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Birth order and breast cancer risk

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It has been hypothesized that prenatal exposure to maternal estrogens may be a risk factor for breast cancer in the offspring. In two recent studies, maternal estradiol levels in the first pregnancy have been compared to those in the second, and in both studies levels were higher in the first pregnancy. If both the hypothesis and the reported findings were true, women born as their mother's second child would be expected to have lower risk for breast cancer than first-born women. Data from 1,468 cases of breast cancer and 4,175 hospital controls from three previously published studies were modelled through multiple logistic regression to evaluate this possibility. The size of the woman's sibship was not related to breast cancer risk. On the other hand, second-born women had, as predicted, lower breast cancer risk than first-born women, although the difference was nominally significant only among premenopausal women. The relative risk for breast cancer, contrasting second-born to first-born women, and the corresponding 95 per cent confidence intervals, were 0.71 (0.54 – 0.94) among premenopausal women, 0.94 (0.76 – 1.17) among postmenopausal women, and 0.86 (0.73 – 1.02) among all women, controlling for menopausal status.

Key words: Birth order, breast cancer, case-control studies, estrogens.

Introduction

It has been suggested recently that breast cancer risk may be influenced by concentrations of maternal estrogens while the woman herself was *in utero*.[1] Little is known, however, of the correlates of pregnancy estrogen levels. In 1986, Bernstein *et al*[2] reported that the percentage and the amount of free estradiol (E2) are significantly higher in the early part of a woman's first pregnancy than at a comparable time-point in her second pregnancy. Panagiotopoulou *et al*[3] later reported similar results, although their study focused on total, rather than bio-available, E2, and on the late, rather than the early, stage of pregnancy. On the basis of these findings, it might be expected that breast cancer risk might be lower in women born of a second pregnancy than in first-born women. The present analysis was undertaken in order to explore this possibility.

Subjects and methods

The data for this analysis derive from a multicenter case-control study conducted in the late 1960s.[4,5] Information concerning birth order and sibship size was collected in only three centers, namely Boston (USA),[6] Glamorgan (Wales),[7] and Tokyo (Japan).[8] In Boston and Glamorgan, the breast cancer cases included most of the female residents of the study areas who were hospitalized for a first diagnosis of breast cancer during the study period, whereas in Tokyo the coverage was about 50 percent. For each breast cancer patient interviewed, three eligible patients in beds closest to the index case were interviewed as controls. A control had to be a resident of the study area, never to have had cancer of the breast, and to be over 35 years of age (except when the index case was under 35, in which instance controls were age-matched within two years). Details of the

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original study and the collective results have been published with respect to lactation;[4] age at first and at any birth;[5,9] maternal age at birth;[10] age at menarche, age at menopause, and anthropometric variables;[11] and breast size and handedness.[12]

The data on sibship size and birth order were based on the number of children in the parental family who lived to be age 40, including the patient (whatever her age). Multiple births were counted as a single pregnancy. Cases and controls were not included if their interviews were judged unreliable, or when information was not available for the study variable (birth order in the corresponding sibship) or any of the following potential confounding variables: age at interview; age at first birth; parity; age at menarche; menopausal status; height; Quetelet's index (obesity); and maternal age at birth. The analysis is therefore based on 1,468 cases of breast cancer and 4,175 controls distributed by center as follows: in Boston, 467 cases (77 percent of all interviewed) and 1,391 controls (77 percent of all interviewed); in Glamorgan, 403 (65 percent) and 1,250 (68 percent), respectively; and in Tokyo, 598 (70 percent) and 1,534 (68 percent), respectively. The age distributions of the original cases are given in the original publications,[6-8] and the cases analyzed here are similarly distributed.

The statistical analysis was carried out by modelling through multiple logistic regression.[13] Separate analyses were conducted for premenopausal and postmenopausal women, as well as for all women (controlling for menopausal status). Birth order was assessed categorically, with birth order 1 as the baseline. Since a prior hypothesis existed only with respect to birth order 2 (compared to birth order 1), birth orders 2, 3, and 4+ were examined separately as well as in combination (2+). Established or likely risk factors for breast cancer[10,11,14,15] were considered as potential confounders and were controlled in the analysis as follows: study center (categorically); parity (categorically:nulliparous = 0, parous = 1); age at first birth (as continuous variable); age at interview (as continuous variable); age at menarche (as continuous variable); height (as continuous variable); obesity (Quetelet's index, weight/height^2, as continuous variable); and maternal age at birth (as continuous variable, with five-year increments). A similar model was used to assess the relation, if any, between sibship size and breast cancer risk, controlling for all the previously indicated potential confounders. Confidence intervals (CI) of rate ratios (RR) were computed from the models and all CI shown are 95 percent intervals.

