Published in final edited form as:

Am J Hum Biol. 2008 ; 20(6): 659–662. doi:10.1002/ajhb.20789.

A Possible Link Between the Pubertal Growth of Girls and Ovarian Cancer in Their Daughters

DAVID J. P. BARKER^{1,*}, CLIVE OSMOND², KENT L. THORNBURG¹, EERO KAJANTIE³, and JOHAN G. ERIKSSON^{3,4}

¹Heart Research Center, Oregon Health and Science University, Portland, Oregon ²Medical Research Council Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, United Kingdom ³National Public Health Institute, Helsinki, Finland ⁴University of Helsinki, Department of Public Health, Helsinki, Finland

Abstract

At puberty, the distance between the iliac crests of the female pelvis, measured by the intercrystal and interspinous diameters, increases rapidly. This is mainly controlled by estrogens. We have followed up 6,370 women who were born in Helsinki during 1934–1944, and whose mothers' pelvic bones were measured during routine antenatal care. We have previously reported that women whose mothers had larger intercrystal diameters had higher rates of breast cancer. We postulated that large intercrystal diameters are markers of high circulating concentrations of estrogen, which are established at puberty, persist through reproductive life and cause genetic instability in differentiating breast cells in female embryos. We now report on ovarian cancer in the same cohort. Our hypothesis was that the risk of this cancer would also be higher in women whose mothers had broader hips. We found that, when compared with all other women, the hazard ratio for ovarian cancer was 3.3 (95% CI 1.6–7.0, $P = 0.004$) in the daughters of mothers whose interspinous diameter was greater than 27 cm. Among mothers who had an early menarche, each measure of broad hips was associated with increased risk of ovarian cancer in their daughters. We postulate that ovarian cancer is initiated by exposure of the fetal ovary to maternal sex hormones. Concentrations of these hormones may be higher in mothers who had an early menarche. The maternal sex hormone profile that initiates ovarian cancer may be the product of poor nutrition and growth in early childhood followed by catch-up pre-pubertal growth.

The size of a woman's hips reflects circulating concentrations of growth hormone and sex hormones at puberty (Ellison, 1998; Tanner, 1962). The pubertal growth of girls is characterized by broadening and rounding of the hips. The width between their iliac crests, the intercrystal diameter, increases more rapidly than in boys and their iliac crests become rounded. Roundness is measured by the difference in the maximal width between the iliac crests, the intercrystal, and the anterior width, the interspinous (Berkeley, 1941). We have followed up women who were born in Helsinki and whose mothers' pelvic bones were measured during routine antenatal care. We found that those whose mothers had large

*Correspondence to: David J. P. Barker, MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, UK. djpb@mrc.soton.ac.uk.

intercrystal widths and large intercrystal-interspinous differences had higher rates of breast cancer (Barker et al., 2008). This effect was stronger in women born after 40 weeks gestation and in women whose mothers were multiparous. The intertrochanteric diameter, the distance between the hip joints, which increases similarly in girls and boys at puberty (Tanner, 1962), did not predict breast cancer. We concluded that the intercrystal width and the intercrystal-interspinous difference are markers of the mothers' circulating female sex hormone concentrations, and we postulated that high concentrations in early gestation cause genetic instability in differentiating breast cells in their daughters.

Little is known about the intra-uterine origins of ovarian cancer, the other common hormonally-dependent cancer in women. We hypothesized that, similarly to breast cancer, it is initiated by exposure to maternal sex hormones in early gestation and would therefore be more common in the daughters of women with broad hips. There is evidence that women whose menarche occurred at an early age have higher concentrations of circulating ovarian sex hormones (Apter et al., 1989; Ellison, 1996). We therefore examined whether associations between mothers' hip width and ovarian cancer in their daughters were stronger in mothers who had an early menarche. Since taller women tend to have menarche at an early age, we also took account of mother's height. Because of the findings for breast cancer, we examined the effects of length of gestation and mothers' parity.

