# Testicular, Other Genital, and Breast Cancers in First-Degree Relatives of Testicular Cancer Patients and Controls

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## Abstract

**Previous studies showed an increased prevalence of testicular cancer among fathers and brothers of testicular cancer patients. We examined whether testicular, other genital, and breast cancers aggregate in parents and siblings of testicular cancer patients in a population-based case-control study, including males, ages 15 to 69 years at diagnosis, with primary malignant tumors of the testes or extragonadal germ cell tumors. Controls were ascertained through the mandatory registries of residents and frequency matched to the cases by age and region of residence. In a face-to-face interview, 269 cases and 797 controls provided health-related information on parents and siblings. We calculated odds ratios (OR) and corresponding 95% confidence intervals (95% CI) based on the generalized estimating equations technique, adjusting for the matching variables and relatives' age. Three (1.1%) fathers and eight (3.2%) brothers of cases were affected with testicular cancer compared with four (0.5%) fathers and two (0.2%) brothers of controls. The OR (95% CI) of familial testicular cancer was 6.6 (2.35-18.77). Only nonseminoma patients had fathers with testicular cancer, whereas the affected brothers were all related to seminoma patients. Overall, we found an increased risk for genital other than testicular cancers (OR 2.5, 95% CI 1.43-4.43). For breast cancer, we detected an increased risk in sisters (OR 9.5, 95% CI 2.01-45.16, adjusted for age of study participant and age of sister) but not in mothers. Our findings support the hypothesis that testicular and other genital cancers have a common familial component that may be due to genetic and shared exogenous factors such as estrogen exposure during fetal development.** (Cancer Epidemiol Biomarkers Prev 2004; 13(8):1316–24)

## Introduction

Testicular cancer, while being a rare disease, is in many populations the most frequent neoplasm in young man (1, 2). Its incidence rate has been increasing in many populations, including Germans (3, 4); crude incidence rate is 7.5 per 100,000, and cumulative incidence until age 74 years is 0.5% (data for the year 2000; ref. 5). Aside from the major risk factor cryptorchism (1, 2, 6), the role of most other risk factors is less well established. However, previous investigations and studies have consistently shown an increased risk of testicular cancer among fathers and brothers of testicular cancer patients (7-14), particularly in twin brothers of testicular cancer patients (15, 16). In addition, cancers of certain genital organs and breast cancer may also occur with a higher frequency (17-20). In addition, association studies, segregation analysis, linkage, and microsatellite analyses have supported the role of genetic mechanisms for this disease (21-26) and have identified potentially relevant gene loci (23-26). Further indication for the meaning of genetic factors are ethnic differences in incidence, a higher than by chance expected proportion of bilateral cases and a higher incidence among individuals with certain disorders of genital development (2, 27).

On the other hand, an association between the disease and the factors related to familial, gestational, and developmental characteristics such as *in utero* estrogen exposure, birth weight, birth order, sibship size, and onset of puberty have been shown in some studies (20, 28-38), especially among seminoma patients (20, 34, 35, 37), pointing at the potential role of prenatal, perinatal, and postnatal hormones in disease development. This is supported by the results from the above-mentioned twin study, which found a higher overall risk of testicular cancer in dizygotic than in monozygotic twins (15).

The aim of the analyses presented here is to examine whether testicular, other genital, and breast cancers aggregate in parents and siblings of testicular cancer patients as compared with relatives of the control population based on data from a population-based case-control study. In addition, we examined other cancer and hernia inguinalis (or simply hernia) in relatives.

## Material and Methods

**Subjects.** The methods relating to planning and conducting this study have been described elsewhere in

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detail (6, 39). Briefly, our study is part of a multinational population-based case-control study on occupational risk factors for eight rare cancers. Eligibility criteria for cases included primary malignant tumors of the testes or extragonadal germ cell tumors, newly diagnosed between July 1, 1995 and December 31, 1997, ages 15 to 69 years at the time of diagnosis, and sufficient command of the German language to complete a personal interview. The study area comprised five German regions (cities of Hamburg, Bremen, Essen, Saarbrücken, and the Federal State of Saarland without Saarbrücken). Cases were ascertained through an active reporting system of clinical and pathology departments in the study regions, supported in Saarland through the infrastructure existing at the population-based Saarland cancer registry, and, for cases living in Hamburg, through the population-based Hamburg Cancer Registry. Tumor histologies were classified according to the guidelines of the IARC (40) and were assured by a reference pathologist (K.A.M.). Of the participating 269 cases, 170 (63.2%) were classified as seminoma and 99 (36.8%) were classified as nonseminoma.

The collective of 797 controls was randomly selected from the mandatory registries of residents in each study region. Controls were frequency matched to cases by region of residence (five strata) and age (5-year age groups). Again, the selection was restricted to men with sufficient German language skills. Because the number of controls was determined by the maximum age stratum–specific number of any of the eight rare cancers considered in the multinational study, age-specific matching ratios varied (41). Therefore, controls were on average slightly older than cases.

