Risk of testicular cancer in men with abnormal semen characteristics: cohort study

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Abstract

Objective To explore the associations between semen characteristics and subsequent risk of testicular cancer.
Design Cohort study.
Participants 32 442 men who had a semen analysis done at the Sperm Analysis Laboratory in Copenhagen during 1963-95.
Main outcome measure Standardised incidence ratios of testicular cancer compared with total population of Danish men.
Results Men in couples with fertility problems were more likely to develop testicular cancer than other men (89 cases, standardised incidence ratio 1.6; 95% confidence interval 1.3 to 1.9). The risk was relatively constant with increasing time between semen analysis and cancer diagnosis. Analysis according to specific semen characteristics showed that low semen concentration (standardised incidence ratio 2.3), poor motility of the spermatozoa (2.5), and high proportion of morphologically abnormal spermatozoa (3.0) were all associated with an increased risk of testicular cancer. The only other cancer group that showed increased incidence was "peritoneum and other digestive organs" (six cases; 3.7, 1.3 to 8.0). Of these, two cases were probably and two cases were possibly extragonadal germ cell tumours.
Conclusions The results point towards the existence of common aetiological factors for low semen quality and testicular cancer. Low semen quality may also be associated with increased incidence of extragonadal germ cell tumours.

Introduction

Over recent decades a possible decrease in semen quality[1 2] and an increase in the incidence of testicular cancer have been reported in many populations.[3–5] It is unclear whether these temporal trends are independent phenomena or somehow connected to each other.[6–8] Case-control studies on subfertility and subsequent risk of testicular cancer have given conflicting results.[8 9] However, a recent Danish population based cohort study found an increased risk of testicular cancer in men with few children for their age.[10] These findings supported the results of an earlier Danish case-control study.[8] Both of these Danish studies used the number of children fathered at a given age as the measure of fertility. Thus some men with normal reproductive potential will inevitably have been classified as having low relative fertility because they had no or few children for reasons that were unrelated to their fertility. Subfertility can be measured more directly by analysis of semen for characteristics such as spermatocyte concentration, motility, and morphology.[11 12]

Men with testicular cancer often have abnormal semen characteristics,[13 14] but the association between abnormal semen characteristics and testicular cancer has not been investigated prospectively. We studied the incidence of testicular cancer in relation to semen characteristics in 32 442 men who had semen analysis at the Sperm Analysis Laboratory in Copenhagen during 1963-95.

Participants and methods

We linked information on all men in couples with fertility problems who had a semen analysis done at the Sperm Analysis Laboratory in Copenhagen during 1963-95 (n = 32 442) with data in the Danish Cancer Registry, which holds information on all cases of cancer in the Danish population from 1943 to 1995.[15] Men who visited the laboratory for other reasons (such as semen analysis after vasectomy) were excluded from the analysis. The Copenhagen laboratory is one of several public semen analysis laboratories in Denmark and examines semen samples mostly from men in the area of Copenhagen. Men are referred to the clinic by general practitioners and urologists, and the investigations are paid for through the public health system. Men with cancer before the date of semen analysis were excluded. For men who had multiple semen tests only their first test was used in the analysis. Similarly, only the first cancer diagnosis in a given man was included in the analysis. The methods used for analysis of semen (sperm concentration and motility and proportion of morphologically abnormal spermatozoa) have been described previously.[16] For each man we also obtained information on date of birth, dates of birth of his children, and date of death from the Central Population Register and the National Death Register.

We calculated the expected numbers of cancer cases in the cohort (by multiplying years at risk with primary cancer rates in the Danish population) and

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Table 1 Standardised incidence ratios and 95% confidence intervals for different cancers in cohort of 32 442 men having sperm analysis in Copenhagen, 1963-95

Type of cancer	Observed No of cases	Expected No of cases	Standardised incidence ratio (95% CI)
All malignant neoplasms	481	452.6	1.1 (1.0 to 1.2)
Peritoneum and other digestive organs	6	1.6	3.7 (1.3 to 8.0)*
Testis	89	57.1	1.6 (1.3 to 1.9)*
Others	386	393.3	1.0 (0.9 to 1.1)

*P<0.05.

standardised incidence ratios and 95% confidence intervals using a Fortran computer program.[17] The standardised incidence ratios were calculated for each type of cancer by time since first semen analysis, stratifying by semen characteristics according to standard definitions of subfertility.[12] The group of azoospermic men was divided into those with and without children in order to address the possibility that some azoospermic men had not given information on sterilisation or other circumstances resulting in a sudden azoospermia. To examine the separate and joint effects of the three semen characteristics, the cohort was stratified into groups according to their combination of semen measures.