METHODS

The study cohort comprised 6,370 women born from 1934 through 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). All except 170 record the mother's age in years at menarche. Among them 4,102 (64%) include measurements, so-called "diameters," of the bony pelvis. These were used to assess the likelihood of obstructed labor (Berkeley, 1941). Mothers whose records included pelvic measurements tended to be younger and more of them were primiparous, but their average height was the same as that of the other mothers. 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 inter-trochanteric diameter, the distance between the greater trochanters, measured the width of the lower hips. The external conjugate diameter was 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 women'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 ovarian cancer during 1971 to 2003. Ovarian cancer was defined by International Classification of Disease code 183 in revisions 8 and 9 and by code C56 in revision 10. The ethics committee at the National Public Health Institute in Helsinki approved the study.

Statistical methods

The end point for our survival analysis was death or registration with ovarian cancer. Subjects were censored in the analysis when they migrated from Finland, died from causes other than ovarian cancer, or reached the end of 2003. We used a Cox proportional hazards model to calculate the hazard ratios for ovarian cancer in relation to maternal characteristics and length of gestation. The measurements of pelvic size, height, gestation period, and age at menarche were analyzed as continuous variables although presented in the tables as groups.

RESULTS

Ovarian cancer had been diagnosed in 55 women, of whom 14 had died from the disease. Among these women 39 whose mothers had measurements of their pelvic bones had ovarian cancer. The mothers' pelvic diameters are shown in Table 1. Table 2 shows hazard ratios for ovarian cancer in relation to mother's height and the three measurements of hip width. Ovarian cancer was not related to mother's height or to mother's weight, but hazard ratios increased with the interspinous diameter. The hazard ratio for ovarian cancer was 3.3 (95% confidence interval 1.6–7.0, $P = 0.004$) in women whose mother's interspinous diameter was greater than 27 cm compared with all other women. The mothers' pelvic diameters correlated with their heights, the correlation coefficient being 0.41 for the intercrystal diameter. After adjustment for height there were statistically significant trends in ovarian cancer with both the interspinous and intertrochanteric diameters (Table 2). Ovarian cancer was not related to the external conjugate diameter or to the difference between the intercrystal and interspinous diameters, with or without adjustment for height.

Mothers age at menarche was not related to the risk of ovarian cancer, but we examined whether it modified the effects of pelvic width. In Table 3, the mothers are divided around their median age of menarche, which was 14 years. The trends in ovarian cancer with pelvic width were confined to 15 women whose mothers had an early menarche. In these women hazard ratios for ovarian cancer increased with the intercrystal, interspinous and intertrochanteric diameters, but were not related to the external conjugate diameter or to the intercrystal-interspinous difference. We next examined whether, among women whose mothers had an early menarche, the mother's height modified the effects of their pelvic size. In Table 4, the mothers who had an early menarche are divided around their median height, which was 160 cm. The trends in ovarian cancer with pelvic width were confined to eight women whose mothers had an early menarche and were below the median height. The interactions between the effects of pelvic width and mother's height were statistically significant for the intercrystal and intertrochanteric diameters ($P = 0.03$ and 0.02 , respectively).

Gestation period

Ovarian cancer was unrelated to the length of gestation in either a linear or quadratic trend. We examined whether the effects of the pelvic diameters differed among the daughters born before or after term, defined as 40 or more weeks of gestation as in our analysis of breast

cancer (Barker et al., 2008). There were no differences in the effects of any pelvic measurement on ovarian cancer in the two groups.

Maternal age and parity

Mother's age was not related to ovarian cancer. The associations between mother's pelvic size and ovarian cancer were similar in the women born to primiparous and multiparous mothers.

Socioeconomic status

Ovarian cancer was not associated with the socioeconomic status of the family, as indicated by the father's occupation at the time of the birth. Neither was it associated with the women's own socioeconomic status, as indicated by their occupation in adult life.