**Exposure Assessment.** Data were collected by interviewers through a standardized interview lasting ~70 minutes (99% face-to-face interview and 1% telephone interview). Interviewers were specifically trained for this project and continuously monitored to ensure uniform data quality. They were unaware of specific study hypotheses. The interview included information on occupational exposure; job history; smoking and alcohol consumption; nutrition; intake of medicine; exposure to radiation and electromagnetic fields; physical constitution and activity; exposure to hormones, pesticides, heat, and light, familial characteristics; medical history of the study participants and their families; and sociodemographic characteristics.

**Family History of Diseases.** Information on the relatives was collected through the study participants. For each parent and sibling, these data included year of birth; history of hernia, multiple sclerosis, and cancer; the organ affected by cancer; and age at diagnosis. The study participants were asked about being a twin, and for siblings, data on the type of sibling (twin, full, or half) were assessed. Additionally, participants were asked about other relatives who had a medical history of testicular diseases such as hernia or cryptorchism.

For cancer in a family member, information on the particular organ was collected and subsequently coded according to *International Classification of Diseases, Ninth Edition* (42). We distinguished four groups of cancers in relatives (*International Classification of Diseases, Ninth Edition* codes in parentheses): (a) testicular cancer (186); (b) breast cancer (174, 175); (c) cancer in any genital organ, except the testes [i.e., uterus (179), cervix (180), placenta (181), corpus uteri (182), ovary (183), vagina (184), prostate (185), and penis (187)]; and (d) all other cancers (140 to 208, except those listed in a to c).

**Statistical Methods.** For each relative, a dichotomous variable was created to code for the history of the types of cancer listed above. After calculating the frequencies of cancer in the various types of relatives, data on all first-degree relatives were simultaneously analyzed using the generalized estimating equation technique to account for intrafamilial phenotypic correlations (43) and for the size of the families. The odds ratios (OR) obtained through procedure GENMOD in SAS (44) are presented with their corresponding 95% confidence intervals (CI).

The risk estimates were usually adjusted for the two matching variables: age of study participants and region of residence (OR1; four strata because there were few observations from Saarbrücken, which was therefore combined with the rest of Saarland) and, additionally, for the age of the relatives (OR2). This was age at onset of disease for diseased relatives, or age at the time of interview, which we used for nondiseased relatives because life status and date of death were not available. Other potential confounders were considered alternatively or additionally such as sex and generation of the relative and highest level of education after school degree. The impact of these variables will be described in the text only. As a rule, we included half-siblings in the analysis presented in the tables; moreover, we did sensitivity analyses excluding them, and we describe the changes in estimates in the text.

We distinguished between seminoma and nonseminoma patients due to underlying differences in disease development and genetic pathways (25, 45, 46) and a potentially different role and relevance of risk factors. To account for differences between these two distinct histologic groups, we present subgroup analyses wherever possible. However, due to small numbers of affected family members, the adjustment for region of residence had to be omitted in some of the analyses. The analyses were repeated for young testicular cancer cases only (ages <35 years), because early age of onset is an additional indicator of the contribution of genetic factors in disease development. In the results presented here, we included the whole control group when analyzing each of the two histologic subgroups, adjusting for age of participants and relatives in addition to region of residence.

To examine a potential dose-response relationship, we did conditional logistic regression stratified by the matching variables using the procedure PHREG in SAS (44) to assess the risk of testicular cancer depending on the number of relatives affected by either testicular, other genital, or breast cancer. The OR was additionally adjusted for the number of relatives to account for family size. In addition, we compared the distributions of the numbers of affected relatives between cases and controls using the Cochrane-Armitage trend test (47). We assessed whether the impact of a previous history of medically confirmed or treated cryptorchism is modified by or interacts with a familial predisposition to these cancers. Therefore, we calculated ORs for those with a family history to these cancers only, with cryptorchism only, and with both.

## Results

Three (1.1%) fathers and eight (3.2%) brothers of cases were affected with testicular cancer compared with four (0.5%) fathers and two (0.2%) brothers of controls. As expected, seminoma patients were on average ~5 years older than nonseminoma patients. Comparing the age distribution of those with a family history of testicular cancer to those without, the mean age is quite similar. However, the age of patients with seminoma is lower for those with a family history compared with those without (ages 34.3 versus 37.0 years). Although based on few observations, the age range is far narrower for participants with a familial predisposition, with ages of study participants ranging from 26 to 48 years (Table 1).

There were 11 (4.1%) cases and 6 (0.8%) controls with a family history of testicular cancer. For the other groups of diseases, these frequencies were as follows: genital, except testicular cancer: 22 (8.2%) cases, 30 (3.8%) controls; female and male breast cancer: 15 (5.6%) cases, 40 (5.0%) controls; any cancer: 83 (30.9%) cases, 214 (26.9%) controls; and hernia: 40 (14.9%) cases, 136 (17.1%) controls. All of the cases with a family history of testicular cancer were unilateral.

