Cryptorchidism and hypospadias are the most common congenital malformations in boys, with prevalence at birth of 1%–9% and 0.4%–0.8%, respectively (1–3). Testicular germ cell cancer (TGCC) is the most common cancer among young men, with a lifetime risk in Denmark of almost 1% (4). Due to reports of increases in male urogenital disorders in the past 50 years, and research showing that these disorders share common risk factors (5–15), a testicular dysgenesis syndrome has been suggested for which hypospadias, cryptorchidism, and TGCC may all be symptoms (16–18).

If these disorders share a common pathogenic pathway that is heritable, they would be expected to coaggregate within families. Indeed, it is well known that boys with cryptorchidism have a three- to eightfold increased risk of developing TGCC (19–22), and there is some weak evidence that a personal history of hypospadias may also be a risk factor for TGCC (21). However, knowledge of whether a family history of one disorder influences the risk of developing any of the other disorders in testicular dysgenesis syndrome is limited to a single study (13), showing that having a child born with cryptorchidism does not increase the risk of having subsequent children born with hypospadias and vice versa.

The aim of this study, which included the entire male population of Denmark, was to address whether testicular dysgenesis syndrome is heritable. We investigated the relative risk (RR) of TGCC according to family history of cryptorchidism or hypospadias.

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The aim of this study, which included the entire male population of Denmark, was to address whether testicular dysgenesis syndrome is heritable. We investigated the relative risk (RR) of TGCC according to family history of cryptorchidism or hypospadias within first-, second-, and third-degree relatives.

Materials and Methods

Study Population
This study was based on a cohort of boys who were identified from the Danish Civil Registration System, which has existed since April 2, 1968, when all residents living in Denmark were assigned a unique personal identification number. Information from various sources, including Danish population–based health registers, can be linked via the personal identification number. Furthermore, information on sex and date and place of birth and continuously

Background
Cryptorchidism, hypospadias, and testicular germ cell cancer (TGCC) may be symptoms of a testicular dysgenesis syndrome that manifests during fetal life. To address the inheritability of this syndrome, we examined whether family history of cryptorchidism or hypospadias is associated with an increased risk of TGCC.

Methods
A total of 2,159,883 men born since 1953, identified through Danish health registers, were followed from April 2, 1968, through May 31, 2008. First-, second-, and third-degree relatives were identified in the Danish Family Relations Database; cryptorchidism and hypospadias patients were identified in the Danish Hospital Discharge Register; and TGCC patients were identified in the Danish Cancer Register. Poisson regression was used to calculate the risk ratio for TGCC by family history of cryptorchidism or hypospadias.

Results
A total of 5,441 patients developed TGCC. A personal history of cryptorchidism or hypospadias was associated with an increased relative risk (RR) of developing TGCC (RR = 3.71, 95% confidence interval [CI] = 3.29 to 4.19; and RR = 2.13, 95% CI = 1.26 to 3.61, respectively). For example, in men in their thirties, the overall rate per 100,000 is 25.1 in the cohort, but 88.6 and 55.4 in men born with cryptorchidism or hypospadias, respectively. In contrast, relatives of a hypospadias patient did not have a statistically significantly increased risk of TGCC nor did the first- and second-degree relatives of cryptorchidism patients. However, we found a small increased risk of TGCC for third-degree relatives of patients with cryptorchidism.

Conclusions
Having hypospadias or cryptorchidism was associated with an increased risk of developing TGCC. However, our finding that family history of hypospadias or cryptorchidism generally was not associated with increased risk of developing TGCC does not support the hypothesis of shared inheritability of cryptorchidism, hypospadias, and TGCC.

**CONTEXTS AND CAVEATS**

**Prior knowledge**
Although a personal history of cryptorchidism or hypospadias is associated with a risk of developing testicular germ cell cancer (TGCC), it is not known whether all three are part of an inheritable dysgenesis syndrome.

