Abstract

To assess the association between adult body size and germ-cell testicular cancer risk and to understand whether this association is independent from perinatal characteristics, a nested case-control study was conducted. Three hundred and seventy-one patients with testicular cancer, registered in the Swedish Cancer Registry between 1958 and 1996 and aged 20–54 years at diagnosis, and 1238 individually matched controls were identified. Information on adult body size at age 18 years was obtained for all subjects through the Military Service Conscription Register, whereas perinatal information was obtained through birth records at the subjects’ respective maternity wards. Height was positively associated with testicular cancer risk, and the association persisted after taking into account perinatal characteristics. The adjusted odds ratio (OR) was 1.55 [95% confidence interval (CI), 1.10–2.17] for the third tertile of height as compared with the first. No association between the risk for testicular cancer and body mass index was found.

Long duration of gestation was negatively associated with testicular cancer risk [OR = 0.64 (95% CI, 0.45–0.91), post-term compared with term], whereas high birth weight appeared to increase the risk [OR = 1.35 (95% CI, 0.99–1.85)]. In conclusion, adult height and perinatal factors acted independently, suggesting that both the fetal life and the childhood and adolescence periods are windows of susceptibility to exposures that influence the risk for testicular cancer.

Introduction

Apart from undescended testis, a certain degree of familiar occurrence, and genetic disorders, there is to date no well-established risk factor for germ-cell testicular cancer. This tumor occurs predominantly among young men (1), and carcinoma in situ has been found in the testis at very young ages (2). It has been hypothesized that the risk of germ-cell tumor development is, to a great extent, determined prenatally. Findings of increased risks associated with perinatal factors, such as low birth order, pre-term birth, and low or high birth weight have given support to a prenatal origin, although the available data are conflicting (3–10).

The rapid growth of the testes during puberty may be another period of vulnerability to carcinogenic exposures. Early age at puberty (11–14) and adult tallness (15–17) have been associated with the risk of testicular cancer, but the exposures and the biological mechanisms behind these associations are not known.

Postnatal growth is known to be correlated with fetal growth. Hence, the association between adult tallness and risk for testicular cancer might be attributable to prenatal factors or vice versa. Furthermore, postnatal catch-up growth, rather than intrauterine growth retardation, could be carcinogenic to the testis. Great attention has been given to the relationship between perinatal characteristics and adult body size in cardiovascular diseases (18), but, to our knowledge, no study has investigated it with concern to testicular cancer risk. Therefore, in a population-based nested case-control study, we evaluated perinatal and adult characteristics simultaneously to enable study of confounding and interaction between these two time windows.

Materials and Methods

In the cohort of all males born in selected hospitals between 1920 and 1976 in two Swedish regions (Uppsala-Örebro Health Care Region and the city of Stockholm) and alive and resident in the country at January 1958, when the Cancer Registry was established, we have previously conducted a nested case-control study on perinatal characteristics and the risk of testicular cancer (19). All subjects in the cohort recorded with malignant germ-cell testicular cancer at the Swedish Cancer Registry, code 178 in the International Classification of Diseases 7th Revision, between 1958 and 1996 were selected as cases. For those born in Uppsala-Örebro, the actual end of follow-up was 1994. Histological information included in the Cancer Registry allowed us to separate testicular cancers into two major groups: seminomas and nonseminomas. Twin cases were not included in the study because being a twin may confound the association between perinatal characteristics and testicular cancer risk, and, due to small numbers, it was not possible to adjust for twin status in the analysis.

The first four singleton males born at the same hospital after a case and alive and without testicular cancer at the time of the patient’s diagnosis served as controls. Overall, 628 cases and 2309 controls aged 15–54 years at diagnosis (or recruitment for controls) were identified. Subjects aged at least 20 years (586 cases and 2132 controls) were included in the study.

Information on several peri- and prenatal characteristics was obtained through the birth records available at the archives...
of the subjects’ respective maternity wards. The hospital of birth and the birth records could be identified using the subjects’ national registration number, which is a unique personal identifier assigned to all residents in Sweden since 1947 (20).

