HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2015 October ; 24(10): 1614–1621. doi: 10.1158/1055-9965.EPI-14-1240.

Prospectively-Identified Incident Testicular Cancer Risk in a Familial Testicular Cancer Cohort

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Abstract

Background—Human testicular germ cell tumors (TGCT) have a strong genetic component and a high familial relative risk. However, linkage analyses have not identified a rare, highly-penetrant familial TGCT (FTGCT) susceptibility locus. Currently, multiple low-penetrance genes are hypothesized to underlie the familial multiple-case phenotype. The observation that two is the most common number of affected individuals per family presents an impediment to FTGCT gene discovery. Clinically, the prospective TGCT risk in the multiple-case family context is unknown.

Methods—We performed a prospective analysis of TGCT incidence in a cohort of multiple-affected-person families and sporadic-bilateral-case families; 1,260 men from 140 families (10,207 person-years of follow-up) met our inclusion criteria. Age-, gender-, and calendar time-specific standardized incidence ratios (SIR) for TGCT relative to the general population were calculated using SEER*Stat.

Results—Eight incident TGCTs occurred during prospective FTGCT cohort follow-up (*versus* 0.67 expected; SIR=11.9; 95% confidence interval [CI]=5.1–23.4; excess absolute risk=7.2/10,000). We demonstrate that the incidence rate of TGCT is greater among bloodline male relatives from multiple-case testicular cancer families than that expected in the general population, a pattern characteristic of adult-onset Mendelian cancer susceptibility disorders. Two of these incident TGCTs occurred in relatives of sporadic-bilateral cases (0.15 expected; SIR=13.4; 95%CI=1.6–48.6).

Conclusions—Our data are the first indicating that despite relatively low numbers of affected individuals per family, members of both multiple-affected-person FTGCT families and sporadic-bilateral TGCT families comprise high-risk groups for incident testicular cancer.

Impact—Men at high TGCT risk might benefit from tailored risk stratification and surveillance strategies.

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Conflicts of interest: No authors on this manuscript have a financial conflict of interest to disclose.

Keywords

testicular cancer; prospective study; familial; incidence

Introduction

Testicular germ cell tumors (TGCT) are the most common form of cancer in men aged 15–35 years. Approximately 8,430 new cases, and 380 TGCT deaths are projected for 2015 (1). The Surveillance, Epidemiology, and End Results (SEER) program reported a US testicular cancer incidence of 5.5 per 100,000 white men between 2006 and 2010 (2). 98% of these tumors are thought to arise from arrested primordial germ cells (3). TGCT presents two main histologic types: the more aggressive non-seminomas (peak incidence: ~25 years of age), and the less aggressive seminomas (peak incidence: ~35 years of age) (4, 5). TGCT incidence has more than doubled during the last 30 years, most notably among men of European ancestry (6). The basis for this pattern of increasing incidence of a malignancy that strikes men in the prime of their productive lives is not well understood.

TGCT has an estimated heritability that ranks as the 3rd highest among all cancers (7), although it does not fit the classical, high penetrance, monogenic paradigm. Compared with most malignancies - which have familial relative risks between 1.5-to-2.5 – retrospective cohort studies with various designs (Table 1) have demonstrated that sons of men with TGCT have a 4- to 6-fold increased risk of TGCT *versus* the general population, while brothers of affected men have an 8- to 14-fold increased risk (8–20). These risks increase to 37-fold and 76-fold in dizygotic and monozygotic twins, respectively (21). While there is a substantial epidemiologic literature aimed at estimating familial risks of TGCT, all prior reports targeted sporadic or unselected TGCT, and employed retrospective, cross-sectional, or record linkage designs. There have been no published reports describing prospective TGCT risk among affected and unaffected members of multiple-case families in which follow-up and cancer validation were performed at the individual level.