Results

Overall, the cohort members had an increased risk of testicular cancer and of cancers of the peritoneum and other digestive organs (table 1). Risk of other types of cancer was not increased in the cohort. Eighty nine men developed testicular cancer, giving a standardised incidence ratio of 1.6 (95% confidence interval 1.3 to 1.9). Of these 89 men, 50 had seminomas (standardised incidence ratio 1.5, 1.1 to 1.9), 37 had non-seminomas (1.8, 1.2 to 2.4), and two were unspecified. For cancer of the peritoneum and other digestive organs the standardised incidence ratio was 3.7 (1.3 to 8.0) based on six observed cases. The standardised incidence ratio for cancers of all other sites combined was 1.0 (0.9 to 1.1).

Table 2 shows the standardised incidence ratios for testicular cancer stratified by time between first semen analysis and cancer diagnosis. The highest risk of testicular cancer was in the first two years after the first semen analysis (standardised incidence ratio 1.8). The risk was 1.5-1.6 for two to 11 years after the first semen analysis and 1.3 for more than 11 years since first semen analysis. The trend in the standardised incidence ratios over the four periods of follow up was not significant (P = 0.46).

Table 2 Standardised incidence ratios and 95% confidence intervals for testicular cancer, stratified by time since semen analysis

Time between semen analysis and diagnosis (years)	Observed No of cases	Expected No of cases	Standardised incidence ratio (95% CI)
0-2	23	12.8	1.8 (1.1 to 2.7)*
-6	30	20.1	1.5 (1.0 to 2.1)*
-11	24	15.3	1.6 (1.0 to 2.3)*
>11	12	9.0	1.3 (0.7 to 2.3)
Trend			P=0.46

*P<0.05.

Table 3 shows the standardised incidence ratios of testicular cancer, stratified by measures of semen quality. In univariate analyses, low semen concentration, poor semen mobility, and a high proportion of abnormal spermatozoa were all associated with increased standardised incidence ratios, whereas the groups with normal semen characteristics had standardised incidence ratios closer to unity. The azoospermic men who had fathered children before semen analysis showed lower risk of testicular cancer than azoospermic men without children (standardised incidence ratio 2.0 *v* 5.3). Men who were not azoospermic but who had sperm concentrations of 20 million/ml or lower had a higher risk of testicular cancer than men with concentrations above 20 million/ml (standardised incidence ratio 2.3 *v* 1.1).

Table 3 Standardised incidence ratios and 95% confidence intervals for testicular cancer according to semen characteristics

Variable	Total No of men	Observed No of cases	Expected No of cases	Standardised incidence ratio (95% CI)
Concentration (10^6/ml)				
0 and no children before analysis	1 031	7	2.0	3.5 (1.4 to 7.2)*
0 and children before analysis	1 644	6	3.0	2.0 (0.7 to 4.3)
0-20	10 509	33	14.4	2.3 (1.6 to 3.2)*
>20	18 668	42	36.9	1.1 (0.8 to 1.5)
Not available	590	1	0.8	1.3 (0.0 to 7.0)
Motility†				
Poor	1 312	7	2.8	2.5 (1.0 to 5.2)*
Good	19 362	44	28.0	1.6 (1.1 to 2.1)*
Not available	9 093	25	21.3	1.2 (0.8 to 1.7)
Proportion abnormal (%)†				
>75	528	4	1.4	3.0 (0.8 to 7.6)
0-75	27 618	64	47.8	1.3 (1.0 to 1.7)*
Not available	1 621	8	2.9	2.7 (1.2 to 5.4)*

*P<0.05. †Excluding 2675 azoospermic men.

