Birth Characteristics and Risk of Prostate Cancer: the Contribution of Genetic Factors

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Abstract

Background: Prostate cancer has a strong hereditary component, but it has been proposed that hormonal influences in utero may contribute to offspring risk. We investigated the associations between birth characteristics and the risk of prostate cancer in twins, and whether possible associations could be confounded by familial factors, such as shared environment and common genes.

Methods: All like-sexed male twins in the Swedish Twin Registry, born from 1926 to 1958 and alive in 1973, were eligible. Data were obtained from birth records, and 11,420 male twins with reliable birth weight data were included in the final study population. Hazard ratios with 95% confidence intervals (CI) from Cox regression models were used to estimate associations between birth characteristics and risk of prostate cancer. Paired analysis was done to account for potential confounding by familial factors.

Results: Compared with twins with a birth weight of 2,500 to 2,999 g, the hazard ratio (95% CI) for twins with a higher birth weight (≥3,000 g) corresponded to 1.22 (0.94-1.57). In analyses within twin pairs, in which both twins had a birth weight of ≥2,500 g, a 500 g increase in birth weight was associated with an increased risk of prostate cancer within dizygotic twin pairs (odds ratio, 1.41; 95% CI, 1.02-1.57), but not within monozygotic twin pairs (odds ratio, 1.06; 95% CI, 0.61-1.84).

Conclusions: High birth weight is associated with an increased risk of prostate cancer. The difference in risk within dizygotic and monozygotic twin pairs may be due to genetic factors playing an important role in this association.

Introduction

Prostate cancer has a strong genetic component (1), and a number of specific genetic factors associated with prostate cancer risk have recently been detected (2). In addition, prostate cancer is a hormone-dependent cancer, and it has been proposed that hormonal influences in utero may contribute to offspring risk (3). Birth weight can, especially when adjusted for gestational age, be considered a proxy for fetal growth. As such, birth weight may be used as an indirect marker for fetal exposure to growth-stimulating factors such as insulin-like growth factors (4-6) and estrogens (7-9), which may also be involved in the carcinogenesis of reproductive cancer diseases (10, 11). High birth weight is associated with breast cancer (12), whereas the association between birth weight and prostate cancer is less certain (13-18).

Fetal growth is, like prostate cancer, largely determined by genetic factors (19). If the same genes influence fetal growth and prostate cancer, a possible association between birth weight and prostate cancer may be confounded by genetic factors. Twin studies enable unique possibilities to study whether the association between exposure and disease is influenced by shared environment and common genes: all twin siblings share intrauterine and early environment, dizygotic twins share, on average, half of their segregating genes and monozygotic twins share all genes. We analyzed information on birth characteristics from birth records in like-sexed male twins with known zygosity to investigate the association between birth weight and risk of prostate cancer, and whether a possible association is confounded by genetic and/or shared environmental factors in early life.

Materials and Methods

Study Population. The Swedish Twin Registry is a population-based registry of twins born in Sweden since 1886 (20). In 1973, all like-sexed twins born from 1926 to 1958 were sent a paper-based questionnaire, including questions of degree of likeness, anthropometric measures, and lifestyle factors. The response rate was 81% (20-22). In this study, we restricted the cohort to male twins with known zygosity, as determined by questions on childhood resemblance. Self-reported zygosity has been validated with DNA markers in a subsample of 199 twin pairs, and was proven correct in 99% of the twin pairs (20). The person-unique national registration number, assigned to all Swedish citizens, permitted linkage between the Swedish Twin Registry, the Cancer and Cause of Death Registers, and also enabled us to retrieve information from birth records. The study was approved by the research ethics committee of the Karolinska Institutet.

