

ORIGINAL ARTICLE

Early life risk factors for testicular cancer: a case-cohort study based on the Copenhagen School Health Records Register

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ABSTRACT

Purpose: One established risk factor for testicular cancer is cryptorchidism. However, it remains unclear whether cryptorchidism is a risk factor in itself or whether the two conditions share common causes in early life (estrogen hypothesis), such as birth weight and birth order. The objective of this study is to utilize data from the Copenhagen School Health Records Register (CSHRR) to evaluate cryptorchidism, birth weight and birth order as risk factors for testicular cancer.

Methods: The study population consisted of 408 cases of testicular cancer identified by a government issued identification number linkage of the entire CSHRR with the Danish Cancer Registry and a random subsample of 4819 males from the CSHRR. The study design was case-cohort and the period of follow-up between 2 April 1968 and 31 December 2003.

Results: Cryptorchidism was significantly associated with testicular cancer in crude analyses [hazard ratio (HR) = 3.60, 95% CI 2.79–4.65]. Birth weight was inversely associated with testicular cancer and no clear association with birth order was observed. The positive association between cryptorchidism and testicular cancer was only slightly attenuated controlling for birth weight and birth order and stratified on birth cohort (HR = 3.46, 95% CI 2.67–4.48).

Conclusion: This study confirmed the robustness of the association between cryptorchidism and testicular cancer even after adjustment for birth weight and birth order. Furthermore, the study showed an inverse association between birth weight and testicular cancer.

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The etiology of testicular cancer is largely unknown, but the early onset of the malignancy has led to focus on factors acting early in life. Besides a family history of testicular cancer and cancer of the contralateral testis, the most established risk factor is cryptorchidism [1]. However, whether cryptorchidism is a risk factor in itself due to the abnormal position of the testes (position theory) or whether the two conditions share common causes (estrogen hypothesis), remains less clear.

According to the 'estrogen hypothesis' high estrogen levels during pregnancy are involved in the pathogenesis of testicular cancer. Studies on proxies for gestational endogenous estrogen levels such as parity/birth order and birth weight [1] have shown that maternal estrogen levels are higher in first relative to subsequent pregnancies [2,3]. Following from this, it has been hypothesized that higher estrogen levels in first pregnancy might explain why firstborn sons seem to be at higher risk of testicular cancer relative to sons born of mothers with a higher parity [4–6]. Birth weight has been shown to be positively associated with estrogen levels during pregnancy, allowing the use of birth weight as a proxy of exposure to estrogens in utero [7]. A meta-analysis from 2007 found a U-shaped association between birth weight

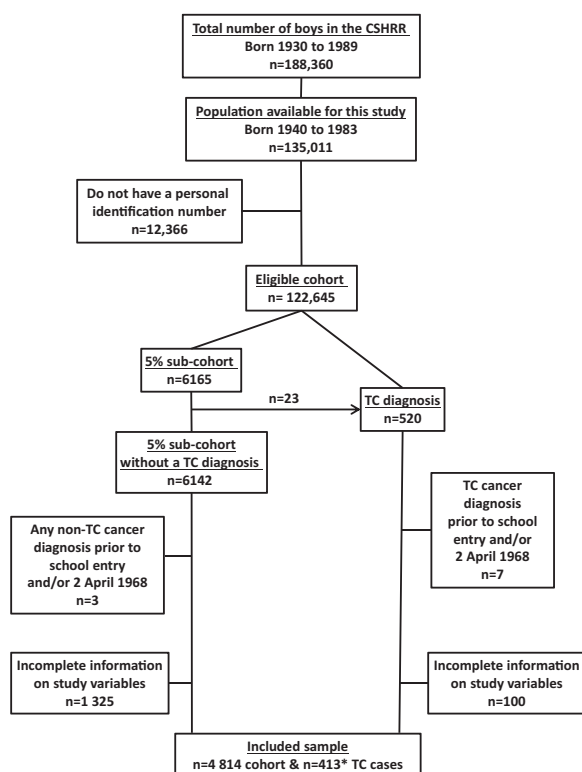
and risk of testicular cancer [8], whereas a meta-analysis from 2010 found an association between low birth weight and risk of testicular cancer [9].

