Fertility and offspring sex ratio of men who develop testicular cancer: a record linkage study

Rune Jacobsen1,6, Erik Bostofte2, Gerda Engholm1, Johnni Hansen3, Niels E.Skakkebæk4 and Henrik Møller5

1Centre for Research in Health & Social Statistics, Sejrsgade 11, DK-2100, 2The Sperm Analysis Laboratory, Health Service Physicians Organisation, Pilestræde, Copenhagen, 3Institute of Cancer Epidemiology, The Danish Cancer Society, Strandboulevarden 49, Box 839, DK-2100, 4Department of Growth and Reproduction, National University Hospital, Blegdamsvej 9, DK-2100, Denmark and 5Thames Cancer Registry, Guy’s, King’s and St Thomas’ School of Medicine, 42 Weston Street, London SE1 3QD, UK

6To whom correspondence should be addressed at: Department of Epidemiology, Institute of Public Health, Faculty of Health Sciences, University of Copenhagen, Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark.
Email: R.jacobsen@pubhealth.ku.dk

Analysis of associations between testicular cancer, subfertility and offspring sex ratio (proportion of males born among newborns) was performed on 3530 Danish men, born 1945–1980, who developed testicular cancer in the period 1960–1993. As the basis of comparison we used the total population of Danish men born in the period 1945–1980 (n = 1 488 957) and their biological children (n = 1 250 989). Men who developed testicular cancer had, prior to the cancer diagnosis, a reduced fertility (standardized fertility rate ratio: 0.93, 95% confidence interval: 0.89–0.97) and a significantly lower proportion of boys (48.9%, P = 0.02) compared with the general population (51.3%). The reduction in fertility was more pronounced in men with non-seminoma but the reduction in offspring sex ratio was independent of histological type. This confirms earlier results from less conclusive studies and indicates that testicular cancer, male subfertility and a female-biased sex ratio among new-born infants are characteristics of male reproduction that are linked by biological mechanisms.

Key words: cohort study/fertility/sex ratio/testicular cancer

Introduction

The increase in incidence of testicular cancer (Coleman et al., 1993; Adami et al., 1994; Forman and Møller, 1994), the decrease in the sex ratio (proportion of males among newborn infants) in many populations (Møller, 1996, 1998) and the possible decrease in semen quality (Carlsen et al., 1992; Swan et al., 1997) lead to the question whether these temporal trends are independent phenomena or, alternatively, are somehow connected to each other (James, 1997; Møller, 1998). Data from a Danish case–control study of testicular cancer, based on interviews with 514 cases and 720 controls, suggested a strong association between subfertility and subsequent risk of testicular cancer (Møller and Skakkebæk 1999), and produced evidence that men who develop testicular cancer have a lower offspring sex ratio than other men, thus suggesting that testicular cancer, subfertility and low offspring sex ratio are interdependent. However, other studies have found no association between testicular cancer and subfertility (Swerdlow et al., 1989) or between testicular cancer and low offspring sex ratio (Swerdlow et al., 1989; Heimdal et al., 1996). The present paper addresses the hypothesis that there is an association between testicular cancer, subfertility and offspring sex ratio using data on a large complete and unselected cohort of 3530 Danish men who developed testicular cancer. This larger study eliminates the potential problems with interview-based case–control studies: information bias due to differential recall or reporting, and selection bias due to non-participation.

Materials and methods

The population of Danish men born 1945–1980 who developed testicular cancer in the period 1960–1993 was identified in the Danish Cancer Registry, which holds information on all cases of cancer in the Danish population (Storm, 1991). The information from the Danish Cancer Registry was linked with data on reproduction from the Fertility Database at Statistics Denmark (Knudsen, 1998). The study population comprised 3530 men who developed testicular cancer and the total population of Danish men born in the period 1945–1980, regardless of whether they had children or not (n = 1 488 957), served as the basis of comparison.

The number of children of the men who developed testicular cancer was 3661 and the number of children of men in the comparison group was 1 250 989. The analyses included both live-born and still-born biological children. The men who were married to the biological mother were identified as the man to whom the biological mother was married or with whom she was living by January 1st in the year of birth of the child. For each child, information was available on sex and date of birth. For each man, information was available on date of birth, date of testicular cancer diagnosis, histological type of testicular cancer and date of death. For each child, information was available on sex and date of birth. The analysis was conducted for the testicular cancer group as a whole and separately for the histological groups seminoma and non-seminoma.

Fertility rate ratios and offspring sex ratios were calculated for the periods: (i) up to 8 full calendar years before testicular cancer diagnosis, (ii) from 8 years before until 4 years before testicular cancer diagnosis, (iii) from 4 years before testicular cancer until
2 years before testicular cancer diagnosis. Offspring sex ratios were further calculated from 2 years before until 2 years after testicular cancer diagnosis, and from two years after testicular cancer and onwards. Age and year of birth of the man (in 5 year groups) were included as co-variates in all analyses. Fertility rates were analysed as a function of the covariates using multiplicative Poisson regression models (Breslow and Day, 1987), and fertility rate ratios and 95% confidence intervals (CI) were thereby estimated. The analyses of the proportion of male offspring were similarly carried out by logistic regression analysis (Breslow and Day, 1980). In the analysis of fertility rates, the best fit to the data was obtained by a Poisson regression model that included an interaction term between age and year of birth. This interaction was due to an increase in age-specific fertility with increasing year of birth. Inclusion or exclusion of the interaction term, however, had no material influence on the analysis of fertility in men who developed testicular cancer. The analysis of offspring sex ratios was carried out with a logistic regression model that included age and year of birth as co-variates. As in the analysis of fertility, the estimated parameters were robust to the details of model parameterization. All statistical analyses were done using the SAS 6.12 package (SAS, 1996).