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Outcome. Information about prostate cancer was retrieved from the population-based Swedish Cancer Register, which includes information from all primary incident cancers in Sweden since 1958. Reporting is mandatory for physicians as well as pathologists and cytologists separately, and 99% of the registered cancers in 2006 have been morphologically verified (23). The registry roughly covers 95% of all cancers reported in the Cause of Death Registry (23, 24), the deficit mainly represented by patients over 75 years of age. The cancers are classified according to the International Classification of Diseases (ICD). Prostate cancer cases were recorded during the time of follow-up (from 1973 to 2006) and identified from the Swedish Cancer Register (ICD-7 code 177, ICD-8 and ICD-9 code 185, and ICD-10 code C61). We found no cases whose underlying cause of death was reported to be prostate cancer in the Cause of Death Register that were not reported in the Swedish Cancer Register. Reports of death in the Cause of Death Register have been computerized since 1952, and are considered reliable from 1961 onwards (25).

Exposures. Information about maternal and birth characteristics were documented at birth by the attending midwife, and recording and preservation of birth records is enforced by law. We retrieved information from original birth records by visiting delivery archives, located all over Sweden. Correct birth identification of each twin within a pair was ensured by restricting the data collection to twin pairs who were both baptized and named at birth, or who reported birth order with mutual within-pair agreement in a telephone interview, conducted in 1998 to 2002 (26). Information from birth records included anthropometric measures at birth, gestational age, maternal age, parity, and occupational status of both parents. Gestational age was based on the date of the first day of the last menstrual period. Socioeconomic status at birth was based on information of parental occupation, and was classified according to the recommendations by Statistics Sweden (27).

For this study, all like-sexed male twins with known zygosity born from 1926 to 1958, were considered. In the 15,418 males who were alive and without previous prostate cancer diagnosis at the start of follow-up in 1973, the birth record coverage was 74%. Restrictions were due to missing birth weight data in birth records (N = 2,809) and not correct identification of each twin within a twin pair at birth (N = 1,189), resulting in a final study population of 11,420 twins (including 5,622 intact twin pairs).

Statistical Analyses. Risk time (person-years) was accrued from the time of entry (January 1, 1973) until a first diagnosis of prostate cancer, or censored at the date of first emigration from Sweden, death, or end of follow-up (December 31, 2006). Cox proportional hazard models were used to estimate hazard ratios (HR) for prostate cancer, with age (measured in months) as the underlying time scale, and robust SE estimates to account for the dependence within twin pairs. The proportional hazards assumption was verified by plotting of scaled Schoenfeld residuals. Splines were used to investigate whether there is a linear relationship between birth weight and risk for prostate cancer.

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,000</td>
<td>3,882 132 3.4 10.4</td>
</tr>
<tr>
<td>2,000-2,999</td>
<td>4,143 121 2.9 8.9</td>
</tr>
<tr>
<td>≥3,000</td>
<td>3,395 129 3.8 10.9</td>
</tr>
</tbody>
</table>

*Age-adjusted incidence rates per 10,000 person-years.
share early environment, dizygotic twins share, on average, 50% of their segregating genes, whereas monozygotic twins share 100% of their segregating genes. If the effect of the within-component is smaller in monozygotic twins compared with dizygotic twins, this indicates that confounding is more related to genetic than to shared environmental factors.

The paired analysis assumes a linear effect of the exposure. Finding an not strictly linear relationship between birthweight and prostate cancer between twins, we proceeded with the paired analyses in the subgroup of twins born above 2,500 g.

**Results**

In the cohort of 11,420 male twins, 382 developed prostate cancer during the time of follow-up. Table 1 shows the distribution of birth characteristics in relation to age-adjusted incidence rates of prostate cancer. The incidence rate was higher in older compared with younger birth cohorts. The incidence rate of prostate cancer was lower among men with a birth weight between 2,500 and 2,999 g than among men with higher or lower birth weight.

The nonlinear relationship between birth weight and risk of prostate cancer is illustrated in Fig. 1. In the spline model, the association between birth weight and risk of prostate cancer started to increase from \( \sim 3,000\) g.