To obtain information on body size in adulthood, we performed a linkage between the study subjects and medical data stored in the Swedish Military Service Conscription Register. For the purpose of military service, a medical examination is mandatory for all male citizens at 18 years of age in Sweden. Charts for subjects born in 1931 onward are recorded in the Military Register according to the national registration number, with the exception of charts for men born between January 1946 and July 1950, which are stored in the archive under the date of the medical examination. For the latter subjects as well as for men born before 1931, we could not perform the linkage. Thus, 457 cases and 1673 controls formed the potential eligible subjects for the present study, of which 82% of cases and 78% of controls were actually traced in the Military Register. Failure of linkage concerned mainly subjects born before 1946 (71% and 60% of these cases and controls, respectively, were linked), whose data in the Military Register are not computerized. In particular, we did not obtain information on subjects who were born before 1946 and exempted from the military service because their charts during some periods were not stored in the central archive but remained in different local or regional archives. Among those born after July 1950, the linkage succeeded for 88% of the 311 cases and 86% of the 1166 controls.

To avoid problems of reverse causality, we excluded from the study subjects (4 cases and 20 controls) who attended the medical examination less than 2 years before the diagnosis of the cancer (or recruitment for controls). The date of the visit was not available for 3.8% of cases and 3.5% of controls. These subjects were included in the study.

When a case subject was excluded from the study, we also excluded the corresponding controls (21). Furthermore, we excluded matching strata that included cases only. Three hundred and seventy-one patients and 1238 controls remained for analysis.

The study was approved by the Ethics Committee at Karolinska Institutet.

Perinatal characteristics considered in the present analyses were birth weight, gestational duration (estimated on the basis of the first day of the last menstruation), SGA, LGA, birth order, maternal age, maternal socioeconomic status, medical problems of the newborn, neonatal jaundice, and history of pre-eclampsia/toxicosis during pregnancy. Medical problems of the newborn included any perinatal medical condition recorded in the birth charts (mainly neonatal asphyxia and cephalic hematoma). The intrauterine growth curves estimated by Marsal et al. (22) were used to define LGA and SGA, with the values corresponding to the mean weight for gestational age ± 2 SDs as the cutoff.

Measures of adult height and weight were retrieved from the charts of the Military Register, and the BMI [BMI = weight (kg)/height (m²)] was calculated.

We used conditional logistic regression to estimate ORs for testicular cancer and derive 95% CIs by using the PHREG procedure available in SAS software (23). Variables were categorized as shown in Tables 1 and 2. In particular, for birth weight, gestational duration, and BMI, we followed a standard categorization, whereas we used tertiles of the distribution among controls for height. When perinatal characteristics were investigated, models included gestational duration, SGA, LGA, birth weight (which was introduced as alternative to SGA and LGA), and maternal age (each 5-year increase) as well as neonatal jaundice (data missing for 24 subjects) and medical problems of the newborn (data missing for 1 subject). Other variables were neither substantial confounders nor a priori risk factors for testicular cancer. Models to investigate adult characteristics included adult height and BMI. Subjects with missing information were excluded from the analysis when the variable with missing values had to be included in the model.

We evaluated perinatal and adult variables in relation to the risk of testicular cancer in two separate models (OR1 in Tables 1 and 2). The two histological subgroups, seminomas and nonseminomas, were analyzed separately as well as together. Then, models including both perinatal and adult characteristics were performed to evaluate their effects on risk after mutual adjustment (OR2 in Tables 1 and 2). The OR1s estimated in the models with perinatal characteristics only or adult