Despite these strong familial relative risks, the largest genome-wide genetic linkage study performed by the International Testicular Cancer Linkage Consortium did not uncover any major, highly-penetrant genes predisposing to TGCT; rather, its data suggested that multiple genes with smaller effect sizes may underlie this familial aggregation (22). The discovery of multiple TGCT-risk variants in recent GWAS studies supports the hypothesis that many genetic loci contribute to TGCT risk (6, 23–29). Despite the apparent heritability of TGCT, families with more than two affected members are unusual, unlike other hereditary cancer syndromes in which a single multigenerational pedigree often harbors many affected individuals. TGCT is thought to be a polygenic disorder caused by the combined effects of multiple, common genetic variants, perhaps acting in concert with certain environmental exposures. To date, 19 genomic susceptibility loci and three candidate genes have been identified, implicating biological pathways involving fertility, spermatogenesis, sex determination and testicular differentiation (6, 23–30). However, the traditional genetic perspective has been that polygenic disorders should not present as familial clusters,

presumably because the penetrance of such variants is low (31). Therefore, FTGCT represents an unusual, and potentially informative, exception to this rule.

Cryptorchidism, infertility, positive family history, previous TGCT and white race are known TGCT clinical risk factors (4, 5, 32, 33). The TGCT relative risk among men with cryptorchidism is 4.8 (95%CI=4.0–5.7) (32). Male infertility also confers a significantly increased risk of testicular cancer (Standardized Incidence Ratio [SIR] 2.8, 95%CI=1.5–4.8) (33). Both our group and British investigators have implicated testicular microlithiasis in TGCT risk (34, 35). There is also evidence that infertility may be increased in males from TGCT families compared with the general population (36).

In an analysis of 985 cases of TGCT from 461 families, we found that the characteristics of FTGCT were largely similar to those observed in sporadic TGCT (37); similarities included: 1) the distribution of seminomas and non-seminomas; 2) the frequency of bilateral cases and; 3) a later age-at-diagnosis for seminomas than non-seminomas. In addition, the genomic regions implicated as susceptibility loci by GWAS have been similar for sporadic and familial TGCT (24, 25, 28, 29, 38). Differences include a 2-to-3-year earlier age of onset for FTGCT *versus* TCGT (39). A younger age at tumor diagnosis is observed in many hereditary cancer syndromes, a pattern thought to reflect the role of genetic factors (40). However, despite the cumulative data suggesting an important role of heritable factors in the etiology of FTGCT, no study to date has evaluated whether there is an increased risk of prospectively-identified incident testicular cancer in an FTGCT cohort, compared with the general population, a knowledge deficit that produces clinical uncertainty when counseling high-risk family members. Given that two is the most common number of TGCTs in multiple-affected-person families, one might anticipate that such risks would be small, if they could be detected at all. We hypothesized that if there indeed were a genetic component to FTGCT, there should be a substantially increased risk of incident testicular cancer in our prospectively-followed FTGCT cohort. This is the first prospective study with long-term follow up that quantifies incident TGCTs in a cohort of FTGCT individuals and bloodline relatives.

Materials and Methods

Study Population

Multiple-case families with (a) ≥two confirmed TGCT subjects, (b) a combination of TGCT and extra-gonadal germ cell tumor (both designated “multiple- affected-person” families), and (c) families containing only a single individual with bilateral TGCT (designated “sporadic-bilateral-subject” families) were enrolled in the “Multidisciplinary Etiologic Study of Familial Testicular Cancer” (NCI Protocol 02-C-0178; NCT-00039598). In the aggregate, these 3 subsets of families were designated “multiple-case” families, since a subject with sporadic bilateral testicular cancer by definition had two cases of TGCT. Kindreds with a female germ cell tumor patient were excluded from the current analysis. The study protocol explicitly included sporadic-bilateral TGCT subjects (*i.e.*, men with bilateral testicular cancer and a *negative* family history of TGCT) because bilateral affection of paired organs has long been regarded as one of clinical features suggesting the presence of an underlying cancer susceptibility disorder. Our original analytic plan was to seek

candidate gene germline mutations identified in multiple-affected-person families, within our sporadic-bilateral- subjects. It was our *a priori* hypothesis that at least a subset of sporadic-bilateral TGCT patients would be found to have germline mutations in the same susceptibility gene(s) identified in multiple-affected-person families, *i.e.*, that they would have the same genetic cause of their cancer.

