Cancer Causes and Control 1996, 7, pp. 264–274

Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: case-control studies in Denmark

Henrik Møller, Anne Prener, and Niels Erik Skakkebæk

(Received 11 July 1995; accepted in revised form 20 November 1995)

To explore risk factors for testicular cancer and cryptorchidism, two parallel case-control studies were conducted in Denmark. The testicular cancer study was population-based and included 514 cases and 720 controls. The cryptorchidism study included 387 cases and 416 controls and was based on two hospital series of men treated for cryptorchidism and a control group sampled among residents in the Copenhagen area. The 2,037 men were interviewed by telephone. The relative risk (RR) of testicular cancer in men with treated or persisting cryptorchidism was 3.6 (95 percent confidence interval = 1.8-6.9), but no increase in risk was seen in the six to seven percent of the men who reported a history of undescended testes that descended spontaneously. The RR in men who were treated for cryptorchidism increased with age at treatment. This effect may be due wholly or in part to increased treatment of boys with testes that would have descended spontaneously if they had not been treated. Cryptorchidism and inguinal hernia may be confused and reported interchangeably. In the absence of cryptorchidism or testicular atrophy, clinical inguinal hernia was not associated with testicular cancer. Testicular atrophy was associated with both testicular cancer and cryptorchidism. Associations with other congenital malformations were few and based on small numbers. *Cancer Causes and Control* 1996, 7, 264-274

Keywords: Cryptorchidism, Denmark, inguinal hernia, men, testicular atrophy, testicular neoplasms.

Introduction

Testicular cancer is the most common type of cancer in young men in Denmark. The incidence rate in the Danish population is among the highest in the world, and increased from 3.1 per 100,000 around 1945 to 8.9 per 100,000 around 1990.[1] The etiology of testicular cancer is poorly understood, and the only commonly occurring, consistent risk factor is cryptorchidism, *i.e.*, undescended testes.[2-16] Among less consistent risk factors are certain other malformations or abnormalities of the genital organs, including inguinal hernia,[2,5,7,16] and atrophic testes.[14,17,18] A number of rare abnormalities also have been associated with an increased risk, including testicular torsion,[19] hydrocele,[7,20,21] varicocele,[22] x-linked ichthyosis,[23] and different intersex conditions.[24-26]

These findings, together with the descriptive epidemiologic data[1] and biologic insights in the process of testicular carcinogenesis,[27] suggest that important etiologic factors for testicular cancer operate during the period of embryonic development. Case-control studies have shown associations with factors relating to the man him-

Henrik Møller is at the Center for Research in Health and Social Statistics, Copenhagen, Denmark. Authors were also affiliated with The Danish Cancer Registry at The Danish Cancer Society, Copenhagen, Denmark (Drs Møller and Prener), and with International Agency for Research on Cancer, Lyons, France (Dr Møller). Dr Skakkebæk is with the Department of Growth and Reproduction, National University Hospital, Copenhagen, Denmark. Address correspondence to Dr Møller, Center for Research in Health & Social Studies, Sejrøgade II, DK-2100 Copenhagen, Denmark. *The study was supported by grants from The Danish Cancer Society and The Danish Medical Research Council.*

self and with factors relating to his mother, such as exogenous estrogens or excessive nausea during the pregnancy,[3,6] bleeding during the pregnancy,[28] high body weight of the mother[6] , being the first-born child of the mother,[29,30] premature birth,[31] low birth weight,[6,28] early puberty of the man,[9,16] orchitis,[7,11,12] sexually transmitted diseases,[32] testicular trauma,[5,11,14,32] and a sedentary lifestyle of the man.[16]

In men with unilateral cryptorchidism, it has been found that there is an increased risk of testicular cancer in the normally descended testis, but the relative risk (RR) is not as high as in the non-descended one.[3,4,12,13,16,33,34] Further, epidemiologic studies of risk factors for cryptorchidism have suggested a pattern of prenatal risk factors similar to testicular cancer, *e.g.*, high levels of estrogens in the first trimester,[35-38] high body weight of the mother,[36,39] bleeding in the pregnancy,[40] threatened abortion,[41] premature birth,[37,39,40,42] low birth weight,[36,39,40,43-45] being the first-born child of the mother,[43,46] hypospadias,[44,46] and inguinal hernia.[43,47] These similarities suggest that the association between cryptorchidism and testicular cancer may be due to the existence of causal factors which are common to the two diseases. Henderson *et al*[3] suggested that exposure of the male embryo to estrogens could be one such possible common risk factor.

To explore common risk factors for testicular cancer and cryptorchidism, two case-control studies were conducted in parallel in Denmark. One was a population based case-control study of testicular cancer in the entire population of Denmark; the other was a case-control study with hospital based case ascertainment and population based sampling of controls in the Copenhagen area.

