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A Possible Link Between the Pubertal Growth of Girls and Prostate Cancer in Their Sons

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Abstract

Objectives—Among women attending antenatal clinics during 1934–1944 a large intercrystal diameter, the maximum distance between the pelvic iliac crests, was associated with a raised incidence of breast and ovarian cancer in the daughters in later life. At puberty, the intercrystal diameter of girls enlarges rapidly under the influence of estrogen. We speculated that high maternal estrogen concentrations during pregnancy initiate hormonal cancers in their daughters. Here, we examine the association between the mothers' intercrystal diameters and prostate cancer in their sons.

Methods—Using the national cancer registry we identified 221 cases of prostate cancer among 6,975 men born during 1934–1944 in Helsinki, Finland. Four thousand four hundred and one of these men had their mother's bony pelvic measurements recorded: there were 149 cases among them.

Results—Hazard ratios for prostate cancer rose as the mother's intercrystal diameter increased; but this association was restricted to men who were born before 40 weeks of gestation. Among these men the hazard ratio was 1.27 (95% CI 1.09–1.48; $P = 0.002$). The hazard ratio was 2.2 (1.3–3.7; $P < 0.001$) in men whose mothers weighed more than 80 kg in late pregnancy compared with those whose mothers weighed 60 kg or less.

Conclusions—These findings are consistent with a conceptual framework for the origins of hormonally dependent cancers that invokes exposure of embryonic tissue to maternal sex hormones followed by resetting of the fetal hypothalamic-gonadotropin axis in late gestation. We hypothesize that compensatory prepubertal growth among girls is associated with hormonal cancers in the next generation.

The pubertal growth of girls is characterized by broadening of the hips in anticipation of childbirth. The intercrystal diameter, the maximal distance between the iliac crests, increases rapidly under the control of estrogens (Ellison, 1998; Tanner, 1962). The interspinous diameter, the distance between the anterior-superior iliac spines, increases less rapidly so that the iliac crest becomes rounder. We have suggested that a large intercrystal diameter reflects high circulating concentrations of estrogens at puberty that persist through reproductive life. In a previous study of women born in Helsinki, Finland we found that the incidence of breast cancer was higher in those whose mothers had a large intercrystal diameter and a large intercrystal-interspinous difference (Barker et al., 2008b). We speculated that, if a female embryo is exposed to high maternal estrogen concentrations, this would produce genetic instability in differentiating breast and ovarian cells and thereby initiate cancer. Catechol estrogen, a metabolite of estradiol, is thought to cause chromosomal instability by breaking DNA strands (Yoshi and Ohshima, 1998; Yue et al., 2003). The literature linking estrogen to breast cancer is specific to the individual who develops cancer and not, as in our studies, the effects on the offspring. The associations between the mother's intercrystal diameter and breast cancer were strongest in women who were born at or after 40 weeks of gestation. We speculated that prolonged exposure to placental estrogens permanently reset the fetal hypothalamic gonadotropic axis.

In contrast to the findings for breast cancer, the mother's of women who developed ovarian cancer were characterized by large intercrystal and intertrochanteric diameters, the distance between the greater trochanters (Barker et al., 2008a). At puberty, the intratrochanteric diameter increases at a similar rate in boys and girls and is controlled by growth hormone and androgens. Ovarian cancer may therefore be initiated by a more masculine hormonal profile than that which initiates breast cancer. These findings raise the possibility that prostate cancer, the commonest hormonally dependent cancer in men, may also be initiated by exposure to maternal or placental sex hormones during gestation. We have examined the effects of mothers' pelvic diameters on prostate cancer among men in the Helsinki Birth Cohort. Because there is evidence that prostate cancer is associated with raised testosterone concentrations in adults (Jung et al., 2011; Rahman et al., 2011), we hypothesized that prostate cancer would be commoner in the sons of women with broad hips, as measured by the intertrochanteric diameter.

METHODS

The study cohort comprised 6,975 men born from 1934 to 1944 in one of the two maternity hospitals in Helsinki, the University Central Hospital, and the City Maternity Hospital. Details of the birth records have been described (Eriksson et al., 2001). They include the body size of the baby at birth, the length of gestation estimated from the date of the mother's last menstrual period, and the mother's height, weight in late pregnancy, age, parity, and age at menarche. Four thousand four hundred and one (63%) of them include measurements of the bony pelvis. These were used to assess the likelihood of obstructed labor (Anderson, 1930; Berkeley, 1941). Mothers whose records included pelvic measurements tended to be younger and more of them were primiparous, and they were 0.6 cm shorter ($P < 0.001$). There were two measurements of the distance between the iliac crests, the intercrystal diameter, the maximal distance between the iliac crests, and the interspinous diameter, the distance between the anterior-superior iliac spines. The difference between the intercrystal and interspinous diameters is used as an index of the roundness of the iliac crest. The intertrochanteric diameter, the distance between the greater trochanters, measures the width of the lower hips. The external conjugate diameter is the distance between the front of the pubic bone and the spine of the fifth lumbar vertebra.