| Table 1 Risk for germ-cell testicular cancer in relation to perinatal characteristics |
|----------------------------------|-----------------|------------------|-----------------|-----------------|
| Perinatal characteristics       | Cases (N = 371) | Controls (N = 1238) | Crude OR (95% CI) | OR1 (95% CI) |
| Birth weight (g)                |                 |                  |                  |                |
| <2500                            | 15 (4.0)        | 43 (3.5)         | 1.25 (0.69–2.29) | 1.14 (0.58–2.25) |
| 2500–3999                       | 274 (73.9)      | 967 (78.1)       | 1.00             | 1.00           |
| ≥4000                           | 82 (22.1)       | 228 (18.4)       | 1.28 (0.95–1.71) | 1.43 (1.05–1.94) |
| Gestational duration (wks)      |                 |                  |                  |                |
| <37                             | 22 (6.1)        | 58 (4.8)         | 1.14 (0.68–1.90) | 1.10 (0.65–1.89) |
| 37–41                           | 287 (79.5)      | 897 (74.6)       | 1.00             | 1.00           |
| ≥41                             | 52 (14.4)       | 147 (20.6)       | 0.65 (0.46–0.92) | 0.66 (0.46–0.93) |
| Missing                         | 10              | 36               |                  |                |
| Dimension for gestational age   |                 |                  |                  |                |
| SGA                             | 19 (5.3)        | 65 (5.4)         | 1.00 (0.59–1.69) | 1.04 (0.61–1.78) |
| Normal                          | 326 (90.3)      | 1098 (91.4)      | 1.00             | 1.00           |
| LGA                             | 16 (4.4)        | 39 (3.2)         | 1.26 (0.69–2.30) | 1.16 (0.62–2.17) |
| Missing                         | 10              | 36               |                  |                |

OR1 is adjusted for variables in the table, maternal age, neonatal jaundice, and medical problems of the newborn. Birth weight was introduced as alternative to SGA and LGA. Cases (n = 15) and controls (n = 54) with missing values in at least one variable included in the model were excluded.

OR2 includes the same variables as OR1 and adult height and BMI. Birth weight was introduced as alternative to SGA and LGA. Cases (n = 21) and controls (n = 85) with missing values in at least one variable included in the model were excluded.

Values = number (percentage of the total excluding subjects with missing values).
characteristics only were compared with the corresponding OR2s obtained from the model with both perinatal and adult characteristics. Finally, the joint effect (interaction) between adult height and perinatal characteristics was investigated in stratified analyses.

**Results**

**Perinatal Characteristics.** As expected from our previous analysis (19), gestational duration was negatively associated with the risk for testicular cancer ($P$ for linear trend = 0.02), whereas a significant increased risk was found for men with a high birth weight (OR1, Table 1). No association was found between the risk for testicular cancer and SGA or LGA. For all perinatal variables, the adjustment for adult height and adult BMI (OR2, Table 1) imposed only a marginal change in the ORs.

**Adult Characteristics.** With respect to adult anthropometric measures, the risk for testicular cancer increased with increasing in height (OR1, Table 2). The association persisted both when the shortest subjects (<170 cm) were excluded from the reference category and when the analysis was restricted to subjects born after 1950, who had a more complete linkage with the records at Military Register (data not shown). Both high and low BMI were negatively but nonsignificantly associated with testicular cancer risk. When perinatal variables were also included in the model (OR2, Table 2), the association between adult height and testicular cancer risk persisted.

There were no major differences in the results when the two histological types of testicular cancer were analyzed separately. The ORs for seminomas (184 cases) were 1.60 (95% CI, 1.02–2.53) and 1.86 (95% CI, 1.18–2.95), respectively, for the second and third tertile of height as compared with the first one, whereas the corresponding ORs for nonseminomas (187 cases) were 1.44 (95% CI, 0.92–2.23) and 1.35 (95% CI, 0.84–2.17).

**Interaction between Perinatal Characteristics and Adult Height.** The comparison between ORs mutually adjusted for adult and perinatal characteristics (OR2, Table 1 and 2) and the ORs estimated in the models with perinatal characteristics only (OR1, Table 1) or adult body size only (OR1, Table 2) indicates independent association for perinatal and postnatal variables. Table 3 summarizes the results obtained when height was evaluated stratified by gestational duration and birth weight. There was no clear indication of heterogeneity.

**Discussion**

The study has several strengths and some limitations. Patients were identified through the Cancer Registry, which is close to 100% complete in Sweden. According to the nested design, all information was prospectively collected. Thus, any misclassification of body size measures ought to be nondifferential. Furthermore, adult weight and height have been measured approximately at the same age for all subjects, irrespective of the age at diagnosis or the case/control status.

In contrast to our previous investigation (19), the present study includes men aged at least 20 years at diagnosis (instead of 15 years) and considers only subjects born during the years...
covered by the Military Register. These selection criteria decreased the number of eligible subjects but are not likely to have introduced any selection bias. Indeed, results on perinatal characteristics from the present study were similar to those obtained in our previous analysis on the whole sample of subjects.

