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Cancer in first-degree relatives and risk of testicular cancer in Denmark

Rikke Baastrup Nordsborg[1,2,*], **Jaymie R. Meliker**[3], **Jan Wohlfahrt**[4], **Mads Melbye**[4], and **Ole Raaschou-Nielsen**[1]

[1] Institute of Cancer Epidemiology, the Danish Cancer Society

[2] National Institute of Public Health, University of Southern Denmark

[3] Graduate Program in Public Health and Department of Preventive Medicine, Stony Brook University

[4] Department of Epidemiology Research, Statens Serum Institut

Abstract

Familial aggregation of testicular cancer has been reported consistently, but it is less clear if there is any association between risk of testicular cancer and other cancers in the family. We conducted a population based case-control study to examine the relationship between risk of testicular cancer and 22 different cancers in first-degree relatives. We included 3297 cases of testicular cancer notified to the Danish Cancer Registry between 1991 and 2003. 6594 matched controls were selected from the Danish Civil Registration System, which also provided the identity of 40,104 first-degree relatives of case and controls. Familial cancer was identified by linkage to the Danish Cancer Registry, and we used conditional logistic regression to analyse whether cancer among first-degree relatives was associated with higher risk of testicular cancer. Rate ratio (RR) for testicular cancer was 4.63 (95% CI: 2.41–8.87) when a father, 8.30(95% CI: 3.81–18.10) when a brother and 5.23 (95% CI: 1.35–20.26) when a son had testicular cancer compared with no familial testicular cancer. Results were similar when analyses were stratified by histologic subtypes of testicular cancer. Familial Non-Hodgkin lymphoma and oesophageal cancer were associated with testicular cancer; however these may be chance findings. The familial aggregation of testicular and possibly other cancers may be explained by shared genes and/or shared environmental factors, but the mutual importance of each of these is difficult to determine.

Keywords

Testicular cancer; familial aggregation; first-degree relatives; Denmark

Introduction

Testicular cancer is a rare disease, accounting for one percent of all incident male cancers worldwide [1]. It is, however, the most common cancer among young men 15–34 years old [2], and Denmark has the highest incidence rate in the world with 9.7 cases per 100,000 inhabitants [3]. Furthermore, incidence has increased over the last decades especially in the developed countries in Western Europe, North America, and Oceania [4]. The few known risk factors for testicular cancer are cryptorchidism (undescended testes) and a family history of

[*]Corresponding Author: Rikke Baastrup Nordsborg, The Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, Dk-2100 Copenhagen, Denmark., Phone: +45 35 25 76 86, Fax: +45 35 25 77 31, baastrup@cancer.dk.

testicular cancer; early-life or *in utero* exposures are also suspected to play an important role [5;6]. The increased risk of testicular cancer in male first-degree relatives of testicular cancer cases is well-documented [7–14]. Some studies suggest that the risk is more pronounced in brothers of testicular cancer cases than in fathers and sons [8;9;11;13;14] and Swerdlow et al reported a relative risk as high as 37.5 in twin brothers of testicular cancer cases [15]. Only few studies distinguish between histological subtypes of testicular cancer i.e. seminoma and nonseminoma providing no clear differences in risk patterns [8;12;16]. Swedish data suggest that the association between testicular cancer in first-degree relatives is much stronger for pure than for mixed histological subtypes, i.e. the risk is higher for seminoma testicular cancer given seminoma testicular cancer in relatives and *vice versa* for nonseminoma testicular cancer [8;10].

While an association, thus, has been established between the risk of testicular cancer and testicular cancer in first-degree relatives, it is an open question whether an association also exists between risk of testicular cancer and non-testicular cancers in relatives. Such possible associations were explored in previous studies of which some indicated higher risk of testicular cancer in association with, among others, cancers of the pancreas, oesophagus, genitals and breast as well as melanomas and lymphomas, whereas other studies did not find such associations [7–12;16–19].

Thus, still little is known about the potential aggregation of cancers other than testicular cancer in families of testicular cancer cases, and large studies using registry data are useful for examining such possible associations. We used a large population-based case-control study from Denmark to explore if cancer among first-degree relatives was associated with the risk of testicular cancer.