The birth records included data on the father's occupation, which was grouped into upper and lower middle class and manual workers, based on a classification from Statistics Finland (Barker et al., 2001). The men's own occupations, recorded at the 1980 census, were obtained through Statistics Finland who grouped them into four classes: higher official, lower official, self-employed, and manual worker. In Finland, cases of cancer are recorded in the national cancer registry. We ascertained all registrations for prostate cancer during 1971 to 2006. Prostate cancer was defined by International Classification of Disease code 185 in revisions 8 and 9 and by code C61 in revision 10. The ethics committee at the National Public Health Institute in Helsinki approved the study.

Statistical methods

The end for our survival analysis was registration with prostate cancer. Men were censored in the analysis when they migrated from Finland, died from causes other than prostate cancer, or reached the end of 2006. We used a Cox proportional hazards model to calculate the hazard ratios for prostate cancer in relation to maternal characteristics and length of gestation. The measurements of mother's height, weight, pelvic size, age at menarche, and the length of gestation were analyzed as continuous variables although presented in the tables as groups.

RESULTS

The cohort comprised 6,975 men. Two hundred twenty-one of them had had prostate cancer, five of whom had died from the disease. For 149 of the men with prostate cancer, there were measurements of the mother's pelvic bones. Characteristics of the mothers and their sons are shown in Table 1. The mothers' pelvic diameters correlated with their heights and weights, the correlation coefficient for the intercrystal diameter and weight being 0.47.

Body size at birth

Prostate cancer was not associated with birthweight, birth length, or head circumference at birth, with or without allowance for the length of gestation.

Mother's body size

Table 2 shows hazard ratios for prostate cancer in relation to mother's height and weight and the three measurements of hip width. There was no trend in hazard ratios with mother's height but the ratios increased with mother's weight in late pregnancy and with her body mass index ($P = 0.005$). Hazard ratios tended to increase with the intercrystal, the interspinous, and the intertrochanteric diameters, although none of the trends was statistically significant. Men whose mothers had intercrystal diameters greater than 29.5 cm were at significantly increased risk (Table 2). Neither the intercrystal-interspinous difference nor the external conjugate diameter was associated with prostate cancer.

Length of gestation

There was an inverted U-shaped association between the length of gestation and later prostate cancer (P for quadratic trend 0.04). The highest risk was among men born at 38 weeks. In Table 3, the men are divided around the median gestation period of 40 weeks, the same division used in our previous analyses of breast cancer (Barker et al., 2008b). Among men born before 40 weeks of gestation high mother's weight and large intercrystal and interspinous diameters were associated with high hazard ratios for prostate cancer. The trend with mother's weight, however, was no longer statistically significant in simultaneous regressions with either of the two pelvic diameters, whose trends remained significant ($P = 0.02$ for both). These trends are shown in Table 4. Among men born at or after 40 weeks

hazard ratios for prostate cancer rose with increasing mother's weight, but there were no trends with the two diameters (Tables 3 and 4). There were no statistically significant trends with mother's height, intertrochanteric or external conjugate diameters, or intercrystal-interspinous difference in either gestation group.

Mother's age, parity, and age at menarche

Mother's age, parity, and age at menarche were not related to prostate cancer. The associations between prostate cancer and the mothers intercrystal and interspinous diameters were similar in men born to primiparous and multiparous mothers, and in men whose mother's menarche was early or late, defined by the median age of 14 years.

Socioeconomic status

Prostate cancer was not associated with the socioeconomic status of the family, as indicated by the father's occupation at the time of the birth. It was, however, associated with the men's own socioeconomic status, defined by their occupations. Higher socioeconomic status was associated with higher hazard ratios for prostate cancer ($P = 0.03$). The trends in prostate cancer within the two gestation groups (Tables 3 and 4) were not changed by allowance for socioeconomic status.

