Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer

BRIEF COMMUNICATIONS

Fecundity and Twinning Rates as Measures of Fertility Before Diagnosis of Germ-Cell Testicular Cancer

Lorenzo Richiardi, Olof Akre, Scott M. Montgomery, Mats Lambe, Ulrik Kvist, Anders Ekbom

Previous studies have suggested an association between subfertility and testicular cancer by using fecundity and semen characteristics to measure fertility. The occurrence of twinning in offspring may be used to investigate male reproductive health, because dizygotic twinning is reduced by male subfertility. We therefore assessed number of children and offspring twinning rates among 4592 Swedish patients with testicular cancer and 12 254 control subjects. Before diagnosis, case patients had a decreased number of children (for testicular cancer, odds ratio [OR] = 0.71, 95% confidence interval [CI] = 0.62 to 0.81; at least three children compared with no children), with a lower frequency of dizygotic twinning (for unlike-sex twins, OR for the father having testicular cancer = 0.49, 95% CI = 0.22 to 1.08). The ratio of unlike-sex to same-sex twins was 0.22 among children of case patients and 0.66 among children of control subjects (adjusted *P* = .03, two-sided Wald test). We also found an increased occurrence of twinning after diagnosis, probably attributable to treatment for iatrogenic subfertility. Our study strongly supports evidence of an association between subfertility and the subsequent risk for testicular cancer. [J Natl Cancer Inst 2004;96:145–7]

It has been suggested that the increased occurrence of testicular cancer and the alleged decline in male fertility are attributable to the same exposure(s) *(1)*. In support of this hypothesis, observational studies have demonstrated associations between a small number of children fathered *(2)* or abnormal semen characteristics *(3)* and the risk of testicular cancer.

Twinning rates can be used as a measure of reproductive health, because dizygotic twinning, but not monozygotic twinning, is reduced by male subfertility *(4)*. Dizygotic twinning rates can be estimated by the occurrence of unlike-sex twins. Unlike the number of children, the twinning rate has the advantage that it is not influenced by decisions about family size.

We therefore assessed the number of children and unlike-sex twins fathered by men who subsequently developed testicular cancer. These two variables are independent indicators of fertility, and they permitted us to evaluate the previously reported association between low fecundity and the risk of testicular cancer.

We used the Swedish Cancer Registry to identify patients with germ-cell testicular cancer [International Classification of Diseases, 7th Revision (ICD-7), code 178 *(5)*] who were diagnosed between January 1, 1958, and December 31, 1998; were born after 1915; and were 18–54 years old at diagnosis. Male control subjects, matched on year of birth, age, and county, were identified through the Swedish Register of Population and Population Changes. We used the Swedish Multi-Generation Registry, which lists known relations between first-degree relatives for citizens born after 1931 who were alive in 1961 *(6)*, to obtain information on date of birth and sex of offspring fathered between January 1, 1932, and February 28, 2000, by case patients and control subjects. Information on fathers and siblings was used to exclude case patients (1.6%) with familial testicular cancer. Information included in the Swedish Register of Population and Population Changes allowed exclusion of subjects with incomplete follow-up because of migration. The study was approved by the Ethics Committee at the Karolinska Institutet.

We identified 4592 case patients and 12 254 control subjects. Two periods were considered: 1) up to 6 months before diagnosis and 2) at least 2 years after diagnosis. The date of diagnosis for each case patient was used as the time reference for the corresponding control subjects. Analyses on number of children were restricted to the first period, because subjects' date of death was unknown. During both periods, 5518 children were fathered by case patients and 18 038 children were fathered by control subjects. Multiple deliveries were identified as siblings born in the same 3-day interval who shared the same father. In total, there were 238 multiple births, including one set of triplets among the children of case patients and two sets of triplets among the children of control subjects. Ninety-eight (41%) of the 238 multiple births were unlike-sex twins.

