control enrollment have been published previously [8–11]. Briefly, cases of GCT were identified through 84 member institutions of the COG and were diagnosed with a malignant GCT (including germinoma, embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, malignant teratoma, and mixed germ cell tumor) in all sites other than the brain between 1 January 1993, and 31 December 2001 at less than 15 years of age. Eligibility criteria required cases to have a telephone in the home and to have an English-speaking biological mother available for an interview. Permission to interview was obtained from the child's physician, and informed consent was obtained from the parents. The study was approved by the Institutional Review Board(s) at each COG institution. A total of 496 cases of GCT were registered with COG for this study, 344 of whom were eligible. Telephone interviews were completed successfully with the mothers of 278 eligible cases (80.8%).

Controls were identified through random digit dialing and were frequency matched to the case by sex, age (year of birth $\pm$ 1), and state of residence. The case–control matching ratio was 1:2 for boys and 1:1 for girls, which was designed to maximize study power given the lower incidence of GCT among boys. The method of random digit dialing used cases' telephone area code and exchange as the primary sampling unit and randomly modified the last four digits [27, 28]. Of the 17,292 randomly selected phone numbers, 5,912 were residential. We were unable to determine if 1,590 of the numbers were residential as we were unable to reach anyone at these numbers during the screening period. Of the residential numbers, 634 were of families with one or more eligible child. The remaining phone numbers were for families who were without eligible children ($n = 3{,}105$), refused to be screened ($n = 325$), or could not be contacted ($n = 1{,}848$). This yielded a screening success rate of 63.2%. If more than one child was eligible, one child was randomly chosen to participate. Telephone interviews were completed successfully with the mothers of 423/634 potential controls (66.6%). Non-response was due to refusal ($n = 182$; 28.7%), changes in phone numbers ($n = 28$; 4.4%) and other reasons ($n = 1$).

Interviews were conducted between 1 January 1997 and 31 December 2002. Data were collected from mothers through a self-administered questionnaire and telephone interview. Data were collected from fathers through a telephone interview for 223 cases (80.2%) and 285 controls (67.4%). The mother provided a surrogate interview for 35 case fathers (12.6%) and 97 control fathers (22.9%).

Parents were asked about their personal medical history, that of their parents (i.e., the child's grandparents), and that of their siblings (i.e., the child's aunts and uncles). Medical history questions included the occurrence of birth defects; diseases of the uterus, ovaries, or testes; malignant tumor or cancer; and causes of death. The family member's age at the occurrence of the medical problem was recorded as well. Cases and controls were excluded from the analysis if data were missing for all maternal and paternal relatives. Parents were not asked to report cancer history in offspring other than the index child, so we were unable to evaluate family history of cancer in siblings of cases and controls.

We used a dichotomous variable for the presence of any cancer in a family. We also grouped cancer sites into the following categories based on *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM)[29] groupings: (1) lip, oral cavity and pharynx (140–149); (2) esophagus, stomach, and small intestine (150–152); (3) colon, rectum (153–154); (4) liver, gallbladder, pancreas (155–157); (5) lung (162); (6) melanoma (172); (7) breast (174); (8) uterus, ovary (179–184); (9) prostate (185); (10) testis (186); (11) bladder, kidney (188–189); (12) lymphatic, hematologic (200–208); and (13) other sites. Cancers of family members were counted once for individual cancer sites but a child could have a positive family history of more than one cancer. We did not evaluate associations for specific cancer types if there were fewer than five relatives with a reported cancer in the case or control group.

In order to capture potential misreporting of malignant reproductive organ cancers as benign conditions, we also evaluated associations between other disorders of the male and female reproductive organs and pediatric GCT in a secondary analysis. Benign disorders of the reproductive organs included the following categories based on ICD-9-CM [29]: uterine leiomyoma (218), other benign neoplasm of uterus (219), benign neoplasm of ovary (220), ovarian dysfunction (256), other disorders of male genital organs (608), endometriosis (617), noninflammatory

disorders of ovary, fallopian tube, and broad ligament (620), disorders of uterus, not elsewhere classified (621), noninflammatory disorders of cervix (622), disorders of menstruation and other abnormal bleeding from female genital tract (626), and congenital anomalies of genital organs, including cryptorchidism (752). We used a dichotomous variable for the presence of any benign reproductive organ disorder in male or female relatives.