The univariate, separate, and joint effects of the three semen quality measures were analysed in the subgroup of 29 177 men who had some spermatozoa in the semen sample (table 4). The separate effect of low concentration on the risk of testicular cancer was roughly the same as the univariate effect (standardised incidence ratio 2.1 and 2.3, respectively). Of 10 509 men with low semen concentration, 9187 had low concentration as the only abnormal characteristic. Very few men had poor motility only or a high proportion of abnormal spermatozoa only, and no case of testicular cancer was observed in these groups. We therefore could not identify a separate effect of poor motility or of having a high proportion of abnormal spermatozoa. However, the risk of testicular cancer increased with increasing number of subfertility measures present. The standardised incidence ratio was 1.9 for one subfertility measure, 2.7 for two measures, and 9.3 for all three subfertility measures.

Table 5 gives the details of the six cases of cancer in the peritoneum and other digestive organs. Case 1 may have had a testicular cancer before his leukaemia, which probably was treatment induced. An extragonadal germ cell tumour is also possible for case 2, who had increased concentrations of tumour markers. The notifications suggest that cases 3 and 5 had extragonadal germ cell tumours. Cases 4 and 6 seemed unlikely to have had extragonadal germ cell cancers.

Table 4 Separate and joint effects of three semen quality measures on risk of testicular cancer among 29 177 men with some spermatozoa in semen

Variable	Total No of men	Observed No of cases	Expected No of cases	Standardised incidence ratio (95% CI)
Univariate effects				
Low concentration ($\leq 20\times10^6$/ml)	10 509	33	14.5	2.3 (1.6 to 3.2)*
Poor motility	1 298	7	2.8	2.5 (1.0 to 5.2)*
Many abnormal (>75%)	528	4	1.4	3.0 (0.8 to 7.6)
Separate effects				
Low concentration (only)	9 187	24	11.6	2.1 (1.3 to 3.1)*
Low motility (only)	187	0	0.4	—
Many abnormal (only)	213	0	0.6	—
Other	19 590	52	39.5	1.3 (1.0 to 1.7)
Joint effects				
One subfertility measure	9 587	24	12.6	1.9 (1.2 to 2.8)*
Two subfertility measures	1 251	7	2.6	2.7 (1.1 to 5.5)*
Three subfertility measures	82	2	0.2	9.3 (1.0 to 33.4)
Other	18 257	43	36.7	1.2 (0.9 to 1.6)

*P<0.05.

Discussion

Our retrospective cohort study, based on more than 30 000 men in infertile couples, found a strong association between subfertility and subsequent risk of testicular cancer. All men of couples with fertility problems were 1.6 times more likely to develop testicular cancer than the Danish male population in general, and the increase was evident for both seminoma and non-seminoma. The overall analysis included some fully fertile men from couples in which only the woman was subfertile, and the observed higher risk of testicular cancer in the cohort overall would be even higher if only subfertile men were included. Men in the cohort with abnormal semen characteristics had a twofold to threefold increased risk. Our findings are consistent with the results of investigations into spermatogenesis in patients with unilateral testicular cancer[18] and risk of testicular cancer in men considered subfertile on the basis of a low number of children for their age.[8 10]

The observation that men with unilateral testicular cancer have impaired spermatogenesis[18] does not preclude the possibility that impaired reproductive capacity is secondary to the cancer. We found that the risk of testicular cancer was relatively constant with increasing time since semen analysis. Impaired spermatogenesis may therefore have been present many years before testicular cancer was diagnosed, pointing towards a permanent state of impaired spermatogenesis.

Our use of semen characteristics to assess subfertility eliminates the misclassification problems in studies based on numbers of children, where men with normal reproductive potential who have no or few children for other reasons may bias the result towards unity. All together, the available data point towards the existence of common risk factors for impaired spermatogenesis and testicular cancer.

Some evidence suggests that testicular cancer has its origin in fetal life. Incidence of testicular cancer is lower among men born during the second world war than men born before and after the war in Denmark, Norway, and Sweden.[19–21] Other risk factors for testicular cancer, such as low birth weight[22] and congenital malformations of the testes,[23 24] also support a fetal origin for testicular cancer. In addition, carcinoma in situ (the precursor of both seminomas and non-seminomas) has several characteristics in common with fetal germ cells.[25] The specific aetiological factors in testicular cancer are unknown, but maternal oestrogens and hormonal disrupting agents have been proposed as causal factors acting on the male fetus.[26 27]

