Published in final edited form as:

Int J Cancer. 2009 February 15; 124(4): 952–957. doi:10.1002/ijc.23971.

Risk of cancer in first- and second-degree relatives of testicular germ cell tumor cases and controls

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Abstract

Risk factors for testicular germ cell tumors (TGCT) have not been well-identified, however, data suggest that risks of cancer in family members of men with TGCT is elevated. Using family history data from 738 cases and 904 controls enrolled in the U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) Study from 2002–2005, the risk of cancer in first- and second-degree family members of these men was examined. Relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models, adjusting for reference age of case or control, race/ethnicity of case or control, sex of family member, and lineage (maternal versus paternal). An increased risk of all cancer among first-degree relatives of cases compared to controls was observed (RR=1.17, 95% CI, 1.01–1.35). There were suggestions of differences in risk when stratifying all relatives by lineage. For maternal relatives, there was a statistically significant increased risk of all cancer (RR=1.16, 95% CI, 1.04–1.30), digestive tract (RR=1.52, 95% CI, 1.15–2.00), and male genital organ cancer (RR=1.70, 95% CI, 1.15–2.51); there was also a suggestion of increased risks of hematopoietic cancers, cancers in the female genital organs, and non-melanoma skin cancer. For paternal relatives, there was a statistically significant association only with decreased risk of lung cancer (RR=0.69, 95% CI, 0.51–0.94). Thus, this study suggests that there may be aggregation of cancer among families of men diagnosed with TGCT.

Keywords

testicular cancer; family; aggregation

Introduction

Testicular germ cell tumors (TGCT) are the most common tumors among men in the U.S. aged 15–35 years, and the incidence of certain subtypes is still rising.¹ However, with the

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Journal Category: Epidemiology

This study examines familial aggregation of cancer in men with testicular cancer, and is the first study to examine risk of cancer in relatives by lineage. We observed an increased risk of cancer among relatives of men with testicular germ cell tumors compared to relatives in men without.

exception of cryptorchidism which has been shown to increase risk substantially, other risk factors for TGCT have not been well-identified,² although there is some evidence that a genetic predisposition to TGCT may exist. Several studies have shown that men with TGCT, compared to those without, are more likely to have a family member also affected with TGCT. Brothers of cases have been shown to have a 5–14-fold increase in risk of having TGCT,^{3–6} and this elevated risk is particularly evident among twins.⁷ Fathers of men with TGCT have also been shown to have elevated risk of having TGCT, although the increase in risk is not as great, ranging from 1.75 to 4.50.^{3, 4, 6, 8–10} Other studies have indicated an elevated risk of other cancers among first- and second-degree family members, including a higher risk of breast cancer^{8, 9, 11–14} and cancer in the female genital organs of mothers or sisters of TGCT cases.^{9, 11} Thus it is reasonable to posit that there may be an increased risk of hormonally-related cancers among family members of men with TGCT.

There have been several studies on aggregation of cancer among families identified by a proband with TGCT, but many of the earlier studies focused primarily on first-degree relatives and few studies have quantitatively examined the spectrum of cancers that may aggregate with TGCT,^{3, 15} nor, to our knowledge, have examined whether there are differences in a relative's cancer risk by lineage (maternal versus paternal). In addition, there are no data from the U.S. on familial aggregation of cancer among relatives of probands with TGCT. Thus, we sought to characterize the risk of cancer among family members of men participating in a U.S.-based case-control study of TGCT. We examined risk of cancer in first- and second-degree relatives, as well as risk by lineage (maternal versus paternal) and by TGCT histologic type.

Materials and Methods

Study population

Study participants, enrolled from April 2002 to January 2005 in the U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) Study, have been previously described in detail.¹⁶ Briefly, all men who had at least one serum sample stored in the Department of Defense Serum Repository (Silver Spring, MD), and who were younger than 45 years of age at diagnosis were eligible for the study. Men who developed TGCT while on active duty were eligible to be enrolled as cases if they were diagnosed at a later date than the date of serum donation. TGCT diagnoses, confirmed by pathology reports or by a pathologist if the pathology report was missing (5%), were limited to classic seminomas or nonseminomas (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratomas, and mixed germ cell tumors). Men who developed spermatocytic seminomas were not eligible for inclusion. Eligible controls were men who did not develop TGCT, and were pair-matched to cases based on age at diagnosis (<1 year), ethnicity (white, black, other), and date serum sample was donated (<30 days).