DISCUSSION

We have found that men whose mothers had large intercrystal and interspinous diameters of the bony pelvis were at increased risk of prostate cancer if they were born before 40 weeks of gestation. Contrary to our hypothesis, prostate cancer was not associated with the mother's intertrochanteric diameter. The skeletal growth of girls at puberty is characterized by rapid expansion of the intercrystal and interspinous diameters under the influence of sex hormones, importantly estrogen (Ellison, 1998; Tanner, 1962). The intratrochanteric diameter expands at a similar rate in boys and girls and is controlled by growth hormone and androgens. We have suggested that the sex hormone profile established in a girl at puberty may persist through her reproductive life, and could initiate breast and ovarian cancers in her daughters during early gestation when the breast and ovarian stem cells are developed (Barker et al., 2008a,b). High catechol estrogen concentrations in the maternal circulation at that time could produce genetic instability in breast and ovarian progenitor cells (Barker et al., 2008a,b; Yoshie and Ohshima, 1998; Yue et al., 2003). This could make the cells vulnerable to cancer in later life. Because ovarian cancer is related to the intertrochanteric diameter as well as the intercrystal, and is not related to the intercrystal-interspinous difference, we speculated that it is initiated by a more masculine hormonal profile than that which initiates breast cancer (Barker et al., 2008a).

Our present findings suggest that similar processes could initiate prostate cancer and that it is the estrogenic component of the mother's sex hormone profile rather than the androgenic component. This conclusion is strengthened by the association between high maternal weight in pregnancy and prostate cancer. Greater maternal fat mass is associated with higher circulating estrogen concentrations. There is evidence that men with prostatic cancer have raised testosterone concentrations (Jung et al., 2011; Rahman et al., 2011). This evidence comes from studies of men's second to fourth digit ratios and is difficult to reconcile with our observations implicating the mother's estrogen concentrations.

We found that there was an inverted U-shaped association between prostate cancer and the length of gestation, such that the highest risk was in men born at 38 weeks. We suggest that this association reflects altered hypothalamic-gonadotropin settings in the fetus in late gestation. Observations in animals provide strong evidence that lifelong patterns of

gonadotropic hormone release are initiated at early development (Barraclough and Gorski, 1961). Among premenopausal women in Sheffield, UK, plasma luteinizing hormone concentrations were raised in those born after 40 weeks of gestation (Cresswell et al., 1997). We have previously shown that the relationship between the intercrystal diameter and breast cancer was strongest in women born at or after 40 weeks, and we speculated that this reflected prolonged fetal exposure to placental estrogens with resetting of the hypothalamic-gonadotropic axis (Barker et al., 2008b). For prostate cancer, however, a large intercrystal diameter increased the risk only among men born before term. We cannot explain this but speculate that it is also linked to fetal exposure to placental estrogens with resetting of the hypothalamic-gonadotropic axis.

The three common hormonal cancers are associated with a similar maternal phenotype though there are differences in detail. Mothers whose daughters developed breast cancer had large intercrystal diameters and a large difference between the intercrystal and interspinous diameters so that the iliac crest was round (Barker et al., 2008b). The mothers were of similar stature to all mothers in the cohort, but had had a larger pubertal growth spurt, as indicated by their large intercrystal diameter. Because the large pubertal growth spurt did not result in tall adult stature we suggested that it was the result of accelerated prepubertal growth following growth faltering in early childhood (Proos et al., 1993). Further evidence supporting this concept came from the studies of ovarian cancer (Barker et al., 2008a). Broad hips only predicted ovarian cancer in the daughters of mothers with below average stature (160 cm or less) and below average age at menarche (14 years or less). An early onset of menstruation and short adult stature occurs when girls are undernourished and grow slowly in the first few years of life and then are well nourished and catch up in size (Proos et al., 1993). Mothers whose sons later developed prostate cancer were similar to those whose daughters developed breast cancer or ovarian cancer in that they had large intercrystal diameters but were similar in stature to all mothers in the cohort. We suggest that, similarly to the mothers whose daughters developed breast or ovarian cancer, the mothers' large pubertal growth spurts resulted from accelerated prepubertal growth after growth faltering in early childhood.

The ability to mount accelerated "compensatory" growth after growth faltering is common in animals and familiar to farmers (Metcalf and Monaghan, 2001). In animals compensatory growth has a wide range of physiological and metabolic costs that include premature death. We hypothesize that compensatory growth in girls is associated with an altered sex hormone profile that is established at puberty and persists through reproductive life. This profile predisposes their offspring to hormonal cancers. In children, compensatory growth becomes more common when societies transition from chronic malnutrition to western nutrition. Our hypothesis is consistent with the rise of hormonal cancers in western countries during the past century.

