Maternal pelvic size not predictive of daughter's breast or ovarian cancer in a large Swedish cohort

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Abstract

Recent studies from Finland reported that maternal pelvic size predicted daughters' breast and ovarian cancer, possibly because maternal pelvic size is a marker for *in utero* hormone exposure. We sought to replicate this association in 3845 women born 1915-1929 in Uppsala, Sweden, and followed from 1960 to 2002. Archived obstetric records provided the standard measures of maternal pelvic size (intercristal distance, interspinous distance, the intercristal-interspinous difference and the external conjugate distance). The Swedish cancer registry ascertained cancer incidence, with 273 cohort members developing primary breast cancer and 52 developing primary ovarian cancer during the follow-up period. There was no evidence ($p>0.1$) of an association between any measure of maternal pelvic size and incidence of either breast or ovarian cancer. This was true both before and after adjustment for various characteristics of the women and their mothers, and in analyses stratified by age at diagnosis (under age 50 vs. age ≥50, as a proxy for pre- and post-menopausal ages). There was also no evidence of an association in subgroup analyses restricted specifically to those groups in which the Finnish data found the greatest effect. Our study is of comparable size to the Finnish studies and highly powered (>99%) to detect effects of the magnitude they reported. Our non-replication therefore casts doubt on the link between maternal pelvic size and risk of breast and ovarian cancer in the offspring.

Key Words: pelvic size, breast cancer, ovarian cancer, intergenerational, developmental origins of health and disease

Introduction

Barker *et al.* recently reported that maternal pelvic size predicted breast and ovarian cancer in 4102 Finnish women born between 1934-1944 and followed from 1971-2003 (1, 2). They investigated four standard measures of maternal pelvic size: intercristal distance (the maximal distance between the iliac crests); interspinous distance (distance between the anterior-superior iliac spines); the difference between the intercristal and interspinous distances; and external conjugate distance (distance from front of the pubic bone to the fifth lumbar vertebrae). 206 of their cohort members developed primary breast cancer, with higher incidence among women whose mother had a larger intercristal distance and a larger interspinous-intercristal difference. 39 developed primary ovarian cancer, with higher incidence among women whose mother had a larger interspinous distance. Barker *et al.* hypothesise that pelvic size is a marker for mother's hormone profile, and that this *in utero* exposure increases the daughter's risk.

Methods

Sample

The Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) has been described previously (3-5). Briefly, the cohort comprises all live births between 1915-1929 in the Uppsala Academic Hospital, Sweden. Archived obstetric records provided information about cohort members and their mothers at birth, and record linkage provided data from routine registers up to 2002. This included the Swedish cancer registry, established 1 January 1960.

Of the 6781 females live births, 751 died before 1960, 63 emigrated before 1960, and 202 were never traced. 3845/5765 (66.7%) of the remainder had maternal pelvis measurements, and these are the starting population for our analyses. Pelvis measurements were more complete after 1924 (31.7-50.1% with data pre-1924 vs. ≥93.4% after) and for primiparous women (72.1% with data vs. 63.2% for multiparous). There was no evidence ($p>0.05$) that missing pelvis measurements predicted breast or ovarian cancer in daughters.

Statistical methods

We fitted Cox proportional hazards models, running separate models for breast and ovarian cancer. Follow-up started on 1 January 1960 and continued until the date of death, emigration, diagnosis with any primary cancer or until 31 December 2002. The woman's age defined the timescale. To adjust for possible cohort or period effects, we divided birth year into three bands (1915-19, 1920-24, 1925-29) and included this as a categorical variable in all models. We used the same cut-offs as Barker *et al.* for categorizing pelvic measurements and also present analyses using the continuous measurements.

We then assessed the effect of adjusting for each potential confounder listed in Table 1 individually, and of adjusting for all of them simultaneously. We banded the continuous confounders into between five and eight categories of approximately equal size, and modeled these as categorical variables.

Barker *et al.* report that the effect of intercristal distance on breast cancer was greatest in multiparous mothers and infants born at ≥40 weeks, and that the effect of interspinous distance on ovarian cancer was greatest in mothers who had menarche before age 14 and were under 160cm tall. We conducted sensitivity analyses restricting our analyses to these subgroups, except for mother's height which was not recorded for our cohort. To assess whether the effect of maternal pelvic size was modified by menopausal status, we also conducted separate analyses for ages <50 and ≥50 years, using these as proxies for pre-menopausal and post-menopausal ages.

Results

The characteristics of the study population and their mothers are summarized in Table 1. Among our 3845 study members, 273 developed primary breast cancer and 52 developed primary ovarian cancer by 31 December 2002 (total person years at risk 142826.3).

Table 1: Characteristics of study population and their mothers (N=3845)

	Number with data	Mean (SD) or proportion	Range
Pelvis measurements of mother			
Intercristal distance (cm)	3845	28.3 (1.6)	20, 35
Interspinous distance (cm)	3845	25.3 (1.7)	17.5, 39
Intercristal minus interspinous distance (cm)	3845	2.9 (1.3)	-10, 9
External conjugate (cm)	3332	20.1 (1.5)	10, 34
Cancer incidence of daughter			
Age at breast cancer diagnosis (years)	273	61.9 (11.1)	36.4, 85.4
Age at ovarian cancer diagnosis (years)	52	60.3 (12.0)	36.6, 86.3
Potential confounders			
Mother's characteristics			
Mother's age at menarche (years)	3811	14.7 (1.5)	11, 22
Mother's age at child's birth (years)	3845	28.1 (6.5)	15, 47
Mother's parity at child's birth	3845	2.6 (2.3)	1, 16
Daughter's characteristics at birth			
Birthweight (g)	3822	3367.8 (521.5)	1180, 5350
Birth length (cm)	3838	50.2 (2.3)	38, 59
Head circumference (cm)	3744	34.3 (1.5)	23, 46
Gestational age (weeks)	3713	39.6 (2.1)	29, 47
Daughter's adult characteristics			
Post-elementary education	3791	4.3%	--
Had at least one child	3845	83.6%	--
Number of children among those who had at least one child	3214	2.3 (1.3)	1, 13
Age at first birth among those who had at least one child (years)	3214	24.1 (4.6)	17, 41