Of the possible case participants (n=853), 22 were in the process of being contacted when the study closed, leaving 831 men who were contacted. Of those, 77 refused to participate and 754 cases (91%) agreed to participate in and completed the study. Of the possible control participants (n=1,182), 32 were in the process of being contacted when the study closed, leaving 1,150 men who were contacted. Of those, 222 refused to participate and 928 (81%) controls agreed to participate in and completed the study. Seven hundred, twenty were matched case-control pairs. Of the cases and controls that agreed to participate, 1,247 participants also gave permission to contact their mothers; 41 mothers were found to be ineligible (primarily due to a language barrier), and 16 could not be located. Of the 1,160 mothers that were contacted, 72 refused to participate (94% participation); the remaining 1,088 women were enrolled into the study and completed a questionnaire. The study was approved by the institutional review boards of the National Cancer Institute and the Walter

Reed Army Institute for Research. All participants provided written informed consent prior to enrolling in the study.

Determination of family history of cancer

Each case/control participant completed a study questionnaire through a computer-assisted telephone interview. Questionnaires elicited information on known or suspected risk factors for TGCT, and a detailed family pedigree of blood relatives, including half-siblings and excluding stepparents or relations by marriage or adoption. Information collected on each relative included their age at interview if alive or age at death, whether the relative ever had a cancer diagnosis, and the types and dates of cancer diagnoses. The mothers of the case/control participants were also interviewed and completed a questionnaire including the same family history information. For our determination of family history of cancer, we used any report of cancer in relatives from either the participant or their mother. If the dates of cancer diagnoses reported by the sons and mothers were discrepant, we used the date reported by the mother.

To maximize the power of our associations, cancer diagnoses were categorized into the following main groups: all malignant neoplasms, head and neck (buccal cavity, head, neck, larynx), lung, breast, digestive tract (esophagus, stomach, colorectal, pancreas, biliary tract, liver), urinary system (bladder, kidney), hematopoietic (leukemia, lymphoma, myeloma), male genital organs (penis, prostate, testis), female genital organs (uterus, vagina, vulva, cervix, ovary, fallopian tube), melanoma, and non-melanoma skin. In men, prostate and testicular cancers were also examined separately.

Statistical Analysis

To assess familial aggregation, we estimated risk of cancer in relatives among men with and without a diagnosis of TGCT, by applying a general stratified Cox model, where t_{ij} denoted the age at onset of cancer or the age at censoring for member j in family i .¹⁷ The outcome t_{ij} was modeled as

$$\lambda_g(t_{ij}, \mathbf{X}_{ij}, Z_{ij}) = \lambda_{0g}(t_{ij}) \exp(\beta \mathbf{X}_{ij} + \gamma Z_{ij})$$

where $\mathbf{X}_{ij}$ denoted measured covariates for member j in family i , and Z_{ij} was an indicator variable of the proband's disease status ($Z_{ij}=1$ if proband of family i is a case, and 0 otherwise). Testing for familial aggregation corresponds to testing the null hypothesis $H_0: \gamma = 0$. The subscript g indicated the g^{th} stratum, and the strata were defined by cohort birth year. g was equal to 1, 2, 3, 4, 5, or 6 if the individual was born before 1920, from 1920 to 1940, from 1941 to 1960, from 1961 to 1980, and after 1980, respectively. The baseline hazard function $\lambda_{0g}(t_{ij})$ was allowed to vary for each stratum; however, the coefficients β and γ were the same for each stratum. The parameters β and γ were estimated by maximizing a partial likelihood function, obtained by multiplying likelihood functions for each stratum under the assumption of no interaction between the stratification variable (cohort birth year) and the covariates ($\mathbf{X}_{ij}$ and Z_{ij}). We estimated the variance-covariance matrix of $\hat{\beta}$ and $\hat{\gamma}$ by the robust sandwich estimator¹⁸ using Proc Survival, in the Sudaan 9.0 program (RTI International, Research Triangle Park, NC), which accounts for the dependence of family members and allows for stratified sampling where cases and controls are treated as being sampled from separate stratum..