The number of the different types of relatives and the frequencies of the neoplasms of interest as well as hernia in these relatives for cases and controls and by histology are presented in Table 2. The cancer forms of interest are more prevalent in relatives of cases than in relatives of controls. These prevalences are on average higher in relatives of seminoma compared with nonseminoma patients. As expected, cancer prevalence is higher in parents than in siblings. For hernia, the prevalences in relatives of cases and controls are quite similar. In addition, the prevalence of ever having had a hernia in the study participants themselves was quite similar [33 (12.3%) cases versus 104 (13.1%) controls].

Reported genital cancers in family members referred to the following organs: controls: uterus ($n$ = 9), unspecified female genital organs ($n$ = 16), prostate ($n$ = 5); cases: uterus ($n$ = 4), cervix ($n$ = 1), ovary ($n$ = 2), unspecified female genital organs ($n$ = 10), prostate ($n$ = 5). In addition to female breast cancer, there was also one case of male breast cancer in a father of a patient with seminoma. However, this was not included in the generalized estimating equation estimation for breast cancer, which focused on female breast cancer only.

None of the study participants with a sibling affected by cancer was a twin. However, there were a few instances were the affected sibling was only a half-sibling. There was one half-brother of a case with testicular cancer, two half-sisters of controls with other genital cancers, and one half-brother and two half-sisters of controls with cancers other than testicular, other genital, or breast cancer. As for the total number of siblings, cases had on average (as expressed by the mean) 1.75 siblings compared with 2.1 in controls, a difference that is accounted for in the analysis.

ORs for the different groups of cancer and hernia in the relatives according to case-control status by generation and for participants ages <35 years are presented in Table 3. The OR (95% CI) of familial testicular cancer was 6.6 (2.35-18.77) after adjusting for the matching variables and age of relative. This OR was particularly high in the subgroup of brothers of cases and controls. The tendency that the association is stronger in siblings than in parents is also seen for female breast cancer and other genital cancers but not in the group of ''other cancers'' where the prevalences among relatives of cases and controls are comparable. We found an increased risk for other genital cancers (OR2 2.5, 95% CI 1.43-4.43). For female breast cancer, we detected an increased risk in sisters (OR1 6.9, 95% CI 1.76-26.96; OR2 9.5, 95% CI 2.01-45.16) but not in mothers. In the analyses of hernia in relatives, no age adjustment was being

**Table 1. Distribution of cases and controls according to demographic characteristics**

| Variable | Controls ($n$ = 797) | | Cases ($n$ = 269) | | Seminoma ($n$ = 170) | | Nonseminoma ($n$ = 99) | |
|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| Age group | | | | | | | | |
| 15-24 | 67 | 8.4 | 25 | 9.3 | 4 | 2.4 | 21 | 21.2 |
| 25-34 | 301 | 37.8 | 116 | 43.1 | 69 | 40.6 | 47 | 47.5 |
| 35-44 | 235 | 29.5 | 96 | 35.7 | 72 | 42.4 | 24 | 24.2 |
| 45-54 | 83 | 10.4 | 19 | 7.1 | 15 | 8.8 | 4 | 4.0 |
| 55-64 | 111 | 13.9 | 13 | 4.8 | 10 | 5.9 | 3 | 3.0 |
| No family history of testicular cancer | $n$ = 791 | | $n$ = 258 | | $n$ = 162 | | $n$ = 96 | |
| Age (years) | | | | | | | | |
| Range | 15-64 | | 17-64 | | 18-64 | | 17-60 | |
| Median | 35 | | 34 | | 35.5 | | 30 | |
| Mean | 38.0 | | 34.8 | | 37.0 | | 31.1 | |
| Standard deviation | 11.7 | | 9.2 | | 8.9 | | 8.5 | |
| Family history of testicular cancer | $n$ = 6 | | $n$ = 11 | | $n$ = 8 | | $n$ = 3 | |
| Age (years) | | | | | | | | |
| Range | 32-48 | | 26-43 | | 26-43 | | 27-37 | |
| Median | 36.5 | | 35 | | 35 | | 31 | |
| Mean | 38.0 | | 33.5 | | 34.3 | | 31.7 | |
| Standard deviation | 5.4 | | 6.1 | | 6.6 | | 5.0 | |