Participants completed family, medical, epidemiologic, and psychosocial questionnaires and donated blood samples. All subjects provided written informed consent. Families with two or more affected males or a sporadic bilateral case were eligible for travel to the National Institutes of Health (NIH) Clinical Center for a protocol-based etiologic evaluation, including detailed history and physical examination, semen and laboratory analyses, ultrasound imaging of the testes or ovaries, and ultrasound imaging or computed tomography of the kidneys (41). This study was approved by the NCI Institutional Review Board. Ninety-three percent of all participants reported their racial category as white. Twelve hundred sixty enrolled individuals from 140 families were included in this study; females and non-bloodline relatives were excluded from the current analysis.

Data Collection

Within each family, we designated the first participant with TGCT to enroll in the study as the index case. Data collected from all participants included gender, vital status, date of birth, and dates of death and/or censorship. Data regarding clinical factors such as microlithiasis and undescended testis (UDT) were also collected. Also, pathology reports were obtained and reviewed for seven of eight (87.5%) incident cases. The relationships between multiple affected persons in a family were classified as “siblings,” “first cousins,” “father-son,” “uncle-nephew,” or “complex,” a term reserved for families with patterns that did not fit neatly into the one of the other categories. We performed annual follow-up of study participants *via* mailed questionnaires and telephone contact.

Statistical Analysis

Referent age-adjusted population cancer rates for white males were computed by 5-year age group and 5-year calendar periods using the NCI SEER9 database (1973–2010). The at-risk interval was defined from the family enrollment date [the date on which the first subject from each family signed the study-related informed consent document] to date of cancer diagnosis, death or end of study. Accrued person-years were calculated, and an observed-to-expected SIR for incident TGCT was calculated using SEER*Stat, as previously described (42). All TGCT (n=224) diagnosed prior to each family’s date of study enrollment were excluded from the incident TGCT calculation.

Results

Twelve hundred sixty men from 140 families with 10,207 person-years of follow-up were included in this study. Eight of the 1,260 subjects developed TGCT during follow-up; six incident cases had no prior testicular cancer history, while two were metachronous TGCTs. Six incident cases occurred in multiple-affected-person families and two incident cases occurred among the relatives of men with sporadic-bilateral TGCT. Table 2 summarizes the

demographic and clinical characteristics of the individuals with TGCT prior to enrollment and characteristics of incident TGCTs, including number of individuals affected in the family, presence of microlithiasis, personal history of undescended testis, familial pattern of affection and TGCT morphology. Prior TGCT cases and incident cases had similar distributions of these variables. Table 3 summarizes the clinical characteristics of study participants with an incident cancer.

Eight TGCTs were observed among the 1,260 familial multiple-case TGCT cohort members during prospective follow-up *versus* 0.67 cases expected (O/E=11.9; 95%CI=5.1–23.4) (see Table 4). Analyzing only the 1,036 family members with no personal history of TGCT prior to cohort entry yielded similar results: observed=6; expected=0.50; O/E=12.0; 95%CI=4.4–26.1. The absolute excess risk of TGCT in this cohort was 7.2 cases per 10,000 ($p<0.001$). Table 4 summarizes SIRs stratified by selected characteristics chosen *a priori* as potential modifiers of TGCT risk. Within the constraints imposed by the small number of events, none of these features identified a subset of study participants as being at markedly greater risk of developing incident TGCT, although the presence of either microlithiasis (O/E=29.3; 95%CI=10.7–63.7) or UDT (O/E=31.1; 95%CI=8.5–79.7) in the family suggested higher risks. However, the 95%CI associated with these point estimates overlapped with those from the respective “no” categories, indicating that these differences were not statistically significant. Of note, 7 of the 8 incident TGCT occurred in the 119 families with ≤2 affected individuals (expected=0.51; O/E=13.7; 95%CI=5.5–28.3) *versus* 1 observed (expected=0.16; O/E=6.2; 95%CI=0.2–35.2) in the 21 families with ≥3 affecteds. Thus, the handful of heavily-loaded families did not drive the occurrence of incident TGCT in this cohort.

Stratifying the data by multiple-affected-person family (n=82 families; 874 family members; 7696.9 person-years of observation) *versus* sporadic-bilateral-subject family (n=56 families; 373 family members; 2437.5 person-years of observation) yielded similarly increased SIRs in both the former (observed=6; expected=0.52; O/E=11.6; 95% CI=4.2–25.1) and the latter (observed=2; expected=0.15; O/E=13.4; 95% CI=1.6–48.6).