Table 2 show birth weight categories and HRs of prostate cancer. Compared with males with birth weights of 2,500 to 2,999 g, males with lower but especially higher birth weight had slightly increased risks of prostate cancer in the age-adjusted model. The association between birth weight and risk of prostate cancer remained essentially unchanged when we also adjusted for gestational age and zygosity.

Next, we wanted to investigate whether familial (genetic or shared environmental) factors influenced the association between birth weight and prostate cancer risk. Table 3 shows the effect of a 500 g increase in birth weight on prostate cancer risk within twin pairs. Within dizygotic twin pairs, the risk of prostate cancer increased with birth weight: a 500 g increase in birth weight was associated with a 25% increased risk of prostate cancer, whereas corresponding increase within monozygotic twins was 12%. Given that the risk of prostate cancer started to increase from \( \sim 3,000\) g (Fig. 1), we also restricted the analyses to twin pairs, in which both twins had a birth weight of \( \geq 2,500\) g. We found that a 500 g increase in birth weight was associated with a 41% increased risk within dizygotic twins. These results were in contrast with the results within monozygotic twins, in which corresponding risk was not increased (Table 3). When we formally tested for an interaction between birth weight and zygosity with regard to the risk of prostate cancer, the interaction was not significant (\( P = 0.61\)).

**Discussion**

We found that an increase in birth weight was associated with a modestly increased risk of prostate cancer within dizygotic (fraternal) but not within monozygotic (genetically identical) twin pairs. These findings suggest a genetic background for the association between birth weight and prostate cancer risk.

In the cohort analysis, we found evidence of a nonlinear relationship between birth weight and prostate cancer, with increasing risks especially among offspring with birth weights from \( \sim 3,000\) g. Given the generally reduced birth weight in twins, we had limited possibilities to study the effects of high birth weight on prostate cancer risk. We also observed a modest nonsignificant risk increase related to low birth weight (odds ratio, 1.12; Table 2), which does not agree with the observation that prenatal exposure to preeclampsia (which reduces fetal growth) is, if anything, associated with a reduced risk of prostate cancer in offspring (14, 15).

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Table 2. Unadjusted and adjusted HRs of prostate cancer in relation to birth weight in the cohort analyses of Swedish like-sexed twins born from 1926 to 1958

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>Crude* (n = 11,420)</th>
<th>Adjusted for birth characteristics† (n = 10,884)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,500</td>
<td>3,882</td>
<td>132</td>
<td>3.4</td>
<td>1.16 (0.91-1.48)</td>
<td>1.12 (0.86-1.46)</td>
</tr>
<tr>
<td>2,500-2,999</td>
<td>4,143</td>
<td>121</td>
<td>2.9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥3,000</td>
<td>3,395</td>
<td>129</td>
<td>3.8</td>
<td>1.22 (0.96-1.56)</td>
<td>1.22 (0.94-1.57)</td>
</tr>
</tbody>
</table>

NOTE: All analyses accounted for the clustered data structure and between-cluster effect.

*Age-adjusted HRs.
†Also adjusted for gestational age and zygosity.

Table 3. Oddsratios of prostate cancer related to a 500 g increase in birth weight within twin pairs

<table>
<thead>
<tr>
<th>Effect of 500 g increase in birth weight</th>
<th>N</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within dizygous pairs</td>
<td>7,107</td>
<td>1.25 (0.96-1.62)</td>
</tr>
<tr>
<td>Within monozygous pairs</td>
<td>4,313</td>
<td>1.12 (0.79-1.59)</td>
</tr>
<tr>
<td>Within pairs ≥2,500 g</td>
<td>4,819</td>
<td>1.41 (1.02-1.95)</td>
</tr>
<tr>
<td>Within dizygous pairs</td>
<td>2,456</td>
<td>1.06 (0.61-1.84)</td>
</tr>
</tbody>
</table>