Contingency table methods were used for comparisons of categorical data. Unconditional logistic regression was used to estimate adjusted associations between family history of disease and GCT using separate analyses for male and female cases. The odds ratios (ORs) for associations between specific cancer types and GCT were adjusted for all other types of cancer. The following variables were included as potential confounders: age of index child (age at diagnosis for cases and age at enrollment for controls), sex of child, number of relatives reported, mother's age at birth of child (15–24 years; 25–29 years; 30–34 years; and 35–42 years), mother's education (less than high school; high school graduate; some college; and college degree or greater), mother's race (white or non-white), and annual family income (<$20,001; $20,001–30,000; $30,001–50,000; ≥ $50,001). We evaluated family history in all relatives (parents, grandparents, and aunts and uncles of index child). We also evaluated family history separately for maternal and paternal relatives. We performed additional analyses excluding cases and controls with missing personal interview data from the father as a sensitivity analysis. In addition, we stratified the tumors by location (gonadal vs. extragonadal) and age category (0–2 years, 3–10 years and 11–14 years). Tests for linear trend were performed by treating a categorical variable as a continuous variable in the logistic regression model. All statistical analyses were performed using SAS (Version 9.1, Cary, NC), and all reported *p*-values are two-sided.

Results

The study population included 278 cases and 423 controls. One case and one control were excluded because family history data were missing for all relatives. Seven additional participants were excluded due to missing values for potential confounders, resulting in a sample of 274 cases and 418 controls available for analysis (Table 1). There were more female cases than male cases, 195 vs. 79, respectively. The number of relatives reported was similar for parents of cases compared with parents of controls in both boys and girls (Table 1).

We observed no overall association between family history of cancer and GCT in either boys or girls (Table 2). There was a decreased risk of GCT in girls with a family history of cancer in a relative diagnosed before age 40 years (OR = 0.50, 95% CI 0.28–0.89). In contrast, we observed an increased risk of GCT in males with a family history of cancer in a relative diagnosed before age 40 years (OR = 2.56, 95% CI 1.02–6.44). When we evaluated family history only in maternal relatives, we observed a similar inverse association for girls and a positive association for boys for family history of cancer with early age at diagnosis. In contrast, when we evaluated family history in paternal relatives, we observed no obvious patterns. We also observed no statistically significant relationship between number of relatives diagnosed with cancer and GCT in either girls or boys (Table 2). In further analyses, we stratified the tumors by location (gonadal vs. extragonadal) and age category. While the small numbers make it difficult to draw definitive conclusions, the data do not suggest substantial differences for gonadal and extragonadal GCTs (data not shown). In analyses stratified by age (0–2 years, 3–10 years and 11–14 years), we observed positive associations between family history of cancer and GCT in boys in all age groups while the inverse association between family history of cancer and GCT in girls was not observed in females age 0–2 years (data not shown).

Further, we evaluated associations between family history of specific types of cancer and pediatric GCT (Table 3). For female cases, we evaluated family history of the following cancer sites: lip and oral cavity, esophagus and stomach, colon and rectum, liver, gallbladder and pancreas, lung, melanoma, breast, uterus and ovary, prostate, bladder and kidney, lymphatic and hematologic malignancies, and all other cancers. For male cases, we evaluated site specific risks only for family history of melanoma, lung, breast, and uterine/ovarian cancers due to the small reported numbers of affected relatives with other types of cancer. We observed a significant association between family history of melanoma and pediatric GCT in boys (OR = 4.65, 95% CI 1.40–15.4). When we stratified the analysis by tumor location, the association between family history of melanoma and GCT was significant for tumors located in the testes (OR = 7.25, 95% CI 1.85–28.4) but not for extragonadal tumors (OR = 2.54, 95% CI 0.47–13.7), although the confidence intervals were wide and overlapping. Similar, although non-significant, associations were seen in each of the three age categories (data not shown). A family history of uterine or ovarian cancer was inversely associated with GCT in girls (OR = 0.45, 95% CI 0.21–0.95). No other statistically significant associations were observed.