Family members had an event if they were reported to have been diagnosed with cancer, and age at cancer diagnosis was the time to event. Those who did not develop cancer were not considered to have had an event, and were censored either at age of death or, if alive, age at

the time of the case/control participant's interview. The risk of cancer was assessed for first-degree relatives, all first- and second-degree relatives combined, and for maternal and paternal relatives, separately. Analyses were also conducted separately by sex. All models were adjusted for age at diagnosis of TGCT for the case/control, race/ethnicity of the case/control, and sex, when appropriate. Models assessing risk for all first- and second-degree relatives combined also adjusted for lineage (maternal versus paternal).

We also examined differences in cancer risk of family members by TGCT histology of the proband (seminoma versus nonseminoma) using data from the cases only. Therefore, Z_{ij} is defined as the indicator of the cases' histology status ($Z_{ij}=1$ if the case of family i has a diagnosis of seminoma, and 0 if the case of family i has a diagnosis of nonseminoma). These models were adjusted for ethnicity, sex (when appropriate), and lineage (when appropriate). Age at diagnosis was not adjusted for in these models, because seminomas occur primarily among older men and histology has been shown to be strongly correlated with age at diagnosis.¹

Results

Family history data was available from 738 cases and 904 controls, and from the mothers of 515 cases and 556 controls. Three hundred fourteen of the cases had been diagnosed with seminomas and 424 with nonseminomas. The mean ages of cases and controls were 28.4 years and 28.3 years, respectively; within cases, the mean ages of men with seminomas and nonseminomas were 30.8 years and 26.3 years, respectively.

Risk of cancer in first-degree relatives of the study participants is presented in Table 1. Among all first-degree relatives of the cases, there were increased risks of all cancer [relative risk (RR)=1.17, 95% CI, 1.01–1.35] and non-melanoma skin cancer (RR=1.48, 95% CI, 1.07–2.06) and a decreased risk of risk of head and neck cancers (RR=0.37, 95% CI, 0.15–0.94). For male first-degree relatives, although there was a statistically significant 4.51-fold increase in total testicular cancer risk, when separated, the risks of testicular cancer in brothers (RR=4.78, 95% CI, 0.99–23.21) and fathers (RR=3.74, 95% CI, 0.39–36.11) were suggestively elevated, but did not reach statistical significance. Among the female first-degree relatives there was a suggestion of an increased risk of cancers of the genital organs (RR=1.44, 95% CI, 0.96–2.15).

Risks of cancer in first- and second-degree relatives of the study participants are presented in Table 2. Again, there was an increased risk of cancer in all relatives, although the association was stronger in females (RR=1.19, 95% CI, 1.07–1.32). Significantly increased risks of digestive tract cancer, hematopoietic cancer, melanoma, and non-melanoma skin cancer were also observed. In contrast, there was a decreased risk of lung cancer, particularly among male relatives (RR=0.78, 95% CI, 0.62–0.99). Again, we observed a statistically significant increased risk of testicular cancer (RR=3.03, 95% CI, 1.47–6.21) and a suggestion of an increased risk of female genital organ cancer (RR=1.27, 95% CI, 0.98–1.65). There was also a significantly increased risk of prostate cancer (RR=1.39, 95% CI, 1.07–1.81).

When stratified by lineage (Table 2), there were increased risks of all cancer (RR=1.16, 95% CI, 1.04–1.30), digestive tract cancer (RR=1.52, 95% CI, 1.15–2.00), testicular cancer (RR=3.85, 95% CI 1.22–12.12), and prostate cancer (RR=1.52, 95% CI 1.00–2.32) among maternal relatives. There were also suggestions of increased risks of hematopoietic cancers, female genital organ cancers, and non-melanoma skin cancer. Among the paternal relatives, there was only a suggestion of an increased risk of all cancer (RR=1.08, 95% CI, 0.95–1.21), prostate cancer (RR=1.32, 95% CI, 0.94–1.84), and non-melanoma skin cancer

(RR=1.41, 95% CI, 0.99–1.99). Risk of testicular cancer was not statistically significantly elevated among the paternal relatives (RR=1.34, 95% CI, 0.38–4.78), however, there was a reduction in lung cancer risk in male paternal relatives (RR=0.71, 95% CI, 0.51–0.98) that was not observed among the male maternal relatives (OR=0.87, 95% CI, 0.62–1.22).