Odds ratios (ORs) and 95% confidence intervals (CIs) for testicular cancer according to number of children were estimated with unconditional logistic regression *(7)*. Among children of case patients and control subjects, we estimated the odds ratio for being unlike-sex twins according to the case–control status of the father. In addition, we calculated the ratio of unlike-sex to same-sex twins, which is an attenuated measure of the dizygotic/monozygotic twin ratio, because dizygotic twins can be of the same sex. Because *in vitro* fertilization began to influence twinning rates in Sweden in the 1990s *(8)*, we performed further analyses stratifying by year of birth of offspring, with 1990 as the threshold. Finally, because a decreased proportion of males was previously found among the offspring of patients with testicular cancer *(9)*, but not among the offspring of subfertile men *(10)*, we calculated and compared the sex ratio among singletons born to case

Affiliations of authors: Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (LR, ML); Unit of Cancer Epidemiology, Centro Ricerca Medicina Sperimentale (CeRMS) and Center for Oncologic Prevention, University of Turin, Turin, Italy (LR); Clinical Epidemiology Unit, Department of Medicine (OA, SMM, AE), Andrology Center, Department of Woman and Child Health (UK), Karolinska Hospital, Stockholm; Department of Epidemiology, Harvard School of Public Health, Boston, MA (AE).

Correspondence to: Lorenzo Richiardi, MD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden (e-mail: lorenzo.richiardi@meb.ki.se).

See "Note" following "References."

DOI: 10.1093/jnci/djh012

Journal of the National Cancer Institute, Vol. 96, No. 2,

Table 1. Basic characteristics of study subjects (Sweden, 1958–1998)

Characteristic	No. of case patients (%)*	No. of control subjects (%)*
Year of birth		
Before 1945	1667 (36)	4108 (34)
1945–1954	1217 (27)	3353 (27)
1955–1964	1068 (23)	3021 (25)
1965–1974	586 (13)	1635 (13)
1975 or after	54 (1)	137 (1)
Study area		
Largest Swedish cities†	1843 (40)	4895 (40)
Northern Sweden	696 (15)	1948 (16)
Southern Sweden	2053 (45)	5411 (44)

*Age at diagnosis among case patients was 33.7 ± 8.58 years (mean ± standard deviation), and age at recruitment among control subjects was 33.5 ± 8.51 years.

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

patients and control subjects. All statistical tests were two-sided.

Table 1 summarizes basic characteristics of the study subjects. The risk of testicular cancer decreased monotonically with increasing number of children fathered before diagnosis (Table 2; OR for testicular cancer = 0.71, 95% CI = 0.62 to 0.81, for at least three children compared with no children). There were no major differences between case patients with seminoma and case patients with nonseminoma, the two major histologic types of testicular cancer, and lag times of 4 or 10 years before diagnosis changed risk estimates only marginally.

Before diagnosis, offspring of case patients were less likely to be unlike-sex twins than offspring of control subjects (for unlike-sex twins, OR for the father having testicular cancer = 0.49, 95% CI = 0.22 to 1.08; Table 3). The ratio of unlike-sex to same-sex twins was 0.22 among children of case patients and 0.66 among children of control subjects (adjusted P for difference = .03, two-sided Wald test). Changing the lag time before diagnosis from 6 months to 4 years did not substantially alter the estimates (for unlike-sex twins, OR for the father having testicular cancer = 0.52, 95% CI = 0.15 to 1.77, from three and 17 sets of twins among children of case patients and control subjects, respectively). After 1989, the probability of being unlike-sex twins increased among offspring of case patients.

Analyses of the period after diagnosis revealed that children of case patients had a higher probability of being unlike-sex twins. The association was stronger among children born after 1989. The ratio of unlike-sex twins to same-sex twins was similar among children of case patients (ratio = 1.23) and among children of control subjects (ratio = 1.06).