Discussion

In 2002, the National Cancer Institute’s Clinical Genetics Branch initiated an observational, etiologic study of familial TGCT (41). During the course of prospective follow-up, eight persons (6 without, and 2 with, a personal history of TGCT at the time of enrollment) developed TGCT, a nearly twelve-fold increase in TGCT risk compared with the number expected from gender-, age- and calendar-time-specific rates from the US white population. These are the first cases of familial TGCT to be documented prospectively, and their occurrence permitted us to generate the first quantitative estimates of TGCT risk in the setting of multiple-case families.

Furthermore, stratified analysis revealed that the risk was similarly increased in multiple-affected-person families (O/E=11.6) and sporadic-bilateral-subject families (O/E=13.4). Our results confirm that men from both multiple-affected-person TGCT families and sporadic-bilateral-subject TGCT families truly do comprise two subsets of the general population that

are at substantially increased TGCT risk. Although the number of cancer events in each group is small, and the excess absolute risks are low, each O/E ratio is statistically significantly elevated relative to general population expectation. Nonetheless, our observations in the relatives of men with sporadic-bilateral TGCT warrant replication, a task that may be approachable using the Scandinavian population-based registry system.

Our results are somewhat surprising given that a combination of low penetrance genes is thought to underlie the etiology of familial testicular cancer, and that about 75% of families contain only two cases, since it is generally believed that polygenic susceptibility does not produce familial aggregations of disease (31). To the best of our knowledge, ours is the only existing longitudinal cohort study targeting men from extended multiple-case TGCT families that could be used to address this fundamental question. In particular, the prospective occurrence of incident TGCT in the relatives of men from sporadic-bilateral-subject families further supports the broader notion that there is a genetic component to this pattern of affection. This unexpected result is consistent with the recognition that men who are homozygous for *KITLG* TGCT-associated risk alleles have a TGCT odds ratio that is greater than 6 (25, 26), the strongest SNP/cancer association yet reported. Familial TGCT may be the first well-documented example of a disease presentation that will become more common now that our ability to identify polygenic disorders has become more tractable. Potential mechanisms for this phenomenon include (a) the existence of intermediate-risk variants, like *KITLG*; (b) the presence of common, low-penetrance variants acting as modifiers of the risks associated with as yet undiscovered rare, high-penetrance variants; and (c) common variants proving to be highly-active functionally.

We attempted to determine whether specific clinical features might permit identification of a subset of family members that was at particular risk of developing incident TGCT. Within the constraints imposed by the small number of prospective cancer events, none of the characteristics we examined (Table 4) were significantly correlated with cancer risk above and beyond the level seen in the entire set of family members. The SIRs associated with a family history of either microlithiasis (O/E=29.3) or undescended testes (O/E=31.1) trended towards greater risks, but these differences were not statistically significant. We are continuing to enroll and follow additional FTGCT kindred, and hope to eventually achieve sufficient statistical power to answer these questions definitively. We should note that our prior report linking microlithiasis to the risk of familial TGCT included many of the same families analyzed here (35); thus, these findings do not comprise independent confirmation of that provocative observation, which does merit corroboration in the context of elucidating the pathogenesis of testicular cancer. The microlithiasis association question is one of the major foci of our ongoing research.

This is the first study to demonstrate quantitatively that the incidence of testicular cancer is substantially increased relative to the general population in a cohort of multiple-case families, including both multiple-affected-person and sporadic-bilateral-subject kindreds. While there is a substantial epidemiologic literature aimed at estimating familial risks of TGCT, all prior reports targeted sporadic/unselected TGCT, and employed retrospective, cross-sectional or record linkage designs (Table 1). In contrast, our study was family-based, prospective, excluded prevalent cases from the risk assessment, had clinical details on a

significant fraction of study participants, included a relatively large number of individuals at risk, had central pathology review of TGCT cases performed (87.5% of incident cases), and was based on an average follow-up of more than 8 years. Nonetheless, the number of cancer events was small, limiting our ability to more precisely define subsets of family members that might be at particularly high risk. In addition, individual level information relative to testicular microlithiasis was available only for the 132 individuals who had undergone testicular ultrasound, either as part of our study or during the course of their routine clinical care. This restricted our stratified SIR analysis of microlithiasis to families rather than individuals. Critical risk factor information, such as history of undescended testicle, was based largely on unconfirmed subject self-report. Medical record documentation of UDT was exceedingly difficult to obtain. The study was not designed to disentangle the relative contributions of genetic, developmental and environmental factors to the etiology of TGCT. Rather, its primary focus was on susceptibility gene discovery, towards which end our annotated DNA samples have been contributed to multiple analyses which have shaped our current understanding of TGCT genomics (4, 6, 22, 23, 29, 37, 38, 41, 43, 44).