Material and Methods

Study population

Cases—Cases were all males notified to the population-based Danish Cancer Registry with a testicular cancer diagnosis between 1991 and 2003. We included only first cancers with International Classification of Diseases for Oncology (ICD-O) morphology behaviour code 3 (malignant, primary site), however preceding diagnosis of non-melanoma skin cancer was allowed. In total, 3297 cases were included. Furthermore, we classified cases as either seminoma or nonseminoma testicular cancer. Seminoma testicular cancer was defined as ICD-O morphology codes: 9060/3, 9061/3, 9062/3 and 9063/3. The remaining testicular cancers were classified as nonseminoma. We identified 1871 seminoma and 1426 nonseminoma cases.

Controls—Eligible controls were all males born on the same day, month and year as cases and alive and living in Denmark at time of diagnosis. For cases 90 years of age or older eligible controls were males born in the same month and year. The wider time range was applied in this age group to ensure enough potential controls alive at the time of diagnosis. Further, eligible controls should have received no cancer diagnosis except from non-melanoma skin cancer at the date of diagnosis of the matched case. The pool of potential controls was identified in the Danish Civil Registration System, which was founded in 1968 and includes information on the whole Danish population. Two controls were randomly selected and matched individually with cases, thus the control group included 6594 individuals.

Family history of cancer—The Danish Civil Registration System is based on a10-digit personal identification number (PIN), which provides a unique identifier for every Danish citizen. Furthermore, the registry contains parental links between persons, which is utilised

in the Danish Family Relations Database [20]. 40,104 first-degree relatives (that is parents, siblings and children) of cases and controls were identified by linkage with this database. Subsequently, we identified cancer among these relatives by linkage with the Danish Cancer Registry, using their PIN. We only counted first primary cancers recorded in the cancer registry in 1943–2003 (ignoring non-melanoma skin cancers), and used the 7th Revision of the International Classification of Diseases (ICD-7) to group the cancer diagnoses of the fist-degree relatives into the following categories: 140–148: Buccal cavity and Pharynx, 150: Oesophagus, 151: Stomach, 153–154: Colorectal cancer, 155.0: Liver, 155.1: Gallbladder, 157: Pancreas, 161: Larynx, 162.0 and 162.1: Lung, 170: Female Breast, 171–176: Female genital organs, 178: Testis, 177 and 179: Other male genital organs, 178: Kidney, 181: Bladder, 190:Melanoma of skin, 193: Brain and nervous system, 197: Connective tissue, 200 and 202: Non-Hodgkin lymphoma (NHL), 201: Hodgkin's disease, 203: Multiple myeloma, 204: Leukemia.

For each cancer site we counted the number of cases among the first-degree relatives. Only few persons had more than one relative with the same cancer type. Therefore, cancer in relatives was noted as 'yes' (for one or more cases) or 'no'.

Statistical analyses

We used conditional logistic regression to analyse whether cancer in first-degree relatives was associated with higher risk of testicular cancer. All analyses were adjusted for number of known first-degree relatives (continuous variable). For sex-specific cancers, analyses were adjusted for number of known male and female relatives, respectively. We estimated rate ratios (RRs) for testicular cancer in association with each type of cancer in the first-degree relatives, and for testicular cancer separately for fathers, brothers and sons as well as for older and younger cases. Wald test was used to evaluate if estimates by age at diagnosis in family member and type of family member were statistically different. We also analysed risk of seminoma and nonseminoma testicular cancer separately. Wilcoxon tests were used to compare age in cases with and without testicular cancer in first-degree relatives and seminoma versus nonseminoma. Furthermore, we tested if age at diagnosis in the first-degree relatives of cases and controls differed. All analyses were performed using SAS 9.1, all tests were two-sided, and a 5 % significance level was used.