Cancer risks among relatives stratified by tumor histology of the proband's TGCT were also examined (Table 3). Due to small numbers, however, there was insufficient power to examine risks of head and neck cancers, urinary system cancers or melanoma. When comparing nonseminoma to seminoma, first-degree relatives of men with nonseminoma had a 20% reduction in risk of all cancer (95% CI, 0.65–1.00). There was also a reduction in risk of lung cancer (RR=0.44, 95% CI, 0.19–0.98) and non-melanoma skin cancer (RR=0.52, 95% CI, 0.33–0.82). For maternal relatives, there was a statistically significant increased risk of all cancer and lung cancer in male relatives and decreased risk of hematopoietic cancer in female relatives of men with nonseminoma. For paternal relatives, there were no differences in cancer risk for relatives of men with nonseminoma versus seminoma, except for a statistically significant inverse association of non-melanoma skin cancer.

Discussion

Our findings of an increased risk of testicular cancer in male first-degree relatives, especially in brothers, is consistent with the majority of studies examining familial aggregation of cancers.^{3, 4, 6, 8-10, 15, 19} First-degree relatives were observed to have increased risks of female genital organ, hematopoietic, and non-melanoma skin cancer, and a decreased risk of head and neck cancer. Associations for female genital cancer have also been inconsistent, with three studies reporting increased risks,^{5, 8, 11} and 4 studies reporting no association.^{3, 9, 15, 19} Risk associated with hematopoietic cancers have been inconsistent, with one study reporting an increased risk in mothers,⁹ one reporting decreased risk,³ and others finding no association.^{6, 15, 19} No studies have previously observed an association with non-melanoma skin cancer,^{3, 9} although two studies have reported an increased risk of melanoma.^{3, 9} The suggestion of an increased risk of melanoma observed in the current study (OR=1.71, 95% CI, 0.79–3.70), however, did not attain statistical significance. Two prior studies have reported the rate of head and neck cancers among relatives of TGCT cases compared to controls. Although Gundy et al.¹⁹ did not calculate a relative risk, there were fewer first-degree family members of cases with head/neck cancer (n=10) than first-degree family members of controls (n=17); however, these differences are not likely to be statistically significant. Another study reporting on mouth and pharynx cancer calculated an observed/expected ratio of 0.5 (95% CI, 0.1–1.8).¹⁵ The findings of these studies and ours may be due to chance because of small numbers of cases.

Other cancers that have been reported to aggregate with testicular tumors in first-degree family members include colorectal cancers,^{3, 9} lung or other respiratory tract cancers,^{5, 9, 15} kidney cancer,³ and breast cancer.^{8, 9, 11} These previous findings have been inconsistent, as other studies have reported a reduction in cancer risk, among first-degree relatives, in the urinary tract,¹⁵ gastrointestinal tract,⁶ and respiratory tract.^{6, 11} Our study was unique in its ability to examine cancer risk among first- and second-degree relatives. With the expanded family size, we also observed familial aggregation of cancers in the digestive tract, and prostate, and a reduced risk of lung cancer. The lack of an association seen with prostate cancer in most other studies may be due, in part, to differential screening practices between the northern European countries and the U.S. Studies of family history also found positive associations between TGCT risk and history of maternal lung cancer,²⁰ maternal breast cancer,¹³ and prostate and breast cancer in first- and second-degree relatives.¹⁴

The observed differences in associations between sex and lineage are interesting, and may be clues to the etiology of TGCT. Aggregation of cancer in families of men with testicular germ cell tumors could be due to inheritance of traits, such as genetic variation or inherited epigenetic modification, and/or common environmental risk factors. It is unknown, though, what proportion of TGCT risk may be explained by each of these components. The observation of stronger increases in all cancer risk among brothers and sisters of men with TGCT than among parents, suggests that a common *in utero* exposure may be associated with increased cancer risk.^{21, 22} Alterations in hormonal concentrations during pregnancy or within the affected individuals themselves, either due to genetics or common environmental exposures among family members, may also explain the increased risk of other hormonally-related cancers that we have observed in family members of TGCT cases. Linkage analyses of TGCT have not identified any single major locus that can account for the majority of the familial aggregation of TGCT, but rather suggest that multiple susceptibility loci with weak effects are involved.²³⁻²⁵ Although there has been a suggestion of a role of X linkage in families with two or more cases of TGCT,²⁴ these results have not yet been verified by other studies.²⁵ Two of our notable findings were the suggestions of increased risks of melanoma and non-melanoma skin cancer. These cancers, like TGCT,²⁶ have substantial variation due to geographic differences,^{26, 27} with men in northern Europe and in the U.S. having the highest rates. These observations again suggest both genetic and environmental factors may be responsible.

