Short Communication

Duration of Gestation and Prostate Cancer Risk in Offspring[1]

Anders Ekbom, Joanne Wuu, Hans-Olov Adami, Chih-Ming Lu, Pagona Lagiou, Dimitrios Trichopoulos, and Chung-cheng Hsieh[2]

Department of Medical Epidemiology, Karolinska Institute, Stockholm S-171 77, Sweden [A. E., H-O. A.]; University of Massachusetts Cancer Center, Worcester, Massachusetts 01605 [J. W., C-M. L., C-c. H.]; Department of Urology, Tian-Sheng Memorial Hospital, Pingtung 928, Taiwan [C-M. L.]; Department of Epidemiology, Harvard School of Public Health and Harvard Center for Cancer Prevention, Boston, Massachusetts 02115 [D. T., C-c. H.]; and University of Athens, Athens 115 27, Greece [P. L., D. T.]

Abstract

This large population-based nested case-control study investigated the importance of perinatal characteristics as risk factors for prostate cancer in later life in a cohort of men who were born between 1889 and 1941 in Stockholm, Sweden. Eight hundred and thirty-four prostate cancer cases over 18 years of age and of singleton birth were identified from the cohort between 1958 and 1994. For each case, singleton males born live to the first four mothers admitted after the case's mother were selected as potential controls; 1880 eligible controls were included in the study. For each study subject, we obtained data on mother's parity, pre-eclampsia or eclampsia before delivery, age at delivery, and socioeconomic status, as well as child's birth length and weight, placental weight, and gestational age. Odds ratio (OR) estimates and 95% confidence intervals (CIs) were derived from logistic regression analyses. We found no statistically significant differences between cases and controls with respect to maternal age, socioeconomic status, or parity. Birth weight, birth length, and placental weight were also not significantly related to prostate cancer risk. Pregnancy toxemia (OR = 0.33; 95% CI, 0.07–1.45) and longer gestation age were associated with a reduced risk of prostate cancer; the OR estimate was 0.94 (95% CI, 0.89–0.99) for each 1-week prolongation of the duration of gestation. Our results suggest that birth size indicators are not important risk factors for prostate cancer in later life. In addition, our data on gestation age indicate that the late *in utero* environment may be as important as the early *in utero* environment in the modulation of prostate cancer risk in offspring.

Introduction

The hypothesis that intrauterine hormones may affect prostate cancer risk in offspring was advanced by Henderson *et al.* (1) and Ross and Henderson (2), who focused on the early *in utero* estrogen and testosterone environment that could affect the hypothalamic-pituitary-testicular feedback system through imprinting. Evidence for perinatal influences on prostate cancer risk was revealed in a small cohort study in Gothenberg, Sweden, where a strong positive association between birth weight and prostate cancer risk was reported (3). Fetal growth and pre-eclampsia or eclampsia are correlated with concentrations of pregnancy hormones (4). In a nested case-control study in Uppsala, Sweden, nonsignificant positive associations of prostate cancer risk with several birth size indicators and a significant inverse association with pregnancy toxemia were reported (4). Furthermore, a retrospective analysis of birth weight in relation to prostate cancer found no overall association between birth weight and prostate cancer incidence and found weak and nonsignificant evidence for a positive association between birth weight and high-stage/grade prostate cancer (5). To assess the importance of perinatal characteristics as risk factors for prostate cancer in later life, we performed a large population-based nested case-control study in Stockholm, Sweden.

Subjects and Methods

Because there is no private inpatient treatment in Sweden, hospital services are population based. We have attempted to identify all men born between 1889 and 1941 at the two major delivery centers in Stockholm who were residents of the city of Stockholm on or after January 1, 1947 and were alive in 1958. The individually unique national registration number used for identification and follow-up was introduced for all Swedish residents in 1947. The first six digits provide the date of birth (year, month, and day), whereas the seventh and eighth digits provide information on county of birth or residency on January 1, 1947.