Results

In total, we included 3297 cases (57% seminomas and 43% nonseminomas), 6594 controls and 40,104 first-degree relatives. Sixty-nine cases and 26 controls had a male first-degree relative with testicular cancer, and the cases having a relative with testicular cancer were younger (mean: 33 years; median: 32 years) at date of diagnosis than cases with no testicular cancer in the family (mean: 37 years; median: 35 years) (Wilcoxon test: p=0.003). Table 1 shows characteristics of cases and controls. Due to the matching criteria, the age distribution of cases and controls was virtually identical. Furthermore, the number of known first-degree relatives was very similar for cases and controls, except that testicular cancer cases tended to have slightly fewer children than controls. Seminoma cases were older (mean: 40 years; median: 38 years) than nonseminoma cases (mean: 33 years; median: 30 years) at the time of diagnosis Wilcoxon test: p <0.001). Age at diagnosis in first-degree relatives was similar for cases and controls, both for all cancers except testicular cancer and when testicular cancer among fathers and brothers was considered (table 2). Sons of cases tended to be younger at date of diagnosis than sons of controls but the difference was not statistically significant (Wilcoxon test: p=0.49). Table 3 shows a RR of 5.97 (95% CI: 3.74–9.53) for testicular cancer in association with testicular cancer in any male first-degree relatives compared with no familial testicular cancer. Higher RRs for testicular cancer were observed when brothers and sons had testicular cancer compared to paternal testicular cancer, but the

difference was not statistically significant (Wald test: p=0.49). RRs were similar for young and older cases (Wald test: p=0.82). We also tested the effect of age at disease onset in the relatives, which showed higher RR for testicular cancer when relatives were diagnosed at young ages (≤35 years) compared to relatives diagnosed at older ages (>35 years), however estimates were not significantly different (Wald test: p=0.35).

Further, the results showed a RR of 1.73 (95% CI: 1.10–2.73) for testicular cancer in association with NHL and a borderline statistically significant RR of 1.83 (95% CI: 0.94–3.58) in association with oesophageal cancer in first-degree relatives compared with no such familial cancer. The results showed no statistically significant association for any other type of cancer. For all cancers combined the risk of testicular cancer was slightly increased; however, this association disappeared when testicular cancer was not included in the total number of cancers. A further breakdown of this category by type of relative showed no statistically significant associations, and results were similar across type of relative (results not shown).

Separate risk estimates for seminoma and nonseminoma testicular cancer are shown in table 4. Cancer of the brain and nervous system in first-degree relatives increased the risk of nonseminoma testicular cancer with 91%, and a borderline significant association between NHL in relatives and risk for seminoma testicular cancer was observed. In general, however, the separate analyses for seminoma and non-seminama testicular cancer showed similar associations, although these estimates were based on relatively few cases and with wide confidence intervals.

Table 5 shows risk of seminoma and nonseminoma testicular cancer in association with seminoma and nonseminoma testicular cancer in fathers, brothers and sons, respectively. Overall, associations were similar across the histologic subtypes and groups of male relatives, however each group counted only few cases and some too few to obtain an estimate.

Discussion

This population-based case control study found increased risk of testicular cancer in association with testicular cancer among first-degree relatives. Similar associations were found when risk of histological subtypes of testicular cancer was evaluated. Furthermore, our findings suggested an association between testicular cancer and familial NHL and oesophageal cancer.

Cases were identified in the virtually complete, high-quality population-based Danish Cancer Registry [21], thus the study has very reliable case ascertainment. Furthermore, the the Danish Civil Registration System provided an ideal frame for control selection as well as identification of first-degree relatives of cases and controls.

The Danish Civil Registration System has some historical limitations, as the identity of parents can (only) be found for persons born since the beginning of the 1950s, and the information is first regarded complete for persons born in 1960 and onwards [6;9]. Consequently, our database had some gaps in information on first-degree relatives among the older cases and controls. To address this issue we adjusted all analyses for number of known first-degree relatives. Furthermore, as testicular cancer is rare and the specificity of the registration of the cancer is very high, the misclassification will only induce a very small downward bias.

Previous studies consistently reported familial aggregation of testicular cancer in agreement with our findings. Most studies found a 4-fold increased risk of testicular cancer, when the

father had testicular cancer, and estimates ranged from 8–13-fold increased risk for brothers and 2–5-fold increased risk when a son had testicular cancer[8;9;11;13;14]. Thus, our results agree with these previous findings. Higher risk among brothers than fathers was also consistently reported; however the difference between fathers and brothers that we observed was less pronounced and not statistically significant.

