Fertility Among Brothers of Patients with Testicular Cancer

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Abstract

Objective: **Patients with testicular cancer have decreased fertility prior to the diagnosis of cancer, although it is not clear whether the subfertility is the result of an emerging tumor, or whether subfertility and testicular cancer share causes. To test if they share causes, we assessed fertility among brothers of patients with testicular cancer.**
Methods: **We compared 5,613 siblings (2,878 brothers) of patients with germ-cell testicular cancer, diagnosed in Sweden from 1960 to 2002, with 6,151 population controls (3,202 men). Using the Swedish Multi-Generation Register, we obtained information on the number of children born (until December 2003) from cases (n = 9,480) and controls (n = 10,739). Fertility was measured using two indicators, (a) offspring twinning rates, as dizygotic twinning is reduced by male subfertility, and (b) number of children. We used unconditional logistic regression, and analyzed brothers and sisters separately. Analyses on the number of children were restricted to subjects (39%) born prior to 1954, for whom information on reproductive life until age 50 was available.**
Results: **Brothers, but not sisters, of patients with testicular cancer were less likely to have unlike-sex twins than controls (for unlike-sex twins, the odds ratio for the father being a sibling of testicular cancer patient was 0.53; 95% confidence interval, 0.26-1.09). The likelihood of being a brother of a patient with testicular cancer decreased monotonically with increasing number of children (P = 0.05), whereas no association was observed for the sisters.**
Conclusion: **The decreased fertility found among brothers of patients with testicular cancer argues in favor of shared causes between cancer-associated subfertility and testicular cancer. Genetic links and shared environment could explain the association.** (Cancer Epidemiol Biomarkers Prev 2005;14(11):2557–62)

Introduction

The incidence of germ-cell testicular cancer is increasing by ~3% to 4% annually in many populations (1). It has been proposed that this surge is part of an ongoing epidemic of a testicular dysgenesis syndrome that includes subfertility problems, cryptorchidism, and hypospadias as well (2, 3), although descriptive data on time trends in male fertility and urogenital malformations are much less consistent than those of testicular cancer. There is, furthermore, no strong candidate environmental cause of the possible epidemic.

It has recently been established that patients with testicular cancer have decreased fertility prior to being diagnosed with cancer (4-6), although it is not clear whether the fertility problems are results of an emerging tumor, or if the subfertility and testicular cancer share causes, as would be the case in a testicular dysgenesis syndrome. Based on the notion of shared causes, we hypothesized that fertility may also be decreased among brothers of patients with testicular cancer. To test this hypothesis, we studied the number of children and twinning rates among brothers and sisters of patients with testicular cancer in a population-based case-control study. Fathering unlike-sex twins is, until the introduction of *in vitro* fertilization in the early 1990s, a possible measure of male fertility that is not affected by decisions about family size (7). By investigating both brothers and sisters, we were able to evaluate the effect of unmeasured socioeconomic factors on fertility. We assumed that if testicular cancer and cancer-associated male subfertility share environmental or genetic causes, then brothers, but not sisters, of patients with testicular cancer should have a decreased fertility.

Patients and Methods

In this case-control study, we used several Swedish population–based registers to identify study subjects and measure their degree of fertility. The study was approved by the local Ethics Committee at Karolinska Institutet (registration number 03-191).

Registry Descriptions. All Swedish residents alive from 1947 onwards have been assigned a 10-digit national registration number (date of birth plus a four-digit code containing information on sex and county of birth), which is a unique personal identifier, referred to in all medical records and official registries. Through the use of the national registration number, it is possible to unambiguously link information from several databases together.

Since 1958, all newly diagnosed malignant tumors in Sweden must be reported to the National Cancer Registry by the physician who makes the diagnosis as well as the pathologist or cytologist who confirms it (8). All patients are entered in the Cancer Registry by use of their national registration number.

The Register of Population and Population Changes, kept by Statistics Sweden, contains the official Swedish population data (since 1960) in a computerized fashion (9). All residents in Sweden alive at the end of each year are included. Since 1969, the Register also contains information on dates of emigration and/or immigration. Furthermore, the Register contains information from the Swedish Censuses, which include occupational and marital statuses. For children living with their parents, the censuses report the parental occupational status.