**Table 2. Number of relatives and frequency of cancers and hernia in family members by case-control status, type of relative, and histology of testicular cancer**

| | Cases | | | | | | | | Controls | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Father | | Mother | | Brother | | Sister | | Father | | Mother | | Brother | | Sister | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Number | | | | | | | | | | | | | | | | |
| Total number | 269 | | 269 | | 249 | | 222 | | 797 | | 797 | | 877 | | 798 | |
| Seminoma | 170 | | 170 | | 160 | | 132 | | | | | | | | | |
| Nonseminoma | 99 | | 99 | | 89 | | 90 | | | | | | | | | |
| age <35 | 141 | | 141 | | 125 | | 95 | | 368 | | 368 | | 341 | | 353 | |
| Total cancer | 38 | 14.1 | 38 | 14.1 | 11 | 4.4 | 13 | 5.9 | 108 | 13.6 | 99 | 12.4 | 11 | 1.3 | 23 | 2.9 |
| Seminoma | 27 | 15.9 | 25 | 14.7 | 11 | 6.9 | 9 | 6.8 | | | | | | | | |
| Nonseminoma | 11 | 11.1 | 13 | 13.1 | 0 | 0 | 4 | 4.4 | | | | | | | | |
| Testes | 3 | 1.1 | | | 8 | 3.2 | | | 4 | 0.5 | | | 2 | 0.2 | | |
| Seminoma | 0 | 0 | | | 8 | 5.0 | | | | | | | | | | |
| Nonseminoma | 3 | 3.0 | | | 0 | 0 | | | | | | | | | | |
| Other genital | 4 | 1.5 | 12 | 4.5 | 1 | 0.4 | 5 | 2.3 | 5 | 0.6 | 20 | 2.5 | 0 | 0 | 5 | 0.6 |
| Seminoma | 4 | 2.4 | 7 | 4.1 | 1 | 0.6 | 4 | 3.0 | | | | | | | | |
| Nonseminoma | 0 | 0 | 5 | 5.1 | 0 | 0 | 1 | 1.1 | | | | | | | | |
| Breast | 1 | 0.4 | 10 | 3.7 | 0 | 0 | 4 | 1.8 | 0 | 0 | 36 | 4.5 | 0 | 0 | 4 | 0.5 |
| Seminoma | 1 | 0.6 | 7 | 4.1 | 0 | 0 | 3 | 2.3 | | | | | | | | |
| Nonseminoma | 0 | 0 | 3 | 3.0 | 0 | 0 | 1 | 1.1 | | | | | | | | |
| Hernia | 27 | 10.0 | 7 | 2.6 | 16 | 6.4 | 1 | 0.5 | 78 | 9.8 | 16 | 2.0 | 49 | 5.6 | 11 | 1.4 |
| Seminoma | 16 | 9.4 | 2 | 1.2 | 13 | 8.1 | 0 | 0 | | | | | | | | |
| Nonseminoma | 11 | 11.1 | 5 | 5.1 | 3 | 3.4 | 1 | 1.1 | | | | | | | | |

done, because the age of onset was provided only in ~64% of the relatives affected by hernia.

Exclusion of the one half-brother from the analyses on familial testicular cancer reduced the risk estimates for the joint analysis of fathers and brothers to OR1 5.8, 95% CI 2.08-16.37 and OR2 5.9, 95% CI 2.06-16.88 (Table 3). The analysis for brothers only resulted in OR1 12.3, 95% CI 2.59-58.76 and OR2 12.6, 95% CI 2.52-62.88. Because all other half-siblings affected by cancer were related to controls, the risk estimates for other genital cancers increased slightly after excluding them from the analysis (OR1 2.8, 95% CI 1.59-4.79; OR2 2.7, 95% CI 1.55-4.85).

The ORs for testicular, breast, and other genital cancers were particularly high in young study participants. However, due to small numbers of affected relatives, the adjustment for some of the analyses for breast and other genital cancers had to be restricted to fewer factors, which needs to be kept in mind when comparing the results. The risk estimates for hernia are comparable for cases and controls and for different generations and for young participants only.

Additional adjustment for sex of the relative and highest level of education of participants and for generation instead of age of the relative did not lead to relevant changes in the ORs presented in this table (data not shown).

Table 4 presents the risk estimates for the above-mentioned types of cancer and hernia in parents and siblings differentiated by histology of the cases. Only cases with nonseminoma had fathers with testicular cancer, whereas the affected brothers of cases were all related to seminoma patients. The risk estimates for seminoma patients and controls are consistently higher in all analyses than in nonseminoma patients and controls. However, the analysis for the patients with nonseminomas and controls suffers from the small number of affected relatives. Therefore, the adjustment in the analyses of testicular cancer had to be modified. Again, additional adjustment for relatives' sex and highest level of education of participants and for generation instead of age of the relative did not lead to relevant changes in the ORs presented in this table (data not shown).

For hernia, we found no risk elevation for cases when looking at the subgroups of seminoma and nonseminoma patients.

The distribution of testicular, other genital, and breast cancer cases per family and corresponding risk estimates are presented in Table 5. The prevalence of at least one relative affected with one of these cancers is 16.4% in cases versus 9.4% in controls. Whereas there are few families with multiple occurrences of these cancers in relatives, families of cases are disproportionately more often affected (1.1% versus 0.1%), with one case even having three affected family members. These differences are expressed in the result of the trend test ($P = 0.0005$) as well as in the risk estimates.