Limitations of the study

The measurements in our study were made during routine obstetric practice 70 years ago. There were no routine checks of the quality of the measurements, just as there are no routine checks of the quality of blood pressure and other measurements made in current clinical practice. Measurement errors would tend to diminish the associations between the pelvic diameters and prostate cancer in later life. The people in our study may not be representative of all people now living in Helsinki, although at birth their social class distribution was similar to that in the city as a whole.

CONCLUSION

These findings are consistent with a conceptual framework for the origins of hormonally dependent cancers that invokes exposure of embryonic tissue to maternal sex hormones followed by resetting of the fetal hypothalamic-gonadotropin axis in late gestation. We hypothesize that rapid compensatory growth among prepubertal girls is associated with an altered sex hormone profile that is established at puberty and persists through reproductive life. This profile predisposes their male and female offspring to hormonal cancers.

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LITERATURE CITED

- Anderson, MC. Lessons in midwifery for nurses and midwives. London: A & C Black; 1930.
- Barker DJP, Forsen TJ, Uutela A, Osmond C, Eriksson JG. Size at birth and resilience to the effects of poor living conditions in adult life: longitudinal study. *Br Med J*. 2001; 323:1273–1276. [PubMed: 11731388]
- Barker DJ, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. A possible link between the pubertal growth of girls and ovarian cancer in their daughters. *Am J Hum Biol*. 2008a; 20:659–662. [PubMed: 18461601]
- Barker DJP, Osmond C, Thornburg KL, Kajantie E, Forsen TJ, Eriksson JG. A possible link between the pubertal growth of girls and breast cancer in their daughters. *Am J Hum Biol*. 2008b; 20:127–131. [PubMed: 17922483]
- Barracough CA, Gorski RA. Evidence that the hypothalamus is responsible for androgen induced sterility in the female rat. *Endocrinology*. 1961; 68:68–79. [PubMed: 13687240]
- Berkeley, C. Pictorial Midwifery. London: Bailliere, Tindall and Cox; 1941.
- Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI, Fraser RB. Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet*. 1997; 350:1131–1135. [PubMed: 9343501]
- Ellison, PT. The Cambridge Encyclopaedia of Human Growth and Development. Cambridge: Cambridge University Press; 1998. p. 473
- Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. Early growth and coronary heart disease in later life: longitudinal study. *Br Med J*. 2001; 322:949–953. [PubMed: 11312225]
- Jung H, Kim KH, Yoon SJ, Kim TB. Second to fourth digit ratio: a predictor of prostate specific androgen level and the presence of prostate cancer. *BJU Int*. 2011; 107:591–596. [PubMed: 20633006]
- Metcalfe NB, Monaghan P. Compensation for a bad start: grow now, pay later. *Trends Ecol Evol*. 2001; 16:254–260. [PubMed: 11301155]
- Proos LA, Kahlberg J, Hofvander Y, Tuvemo T. Pubertal linear growth of Indian girls adopted in Sweden. *Acta Paediatr*. 1993; 82:641–644. [PubMed: 8374210]
- Rahman AA, Lophatananon A, Stewart-Brown S, Harriss D, Anderson OJ, Parker T, Easton D, Kote-Jarai Z, Pocock R, Dearnaley D, Guy M, O'Brien L, Wilkenson RA, Hall AL, Sawyer E, Page E, Liu JF, Eeles RA, Muir K. Hand pattern indicates prostate cancer risk. *Br J Canc*. 2011; 104:175–177.
- Tanner, JM. Growth at Adolescence. Oxford: Blackwell; 1962. p. 340

- Yoshie Y, Ohshima H. Synergistic induction of DNA strand breakage by catechol-estrogen and nitric oxide: implications for hormonal carcinogenesis. *Free Radic Biol Med*. 1998; 2:341–348. [PubMed: 9433910]
- Yue W, Santen RJ, Wang JP, Li Y, Verderane MF, Bocchinfuso DP, Korach KS, Devanesan P, Todorovic R, Rogan EG, Cavalieri EL. Genotoxic metabolites of estradiol in breast: potential of estradiol induced carcinogenesis. *J Steroid Biochem Mol Biol*. 2003; 86:477–486. [PubMed: 14623547]