We also evaluated reported family history of benign reproductive organ disorders as described above. We observed a statistically significant association between family history of any benign reproductive organ disorder and GCT in boys (OR = 2.39, 95% CI 1.23–4.64) and no

Table 1 Selected characteristics of the study participants

	Female		Male	
Total	Cases N (%)[a] 195	Controls N (%)[a] 237	Cases N (%)[a] 79	Controls N (%)[a] 181
Tumor histology				
Dysgerminoma/Seminoma	43 (22)		2 (2.5)	
Yolk sac tumor (Endodermal sinus tumor)	80 (41)		44 (56)	
Mixed GCT/Other[b]	15 (7.7)		19 (24)	
Malignant Teratoma	56 (29)		13 (16)	
Not specified	1 (0.5)		1 (1.3)	
Tumor location				
Gonadal	96 (49)		45 (57)	
Extragonadal	90 (46)		29 (37)	
Unknown	9 (4.6)		5 (6.3)	
Age of index child (years)				
0	35 (18)	45 (19)	21 (27)	49 (27)
1–2	43 (22)	42 (18)	34 (43)	34 (19)
3–10	55 (28)	83 (35)	10 (13)	46 (25)
11–14	62 (32)	67 (28)	14 (18)	52 (29)
Family income				
<$20,001	60 (31)	46 (19)	25 (32)	37 (20)
$20,001–30,000	46 (24)	65 (27)	14 (18)	44 (24)
$30,001–50,000	42 (22)	71 (30)	21 (27)	53 (29)
>$50,000	47 (24)	55 (23)	19 (24)	47 (26)
Mother's age at birth of child				
15–24	59 (30)	71 (30)	19 (24)	42 (23)
25–29	77 (39)	78 (33)	27 (34)	74 (41)
30–34	37 (19)	61 (26)	20 (25)	48 (27)
35–42	22 (11)	27 (11)	13 (16)	17 (9.4)
Mother's education				
Less than high school	17 (8.7)	12 (5.0)	10 (13)	11 (6.1)
High school graduate	63 (32)	64 (27)	15 (19)	34 (19)
College, no degree	57 (29)	80 (34)	27 (34)	61 (34)
College degree and graduate school	58 (30)	81 (34)	27 (34)	75 (41)
Mother's race				
White	144 (74)	201 (85)	67 (85)	152 (84)
Other	51 (26)	36 (15)	12 (15)	29 (16)
Father's age at birth of child				
17–24	38 (22)	38 (18)	9 (12)	20 (13)
25–29	58 (34)	65 (31)	23 (30)	54 (34)
30–34	37 (21)	68 (32)	21 (27)	53 (33)
35–56	40 (23)	39 (19)	24 (31)	33 (21)
Father's education				
Less than high school	25 (14)	21 (9.9)	14 (18)	11 (6.8)
High school graduate	53 (30)	62 (29)	17 (22)	53 (33)
College, no degree	37 (21)	59 (28)	18 (23)	38 (23)
College degree and graduate school	59 (34)	70 (33)	29 (37)	60 (37)
Father's race				
White	133 (76)	181 (85)	65 (82)	139 (84)
Other	42 (24)	32 (15)	14 (18)	26 (16)

Table 1 continued

	Female		Male	
Total	Cases N (%)[a] 195	Controls N (%)[a] 237	Cases N (%)[a] 79	Controls N (%)[a] 181
Number of relatives	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Total	12.3 (4.3)	12.2 (4.3)	12.7 (4.2)	11.8 (4.3)
Parents	1.9 (0.3)	1.9 (0.3)	2 (0)	1.9 (0.3)
Grandparents	3.7 (0.7)	3.7 (0.7)	3.9 (0.4)	3.8 (0.6)
Maternal Aunts	1.7 (1.6)	1.6 (1.5)	1.6 (1.4)	1.6 (1.4)
Maternal Uncles	1.7 (1.6)	1.5 (1.3)	1.9 (1.7)	1.6 (1.4)
Paternal Aunts	1.6 (1.5)	1.7 (1.7)	1.6 (1.6)	1.5 (1.6)
Paternal Uncles	1.7 (1.6)	1.8 (2.0)	1.7 (1.5)	1.5 (1.8)

[a] Ns may not sum to total due to missing data

[b] Other includes embryonal carcinoma, choriocarcinoma, and polyembryoma

significant association in girls (OR = 1.43, 95% CI 0.91–2.23).

