Family history of cancer in children and adolescents with germ cell tumours: a report from the Children's Oncology Group

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Background: Studies of family history of cancer in paediatric germ cell tumours (GCTs) are few, and none has had sufficient sample size to specifically evaluate family history of GCT.

Methods: We utilised family history data from a paediatric GCT study to calculate standardised incidence ratios (SIR) for GCT and other cancers using age- and sex-specific incidence rates from the SEER Program.

Results: This analysis included 7998 relatives of paediatric GCT probands. We observed a higher number of GCT cases than expected in male and female relatives of probands (SIR = 2.38, 95% CI 1.25, 3.51 for males; SIR = 14.3, 95% CI 0.29, 28.4 for females). Further, we observed a particularly strong SIR for relatives of probands with intracranial GCT (SIR = 8.07, 95% CI 3.51, 12.6). The SIR for relatives of probands with ovarian GCT was also elevated but did not reach statistical significance (SIR = 4.35, 95% CI 0-9.27). Other notable associations include elevated SIRs for melanoma in male relatives and reduced SIRs for lymphatic/haematologic malignancies in male and female relatives.

Conclusions: These results support the hypothesis that familial aggregation of GCT occurs in males and females.

Family history is one of the few well-established risk factors for adult testicular germ cell tumour (TGCT) (Heimdal et al, 1996; Westergaard et al, 1996; Kharazmi et al, 2015; Litchfield et al, 2015). Among cancers, TGCT has one of the highest reported heritability estimates (Czene et al, 2002; Sampson et al, 2015), although a positive family history represents only 1–3% of all cases (Dieckmann and Pichlmeier, 1997).

The evidence for a heritable component of ovarian GCT (OGCT) is less conclusive. A study of 74 cases of ovarian GCT found none with a family history (Shulman et al, 1994) while other reports have described families with cases of both ovarian GCT and either TGCT or extravagadal GCT (Giambartolomei et al, 2009). Population-based studies of familial aggregation do not exist due to the rarity of the disease.

Similarly, there are few studies on family history of cancer in paediatric GCTs, and none with a sufficient sample size to specifically evaluate family history of GCT (Johnston et al, 1986; Walker et al, 1988; Shu et al, 1995; Poynter et al, 2010). In our previous analysis in an independent set of 274 GCT cases, relatives of male cases but not female cases had higher risk of melanoma (OR = 4.65, 9% CI 1.40–15.4 for males; OR = 1.30, 95% CI 0.55, 3.08 for females; Poynter et al, 2010).

In this analysis, we estimated risk of GCT and other cancers in relatives of paediatric GCT cases. Owing to our relatively large...
sample size of paediatric GCTs, we were able to evaluate associations for GCT overall and stratified by characteristics of the proband.

**MATERIALS AND METHODS**

**Study participants.** Children diagnosed with GCT were identified through the Children’s Oncology Group Childhood Cancer Research Network (CCRN) (Musselman et al., 2014) and invited to participate in this case-parent triad study. The CCRN was established by the COG in 2008 to provide a centralised paediatric cancer registry in the United States to facilitate aetiologic and survivorship studies. Children were eligible for the study if they had a primary diagnosis of GCT including germinoma (ICCC code 9060-9065), teratoma (9080-9084), embryonal carcinoma (9070-9072), yolk sac tumour (9071), choriocarcinoma (9100, 9103, 9104), and mixed GCT (9085, 9101, 9102, 9105) between 1 July 2008 and 31 December 2015. Additional eligibility criteria included age <20 years at diagnosis, the availability of at least one biological parent alive and willing to participate, and ability to complete a questionnaire in English or Spanish. Pathology reports were provided by the participating Children’s Oncology Group institutions per the CCRN protocol. All study procedures were approved by the University of Minnesota Institutional Review Board. Parents provided written informed consent prior to completion of questionnaires. GCT probands aged 18 years and older provided informed consent for participation in the study. Assent was obtained from children aged 8–17 years.