Given the rarity of testicular cancer and its favorable prognosis even at advanced stages, the United States Preventive Services Task Force (USPSTF) has recommended against testicular cancer screening, concluding that the limited benefits do not outweigh the potential screening-related harms (45, 46). We concur that there is no proven testicular cancer screening strategy available for clinical use, and further believe that the relative rarity of TGCT coupled with its high curability rate make it unlikely that such a strategy will be developed and formally validated. The USPSTF concluded that these characteristics make it unlikely that screening asymptomatic men *from the general population* will produce additional benefits above and beyond clinical detection (45, 46). However, for the first time, our study has demonstrated prospectively that men from multiple-affected-person and sporadic-bilateral-subject TGCT families are at substantially elevated risk relative to the general population.

What can one do with this information in the absence of a clinically validated risk-reducing strategy? This conundrum is becoming increasingly prevalent, as our ability to identify persons at increased genetic cancer risk is outstripping the development of evidence-based cancer site-specific screening and risk-reducing capabilities. First, the results are of etiologic importance in that we have documented high TGCT risk in a genetic context where the presence of a rare, highly-penetrant, single gene Mendelian trait seems very unlikely (22). If the currently-accepted polygenic model of TGCT heritability is correct, our findings suggest that substantial cancer risks can result nonetheless.

Second, even in the absence of proven benefit, best clinical judgment would seem to support advising members of multiple-affected-person and sporadic-bilateral-subject families to perform testicular self-examination on a regular basis, and to bring new abnormalities (testicular mass; persistent testicular pain) to the attention of their health care providers promptly. Outside the research setting, we do not advise periodic, routine testicular ultrasound examination for high-risk individuals. We reserve such imaging for the evaluation and management of testicular cancer signs or symptoms, an approach that is practical given the very high rates of cure among patients with advanced stage TGCT.

Nonetheless, there is real potential to avoid the acute and chronic toxicities (*e.g.*, coronary artery disease, neurotoxicity, nephrotoxicity, ototoxicity, pulmonary fibrosis and treatment-related second cancers) (47) related to 3–4 cycles of platinum-based chemotherapy if TGCT can be detected at a sufficiently early stage to permit management with surgery and surveillance rather than chemotherapy and/or radiation. And treatment delay has been associated with reduced TGCT survival (48, 49). Thus, a family history of bilateral TGCT or ≥2 TGCT cases might be considered clinically actionable, despite the absence of an effective screening program.

Finally, modeling exercises have suggested that combining data from GWAS risk loci and strong clinical risk factors (*e.g.*, family history, undescended testis, infertility) might permit the development of risk stratification models that could identify specific subsets of men with even more dramatic elevations in risk, upon whom more aggressive education and surveillance activities might be appropriately focused (50, 51), especially if it could be demonstrated that the GWAS risk SNPs were not also associated with the clinical risk factors, a question for which limited data are contradictory (52, 53). Thus, for example, men aged 30–34 in our study who were in the top 1% of genetic risk and who also had a personal history of cryptorchidism were estimated to be at a 50-fold increase in TGCT risk relative to average population risk, *assuming* that the TGCT risk SNPs were not also associated with undescended testicle risk (50). We are continuing to develop this line of research in the hope that clinically actionable levels of risk can be defined.

This study presents the first prospectively-collected data on incident testicular cancer in a multiple-case familial testicular cancer cohort, providing strong evidence that TGCT incidence is substantially higher in this group than in the general population. These findings support the notion that the combined effect of common, low-penetrance mutations can confer a significant risk of cancer, and provide a rationale for developing more sophisticated risk stratification strategies that might unambiguously identify subsets of men which warrant enhanced education and TGCT surveillance.

