

# Undescended testis and the risk of testicular cancer: importance of source and classification of exposure information

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<b>Background</b>	The strength of the association between undescended testis and testicular cancer varies considerably across studies. Here we report the effect of various classifications of self-reported history of undescended testis and different data sources on the estimates of the risk of testicular cancer from a case-control study.
<b>Methods</b>	We performed a population-based case-control study including 269 testicular cancer cases and 797 controls matched on age and region. Medical history was assessed by interviews (index persons) and mailed questionnaires (mothers). We used conditional logistic regression to calculate odds ratios (OR) and kappa coefficients to assess agreement between different sources of information.
<b>Results</b>	Odds ratios for testicular cancer ranged between 2.4 and 5.4 based on the sons' self-reports and between 1.1 and 1.9 based on the mothers' reports. The agreement between the sons and mothers on undescended, gliding or retractile testis was fair (kappa 0.53) and was good when these conditions were treated by surgery (kappa 0.89). The rating of a history of undescended testis by two urologists was fair (kappa 0.54).
<b>Conclusions</b>	The questionnaire design, the classifications of undescended testis and data sources have an important impact on the OR for the association of undescended testis and testicular cancer. These factors may partially explain the heterogeneity of the OR for this association in case-control studies relying on self-reports.
<b>Keywords</b>	Case-control studies, multicentre study, testicular neoplasms, cryptorchidism, epidemiologic methods, questionnaires, Germany
<b>Accepted</b>	16 February 2001

Testicular cancer is a rare disease. However, it is the most frequent malignancy in young men, and the incidence has increased in several populations, including Germans.<sup>1</sup>

As early as 1777, physicians suspected that undescended testis was associated with an increased risk of testicular cancer.<sup>2</sup> Although cryptorchidism is nowadays one of the best established risk factors for testicular cancer,<sup>3</sup> the strength of the association

varies considerably across the epidemiological studies that have been published.

There are several degrees of maldescensus testis including undescended testis (i.e. testis that is permanently within the groin or abdomen), gliding testis (i.e. testis that descends into the scrotum after pressure on the femoral artery in the groin but immediately upon release returns to the prescrotal position), and retractile testis that need not to be treated (i.e. testis that descends into the scrotum after pressure on the femoral artery in the groin and remains in this position for a while).<sup>4</sup> In a review from 1992 Whitaker wrote 'several attempts at classifying undescended testes have been made but none has provided the clinician with a comprehensive, simple and practical guide that everyone could accept'.<sup>5</sup> As a consequence, no unique definition of maldescensus testis has been used in case-control studies. For example, the United Kingdom Testicular Cancer Study Group regarded undescended testis as definite only if there was evidence of successful orchidopexy or of surgical

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investigation at which a testis was found to be missing or impossible to correct. Gliding or retractile testes in either childhood or adulthood or testes that descended spontaneously were not regarded as undescended.<sup>6</sup> Moller *et al.*<sup>7</sup> asked their study participants whether 'one or both testes were not descended to the scrotum in early childhood' and therefore included conditions like spontaneously descended testes, gliding, retractile and ascending testes. In many other case-control studies, the definition or wording of the questionnaire regarding a history of undescended testis is not even given.<sup>8-21</sup>

We hypothesized that the variability of odds ratios (OR) associated with maldescensus testis can be partially explained by the different questionnaires and classifications of undescended testis that have been used. Based on several classifications of undescended testis, different information sources (index subjects and their mothers), and ratings of two experienced urologists, we examined by how much the OR for the association between undescended testis and testicular cancer varies within a population-based case-control study that relied on self-report of undescended testis.

## Material and Methods

Eligibility criteria for cases included diagnosis of testicular cancer or extragonadal germ cell tumours between 1 July 1995 and 31 December 1997, age 15–69 years at the time of diagnosis, and sufficient command of the German language to complete the personal interview. The study area comprised five German regions (the cities of Bremen, Essen, Hamburg, and Saarbrücken and the Federal State of Saarland) covering a population of about 1.5 million male residents at risk. Cases were reported through an active reporting system from clinical and pathological departments in the study regions. In addition, cases residing in Hamburg were identified through the population-based cancer registry. Based on data of the population-based Saarland Cancer Registry, we expected to identify about 320 cases and observed 353 eligible cases.

