Published in final edited form as:

Cancer Epidemiol. 2018 April ; 53: 184–186. doi:10.1016/j.canep.2018.02.005.

Hereditary association between testicular cancer and familial ovarian cancer: a Familial Ovarian Cancer Registry study

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Abstract

Background: Although family history of testicular cancer is well-established as a risk factor for testicular cancer, it is unknown whether family history of ovarian cancer is associated with risk of testicular cancer.

Materials and Methods: Using data from the Familial Ovarian Cancer Registry on 2,636 families with multiple cases of ovarian cancer, we systematically compared relative frequencies of ovarian cancer among relatives of men with testicular and non-testicular cancers.

Results: Thirty-one families with cases of both ovarian and testicular cancer were identified. We observed that, among men with cancer, those with testicular cancer were more likely to have a mother with ovarian cancer than those with non-testicular cancers (OR=3.32, p=0.004). Zero paternal grandmothers of men with testicular cancer had ovarian cancer.

Conclusion: These observations provide compelling preliminary evidence for a familial association between ovarian and testicular cancers. Future studies should be designed to further investigate this association and evaluate X-linkage.

Keywords

Testicular cancer; ovarian cancer; familial cancer; Familial Ovarian Cancer Registry; X-linkage

INTRODUCTION

Testicular germ cell tumors (TGCT), although rare in the overall population, are the most common malignancies among men aged 15 to 44 in the United States and account for 98% of all testicular malignancies [Ghazarian et al, 2015]. Incidence of TGCT has been increasing in the United States since the early 21st century; however, the underlying basis for this trend remains unclear [Shah et al, 2007; Zheng et al, 1996].

Well-established TGCT risk factors include cryptorchidism [Cook et al, 2010], prior testicular cancer [Fossa et al, 2005], greater adult height [Lerero et al, 2010], and family history of TGCT. The heritability of TGCT is estimated at 35-50% [Litchfield et al, 2015; Mucci et al, 2016] with evidence for several susceptibility genes, including 27 identified autosomal loci [Pyle & Nathanson, 2016] and a putative X-linked gene at Xq27, *TGCT1* [Rapley et al, 2000]. Although familial TGCT studies have yet to characterize TGCT syndromic patterns [Mueller et al, 2014], a biologically plausible link between TGCT and ovarian germ cell tumors has been posited [Giambartolomei et al, 2009].

MATERIALS AND METHODS

The Familial Ovarian Cancer Registry (FOCR) at Roswell Park Comprehensive Cancer Center contains clinical and epidemiological information from 2,636 families enrolled continuously from 1981 to present. Qualifying families meet at least one of the following criteria: 1) two or more cases of ovarian cancer; 2) one ovarian cancer and two or more other cancers; 3) an early-onset (<45) ovarian cancer and at least one other cancer; or, 4) a personal history of ovarian cancer and at least one other cancer [Piver, 2002; Tayo et al, 2009]. All cancer diagnoses are self- or family-reported via a family history questionnaire. Eligibility is verified by registry review of completed family history surveys and pro-band medical records. Familial cases reported by the pro-band may themselves be referred to the registry for completion of surveys and medical record evaluation.

Using data from FOCR, we compared relative frequencies of first-degree relatives with ovarian cancer among men with testicular cancer to men with non-testicular cancers via univariate logistic regression to test for unusual familial aggregation of testicular and ovarian cancers. Additional covariates, including age of diagnosis and histology, were not included in multivariate models due to missingness in the registry. Relative frequencies of ovarian cancer among maternal and paternal grandmothers were also compared to explore for possible X-linkage. All analyses were conducted in R version 3.4.

RESULTS

The registry contained records for 34 men with testicular cancer. Table 1 contains information on the number and types of relatives of men with testicular and non-testicular cancers in the registry. We observed that men with testicular cancer in the registry were more likely to have a mother (OR=3.32, 95%CI: 1.46-7.55) or sister (OR=1.66, 95%CI: 0.87-3.15) with ovarian cancer than men with non-testicular cancers (Table 2). Men with testicular cancer in FOCR fathered 13 daughters; however, these daughters either were too young to be at significant risk for ovarian cancer as of their last registry contact or lacked

follow-up. Four of 16 maternal grandmothers (25.00%) of men with testicular cancer were diagnosed with ovarian cancer, while zero of nine paternal grandmothers (0.00%) were affected.

DISCUSSION

Researchers have reported evidence linking the X-chromosome to testicular cancer for the last two decades [Looijenga et al, 1997]. Unsilenced supernumerical X-chromosomes have been reported in TGCT patients [Kawakami et al, 2003; Spatz et al, 2004] and men with TGCT have been observed to confer a four-fold increased risk of TGCT to their sons as opposed to an eight-fold increased risk to their brothers [Hemminki & Chen, 2006; McGlynn & Trabert, 2012; Nordsborg et al, 2011]. Furthermore, a genome-wide linkage analysis reported strong evidence for an unidentified X-linked TGCT susceptibility gene on Xq27 [Rapley et al, 2000].