Materials and methods

The following four groups of men were approached:

(i) *Testicular cancer cases.* Cases were identified in the Danish Cancer Registry which since 1943 has recorded information on all cases of cancer in the Danish population.[48] We attempted to include as cases all men born in Denmark in the period from 1916 to 1970, who were given a diagnosis of testicular cancer in Denmark in the period 1986-88. Men with multiple occurrences of testicular cancer after 1986 were included in the study by the first tumor. Men who had had a first occurrence of testicular cancer before 1986 were not considered eligible;

(ii) *Controls, frequency matched to the testicular cancer cases by year of birth.* These men were identified in the Danish Central Population Register, which since 1968 has kept a computerized roster of the Danish population. The sampling frame consisted of all men born in Denmark between 1916 and 1970, who were alive at the time of inquiry. Men who had had testicular cancer diagnosed before 1986 were not considered eligible. Men with testicular cancer in 1986-88 were included as cases and were not considered eligible as controls;

(iii) *Cryptorchidism cases.* No population-based registry of men with cryptorchidism exists in Denmark, and these men were therefore identified through two hospital-based case series, previously described.[10,49] The first series (Series 1) consisted of 506 consecutive patients hospitalized for cryptorchidism in the period 1949-60 at Rigshospitalet in Copenhagen.[10] The second group (Series 2) consisted of 300 men who were admitted to one of three surgical departments in the Copenhagen area between 1964 and 1976, and who between 1984 and 1987 participated in a clinical study of testicular carcinoma *in situ* in adult men previously treated for cryptorchidism.[49] The men were considered eligible for the present study if they were born in Denmark between 1946 and 1970, alive at the time of inquiry, and not diagnosed with testicular cancer prior to 1988;

(iv) *Controls, frequency matched by year of birth to cryptorchidism cases.* These men were identified in the Danish Central Population Register. They had to be born in Denmark between 1946 and 1970 and had to be alive and residents of the greater Copenhagen area at the time of inquiry.

There were 698 incident cases of testicular cancer in Denmark in the period from 1986 to 1988 in men born from 1916 to 1970. Of these, 584 were approached and 514 participated. The reasons for not approaching 114 men were: 52 (seven percent) were dead; 23 (three percent) were born outside Denmark; three (zero percent) had emigrated; six (one percent) had had testicular cancer before 1986; 19 (three percent) were notified to the Danish Cancer Registry too late to be identified; and 11 (two percent) were missed in the manual retrieval of notification forms in the Cancer Registry. The interviewed testicular cancer cases cover 74 percent of the relevant total incidence of testicular cancer in Denmark, and the participation rate (interviewed/approached) among cases was 88 percent. Among 1,049 testicular cancer controls who were approached, 720 (69 percent) agreed to participate and were interviewed. According to the histology data collected routinely at the cancer registry, the 514 cases included 262 men with seminoma, 239 with non-seminoma and 13 with other or unspecified testicular cancers. Fifty-four and 46 percent of the tumors were in the right and left testis, respectively.

Of the 806 cases of cryptorchidism available, 549 were born in the period 1946 to 1970. Of these, 506 were approached and 387 (76 percent) participated. Of the 43 men who were not approached, 23 were dead at the time of inquiry, 11 had emigrated, three were born outside Denmark, and six had had testicular cancer in 1988 or earlier. As cryptorchidism controls, 556 men were approached and 416 (75 percent) participated.

All men were contacted by mail and asked to return a form on with they could indicate their telephone number and a convenient time to be called, or refuse to participate. Nonrespondants were sent a reminder and additionally were contacted by telephone if possible. Telephone interviews lasting 20 to 30 minutes were conducted in 1989-90 by specially trained personnel. The interview form provided a list of short, concise questions to be asked in a similar fashion to all participants. It was not possible to blind the interviewers with respect to the case-control status of the participants. The present article describes the analysis of information on cryptorchidism ('one or both testes not descended to the scrotum in early childhood'), inguinal hernia ('a rupture in the groin area'), testicular atrophy ('one testis much smaller than the other'), and other congenital malformations of the genital organs or other organs. The information was substantiated further with questions about laterality and treatment of the conditions, and the age at which they occurred.

The data were analyzed using contingency tables and unconditional logistic regression analysis.[50] Controls were frequency-matched to the cases, and the stratification variable year-of-birth (in nine categories) was included in all statistical analyses. The logistic regression analysis provides the odds ratio (OR) associated with a given risk factor or level of a categorical variable, along with its 95 percent confidence interval (CI). The ORs are estimates of the incidence rate ratio between individuals exposed to a given risk factor and unexposed individuals. Statistical tests for trends over several categories were carried out by assigning values 1, 2, 3, *etc.* to successive categories and including the resulting single variable in the regression analysis. Separate ORs for the effects of ipsilateral and contralateral cryptorchidism were calculated by a simple partitioning of the relative risk in unilateral cryptorchidism as described by Henderson *et al.*[3]

The population basis of the testicular cancer study ensures comparability of the cases and controls. This is not the situation in the cryptorchidism study in which the cases were residents in Copenhagen when they were children and the controls were residents in the Copenhagen area at the time of interview. The results for this study therefore were checked by restriction of the analysis to cryptorchidism cases and controls who, in the interview, stated that they were born in Copenhagen or had lived the greater part of their childhood there. In order not to compromise the population-based design of the testis cancer study, it was decided not to combine the two control groups.

A date of diagnosis was available for the testicular cancer cases. Men in the other three groups were assigned a date of diagnosis with a distribution equivalent to that among the testicular cancer cases, and all time-related exposures were truncated to the time before testicular cancer diagnosis in the cases or to the equivalent point in time for men in the other three groups.

Results

The association between testicular cancer and cryptorchidism is analyzed in Table 1. A history of cryptorchidism was reported by 15.8 percent of testicular cancer cases and 9.6 percent of controls, giving an OR of 1.6 (CI = 1.2-2.3). When cryptorchidism was subdivided into treated or persisting conditions and spontaneously descended testes, the increased risk was concentrated on treated or persisting cryptorchidism (6.6 percent of cases, 1.8 percent of controls; OR = 3.6; CI = 1.8-6.9), while there was hardly any increase in risk associated with spontaneously descended testes (8.0 percent of cases, 6.7 percent of controls; OR = 1.2, CI = 0.8-1.9).