**Table 1. Demographic and clinical characteristics of the germ cell tumour probands**

| Age at diagnosis | Male probands N=340 | Female Probands N=330 |
|------------------|---------------------|-----------------------|
| 0–4              | 66 (19)             | 105 (32)              |
| 5–9              | 17 (5)              | 50 (15)               |
| 10–14            | 77 (23)             | 114 (35)              |
| 15–19            | 180 (53)            | 61 (19)               |

| Tumour Histology | Male probands | Female Probands |
|------------------|---------------|-----------------|
| Germinoma        | 103 (30)      | 67 (20)         |
| Teratoma         | 51 (15)       | 105 (32)        |
| Yolk Sac Tumour | 42 (12)       | 73 (22)         |
| Mixed/Other      | 126 (37)      | 50 (15)         |
| Teratoma and YST | 6 (2)         | 27 (8)          |
| Unknown          | 12 (4)        | 8 (2)           |

| Tumour location | Male probands | Female Probands |
|-----------------|---------------|-----------------|
| Ovary           | —             | 177 (54)        |
| Testis          | 136 (40)      | —               |
| Intracranial    | 133 (39)      | 52 (16)         |
| Extragonadal    | 71 (21)       | 101 (31)        |

| Cryptorchidism  | Yes | N/A |
|-----------------|-----|-----|
| Number relatives per family | Mean # (SD) | 12.5 (4.5) | 11.4 (3.9) |

| Relatives by type | Male probands | Female Probands |
|-------------------|---------------|-----------------|
| Mothers           | 336           | 326             |
| Fathers           | 322           | 303             |
| Siblings*         | 591           | 585             |
| Grandparents      | 1241          | 1196            |
| Aunts/uncles*     | 1754          | 1344            |

*Numbers may not sum to total due to missing values.
*Includes full and half siblings.
*Does not include half-aunts and half-uncles.

**RESULTS**

Family history data were available for 670 GCT probands (Table 1). Age at diagnosis differed by sex of the proband, with more male cases than female cases diagnosed after age 10 years (76 vs 54%). Differences were also observed by tumour location and histology. Parents of male and female probands reported cancer history for 12 family members on average (Table 1).

The number of observed cases of GCT was higher than the expected number of cases in both male and female relatives (SIR = 2.38, 95% CI 1.25, 3.51; SIR = 14.3, 95% CI 0.29, 28.41, respectively), although the SIR in female relatives had wide confidence limits and did not reach statistical significance (Table 2). In male relatives, we also observed a statistically significantly higher number of melanomas (SIR = 1.78, 95% CI 1.20, 2.36) than expected. A lower than expected number of lymphatic/haematologic cancers was observed in both male and female relatives (Table 2).

We observed a higher than expected number of GCTs in relatives of both male and female probands. In males, we were only able to quantify the excess number of cancers in relatives of probands diagnosed at age 11 years or older (SIR = 4.05, 95% CI 1.54, 6.56) due to small numbers of probands <11. An excess number of cases were reported in relatives of girls diagnosed at any age, although the SIRs did not reach statistical significance (Table 3). SIRs were significantly elevated for relatives of probands with germinoma (Table 3). More than half of the affected relatives were from a family where the proband had an intracranial GCT. Pedigrees for the 21 families with a history of GCT are included in the Supplementary Information. No family had more than two
individuals with GCT. Tumour location was the same in the proband and the affected relative in 9/21 families (43%).

**DISCUSSION**

In this population-based study, we were able to evaluate family history of GCT and other cancers in relatives of paediatric GCT probands. Male and female relatives of probands had a higher number of GCTs than expected when compared with incidence data from the NCI’s SEER programme, although this reached statistical significance only among male relatives. This increase in reported GCTs was observed in relatives of both male and female probands. Notably, the majority of reported GCTs occurred in relatives of probands with an intracranial tumour (IGCT).