In 2000, Statistics Sweden started a linkage between several data sources from the national registration and created the Swedish Multi-Generation Register, which contains information on the parents of all individuals in Sweden born from 1932

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onwards and surviving until 1961 (10). Using this Register, it is thus possible to identify siblings and offspring of each index person through the parents. The completeness of the Register increases rapidly with increasing year of birth—for those born in 1935, 80% of the parents can be identified, and parent information is virtually complete for those born from 1945 onwards. Adoption or other nonbiological relations are flagged in the Register.

Identification of Cases and Controls and Data Collection. We identified testicular cancer index patients (International Classification of Diseases-7 code: 178) diagnosed from January 1960 to December 2002 from the Swedish Cancer Register. For each testicular cancer index patient, we identified a male index population subject through the Swedish Register of Population and Population Changes, frequency-matched on year of birth in 10-year intervals, and county. The Cancer Register allowed us to verify that the index population subjects were not diagnosed with testicular cancer before the date of diagnosis of the corresponding index testicular cancer patient. In order to select a homogeneous group of testicular cancers, we restricted the index subjects to individuals born after 1940 and aged 15 to 54 years at identification. Moreover, the testicular cancer index patients were restricted to individuals with a germ-cell cancer. Testicular cancer index patients and population subjects who migrated during follow-up were excluded to minimize underascertainment of cancer occurrence (Fig. 1).

Using the Swedish Multi-Generation Register, we identified all brothers and sisters (born from 1932 to 1987) of the testicular cancer index patients and population subjects. These siblings are the actual cases (siblings of patients with testicular cancer) and controls (siblings of the population subjects) of the study (Fig. 1). Nonbiological and half-siblings were excluded.

We identified the children of the brothers and sisters of patients with testicular cancer and controls that were fathered/given birth to until the age of 50 years, using data from the Multi-Generation Register up to December 2003. Among the children, twins were identified as siblings born in the same 3-day period. Brothers and sisters of patients with testicular cancer and population subjects who emigrated or immigrated during follow-up were excluded to minimize underascertainment of children. We also excluded subjects who received a diagnosis of testicular cancer (Fig. 1).

Because occupational status varies over lifetime, census data obtained at ages 35 to 45 years were used whenever available. Otherwise, we used census data obtained at ages 46 to 50 years or 25 to 34 years, in that order. This occurred for 3.6% of the siblings of testicular cancer patients and 2.7% of the controls born prior to 1954, which were thus followed-up until the age of 50.

Statistical Analyses. We carried out all analyses stratifying by sex to investigate brothers and sisters of testicular cancer, separately. Twinning rates and number of children were used as two independent indicators of fertility.