Comparison with breast cancer

We compared the maternal characteristics of the women who developed ovarian cancer and the women who developed breast cancer. The two groups of mothers were of similar height. The mothers whose daughters had ovarian cancer had larger interspinous diameters (26.5 cm vs 25.8 cm; $P = 0.04$), but smaller intercrystal interspinous differences (2.3 cm vs. 2.9 cm, $P = 0.01$). There were no differences in other pelvic measurements.

DISCUSSION

We have found that women whose mothers had broad hips were at increased risk of ovarian cancer. Despite the rarity of ovarian cancer, and hence the small number of cases, the associations were statistically strong. The skeletal growth of girls at puberty is characterized by broadening of the hip bones under the influence of sex hormones (Ellison, 1998; Tanner, 1962). We suggest that the sex hormone profile established in a girl at puberty may initiate ovarian cancer in her daughters. We have previously suggested that breast cancer is initiated through a similar process (Barker et al., 2008). We found that the association between mothers' hip width and ovarian cancer in the daughters was confined to mothers whose menarche occurred below the median age. This is consistent with the increased levels of circulating levels of sex hormones in adult women whose menarche occurred early (Apter et al., 1989; Ellison, 1996).

Breast cancer is linked to a female pattern of pelvic pubertal growth in the mothers, characterized by a large intercrystal diameter and a round iliac crest, reflected in a large intercrystal-interspinous difference. We have suggested that the disease is driven by the mother's estrogen profile (Barker et al., 2008). Ovarian cancer is linked to large intercrystal and interspinous diameters, but not to a round iliac crest. Unlike breast cancer, ovarian cancer is also linked to a large intertrochanteric diameter which, at puberty, increases at a similar rate in boys and girls (Tanner, 1962). The disease may therefore be related to a more masculine pattern of pubertal growth in the mothers. The pubertal growth of boys is controlled by growth hormone and androgens. We speculate that ovarian cancer is initiated by a more masculine hormonal profile than that which initiates breast cancer.

We have suggested that high catechol estrogen concentrations in the maternal circulation could produce genetic instability in differentiating breast epithelial cells in the daughter in early gestation (Barker et al., 2008; Yoshie and Ohshima, 1998). This could make the breast vulnerable to cancer in later life. Epithelial cancer of the ovary originates through malignant transformation of the epithelium of the ovarian surface (Medical Progress, 2004). Aromatase is present in the ovary in early gestation, and circulating androgens could therefore be converted to estrogens within the ovary. We speculate that circulating estrogens and androgens cause genetic instability in differentiating ovarian epithelial cells. Late menarche, multiple pregnancies, and early menopause protect against ovarian cancer, which has led to the hypothesis that the disease is linked to the lifetime number of ovulation cycles (Medical Progress, 2004; Schildkraut, 1988; Whittemore, 1994). Ovarian surface epithelial cells undergo repair with every ovulation, and this requires an increased level of cell replication. We speculate that if these cells were made genetically unstable early in the formation of the ovary they are more vulnerable to becoming neoplastic during the period of repair.

Broad mothers' hips only predicted ovarian cancer in women whose mothers had an early menarche. Because early menarche is preceded by rapid child growth, one might expect that broad hips would predict ovarian cancer in the daughters of tall mothers. We found, however, that broad hips predicted ovarian cancer in the daughters of short mothers. 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 are then well nourished and catch up in size. A well-known example of this was when a group of young Indian girls were adopted by Swedish families and went to live in Sweden (Proos et al., 1993). On arrival they were stunted, but their heights thereafter increased rapidly, though they remained below the reference mean for Indian girls. The onset of puberty occurred on average 1.5 years earlier than in the Swedish reference population and 2 years earlier than in Indian girls from similar backgrounds. Early menarche led to early cessation of growth and short final height. We speculate that mothers whose daughters developed ovarian cancer followed a similar path of growth.

Limitations of the study

We have previously discussed limitations of the Helsinki birth cohort (Barker et al., 2005; Eriksson et al., 2001). The mean values for the mother's pelvic diameters in our study are similar to those reported elsewhere (Hamilton, 1966). At birth, the distribution of social class in the cohort, as indicated by father's occupation, was similar to that in the city as a whole. The mothers who had measurements of the bony pelvis tended to be younger and more of them were primiparous. Neither of these variables was associated with ovarian cancer. Although the mother's median age of menarche, 14 years, is late by the standards of western countries today it was typical for Scandinavian countries in the early years of the last century (Eveleth and Tanner, 1990).