A previous history of cryptorchism and/or a history of gliding or retractile testis was reported by 18.6% of the cases and 5.4% of the controls in our study. When counting only those instances where cryptorchism was medically confirmed or treated, these figures went down to 9.7% and 3.5%, respectively (6). The joint effect of a familial predisposition and cryptorchism was stronger than the product of the individual effects; however, only three cases and one control were exposed to both factors (Table 5).

**Table 3. ORs for various types of cancer and hernia in parents and siblings by generation and for young study participants only (age <35 years)**

| Cancer | Relative | Cases, *n* (%) | Controls, *n* (%) | OR1 | 95% CI | OR2 | 95% CI |
|---|---|---|---|---|---|---|---|
| **All ages** | | | | | | | |
| Testis | Male | 11 (2.1) | 6 (0.4) | 6.4 | 2.34-17.77 | 6.6 | 2.35-18.77 |
| | Father | 3 (1.1) | 4 (0.5) | 2.1* | 0.49-9.40 | 2.1† | 0.16-26.55 |
| | Brother | 8 (3.2) | 2 (0.2) | 14.2* | 3.02-67.22 | 18.5† | 3.09-110.38 |
| Female breast | Female | 14 (2.9) | 40 (2.5) | 1.2 | 0.65-2.21 | 1.2 | 0.65-2.26 |
| | Mother | 10 (3.7) | 36 (4.5) | 0.8 | 0.41-1.71 | 1.2 | 0.54-2.72 |
| | Sister | 4 (1.8) | 4 (0.5) | 6.9 | 1.76-26.96 | 9.5† | 2.01-45.16 |
| Other genital | All | 22 (2.2) | 30 (0.9) | 2.5 | 1.48-4.39 | 2.5 | 1.43-4.43 |
| | Parents | 16 (3.0) | 25 (1.6) | 2.0 | 1.06-3.65 | 2.2 | 1.05-4.49 |
| | Siblings | 6 (1.3) | 5 (0.3) | 5.6 | 1.50-20.70 | 5.4 | 1.49-19.72 |
| Other cancer | All | 52 (5.2) | 166 (5.1) | 1.1 | 0.81-1.63 | 1.1 | 0.79-1.62 |
| | Parents | 46 (8.6) | 143 (9.0) | 1.1 | 0.74-1.57 | 1.3 | 0.82-1.93 |
| | Siblings | 6 (1.3) | 23 (1.4) | 1.1 | 0.44-2.90 | 0.9 | 0.35-2.51 |
| Hernia | All | 51 (5.1) | 154 (4.7) | 1.1 | 0.71-1.57 | | |
| | Parents | 34 (6.3) | 94 (5.9) | 1.1 | 0.71-1.73 | | |
| | Siblings | 17 (3.6) | 60 (3.6) | 0.9 | 0.51-1.73 | | |
| **Ages <35 y** | | | | | | | |
| Testis | Male | 5 (1.9) | 1 (0.1) | 15.3 | 1.96-118.4 | 18.2 | 2.07-160.0 |
| Female breast | Female | 7 (1.4) | 11 (0.8) | 2.0* | 0.75-5.11 | 1.8† | 0.69-4.81 |
| Other genital | All | 13 (2.6) | 12 (0.8) | 3.2* | 1.47-6.82 | 3.2† | 1.43-7.27 |
| Other cancer | All | 12 (2.4) | 40 (2.8) | 0.9 | 0.45-1.62 | 0.8 | 0.42-1.56 |
| Hernia | All | 28 (5.6) | 84 (5.9) | 0.9 | 0.55-1.55 | | |

NOTE: OR1 adjusted for matching variables; OR2 adjusted for matching variables and age of relative.
*Adjusted for age of study participant but not for region.
†Adjusted for age of study participant and age of relative but not for region.

About 11.4% of cases and 13.1% of controls had a previous, medically confirmed history of hernia. According to the information provided by the participants, the prevalence of hernia in relatives with testicular cancer was 23.5% compared with 7.6% in relatives without testicular cancer. Therefore, we found a higher prevalence of hernia in relatives of familial study participants (i.e., with a family history of testicular cancer) than in nonfamilial participants (i.e., without a family history of testicular cancer) but did not detect a difference between cases and controls (prevalence: familial cases 36.4%, familial controls 33.3%; nonfamilial cases 14%, nonfamilial controls 16.9%).

## Discussion

Our results indicate that testicular cancer aggregates in families. Furthermore, it supports the hypothesis that cancers of other genital organs occur more frequently in first-degree relatives of testicular cancer patients than expected. For sisters only, we even found a higher prevalence of breast cancer in the cases' families. The risk estimates for these cancer forms were particularly pronounced in young subjects. Finally, we found ''clusters'' of genital and breast cancers for the most part in relatives of cases.