Family history has not been evaluated extensively in OGCT. Case reports of families with affected male and female relatives and also several studies reporting multiple affected female cases in the same family have been described in the literature (reviewed in Giambartolomei et al, 2009). The three GCTs reported relatives of OGCT cases in our study is higher than the expected number based on SEER incidence rates; however, the confidence intervals for our SIR calculation were very wide given the limited number of probands. This underscores the need for additional studies to confirm our findings; however, our analysis does provide the first quantitative information regarding this association.

Studies of family history of cancer in children with malignant GCTs are limited in number, with only four previous studies reporting associations between family history of cancer and paediatric GCT (Johnston et al, 1986; Walker et al, 1988; Shu et al, 1995; Poynter et al, 2010). No clear associations between risk of GCT and family history of cancer emerged. The lack of previous associations for prostate cancer and lymphatic/haematologic malignancy suggests that these findings should be considered hypothesis-generating and provide future avenues for research. In contrast, previous studies have provided some evidence for a relationship with family history of melanoma and adult testicular cancer (Hemminki and Chen, 2006; Larson et al, 2007; Serrano et al, 2016). In support of our previous findings suggesting an elevated risk of melanoma in relatives of paediatric GCT cases (Poynter et al, 2010), we observed an elevated risk of melanoma in male relatives of probands and an elevated, but non-significant risk of melanoma in female relatives of probands. Hormones have been hypothesised to play a role in both melanoma and GCT (Henderson et al, 1979; Walker et al, 1988; Mitkov et al, 2015) and could potentially explain this relationship. KITLG, the genetic locus with the strongest per allele association in testicular GCT (Wang et al, 2017), plays a role in determining pigmentation (Miller et al, 2007), suggesting another potentially shared aetiological factor.

None of the previous studies of family history in paediatric GCT has had power to specifically evaluate the relationship with family history of GCT. In the current analysis, we were able to evaluate risk of GCT specifically in relatives of male and female GCT cases. GCTs in adolescent males exhibit molecular and clinical features that more closely resemble adult TGCT than prepubertal GCT; thus, it is not surprising that we observed familial aggregation in relatives of these cases. The majority of reported GCTs occurred in male relatives (17/21); however, we did also observe a higher than expected number of GCTs in female relatives. Three of the four female relatives with GCT were related to a female proband. No family in the study had more than two affected individuals. In this respect, the association with family history in paediatric GCT is very similar to what is known about family history in adult testicular GCT, where the majority of families have two affected cases (Mai et al, 2010).

A majority of the reported GCTs this study occurred in relatives of a proband with an intracranial tumour. Little is known about the aetiology of IGCT; however, genetic aetiology is likely given international incidence patterns (Poynter et al, 2014) and is supported by recent publications identifying *JMJD1C1* as a susceptibility locus (Wang et al, 2014). Family history has not
been evaluated systematically as a risk factor for IGCT, although several case reports of familial IGCT have been published (Nakasu et al, 1983; Kido et al, 1984; Aoyama et al, 1994; Shimizu et al, 2014). These data suggest that family history is likely to be important and should be evaluated further in additional studies. If confirmed, these findings could have clinical implications as the diagnosis of intracranial GCT may prompt evaluation of GCT in other family members.

There are several strengths associated with this study, including the large number of cases assembled for this rare paediatric cancer and the inclusion of GCTs at all locations in males and females in the paediatric and adolescent age groups. There are also several limitations that must be taken into account. The most serious limitation is the reliance on self-report of cancer diagnoses. Validation data suggest that reporting is accurate for common cancers (Kerber and Slattery, 1997; Airewele et al, 1998; Ziegas and Anton-Culver, 2003; Murff et al, 2004); however, at least one report has identified lower accuracy for reporting of testicular cancer (Pinsky et al, 2003). We did not obtain medical records to validate any reported cancer diagnoses; however, we did contact families with a reported history of GCT to obtain additional information on tumour location and age at diagnosis. As expected, report of cancer history in first-degree relatives is typically more accurate compared with reports for more distant relatives (Airewele et al, 1998; Ziegas and Anton-Culver, 2003; Murff et al, 2004; Mai et al, 2011). Although we evaluated associations between both first (parents) and second (grandparents and aunts/uncles) degree relatives of the probands, it is important to note that the parents provided family history information 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. The young age of the relatives in our study population is also a limitation, as most have not reached the peak age for risk of cancer.