Acknowledgements

The authors gratefully acknowledge the participation of our patients, without whom this work could not have been done.

Grant Support

All authors were supported by the NCI Intramural Research Program, Division of Cancer Epidemiology and Genetics, Human Genetics Program, under NIH Project Z01-CP010144-16, Clinical Genetic Studies of Familial and Hereditary Cancer Syndromes.

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Table 1

Literature Review of Testicular Cancer Cohort and Case-Control Studies

First Author	Country	Year	Study Design	Testicular Cancer (TC) Cases	Controls	TC in 1° or 2° Relative	Families Reported	Risk Estimate
Tollerud, DJ (19)	U.S.	1985	Retrospective multicenter	269	259	Cases=6 Control=1	NR	RR=5.9 (95%CI:0.7–49.1)
Forman, D (14)	U.K.	1992	Retrospective multicenter	794	749	Cases=12 Control=2	42	RR=9.8 (95%CI:2.8–16.7)
Westergaard, T (20)	Denmark	1996	Retrospective Population-based cohort	Father cohort=2113 Brother's sub cohort=702	NA	Fathers=12 Brothers=4	NR	RR of father of affected=2.0 (95%CI:1.01–3.43) RR of brother of affected=12.3 (95%CI:3.3–31.5)
Heimdal, K (15)	Norway & Sweden	1996	Retrospective multicenter hospital-based cohort	1159	NA	N1°=32 N2°=24	NR	SIR of fathers=4.3 (95%CI:1.6–9.3) SIR of brothers=10.2 (95%CI:6.2–15.8) SIR of sons=5.7 (95%CI:0.7–23.2)
Dieckmann, K (12)	Germany	1997	Prospective multicentric cohort	1692	NA	28	NR	Prevalence=1.7 (95%CI:1.20–2.5)
			Retrospective case/control	518	531	Cases=13 Control=3	NR	OR=4.5 (95%CI:1.2–24.9)
Sonneveld, D (18)	Netherlands	1999	Retrospective single center	693	NA	24	17	RR brother=8.5–12.7 (95%CI:4.3–22.6) RR father= 1.7 (95%CI:0.6–3.8)
Dong, C (13)	Sweden	2001	Retrospective family cancer database	4640	NA	62	NR	SIR brother=8.3 (95%CI:5.7–12.2) SIR father to son=3.9 (95%CI:2.0–6.8) SIR son to father=3.8 (95%CI:2.0–6.7)
Hemminki, K (17)	Sweden	2004	Retrospective multigenerational registry	Sons=4082 Fathers=3878	0		67	RR of son=3.8 (95%CI:2.2–6.2) RR of brother=8.6 (95%CI:6.4–11.3) RR of brother <5yrs younger than affected=10.8 (95%CI:7.3–15.4) RR of brother>5yrs older than affected=6.7 (95%CI:4.2–10.2)
Bromen K(11)	Germany	2004	Retrospective multi-national population-based case/control	269	797	Cases=11 Controls=6	NR	OR w/brother=14.2 (95%CI:3.0–67.3); OR w/father =2.1 (95%CI:0.5–9.4)
Hemminki, K (16)	Sweden	2006	Retrospective population registry	Sons=4586 Fathers=4314	0	NR	43	SIR w/father only=3.8 (95%CI:1.9–6.6) SIR w/brother only=7.6 (95%CI:5.1–10.7)
Walschaerts, M (10)	France	2007	Retrospective hospital-based case/control	229	800	NR	Cases=19 Controls=8	OR=9.6 (95%CI: 4.0–22.9)
Nordsborg, RK (8)	Denmark	2011	Retrospective population-based case/control	3297	6594	40,104 in cases and controls	N/A	RR w/affected father=4.6 (95%CI:2.4–8.9) RR w/affected brother=8.3 (95%CI:3.8–18.1) RR w/affected son 5.23 (95%CI:1.35–20.25)

First Author	Country	Year	Study Design	Testicular Cancer (TC) Cases	Controls	TC in 1° or 2° Relative	Families Reported	Risk Estimate
Valberg, M (9)	Norway	2013	Retrospective Hierarchical Frailty Modeling	1,135,320	NA		7524 families with >1 TGCT	FRR of son=4.0 (95%CI:3.1–5.2); FRR w/1 affected brother=5.9 (4.7–7.4) FRR w/2 affected brothers=21.7 (95%CI:8.9–52.8)