Analysis by age at the time of treatment for cryptorchidism showed a tendency of increasing OR with increasing age ($P = 0.07$). A persisting non-descended testis in particular, was associated strongly with risk of testicular cancer (nine cases; one control; OR = 14.4, CI = 1.8-115.3).

The increased risk associated with treated or persisting cryptorchidism was higher in bilateral than in unilateral cryptorchidism (ORs were 4.9 and 2.9, respectively). Of the 21 cases with unilateral cryptorchidism, the cancer occurred in the undescended (ipsilateral) testis in 14 cases and in the normally descended (contralateral) testis in seven cases. The estimated relative risks (RR) of testicular cancer were, therefore, 3.9 in the ipsilateral testis and 1.9 in the contralateral testis. The associations with non-seminoma and seminoma were similar. In men with spontaneously descended testes, there was a tendency of increasing risk of testicular cancer with increasing age at spontaneous descent, but the trend was not statistically significant.

Table 2 shows the results regarding associations between testicular cancer and inguinal hernia and testicular atrophy. Inguinal hernia was associated weakly with testicular cancer overall (11.3 percent of cases, 9.3 percent of controls; OR = 1.4, CI = 1.0-2.1), but when restriction was made to reported inguinal hernia in the absence of cryptorchidism or testicular atrophy, the association dis-

Table 1. Testicular cancer risk in relation to cryptorchidism, Denmark

Cryptorchidism	Cases ($n=514$) %	Controls ($n=720$) %	OR[a]	(CI)[b]
No	78.2	83.2	1.0	—
Yes	15.8	9.6	1.6	(1.2-2.3)
Treated or persisting cryptorchidism	6.6	1.8	3.6	(1.8-6.9)
Age at time of treatment (yrs)				
0-9	0.4	0.3	1.1	(0.2-8.2)
10-14	3.1	1.0	2.9	(1.2-7.1)
15+	1.4	0.4	3.5	(0.9-13.8)
Persisting	1.8	0.1	14.4	(1.8-115.3)
			$P=0.07$[c]	
Extent of cryptorchidism				
Bilateral	2.1	0.4	4.9	(1.3-18.1)
Unilateral	4.1	1.4	2.9	(1.3-6.3)
Unknown extent	0.4	0.0	—	—
Histologic type				
Non-seminoma	6.7	1.8	3.3	(1.5-7.4)
Seminoma	6.5	1.8	3.8	(1.8-8.1)
Other and unspecified	7.7	1.8	4.6	(0.5-40.8)
Spontaneously descending testes	8.0	6.7	1.2	(0.8-1.9)
Age at time of spontaneous descent (yrs)				
0-9	1.9	2.2	0.8	(0.4-1.9)
10-14	3.1	2.6	1.3	(0.6-2.5)
15+	1.2	0.6	2.1	(0.6-7.6)
Unknown age	1.8	1.3	—	—
			$P=0.17$	
Extent of cryptorchidism				
Bilateral	1.2	1.5	0.8	(0.3-2.3)
Unilateral	5.1	3.6	1.4	(0.8-2.4)
Unknown extent	1.8	1.5	—	—
Histologic type				
Non-seminoma	9.2	6.7	1.4	(0.8-2.5)
Seminoma	7.3	6.7	1.1	(0.6-1.9)
Other and unspecified	0.0	6.7	—	—
Unknown status of treatment/descent	1.2	1.1	—	—
Unknown cryptorchidism	6.0	7.2	—	—

[a] OR = odds ratio.
[b] CI = 95% confidence interval.
[c] The categories '15+' and 'persisting' were combined in the trend test.

appeared (OR = 0.9, CI = 0.5-1.4). Testicular atrophy was associated with testicular cancer risk (OR = 3.2, CI = 2.3-4.5), and this association persisted after restriction to men who did not report cryptorchidism or inguinal hernia (12.1 percent of cases, 5.7 percent of controls; OR = 2.8; CI = 1.8-4.2). The smaller, atrophic testis was equally often the contralateral and the ipsilateral one; hence, the estimated RR applies to both testes. The association between testicular atrophy and testicular cancer depended on age at diagnosis. In men born 1916-45, 1946-55 and 1956-70, the RRs were 4.6, 2.5, and 1.7, respectively.

Self-reported hydrocele occurring after the age of 20 years was associated with testicular cancer. Varicocele before the age of 20 years tended to be associated with testicular cancer but the RR of 4.8 (CI = 0.5-43.6) was based on four cases only. There was no significant association with testicular torsion, hydrocele before the age of 20, varicocele after the age of 20, phimosis, hypospadia or other congenital malformations.

The results of the case-control study of cryptorchidism are described in Tables 3 and 4. Table 3 describes the frequency of self-report of cryptorchidism in these men who are known to have been treated for cryptorchidism. In the men from Series 1, 82.8 percent reported cryptorchidism and 79.0 percent reported treated or persisting cryptorchidism. Sixteen percent in this series reported no history of cryptorchidism. In Series 2, the distribution was different, with 97.0 percent reporting cryptorchidism, 90.0 percent reporting treated or persist-

Table 2. Testicular cancer risk in relation to inguinal hernia, testicular atrophy and other conditions and malformations, Denmark