**Study design**
A cohort of all men living in Denmark between 1968 and 2008 was matched with health information from Danish health and hospital registries to identify boys who were born with cryptorchidism or hypospadias. Relatives of these patients were then identified through the Danish Family Relations Database to assess the risk of TGCC in relatives of cryptorchidism or hypospadias patients.

**Contribution**
These results confirm that boys with hypospadias are at risk of developing TGCC, but their first-, second-, and third-degree relatives are not. The first- and second-degree relatives of boys with cryptorchidism are also not at risk of developing TGCC.

**Implications**
Large linked databases such as those in Denmark are useful for assessment of population-level genetics of disease. Access to a national cohort allowed this study to rule out a strong familial predisposition to developing TGCC when some family members are born with hypospadias or cryptorchidism.

**Limitations**
Misclassification of legal and biological fathers because of privacy could lead to bias in coding of relatives. Diagnoses of cryptorchidism and hypospadias were not recorded for births until 1977, and only later diagnoses made during adolescence could be used. The very small risk of developing TGCC by third-degree relatives of cryptorchidism patients is not biologically realistic, given that it is not found in closer relatives and thus may be because of chance.

*From the Editors*

Updated information on date of death or emigration are registered in the Civil Registration System (23).

We used the Danish Family Relations Database, which is based on data from the Civil Registration System, to link children born since 1953 with their parents and siblings, and, for later birth cohorts, with second- and third-degree relatives. First-degree relatives were defined as sons or brothers; second-degree relatives as grandparents, half brothers, or nephews; and third-degree relatives as first cousins. To identify TGCC patients among cohort members and their relatives, we used the Danish Cancer Register (1943–2004), the Pathology Register (1996–2008), and the Danish Hospital Discharge Register (1977–2008). For data on hypospadias and cryptorchidism, we used the Danish Hospital Discharge Register (1977–2008).

We analyzed the relative risk of TGCC according to family history of cryptorchidism or hypospadias in a cohort of all men born in 1953 or later, who had lived in Denmark between April 2, 1968, and May 31, 2008. The study was approved by the Danish Data Protection Agency.

**Identification of Relatives**
Relatives born before June 1, 2005, were identified from the Danish Family Relations Database. This database records parental links as registered in the Civil Registration System, in which parents were identified by shared address for individuals living at home in 1968. The Civil Registration System was revised in 1978, and links were changed to reflect legal relationships, that is, all newborn children were registered with a link to their biological parents and, if adopted, to their adoptive parents. Thus, most individuals born in Denmark from 1953 to 2008 had parental links reflecting legal parents. Using the parental link also allows the identification of grandfathers, cousins, uncles, and nephews. However, among all boys born in Denmark from 1953 to 1967 and from 1968 to 1989, 2.6% and 35.9%, respectively, had links to their grandfathers (see Supplementary Table 1, available online). Almost all boys (92.7%) born in Denmark since 1990 had registered links for grandparents and thus also for uncles and first cousins. It should be emphasized that whereas the cohort was restricted to men born since 1953 and who lived in Denmark between 1968 and 2008, there were no restrictions on the birth cohorts of relatives other than those imposed by the way parental links were constructed in the Civil Registration System (ie, relatives who died before 1968 have no parental links, and therefore, these relatives were not included in the study).

**Identification of TGCC**
Information on TGCC status was identified by linkage with the Danish Cancer Register, which has recorded almost all cancer patients in Denmark during 1943–2003 (24). Additional information on TGCC in the period 2004–2008 was available through the Danish Hospital Discharge Register, in combination with data obtained from the Danish Pathology Register. Only patients with a TGCC diagnosis in both registers were coded as TGCC patients. In total, 5441 TGCC patients were identified among cohort members during the period 1968–2008.