RR: relative risk; **SIR:** standardized incidence ratio; **OR:** odds-ratio; **FRR:** frailty relative risk

Table 2

Demographic and Clinical Characteristics of the Familial Testicular Germ Cell Tumor Cohort

Age at Entry (Mean, SD)		
Prior Personal History of TGCT (n=224)	38.9 (12.2)	
Incident Cases[a] (n=8)	30.5 (10.6)	
No Incident or Prior TGCT (n=1030)	34.7 (27.4)	
Personal History of TGCT Prior to Family Enrollment		
YES	224 (17.8%)	
NO	1036 (82.2%)	
	Families of those with prior personal history of TGCT (excluding incident families), n=132	Incident Families, n=8
Numbers of Individuals Affected in Family		
1	56 (42.4%)	2 (25.0%)
2	56 (42.4%)	5 (62.5%)
3	18 (13.6%)	1 (12.5%)
4	1 (0.8%)	0 (0.0%)
5	1 (1.8%)	0 (0.0%)
	For those with prior personal history of TGCT (excluding incident cases), n=222	Incident Cases, n=8
Microlithiasis		
Classical Testicular Microlithiasis (CTM)	17 (7.7%)	0 (0.0%)
CTM/LTM	2 (0.9%)	1 (12.5%)
Limited Testicular Microlithiasis (LTM)	25 (11.3%)	2 (25.0%)
No Microlithiasis	25 (11.3%)	1 (12.5%)
Microlithiasis Status Unknown	153 (68.9%)	4 (50.0%)
Personal History of Undescended Testicle		
Yes	14 (6.3%)	1 (12.5%)
No	208 (93.7%)	7 (87.5%)
Family Pattern of Affection At Enrollment		
Bilateral Affected Case	56 (25.2%)	2 (25.0%)
Complex	25 (11.3%)	2 (25.0%)
Cousins	16 (7.2%)	1 (12.0%)
Father/Son	34 (15.3%)	0 (0.0%)
One of a set of identical twins	2 (0.9%)	0 (0.0%)
Siblings	83 (37.4%)	3 (37.5%)
Uncle/Nephew	6 (2.7%)	0 (0.0%)
TGCT Morphology		
Carcinoma, NOS	8 (3.6%)	1 (12.5%)
Mixed Germ Cell Tumor	36 (16.2%)	1 (12.5%)

Seminoma, NOS	102 (46.0%)	4 (50.0%)
Nonseminoma, NOS	76 (34.2%)	2 (25.0%)

[a]Two of 8 incident cases also had a prior history of TGCT; the remaining 6 did not.

TGCT: testicular germ cell tumor; **NOS:** not otherwise specified

Table 3

Summary of Study Participants who Developed Incident TGCT during Prospective Follow-up

Case #	Study Subset	UDT	Testicular Micro-Lithiasis	# of TGCT in Family[3]	Prior TGCT Histology[4] (Laterality)	Age at Dx[5]	Incident TGCT Histology (Laterality)	Age at Dx[5]	Vital Status
1	MAP[1]	No	Unknown	2	Non-Seminoma (L)	14	Non-Seminoma (R)	25	Alive
2	MAP[1]	No	Yes	2	Seminoma (L)	34	Seminoma (R)	40	Alive
3	MAP[1]	No	Unknown	2	None	---	Non-Seminoma	17	Alive
4	MAP[1]	No	Unknown	2	None	---	Unknown	32	Alive
5	MAP[1]	No	Yes	2	None	---	Seminoma (R)	35	Alive
6	MAP[1]	No	Yes	3	None	---	Mixed Germ Cell (R)	39	Alive
7	SB[2]	No	No	1	None	---	Seminoma (L)	47	Alive
8	SB[2]	Yes	Unknown	1	None	---	Seminoma (R)	41	Alive

[1] MAP: multiple-affected-person family

[2] SB: sporadic-bilateral-case family

[3] Number of individuals with TGCT in family at the time of enrollment

[4] For the two subjects who had a unilateral TGCT at the time of study entry, and then developed an incident TGCT during prospective follow-up