TABLE 1

Numbers and types of measurements made on mothers and sons

	Numbers	Mean	SD
Mothers			
Age at menarche (years)	6,760	14.7	1.7
Age at delivery (years)	6,970	28.3	5.4
Height (cm)	6,385	159.8	5.7
Weight (kg)	6,305	67.0	8.2
Body mass index (kg/m ²)	6,279	26.2	2.9
Parity	6,973	1.9	1.3
Intercristal (cm)	4,393	28.4	1.5
Interspinous (cm)	4,396	25.8	1.5
Intercristal-interspinous (cm)	4,393	2.5	1.1
Intertrochanteric (cm)	4,380	31.3	1.6
External conjugate (cm)	4,380	19.4	1.1
Sons			
Length of gestation (days)	6,707	279	13
Age at prostate cancer (years)	221	61	3

TABLE 2

Hazard ratios for prostate cancer according to mothers' heights, weights, and pelvic diameters

	Hazard ratio	95% CI	No. of cases	No. of men
Mother's height (cm)				
156.0	1.0	Baseline	57	1,814
156.1 – 160.0	0.8	0.6–1.2	47	1,722
160.1 – 164.0	1.2	0.8–1.7	55	1,524
>164.0	1.3	0.9–1.8	52	1,325
<i>P</i> for trend	0.11			
Mother's weight (kg)				
60.0	1.0	Baseline	41	1,321
60.1 – 70.0	0.9	0.6–1.4	88	3,079
70.1 – 80.0	1.2	0.8–1.8	56	1,548
>80.0	2.2	1.3–3.7	24	357
<i>P</i> for trend	<0.001			
Intercristal diameter (cm)				
27.5	1.0	Baseline	42	1,331
27.6 – 28.5	0.9	0.5–1.4	31	1,199
28.6 – 29.5	1.0	0.6–1.5	32	1,064
>29.5	1.7	1.1–2.5	44	799
<i>P</i> for trend	0.08			
Interspinous diameter (cm)				
25.0	1.0	Baseline	48	1,635
25.1 – 26.0	1.2	0.7–1.8	37	1,206
26.1 – 27.0	1.4	0.9–2.2	38	940
>27.0	1.4	0.8–2.2	26	615
<i>P</i> for trend	0.13			
Intertrochanteric diameter (cm)				
30.5	1.0	Baseline	46	1,456
30.6 – 31.5	1.5	1.0–2.2	50	1,168
31.6 – 32.5	0.8	0.5–1.3	22	958
>32.5	1.3	0.8–2.0	31	798
<i>P</i> for trend	0.13			

TABLE 3

Hazard ratios (HR) for prostate cancer according to mothers' heights, weights, and pelvic diameters and the length of gestation

Maternal measurements	Length of gestation (weeks)					
	<40			40		
	HR	95% CI	P-value	HR	95% CI	P-value
Height (cm)	1.02	0.98–1.05	0.28	1.02	0.98–1.05	0.31
Weight (kg)	1.02	1.00–1.05	0.03	1.03	1.00–1.05	0.02
Intercristal (cm)	1.27	1.09–1.48	0.002	0.95	0.82–1.11	0.51
Interspinoous (cm)	1.28	1.10–1.49	0.001	0.90	0.78–1.05	0.18
Intertrochanteric (cm)	1.12	0.96–1.30	0.15	1.05	0.91–1.21	0.54
						0.84
						0.73
						0.02
						0.002
						0.52

TABLE 4
Hazard ratios for prostate cancer according to mothers' weights and pelvic diameters and the length of gestation

Maternal measurements	Length of gestation (weeks)					
	<40			40		
	Hazard ratio	95% CI	No of cases	No of men	Hazard ratio	95% CI
Weight (kg)						
60.0	1.0	Baseline	21	694	1.0	Baseline
60.1–70.0	1.1	0.7–1.9	49	1,456	0.7	0.4–1.3
70.1–80.0	1.5	0.9–2.7	29	667	0.9	0.5–1.7
>80.0	2.0	0.9–4.7	8	129	2.0	1.0–4.0
<i>P</i> for trend	0.03				0.02	
Intercristal diameter (cm)						
27.5	1.0	Baseline	14	632	1.0	Baseline
27.6–28.5	1.5	0.7–3.2	16	528	0.6	0.3–1.1
28.6–29.5	1.8	0.9–3.7	17	473	0.6	0.3–1.1
>29.5	3.0	1.5–5.9	23	355	1.0	0.5–1.8
<i>P</i> for trend	0.002				0.51	
Interspinoous diameter (cm)						
25.0	1.0	Baseline	16	769	1.0	Baseline
25.1–26.0	2.3	1.2–4.5	22	557	0.5	0.3–1.0
26.1–27.0	2.4	1.2–4.7	19	407	1.0	0.5–1.7
>27.0	2.5	1.2–5.1	13	255	0.8	0.4–1.5
<i>P</i> for trend	0.001				0.18	