In Sweden, all patients newly diagnosed with malignant tumors must be reported by both the diagnosing physician and the pathologist or cytologist to one of six regional cancer registries, which pass data to the national cancer registry established in 1958. At the time of this study, the national cancer registry was complete through December 31, 1994.

All men in the national cancer registry with a diagnosis of prostate cancer (International Classification of Diseases 7, code 177) and a city code for Stockholm in their national registration number were included in the study. Cases may have been missed if a man born at one of the two delivery centers moved out of the city before 1947 and subsequently developed prostate cancer. From the county in which each patient lived when prostate cancer was diagnosed, we were able to establish his place of birth and family name at birth. At this stage, patients not born at one of the two delivery centers were excluded. Fatal cases, whose underlying cause of death on the death certificate was stated to be prostate cancer, were identified by linkage with the Death Registry.

Received 7/13/99; revised 10/15/99; accepted 11/15/99.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by American Cancer Society Grant EDT-120.
[2] To whom requests for reprints should be addressed, at University of Massachusetts Cancer Center, 373 Plantation Street, Suite 211, Worcester, MA 01605. Phone: (508) 856-4780; Fax: (508) 856-2212; E-mail: chung.hsieh@umassmed.edu.

Table 1 Conditional logistic regression-derived ORs (and 95% CIs) for prostate cancer in relation to a series of maternal and perinatal characteristics

Characteristics	Cases $n = 834$[a]	Controls $n = 1880$[a]	Category or incremental unit for OR	OR (95% CI)[b]	P (two-sided)
Maternal age (yrs)					
<20	35 (4.2)	93 (5.0)	<20	1.00 (reference)	
20–24	184 (22.1)	521 (27.8)	20–24	1.01 (0.65–1.58)	0.95
25–29	284 (34.1)	596 (31.8)	25–29	1.31 (0.84–2.05)	0.24
30–34	207 (24.8)	369 (19.7)	30–34	1.51 (0.94–2.41)	0.09
≥35	124 (14.9)	298 (15.9)	≥35	0.97 (0.59–1.61)	0.92
Socioeconomic status (%)[c]					
Low	695 (84.0)	1535 (82.3)			
Medium	97 (11.7)	271 (14.5)	1 class	1.02 (0.85–1.23)	0.81
High	35 (4.2)	59 (3.2)			
Parity (%)					
1	331 (39.7)	856 (45.6)	1	1.00 (reference)	
2–3	345 (41.4)	759 (40.4)	2–3	1.12 (0.91–1.38)	0.29
≥4	158 (18.9)	265 (14.1)	≥4	1.36 (1.01–1.83)	0.04
Pre-eclampsia or eclampsia (%)					
No	832 (99.8)	1864 (99.1)	No	1.00 (reference)	
Yes	2 (0.2)	16 (0.9)	Yes	0.33 (0.07–1.45)	0.14
Mean (SD) gestational age (wks)[b]	39.8 (2.3)	39.9 (2.3)	1	0.98 (0.94–1.02)	0.22
Mean (SD) birth weight (g)	3491.6 (508.9)	3497.5 (504.2)	500	0.99 (0.90–1.09)	0.86
Mean (SD) gestational age (wks)[b]	39.8 (2.3)	39.9 (2.3)	1	0.96 (0.92–1.00)	0.07
Mean (SD) birth length (mm)	508.2 (21.4)	507.9 (22.7)	20	1.05 (0.96–1.15)	0.32
Mean (SD) gestational age (wks)[b]	39.6 (2.3)	39.9 (2.3)	1	0.94 (0.89–0.99)	0.03
Mean (SD) placental weight (g)	620.7 (128.9)	619.2 (133.4)	150	1.06 (0.92–1.24)	0.41

[a] There were 22 subjects with missing information on socioeconomic status, 3 subjects with missing information on maternal age, and 65 subjects with missing information on gestational age. Placental weight was available only for 461 cases and 1002 controls from one of the two delivery centers.
[b] ORs were from a conditional logistic regression model that included maternal age, socioeconomic class, parity, pre-eclampsia/eclampsia, gestational age, and birth weight. The last four ORs were from similar models replacing birth weight with birth length or placental weight.
[c] Low, blue collar workers and farmhands; Medium, white collar workers and farm owners with no college education; High, college education.