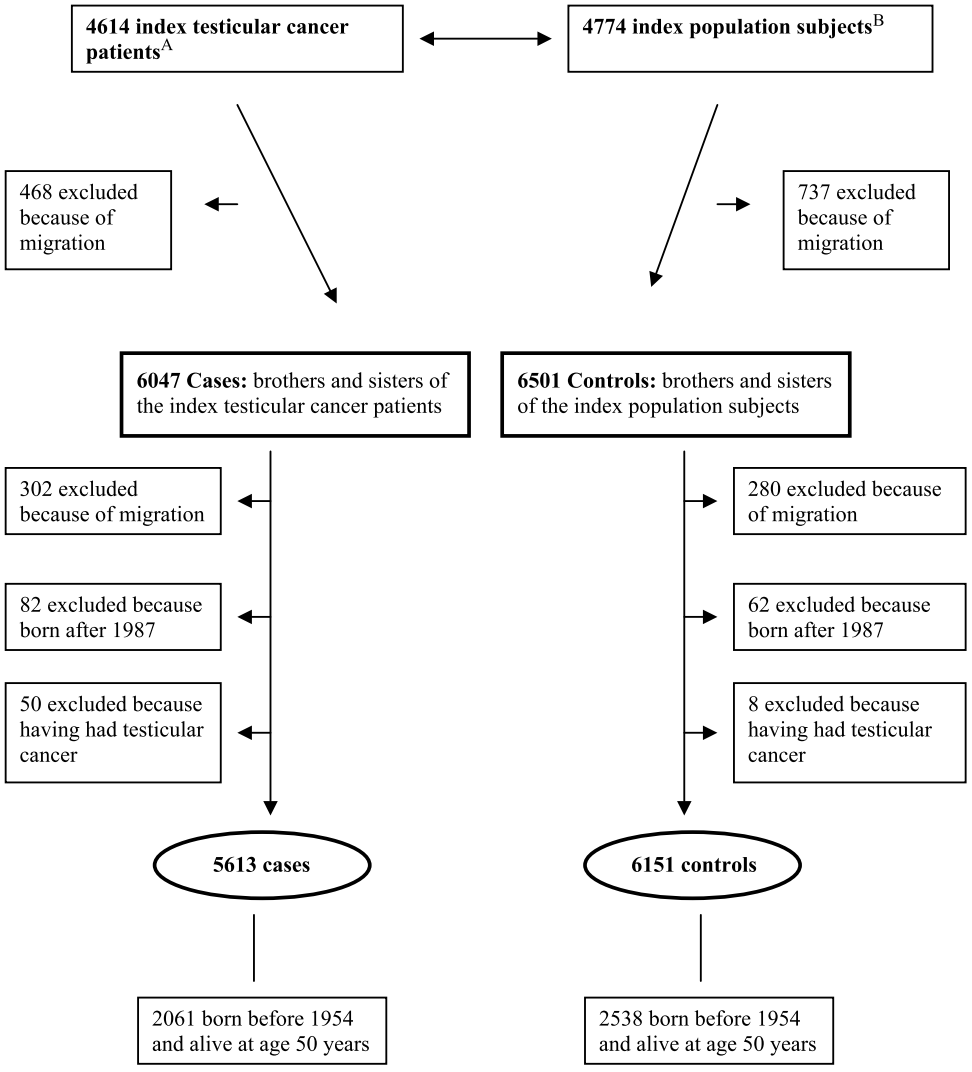

Figure 1. Selection of study cases and controls. **A.** Swedish individuals born after 1940 and ages 15 to 54 years at diagnosis of a germ-cell testicular cancer between 1960 and 2002 (see text). **B.** Population subjects born after 1940 and ages 15 to 54 years—frequency-matched with patients with testicular cancer on year of birth in 10-year intervals, and county—alive and with no testicular cancer at the time of diagnosis of the corresponding testicular cancer index patient (see text).

Table 1. Demographic characteristics of siblings of patients with testicular cancer and controls

	Brothers of patients with testicular cancer, n = 2,878, n (%)	Controls, n = 3,202, n (%)	Sister of patients with testicular cancer, n = 2,735, n (%)	Controls, n = 2,949, n (%)
Cohort				
<1936	37 (1.3%)	57 (1.8%)	35 (1.3%)	44 (1.5%)
1936-1940	127 (4.4%)	170 (5.3%)	126 (4.6%)	165 (5.6%)
1941-1945	255 (8.9%)	361 (11.3%)	233 (8.5%)	288 (9.8%)
1946-1950	387 (13.4%)	473 (14.8%)	406 (14.8%)	445 (15.1%)
1951-1955	425 (14.8%)	494 (15.4%)	397 (14.5%)	455 (15.4%)
1956-1960	475 (16.5%)	470 (14.7%)	429 (15.7%)	459 (15.6%)
1961-1965	419 (14.6%)	445 (13.9%)	435 (15.9%)	426 (14.4%)
1966-1970	338 (11.7%)	330 (10.3%)	314 (11.5%)	291 (9.9%)
1971-1975	235 (8.2%)	214 (6.7%)	189 (6.9%)	219 (7.4%)
1976-1980	115 (4.0%)	120 (3.8%)	109 (4.0%)	92 (3.1%)
1981+	65 (2.3%)	68 (2.1%)	62 (2.2%)	65 (2.2%)
Sibship size				
2	757 (26.3%)	724 (22.6%)	753 (27.5%)	782 (26.5%)
3	988 (34.4%)	1,021 (31.9%)	917 (33.5%)	875 (29.7%)
4	591 (20.5%)	595 (18.6%)	537 (19.6%)	537 (18.2%)
5+	542 (18.8%)	862 (26.9%)	528 (19.3%)	755 (25.6%)
Study area				
Largest Swedish cities*	880 (30.6%)	947 (29.6%)	873 (31.9%)	879 (29.8%)
Southern Sweden	1,446 (50.2%)	1,588 (49.6%)	1,369 (50.1%)	1,468 (49.8%)
Northern Sweden	552 (19.2%)	667 (20.8%)	493 (18.0%)	602 (20.4%)