Singleton sex ratio was not altered before diagnosis of testicular cancer (percentage of males among children of case patients = 51.1% and that among children of control subjects = 50.9%; P = .85), and it was slightly reduced after diagnosis (49.2% and 51.8%, respectively; P = .14). In the latter analysis, we had an 80% power to detect a statistically significant reduction in the proportion of male children (α level = .05), if the male offspring proportion was 47% or less.

Subfertility, usually defined as at least 1 year of unprotected intercourse without conception *(11)*, may decrease the probability of having a child and of fathering unlike-sex twins. Our findings therefore indicate that fertility is impaired among men who will subsequently develop testicular cancer. Most causes of male subfertility are unknown, but genetic disorders, congenital diseases (including cryptorchidism), lifestyle factors (such as smoking and nutrition), medical procedures (including radiation and chemotherapy), and environmental exposures are, or may be, implicated in its etiology *(12,13)*.

An association between the number of children and the risk of testicular cancer has been reported previously *(2,3,9,14)*, whereas our findings on twinning rates are novel. A decreased occurrence of dizygotic twinning is associated with male subfertility because of the decreased ability of sperm to fertilize oocytes and to sustain their embryonic development. Furthermore, the difference in frequency of twinning before and after 1990, when use of *in vitro* fertilization techniques became common in Sweden, suggests that subfertility problems among future testicular cancer patients may, to some extent, have resulted in assisted reproduction. *In vitro* fertilization is a strong iatrogenic cause of twinning, mostly, but not exclusively, of the dizygotic type *(15)*.

Because testicular cancer occurs at young ages, subfertility after treatment is of concern for many patients, irrespective of its being iatrogenic or already present at the time of cancer diagnosis *(16,17)*. Our findings of a higher likelihood of twinning among patients with a history of testicular cancer probably reflect their need for assisted reproduction, including sperm banking followed by *in vitro* fertilization or intracytoplasmatic sperm injection techniques *(18)*.

Table 2. Association between number of children and risk for germ-cell testicular cancer (Sweden, 1958–1998)

No. of children	6 months before diagnosis*		4 years before diagnosis*		10 years before diagnosis*	
	No. of case patients	OR (95% CI)	No. of case patients	OR (95% CI)	No. of case patients	OR (95% CI)
0	2331	1.00 (referent)	2760	1.00 (referent)	3417	1.00 (referent)
1	802	0.84 (0.76 to 0.93)	694	0.81 (0.73 to 0.90)	544	0.88 (0.78 to 0.99)
2	997	0.77 (0.70 to 0.85)	797	0.78 (0.70 to 0.87)	464	0.80 (0.70 to 0.91)
≥3	462	0.71 (0.62 to 0.81)	341	0.72 (0.62 to 0.83)	167	0.69 (0.57 to 0.85)

*The number of case patients and the odds ratio (OR) adjusted for year of birth, age at diagnosis/recruitment (2-year age groups), and study area (three categories = the largest Swedish cities [Stockholm, Göteborg, and Malmö], northern Sweden, and southern Sweden) were shown. For all time groups, P for linear trend <.001, two-sided Wald test. CI = confidence interval.

Table 3. Association of unlike-sex birth with paternal germ-cell testicular cancer (Sweden, 1958–1998)

Type of delivery	Case patients	Control subjects	Odds ratio (95% confidence interval)*		
			Entire period	Born before 1990	Born in 1990 or after
Before diagnosis (≥6 mo)					
Singleton, No.	4316	12 542	1.00 (referent)	1.00 (referent)	1.00 (referent)
Unlike-sex twins, No.	7	42	0.49 (0.22 to 1.08)	0.40 (0.16 to 1.01)	1.08 (0.21 to 5.66)
Frequency, No. per 1000 births	1.6	3.3			
After diagnosis (≥2 y)					
Singleton, No.	1065	5154	1.00 (referent)	1.00 (referent)	1.00 (referent)
Unlike-sex twins, No.	16	33	2.03 (1.11 to 3.73)	1.53 (0.42 to 5.55)	2.10 (1.04 to 4.25)
Frequency, No. per 1000 births†	14.6	6.3			

*Odds ratios were adjusted for year of birth, paternal age (each 5-year increase), and number of older siblings (0 or ≥1, for the period before diagnosis; 0, 1, 2, or ≥3, for the period after diagnosis).