A reference pathologist independently assessed the diagnosis by reviewing clinical data, histological conclusions of the local pathologists and by re-examining available tissue specimens including slides or tissue blocks in about 95% of the cases. Interviews were conducted with 269 of the 353 eligible cases or their closest available relatives (2 surrogate interviews). The reasons for non-participation were refusal (23 cases), our inability to contact cases because the treating physicians refused contacting the cases (37 cases), and other reasons (24 cases). After excluding cases that had moved away or died before first contact, the response rate was 78%.

Controls were selected randomly from mandatory registries of residence. For each case, about three potential controls matched on age (15–19, 20–24, ..., 65–69 years) and region of residence (Essen, Bremen, Hamburg, Saarbrücken, Saarland) were interviewed. Of 1982 eligible controls, 918 (8 surrogate interviews) were interviewed. The reasons for non-participation were refusal (515 controls), our inability to contact controls because they had moved away or died before first contact (354 controls) or were never reached at home (149 controls), and other reasons (49 controls). After excluding controls that had moved away or died before first contact, the response rate was 57%. We excluded 121 control interviews from the analysis

because no matched cases were available in the corresponding strata, leaving 797 control interviews for the analysis.

Data were collected from study participants by interviewers trained specifically for this project and monitored throughout the study to ensure uniform quality of the questionnaire data. They were unaware of specific study hypotheses as they administered structured questionnaires. The interview took approximately 70 minutes to complete. Of all the interviews, 99% were face-to-face and the remaining interviews (1%) were conducted by telephone.

Questionnaires were mailed to living mothers if the informed consent of the interviewees was obtained. Thirty-four mothers of interviewed cases and 173 mothers of the interviewed controls had died before the son's interviews. About 168 mothers of the 235 living mothers of interviewed cases (71%) and 358 mothers of the 745 living mothers of interviewed controls (48%) sent back our questionnaire. The major reasons for non-participation were refusals of the sons (41 cases, 184 controls) or their mothers (8 cases, 69 controls). We excluded 45 mother questionnaires from the control group because they did not match on age or region.

## Exposure Assessment

First, we asked about undescended testis (UT). Second, we asked about gliding or retractile testis (GRT). The order of these questions enabled us to reclassify UT as GRT. Gliding or retractile testis at the same side and age as a UT were reclassified as GRT. Third, we asked for details regarding laterality, treatment and result of the treatment. (The questionnaire is available on request from the corresponding author.)

Blinded to case-control status, we classified subjects as exposed (i.e. a history of UT) in several ways with an anticipated increasing level of specificity for both the sons' and the mothers' questionnaires: (1) ever having had UT and/or GRT, (2) UT and/or GRT treated or at least confirmed by a physician, (3) UT treated or at least confirmed by a physician with reclassified GRT rated as unexposed, (4) having been treated for UT, and (5) history of surgery for UT.

We used the method of series dual responses to correct for misclassification bias within the subset of index persons with corresponding mother questionnaire data.<sup>22</sup> Only those subjects with a history of UT or GRT that were treated by a physician in both data sets (mothers' and sons' data) were considered positive. All discordant and dual negative responses were considered negative.

For 61 controls (8%) and 33 cases (12%) the information about GRT was missing. This item non-response was caused by the interviewer training. We had temporarily suggested to the interviewer that the questions following UT could be skipped if interviewees did not suggest any history of UT. We regarded these subjects as unexposed in our analyses on GRT, when subjects did not report a history of UT.

Two experienced urologists independently reviewed the questionnaire sections on UT and GRT for all subjects (sons only) who reported a history of at least one of these conditions. They were asked to rate the information on UT and GRT on a 5-item Likert scale (impossible, unlikely, possible, likely, definitely) and were masked to case-control status.

Body mass index was based on self-reported current height (cm) and average weight (kg) between 1–5 years before

interview. Social class was assessed on the basis of highest school degree and highest professional degree.