[5] Dx: diagnosis

Table 4

Observed/Expected Analysis of Incident Cases in Familial Testicular Germ Cell Tumor Cohort

Strata	Observed	Expected	O/E (95% Confidence Interval)	Persons	Person Years at Risk	Absolute Excess Risk[e]	P-value
All Subjects	8	0.67[a]	11.9[b] (5.1–23.4)	1,260	10,207.2	7.2	1.11E-06
Family History of Microlithiasis: Yes	6	0.20[a]	29.3[b] (10.7–63.7)	422	3,215.8	18.0	1.5E-07
Family History of Microlithiasis: No	1	0.17[a]	5.9 (0.2–33.0)	194	2,409.6	3.5	0.31267
Family History of Microlithiasis: Unknown	1	0.30[a]	3.4 (0.1–18.7)	644	4,581.7	1.5	0.518364
UDT in Family: Yes	4	0.13[a]	31.1[b] (8.5–79.7)	261	1,824.4	21.2	2.15E-05
UDT in Family: No	4	0.54[a]	7.4[c] (2.0–18.8)	999	8,382.8	4.1	0.004619
Familial Histology Type: Seminoma	2	0.14[a]	14.3[d] (1.7–51.7)	317	2,258.2	8.2	0.017863
Familial Histology Type: Nonseminoma	1	0.12[a]	8.6 (0.2–47.7)	155	1,769.3	5.0	0.226159
Familial Histology Type[f]: Mixed	5	0.42[a]	12.0[b] (3.9–28.1)	788	6,179.8	7.4	0.000154
Pattern of Cancer: Siblings	3	0.24[a]	12.4[c] (2.6–36.2)	452	3,850.33	7.2	0.003853
Pattern of Cancer: Cousins	1	0.05[a]	20.4 (0.5–111.6)	86	623.1	15.3	0.097541
Pattern of Cancer: Complex	2	0.13[a]	15.1[d] (1.8–54.4)	157	1,860.1	10.0	0.015504
Pattern of Cancer: Father/Son	0	0.09[a]	0 (0.0 –42.1)	152	1,266.5	−0.7	1
Pattern of Cancer: Other	2	0.16[a]	12.83[d] (1.6–46.3)	400	2,534.3	7.3	0.023026
Pedigree Type: Multiple-Affected-Person	6	0.52[a]	11.6[b] (4.2–25.1)	874	7,696.9	7.1	3.52E-05
Pedigree Type: Sporadic-Bilateral	2	0.15[a]	13.4[d] (1.6–48.6)	373	2,437.5	7.6	0.020372
Age at Entry: 0–19	1	0.15[a]	6.6 (0.2–37.0)	399	3,534.2	2.4	0.278584
Age at Entry: 20–39	5	0.40[a]	12.5[b] (4.1–29.2)	325	3,023.2	15.2	0.000122
Age at Entry: 40–59	2	0.10[a]	19.2[c] (2.3–69.2)	295	2,121.2	8.9	0.009358
Age at Entry: 60+	0	0.02[a]	0 (0.0–207.0)	241	1,528.6	−0.1	1
TGCT Subjects in Family: One	2	0.15[a]	13.0[d] (1.6–47.0)	388	2,532.0	7.3	0.020372

Strata	Observed	Expected	O/E (95% Confidence Interval)	Persons	Person Years at Risk	Absolute Excess Risk[e]	P-value
TGCT Subjects in Family: Two	5	0.36[a]	13.9[b] (4.5–32.4)	615	5,200.9	8.9	7.48E-05
TGCT Subjects in Family: ≥Three	1	0.16[a]	6.3 (0.2–35.2)	257	2,474.2	3.4	0.295712

[a] The specific age or year was not found in the referent rate table; the closest age/year was used to obtain the rate.

[b] $P < 0.001$;

[c] $P < 0.01$;

[d] $P < 0.05$.

[e] Excess absolute risk is expressed as cases per 10,000

[f] "Familial histology, mixed" signifies families in which at least one man with seminoma and one man with non-seminoma TGCT have each been diagnosed.

UDT: undescended testis; **TGCT:** testicular germ cell tumor; **0/E:** observed/expected