**Identification of Hypospadias and Cryptorchidism Patients**
Information on hypospadias and cryptorchidism status, other congenital malformations, chromosomal abnormalities, and surgeries in the relatives of the cohort members was obtained from the Danish Hospital Discharge Register, which contains nationwide registration of all hospital discharge diagnoses and performed operations from 1977 through 2008, as well as outpatient diagnoses since 1995 (25). Cohort members were classified as hypospadias case subjects if a diagnosis of hypospadias was registered in the Danish Hospital Discharge Register; further subdivision according to severity was not possible. Cohort members were classified as cryptorchidism case subjects if a diagnosis of cryptorchidism was registered in the Danish Hospital Discharge Register after 6 months of age; classification according to anatomic location and laterality was not possible. Hypospadias and cryptorchidism are congenital malformations; thus, the date of diagnosis was set to the date of birth.

**Statistical Analysis**
The risk of TGCC in first-, second-, and third-degree relatives of a patient with hypospadias or cryptorchidism was evaluated as
the ratio between the risk of TGCC in individuals with a relative with known hypospadias or cryptorchidism and the risk in individuals with known relatives of the same type of whom none had cryptorchidism or hypospadias. Thus, for example, the relative risk of developing TGCC when having an affected nephew was estimated as the risk of TGCC in uncles with affected (cryptorchidism or hypospadias) nephews compared with the risk in uncles with known and only unaffected nephews. Comparing only individuals with the same types of relatives reduces bias because of incomplete registration of family members in older birth cohorts in the Danish Family Relations Database and furthermore adjusts the relative risk for the effect of having a specific relative. The association between having cryptorchidism or hypospadias and risk of TGCC in individuals was evaluated by the relative risk of TGCC, according to a personal history of cryptorchidism or hypospadias.

Relative risks were estimated by using Poisson regression with the logarithm of person-years as offset and with adjustment for age and birth period in 5-year intervals. The cohort members were followed from April 2, 1968, until death, emigration, or 2008, whichever came first. Thus, persons diagnosed with TGCC before April 2, 1968, were not included in the study. All statistical tests were two-sided, and associations with 95% confidence intervals (CIs) for the relative risk that did not include one were considered statistically significant. The same statistical approach was used in the additional analyses performed to assess the robustness of the results when case definitions were changed (including only those with cryptorchidism or hypospadias but not other abnormalities or including only those born in Denmark) and the definitions of relatives were changed (excluding all relatives born before 1968).

Results

Of the 2159883 men in the cohort who were followed during the period 1968–2008 for 58021640 person-years, a total of 5441 developed TGCC. Overall, 6393 men were identified with a diagnosis of hypospadias; of these, 785 (12.2%) had malformations other than hypospadias. In addition to the diagnosis for hypospadias, 2945 cohort members had an additional operation code in the Danish Hospital Discharge Register (ie, had surgery). Of 41837 patients with cryptorchidism identified after 6 months of age, 1767 (4.2%) also had congenital malformations other than cryptorchidism and 25655 (61.3%) had an operation code in addition to their diagnosis in the Danish Hospital Discharge Register. Fourteen had a diagnosis of both hypospadias and TGCC; 276 had both cryptorchidism and TGCC; and one had cryptorchidism, hypospadias, and TGCC. The TGCC cases had 57 relatives with a diagnosis of hypospadias and 379 relatives with a diagnosis of cryptorchidism, which were distributed as follows: two brothers, 17 sons, three half brothers, two grandsons, 31 nephews, and two first cousins with hypospadias; and 65 brothers, 107 sons, 25 half brothers, three grandsons, 154 nephews, and 37 first-cousin pairs with cryptorchidism.

Being born with either hypospadias or cryptorchidism was associated with an increased relative risk of TGCC (Table 1). Adjusted for diagnosis of cryptorchidism, period, and age, RR for a hypospadias patient = 1.88, 95% CI = 1.11 to 3.18. Adjusted for diagnosis of hypospadias, period, and age, RR for a cryptorchidism patient = 3.70, 95% CI = 3.27 to 4.18. For example, in men in their thirties, the overall rate per 100000 is 25.1 in the cohort, but 88.6 and 55.4 in persons with personal history of cryptorchidism or hypospadias, respectively.