Lastly, family history of disease and GCT associations were examined by excluding those cases and controls whose father did not provide an interview (data not shown). These results did not differ materially from those shown above.

Discussion

In this analysis, we did not observe any significant associations between GCT in girls or boys and family history of cancer overall; but we did observe some interesting results by age at diagnosis in the relatives. A family history of cancer with an early age of onset is suggestive of genetic susceptibility to disease. In our study, male children displayed a statistically significant increased risk of GCT if they had a family history of cancer in a relative diagnosed before the age of 40 years. In contrast, we observed a significant inverse association in girls with a family history of cancer diagnosed before age 40. We also observed a significant association between GCT in boys and melanoma in a family member, suggesting that these cancers may share common genetic or environmental risk factors.

Our results on the overall association between family history of cancer and risk of pediatric GCT are consistent with the few studies that have evaluated this relationship. A study of 41 GCT cases reported similar numbers of neoplasms in relatives of case and control children; however, they observed an excess of first- and second-degree case relatives with multiple tumors [4]. A study of 73 cases with ovarian GCT reported no excess diagnoses of any cancer, breast and cervical cancer, or ovarian cysts among mothers of cases compared with mothers of controls [5]. A third study of 105 cases of pediatric GCT reported a non-significant increase in risk of malignant GCT in children with a family history of cancer in a first-degree relative (OR = 2.9, 95% CI 0.9–9.1)[6]. Taken together, these results suggest that a family history of cancer in general is not strongly associated with the risk of pediatric GCT, although the small sample size of these studies limits the power to detect associations.

The evidence for a heritable component of ovarian GCT has not been conclusive [30–33]. In our study, we observed a statistically significant inverse association between family history of ovarian or uterine cancer and risk of GCT in girls. The explanation for this association is not obvious. We did observe a slightly elevated, although non-significant, association between family history of other benign reproductive organ disorders and GCT in girls. Previous studies have demonstrated that family history of female reproductive cancers is not accurately reported in case–control studies [34, 35]; therefore, it is possible that history of cancer is inaccurately reported as reproductive organ disease in these families. We were unable to account for female relatives who had hysterectomies or oophorectomies and were subsequently not at risk for uterine or ovarian cancer.

In contrast to the limited studies of family history in pediatric GCT and adult ovarian GCT, numerous studies have evaluated the association with adult testicular GCT. The strong family history of testicular cancer in fathers and brothers of testicular cancer cases suggests that there is a heritable component of this disease [15–18, 36, 37], although a positive family history represents only 1–3% of all cases [38]. The association between family history of testicular cancer and risk of pediatric GCT in boys was of interest in our study; however, we could not test the hypothesis that pediatric GCT in boys was associated with a family history of testicular cancer because of the small number of reported cases of testicular cancer in family members ($n = 2$).

A family history of other types of cancers in relatives of testicular cancer patients could suggest common genetic or

Table 2 Family history of cancer in 1st and 2nd degree relatives and risk of malignant germ cell tumors in children