CONCLUSION

The skeletal growth of girls at puberty is characterized by an increase in the distance between the iliac crests. We found that the daughters of women with a large distance

between the crests were at increased risk of ovarian cancer. We suggest that ovarian cancer is initiated by exposure of the fetal ovary to maternal sex hormones. The maternal sex hormone profile that initiates the disease is the product of poor nutrition in early childhood followed by improved nutrition and catch-up pre-pubertal growth.

Acknowledgments

Contract grant sponsors: Academy of Finland, British Heart Foundation, Finnish Diabetes, Foundation, Finnish Foundation for Cardiovascular Research, Finnish Medical Society, Duodecim, Finska Läkaresällskapet, Foundation for Pediatric Research, Jalmari and Rauha Ahokas Foundation, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation, Signe and Ane Gyllenberg Foundation, Royal Society, Yrjö Jahnsson Foundation, M. Lowell Edwards Endowment.

LITERATURE CITED

- Apter D, Reinila M, Vihco R. Some endocrine characteristics of early menarche, a risk factor for breast cancer are preserved into adulthood. *Int J Canc.* 1989; 44:783–787.
- Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med.* 2005; 353:1802–1809. [PubMed: 16251536]
- 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 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.* 2008; 20:127–131. [PubMed: 17922483]
- Berkeley, C. Pictorial midwifery. Bailliere, Tindall and Cox; London: 1941.
- Elison PT. Developmental influences on adult ovarian hormonal function. *Am J Hum Biol.* 1996; 8:725–734.
- Ellison, PT. The Cambridge Encyclopaedia of Human Growth and Development. Cambridge University Press; Cambridge: 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]
- Eveleth, PB., Tanner, JM. Worldwide variation in human growth. 2nd ed. Cambridge University Press; Cambridge: 1990.
- Hamilton, W. Hamilton Textbook of Anatomy. Macmillon; London: 1966.
- Medical Progress. Cancer of the ovary. *N Eng J Med.* 2004; 351:2519–2529.
- 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]
- Schildkraut JM, Thompson WD. Familial ovarian cancer: a population-based case-control study. *Am J Epidemiol.* 2008; 128:456–466.
- Tanner, JM. Growth at adolescence. Blackwell; Oxford: 1962. p. 340
- Whittemore AS. Characteristics relating to ovarian cancer risk: Implications for prevention and detection. *Gynecol Oncol.* 1994; 55:S15–S19. [PubMed: 7835800]
- 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; 24:341–348. [PubMed: 9433910]

TABLE 1

Numbers and types of measurements made on 6,370 mothers and daughters

	Numbers	Mean	SD
Mothers			
Age at menarche (years)	6,200	14.6	1.7
Age at delivery (years)	6,367	28.5	5.5
Height (cm)	5,837	160.0	5.6
Weight (kg)	5,769	67.0	8.4
Body mass index (kg/m ²)	5,748	26.2	2.9
Parity	6,367	2.0	1.4
Pelvic diameters			
Intercristal (cm)	4,091	28.4	1.5
Interspinous (cm)	4,096	25.8	1.5
Intercristal-interspinous (cm)	4,070	2.6	1.1
Intertrochanteric (cm)	4,081	31.3	1.6
External conjugate (cm)	4,084	19.4	1.1
Daughters			
Length of gestation (days)	6,169	280	13
Age at ovarian cancer (years)	46	52	10

TABLE 2

.Hazard ratios for ovarian cancer according to mothers' heights and pelvic diameters