There are several considerations that must be taken into account when interpreting the results of our study. This case-control study of TGCT in the U.S. had a large number of person-years, and we were able to assess risk of cancer among first- and second-degree relatives. We were also able to examine a spectrum of cancers, although power was limited in some of the rarer cancers. Although our participation rates were generally high, there is the possibility that selection bias may affect our results as participation proportions between cases and controls were different. This is the first study to examine familial aggregation in maternal and paternal relatives separately. There is a chance, however, that retrospective determination of family history of cancer could lead to misclassified outcomes, as cancer diagnoses were not able to be verified and agreement between the proband's and their mother's reports of cancer among relatives was 63%. In addition, because family history was collected from the proband's mother, but not his father, there is the possibility that reporting may be more accurate for the maternal lineage. This could have led to the differential risk estimates observed when cancer outcomes were stratified by lineage. However, studies have shown that the accuracy of a proband reporting on cancer among first-degree relatives is high, ranging from 83–95%, although accuracy of reporting on a second-degree relative was significantly lower.^{28, 29}

Our study results suggest that there may be familial aggregation of cancer in men with TGCT, and there are suggestions that there may be differences by lineage. Although no single major locus has been found to explain the high risk of TGCT in brothers of men with TGCT, there is a strong suggestion that either many loci contribute to the familial aggregation of TGCT and other cancers, or that shared environmental exposures, including the determination of hormonal concentrations, are responsible.

Acknowledgments

The authors thank Emily Steplowski of Information Management Services, Inc. (Rockville, Maryland) for her contributions to data management. This work was supported by the Intramural Research Program of the NIH, National Cancer Institute. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Abbreviations

CI	confidence interval
RR	relative risk
TGCT	testicular germ cell tumor

References

1. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer*. 2003; 97:63–70. [PubMed: 12491506]
2. McGlynn KA. Environmental and host factors in testicular germ cell tumors. *Cancer Invest*. 2001; 19:842–53. [PubMed: 11768038]
3. Hemminki K, Chen B. Familial risks in testicular cancer as aetiological clues. *Int J Androl*. 2006; 29:205–10. [PubMed: 16466541]
4. Heimdal K, Olsson H, Tretli S, Flodgren P, Borresen AL, Fossa SD. Familial testicular cancer in Norway and southern Sweden. *Br J Cancer*. 1996; 73:964–9. [PubMed: 8611416]
5. Heimdal K, Olsson H, Tretli S, Flodgren P, Borresen AL, Fossa SD. Risk of cancer in relatives of testicular cancer patients. *Br J Cancer*. 1996; 73:970–3. [PubMed: 8611417]
6. Westergaard T, Olsen JH, Frisch M, Kroman N, Nielsen JW, Melbye M. Cancer risk in fathers and brothers of testicular cancer patients in Denmark. A population-based study. *Int J Cancer*. 1996; 66:627–31. [PubMed: 8647624]
7. Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NE. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet*. 1997; 350:1723–8. [PubMed: 9413462]
8. Broman K, Stang A, Baumgardt-Elms C, Stegmaier C, Ahrens W, Metz KA, Jockel KH. Testicular, other genital, and breast cancers in first-degree relatives of testicular cancer patients and controls. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1316–24. [PubMed: 15298952]
9. Dong C, Lonnstedt I, Hemminki K. Familial testicular cancer and second primary cancers in testicular cancer patients by histological type. *Eur J Cancer*. 2001; 37:1878–85. [PubMed: 11576844]
10. Sonneveld DJ, Sleijfer DT, Schrafford Koops H, Sijmons RH, van der Graaf WT, Sluiter WJ, Hoekstra HJ. Familial testicular cancer in a single-centre population. *Eur J Cancer*. 1999; 35:1368–73. [PubMed: 10658529]
11. Bajdik CD, Phillips N, Huchcroft S, Hill GB, Gallagher RP. Cancer in the mothers and siblings of testicular cancer patients. *Can J Urol*. 2001; 8:1229–33. [PubMed: 11375786]
12. Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN. Effect of twinship on incidence of cancer of the testis, breast, and other sites (Sweden). *Cancer Causes Control*. 1995; 6:519–24. [PubMed: 8580300]
13. Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case-control study. *Am J Epidemiol*. 1986; 124:39–52. [PubMed: 2872797]
14. Walschaerts M, Muller A, Auger J, Bujan L, Guerin JF, Le Lannou D, Clavert A, Spira A, Jouannet P, Thonneau P. Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. *Int J Androl*. 2007; 30:222–9. [PubMed: 17708752]
15. Spermon JR, Witjes JA, Nap M, Kiemeny LA. Cancer incidence in relatives of patients with testicular cancer in the eastern part of the Netherlands. *Urology*. 2001; 57:747–52. [PubMed: 11306395]
16. McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol*. 2007; 165:355–63. [PubMed: 17110638]
17. Pfeiffer RM, Goldin LR, Chatterjee N, Daugherty S, Hemminki K, Pee D, X LI, Gail MH. Methods for testing familial aggregation of diseases in population-based samples: application to Hodgkin lymphoma in Swedish registry data. *Ann Hum Genet*. 2004; 68:498–508. [PubMed: 15469426]