Our findings may even fit the hypothesis that genetic and not merely any other familial mechanisms contribute to this aggregation: (1) Familial testicular cancer risk is particularly increased in young cases, although this risk difference is not very high; (2) we detected an increased familial risk for testicular cancer and for other cancer of the genital organs but not for cancer in general when excluding those in breast and the genital organs; and (3) familial testicular cancer risk remains elevated after adjustment for other risk factors. On the other hand, the finding that the ORs are always higher in siblings than in parents of the study population hints at the potential influence of other nongenetic factors shared by sibships such as gestational characteristics (e.g., *in utero* estrogen exposure).

Some of our findings are in line with results reported previously. Thus far, only few studies have investigated and provided risk estimates for a family history of testicular cancer in testicular cancer patients (7-14). The investigators of those studies consistently found a higher prevalence of a family history in patients than in the investigated comparison collective. In addition, they detected a higher relative risk to develop the disease in brothers than in fathers of the patients. Both these findings were confirmed by our results. In these studies, the prevalences of having an affected first-degree relative, which sometimes included offspring, varied between 1.1% (7) and 2.8% (10). Overall, relative risk estimates varied between 3.1 (7) and 7.6 (10) for family history in any first-degree relative. For sons, relative risk estimates were in a similar order of magnitude (8, 48). These estimates of testicular cancer patients to develop this disease varied between 5.9 (14) and 12.7 (11) for brothers and between 1.8 (11) and 4.3 (10) for fathers.

The prevalence of family history in our study (4.1% in patients) is somewhat higher than in these earlier studies, which might be due to increasing testicular cancer rates over time, but is more likely to reflect differences in the populations studied, with Germany having one of the highest incidence rates. However, our

**Table 4. ORs for various types of cancer and hernia in parents and siblings by histology of cases**

| Cancer | Histology | Cases, *n* (%) | Controls, *n* (%) | OR1 | 95% CI | OR2 | 95% CI |
|---|---|---|---|---|---|---|---|
| Testis | All | 11 (2.1) | 6 (0.4) | 6.4 | 2.34-17.77 | 6.6 | 2.35-18.77 |
| | Seminoma | 8 (2.4) | | 8.0 | 2.75-23.22 | 7.6 | 2.53-22.79 |
| | Nonseminoma | 3 (1.6) | | 4.4* | 1.07-17.94 | 4.7† | 1.15-18.87 |
| Female breast | All | 14 (2.9) | 40 (2.5) | 1.2 | 0.65-2.21 | 1.2 | 0.65-2.26 |
| | Seminoma | 10 (3.3) | | 1.4 | 0.70-2.86 | 1.5 | 0.71-2.98 |
| | Nonseminoma | 4 (2.1) | | 0.9 | 0.31-2.49 | 0.9 | 0.31-2.49 |
| Other genital | All | 22 (2.2) | 30 (0.9) | 2.5 | 1.48-4.39 | 2.5 | 1.43-4.43 |
| | Seminoma | 16 (2.5) | | 2.8 | 1.56-5.16 | 2.8 | 1.47-5.14 |
| | Nonseminoma | 6 (1.6) | | 2.2 | 0.88-5.26 | 2.2 | 0.91-5.50 |
| Other cancer | All | 52 (5.2) | 166 (5.1) | 1.1 | 0.81-1.63 | 1.1 | 0.79-1.62 |
| | Seminoma | 37 (5.9) | | 1.2 | 0.83-1.76 | 1.2 | 0.81-1.75 |
| | Nonseminoma | 15 (4.0) | | 1.0 | 0.52-1.88 | 1.0 | 0.51-1.85 |
| Hernia | All | 51 (5.1) | 154 (4.7) | 1.1 | 0.71-1.57 | | |
| | Seminoma | 31 (4.9) | | 1.0 | 0.67-1.63 | | |
| | Nonseminoma | 20 (5.3) | | 1.0 | 0.53-1.91 | | |

NOTE: OR1 adjusted for matching variables; OR2 adjusted for matching variables and age of relative.
*Adjusted for age of study participant but not for region.
†Adjusted for age of study participant and age of relative but not for region.

risk estimates for family history of testicular cancer in general as well as for the two subgroups (i.e., fathers and brothers) are quite in line with these previous findings. After exclusion of the one half-brother from our analyses, our results are even more similar to those published previously.