Eight hundred and thirty-four prostate cancer cases over age 18 years and of singleton birth were identified. For each case, singleton males born live to the first four mothers admitted after the case's mother were selected as potential controls. We used the cancer and death registries to check that potential control subjects were alive and had not had prostate cancer diagnosed at the time of diagnosis of the corresponding case; 1880 eligible controls were included in the study.

For all cases and their matched controls, we manually abstracted information on mother's parity, pre-eclampsia or eclampsia before delivery, age at delivery, and socioeconomic status from the standardized hospital chart. We also recorded the child's birth length and weight, placental weight, and gestational age in completed weeks calculated from the first day of last menstruation. The completeness of records exceeded 95% for every item in the study, with the exception of placental weight, which was only recorded at one of the two delivery centers.

We analyzed the data using logistic regression conditional on the matching process (6). Different sets of models were fitted to assess the effect of birth size indicators including birth weight, birth length, and placental weight. Each of the birth size indicators was introduced alternatively into a core model to avoid problems of collinearity. The core model included maternal age (<20, 20–24, 25–29, 30–34, ≥35 years; as a categorical variable), socioeconomic status (low, medium, high; as an ordinal variable), parity (1, 2–3, ≥4; as a categorical variable), pregnancy toxemia (pre-eclampsia or eclampsia; yes or no), and gestation age (in weeks; as a continuous variable). OR[3] estimates and 95% CIs were derived from the fitted regression (7). The level of significance was set at $P < 0.05$ (two-sided P).

Results

Of 834 cases, 1.8% were born before 1900, 55.6% were born between 1900 and 1919, and 42.6% were born in 1920 or later. The corresponding numbers among the 1880 control subjects were 1.1%, 47.6%, and 51.3%, respectively. Maternal age had an inverse U-shaped relation with prostate cancer risk; subjects born to younger (<25 years) and older mothers (≥35 years) were at lowered risk (Table 1). We found no statistically significant differences between cases and controls with respect to socioeconomic status. High birth order, as indicated by high maternal parity, was associated with an increased risk. A recorded pre-eclampsia or eclampsia appeared to be associated with a reduced risk for prostate cancer, but the risk estimate was based on a few exposed subjects and was hence statistically imprecise. Birth weight, birth length, and placental weight, adjusted one at a time for gestational age, were also not significantly related to prostate cancer risk. The effect estimates for birth size indicators varied over different strata of gestation age: near null associations were seen in the strata of 37–41 and ≥42 weeks of gestation, and positive associations were seen in preterm (<37 weeks) stratum. However, with a smaller number of preterm subjects (7.4% of cases and 6.1% of controls), stratum-specific OR estimates had CIs that were wide and included null value (data not shown). Gestational age, however, tended to be inversely associated with risk for prostate cancer: OR associated with each additional week of gestation was 0.97 (95% CI, 0.94–1.01); and it was 1.31 (95% CI, 0.93–1.84) comparing preterm (<37 weeks) to full-term (≥37 weeks) subjects. The inverse association was not changed after adjust-

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

ment for the alternative birth size indicators to remove potential confounding (Table 1). Indeed, when placental weight, rather than birth weight or length, was adjusted for, the inverse association of gestational age with prostate cancer risk became statistically significant, indicating that prolongation of the duration of gestation by 1 week is associated with a 6% reduction in prostate cancer risk (Table 1). Preterm subjects had an OR of 1.76 (95% CI, 1.15–2.71) as compared to full-term subjects in the analysis adjusting for placental weight. To potentially separate the effects of intrauterine growth retardation from prematurity, we examined the effect associated with small-for-gestational-age subjects, defined as those below the 10th percentile of birth weight for a given gestational age according to Swedish population distribution (8), and found an insignificant OR of 1.05 (95% CI, 0.76–1.47) compared to normal-for-gestational-age subjects. Risk estimates similar to those found in the main analysis on birth size variables and gestational age were obtained when subjects were stratified by age ($<$70 years, $\geq$70 years), as well as when the alternative outcome of fatal cases was examined.