	Female				Male			
	Cases N (%)	Controls N (%)	OR[a,b]	95% CI[a,b]	Cases N (%)	Controls N (%)	OR[a,b]	95% CI[a,b]
All relatives								
Any cancer[c]								
No	93 (48)	89 (38)	1.0		35 (44)	89 (49)	1.0	
Yes	102 (52)	148 (62)	0.72	0.47–1.10	44 (56)	92 (51)	1.54	0.81–2.91
Youngest age at cancer diagnosis[d]								
No cancer	93 (48)	89 (38)	1.0		35 (44)	89 (49)	1.0	
< 40 Years	26 (13)	51 (22)	0.50	0.28–0.89	14 (18)	17 (9.4)	2.56	1.02–6.44
40–49 Years	23 (12)	30 (13)	0.83	0.43–1.58	9 (11)	22 (12)	1.24	0.45–3.43
≥ 50 Years	52 (27)	65 (28)	0.91	0.54–1.52	21 (27)	52 (29)	1.28	0.60–2.73
Number of cancers								
0	93 (48)	89 (38)	1.0		35 (44)	89 (49)	1.0	
1	60 (31)	83 (35)	0.71	0.44–1.13	21 (27)	46 (25)	1.47	0.71–3.03
2–6	42 (22)	65 (27)	0.74	0.43–1.27	23 (29)	46 (25)	1.64	0.75–3.59
p-value trend				0.21				0.20
Maternal relatives[e]								
Any cancer[c]								
No	134 (69)	134 (57)	1.0		48 (61)	120 (67)	1.0	
Yes	60 (31)	103 (43)	0.60	0.40–0.92	31 (39)	60 (33)	1.61	0.86–3.04
Youngest age at cancer diagnosis[d]								
No cancer	134 (69)	134 (57)	1.0		48 (61)	120 (67)	1.0	
< 40 Years	19 (10)	37 (16)	0.47	0.25–0.88	11 (14)	10 (5.6)	3.28	1.16–9.27
40–49 Years	13 (6.7)	16 (6.8)	0.94	0.42–2.09	5 (6.4)	8 (4.5)	2.32	0.62–8.70
≥ 50 Years	28 (14)	49 (21)	0.64	0.36–1.11	14 (18)	40 (22)	1.03	0.46–2.29
Number of cancers								
0	134 (69)	134 (57)	1.0		48 (61)	120 (67)	1.0	
1	43 (22)	75 (32)	0.59	0.37–0.95	20 (25)	44 (24)	1.36	0.67–2.75
2–3	17 (8.8)	28 (12)	0.63	0.32–1.24	11 (14)	16 (8.9)	2.47	0.94–6.45
p-value trend				0.04				0.07
Paternal relatives[f]								
Any cancer[c]								
No	113 (66)	133 (63)	1.0		52 (67)	108 (67)	1.0	
Yes	59 (34)	79 (37)	0.96	0.61–1.51	26 (33)	54 (33)	1.02	0.52–2.02
Youngest age at cancer diagnosis[d]								
No cancer	113 (66)	133 (63)	1.0		52 (67)	108 (67)	1.0	
< 40 Years	7 (4.1)	19 (9.1)	0.43	0.17–1.11	3 (3.9)	7 (4.3)	1.16	0.23–5.81
40–49 Years	12 (7.1)	16 (7.6)	0.92	0.39–2.13	7 (9.0)	16 (10)	0.84	0.28–2.54
≥ 50 Years	38 (22)	42 (20)	1.28	0.73–2.23	16 (21)	31 (19)	1.08	0.49–2.40
Number of cancers								
0	113 (66)	133 (63)	1.0		52 (67)	108 (67)	1.0	
1	38 (22)	60 (28)	0.75	0.45–1.25	16 (21)	34 (21)	0.92	0.42–2.04
2–3	21 (12)	19 (9.0)	1.92	0.91–4.05	10 (13)	20 (12)	1.22	0.47–3.17
p-value trend				0.43				0.79

[a] OR, odds ratio; CI, confidence interval

[b] All odds ratios were adjusted for number of relatives reported, child's sex and age, mother's age, education, and race, and family income

[c] Presence of cancer counted once per family

[d] Number of cases and controls do not sum to total because age at diagnosis was missing for 4 affected relatives

[e] One female case and one male control were missing information on maternal cancer history

[f] Cancer history in paternal relatives was missing for 24 cases and 44 controls

Table 3 Family history of specific cancers and risk of pediatric germ cell tumors

	ICD9 Code	Female						Male					
		Cases ($n = 195$)		Controls ($n = 237$)		OR[a,b,c]	95% CI[a]	Cases ($n = 79$)		Controls ($n = 181$)		OR[a,b,c]	95% CI[a]
Family history		Yes	No	Yes	No			Yes	No	Yes	No		
Lip, oral cavity	140–149	4	191	7	230	ND		2	77	4	177	ND	
Esophagus, stomach	150–152	5	190	6	231	1.06	0.28–4.06	1	78	5	176	ND	
Colon, rectum	153–154	14	181	23	214	0.80	0.37–1.73	3	76	5	176	ND	
Liver, gallbladder, pancreas	155–157	12	183	7	230	2.56	0.92–7.10	1	78	8	173	ND	
Lung	162	22	173	18	219	1.79	0.87–3.70	8	71	20	161	1.14	0.43–2.98
Melanoma	172	12	183	13	224	1.30	0.55–3.08	8	71	7	174	4.65	1.40–15.4
Breast	174	16	179	33	204	0.64	0.32–1.29	15	64	22	159	1.65	0.71–3.83
Uterus, ovary	179–184	12	183	31	206	0.46	0.22–0.96	9	70	20	161	1.60	0.59–4.37
Prostate	185	9	186	13	224	1.07	0.42–2.77	4	75	12	169	ND	
Testes	186	2	193	4	233	ND		1	78	1	180	ND	
Bladder, kidney	188–189	7	188	6	231	1.61	0.51–5.08	1	78	6	175	ND	
Lymphatic/Hematologic	200–208	10	185	19	218	0.72	0.31–1.66	4	75	7	174	ND	
Other sites		29	166	43	194	0.84	0.48–1.48	13	66	32	149	0.84	0.38–1.86