### Statistical Methods

We calculated OR and corresponding 95% CI for testicular cancer by conditional logistic regression using SAS.<sup>23</sup> The matching factors age and region of residence formed 55 strata for the conditional logistic regression.

We assessed the agreement between the two raters on a 3-item scale defined as unlikely (including impossible and unlikely), possible, and likely (including likely and definitely) and the agreement between the sons' and mothers' questionnaires on a 2-item scale (yes/no). We used kappa statistics with 95% CI to assess the agreement between the raters or data sources.<sup>24</sup>

### Results

Germ cell tumours were grouped as seminomas ( $n = 170$ ), and non-seminomas ( $n = 99$ ) according to Parkin *et al.*<sup>25</sup> Major histological groups among non-seminomas were teratocarcinoma

( $n = 71$ ) and embryonal carcinoma ( $n = 27$ ). About 43% of the cases were between 25 and 34 years old. The risk for testicular cancer was slightly increased for subjects with professional degrees (i.e. apprenticeship, technical colleges, study at universities and universities for applied sciences) (Table 1).

Table 2 presents the OR according to various classifications of UT based on the sons' questionnaires. As expected, a higher proportion of cases than controls reported a history of UT. From the least to the most restrictive exposure classification, we observed a relevant increase of the OR for the history of undescended testis (test for trend,  $P = 0.0001$ ). Cases reported more often a history of UT and/or GRT neither being treated nor confirmed by a physician (20 out of 50, 40%) than controls (9 out of 43, 21%). The exclusion of these subjects from the exposed group resulted in a decrease in the effect estimate. Several subjects reported a medically treated or confirmed undescended testis that temporarily descended into the scrotum that should be regarded as either a gliding or retractile testis.<sup>4</sup> This proportion was higher among controls (15 out of 28, 54%) than among cases (8 out of 26, 31%). After rating these subjects as unexposed, the OR substantially increased. Furthermore,

**Table 1** Characteristics of the interviewed study subjects

	Controls n = 797		Cases n = 269		OR <sup>a</sup>	95% CI
	n	%	n	%		
<b>Age (years)</b>						
15–24	67	8	25	9		
25–34	301	38	116	43		
35–44	235	30	96	36		
45–54	83	10	19	7		
55–64	111	14	13	5		
<b>Years at school</b>						
Schoolboy	5	1	1	0		
≤9 <sup>b</sup>	304	38	89	33	Ref.	
10	192	24	61	23	0.8	0.6, 1.3
12	78	10	25	9	0.9	0.5, 1.5
13	217	27	93	35	1.1	0.7, 1.5
Unknown	1		0			
<b>Highest professional degree</b>						
None	95	12	24	9	Ref.	
Apprent. <sup>c</sup>	485	61	164	61	1.5	0.9, 2.5
University <sup>d</sup>	154	19	62	23	1.5	0.9, 2.6
Other <sup>e</sup>	63	8	19	7	0.9	0.4, 1.9
<b>Body mass index (kg/m<sup>2</sup>)<sup>f</sup></b>						
<21.9	147	18	66	25	1.3	0.9, 2.1
(21.9–23.7)	149	19	59	22	1.4	0.9, 2.1
(23.7–25.3)	148	19	46	17	Ref.	
(25.3–27.1)	143	18	47	17	1.4	0.9, 2.2
>27.1	147	18	40	15	1.3	0.8, 2.0
Unknown	63	8	11	4		

<sup>a</sup> Odds ratios (OR) and 95% CI from the conditional logistic regression model with the matching factors age and region of residence, adjusted for the highest professional degree; subjects with unknown values were excluded from the OR calculation.

<sup>b</sup> ≤9: reference group including: no school degree, 'Sonderschulabschluss, Volksschulabschluss, Hauptschulabschluss'.

<sup>c</sup> Apprenticeship including technical colleges degrees ('Fachschule').

<sup>d</sup> University or college degrees ('Abitur oder Fachabitur').

<sup>e</sup> Includes schoolboys, apprentices, students, people in the community service or military services.

<sup>f</sup> Body mass index based on average weight 1–5 years before interview and on current height.