Early onset of disease is considered one of the established factors that characterize genetic predisposition for cancer in families [22]. In agreement with such genetic predisposition, we found that cases with testicular cancer in the family were on average four years younger at time of diagnosis than cases with no history of familial testicular cancer, which is in agreement with a an age difference of 3.5 years previously reported [23]. Two other studies did not observe such age differences; these studies were, however, based on few cases with testicular cancer in the family [9;24]. Further, risk of testicular cancer in association with testicular cancer in first-degree relatives tended to be higher if relatives were diagnosed at young ages compared to relatives, who were older at time of diagnosis, but the difference was not statistically significant.

We found that a family history of NLH was associated with a73% higher risk of testicular cancer. Results from a Swedish study population similarly suggested a slightly increased risk of testicular cancer in association with familial NHL [10;11], which to our knowledge is the only previous investigation of this association. Furthermore, we observed a borderline statistically significant association between familial oesophageal cancer and testicular cancer, which is in agreement with prior studies [10;17]. A similar tendency was found in a previous Danish study of cases from an earlier time period, however statistically insignificant and based on very few cases [9]. Others have not been able to detect such association [16]. In addition, we found that cancer of the brain and nervous system in first-degree relatives increased the risk of nonseminoma testicular cancer. Only few others have investigated and found such association, however Dong et al found a similar association between seminoma testicular cancer and cancer of the nervous system [8], and Hemminki et al between testicular cancer as a whole and paternal nervous system cancer [10]. Thus little evidence exists to support our finding of associations between testicular cancer and NHL and cancer of the oesophagus and brain and nervous system, and it cannot be ruled out that these results are chance findings, due to multiple testing.

Explanations for familial aggregation of testicular (and other cancers) involve genetic and environmental components, however the mutual importance of each of these is difficult to determine. Some interpret the consistent findings of familial aggregation of testicular cancer as evidence for a genetic predisposition, while others emphasize environmental factors.

It has been pointed out that the familial risk of testicular cancer is much higher than the familial risk of other cancers, which suggest the involvement of some genetic mechanisms, as it is considered unlikely that environmental factors alone can explain such strong familial aggregation [14;23;24]. Consistent with a genetic element in testicular carcinogenesis, a higher risk of testicular cancer was found in monozygotic twins of men with testicular cancer compared to dizygotic twins [15]. On the other hand, specific heritable genes have not been identified [22], and the fast increase in the incidence of testicular cancer observed in the industrialized countries indicates that environmental factors are of primary importance, because genetic factors change at a much slower rate. Migrant studies of testicular cancer also argue for a substantial environmental influence, because individuals who migrate from low-risk areas to areas of high risk adopt the rate in the host country within few generations[6].

Twins were found to have larger risk of testicular cancer than the general population, which could be due to higher levels of maternal hormones associated with twin-pregnancies compared to singleton-pregnancies [15;25], which is referred to as the maternal-hormone aetiology hypothesis. Such shared *in utero* environment has also been used to explain the higher risk of testicular cancer among brothers than fathers of cases of testicular cancer [8;10]. One study found higher risk among brothers close in age compared to those further apart, indicating that shared childhood environment may also play an important role [10]. In summary, is seems plausible that multiple factors causes familial clustering of testicular cancer. The existing literature offers reliable arguments for both genetic and environmental influence, but these have not convincingly been separated into more specific contributions, suggesting that the aggregation is perhaps rather a product of complex gene-environment interactions. Except for a few known risk factors the aetiology of testicular cancer still remains unclear.

This large population-based study confirmed familial aggregation of testicular cancer and suggested an association between testicular cancer and familial NHL and oesophageal cancer.