[a] OR, odds ratio; CI, confidence interval

[b] All odds ratios were mutually adjusted by cancer site and by number of relatives, child's age, mother's age, mother's education, mother's race, and family income

[c] ND, not done. ORs and 95% CIs were not estimated for cancers where fewer than 5 cases were reported in the case or control group

environmental risk factors. Because of the limited numbers of cancers reported in relatives, we were able to evaluate site specific associations only between family history of melanoma, lung, breast, prostate, and uterine/ovarian and GCT in boys. Melanoma was the only cancer for which a family history was significantly associated with GCT in boys. A possible association between family history of melanoma and risk of testicular GCT has been reported previously in an analysis from the Swedish Family-Cancer database [25, 26]; however, the reported associations were not consistent across all types of relatives. In another study, an increased number of testicular cancers was not observed in relatives of 4,079 cases of melanoma; however, there was an increased number of testicular cancers when second cancers were evaluated in the melanoma cases themselves [39]. Hormonal and reproductive factors have been suggested to play a role both in testicular cancer and melanoma [5, 40–43], which could provide one potential explanation for this relationship. However, the role of hormonal and reproductive factors in the pathogenesis of melanoma has been controversial, and a recent review of the literature suggested that there is no conclusive evidence to suggest that pregnancy or hormonal factors influence the development of melanoma in women [40]. The potential relationship between family history of melanoma and GCT should be evaluated in future studies.

A major strength of this study was the *relatively* large number of pediatric GCT cases assembled; however, several limitations must also be considered. First, family history of disease was obtained by self-report. Validation studies have shown that reporting of family history of cancer is relatively accurate, especially for the more common cancer sites [34, 35, 44–46]. However, studies have shown that reporting may be less accurate for several of the cancers of interest here, including testicular cancer [47], melanoma [48], and cancer of the female reproductive organs [34]. As expected, a higher reliability of report has been observed for first-degree relatives compared with more distant relatives [34, 45, 46]. Although we evaluated associations between both first (parents) and second (grandparents and aunts/uncles) degree relatives of the cases, it is important to note that family history information was provided by the parents about their first degree relatives. We might then expect the information about children's second degree relatives to be more accurate than in comparable studies of adult cancers. Parents of cases might also be expected to give a more thorough history than control parents, although there was no difference in sensitivity of reporting between cases and controls in two previous studies [35, 49]. There was not a tendency for parents of cases to report more cancers among family members in our study, and significant associations of GCT

with a positive family history of cancer and reproductive organ disease differed by sex.

Another limitation that must be considered is the lower participation rate among controls (66.6%) compared with cases (80.8%) in this study. Significant differences between cases and controls for family income, race and parental education have been reported in this study population [8]. In order to account for these potential variations among the groups, we adjusted our analyses for annual family income, maternal education, maternal race, and maternal age at birth of the index child; however, we must consider the possibility of residual confounding by SES. The young age of the relatives of our study population is also a limitation as most of these individuals have not reached the peak age for risk of cancer. Lastly, we cannot rule out chance as an explanation for these results due to the many comparisons we made between family history of cancer and GCT.

In conclusion, we did not find strong evidence that a family history of cancer in general is associated with pediatric GCT in boys or girls. We did find evidence that having a relative with an early age at diagnosis may be associated with childhood GCTs in a sex-specific manner, although these results should be evaluated in additional studies. Analysis of family history of other cancers may provide clues to mechanistic pathways involved in GCT and could also be used to help define cancer screening practices for relatives of children with GCT.

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