*Largest Swedish cities include Stockholm, Malmö, and Göteborg.

All analyses were carried out using SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC). To evaluate twinning rates, we estimated the odds ratio (OR) and 95% confidence interval (CI) for same-sex and unlike-sex twin birth, according to the case-control status of the parent, using unconditional logistic regression (11). Models included year of birth (continuous variable), parental age (continuous variable), and birth order (three categories, 1, 2, and 3+). Unlike-sex twins were excluded from the analysis of same-sex twins and vice versa. Because *in vitro* fertilization started influencing twinning rates in Sweden significantly in the 1990s (12), we did further analyses stratifying by year of birth of offspring using 1990 as the threshold.

We estimated ORs and 95% CIs of being a sibling of a testicular cancer patient for the cumulative number of children born until age 50 years. We used unconditional logistic regression models (11). Variables evaluated as potential confounders and kept in the final models were cohort of birth, sibship size, socioeconomic status, place of birth, and marital status. The demographic variables were categorized as in Table 1. Marital status, which had virtually no missing values, was included as a dichotomous variable for having never been married according to all censuses carried out during the study period. Socioeconomic status was classified into three categories according to occupation: (*a*) non–manual workers, (*b*) manual workers, and (*c*) ''others,'' which included occupational categories, such as pensioner, home-worker, student, part-time worker, unemployed, as well as missing values (1.6% of the siblings of patients with testicular cancer and 1.0% of the controls born prior to 1954).

Although our study subjects were siblings sampled from the same families, the SE estimates did not change when we carried out analyses taking into account the family clustering. Therefore, we present results obtained using a standard logistic regression approach.

Results

We identified 5,613 siblings (2,878 brothers and 2,735 sisters) of patients with testicular cancer and 6,151 controls (3,202 men and 2,949 women; Table 1). As expected from the testicular cancer epidemiology, siblings had a smaller sibship size (13).

During the study period, and until 50 years of age, the siblings had 9,480 children, whereas controls had 10,739 children. Overall, there were 229 multiple deliveries including two triplets among controls' children.

Twinning Rates. Brothers of patients with testicular cancer were less likely to father opposite-sex twins than controls (for

Table 2. Twinning rates among brothers and sisters of patients with testicular cancer

Type of delivery	Siblings of patients with testicular cancer	Controls	OR (95% CI)*	Born <1990	Born in 1990+
Men					
Singleton (no.)	4,339	5,088	1.00	1.00	1.00
Unlike-sex twins	11	23	0.53 (0.26-1.09)	0.61 (0.21-1.80)	0.48 (0.18-1.26)
Same-sex twins	33	37	1.00 (0.62-1.60)	1.08 (0.57-2.08)	0.90 (0.45-1.79)
Unlike-sex twinning rate (per 1,000 births)	2.5	4.5			
Women					
Singleton	4,915	5,417	1.00	1.00	1.00
Unlike-sex twins	19	14	1.41 (0.70-2.82)	1.55 (0.49-4.90)	1.35 (0.57-3.23)
Same-sex twins	50	42	1.27 (0.84-1.92)	1.24 (0.73-2.11)	1.34 (0.69-2.57)
Unlike-sex twinning rate (per 1,000 births)	3.8	2.6			

*OR adjusted by year of birth (continuous), parental age (continuous), and birth order (1, 2, 3+).