Discussion

Selection and information biases are unlikely in our nested case-control study because this design preserved the validity of a cohort study. However, data on maternal diabetes were not available. During the period when the study subjects were born, most diabetic women were unlikely to complete the pregnancies, and very few subjects would be born to diabetic mothers. On the other hand, having information on perinatal characteristics available from birth records is a major strength of this study.

For most exposures, the study was sufficiently large to document risk gradients of even moderate size. Taken together with the results of the two previous large studies (4, 5), our results suggest that birth size indicators are not important risk factors for prostate cancer in later life. Our findings do not refute a possible inverse association between pregnancy toxemia and prostate cancer risk and agree with those in a previous study. If results from the two studies we have thus far conducted are pooled to gain statistical power, the combined OR is 0.16 (95%CI, 0.03–0.72; $P = 0.01$), but evidence from other populations is clearly needed to establish (or refute) this association.

The novel result of the present study was the inverse association between gestational age and prostate cancer risk after adjustment for birth size indicators and, in particular, placental weight. Placental weight is an important correlate of pregnancy hormone levels, and its adjustment is likely to better unmask the effect of gestation age (4, 9). Although chance cannot be ruled out as a possible explanation for this finding, and maternal levels of other hormones also change with gestational age, to the extent that pregnancy estrogen increases exponentially with gestational age, pregnancy estrogens are higher in women with low parity, and estrogen plays an inhibitory role in the natural history of prostate cancer, this finding appears to support the hypothesis that the intrauterine hormonal environment modulates prostate cancer risk (1, 2). However, our data suggest that the late *in utero* environment may be as important as the early *in utero* environment in the modulation of prostate cancer risk in offspring.

Acknowledgments

We thank Ulrika Lund and Ann Almqvist for the retrieval process and anonymous reviewers for helpful comments.

References

1. Henderson, B. E., Bernstein, L., Ross, R. K., Depue, R. H., and Judd, H. L. The early *in utero* oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. Br. J. Cancer, *57:* 216–218, 1988.

2. Ross, R. K., and Henderson, B. E. Do diet and androgens alter prostate cancer risk via a common etiologic pathway? J. Natl. Cancer Inst., *86:* 252–254, 1994.

3. Tibblin, G., Eriksson, M., Cnattingius, S., and Ekbom, A. High birth weight as a predictor of prostate cancer risk. Epidemiology, *6:* 423–424, 1995.

4. Ekbom, A., Hsieh, C-c., Lipworth, L., Wolk, A., Ponten, J., Adami, H-O., and Trichopoulos, D. Perinatal characteristics in relation to incidence of and mortality from prostate cancer. Br. Med. J., *313:* 337–341, 1996.

5. Platz, E. A., Giovannucci, E., Rimm, E. B., Curhan, G. C., Spiegelman, D., Colditz, G. A., and Willett, W. C. Retrospective analysis of birth weight and prostate cancer in the Health Professionals Follow-up Study. Am. J. Epidemiol., *147*: 1140–1144, 1998.

6. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research. Vol. I. The Analysis of Case-Control Studies. Lyon, France: IARC, 1980.

7. Statistical Analysis Systems. SAS User's Guide, Statistics, version 6.04. Cary, NC: SAS Institute Inc., 1995.

8. Cnattingius, S., Haglund, B., and Kramer, M. S. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population-based cohort study. Br. Med. J., *316:* 1483–1487, 1998.

9. Ekbom, A., Trichopoulos, D., Adami, H-O., Hsieh, C-c., and Lan, S-J. Evidence of prenatal influences on breast cancer risk. Lancet, *340:* 1015–1018, 1992.