First-, second-, and third-degree relatives of a patient with hypospadias did not have a statistically significantly increased risk of developing TGCC (Table 2). Similarly, being a first- and second-degree relative of a patient with cryptorchidism was not associated with an overall increased risk of TGCC, whereas it was among third-degree relatives (RR = 1.73, 95% CI = 1.23 to 2.43). Among first-degree relatives of cryptorchidism patients, being a father of an affected son was initially associated with a slightly increased risk of TGCC (RR = 1.30, 95% CI = 1.07 to 1.57). However, in the analysis adjusted for personal history of cryptorchidism in TGCC patients and restricted to include relatives with confirmatory operations only (ie, those who had an operation code in the register) in addition to the cryptorchidism diagnosis in the Danish Hospital Discharge Register, the association was no longer statistically significant (RR = 1.17, 95% CI = 0.90 to 1.51).

We performed several additional analyses to assess the robustness of the results. First, we tested different case definitions in the following sub-analyses: 1) including only case subjects of hypospadias or cryptorchidism with no other congenital malformations or chromosomal abnormalities and 2) including only case subjects of hypospadias or cryptorchidism who were born in Denmark (rather than just having lived in Denmark during the study period). Using these criteria did not change the results. Moreover, to investigate the importance of the completeness of hypospadias and cryptorchidism status, the analyses were also made with a restriction on the relatives including only relatives born later than 1968. This change in the definition of relatives did not change the overall results (data not shown).

Discussion

In this nationwide cohort study, we investigated the risk of TGCC in individuals with a family history of cryptorchidism or

Table 1. Relative risk (RR) of developing testicular germ cell cancer (TGCC) in individuals who are born with cryptorchidism or hypospadias*

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Person-years</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypospadias</td>
<td>14</td>
<td>114115</td>
<td>2.13 (1.26 to 3.61)</td>
<td>1.88 (1.11 to 3.18)†</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>278</td>
<td>1009194</td>
<td>3.71 (3.29 to 4.19)</td>
<td>3.70 (3.27 to 4.18)‡</td>
</tr>
</tbody>
</table>

* All RRs were adjusted for age and birth period in 5-year intervals. CI = confidence interval.
† Adjusted for the TGCC case subjects’ personal status of cryptorchidism.
‡ Adjusted for the TGCC case subjects’ personal status of hypospadias.
Table 2. Relative risk (RR) of testicular cancer in individuals with a family history of cryptorchidism or hypospadias*

<table>
<thead>
<tr>
<th>Relationship</th>
<th>N</th>
<th>RR (95% CI)†</th>
<th>N</th>
<th>RR (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>175</td>
<td>1.14 (0.98 to 1.33)</td>
<td>103</td>
<td>1.04 (0.85 to 1.26)</td>
</tr>
<tr>
<td>Son</td>
<td>107</td>
<td>1.30 (1.07 to 1.57)</td>
<td>59</td>
<td>1.17 (0.90 to 1.51)</td>
</tr>
<tr>
<td>Brother</td>
<td>65</td>
<td>1.12 (0.89 to 1.44)</td>
<td>43</td>
<td>1.00 (0.74 to 1.35)</td>
</tr>
<tr>
<td>Grandson</td>
<td>3</td>
<td>3.26 (0.40 to 3.94)</td>
<td>1</td>
<td>0.93 (0.13 to 6.62)</td>
</tr>
<tr>
<td>Half brother</td>
<td>25</td>
<td>1.32 (0.89 to 1.96)</td>
<td>18</td>
<td>1.35 (0.85 to 2.16)</td>
</tr>
<tr>
<td>Nephew</td>
<td>148</td>
<td>1.00 (0.85 to 1.18)</td>
<td>93</td>
<td>0.99 (0.84 to 1.17)</td>
</tr>
<tr>
<td>Third degree</td>
<td>37</td>
<td>1.73 (1.23 to 2.43)</td>
<td>23</td>
<td>1.56 (1.02 to 2.39)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>RR (95% CI)†</th>
<th>N</th>
<th>RR (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidism</td>
<td>19</td>
<td>0.77 (0.49 to 1.21)</td>
<td>8</td>
<td>0.68 (0.34 to 1.36)</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>21</td>
<td>1.01 (0.63 to 1.63)</td>
<td>7</td>
<td>0.83 (0.39 to 1.74)</td>
</tr>
</tbody>
</table>