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Abbrevations

RR	Rate Ratio
CI	Confidence Interval
ICD-O	International Classification of Diseases for Oncology
ICD-7	7th Revision of the International Classification of Diseases
PIN	Personal Identification Number
NHL	Non-Hodgkin lymphoma

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Novelty and impact

The study is among the largest case-control studies of familial cancer and risk of testicular cancer, and it is an important contribution to the limited number of population-based studies that examine association between testicular cancer and familial cancer other that testicular cancer.

Table 1

Characteristics of testicular cancer cases and controls

Variable	cases (n=3297)	controls (n=6594)
Age at diagnosis/censoring		
Min	0	0
5%	21	21
25%	28	28
50% (mean)	35(36.7)	35(36.6)
75%	43	43
95%	59	59
Max	96	96
Identified family members		
Father	2496(76%)	5001 (76%)
Mother	2547(77%)	5118 (78%)
Brothers		
0	1957 (59%)	3802(58%)
1	977 (30%)	1941(29%)
2	288 (9%)	660(10%)
3	57 (2%)	149(2%)
4+	18 (1%)	42(1%)
Sisters		
0	2015(61%)	4011(61%)
1	998(30%)	1936(29%)
2	226(7%)	542(8%)
3	53(2%)	76(1%)
4+	5(0%)	29(0%)
Sons		
0	1739(53%)	3141 (48%)
1	979 (30%)	2164 (33%)
2	497 (15%)	1058 (16%)
3	67(2%)	198 (3%)
4+	15(0%)	33 (1%)
Daughters		
0	1735 (53%)	3237 (49%)
1	1037 (31%)	2177 (33%)
2	428 (13%)	949 (14%)
3	81 (2%)	199 (3%)
4+	16(0%)	32(0%)

Table 2

Age at cancer diagnosis in first-degree relatives of testicular cancer cases and controls.

Cancer type in relatives	Age at cancer diagnosis in relatives (years)						
	Testicular cancer cases			Controls			Wilcoxon test[a]
	n	mean	median	n	mean	median	*p* value
All cancer ex. testicular cancer	864	57.8	59.5	1687	57.5	59.5	0.55
Testis	69	33.8	30.8	26	33.1	33.0	0.75
Father	30	41.0	40.0	13	37.4	37.4	0.32
Brother	32	28.5	27.8	10	26.9	25.6	0.45
Son	7	26.8	25.5	3	35.0	36.9	0.49

[a]Test for difference between age at cancer diagnosis in first-degree relatives of cases and controls.

Table 3

Rate ratio (RR) of testicular cancer according to site-specific familial cancer in first-degree relatives.

Cancer in first-degree relative (ICD-7)	n_{ca}/n_{co}	RR (95% CI)	*p*
Buccal cavity and Pharynx (140–148)	20/40	1.02 (0.59–1.75)	0.95
Oesophagus (150)	17/19	1.83 (0.94–3.58)	0.08
Stomach (151)	19/35	1.10 (0.62–1.93)	0.75
Colorectal cancer (153–154)	91/189	0.97 (0.75–1.26)	0.83
Liver (155.0)	7/11	1.27 (0.49–3.27)	0.63
Gallbladder (155.1)	3/8	0.81 (0.22–3.09)	0.76
Pancreas (157)	31/45	1.38 (0.87–2.18)	0.17
Larynx (161)	7/28	0.50 (0.22–1.14)	0.10
Lung (162.0,1)	120/249	0.98 (0.78–1.22)	0.84
Breast, female (170)[a]	135/258	1.06 (0.85–1.31)	0.62
Female genital organs (171–176)[a]	78/177	0.89 (0.68–1.16)	0.37
Testis (178)			
All male relatives[b]	69/26	5.97 (3.74–9.53)	<0.0001
Cases ≤ 35 years of age[b,c]	43/15	6.24 (3.41–11.43)	<0.0001
Cases > 35 years of age[b,c]	26/11	5.59 (2.68–11.67)	<0.0001
Relatives ≤ 35 years of age[b,d]	44/14	7.18 (3.86–13.36)	<0.0001
Relatives > 35 years of age[b,d]	25/12	4.57 (2.24–9.32)	<0.0001
Fathers[e]	30/13	4.63 (2.41–8.87)	<0.0001
Brothers[f]	32/10	8.30 (3.81–18.10)	<0.0001
Sons[g]	7/3	5.23 (1.35–20.26)	0.02
Other male genital organs (177,179)	47/101	0.95 (0.67–1.34)	0.75
Kidney (180)	17/49	0.70 (0.40–1.22)	0.20
Bladder (181)	52/108	0.98 (0.70–1.37)	0.91
Melanoma of skin (190)	36/70	1.06 (0.70–1.59)	0.79
Brain and nervous system (193)	35/57	1.30 (0.84–1.99)	0.24
Connective tissue (197)	8/14	1.15 (0.48–2.74)	0.75
Non-Hodgkin lymphoma (200,202)	35/41	1.73 (1.10–2.73)	0.02
Hodgkin's disease (201)	6/19	0.65 (0.26–1.64)	0.37
Multiple myeloma (203)	11/15	1.51 (0.69–3.30)	0.30
Leukemia (204)	23/42	1.10 (0.66–1.83)	0.72
All cancer	814/1513	1.13 (1.02–1.26)	0.02
All cancer excl. testis	766/1492	1.06 (0.95–1.17)	0.30