We obtained information on adult anthropometric measures on approximately 80% of the potentially eligible subjects. This failure of linkage may have introduced some bias if the mechanism of failure was associated both with testicular cancer and body size. However, cases were diagnosed at least 2 years after the medical examination, and there are no known common medical conditions associated with testicular cancer that (a) prevent one from doing the military service and (b) are associated with adult height. Moreover, it is reassuring that results from the analysis restricted to subjects born after July 1950, of whom nearly 90% were linked to the records at Military Register, confirm the findings obtained on the whole study sample.

The association between adult height and risk for testicular cancer has been reported previously (15, 16). One further study found an excess risk confined to tall seminoma patients (14), whereas three other studies did not find any evidence of an association (8, 24, 25). Because the association between height and testicular cancer risk (OR1, Table 2) persisted when perinatal factors were taken into account (OR2, Table 2), our study indicates an association with height that is independent of fetal growth. The adjustment for gestational age and birth weight resulted in little change in the ORs for height, indicating that these variables were not strong confounders. Moreover, because these two variables are meticulously recorded by midwives (as indicated by the very few missing values) and rather easily measured, we do not believe that the association between height and testicular cancer risk was due to residual confounding from perinatal variables.

The result from this study suggests that both prenatal and postnatal exposures have a role in testicular cancer etiology. One recent twin study also obtained anthropometric measures at different period of life, including birth and 18 years of age (17). However, the different measures were not included in the same model, perhaps because of power limitations. In the study, height at 18 years old had a nonsignificant 40% excess risk for testicular cancer, whereas arm and leg length were significantly associated.

Previous results on adult BMI and the risk for testicular cancer are more conflicting, and no study has found any statistically significant association (14–16, 24–26), with the exception of one study showing an increased risk among men with low BMI (8). Most of these studies used retrospectively collected data, and only one obtained information on weight at the same age for all subjects (17). However, the lack of association seemed to be irrespective of the study design. Likewise, BMI and risk for testicular cancer were not associated in our data.

The underlying biology of our findings on height is unknown. The incidence of testicular cancer has increased steadily in several populations over the last 50 years (1), concurrent with a parallel secular trend of increasing height (27). Therefore, factors affecting adult height are possible candidates to explain part of the trend in incidence of testicular cancer.

Finally, adult height is influenced by several factors, which may also interact with each other. Firstly, growth after birth is hormonally regulated, mainly by sex steroids (testosterone in men), and growth hormones. One hormone of particular interest might be insulin-like growth factor I, whose plasma levels correlate with height (28). In turn, high levels of insulin-like growth factor I have been associated with the risk for a number of tumors (29), including prostatic cancer (30, 31) and premenopausal breast cancer (32).

Parental measures and fetal growth are predictors of adult body size (33, 34). Body size at birth was considered in our analysis and ruled out as a possible explanation for our findings on postnatal growth. However, we had no information on parental body size, which is also related to adult height. An inverse association between late age at puberty and the risk for testicular cancer has been suggested by some previous studies (11–14). Because early puberty results in shorter stature (35), our results on adult height cannot be attributed to pubertal age.

Intake of fat, animal proteins, and micronutrients during childhood and adolescence are associated with an increased height (27). A recent ecological study including 42 countries showed a high correlation between incidence of testicular cancer and per capita consumption of cheese, milk, and animal fats (36). In the same study the correlation coefficient for some other foods, such as fish or vegetables, was close to zero. A few observational studies on diet and testicular cancer have been conducted, with problems of low power, recall bias, and low response rate. One study reported increased milk consumption in adolescence, but not consumption of dairy products, among testicular cancer patients (37). Another study reported an association with total fat and saturated fat consumption (38). A twin study did not find evidence of an association, but most of the twin couples were concordant for diet patterns (17). Interestingly, in the search for candidate causal exposures, milk and dairy products contain high levels of sex hormones, such as estrogens and progestrone (39).

In conclusion, we found that the risk for germ-cell testicular cancer was increased among men with a high weight at birth and decreased among those born post-term and those who were short at 18 years old. No clear association was found with adult BMI. Perinatal factors and adult height appeared to act independently, suggesting that both the fetal life and the childhood and adolescence periods are windows of susceptibility to exposures that influence the risk for testicular cancer.

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References
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