* Risk of testicular germ cell cancer in individuals with a family history of hypospadias or cryptorchidism was compared with the risk in individuals with known relatives of the same type of whom none had cryptorchidism or hypospadias.
† Adjusted for age and birth period in 5-year intervals.
‡ Only cryptorchidism case subjects with confirmatory surgery were included in the analyses. The analyses were adjusted for age and birth period in 5-year intervals and personal status of cryptorchidism in the person at risk.
§ Only hypospadias case subjects with confirmed surgery were included in the analyses. The analyses were adjusted for age and birth period in 5-year intervals and personal status of hypospadias in the person at risk.

Our findings confirm that there is an association between being born with hypospadias or cryptorchidism and developing TGCC on an individual level. However, a family history of hypospadias or cryptorchidism is not associated with an increased risk of developing TGCC.

We acknowledge that we did find an increased risk of TGCC in first cousins of cryptorchidism case subjects. However, this difference is most likely because of chance. We investigated whether the observed relative risk was because of large clusters of TGCC and cryptorchidism within a few families, but no such clusters were found in the cohort. Furthermore, the lack of an increased risk of TGCC in sibling pairs and second-degree relatives with cryptorchidism makes it highly unlikely that the association found for cousins is biologically plausible.

Regarding the initial finding of an increased risk of TGCC among fathers of cryptorchidism case subjects, the observed effect can be explained by familial aggregation of cryptorchidism because cryptorchidism both aggregates within families (26) and is associated with TGCC on an individual level (20). In other words, the fact that cryptorchidism is heritable and cryptorchidism in itself is associated with an increased risk of TGCC explains the apparent increased risk of TGCC among fathers of cryptorchidism case subjects.

Missing registrations of cryptorchidism before 1977 resulted in an incomplete adjustment for personal cryptorchidism status (Table 2). However, even with unreported cases of cryptorchidism, this partial adjustment resulted in an overall decrease in relative risk of TGCC, suggesting that a complete registration of cryptorchidism status among TGCC case subjects would probably have resulted in even greater decreases in the estimates. In addition to adjustment for personal history of cryptorchidism, restricting the analyses to those who had confirmed surgery resulted in a further decrease in the relative risk of TGCC (Table 2).

Very few studies have investigated the familial aggregation of TGCC in families with a history of cryptorchidism or hypospadias. In a small case–control study, cryptorchidism was reported in one (17%) of the six first-degree relatives of TGCC patients who had a family history of TGCC compared with seven (2.7%) of the 259 and 14 (5.3%) of the 263 first-degree relatives of control and TGCC patients, respectively, who did not have a family history of TGCC (27). In a recent case–control study of 229 case subjects of TGCC and 800 control subjects (28), associations were reported between TGCC incidence among persons with a family history of cryptorchidism (odds ratio [OR] = 2.85, 95% CI = 1.70 to 4.79) and among persons with fathers with cryptorchidism (OR = 6.85, 95% CI = 1.52 to 30.79).

This large register-based cohort study that included the entire male population living in Denmark did not support the previously reported association (27,28) between a family history of cryptorchidism and TGCC. The conflicts with previous reports may in part be due to the small numbers in those studies and to the fact that they were case–control studies based on questionnaires and interview data. Such a study design is particularly prone to recall bias and differential misclassification. In addition, the previous studies may also suffer from selection bias because of selection of case patients with more severe disease or with a family history of cryptorchidism.