	Cases (n=514) %	Controls (n=720) %	OR[a]	(CI)[b]
Inguinal hernia				
No	87.0	90.3	1.0	—
Yes	11.3	9.3	1.4	(1.0-2.1)
With cryptorchidism or testicular atrophy	5.8	1.7	3.7	(1.9-7.4)
Age in years:				
0-9	2.9	0.4	6.4	(1.8-22.5)
10+	2.7	1.1	3.0	(1.2-7.3)
Unknown age	0.2	0.1	—	—
Without cryptorchidism or testicular atrophy	5.4	7.6	0.9	(0.5-1.4)
Age in years:				
0-9	2.1	2.6	0.8	(0.4-1.7)
10+	3.3	4.6	1.0	(0.5-1.9)
Unknown age	0.0	0.4	—	—
Unknown inguinal hernia	1.8	0.4	—	—
Testicular atrophy				
No	70.4	87.1	1.0	—
Yes	21.8	8.5	3.2	(2.3-4.5)
With cryptorchidism or inguinal hernia	9.7	2.8	4.2	(2.4-7.1)
Without cryptorchidism or inguinal hernia	12.1	5.7	2.8	(1.8-4.2)
Unknown testicular atrophy	7.8	4.4	—	—
Testicular torsion	2.1	3.3	0.5	(0.3-1.1)
Hydrocele				
Age in years:				
0-19	1.4	1.0	1.3	(0.5-3.8)
20+	1.2	0.1	10.4	(1.2-88.4)
Unknown age	0.4	0.0	—	—
Varicocele				
Age in years:				
0-19	0.8	0.1	4.8	(0.5-43.6)
20+	1.4	0.8	1.9	(0.6-5.7)
Unknown age	0.0	0.1	—	—
Phimosis	7.6	6.9	1.0	(0.7-1.6)
Hypospadias	0.4	0.0	—	—
Other genital malformations	0.6	0.8	0.7	(0.2-2.9)
Malformations of any other organ	4.1	5.6	0.7	(0.4-1.3)

[a] OR = odds ratio.
[b] CI = 95% confidence kinterval.

ing cryptorchidism, and only 3.0 percent reporting no history of cryptorchidism. The distribution of answers in the cryptorchidism controls was similar to the distribution in the population based controls (Table 1).

Both inguinal hernia and testicular atrophy was associated with cryptorchidism (Table 4). The association with inguinal hernia, however, was much stronger in Series 1 (OR = 10.3) than in Series 2 (OR = 1.8). An association was seen between phimosis and cryptorchidism (OR = 1.6, CI = 1.0-2.5), and there were tendencies towards associations with hypospadia (OR = 4.8, CI = 0.5-43.1) and congenital malformations of organs other than the genital organs (OR = 1.7, CI = 1.0-3.0). The latter excess was not due to any particular type of malformation.

Discussion

Cryptorchidism and testicular cancer

The present data confirm the well-known association between cryptorchidism and testicular cancer. We note that the excess risk of testicular cancer is confined to the condition of treated or persisting cryptorchidism, and there is no association between spontaneously descended testes and testicular cancer[51] risk. Another case-control study of testicular cancer that was based on information from records from school health examinations found RRs of 5.2 (CI = 2.1-13.0) for treated or persisting cryptorchidism and 1.2 (CI = 0.6-2.6) for spontaneously descended testes. A survey of these school health-examination records in-

dicated cryptorchidism in 7.0 percent of 2,516 boys, which is comparable to our interview data.[52]

It is of particular interest to note the very high proportion (six to seven percent) of men in the Danish population who have a history of cryptorchidism, but in whom the testes descended spontaneously without any treatment. We are not in a position to clarify the exact nature of this condition. It may be similar or identical to ascending testes.[53] 'retractile testes,[54,55] or 'late descending testes.'[16] Some of these testes may not be truly ectopic, but merely located in a high position in the scrotum. Others may be ascending testes, *i.e.*, testes that were in the scrotum at the time of birth, but have ascended to a position high in the scrotum or at a position above the external ring. The existence of ascending testes is beyond doubt, but little is known about how frequently it occurs.

Villumsen and Zachau-Christensen[53] studied records of 4,300 boys who had the testes normally descended at birth and found, by examination at the age of three years, that 69 boys (1.6 percent) had one or both testes in an ectopic position. The investigators stated that they only considered a testis ectopic after painstaking attempts at manipulating the testis down into the scrotum. In a review of several studies, Scorer and Farrington[54] concluded that the apparent incidence of undescended testis in schoolboys was around six percent, with large variation between observers (two to nine percent). They suggested that the majority of these cases were testes that had been descended around the time of birth, but had later retracted (most commonly at the age of five to six years), and stated that such retracted testes in all cases descend again before or at the time of puberty. Our case-control data and the data from school health-examination records on 'spontaneously descended testes' fit well with the pattern of events suggested by Scorer and Farrington.

The high prevalence of spontaneously descended testes, and the increasing prevalence of men with treated cryptorchidism are important for our understanding of the strength of the association between cryptorchidism and testicular cancer, as well as the influence of the age at the time of treatment for cryptorchidism on the estimated RR. Our RR estimate of 3.6 (CI = 1.8-6.9) is lower than some[2,3,5-7,9,12-14,51] but not all[4,8] estimates from previous case-control studies, but agrees well with the results from another recent, large case-control study in the United Kingdom that reported an RR of 3.8 (CI = 2.2-6.5).[16] Two prospective cohort studies of the association between cryptorchidism and testicular cancer have yielded estimates of 4.7 (CI = 1.7-10.2) and 7.4 (CI = 2.0-19.0),[10,15] but both were based on a small number of cases. We propose that the move towards treatment of boys with cryptorchidism at an early age[56] may have contributed to the somewhat low RRs found in the most recent case-control studies. As, in the most recent years, more boys are treated at a young age, an increasing proportion of those treated may have had retractile testes that would have descended spontaneously if the boy had not been treated. Since these boys with spontaneously descended testes are at no increased risk of testicular cancer, their inclusion in the group classified as cases of cryptorchidism will have led to a dilution of the effect of true cryptorchidism.