18. Binder DA. Fitting Cox's proportional hazards models from survey data. *Biometrika*. 1992; 79:139–47.
19. Gundy S, Babosa M, Baki M, Bodrogi I. Increased predisposition to cancer in brothers and offspring of testicular tumor patients. *Pathol Oncol Res*. 2004; 10:197–203. [PubMed: 15619639]
20. Kaijser M, Akre O, Cnattingius S, Ekblom A. Maternal lung cancer and testicular cancer risk in the offspring. *Cancer Epidemiol Biomarkers Prev*. 2003; 12:643–6. [PubMed: 12869404]
21. Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int J Cancer*. 2000; 87:438–43. [PubMed: 10897052]
22. Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: an overview. *Int J Cancer*. 2005; 116:331–9. [PubMed: 15818625]
23. Crockford GP, Linger R, Hockley S, Dudakia D, Johnson L, Huddart R, Tucker K, Friedlander M, Phillips KA, Hogg D, Jewett MA, Lohynska R, et al. Genome-wide linkage screen for testicular germ cell tumour susceptibility loci. *Hum Mol Genet*. 2006; 15:443–51. [PubMed: 16407372]
24. Rapley EA, Crockford GP, Teare D, Biggs P, Seal S, Barfoot R, Edwards S, Hamoudi R, Heimdal K, Fossa SD, Tucker K, Donald J, et al. Localization to Xq27 of a susceptibility gene for testicular germ-cell tumours. *Nat Genet*. 2000; 24:197–200. [PubMed: 10655070]
25. Rapley E. Susceptibility alleles for testicular germ cell tumour: a review. *Int J Androl*. 2007; 30:242–50. [PubMed: 17705805]
26. Ferlay, J.; Bray, F.; Pisani, P.; Parkin, DM. *GLOBOCAN 2000: Cancer incidence, mortality, and prevalence worldwide*. International Agency for Research on Cancer; Lyon, France: 2001.
27. de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. *Int J Cancer*. 2003; 107:119–26. [PubMed: 12925966]
28. Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. *Am J Prev Med*. 2003; 24:190–8. [PubMed: 12568826]
29. Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. *J Chronic Dis*. 1985; 38:289–93. [PubMed: 3998045]

Table 1
Risk of cancer in first-degree family members of men with testicular germ-cell tumors compared with controls, overall and stratified by sex

	All first-degree relatives			All male first-degree relatives			All female first-degree relatives		
	Cases	Controls	RR (95% CI)*	Cases	Controls	RR (95% CI)*	Cases	Controls	RR (95% CI)*
	(159,394 person-years) n	(201,765 person-years) n		(81,289 person-years) n	(102,908 person-years) n		(78,105 person-years) n	(98,857 person-years) n	
All malignant neoplasms	361	393	1.17 (1.01–1.35)	167	192	1.07 (0.86–1.32)	194	201	1.25 (1.02–1.53)
Head and neck	6	20	0.37 (0.15–0.94)	3	13	0.27 (0.08–0.95)	3	7	0.54 (0.14–2.14)
Lung	24	36	0.84 (0.51–1.41)	11	24	0.55 (0.27–1.14)	13	12	1.44 (0.66–3.17)
Breast							39	51	0.99 (0.65–1.50)
Digestive tract	31	45	0.86 (0.53–1.37)	17	26	0.73 (0.39–1.34)	14	19	1.02 (0.51–2.07)
Urinary system	8	12	0.82 (0.30–2.20)	6	10	0.71 (0.25–2.04)	2	2	1.24 (0.17–9.33)
Hematopoietic	19	21	1.15 (0.60–2.22)	11	18	0.77 (0.36–1.65)	8	3	3.46 (0.90–13.29)
Male genital organs									
Testis				47	41	1.41 (0.91–2.16)			
Prostate				14	4	4.51 (1.21–16.81)			
				32	36	1.06 (0.65–1.71)			
Female genital organs							54	48	1.44 (0.96–2.15)
Melanoma skin	16	12	1.71 (0.79–3.70)	7	5	1.85 (0.60–5.74)	9	7	1.69 (0.63–4.56)
Non-melanoma skin	81	69	1.48 (1.07–2.06)	50	38	1.66 (1.09–2.54)	31	31	1.28 (0.78–2.09)