What is already known on this topic

The incidence of testicular cancer has increased in the past 50 years, and some evidence suggests that sperm quality has decreased in the same period

Common aetiological factors may exist for testicular cancer and male subfertility

What this study adds

This study confirms that incidence of testicular cancer is increased in men with few children for their age

The association between testicular cancer and abnormal semen characteristics is statistically robust and consistent with the hypothesis of a common aetiology

Abnormal semen characteristics may be associated with extragonadal germ cell tumours

Table 5 Evaluation of the six cases of cancers of peritoneum and other digestive organs based on notification forms received from Danish Cancer Registry

Case	Year of birth	Age (years): At semen analysis	Age (years): At cancer diagnosis	Age (years): At death	Topography	Morphology	Comment, based on notification forms	Consistent with extragonadal germ cell cancer?
1	1949	30	39	45	1580 Retroperitoneum	90643 Germinoma	Uncertain diagnosis. Died 1994 from leukaemia. Notification indicates "leukaemia secondary to testicular cancer"	Possibly
2	1953	19	30	—	1580 Retroperitoneum	81403 Adenocarcinoma, not otherwise specified	Uncertain diagnosis. Notification form indicates: "partly differentiated adenocarcinoma" as well as "extragonadal germ cell tumour" and "tumour marker concentrations increased"	Possibly
3	1956	32	33	34	1580 Retroperitoneum	80003 Neoplasm unclassified, malignant	Three notifications suggest extragonadal germ cell tumour	Probably
4	1926	52	68	68	1589 Peritoneum	99903 No microscopic confirmation; clinically benign tumour	Metastatic tumour of unknown origin	Unlikely
5	1948	29	35	—	1580 Retroperitoneum	90803 Teratoma, malignant, not otherwise specified	Diagnosis on notification form is: "extragonadal germ cell tumour" and "embryonal carcinoma." Testicular biopsy samples were negative for carcinoma in situ	Probably
6	1950	30	33	34	1580 Retroperitoneum	88003 Sarcoma, not otherwise specified	Sarcoma, not otherwise specified	Unlikely

We also found an increased risk of cancer of the peritoneum and other digestive organs. One explanation for this association is that some of the observed cancers in this category were misclassified testicular or extragonadal germ cell tumours. Extragonadal germ cell tumours have been associated with testicular carcinoma in situ,[28 29] suggesting a common aetiology with testicular cancer.

From a public health perspective, our study provides some reassurance to men identified with abnormal semen characteristics, despite the increased relative risks. The absolute excess of cancers is about 36 cases per 32 442 men followed for 297 750 person years. The absolute increase in risk for the individual is therefore very small.