Our data suggest that the increased risk of testicular cancer in men treated for cryptorchidism may depend on the age at the time of treatment for cryptorchidism. The excess risk seems to be stronger for men who were treated later rather than earlier in life, and a particularly high risk is indicated in the small group of men in whom the testes were persistently retained, *i.e.*, in men who were not treated or in whom the treatment was unsuccesful in bringing the testes down in the scrotum. Very similar data have been published previously in other case-control studies,[8,13,16] one of which validated the self-reported cryptorchidism against family doctor's notes.[16] It

Table 3. Self-reported history of cryptorchidism in two case series of men who are known to have been treated for cryptorchidism in childhood, Denmark

Cryptorchidism	Cases (n=157) Series 1		Cases (n=230) Series 2		Controls (n=416)	
	No.	%	No.	%	No.	%
No	25	15.9	7	3.0	350	84.1
Yes	130	82.8	223	97.0	30	7.2
Treated or persisting cryptorchidism	124	79.0	207	90.0	5	1.2
Spontaneously descening testes	4	2.5	16	7.0	24	5.8
Unknown treatment/descent	2	1.3	0	0.0	1	0.2
Unknown euyptorchidism	2	1.3	0	0.0	36	8.7

Table 4. Associations between cryptorchidism and inguinal hernia, testicular atrophy and other conditions and malformations, Denmark

	Cases (n=387) %	Controls (n=416) %	OR[a]	(CI)[b]
Inguinal hernia				
No	71.1	90.6	1.0	—
Yes	25.1	8.2	4.0	(2.6-6.1)
Cryptorchidism, series 1	39.5	8.2	10.3	(5.6-18.8)
Cryptorchidism, series 2	15.2	8.2	1.8	(1.1-3.2)
Unknown inguinal hernia	3.9	1.2	—	—
Testicular atrophy				
No	40.8	85.1	1.0	—
Yes	45.5	7.2	13.8	(8.9-21.3)
Cryptorchidism, series 1	45.2	7.2	11.9	(6.7-21.3)
Cryptorchidism, series 2	45.7	7.2	13.2	(7.7-22.3)
Unknown testicular atrophy	13.7	7.7	—	—
Testicular torsion	5.7	4.8	1.2	(0.6-2.2)
Hydrocele (age in yrs)				
0-19	2.1	1.7	1.2	(0.4-3.4)
20+	0.0	0.0	—	—
Unknown age	0.3	0.0	—	—
Varicocele (age in yrs)				
0-19	0.3	1.0	0.3	(0.0-2.3)
20+	0.8	0.0	—	—
Unknown age	0.3	0.0	—	—
Phimosis	13.2	8.9	1.6	(1.0-2.5)
Hypospadias	1.0	0.2	4.8	(0.5-43.1)
Other genital malformations	1.6	1.2	1.2	(0.4-4.1)
Malformations of any other organ	8.3	5.0	1.7	(1.0-3.0)

[a] OR=odds ratio.
[b] CI=95% confidence interval.

is possible that the high prevalence of spontaneously descended testes may contribute to this effect. If, as discussed above, the category of men who are considered to have a history of cryptorchidism also includes some proportion of men who were treated for a condition which would have resolved spontaneously and which is not associated with an increased risk of testicular cancer, then this proportion is likely to be greater in the group of men who were treated early than in the group who were treated later, and the result would be a trend in the RR with age at the time of treatment. In the present data, there is a tendency for the RR for cryptorchidism to be higher for the older than for the younger men (men born 1916-45: OR = 4.5; 1946-55: OR = 3.5; 1956-70: OR = 3.4).

We can imagine two different types of explanation for the association between cryptorchidism and testicular cancer. One possibility is that the risk of testicular cancer is a consequence of the abnormal position of the testis ('the position model'); the other possibility is that the association is due to the existence of common risk factors for cryptorchidism and testicular cancer ('the common cause model'). These models are clearly not mutually exclusive. Exposure of the embryo to maternal or exogenous estrogens has been proposed as a possible common cause of cryptorchidism and testicular cancer.[3,57] Other evidence in support of this explanation includes the associations between low birthweight and both testicular cancer and cryptorchidism,[6,28,36,39,40,43–45] which suggest that both testicular cancer and cryptorchidism may be consequences of a suboptimal pattern of growth of the embryo. A case can be made for a role of not only estrogens but also androgens and gonadotropins in causal pathways common to cryptorchidism and testicular cancer.[58] It should be noted, however, that although cryptorchidism is a consistent risk factor for testicular cancer, the proportion of testicular cancer cases that can be attributed statistically to cryptorchidism is not large, in the present data around five percent.

If the 'position model' is correct, we would expect a lower RR of testicular cancer in boys treated for cryptorchidism at an early age; if the 'common cause model' is correct, there should be no such trend. This argument, however, requires that any confounding effect of treatment of spontaneously descended testes could be ruled out or controlled accurately. If we turn to the effect of age at spontaneous descent of the testes on the RR of

testicular cancer, there is a weak tendency of a higher RR in men with a late spontaneous descent. This suggests that the increased risk of testicular cancer in cryptorchidism in some way is related to the abnormal position of the testis and hereby adds some weight to the interpretation that the association with age at the time of treatment for cryptorchidism as a real phenomenon. Finally, our data suggest that men with unilateral cryptorchidism have an increased risk of testicular cancer in the normally descended testicle although not as high as in the undescended one. This has been reported also in previous studies which addressed this question.[3,4,12,13,16,33,34] Taking all these observations into consideration, it seems possible that effects of both 'position' and 'common causes' may contribute to the association between cryptorchidism and testicular cancer.