* Adjusted for reference age and race/ethnicity of cases/controls, and sex (for non-sex-stratified analyses)

Risk of cancer in family members of men with testicular germ-cell tumors compared with controls, overall and stratified by sex

Table 2

	All first- and second-degree relatives				Maternal relatives				Paternal relatives			
	Cases		Controls		Cases		Controls		Cases		Controls	
	(592,888 person-years)	n	(742,986 person-years)	n	(312,495 person-years)	n	(254,449 person-years)	n	(227,881 person-years)	n	(288,622 person-years)	n
All malignant neoplasms	1,574	1,735	1,735	1,735	831	879	879	879	657	776	776	776
Male	753	849	849	849	329	349	349	349	389	473	473	473
Female	821	886	886	886	502	530	530	530	268	303	303	303
Head and neck	46	68	68	68	26	34	34	34	18	28	28	28
Male	30	48	48	48	16	19	19	19	13	25	25	25
Female	16	20	20	20	10	15	15	15	5	3	3	3
Lung	186	282	282	282	106	136	136	136	78	143	143	143
Male	122	189	189	189	63	85	85	85	58	102	102	102
Female	64	93	93	93	43	51	51	51	20	41	41	41
Breast	209	244	244	244	127	151	151	151	77	85	85	85
Digestive tract	223	213	213	213	127	101	101	101	94	108	108	108
Male	111	119	119	119	54	46	46	46	55	70	70	70
Female	112	94	94	94	73	55	55	55	39	38	38	38
Urinary system	42	48	48	48	26	27	27	27	15	19	19	19
Male	31	29	29	29	18	13	13	13	12	14	14	14
Female	11	19	19	19	8	14	14	14	3	5	5	5
Hematopoietic	86	86	86	86	47	39	39	39	31	43	43	43
Male	44	53	53	53	23	18	18	18	16	33	33	33
Female	42	33	33	33	24	21	21	21	15	10	10	10
Male genital organs	175	144	144	144	70	50	50	50	94	91	91	91
Testis	28	12	12	12	12	4	4	4	5	5	5	5
Prostate	146	130	130	130	58	46	46	46	88	84	84	84
Female genital organs	132	132	132	132	85	82	82	82	22	26	26	26
Melanoma skin	29	40	40	40	16	25	25	25	8	11	11	11

	All first- and second-degree relatives				Maternal relatives				Paternal relatives			
	Cases		Controls		Cases		Controls		Cases		Controls	
	(592,888 person-years)	n	(742,986 person-years)	n	(312,495 person-years)	n	(254,449 person-years)	n	(227,881 person-years)	n	(288,622 person-years)	n
				RR (95% CI)*				RR (95% CI)*				RR (95% CI)*
Male	13	22		0.75 (0.37–1.52)	4	12		0.41 (0.13–1.25)	6	8		0.97 (0.31–2.98)
Female	16	18		1.34 (1.01–1.77)	12	13		1.19 (0.53–2.63)	2	3		0.91 (0.16–5.27)
Non-melanoma skin	184	169		1.40 (1.10–1.77)	92	85		1.35 (0.96–1.91)	79	73		1.41 (0.99–1.99)
Male	109	102		1.17 (0.59–2.31)	38	35		1.31 (0.79–2.18)	62	62		1.29 (0.90–1.84)
Female	75	67		1.49 (1.04–2.11)	54	50		1.39 (0.92–2.10)	17	11		2.20 (0.98–4.93)

* Adjusted for reference age and race/ethnicity of cases/controls, sex (for non-sex-stratified analyses), and side of family (for analyses of all first- and second-degree relatives)