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1 Carlsen E, Giwercman A, Keiding N, Skakkebæk NE. Evidence for decreasing quality of semen during past 50 years. *BMJ* 1992;305:609-13.
2 Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A reanalysis of global trend data. *Environ Health Perspect* 1997;105:1228-32.
3 Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. *Trends in cancer incidence and mortality*. Lyons: International Agency for Research on Cancer, 1993. (IARC Scientific Publication No 121.)
4 Forman D, Møller H. Testicular cancer. *Cancer Surv* 1994;19-20:323-41.
5 Adami HO, Bergström R, Mohner M, Zatonski W, Storm H, Ekbom A, et al. Testicular cancer in nine northern European countries. *Int J Cancer* 1994;59:33-8.
6 James WH. Secular trends in monitors of reproductive hazard. *Hum Reprod* 1997;12:417-21.
7 Møller H. Trends in sex-ratio, testicular cancer and male reproductive hazards: are they connected? *APMIS* 1998;106:232-39.
8 Møller H, Skakkebæk NE. Risk of testicular cancer in subfertile men: case-control study. *BMJ* 1999;318:559-62.
9 Swerdlow AJ, Huttly SR, Smith PG. Testis cancer: post-natal hormonal factors, sexual behaviour and fertility. *Int J Cancer* 1989;43:549-53.
10 Jabsen R, Antoniades B, Bostofte E, Engholm G, Hansen J, Skakkebaek NE, et al. Fertility and offspring sex ratio of men who develop testicular cancer: a record linkage study. *Hum Reprod* 2000;15:1958-61.
11 Bostofte E, Serup J, Rebbe H, Interrelations among the characteristics of human semen, and a new system for classification of male infertility. *Fertil Steril* 1989;41:95-102.
12 World Health Organization. *Laboratory manual for examination of human semen and sperm-cervical mucus interaction*. Cambridge: Cambridge University Press, 1999.
13 Nijman JM, Schraffordt Koops H, Kremer J, Willemse PHB, Sleijfer DT, Oldhoff J. Fertility and hormonal function in patients with nonseminomatous tumor of the testis. *Arch Andrology* 1985;14:239-46.
14 Carroll P, Whitmore WF Jr, Herr HW, Morse MJ, Sogani PC, Bajorunas D, et al. Endocrine and exocrine profiles of men with testicular tumors before orchidectomy. *J Urol* 1987;137:420-3.
15 Storm HH. *The Danish Cancer Registry, a self-reporting national cancer registration system with elements of active data collection*. Lyons: International Agency for Research on Cancer, 1991:220-36. (IARC Scientific Publication No 95.)
16 Bostofte E, Bagger P, Michael A, Stakemann G. Fertility prognosis for infertile men: results of follow-up study of semen analysis in infertile men from two different populations evaluated by the Cox regression model. *Fertil Steril* 1990;54:1100-6.
17 Coleman M, Douglas A, Hermon C, Peto J. Cohort study analysis with a Fortran computer program. *Int J Epidemiol* 1986;15:134-7.
18 Berthelsen JG, Skakkebæk NE. Gonadal function in men with testis cancer. *Fertil Steril* 1983;39:68-75.
19 Møller H. Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. *Eur Urol* 1993;23:8-13.
20 Bergström R, Adami HO, Mohner M, Zatonski W, Storm H, Ekbom A, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. *J Natl Cancer Inst* 1996;88:727-33.
21 Wanderås EH, Grotmol T, Fossa SD, Tretli S. Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective population- and register-based study on Norwegian males born between 1967 and 1995. *Cancer Causes Control* 1998;9:475-86.
22 Møller H, Skakkebæk NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. *Cancer Causes Control* 1997;8:904-12.
23 United Kingdom Testicular Cancer Study Group. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. *BMJ* 1994;308:1393-9.
24 Møller H, Prener A, Skakkebæk NE. Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: Case control studies in Denmark. *Cancer Causes Control* 1995;7:264-74.
25 Skakkebæk NE, Berthelsen JG, Giwercman A, Müller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumors except spermacytoma. *Int J Andrology* 1987;10:19-28.
26 Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993;341:1392-5.
27 Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. *Int J Cancer* 1979;23:598-602.
28 Daugaard G, Rorth M, von der Maase H, Skakkebaek NE. Management of extragonadal germ-cell tumors and the significance of bilateral testicular biopsies. *Ann Oncol* 1992;3:283-9.
29 Daugaard G, von der Maase H, Olsen J, Rorth M, Skakkebaek NE, Carcinoma-in-situ testis in patients with assumed extragonadal germ-cell tumours. *Lancet* 1987;ii:528-30.

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Towards evidence based circumcision of English boys: survey of trends in practice

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Introduction

Although the proportion of English boys circumcised for medical reasons fell from 35% in the early 1930s to 6.5% by the mid-1980s, even latterly it was argued that some two thirds underwent the procedure unnecessarily,[1] a judgment consistent with practice in Scandinavia, where less than 2% of boys are circumcised.[2] Has any further change occurred in English practice, and, if so, is this evidence based? We examined trends in the catchment population of a children's hospital, in its surrounding region, and in England as a whole.

Subjects, methods, and results

The study was confined to medically indicated operative circumcisions. Statistics for circumcisions for the NHS, including diagnostic codings, were obtained for the Mersey region and its health districts for 1975-97 and for England for 1984-6 and 1990-8. Data for 1996-8 may slightly underestimate the number of procedures performed.[3] Corresponding population figures were supplied by the Office for National Statistics. The catchment population of the Liverpool children's hospital has been taken as that of the Liverpool and Sefton health districts.

During the study period, similar proportions of procedures were indicated for phimosis in the Mersey region (89.5%) and in England as whole (90.2%). Rates of circumcision, overall and stratified by age, are shown in the figure. During the earlier years these rates differed little between the Mersey region and the Liverpool children's hospital, and by the mid-1980s both overall rates closely matched the figure for all