Table 3. Number of children among brothers and sisters of patients with testicular cancer

No. of children	Brothers of patients with testicular cancer (no.)	Controls (no.)	OR (95% CI)*	Sisters of patients with testicular cancer (no.)	Controls (no.)	OR (95% CI)*
0	193	218	1.00	116	120	1.00
1	159	199	0.91 (0.67-1.24)	130	163	0.86 (0.60-1.23)
2	396	489	0.88 (0.66-1.16)	430	531	0.88 (0.64-1.21)
3	202	293	0.78 (0.57-1.06)	254	282	0.98 (0.70-1.38)
4+	80	121	0.74 (0.51-1.08)	101	122	0.95 (0.64-1.41)
Linear trend	1,030	1,320	$P = 0.05$	1,031	1,218	$P = 0.72$

NOTE: Individuals born prior to 1954.
*OR adjusted by cohort and place of birth, socioeconomic status, single status, and sibship size.

unlike-sex twins, OR for the father being a sibling of testicular cancer patient was 0.53; 95% CI, 0.26-1.09), whereas there were no differences in the same-sex twinning rates (Table 2). Among women, both unlike-sex and opposite-sex twinning rates were similar between the children of the sisters of patients with testicular cancer and controls' offspring. Stratification by year of birth, either among men or among women, did not modify the OR estimates.

Number of Children. Analyses on number of children were restricted to the 2,061 siblings of patients with testicular cancer and 2,538 controls born prior to 1954, and alive at age 50 years, for whom information on virtually the whole reproductive life was available. The likelihood of being a brother of a patient with testicular cancer decreased monotonically with increasing number of children fathered ($P = 0.05$), whereas no such association was observed for the sisters of patients with testicular cancer (Table 3).

To disentangle between genes and shared early environment as an explanation for the decreased fertility among brothers of patients with testicular cancer, we carried out analyses stratifying by the age distance from the testicular cancer patient (index subject for controls). We found no clear effect of age distance (Table 4). Table 4 also summarizes the results of analyses stratified by sibship size. Among men, the strength of the association between number of children fathered and being a brother of a patient with testicular cancer increased with increasing sibship size.

Discussion

We have found that fertility is impaired among brothers, but not sisters, of patients with testicular cancer, measuring fertility both as the number of children and as unlike-sex twinning rates. Although associations were of borderline statistical significance only, results of the different indicators of fertility were consistent.

We used nationwide high-quality registers to identify study subjects as well as to collect data, and bias is an unlikely explanation of the results. There is a survival-dependent underascertainment of parents in the Multi-Generation Register, but because we included only subjects for whom both parents could be identified, and because the mortality in the age group we were studying was very low, this potential problem is not a relevant issue in our study.

Whereas the lack of a direct measure of male fertility is the major weakness of this study, the use of two different indirect measures is a strength. The hypothesis that dizygotic twinning rate is a measure of sperm quality and male reproductive health has recently been supported by empirical evidence (14). Among women, on the other hand, the level of follicle stimulating hormones—determined by genetic, individual, or environmental factors—plays a central role in causing double ovulation (15). We identified dizygotic twins through unlike-sex twins, which introduced an underestimation of the dizygotic twinning rates. Overall twinning rates were slightly >1%, which is consistent with Swedish population data (16). Thus, although our study is nationwide, the absolute number of twins is low, resulting in low statistical power to detect associations.

For some reason, we find the data altogether persuasive of an actually decreased fertility among brothers of men with testicular cancer. First, unlike-sex twinning is unaffected by social status, and we were able to adjust for birth order and maternal age (paternal age was used as a proxy of maternal age), which are the two most important known predictors of dizygotic twinning. We found a nonsignificantly decreased

Table 4. Number of children among brothers and sisters of patients with testicular cancer, by selected characteristics