Studies strongly support the hypothesis that precursor cells of TGCC are developed during the fetal period. Accordingly, TGCC, cryptorchidism, and hypospadias all have their origin in fetal life. The simultaneous increase in cryptorchidism and hypospadias during the past decades and the shared gestational and maternal risk factors between these abnormalities and TGCC (5–15) suggest that cryptorchidism, hypospadias, and TGCC are all symptoms of what is called testicular dysgenesis syndrome, which may be associated with environmental toxins, such as estrogenic or antiandrogenic chemicals that act in utero in genetically susceptible individuals (16–18).

We would expect to find familial coaggregation of the symptoms belonging to this syndrome if the disorders are caused by genetic susceptibility, familial environmental factors, or gene–environment interactions. Such a coaggregation would be strongest for full brothers who share 50% of their genes and common (genetic and environmental) gestational environments. Indeed,
intrauterine factors, for example, gestational hormone levels, have previously been found to be strongly associated in successive pregnancies of the same women (29). However, we did not find any association between a family history of hypospadias or cryptorchidism and TGCC.

A possible explanation for the coaggregation of these disorders on an individual level could be a cascade of seemingly unrelated consequences proceeding from one primary defect. During intrauterine life, this primary abnormality within the urogenital system may interfere with normal embryological and fetal development. Data in this study suggest that this syndrome is not inherited. Rather, it may be associated with a combination of genetic and environmental factors, but these results suggest that it is unlikely that the primary defect is because of genetic predisposition alone.

This cohort study has several strengths. It not only had good statistical power (large cohort) but also had a minimum of differential information bias and good validity (24,25). It is based on the entire population of Danish men with very complete information on follow-up, which minimizes selection bias. The personal identification number given to all Danish residents is the key to information on individuals that is stored in national registers and enables linkage between familial status and disease outcome. These data were obtained independently of each other and are based on mandatorily reported information. The validity of this information is underscored by our findings of an association of increased risk of TGCC in persons born with hypospadias and cryptorchidism, which is in agreement with previous studies (21,30).

The study also had potential limitations. Potential misclassifications because of registration of the legal father only of adopted children, children conceived with donor semen, or paternal discrepancy in general (31,32) cannot be ruled out. Furthermore, registration in the Danish Family Relations Database of relatives in older birth cohorts is not complete, and this may have influenced our estimates. However, minor misclassifications of family relations cannot explain our results, and potential information bias was reduced by comparing only individuals with the same types of relatives. In addition, this approach adjusts the relative risks for the effect of having a specific relative, for example, being a twin.

Another potential limitation is the collection of cryptorchidism or hypospadias data about relatives born before 1977 because diagnosis of cryptorchidism or hypospadias was not recorded until that year. However, although cryptorchidism and hypospadias are congenital malformations, treatment and thus registration of hypospadias and cryptorchidism occurred at adolescence or later in a large proportion of the older birth cohorts. Using this information, it was also possible to identify cases of cryptorchidism or hypospadias among relatives born before 1977. Furthermore, a simulation study based on data from the Danish Hospital Discharge Register has shown that information bias because of incomplete registration of the relatives (before initiation of a register) is negligible when the frequency of the disorder is low (33). Because both cryptorchidism and hypospadias are rare disorders, we consider such an information bias of minor importance to our results. Nevertheless, missing registration of case subjects with cryptorchidism and hypospadias before 1977 leads to incomplete adjustment for personal history of cryptorchidism or hypospadias status. However, both incomplete and complete adjustment for personal history of cryptorchidism or hypospadias would make the estimate in Table 2 attenuate toward 1.0 because a personal history of cryptorchidism or hypospadias is associated with TGCC and a personal history of cryptorchidism or hypospadias is associated with family history of cryptorchidism or hypospadias.

In conclusion, diagnosis of hypospadias and cryptorchidism was associated with incidence of TGCC at an individual level. However, a family history of hypospadias or cryptorchidism was not associated with a general increase in the risk of developing TGCC. Thus, our data do not support the hypothesis of shared inheritability of the disorders described under testicular dysgene

References


**Funding**

Danish Research Council (2107-04-0004 to M.M.).

**Note**

The sponsors had no role in the study design, the collection and interpretation of data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

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