SD = standard deviation

Table 2 presents the hazard ratios for breast and ovarian cancer for each of the pelvic measures. In no case was there evidence of an association ($p>0.1$); this remained true when entering the pelvic measurements as categorical variables or with quadratic terms. There was likewise no evidence at the 5% level of an association after adjusting for any potential confounder listed in Table 1, after stratifying our analyses between women aged <50 and those aged ≥50 years, or after restricting our analyses to the subgroups in which Barker *et al.* report the greatest effect.

Table 2: Hazard ratios for breast and ovarian cancer by maternal pelvic measurements

	Breast cancer			**Ovarian cancer**		
	Hazard ratio & 95% CI	**No. cases (N=273)**	**No. women (N=3845)†**	**Hazard ratio & 95% CI**	**No. cases (N=52)**	**No. women (N=3845)**
Intercristal distance (cm)						
≤28.0	1	145	2122	1	28	2122
28.5-30.0	1.18 (0.92 – 1.51)	111	1391	1.05 (0.59 – 1.89)	19	1391
≥30.5	0.76 (0.46 – 1.26)	17	332	1.20 (0.46 – 3.11)	5	332
P-value for heterogeneity	*0.16*			*0.93*		
Change per 1cm increase	1.00 (0.93 – 1.07)	273	3845	1.05 (0.89 – 1.24)	52	3845
P-value for linear trend	*0.96*			*0.55*		
Interspinous (cm)						
≤28.0	1	72	1037	1	10	1037
28.5-30.0	1.11 (0.83 – 1.48)	141	1933	1.69 (0.81 – 3.53)	28	1933
≥30.5	1.03 (0.73 – 1.47)	60	875	1.92 (0.84 – 4.42)	14	875
P-value for heterogeneity	*0.77*			*0.27*		
Change per 1cm increase	0.98 (0.92 – 1.05)	273	3845	1.11 (0.96 – 1.29)	52	3845
P-value for linear trend	*0.60*			*0.17*		
Intercristal minus interspinous (cm)						
≤2.0	1	84	1228	1	20	1228
2.5	1.21 (0.76 – 1.92)	23	268	0.99 (0.37 – 2.65)	5	268
3.0	0.87 (0.63 – 1.19)	74	122	0.66 (0.33 – 1.30)	15	122
≥3.5	1.16 (0.85 – 1.58)	92	1129	0.54 (0.25 – 1.15)	12	1129
P-value for heterogeneity	*0.25*			*0.35*		
Change per 1cm increase	1.03 (0.94 – 1.13)	273	3845	0.90 (0.74 – 1.09)	52	3845
P-value for linear trend	*0.53*			*0.27*		
External conjugate distance (cm)						
≤19.0	1	72	1000	1	14	1000
19.5-21.0	0.99 (0.74 – 1.32)	129	1831	0.81 (0.41 – 1.61)	20	1831
≥21.5	1.08 (0.72 – 1.60)	38	501	0.92 (0.35 – 2.41)	6	501
P-value for heterogeneity	*0.90*			*0.83*		
Change per 1cm increase	1.02 (0.94 – 1.11)	239	3332	0.98 (0.79 – 1.22)	40	3332
P-value for linear trend	*0.64*			*0.88*		

† 513 women had missing data on external conjugate distance, giving a total of 3332.

All analyses adjust for birth year with age defining the timescale.

Discussion

UBCoS Multigen provides a unique opportunity to test the hypotheses proposed by Barker *et al.* (1, 2). Unlike their findings from Finland, our Swedish cohort provided no evidence that maternal pelvic size predicts daughters' breast or ovarian cancer. This is despite a close similarity in our methods, and a close similarity between our study populations in terms of pelvic sizes and cancer incidence. Our null findings were robust to adjustment for confounders and sensitivity analyses, including analyses restricted to the subgroups in which Barker *et al.* report the largest effect. The one subgroup analysis we did not have the data to replicate was restricting the analysis of interspinous distance and ovarian cancer to shorter mothers. We found no evidence (p=0.17) for this effect in the whole population, however, whereas in the Finnish cohort the whole-population p-value was 0.008 (1).

This non-replication cannot be attributed to insufficient power. Our cohort is of a similar size to the Finnish cohort (3854 vs. 4201 females) and, because of the longer follow-up, contains somewhat more cancer cases (273 vs. 206 breast cancers, 52 vs. 39 ovarian cancers). For example, Barker *et al.* report a hazard ratio for breast cancer of 1.23 per 1cm increase in the intercristal-interspinous difference. With 273 cancers among 3845 women, and a standard deviation of 1.3, our cohort would have 99.4% power to detect this at the 5% significance level. This non-replication likewise cannot be attributed to poor measurement of exposure or outcome, as both have previously shown positive findings in other studies. For example, larger maternal pelvic size does protect against stroke in our cohort (6) in a way which replicates findings from the Finnish cohort (7). Similarly, breast cancer in our cohort is predicted by birth size (3) in a way consistent with the existing literature (8).

In summary, this cohort provides no evidence that maternal pelvic size predicts daughters' incidence of breast or ovarian cancers. This therefore casts doubt on a relationship between these factors.

Conflict of interest

None

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