Other limitations include the low participation rate among eligible GCT cases based on CCNR data (56%); however, the distribution of demographic and tumour characteristics is similar in the participating and non-participating cases. In addition, our previous analyses demonstrate that the CCNR includes only a subset of the GCT cases diagnosed in the United States (Musselman et al, 2014). The eligible cases in the CCNR were more likely to be female, younger at diagnosis, more likely to have YST, and less likely to have a testicular tumour when compared with the distribution of cases in SEER (data not shown). This is not surprising given the knowledge that adolescent patients with TGCT are often treated by adult oncologists (Olson et al, 2015). If non-participating COG cases or GCT cases treated at a non-COG institution differ with respect to family history of GCT, it is possible that our findings may be biased.

In conclusion, we report higher than expected numbers of GCTs in relatives of probands enrolled in our series of GCT cases recruited through the Childhood Cancer Research Network. These results were observed in both males and females and in tumours of differing tumour location and histologic subtypes, suggesting that the familial aggregation of GCT is not restricted to adult TGCT. This familial aggregation suggests that paediatric GCT may also have genetic aetiology that should be evaluated in future studies.

**Table 3. Standardised incidence ratios for GCT in relatives by proband characteristics**

| Characteristic of proband | N\text{OBSERVED} | N\text{EXPECTED} | SIR (95% CI)\text{b} |
|---------------------------|------------------|------------------|---------------------|
| **Sex**                   |                  |                  |                     |
| Males                     | 11               | 3.2              | 3.47 (1.42–5.52)    |
| Females                   | 10               | 2.5              | 3.94 (1.50–6.38)    |
| **Age at diagnosis**      |                  |                  |                     |
| < 11                      | 6                | 1.3              | 4.63 (0.93–8.34)    |
| ≥ 11                      | 15               | 5.2              | 2.89 (1.43–4.35)    |
| **Sex and age**           |                  |                  |                     |
| Males <11                 | 1                | 0.1              |                     |
| Males ≥11                 | 10               | 2.5              | 4.05 (1.54–6.56)    |
| Females <11               | 5                | 0.8              | 6.11 (0.75–11.5)    |
| Females ≥11               | 5                | 1                | 5.16 (0.64–9.68)    |
| **Race**                  |                  |                  |                     |
| Non-Hispanic, white       | 19               | 4.5              | 4.26 (2.34–6.17)    |
| Other                     | 2                | 0.6              | 3.00 (0–7.17)       |
| **Tumour histology**      |                  |                  |                     |
| Germinoma                 | 10               | 1.4              | 7.15 (2.72–11.59)   |
| Teratoma                  | 4                | 0.8              | 4.76 (0.10–9.42)    |
| Yolk sac tumour           | 2                | 0.4              | 5.45 (0–13.1)       |
| Mixed/other               | 4                | 0.4              | 9.14 (0.18–18.10)   |
| **Tumour location**       |                  |                  |                     |
| Intracranial              | 12               | 1.5              | 8.07 (3.51–12.6)    |
| Extracranial and extragonadal | 2     | 0.5              | 3.78 (0–9.03)       |
| Testis                    | 4                | 0.4              | 11.15 (0.22–22.08)  |
| Ovary                     | 3                | 0.7              | 4.35 (0–9.27)       |

Abbreviations: CI = confidence interval; IR = incidence rate per 100 000 person-years; SEER = Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov); SIR = standard incidence ratio.

a GCT includes germinoma (ICD-7 9060-9065), malignant teratoma (9080-9084), embryonal carcinoma (9070-9072), yolk sac tumour (9071), choriocarcinoma (9100, 9103, 9104), and mixed GCT (9085, 9101, 9102, 9105) in all sites.

b SIR using indirect standardisation. Reference population is SEER 13 population.

c Tumour histology was missing for one GCT proband.

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The authors declare no conflict of interest.

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