Inguinal hernia

Inguinal hernia is an anatomic defect which may prevent normal testicular descent, and an inguinal hernia, whether clinically apparent or not, is found in a large proportion of boys operated for cryptorchidism.[59]

Inguinal hernia has been associated with an increased risk of testicular cancer in some studies,[2,5,7,16] but it remains to be established as a risk factor independent of cryptorchidism.[60] The present data show no excess risk of testicular cancer associated with a history of inguinal hernia in men who did not also report a history of cryptorchidism or testicular atrophy. Our data further indicate that spurious associations between inguinal hernia and testicular cancer can occur easily because of confusion of the two conditions when the data are obtained by interview. A strong association is seen in these data between inguinal hernia and cryptorchidism, but it is most pronounced in the cryptorchidism cases from Series 1, and much weaker in those from Series 2. An important difference between the two series is that the men in Series 1 were not informed as adults about their condition; the study in which they were followed was a record linkage without personal contact. The men in Series 2, in contrast, took part in clinical examinations as adults and were informed fully about their history of treatment for cryptorchidism. In consequence, the latter group reported inguinal hernia much less frequently than the former. Further, the proportion of men in Series 1 who reported not to have had cryptorchidism was higher than in Series 2, and a high proportion of the men who erroneously reported no history of cryptorchidism reported a history of inguinal hernia. These observations show that there is a great potential for confusion of the two conditions. The present data do not indicate any increase in risk of testicular cancer associated with a clinical history of inguinal hernia. Similarly, a cohort study in Sweden of 30,000 patients operated for inguinal hernia showed no increased risk of testicular cancer.[15]

Testicular atrophy

A history of testicular atrophy, as indicated by the response that one testis was much smaller than the other in childhood, was associated with a threefold increase in testicular cancer risk. The excess risk was not altered materially by stratification for cryptorchidism or inguinal hernia. Similar findings have been reported from one case-control study.[14] In testicular cancer patients, an association has been found between testicular atrophy and the presence of carcinoma *in situ* in the remaining, contralateral testicle.[17,18] This supports that the observed association in the present data is a real phenomenon. However, the finding that, in men with testicular atrophy who developed testicular cancer, a similar proportion of cases developed in the smaller and in the larger testicle raises the possibility that the association may be due in part to recall bias. In our data, the association between testicular atrophy and testicular cancer was strongest for older men. Oliver has suggested that testicular atrophy may be a common manifestation of several different causes of testicular cancer.[61]

As discussed above in the case of cryptorchidism and testicular cancer, association between atrophy and testicular cancer may occur if atrophy itself is a cause of testicular cancer, and/or if there are common causes of atrophy and testicular cancer. In the latter case, it is less surprising that testicular cancer seems to occur with equal frequency in the smaller and the larger testicle. The strongest evidence for the existence of common causes of testicular atrophy and testicular cancer come from studies of the contralateral testis in men who have had testicular cancer. It has been demonstrated clearly that there is an elevated risk of testicular malignancy in the contralateral testicle, both when assessed by the presence of carcinoma *in situ*[17,18] and invasive cancer.[62] The contralateral testicle is often atrophic. For example, Berthelsen and Skakkebæk,[63] in a study of 200 biopsies, found spermatogenic arrest in 10 percent, Sertoli cell-only histology in 12 percent, and hyalinized tubules in 11 percent, in addition to carcinoma *in situ* in 5 percent of the testes.[63] This suggests that atrophy frequently accompanies testicular cancer, in either the ipsilateral or the contralateral testis (or both). In certain individuals with severe gonadal dysgenesis (46,XY and 46XY/45X genotypes), the testes are atrophic and a high proportion develop cancer in the gonads.[26]

An association also was seen between testicular atrophy and cryptorchidism, and, in men with unilateral cryptorchidism, it was most often the undescended testicle that was reported to be the smaller one.

Other congenital malformations

Associations between both testicular cancer and cryptorchidism and other malformations were not found except for a report of hydrocele in adulthood which was associated with testicular cancer, and a weak association between phimosis and cryptorchidism. In our analysis, we excluded a record of hydrocele if it was within three years of the date of diagnosis of testicular cancer. Despite this, hydrocele possibly may occur as an early symptom of testicular cancer,[64] and a spurious association could be introduced hereby. The possibility of recall bias cannot be excluded either.

Most of the congenital malformations we analyzed are so rare that our study has little statistical power to detect associations when they exist. It therefore cannot be ruled out that some of the associations reported in other studies are true, but on the other hand, the few positive associations seen here and in other studies also may be the result of information bias or chance. The high proportions of men who report a history of testicular torsion is probably an artifact and due to a nonspecific question in the interview.

Conclusion

These data confirm the increased risk of testicular cancer in men with treated or persisting cryptorchidism. About five percent of testicular cancer in Denmark is attributable to cryptorchidism. The condition of spontaneous descending testes, which occurs in six to seven percent of Danish men, is not associated with an increased risk of testicular cancer. In men who were treated for cryptorchidism, the RR of testicular cancer increased with age at treatment for cryptorchidism. This effect may be due wholly or in part to increased treatment of boys with testes that would have descended spontaneously if they had not been treated.