**Results**

The average age at diagnosis and average age at first child for men who developed testicular cancer were 31.2 and 27.0 years respectively. For all Danish men the mean age at first child was 26.6 years. The percentage multiple births were 1.0 and 1.1% and the percentage still-births were 1.1 and 1.2% for men who developed testicular cancer and for all Danish men respectively. The interaction between age and year of birth of the man was due to men in the more recent birth cohorts having children later in life. The inclusion of the interaction term improved the goodness of fit but had no influence on the fertility rate ratio or sex ratio estimates when compared to models only including age and year of birth of the man as separate effects.

Fertility rate ratios in men who developed testicular cancer compared with all men are shown in Table I. Prior to testicular cancer diagnosis, the fertility rate ratios of men who subsequently developed testicular cancer were significantly reduced in the period up to 2 years before testicular cancer diagnosis (fertility rate ratio: 0.93), more strongly so in men who developed non-seminoma (0.87) than seminoma (0.97).

Stratification of the period prior to testicular cancer showed the same overall lower fertility even though not significant in some categories (Table I). For both histological groups of testicular cancer the general pattern of fertility in relation to the time of testicular cancer diagnosis was the same.

Table II shows that men who developed testicular cancer had an offspring sex ratio that was lower than the expected value of 51.3% male offspring ($P = 0.01$), both overall (49.2%) and in the strata defined by time relative to testicular cancer diagnosis. Results were similar for seminoma and non-seminoma.

**Discussion**

The present register-based, complete and unselected study of Danish men found rather strong and internally robust associations between low fertility and testicular cancer (particularly non-seminoma), and between low offspring sex ratio and testicular cancer. Men who developed testicular cancer had a lower fertility before the time of diagnosis, and when they had children they had daughters more often than other men. The reduction in offspring sex ratio from 51.3 to 49.2% males is a rather strong effect in comparison with other sources of variation in this parameter (Jacobsen et al., 1999). These observations confirm previous findings from a smaller Danish case–control study, which had detailed information on a number of relevant covariates (e.g. cryptorchidism, duration of education, homosexuality, cohabitation with a woman) and effectively ruled these out as possible explanations for the observed association with subfertility (Møller and Skakkebak, 1999).

Our results are consistent with the hypothesis that the temporal trends in testicular cancer incidence (Coleman et al., 1993; Adami et al., 1994; Forman and Møller, 1994), sex ratio among new-born infants (Møller, 1996, 1998) and (less certain) male subfertility (Carlsen et al., 1992; Swen et al., 1997) are not merely separate, unrelated phenomena, but characteristics of male reproduction that are linked by biological mechanisms. The relatively strong and statistically robust associations point towards the existence of common factors acting on the male reproductive system, probably prior to reproductive age, which

### Table I. Fertility rate ratios for men who developed testicular cancer in relation to period from testicular cancer diagnosis

<table>
<thead>
<tr>
<th>Period from testicular cancer diagnosis (years)</th>
<th>Histological type of testicular cancer</th>
<th>Fertility rate ratio and 95% CI</th>
<th>P</th>
<th>No. of children</th>
<th>Fertility rate ratio and 95% CI</th>
<th>P</th>
<th>No. of children</th>
<th>Fertility rate ratio and 95% CI</th>
<th>P</th>
<th>No. of children</th>
<th>Fertility rate ratio and 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>-32 to -8</td>
<td>Seminoma (n = 1607)</td>
<td>0.98 (0.91–1.05) NS</td>
<td></td>
<td>789</td>
<td>0.98 (0.91–1.05) NS</td>
<td></td>
<td>354</td>
<td>0.86 (0.80–0.92) P</td>
<td></td>
<td>214</td>
<td>0.95 (0.87–1.05) NS</td>
<td></td>
</tr>
<tr>
<td>-8 to -4</td>
<td>Non-seminoma (n = 1835)</td>
<td>0.97 (0.92–1.02) NS</td>
<td></td>
<td>403</td>
<td>0.95 (0.87–1.05) NS</td>
<td></td>
<td>255</td>
<td>0.84 (0.74–0.95) &lt; 0.01</td>
<td></td>
<td>170</td>
<td>0.95 (0.83–1.09) NS</td>
<td></td>
</tr>
<tr>
<td>-4 to -2</td>
<td>Total (n = 3530) a</td>
<td>0.95 (0.90–1.01) NS</td>
<td></td>
<td>1169</td>
<td>0.95 (0.90–1.01) NS</td>
<td></td>
<td>674</td>
<td>0.91 (0.84–0.98) 0.01</td>
<td></td>
<td>393</td>
<td>0.92 (0.83–1.02) NS</td>
<td></td>
</tr>
<tr>
<td>-32 to -2</td>
<td></td>
<td></td>
<td></td>
<td>1406</td>
<td>0.87 (0.81–0.94) 0.01</td>
<td></td>
<td>2236</td>
<td>0.93 (0.89–0.97) &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aIncludes 88 cases with unspecified histology.

bCompared with paternal fertility rates in the total Danish population, adjusted for paternal age and year of birth and their interaction.