**Table 2** Influence of increasingly restrictive definitions of exposure on odds ratios (OR) in a case-control study of maldescensus testis and testicular cancer: Analysis based on the sons' responses

Exposure definition	Controls (n = 797)			Cases (n = 269)			OR <sup>a</sup>	(95% CI)
	No data <sup>b</sup>	Exposed	Unexposed	No data	Exposed	Unexposed		
UT <sup>c</sup> and/or GRT <sup>d</sup> ever had	13	43	741	3	50	216	3.3	(2.1, 5.2)
Confirmed or treated by a physician	19	28	750	7	26	236	2.4	(1.4, 4.2)
GRT reclassified as unexposed <sup>e</sup>	19	13	765	7	18	244	3.6	(1.7, 7.6)
Untreated UT reclassified as unexposed	21	8	768	9	13	247	4.6	(1.8, 11.5)
Treated by surgery	21	5	771	9	9	251	5.4	(1.7, 17.1)

<sup>a</sup> Odds ratio (OR) and 95% CI from the conditional logistic regression model with the matching factors age and region of residence; subjects with the answers 'do not know' or with missing values were excluded from the OR calculation.

<sup>b</sup> No data: subjects with the answer 'do not know' or with missing values.

<sup>c</sup> Undescended testis.

<sup>d</sup> Gliding or retractile testis.

<sup>e</sup> GRT at the same side and age as a UT rated as unexposed.

**Table 3** Influence of increasingly restrictive definitions of exposure on odds ratios (OR) in a case-control study of maldescensus testis and testicular cancer: Analysis based on the mothers' responses

Exposure definition	Controls (n = 313)			Cases (n = 168)			OR <sup>a</sup>	(95% CI)
	No data <sup>b</sup>	Exposed	Unexposed	No data	Exposed	Unexposed		
UT <sup>c</sup> and/or GRT <sup>d</sup> ever had	6	45	262	4	38	126	1.6	(1.0, 2.6)
Confirmed or treated by a physician	7	30	276	5	20	143	1.1	(0.6, 2.0)
UT treated, GRT reclassified as unexposed <sup>d</sup>	10	5	298	6	5	157	1.9	(0.5, 6.9)

<sup>a</sup> Odds ratio (OR) and 95% CI from the conditional logistic regression model with the matching factors age and region of residence; subjects with the answers 'do not know' or with missing values were excluded from the OR calculation.

<sup>b</sup> No data: subjects with the answer 'do not know' or with missing values.

<sup>c</sup> Undescended testis.

<sup>d</sup> Gliding or retractile testis.

<sup>d</sup> GRT at the same side and age as a UT rated as unexposed.

when we restricted this exposed group to subjects who had been treated for UT, the effect estimate further increased to an OR of 4.6. We observed the highest OR among subjects treated for undescended testis by surgery (OR = 5.4) (Table 2).

Considering treated UT as a positive history of UT (excluding GRT), we found a higher proportion of bilateral UT among cases (5 out of 13) than among controls (0 out of 8). Among the cases with a history of treated unilateral UT (8 out of 13), all cases had the condition at the same side as the testicular cancer. Surgery for UT was reported in 10 out of 13 cases and 6 out of 8 controls.

Odds ratios tended to be higher within the subgroup of seminoma compared to non-seminoma for some but not all of the different exposure classifications (confirmed or treated UT and/or GRT: seminoma: OR = 2.7, 95% CI: 1.4, 5.2; non-seminoma: OR = 1.9, 95% CI: 0.9, 4.4; treated UT, excluding GRT: seminoma: OR = 7.8, 95% CI: 2.6, 23.2; non-seminoma: OR = 2.1, 95% CI: 0.5, 9.0).

Within the subset of mothers' questionnaires, the OR were considerably lower compared to the sons' questionnaires, ranging from 1.1 to 1.9. The OR associated with a report of ever having had a history of UT and/or GRT within the sons' subset of the corresponding mothers' interviews is 3.6 (95% CI: 2.1, 6.1) as compared to 1.6 within the mothers' interviews. This higher effect estimate based on the sons' interviews is due to a higher exposure prevalence among the cases (sons: 28%,

mothers: 23%) and a lower exposure prevalence among the controls (sons: 9%, mothers: 14%) compared to the mothers' interviews (Table 3).