Only few of these and some other studies (17-20) examined the risk of other cancers and hernia in relatives. Tollerud et al. (12) found that familial (i.e., persons with a family history of testicular cancer) cases have a particularly high prevalence of hernia in relatives compared with nonfamilial (i.e., persons without a family history of testicular cancer) cases and controls. We also found this difference between familial and nonfamilial participants but not between cases and controls. As for other genital cancers, Dong et al. (8) found a clearly elevated risk of uterus cancer and a very small increase in breast cancer risk in mothers of testicular cancer patients. Like Heimdal et al. (18) and Westergaard et al. (13) who looked specifically at fathers, they did not see a risk elevation of prostate cancer in first-degree relatives. The latter two groups even found a decreased prostate cancer risk in fathers of testicular cancer patients (13, 18). Dong et al. (8) also found elevated risks of cancers of the nervous tissue in first-degree relatives and of colon, lung, melanoma, and connective tissue in mothers of testicular cancer patients. Finally, Heimdal et al. (18) found a higher than expected number of endometrial and, like Swerdlow et al. (34) and Kaijser et al. (49), lung cancer among mothers of these patients. Kroman et al. (19) found the opposite for endometrial cancers in mothers. In addition, the evidence for breast cancer was quite controversial. Aside from the study by Dong et al. (8), Anderson et al. (17) found a small risk elevation for testis cancers in sons of women with breast cancer, Kroman et al. (19) found a small risk reduction for mothers of testicular cancer patients, and Moss et al. (20) found a marked risk elevation in

**Table 5. ORs for testicular cancer according to the number of first-degree relatives (parents and siblings) affected by testicular, other genital, or breast cancer and according to family history of testicular, other genital, or breast cancer and/or cryptorchism**

| | Cases | | Controls | | OR1 | 95% CI | OR2 | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | | | |
| Affected relatives | | | | | | | | |
| 0 | 225 | 83.6 | 722 | 90.6 | 1.0 | | 1.0 | |
| 1 | 41 | 15.2 | 74 | 9.3 | 2.0 | 1.29-3.03 | 2.0 | 1.31-3.08 |
| 2 | 2 | 0.7 | 1 | 0.1 | } 7.5 | 0.77-73.67 | 8.7 | 0.89-86.14 |
| 3 | 1 | 04 | 0 | 0 | } | | | |
| | 269 | 100 | 797 | 100 | | | | |
| *P** | 0.0005 | | | | | | | |
| Joint analysis | | | | | | | | |
| FH no/CR no | 195 | 72.5 | 678 | 85.1 | 1.0 | | 1.0 | |
| FH yes/CR no | 41 | 15.2 | 72 | 9.0 | 2.3 | 1.29-4.19 | 2.2 | 1.22-4.01 |
| FH no/CR yes | 23 | 8.6 | 27 | 3.4 | 2.1 | 1.38-3.28 | 2.2 | 1.40-3.33 |
| FH yes/CR yes | 3 | 1.1 | 1 | 0.1 | 11.0 | 1.10-110.88 | 11.4 | 1.12-115.42 |

NOTE: OR1, matched evaluation (age and region of residence), unadjusted; OR2, matched evaluation (age and region of residence), adjusted for number of relatives.
*Cochrane-Armitage trend test.

mothers of nonseminoma patients. Finally, Bajdik et al. (50) found an increased overall cancer risk in mothers and siblings of testicular cancer patients that is quite comparable with our results.

It is well established that the average age at onset of disease is higher for patients with seminoma than with nonseminoma (1, 51-53), and this is shown in our data as well. Most of the studies touch on differences between different histologic subgroups of patients (7-11, 13); however, only Dong et al. (8) present risk estimates for these groups. Unlike us, they did not obtain higher relative risk estimates for family history in patients with seminomas, but only when limiting the analysis to the family history in brothers or when restricting the analysis to relatives who had seminoma as well. However, the lower risk elevation for familial testicular cancer when focusing on nonseminoma patients may be caused by the earlier age of onset, potentially reflecting a faster growth and more aggressive tumor development of nonseminomas compared with seminomas (52), reducing the probability for affected men to produce offspring and subsequently for researchers to detect the familial predisposition.

Except for Dong et al. (8), all investigations, which distinguished between histologic types, found an earlier age of onset in seminoma familial cases compared with seminoma nonfamilial cases (7, 9-11, 13), thereby confirming our result. For nonseminoma patients, an earlier age of onset in familial cases was only found by Dieckmann and Pichlmeier (7), Forman et al. (9), and Sonneveld et al. (11), whereas Heimdal et al. (10) and Westergaard et al. (13), like us, found a slight difference in the opposite direction.