CI = confidence interval; NS = not significant.
Table II. Offspring sex ratios for men who developed testicular cancer in relation to period from testicular cancer diagnosis

<table>
<thead>
<tr>
<th>Period from testicular cancer diagnosis (years)</th>
<th>Histological type of testicular cancer</th>
<th>Non-seminoma (n = 1835)</th>
<th>Total (n = 3530)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seminoma (n = 1607)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of children</td>
<td>% boys\textsuperscript{b}</td>
<td>P</td>
</tr>
<tr>
<td>-32 to -8</td>
<td>789</td>
<td>49.2</td>
<td>NS</td>
</tr>
<tr>
<td>-8 to -4</td>
<td>403</td>
<td>48.4</td>
<td>NS</td>
</tr>
<tr>
<td>-4 to -2</td>
<td>214</td>
<td>48.9</td>
<td>NS</td>
</tr>
<tr>
<td>Subtotal (-32 to -2)</td>
<td>1406</td>
<td>48.9</td>
<td>NS</td>
</tr>
<tr>
<td>-2 to +2</td>
<td>290</td>
<td>51.0</td>
<td>NS</td>
</tr>
<tr>
<td>+2 to +34</td>
<td>276</td>
<td>45.7</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>1972</td>
<td>48.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Includes 88 cases with unspecified histology.

\textsuperscript{b}Compared with a value of 51.3% based on 1 250 989 children, adjusting for paternal age and year of birth. NS = not significant.

lead to the constitutional characteristic of high testicular cancer risk, subfertility and low offspring sex ratio.

There are strong clues that testicular cancer is a process that starts in utero. The incidence of testicular cancer among men born during the second world war in Denmark, Norway and Sweden was markedly lower than in men born before and after the war (Bergström et al., 1996; Möller and Skakkebæk 1997). Associations with low birthweight (Møller et al., 1994) and congenital malformations of the male genital organs (United Kingdom Testicular Cancer Study Group, 1994; Möller et al., 1995) indicate that the causes of testicular cancer probably act early in fetal life. In addition, the carcinoma in-situ cells (precursor of seminomas and non-seminomas) have several characteristics of fetal germ cells (Skakkebæk et al., 1987). The relevant factors remain to be identified, but it has been postulated that maternal oestrogens or other agents that can disrupt normal hormonal conditions in the developing male fetus may be involved (Sharpe and Skakkebæk, 1993).

Low offspring sex ratio has been proposed as an indicator of male reproductive hazards, particularly in occupationally exposed groups (James, 1996a). One chemical compound, the pesticide dibromochloropropane (DBCP), is known to lead to subfertility and low offspring sex ratio in exposed adult men (Potashnik et al., 1984). Exposure to the dioxin TCDD in the population of Seveso in Italy was associated with a low sex ratio among offspring (Mocarelli, 1993). Neither of these two exposures is a good candidate to explain the associations between testicular cancer, male subfertility and low sex ratios, but these findings point to the possible existence of relevant biological mechanisms, yet to be elucidated.

One possible explanation for low offspring sex ratio of men who develop testicular cancer could be a hormonal imbalance of men with carcinoma in-situ. Low concentrations of testosterone in men with contralateral carcinoma in-situ among testicular cancer patients before their treatment (Petersen et al., 1999). If the low testosterone levels are not merely a consequence of the cancer itself but represent a more permanent condition related to bilateral carcinoma in-situ, this could explain the observed lower sex ratio in the present study, as low testosterone concentrations have been associated with a low sex ratio among offspring (James, 1996b).

The measure of fertility used in the present study was the number of children born fathered by each man. This is not a perfect measure as men could, for example, choose not to have children for reasons other than fertility problems. If this misclassification is non-differential, then the resulting bias, on average, would be towards the null. The classification of men’s biological children in the study is based on the men’s relationship to the mother of the child. This could lead to misclassification of some children due to donor insemination or due to the man not being the biological father for other reasons. However, this misclassification would again decrease differences between the testicular cancer cohort and the population, rather than increase them.

Good registration systems exist in many populations for the monitoring of testicular cancer incidence and births of male and female infants. While medical treatment for involuntary childlessness is certainly increasing, no correspondingly good registration system exists for subfertility. If a general association between subfertility and low offspring sex ratio can be confirmed by future research, the infant sex ratio may potentially be a useful epidemiological tool for research in the causes of both testicular cancer and male subfertility.

References


Fertility, offspring sex ratio and testicular cancer


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