We investigate whether the relatively well established association between cryptorchidism and testicular cancer could be verified in a case-cohort study based on the Copenhagen School Health Records Register (CSHRR), controlling for the potential confounding effects of birth weight and birth order. Second, we explore the associations of birth weight and birth order with testicular cancer risk in further detail, as previous studies on these proxies for gestational estrogen levels have shown conflicting findings [6].

Material and methods

Study population

The details of the CSHRR have been described elsewhere [10]. In short, the register contains school health records of virtually every child born between 1930 and 1992 attending public or private schools in the municipality of Copenhagen. More than 350 000 schoolchildren are included in CSHRR. Testicular cancer cases were identified by linkage of the entire CSHRR with



*5 subjects had a non-TC cancer diagnosis prior to the TC diagnosis; they are included in the analyses until the time of the non-TC cancer diagnosis, thus 408 TC cases are included in the analytic sample

Figure 1. Flowchart describing inclusion and exclusion of individuals in the study.

the Danish Cancer Registry made possible by a personal identification number assigned to each citizen in Denmark since 2 April 1968. Included testicular cancer cases were diagnosed from 2 April 1968 until 31 December 2003, which was the latest update of the cancer registry available at the time of the data extraction (Figure 1). Although the Cancer Registry has systematically collected information about all incident cancers in the Danish population since 1943 [11], only testicular cancer cases diagnosed 2 April after 1968 were included to ensure an inclusion that was irrespective of surviving cancer to obtain a personal identification number in 1968. Cases were identified by The International Classification of Diseases (ICD) version 7 and ICD-10 codes for testicular cancer, which are 178 and C62, respectively.

From the entire CSHRR a random and representative 5% sub-cohort of each sex was drawn. As shown in Figure 1, the final study population consisted of 5227 men including 408 cases of testicular cancer. The inclusion criteria for the study population were: a personal identification number assigned, year of birth between 1940 and 1983, available information on all key study variables (genital abnormalities, birth weight and birth order).

Information on early life risk factors

Information on cryptorchidism, birth weight and birth order was obtained from individual school health records. Specifically, information on genital abnormalities was

obtained from predefined schemes filled in by the school doctors and grouped in main categories accordingly. It is not noted in the school records if the genital abnormality is reported by the parents, observed by the doctor or both. Cryptorchidism was in the present study defined as the absence of one or both testes from a low scrotal position and classified as either unilateral or bilateral.

Information on birth weight and birth order from the health cards were based on report and recall by the parent present at the first school health examination. Birth weight was categorized in five categories: <2500 g, 2500–2999 g, 3000–3999 g, 4000–4499 g, 4500 + g.

Statistical analyses

The analyses of associations between early life risk factors (cryptorchidism, birth weight and birth order) and testicular cancer were analyzed using survival analysis. A weighted Cox Proportional Hazards regression model, intended for case-cohort designs [12], was applied to accommodate the sampling frame. In this model, each member of the 5% sub-cohort was assigned a weight of 20 and the rest of the study population was assigned a weight of 1. Members of the 5% sub-cohort who developed testicular cancer were assigned a weight of 1. The underlying time scale was age.

Follow-up for testicular cancer was from 2 April 1968 or the date of the first school health examination, whichever came last till the date of testicular cancer diagnosis or diagnosis of other malignancy (except non-melanoma skin cancer), emigration, death or 31 December 2003, whichever came first.

All models were adjusted for age including the crude model. Potential confounding effects of birth weight and birth order on the association between cryptorchidism and testicular cancer were evaluated by the change-of-estimate approach. Birth cohort (categorized in eight levels) was included as a stratification variable in the multivariate models, which also tested for relevant potential interaction effects. Interactions were tested between birth weight and cryptorchidism, and birth cohort and cryptorchidism. Evaluation of the overall significance of categorical variables and interaction terms was done by means of likelihood ratio tests with p-values <0.05 defined as statistically significant. Model control by Schoenfeld residuals confirmed that the proportional hazards assumption was met for all models. The statistical software package R version 2.15.0 and the package ‘survival’ were applied.