In the absence of cryptorchidism or testicular atrophy, clinical inguinal hernia was not associated with testicular cancer. Our data from men who were known to have been treated for cryptorchidism show that cryptorchidism and inguinal hernia may be confused and reported interchangeably in an interview.

Acknowledgement —The authors acknowledge the contribution of the late Ole Møller Jensen to this work which was initiated and carried out under his leadership as Director of the Danish Cancer Registry.

References

1. Møller H. Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. *Eur Urol* 1993; **23**: 8-13.
2. Morrison AS. Cryptorchidism, hernia, and cancer of the testis. *JNCI* 1976; **56**: 731-3.
3. 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.
4. Schottenfeld D, Warshauer ME, Sherlock S, Zauber AG, Leder M, Payne R. The epidemiology of testicular cancer in young adults. *Am J Epidemiol* 1980; **112**: 232-46.
5. Coldman AJ, Elwood JM, Gallagher RP. Sports activities and risk of testicular cancer. *Br J Cancer* 1982; **46**: 749-56.
6. Depue RH, Pike MC, Henderson BE. Estrogen exposure during gestation and risk of testicular cancer. *JNCI* 1983; **71**: 1151-5.
7. Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. *Lancet* 1984; **i**: 207-10.
8. Pottern LM, Brown LM, Hoover RN, *et al*. Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. *JNCI* 1985; **74**: 377-81.
9. Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case-control study. *Am J Epidemiol* 1986; **124**: 39-52.
10. Giwercman A, Grindsted J, Hansen B, Jensen OM, Skakkebæk NE. Testicular cancer risk in boys with maldescended testis: a cohort study. *J Urol* 1987; **138**: 1214-6.
11. Brown LM, Pottern LM, Hoover RN. Testicular cancer in young men: the search for causes of the epidemic increase in the United States. *J Epidemiol Comm Health* 1987; **41**: 349-54.
12. Swerdlow AJ, Huttly SR, Smith PG. Testicular cancer and antecedent diseases. *Br J Cancer* 1987; **55**: 97-103.
13. Strader CH, Weiss NS, Daling JR, Karagas MR, McKnight B. Cryptorchism, orchiopexy, and the risk of testicular cancer. *Am J Epidemiol* 1988; **127**: 1013-8.
14. Haughey BP, Graham S, Brasure J, Zielezny M, Sufrin G, Burnett WS. The epidemiology of testicular cancer in upstate New York. *Am J Epidemiol* 1989; **130**: 25-36.
15. Pinczowski D, McLaughlin JK, Lackgren G, Adami HO, Persson I. Occurrence of testicular cancer in patients operated on for cryptorchidism and inguinal hernia. *J Urol* 1991; **146**: 1291-4.
16. 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.
17. Berthelsen JG, Skakkebæk NE, von der Maase H, Sørensen BL, Mogensen P. Screening for carcinoma in situ of the contralateral testis in patients with germinal testicular cancer. *Br Med J Clin Res Ed* 1982; **285**: 1683-6.
18. Harland SJ, Cook PA, Fossa SD, *et al*. Risk factors for carcinoma in situ of the contralateral testis in patients with testicular cancer. An interim report. *Eur Urol* 1993; **23**: 115-8.
19. Chilvers CE, Pike MC, Peckham MJ. Torsion of the testis: a new risk factor for testicular cancer. *Br J Cancer* 1987; **55**: 105-6.
20. Vahlensieck W, Weissbach L, Hildenbrand G. Five-year register and multicenter study for testicular tumours Bonn. *Int Urol Nephrol* 1984; **16**: 149-56.
21. Tollerud DJ, Blattner WA, Fraser MC, *et al*. Familial tes-