The hypothesis that genetic mechanisms are involved in testicular cancer development is supported by several lines of evidence. Apart from classic epidemiologic studies, an association study by Harries et al. (21) found a strong association between the disease and the *GSTP1b* allele, whereas an association to *GSTM1* (54), *TP53* (55), or polymorphisms within the estrogen receptor gene (56) could not be confirmed thus far. In addition, the relation to the human leukocyte antigen system seems to be ambiguous (1, 9, 57). A segregation analysis conducted by Heimdal et al. (22) in a Scandinavian population found the best fit for a recessive model, which fits well to the consistent finding that the risk elevation is more pronounced in brothers than in fathers. Czene et al. (58) estimated genetic factors to account for 25% of testicular cancer development. Most importantly, linkage and microsatellite analyses have identified potentially relevant gene loci [e.g., on chromosome 12 and on the X chromosome (Xq27; refs. 23-26)]. The latter may even be associated with cryptorchism (23), which is a risk factor for testicular cancer and may even have a causal effect as the result of a recent twin study suggests (59). On the other hand, cryptorchism may have underlying causal mechanisms (e.g., genes that are similar to those of testicular cancer). Although based on small numbers, our results indicate a potential synergism between cryptorchism and a family history of testicular, other genital, or breast cancer, which, however, is based on small numbers. Ethnic variation in incidence and lack of an effect of migration (60) has been interpreted as supporting the role of genetic factors (1, 2, 27) and factors having an effect early in life (60). In addition, an increased testicular cancer incidence among individuals with certain disorders of genital development with a definite genetic component (i.e., gonadal dysgenesis; refs. 2, 27), provides further evidence for the causal role of genetic factors. Results of a twin study support both the meaning of genetic factors and a prenatal etiology (15). Finally, early age of onset of the disease (1, 2, 27) and a higher than by chance expected proportion of bilateral cases suggest an involvement of genetic factors (1, 9, 27). Nicholson and Harland (61) even state that patients with bilateral disease and those with a family history carry the same genetic predisposition and estimate that approximately one third of all patients with testicular cancer carry such a genetic predisposition. Kraggerud et al. (45) suggest that tumor development of both familial/bilateral and sporadic testis cancers follows the same genetic pathways. In a recent review article, Oosterhuis and Looijenga (26) describe the likely scenario of many susceptibility genes with low penetrance involved in disease development.

Results of epidemiologic studies on familial disease aggregation require careful interpretation. With family members sharing lifestyle, other environmental factors, and sibships sharing gestational characteristics, it is difficult to attribute disease accumulation to genes. Another limitation of this approach is that information on exposure (i.e., having a family history of a particular disease) is often provided by the study participants themselves without the possibility to verify the diagnosis through other sources, which may lead to misclassification. However, nondifferential misclassification of familial cancer would usually lead to an underestimation of the true risk and would therefore not explain the risk elevation. In addition, because, particularly in the past, testicular cancer was associated with a reduction in fertility and an increase in mortality early in life, the degree of familial aggregation seen in our and other's data sets is likely to be an underestimation of the real situation. This may also explain the lower association between fathers and offspring compared with the association between siblings. Another serious concern is the possibility of recall bias causing differential misclassification. We cannot rule this out entirely, especially because a family history of testicular cancer is underreported by participants of a large screening trial (62), but we do not believe that it has severely distorted our results: Testicular cancer in a father or brother is a disease severe enough to be recalled by both cases and controls, especially if it occurred only a short time beforehand; moreover, the participants in our study were quite a bit younger than the 55- to 74-year-old members of the screening study (62) and therefore should have a decent capability for remembering. In addition, we have assessed this issue in our study by asking participants about multiple sclerosis in their relatives, a disease that is also severe but supposedly unrelated to cancer development. We found 10 cases of multiple sclerosis in relatives, all of which were related to controls. Finally, the difference in cancer prevalence between relatives of cases and relatives of controls was limited to certain cancers. If recall bias were present, we would expect to see this difference for cancers in general as well.

Although the exclusion of the one half-brother with testicular cancer would lower the risk estimate, we believe that in general we have rather provided conservative

risk estimates. First, there is a higher proportion of half-siblings affected with cancer among the control collective, which we had left in the analysis. Second, the age of the controls, their parents, and their siblings is on average a few years higher than that of the cases and their relatives. Therefore, the chance of developing one of the diseases of interest is higher in the control population. Whereas we have adjusted for this difference through the age adjustment, this might have rather led to an underestimation than an overestimation of the true risk.

Another factor that could have resulted in a further underestimation of the true risk if not considered appropriately is the fact that, in our study population, cases have on average less siblings than controls (1.75 versus 2.1). A part of this difference stems from the variation in matching ratios. It was reduced when the disparate matching was taken into account and diminished further when social class was considered additionally (data not shown). Given that the matching is controlled for in the analysis and adjustment for social class did not change our results, we are confident that this weak imbalance did not distort our results. Another part of this difference may be due to reproductional characteristics in the parents that may be (causally or noncausally) associated with testicular cancer in the offspring. An example is genital cancer in the parents that is somewhat more frequent in the parents of cases. When focusing on the families of cases and controls where at least one parent himself or herself had a genital cancer, the number of siblings is quite comparable (arithmetic mean controls 1.79 versus arithmetic mean cases 1.73).

Compared with some of the previous studies, ours has some advantages. We have taken several measures to prevent some of the biases that may arise when summarizing family history of disease in one dummy variable (63). For instance, we have applied generalized estimating equations to account for intrafamilial phenotypic correlations and for differences in family size. In addition, we not only have focused on testicular cancer but also have included other genital and breast cancer in the scope of this article to get a broader picture of other potentially relevant cancer diseases in relatives.

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# Testicular, Other Genital, and Breast Cancers in First-Degree Relatives of Testicular Cancer Patients and Controls

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