Results

In the total study population of 5227 subjects, 408 had a diagnosis of testicular cancer. The age-standardized period incidence rate of 15.8 per 100 000 person-years in the 5% sub-cohort very closely resembled the rate in the Danish population of 13.8 per 100 000 person-years (1970–1999, 20–24 years) [13]. The exact ages at diagnosis of testicular cancer in this study population were in the interval 6.6–60.7 years, with a median of 33.2 years.

Results from descriptive analyses showed that cryptorchidism (all subtypes) was more prevalent in the group of subjects with testicular cancer, relative to the total study

Table 1. Descriptive statistics on the prevalence of early life risk factors for testicular cancer among 5227 men from the Copenhagen school health records registry and thereof 408 subjects with testicular cancer.

N	Total study population		Subjects with testicular cancer	
	(N)	(%)	(N)	(%)
	5227		408	
Cryptorchidism				
Unilateral	212	4.06	49	12.01
Bilateral	41	0.78	8	1.96
Miscellaneous ^a	80	1.53	14	3.43
Any kind	333	6.37	71	17.40
Birth weight (g)				
<2500	250	4.78	29	7.11
2500–2999	619	11.84	56	13.73
3000–3999	3398	65.01	256	62.75
4000–4499	707	13.53	51	12.50
4500+	253	4.84	16	3.92
(Mean $\pm$ SD) ^a	(3422.9 $\pm$ 604.6)		(3351.5 $\pm$ 610.9)	
Birth order				
1	2381	45.55	180	44.12
2	1768	33.82	154	37.75
3	692	13.24	52	12.75
4+	386	7.38	22	5.39

SD: standard deviation. ^aMiscellaneous: laterality of cryptorchidism not stated in health cards.

Table 2. Hazard ratio for the age- and multiple-adjusted associations between early life risk factors and testicular cancer among 5227 men from the Copenhagen School Health Records Registry.

Risk factor	Age adjusted HR (95% CI)	Multiple adjusted ^b HR (95% CI)
Cryptorchidism (any kind)	3.60 (2.79–4.65)	3.46 (2.67–4.48)
Birth weight (g)		
<2500	1.71 (1.16–2.50)	1.48 (1.00–2.17)
2500–2999	1.28 (0.96–1.71)	1.22 (0.91–1.63)
3000–3999	Reference	Reference
4000–4499	0.93 (0.69–1.25)	0.98 (0.73–1.33)
4500+	0.82 (0.49–1.36)	0.90 (0.54–1.49)
Birth order		
1	Reference	Reference
2	1.16 (0.94–1.44)	1.16 (0.94–1.44)
3	0.98 (0.72–1.34)	0.96 (0.71–1.31)
4+	0.68 (0.44–1.06)	0.70 (0.45–1.09)

CI: confidence interval; HR: hazard ratio. ^ap-Value for likelihood ratio test; ^bAll models adjusted for the other covariates and stratified by birth cohort.

population (Table 1). In general, differences in distribution of birth weight categories between subjects with testicular cancer and the study population as a whole were in the magnitude of a few percentage points. The prevalence of firstborns in the group of subjects with testicular cancer was quite similar to that in the total study population.

Any kind of cryptorchidism was significantly associated with an increased risk of testicular cancer in age-adjusted analyses [hazard ratio (HR) = 3.60, 95% CI 2.79–4.65] (Table 2). The association attenuated only slightly in multivariate models with adjustments for birth weight and birth order and stratification by birth cohort (HR = 3.46, 95% CI 2.67–4.48). Interactions between birth weight and cryptorchidism and between birth cohort and cryptorchidism were not significant (data not shown) and hence excluded from the model. In age-adjusted analyses there was an inverse association between birth weight and testicular cancer ($p = 0.04$). The group with the lowest birth weight (<2500 g) had a significantly higher hazard of testicular cancer (HR = 1.71, 95% CI 1.16–2.50) compared to the reference group although this

was only of borderline significance, when adjusted for other covariates (HR = 1.48, 95% CI 1.00–2.17). There was no clear or significant association between birth order and testicular cancer in neither age-adjusted nor multiple-adjusted analyses.