ticular cancer and urogenital developmental anomalies. *Cancer* 1985; **55**: 1849-54.
22. Karagas MR, Weiss NS, Strader CH, Daling JR. Elevated intrascrotal temperature and the incidence of testicular cancer in noncryptorchid men. *Am J Epidemiol* 1989; **129**: 1104-9.
23. Lykkesfeldt G, Bennett P, Lykkesfeldt AE, *et al*. Testis cancer. Ichthyosis constitutes a significant risk factor. *Cancer* 1991; **67**: 730-4.
24. Collins GM, Kim DU, Logrono R, Rickert RR, Zablow A, Breen JL. Pure seminoma arising in androgen insensitivity syndrome (testicular feminization syndrome): a case report and review of the literature. *Mod Pathol* 1993; **6**: 89-93.
25. Müller J, Skakkebæk NE. Gonadal malignancy in individuals with sex chromosome anomalies. *Birth Defects* 1990; **26**: 247-55.
26. Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia. *Cancer Genet Cytogenet* 1987; **25**: 191-218.
27. 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 tumours except spermatocytoma. *Int J Androl* 1987; **10**: 19-28.
28. Brown LM, Pottern LM, Hoover RN. Prenatal and perinatal risk factors for testicular cancer. *Cancer Res* 1986; **46**: 4812-6.
29. Swerdlow AJ, Huttly SR, Smith PG. Prenatal and familial associations of testicular cancer. *Br J Cancer* 1987; **55**: 571-7.
30. Prener A, Hsieh C-c, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes Control* 1992; **3**: 265-72.
31. Gershman ST, Stolley PD. A case-control study of testicular cancer using Connecticut tumour registry data. *Int J Epidemiol* 1988; **17**: 738-42.
32. UK Testicular Cancer Study Group. Social, behavioural and medical factors in the aetiology of testicular cancer: results from the UK study. *Br J Cancer* 1994; **70**: 513-20.
33. Depue RH, Pike MC, Henderson BE. Cryptorchidism and testicular cancer. *JNCI* 1986; **77**: 830-3.
34. Chilvers C, Pike MC. Epidemiology of undescended testis. In: Oliver RTD, Blandy JP, Hope-Stone HF, eds. *Urological and Genital Cancer*. Oxford, UK: Blackwell Scientific Publications; 1989; 306-21.
35. Coscrove MD, Benton B, Henderson BE. Male genitourinary abnormalities and maternal diethylstilbestrol. *J Urol* 1977; **117**: 220-2.
36. Depue RH. Maternal and gestational factors affecting the risk of cryptorchidism and inguinal hernia. *Int J Epidemiol* 1984; **13**: 311-8.
37. Depue RH. Cryptorchidism, and epidemiologic study with emphasis on the relationship to central nervous system dysfunction. *Teratology* 1988; **37**: 301-5.
38. Bernstein L, Pike MC, Depue RH, Ross RK, Moore JW, Henderson BE. Maternal hormone levels in early gestation of cryptorchid males: a case-control study. *Br J Cancer* 1988; **58**: 379-81.
39. Berkowitz GS, Lapinsky RH, Godbold JH, Dolgin SE, Holzman IR. Maternal and neonatal risk factors for cryptorchidism. *Epidemiology* 1995; **6**: 127-31.
40. Beard CM, Melton LJ, O'Fallon WM, Noller KL, Benson RC. Cryptorchism and maternal estrogen exposure. *Am J Epidemiol* 1984; **120**: 707-16.
41. Davies TW, Williams DR, Whitaker RH. Risk factors for undescended testis. *Int J Epidemiol* 1986; **15**: 197-201.
42. Bjoro K, Dybvik T. Testicular retention. Age at diagnosis and surgical correction at a county hospital. *Tidsskr Nor Laegeforen* 1984; **104**: 14-6.
43. Swerdlow AJ, Wood KH, Smith PG. A case-control study of the aetiology of cryptorchidism. *J Epidemiol Comm Health* 1983; **37**: 238-44.
44. John Radcliffe Hospital Cryptorchidism Study Group. Cryptorchidism: a prospective study of 7500 consecutive male births, 1984-8. *Arch Dis Child* 1992; **67**: 892-9.
45. Jackson MB. The epidemiology of cryptorchidism. John Radcliffe Hospital Cryptorchidism Research Group. *Horm Res* 1988; **30**: 153-6.
46. Hjertkvist M, Damber JE, Bergh A. Cryptorchidism: a registry based study in Sweden on some factors of possible aetiological importance. *J Epidemiol Comm Health* 1989; **43**: 324-9.
47. Mori M, Davies TW, Tsukamoto T, Kumamoto Y, Fukuda K. Maternal and other factors of cryptorchidism—a case-control study in Japan. *Kurume Med J* 1992; **39**: 53-60.
48. Storm HH. *The Danish Cancer Registry, a Self-reporting National Cancer Registration System with Elements of Active Data Collection*. Lyon, France: International Agency for Research on Cancer, 1991; IARC Sci Pub. No. **95**: 220-36.
49. Giwercman A, Bruun E, Frimodt Møller C, Skakkebæk NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol* 1989; **142**: 998-1001.
50. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume I. The Analysis of Case-control Studies*. Lyon, France: International Agency for Research on Cancer, 1980. IARC Sci Pub. No. **32**: 5-338.
51. Prener A, Engholm G, Jensen OM. Genital anomalies and risk for testicular cancer in Danish men. Epidemiology 1996 (in press).
52. Blom K. Undescended testis and time of spontaneous descent in 2516 schoolboys. *Ugeskr Laeger* 1984; **146**: 616-7.
53. Villumsen AL, Zachau-Christiansen B. Spontaneous alterations in position of the testes. *Arch Dis Childhood* 1966; **41**: 198-200.
54. Scorer CG, Farrington GH. *Congenital Deformities of the Testis and Epididymis*. London, UK: Butterworths, 1971.
55. Palmer JM. The undescended testicle. *Endocrinol Metab Clin North Am* 1991; **20**: 231-40.
56. Chilvers C, Pike MC, Forman D, Fogelman K, Wadsworth ME. Apparent doubling of frequency of undescended testis in England and Wales in 1962-81. *Lancet* 1984; **ii**: 330-2.
57. Sharpe RM, Skakkebæk NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993; **341**: 1392-5.

58. Rajpert-De Meyts E, Skakkebæk NE. The possible role of sex hormones in the development of testicular cancer. *Eur Urol* 1993; **23**: 54-9.
59. Lee PA. Fertility in cryptorchidism. Does treatment make a difference? *Endocrinol Metab Clin North Am* 1993; **22**: 479-90.
60. Forman D, Gallagher R, Møller H, Swerdlow TJ. Aetiology and epidemiology of testicular cancer: report of consensus group. *Prog Clin Biol Res* 1990; **357**: 245-53.
61. Oliver RT. Atrophy, hormones, genes and viruses in aetiology of germ cell tumours. *Cancer Surv* 1990; **9**: 263-86.
62. Østerlind A, Berthelsen JG, Abildgaard N, *et al*. Risk of bilateral testicular germ cell cancer in Denmark: 1960-1984. *JNCI* 1991; **83**: 1391-5.
63. Berthelsen JG, Skakkebæk NE. Gonadal function in men with testis cancer. *Fertil Steril* 1983; **39**: 68-75.
64. Swerdlow AJ, Huttly SR, Smith PG. Testicular cancer and antecedent diseases. *Br J Cancer* 1987; **55**: 97-103.