†Twin births are included in the denominator of the proportion.

To our knowledge, this is the largest study to investigate fertility before the diagnosis of testicular cancer. The use of population-based registries permitted us to decrease the likelihood of information bias. We did not have information on some possible confounders, such as socio-economic class or history of cryptorchidism, but the consistency of our results on the two independent indicators of fertility decreases the chance of spurious associations. Maternal parity and age influence dizygotic twinning rates *(19)*. We adjusted for the former variable in the analyses and used paternal age as a proxy for the latter variable.

In conclusion, our study strongly supports an association between male subfertility and the risk of subsequent testicular cancer, possibly indicating common etiologic risk factors, probably acting early in life, that interfere with spermatogenesis resulting in subfertility and/or testicular cancer.

References

(1) Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001;16:972–8.

(2) Moller H, Skakkebaek NE. Risk of testicular cancer in subfertile men: case-control study. BMJ 1999;318:559–62.

(3) Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE, et al. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ 2000; 321:789–92.

(4) Tong S, Caddy D, Short RV. Use of dizygotic to monozygotic twinning ratio as a measure of fertility. Lancet 1997;349:843–5.

(5) International Classification of Diseases. Manual of the international statistical classification of diseases, injuries, and causes of death. Vol 1, 7th ed. Geneva (Switzerland): World Health Organization; 1957. p.86.

(6) Statistics Sweden. Bakgrundsfakta till befolknings-och välfärdsstatistik. The Multi-Generation Registry. Örebro (Sweden): Statistska Centralbyrån (SCB); 2001. p. 22–29.

(7) Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. IARC Sci Publ;(32):5–338.

(8) Bergh T, Ericson A, Hillensjo T, Nygren KG, Wennerholm UB. Deliveries and children born after in-vitro fertilisation in Sweden 1982–95: a retrospective cohort study. Lancet 1999;354:1579–85.

(9) Jacobsen R, Bostofte E, Engholm G, Hansen J, Skakkebaek NE, Moller H. Fertility and offspring sex ratio of men who develop testicular cancer: a record linkage study. Hum Reprod 2000;15:1958–61.

(10) Jacobsen R, Bostofte E, Skakkebaek NE, Hansen J, Moller H. Offspring sex ratio of subfertile men and men with abnormal sperm characteristics. Hum Reprod 2000;15:2369–70.

(11) Evers JL. Female subfertility. Lancet 2002; 360:151–9.

(12) de Kretser DM. Male infertility. Lancet 1997;349:787–90.

(13) Wong WY, Thomas CM, Merkus JM, Zielhuis GA, Steegers-Theunissen RP. Male factor subfertility: possible causes and the impact of nutritional factors. Fertil Steril 2000; 73:435–42.

(14) Fossa SD, Kravdal O. Fertility in Norwegian testicular cancer patients. Br J Cancer 2000; 82:737–41.

(15) The ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000; 15:1856–64.

(16) Petersen PM, Skakkebaek NE, Rorth M, Giwercman A. Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. J Urol 1999;161: 822–6.

(17) Lampe H, Horwich A, Norman A, Nicholls J, Dearnaley DP. Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 1997;15:239–45.

(18) Hallak J, Kolettis PN, Sekhon VS, Thomas AJ Jr, Agarwal A. Sperm cryopreservation in patients with testicular cancer. Urology 1999;54:894–9.

(19) Tong S, Short RV. Dizygotic twinning as a measure of human fertility. Hum Reprod 1998;13:95–8.

Notes

Partially supported by the Special Project "Oncology," Compagnia San Paolo/Fondazione Internationale Ricerca Medicina Sperimentale (FIRMS), Turin, Italy.

Manuscript received June 24, 2003; revised November 12, 2003; accepted November 26, 2003.