Characteristic	Brothers of patients with testicular cancer (no.)	OR (95% CI)*	Sisters of patients with testicular cancer (no.)	OR (95% CI)*
Age distance with the testicular cancer patient				
10+ years older	164	0.96 (0.79-1.17)	166	0.92 (0.74-1.15)
2 to 9 years older	407	0.94 (0.82-1.06)	433	0.96 (0.85-1.09)
2 to 0 years older	168	0.86 (0.70-1.07)	162	1.16 (0.92-1.45)
1 to 2 years younger	143	1.02 (0.80-1.28)	118	1.01 (0.78-1.30)
3 to 4 years younger	79	0.74 (0.55-1.00)	95	1.25 (0.92-1.72)
5+ years younger	69	1.09 (0.79-1.50)	57	1.19 (0.82-1.75)
Sibship size				
2	242	0.99 (0.83-1.18)	237	1.39 (1.15-1.70)
3	316	0.99 (0.85-1.15)	312	0.93 (0.79-1.10)
4	220	0.91 (0.76-1.09)	210	0.95 (0.79-1.14)
5+	280	0.84 (0.73-0.97)	284	0.95 (0.82-1.10)

NOTE: Individuals born prior to 1954.
*OR adjusted by cohort and place of birth, socioeconomic status, single status, and when applicable, sibship size.

rate of unlike-sex twinning. Second, the association of number of children with being a brother of a patient with testicular cancer had a regular trend, although number of children is influenced more by social factors other than twinning. Third, had the association with number of children been explained by differences in social factors, we would likely have seen a similar association among sisters. The fact that the association with decreased number of children was stronger among men coming from large sibships—a category that would be expected to have higher fecundity—is somewhat of further support to decreased fertility being a true finding.

It has recently been established that the fertility of patients with testicular cancer is impaired prior to the diagnosis of testicular cancer. Case-control studies with questionnaire-based information on past fertility have, in general, found an association (5, 17-19), although there are exceptions (20, 21). Three register-based studies conducted in Scandinavian countries found a decreased fertility among testicular cancer cases, already evident ten years before diagnosis (6, 22, 23). A cohort study conducted among men who received a semen analysis for fertility problems found an overall excess risk for testicular cancer of 60% (95% CI, 30-90%), which was 80% in the first 2 years after the first semen analysis, but was 30% >11 years following it (4). Although the association is established, the direction of causality between cancer and subfertility is not yet clear, because an early undetected tumor may affect testicular function. The results of the present study implicate that fertility problems prior to diagnosis are not just a sign of an emerging tumor, providing arguments in favor of shared causes between subfertility and testicular cancer. This also gives some support to the notion of a testicular dysgenesis syndrome. However, apart from direct evidence from studies of the contralateral testis of patients with testicular cancer (24), there are still several assumptions implicit in the notion that need to be substantiated to conclude that it really exists. For instance, there is no established association between hypospadias and testicular cancer.

If the association between fraternal testicular cancer and decreased fertility will be confirmed, it would be of interest to understand whether it is explained by a genetic link or by shared environment. We aimed to address this question by stratifying the analysis by age distance to the brother affected with testicular cancer, assuming that if shared early environment were the explanation, the fertility among those born shortly before or after the affected brother could be more influenced. The underlying assumption is that if the relevant exposures change over time, siblings born within a short period of time are more likely to be similarly exposed. We found no heterogeneity between age-distance strata, and because this is no sensitive way of disentangling between genes and the environment, no conclusion can be drawn from the lack of association.

Although there are no studies similar to this, there is some indirect support for our results in the literature. In the countries around the Baltic Sea, where testicular cancer incidence varies markedly, there are studies reporting parallel descriptive patterns with respect to semen variables (25, 26). Moreover, testicular cancer (27-30) and subfertility (31, 32) both have familial components, with indications of a recessive mode of inheritance. Studies conducted both in Sweden (29) and in other populations (27, 33) have found increased risks of testicular cancer of 2- to 4-fold among testicular cancer patients' father/son, and by 8- to 10-fold among patients' brothers. Little is known about possible susceptibility genes. Among the few positive findings, the locus *Xq27* has been identified in a study of several families with at least two testicular cancer patients (34). The role of the Y chromosome, which is directly involved in spermatogenesis and male fertility, in sporadic testicular cancers is currently being investigated (35, 36).

In summary, we report decreased fertility among brothers of patients with testicular cancer. The finding argues in favor of shared causes between cancer-associated subfertility and testicular cancer, and give some support to the notion of a testicular dysgenesis syndrome, but it remains to be elucidated whether these causes are genetic or environmental.

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