	Hazard ratio	95% CI	No. of cases	No. of women
Mother's height (cm)				
156.0	1.0	Baseline	8	1,582
156.1–160.0	1.7	0.7–4.1	14	1,610
160.1–164.0	1.6	0.7–4.0	12	1,455
>164.0	1.4	0.5–3.7	8	1,190
<i>P</i> for trend	0.41			
Intercristal diameter (cm)				
27.5	1.0	Baseline	8	1,191
27.6–28.5	1.0	0.4–2.6	8	1,154
28.6–29.5	1.1	0.4–3.0	7	953
>29.5	1.3	0.5–3.5	7	793
<i>P</i> for trend	0.12			
Adjusted for height	0.09			
Interspinous diameter (cm)				
25.0	1.0	Baseline	8	1,524
25.1–26.0	1.1	0.4–3.1	7	1,144
26.1–27.0	0.9	0.3–3.0	4	840
>27.0	3.4	1.3–8.5	11	588
<i>P</i> for trend	0.008			
Adjusted for height	0.006			
Intertrochanteric diameter (cm)				
30.5	1.0	Baseline	5	1,258
30.6–31.5	2.1	0.7–6.2	9	1,100
31.6–32.5	2.6	0.9–7.7	10	952
>32.5	1.9	0.6–6.2	6	771
<i>P</i> for trend	0.10			
Adjusted for height	0.02			

TABLE 3

Hazard ratios for ovarian cancer according to mothers' pelvic diameters and age at menarche

	Menarche at age 14 years or less				Menarche at age 15 years or more			
	Hazard ratio	95% CI	No. of cases	No. of women	Hazard ratio	95% CI	No. of cases	No. of women
Intercristal diameter (cm)								
27.5	1.0	Baseline	1	575	1.0	Baseline	7	610
27.6–28.5	4.8	0.6–41	5	579	0.4	0.1–1.7	3	570
28.6–29.5	4.9	0.5–44	4	479	0.6	0.1–2.3	3	469
>29.5	7.3	0.8–63	5	391	0.4	0.1–1.9	2	397
<i>P</i> for trend	0.01				0.75			
Adjusted for height	0.004				0.65			
Interspinous diameter (cm)								
25.0	1.0	Baseline	2	746	1.0	Baseline	6	773
25.1–26.0	2.1	0.4–13	3	558	0.8	0.2–2.9	4	577
26.1–27.0	2.8	0.5–17	3	435	0.3	0.0–2.6	1	403
>27.0	9.5	2.0–46	7	285	1.5	0.4–5.5	4	298
<i>P</i> for trend	0.002				0.63			
Adjusted for height	0.001				0.79			
Intertrochanteric diameter (cm)								
30.5	1.0	Baseline	1	583	1.0	Baseline	4	671
30.6–31.5	3.3	0.3–32	3	547	2.3	0.6–8.7	6	546
31.6–32.5	8.2	1.0–67	7	486	1.5	0.3–7.1	3	460
>32.5	5.4	0.6–49	4	399	1.0	0.2–5.4	2	368
<i>P</i> for trend	0.02				0.79			
Adjusted for height	0.003				0.64			

TABLE 4

Hazard ratios for ovarian cancer according to mother's pelvic diameters and height among women whose mother's age at menarche was 14 years or less

	Mother's height 160 cm or less				Mother's height 160 cm or more			
	Hazard ratio	95% CI	No. of cases	No. of women	Hazard ratio	95% CI	No. of cases	No. of women
Intercristal diameter (cm)								
28.5	1.0	Baseline	2	702	1.0	Baseline	4	403
>28.5	7.0	1.4–35	6	293	0.5	0.1–2.4	3	539
<i>P</i> for trend	0.001				0.79			
Interspinous diameter (cm)								
26.0	1.0	Baseline	2	736	1.0	Baseline	3	512
>26.0	9.7	1.9–49	6	260	1.5	0.3–6.8	4	430
<i>P</i> for trend	0.001				0.25			
Intertrochanteric diameter (cm)								
31.5	1.0	Baseline	1	700	1.0	Baseline	3	385
>31.5	17.3	2.1–143	7	292	0.8	0.2–3.7	4	551
<i>P</i> for trend	<0.001				0.83			