Intriguingly, this unidentified X-linked testicular cancer susceptibility gene, *TGCT1*, exists in the same region as an ovarian cancer susceptibility gene previously identified in FOCC by our group [Eng *et al*]. It is possible that this X-linked gene may also confer increased testicular cancer susceptibility and drive observed testicular-ovarian cancer associations. Nevertheless, while the observed absence of ovarian cancer in paternal grandmothers of men with testicular cancer is consistent with X-linked transmission, analyses were limited by small sample sizes and X-linkage could not be conclusively established. The registry has begun re-contacting families to update family histories and collect biospecimens to further test for X-linkage.

Greater missingness of ovarian cancer status among mothers and grandmothers of men with non-testicular cancers (Table 1) may reflect the difference in average age of diagnosis of testicular (39.95) and non-testicular (62.81) cancers. Age of diagnosis, however, was not associated with odds of having a mother or grandmother with ovarian cancer in univariate analysis of men with all cancers (OR = 1.00) and did not significantly alter observed odds ratios when included in multivariate analyses of men with testicular and non-testicular cancers (OR = 3.34). Age of diagnosis and histology were unknown for the majority of testicular and ovarian cancer cases in the registry as family-reported cases were mostly without follow-up.

Although our analyses are limited by small sample sizes, it should be emphasized that this study was conducted in an exceedingly rare and specific study population: families with multiple cases of ovarian cancer and at least one case of testicular cancer. Even with small numbers, we observed a statistically significant association in our primary analysis between mothers with ovarian cancer and sons with testicular cancer and a strong signal for a similar association between sisters and brothers. Validation of these results may prove challenging. It is possible that these observations are unique to a familial ovarian cancer-enriched study population and accrual of this population into a validation study may be impractical. While familial testicular cancer registries may contain families with both ovarian and testicular cancers, it is unlikely that many families will have multiple ovarian cancers. Moreover, these

studies primarily recruit multiple familial testicular cancer cases, including father-son pairs, and thus may systematically exclude X-linked testicular cancers [Mai et al, 2010].

The results of this study provide compelling preliminary evidence for an association between familial ovarian cancer and testicular cancer that may be attributable to an X-linked model of transmission. Moving forward, FOCCR has begun targeting families with multiple cases of ovarian cancer and at least one case of testicular cancer for recruitment and re-contacting existing such families to update information and collect biospecimens for genetic analyses. These analyses may provide insight into the etiology and transmission patterns of both cancers and expose novel gene targets for prevention and therapy.

Abbreviations:

TGCT	Testicular Germ Cell Tumor
FOCR	Familial Ovarian Cancer Registry
OR	Odds Ratio
CI	Confidence Interval

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Table 1:

Number of female relatives of men with testicular and non-testicular cancers. Columns include the number of relatives with known ovarian cancer status, the number of relatives with records in the registry, and the number of relatives expected by family structure.

	Men with Testicular Cancer (N = 34)			Men with Non-Testicular Cancers (N = 2894)		
	N of Known Ovarian Cancer Status	N in Database	N Expected	N of Known Ovarian Cancer Status	N in Database	N Expected
Mothers	24	27	34	1809	1983	2894
Maternal Grandmothers	16	16	34	347	406	2894
Paternal Grandmothers	9	9	34	215	278	2894
Sisters	43	45	-	3119	3319	-
Daughters	12	13	-	2969	3049	-

Table 2:

A) Frequencies of men with testicular cancer and men without testicular cancer stratified by maternal ovarian cancer status. The odds ratio represents the odds of testicular cancer among men whose mothers have ovarian cancer as compared to men whose mothers do not have ovarian cancer. B) Frequencies of men with testicular cancer and men without testicular cancer stratified by sister ovarian cancer status. The odds ratio represents the odds of testicular cancer among men whose sisters have ovarian cancer as compared to men whose sisters do not have ovarian cancer.

		Men with testicular cancer	Men with non-testicular cancer	Statistic	P-value
A	Mothers with ovarian cancer	10 (41.67%)	320 (17.69%)	OR = 3.32 (95% CI: 1.46-7.55)	0.004
	Mothers without ovarian cancer	14 (58.33%)	1489 (82.31%)	Reference	
B	Sisters with ovarian cancer	14 (32.56%)	704 (22.57%)	OR = 1.66 (95% CI: 0.87-3.15)	0.124
	Sisters without ovarian cancer	29 (67.44%)	2415 (77.43%)	Reference	