n_{ca}: number of cases with the particular cancer in the family

n_{co}: number of controls with the particular cancer in the family

p: P-value

RR: rate ratio

95 % CI: 95 percent confidence interval

All analyses were adjusted for number of known first-degree relatives, unless otherwise stated. The numbers in the table do not add up, because cancer in relatives was only noted as ‘yes’ (for one or more cases) or ‘no’.

[a] adjusted for number of known female first-degree relatives

[b] adjusted for number of known male first-degree relatives

[c] age at diagnosis for cases and the matched controls

[d] age at diagnosis in relatives

[e] adjusted for identification of father or not

[f] adjusted for number of known brothers

[g] adjusted for number of known sons

Table 4

Rate ratio (RR) of seminoma and non-seminoma testicular cancer according to site-specific familial cancer in first-degree relatives.

	seminoma testicular cancer			non-seminoma testicular cancer		
Cancer in first-degree relative (ICD-7)	**n_{ca}/n_{co}**	**RR (95% CI)**	***p***	**n_{ca}/n_{co}**	**RR (95% CI)**	***p***
Buccal cavity and Pharynx (140–148)	9/23	0.81 (0.38–1.76)	0.60	11/17	1.28 (0.60–2.75)	0.52
Oesophagus (150)	12/13	1.87 (0.83–4.20)	0.13	5/6	1.77 (0.54–5.82)	0.35
Stomach (151)	12/22	1.11 (0.54–2.28)	0.77	7/13	1.07 (0.42–2.68)	0.89
Colorectal cancer (153–154)	55/117	0.95 (0.69–1.33)	0.78	36/72	1.00(0.66–1.51)	0.99
Liver (155.0)	2/5	0.79 (0.15–4.10)	0.78	5/6	1.66 (0.51–5.47)	0.40
Gallbladder (155.1)	2/4	1.09 (0.20–5.96)	0.93	1/4	0.54(0.06–4.89)	0.59
Pancreas (157)	19/28	1.37 (0.76–2.46)	0.29	12/17	1.38 (0.66–2.90)	0.39
Larynx (161)	3/15	0.41 (0.12–1.40)	0.15	4/13	0.59(0.19–1.83)	0.36
Lung (162.0,1)	68/141	0.99 (0.74–1.33)	0.94	52/108	0.96 (0.68–1.35)	0.80
Breast, female (170)[a]	74/147	1.02 (0.77–1.36)	0.89	61/111	1.10(0.80–1.52)	0.55
Female genital organs (171–176)[a]	46/106	0.87 (0.61–1.24)	0.45	32/71	0.90 (0.59–1.37)	0.63
Testis (178)						
All male relatives[b]	39/13	6.43 (3.42–12.08)	<0.0001	30/13	5.40(2.69–10.83)	<0.0001
Fathers[c]	16/6	5.36 (2.10–13.70)	0.0005	14/7	4.00(1.62–9.92)	0.003
Brothers[d]	17/5	7.54 (2.77–20.54)	<0.0001	15/5	9.58 (2.75–33.41)	0.0004
Sons[e]	6/2	6.44 (1.30–31.93)	0.02	1/1	2.62 (0.16–42.15)	0.50
Other male genital organs (177,179)[b]	27/65	0.85 (0.54–1.33)	0.47	20/36	1.12 (0.64–1.94)	0.70
Kidney (180)	10/30	0.69 (0.33–1.41)	0.30	7/19	0.71 (0.29–1.73)	0.45
Bladder (181)	31/55	1.16 (0.74–1.82)	0.51	21/53	0.79 (0.48–1.33)	0.38
Melanoma of skin (190)	19/39	0.99 (0.57–1.73)	0.98	17/31	1.14 (0.63–2.08)	0.67
Brain and nervous system (193)	15/34	0.92(0.50–1.70)	0.80	20/23	1.91 (1.01–3.58)	0.05
Connective tissue (197)	3/8	0.78(0.21–2.93)	0.71	5/6	1.61 (0.49–5.30)	0.43
Non-Hodgkin lymphoma (200,202)	21/24	1.76 (0.97–3.18)	0.06	14/17	1.70 (0.84–3.46)	0.14
Hodgkin's disease (201)	4/9	0.90 (0.28–2.92)	0.85	2/10	0.43 (0.09–1.97)	0.28
Multiple myeloma (203)	7/10	1.45 (0.55–3.83)	0.45	4/5	1.62 (0.43–6.06)	0.47
Leukemia (204)	14/30	0.96 (0.51–1.82)	0.90	9/12	1.40 (0.59–3.33)	0.45