The largest OR (1.9; 95% CI: 0.9, 4.0) occurred when study subjects were classified according to the method of series dual responses, (i.e. only those subjects with a history of UT and/or GRT who have been treated by a physician in both data sets [mothers' and sons' data]) were considered positive.

The agreement between the mothers and sons for ever having had UT or GRT was fair (kappa 0.53). The agreement was excellent (kappa 0.89) when exposure was defined as a history of surgery due to UT or GRT. The agreement of history of treatment for UT or GRT was lower among control sons and their mothers compared to case sons and their mothers. This difference was mainly due to a larger proportion of control sons who did not report a history although their mothers reported a history compared to case sons (Table 4). The measures of agreement changed little when we stratified the analyses by age of the mothers, sons, age at correction and socioeconomic status of the sons as measured by years at school (data not shown).

The urologists' agreement for the history of UT was fair (weighted kappa 0.54, 95% CI: 0.42, 0.67). This result differed little when examined by various characteristics including case-control status, age group, therapy or missing information on GRT. When we excluded subjects from the OR estimation for whom the raters disagreed on the history of UT, we found an

**Table 4** Agreement between mothers and sons on the history of maldescensus testis

Exposure classification	n <sup>a</sup>	nmiss	Son (+) <sup>b</sup>		Son (-)		Agreement %	Kappa %	95% CI <sup>d</sup>
			Mother (+) <sup>c</sup>	Mother (-)	Mother (+)	Mother (-)			
<b>Undescended testis, gliding or retractile testis ever had</b>	467	14	48	26	35	358	87	53	43, 64
Cases only	161	7	26	20	12	103	80	49	33, 64
Controls only	306	7	22	6	23	255	91	55	41, 70
15–34 years	306	9	32	15	28	231	86	52	39, 64
35+ years	161	5	16	11	7	127	89	57	40, 75
<b>Treatment for undescended testis, gliding or retractile testis</b>	457	24	29	6	18	404	95	68	60, 80
Cases only	155	13	15	3	3	134	96	81	67, 96
Controls only	302	11	14	3	15	270	94	58	41, 75
<b>History of operation due to undescended testis, gliding or retractile testis</b>	408	73	17	1	3	387	99	89	78, 99

<sup>a</sup> n: number of mother-son pairs in the analysis; nmiss: number of mother-son pairs with missing information.

<sup>b</sup> Son (+): positive history of the son; Son (-): no history of the son.

<sup>c</sup> Mother (+): positive history of the mother; Mother (-): no history of the mother.

<sup>d</sup> 95% CI: 95% confidence interval for kappa.

OR of 4.0 (95% CI: 2.1, 7.9) for the history of UT. The agreement for the history of GRT was poor (weighted kappa 0.08, 95% CI: -0.03, 0.19) (data not shown).

## Discussion

We identified 20 published case-control studies that assessed the risk of testicular cancer associated with a history of undescended testis.<sup>6–21,26–29</sup> In 16 studies the exposure assessment (history of undescended testis) was based on self-reports either by interviews or by mailed questionnaire.<sup>6–21</sup> The OR of these 16 studies ranged from 1.6<sup>7</sup> to 17.1.<sup>10</sup> With the exception of one published case-control study relying on self-reports,<sup>7</sup> no publication presents the wording of the questions regarding a history of maldescensus testis. About 7 of the 16 case-control studies based on self-reports included mothers' or parents' interview data.<sup>6,8–9,11–13,16</sup> Only one study<sup>13</sup> presents separate analyses for the sons and their mothers and corroborates our finding that OR based on mothers' interviews tend to be lower than those based on sons' interviews. A higher proportion of non-differential misclassification and/or a lower proportion of recall bias within the mothers' interviews compared to the sons' interviews might explain this finding. The remaining six studies either do not present separate analyses<sup>8,11</sup> or only present analyses based on combinations of the mothers' and sons' interviews<sup>9,16</sup> with some studies supplementing the data by medical record reviews.<sup>6,12</sup>

Several factors might explain the variability of the OR estimates including the definition of undescended testis,<sup>5</sup> age of spontaneous descent,<sup>28</sup> age at correction,<sup>6,12,28</sup> degree of maldescensus (abdominal versus inguinal), uni- or bilaterality of undescended testis,<sup>7,12</sup> histological tumour type,<sup>26,28,30,31</sup> premature birth<sup>29</sup> and others. The different distributions of these factors among the studies may in part explain the substantial heterogeneity of the OR estimates.