Discussion

In agreement with previous studies, the present study shows that cryptorchidism and low birth weight are risk factors for testicular cancer. The 3.6-fold increased risk for testis cancer after cryptorchidism resembles crude estimates obtained in other recent studies: a hospital-based case-control study from France (N = 1029), which adjusted only for age [odds ratio (OR) = 3.02, 95% CI 1.90–4.79] [14], a Danish population-based cohort study (N = 2 159 883), which adjusted for birth period and age [relative risk (RR) = 3.71, 95% CI 3.29–4.19] [15], and a case-control study from Sweden (N = 39 548), which matched cases and controls on year and county of birth (OR = 3.18, 95% CI 2.50–4.04) [16]. Furthermore, a meta-analysis based on nine case-control studies and three cohort studies examining the association between isolated cryptorchidism and testicular cancer, found a pooled RR of 2.90 (95% CI 2.21–3.82) [17]. An earlier case-control study from our institution applied information from the CSHRR, and distinguished between cryptorchidism persistent at school examination and cryptorchidism with spontaneous descent made possible by a collection and specific scrutiny of the information from successive examinations on 183 cases of testicular cancer and 366 controls from the archive [18]. The study found a higher and significant estimate of RR of testicular cancer among men with persistent cryptorchidism (OR = 4.3, 95% CI 1.9–9.7) than with cryptorchidism with spontaneous descent (OR = 1.4, 95% CI 0.6–2.9) relative to a reference group with no cryptorchidism. Albeit, it can be considered a limitation that the present study does not distinguish between these subtypes of cryptorchidism, it, however, includes more cases, has a larger study sample overall and a longer period of follow-up.

It is hypothesized that high estrogen levels during pregnancy might be a causal factor for testicular cancer, however, in the present study only low birth weight was associated with an increased risk of testis cancer. As low birth weight has previously been associated with a low estrogen level, the present results do not support this hypothesis. However, birth weight alone might not be sufficient information to use to determine exposures to estrogens in the utero so the results must be interpreted with caution. This finding of an inverse association between birth weight and testis cancer is in accordance with a previous study done on a different subset of the CSHRR [19], and contradicts others that find either a positive [20] or a U-shaped association [21,22].

In the present study, birth weight and birth order were hypothesized to be confounders of the main association between cryptorchidism and testicular cancer, but this was not confirmed in the findings. As imperfect proxies of hormonal exposures during pregnancy, they may render the estimates of this main association a subject of residual

confounding. Furthermore, there may be residual confounding by yet other factors not taken into account in the present study, such as maternal age at birth and gestational age at birth. Information on the gestational age at birth was not available in the CSHRR. However, it would have been valuable, as it would enable the distinction between children who had low birth weight because they were born preterm and children who had low birth weight due to, for instance intrauterine growth retardation. This is of interest also because a recent review claimed that the risk of cryptorchidism is significantly elevated in boys born preterm with a correspondingly low birth weight, possibly due to the early delivery itself [23].

Among the strengths of this historical case-cohort study is the validity of the unique population-based registration of all school health examinations of nearly all children in Copenhagen from 1930 to 1992 [10], and thus selection bias is of limited concern when utilizing these data. The registry-based design ensures almost complete follow-up for testicular cancer in the Danish Cancer Registry from the introduction of the personal identification number system and onwards and the wide time span made it possible to take birth cohort into account. Furthermore, school doctors ascertained presence of any genital abnormalities and the information was collected prior to development of testicular cancer. This is in contrast to many other studies, which have relied on self-report and recall of cryptorchidism status in childhood. Also, information on cryptorchidism was collected at school age relative to at birth, thus providing a better indication of persistent cryptorchidism.

In conclusion, the findings of the present study verify the well established association between cryptorchidism and testicular cancer in a large population-based dataset spanning several decades of birth cohorts. Furthermore, the study contributes with the finding that this association persists after taking birth weight and birth order into account, and thus these factors do not seem to be important confounders. The study finds supporting evidence of an inverse association between birth weight and testicular cancer, and no clear association between birth order and testicular cancer.

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Disclosure statement

The authors report no conflicts of interest.

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