n_{ca}: number of cases with the particular cancer in the family

n_{co}: number of controls with the particular cancer in the family

p: P-value

RR: rate ratio

95 % CI: 95 percent confidence interval

All analyses were adjusted for number of known first-degree relatives, unless otherwise stated

The numbers in the table do not add up, because cancer in relatives was only noted as 'yes' (for one or more cases) or 'no'.

[a] adjusted for number of known female first-degree relatives

[b] adjusted for number of known male first-degree relatives

[c] adjusted for identification of father or not

[d] adjusted for number of known brothers

[e] adjusted for number of known sons

Table 5

Rate ratio (RR) of seminoma and non-seminoma testicular cancer according to familial testicular cancer by type of testicular cancer and type of relative.

	seminoma testicular cancer			non-seminoma testicular cancer		
Cancer Site (ICD-7)	**n_{ca}/n_{co}**	**RR (95% CI)**	***p***	**n_{ca}/n_{co}**	**RR (95% CI)**	***p***
All Seminomas[a]	17/4	9.10(3.05–27.13)	<0.0001	20/6	9.63(3.27–28.37)	<0.0001
Seminoma, father[b]	8/3	5.35 (1.42–20.18)	0.01	9/4	4.51(1.39–14.63)	0.01
Seminoma, brother[c]	5/0	- -	-	10/2[e]	- -	-
Seminoma, son[d]	4/1	8.73(0.97–78.26)	0.05	1/0	- -	-
All Non-seminoma[a]	22/9	5.23 (2.40–11.36)	<0.0001	10/7	2.97 (1.13–7.82)	0.03
Non-seminoma, father[b]	8/3	5.33(1.42–20.08)	0.01	5/3	3.33(0.80–13.92)	0.10
Non-seminoma, brother[c]	12/5	5.27(1.85–15.02)	0.002	5/3	3.48(0.83–14.58)	0.09
Non-seminoma, son[d]	2/1	4.18 (0.38–46.06)	0.24	0/1	- -	-

n_{ca}: number of cases with the particular cancer in the family

n_{co}: number of controls with the particular cancer in the family

p: P-value

RR: rate ratio

95 % CI: 95 percent confidence interval

[a] adjusted for number of known male first-degree relatives

[b] adjusted for identification of father or not

[c] adjusted for number of known brothers

[d] adjusted for number of known sons

[e] both controls with a brother having seminoma testicular cancer were matched with a case also having an affected brother, consequently no estimates could be obtained.