Our findings suggest that questionnaire design, classifications of undescended testis and data sources used have an important impact on the OR for the association of undescended testis

and testicular cancer. These factors may partially explain the heterogeneity of the OR for this association in studies relying on self-reports. There is some evidence in our study that increasing specificity of exposure classification based on self-reported medical history increased the OR for testicular cancer. This may indicate that bias due to non-differential misclassification is reduced through more specific classifications of undescended testis. Alternatively, it may indicate that differential misclassification (i.e. recall bias) is associated with the more strict definitions of undescended testis. In addition, the different definitions of cryptorchidism based on self-reports might reflect several degrees of maldescensus testis that differ biologically regarding testicular cancer risk.

The accuracy of the anamnestic information from adult men with regard to a history of early childhood maldescensus is limited by at least two factors: (1) limited recall of the early childhood events and (2) understanding the distinction between the different degrees of maldescensus testis. We found a relatively large number of subjects reporting a history of bilateral treated undescended testis that may reflect overreporting. A large proportion of cases and controls reported a history of gliding or retractile testis that was never treated or confirmed by a physician in our study. In addition, a large proportion of subjects reported a history of undescended testis and gliding or retractile testis at the same side and same time indicating that this distinction is not fully understood by the study participants.

The rating of the anamnestic information on maldescensus testis by two experienced urologists showed that the agreement is only fair as measured by kappa. Although a physical examination can provide further evidence for a history of maldescensus testis (if a typical scar in the inguinal region can be found or a testis is in a maldescended position or removed), there is still a considerable proportion of subjects with testes well down in the scrotum and without scars who might have had a maldescensus testis in childhood.

There are several factors in the study that may have affected our results. First, we were not able to validate data on undescended testes by medical chart reviews and therefore we do

not know which classification of undescended testis most likely represents the truth.

Second, our questionnaire did not allow a distinction between gliding and retractile testis, with only the former considered to be a risk factor for testicular cancer. Therefore, our effect estimates for the history of gliding or retractile testis are based on two conditions that probably differ with regard to the cancer risk.

Third, the response proportion in the control group was low and might have increased the heterogeneity of the OR in the different analyses.

In conclusion, the kind of questions regarding a history of maldescensus testis, the exposure classifications, and the data sources (sons or their mothers) substantially influence the strength of the association between cryptorchidism and testicular cancer. Additional questions on medical confirmation,

treatment, laterality and age give important insights into the robustness of medical self-reports and should be applied in studies that rely on self-reported medical conditions that are not easy to remember or to understand by the interviewees or that are not clearly defined.

## Acknowledgements

The study was funded by the Federal Ministry for Education and Research (BMBF No. 01HP 684/8). We are grateful to the clinicians and pathologists who reported cases for the study. We thank Dr Klaus Alfred Metz, Department of Pathology, University of Essen, for reviewing clinical data, slides and tissue specimens of the testicular cancers. In addition, we thank Dr Börgermann, Department of Urology, University Hospital of Essen, for his ratings of the questionnaires.

### KEY MESSAGES

- The odds ratio of the association between undescended testis and testicular cancer varies between 1.6 and 17.1 in the published case-control studies.
- In our study, we found odds ratios between 1.1 and 5.4 depending on the information source (sons or their mothers) and the exposure classification.
- Additional questions on medical confirmation, treatment, laterality and age give important insights into the robustness of medical self-reports and should be applied in studies that rely on self-reported medical conditions that are not easy to remember or to understand by the interviewees or that are not clearly defined.

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