NOTE: The analysis has accounted for the clustered data structure and between-cluster effect.
Our finding, that high birth weight may be associated with a modestly increased risk of prostate cancer in the twin cohort, has previously been reported. A strong positive association between birth weight and prostate cancer was initially reported by a Swedish cohort study, only including 21 cases of prostate cancer (18). Later, a Swedish study found nonsignificant positive associations between high birth weight and risk of prostate cancer (14) and a Norwegian study found a positive association between increasing birth length and risk of metastatic prostate cancer (16). However, in two studies from the United States and in one Swedish study, there was no overall support for an association (13, 15, 17), although one of the studies could not rule out a modest positive association between birth weight and high stage/grade prostate cancer (17). Differences in study size and designs may account for these discrepant results.

Given that both fetal growth (19) and prostate cancer (1) have strong genetic components, we did a twin study, which allowed us to investigate whether a possible association between birth weight and prostate cancer may be confounded by genetic factors. Our findings of a positive association within dizygotic (fraternal) twins and a lack of association within monozygotic twins support the hypothesis of genetic confounding. We acknowledge that our results were hampered by statistical power and need to be confirmed. Still, because genetic confounding was our a priori hypothesis, we feel entitled to speculate about possible underlying reasons.

Genetic factors could be important for the association between high birth weight and prostate cancer in several ways. A locus in the HNF1B gene in chromosome 17 has repeatedly been associated with increased risk of prostate cancer (29, 30). This gene is also associated with reduced risk of type 2 diabetes (29), and we recently reported that the association between low birth weight and risk of type 2 diabetes may be explained by genetic factors (31). Type 2 diabetes has also been reported to reduce the risk of prostate cancer (32). Thus, it is plausible that the same set of genetic factors contribute to the association between high birth weight and increased prostate cancer risk and to the association between low birth weight and increased risk of type 2 diabetes. As far as we know, it has not been studied whether the locus in the HNF1B gene in chromosome 17 is connected to the regulation of fetal growth. In addition, genotypes related to reduced insulin secretion or insulin resistance has been associated with both low birth weight and glucose intolerance (33), whereas corresponding associations with prostate cancer are less certain (11).

Our study of twins offers a major advantage as the associations in the within-pair analyses were not confounded by unmeasured shared environmental or socioeconomic influences and, in monozygotic twins, they were also independent of genetic factors. Furthermore, differences in birth weight within twin pairs reflect differences in fetal growth. Information on perinatal and parental sociodemographic characteristics was retrieved from original birth records, which precludes recall bias on the exposures.

Our cohort analysis was limited in number of prostate cancer cases, and a hampered statistical power was obvious from the wide confidence intervals. We also acknowledge that we cannot exclude the possibility that the association between birth weight and risk of prostate cancer within dizygotic, but not within monozygotic twin pairs, is due to chance. However, the lack of a significant interaction between birth weight and zygosity could also be explained by the small sample size.

The generalizability of results from twin studies may be questionable because twins are, in general, more growth-restricted than singletons, have shorter gestational age, and because they may differ in prenatal environment and upbringing. However, the incidence of prostate cancer does not seem to be different in twins compared with singletons (34). An important question is also whether results within dizygotic and monozygotic twin pairs can be compared. Dizygotic twin pairs have two placenta, whereas 70% of monozygotic twins are monochorionotic, i.e., they share one placenta. Unequal sharing of the placenta is also a primary contributor of birth weight discordance within monochorionotic (monozygotic) twin pairs (35). This suggests that the etiology behind birth weight discordance is similar and due to placental constraint in both dizygotic and monozygotic twin pairs.

To our knowledge, no previous study has investigated the association between birth weight and prostate cancer in a genetically informative population, such as like-sexed twins with known zygosity. We found a positive association between birth weight and prostate cancer within dizygotic but not within monozygotic twins, suggesting that this association may be confounded by genetic factors. Together with recent progress in genetic cancer research, our findings lend support to the hypothesis of an interaction between prostate cancer–regulating genes and the intrauterine environment with respect to prostate cancer development.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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