Results

No relationship was found with size of sibship (data not given). With sibship size 1 as baseline, RR (CI) among all women were: for sibship size 2, 1.09 (0.86 – 1.38); for sibship size 3, 0.98 (0.76 – 1.26); and for sibship size

Table 1. Adjusted[a] rate ratio (RR) with 95% confidence interval (CI), and distribution of women with breast cancer and control women by menopausal status and birth order

Birth order	Number of		RR		CI	P^b
	Cases	Controls	Crude	Adjusted		
Premenopausal						
1	253	598	1.00	1.00	Baseline	
2	115	345	0.79	0.71	0.54 – 0.94	0.02
3	91	231	0.93	0.79	0.57 – 1.09	0.15
4+	136	322	1.00	0.84	0.61 – 1.16	0.30
2+	342	898	0.90	0.76	0.60 – 0.96	0.02
Postmenopausal						
1	288	961	1.00	1.00	Baseline	
2	203	667	1.02	0.94	0.76 – 1.17	0.60
3	152	401	1.26	1.20	0.94 – 1.52	0.19
4+	230	650	1.18	1.02	0.80 – 1.29	0.89
2+	585	1,718	1.14	1.03	0.86 – 1.23	0.78
All women						
1	541	1,559	1.00	1.00	Baseline	
2	318	1,012	0.91	0.86	0.73 – 1.02	0.08
3	243	632	1.11	1.05	0.87 – 1.27	0.62
4+	366	972	1.09	0.98	0.81 – 1.18	0.84
2+	927	2,616	1.02	0.94	0.82 – 1.08	0.39

[a]Multiple logistic regression based; controlling for study center, age at interview, age at first birth, parity, age at menarche, height, Quetelet's index, maternal age at birth, and (for the all-women group) menopausal status.
[b]P value, two tails.

4+, 0.99 (0.77 – 1.28). Furthermore, among premenopausal and postmenopausal women, examined separately, sibship size similarly was not associated with breast cancer risk, irrespective of the individual sibship size or combination of sibship sizes considered (*P* values in all instances were larger than 0.25).

Table 1 shows the distribution of cases and controls by study center, menopausal status, and birth order, together with crude and adjusted RR and CI. Second-born women had lower RR than first-born women, although the difference was substantial and statistically significant only among premenopausal women. Premenopausal women of birth order 3 or 4+ also had lower RR than those of birth order 1, but this was not evident among postmenopausal women; furthermore, the corresponding RRs were not significantly different from the null value of 1, and there was no evidence of a consistent trend. For premenopausal women, the findings were consistent over different centers. RRs associated with the second birth order were 0.51, 0.89, and 0.66 in Boston, Glamorgan, and Tokyo, respectively. Among postmenopausal women, RRs were 1.02, 1.02, and 0.77 in the three centers.

Table 2 shows RRs for a five-year increment of maternal age at birth adjusted for all the previously indicated potential confounders, excluding and including birth order. As expected, maternal age at birth is a risk factor for breast cancer and, among premenopausal women, birth order is a negative confounder of the association. Conversely, maternal age at birth is a confounder of the birth order associations. Thus, if maternal age were not included among the factors controlled for in Table 1, the RR among women with birth order 2 would increase from 0.71 to 0.74 for premenopausal, from 0.94 to 0.99 for postmenopausal, and from 0.86 to 0.89 for all women; among women with birth order 2+, the RR would increase from 0.76 to 0.83 for premenopausal women, from 1.03 to 1.12 for postmenopausal women, and from 0.94 to 1.01 for all women.

Table 2. Adjusted[a] rate ratios (RR) with 95% confidence interval (CI) for breast cancer corresponding to a five-year increase in maternal age at birth

	RR[a]	(CI)	RR[b]	(CI)
Premenopausal	1.02	(0.95 – 1.10)	1.07	(0.98 – 1.17)
Postmenopausal	1.08	(1.02 – 1.14)	1.08	(1.01 – 1.15)
All women	1.06	(1.01 – 1.10)	1.07	(1.01 – 1.12)

[a]Multiple logistic regression based; controlling for study center, age at interview, age at first birth, parity, age at menarche, height, Quetelet's index, maternal age at birth, and (for the all-women group) menopausal status.
[b]Adjusted for all variables indicated above, plus birth order.

Discussion

The present study was an attempt to evaluate the hypothesis that intrauterine exposure to high levels of endogenous estrogens may increase the risk of breast cancer.[1] The study was premised on the assumption that maternal estrogens are higher during the first than during the second pregnancy, with no information available with respect to subsequent pregnancies. There are only two studies which examined the association between pregnancy estrogens and pregnancy ranks[2,3] and, although their results were in broad agreement, they cannot be thought of as definitive. Even if they were, they would not necessarily generate conditions for a critical test of the hypothesis, since there are certainly credible alternative explanations for a lower risk of breast cancer among second-born women. Finally, the results of the present study are no more than suggestive of a breast-cancer risk difference between first-born and second-born women. These reservations notwithstanding, the present analysis indicates that it would be useful to explore further whether birth order is indeed a risk factor for breast cancer—particularly if estrogens or other endocrine variables were confirmed to be dependent on the order of pregnancy.

With respect to the results of the present study, three issues raise concern: the restriction of sibship size and birth order determination to those siblings who survived to the age of 40; the lack of overall statistical significance; and the absence of a discernible risk pattern across successive birth orders (birth orders 3 and 4+). The probability of dying before 40 is low (around six percent for US whites in 1965 and 1966)[16,17] and the resulting errors in classification are expected to be minimal and likely to be nondifferential. On the lack of overall statistical significance, the difference in maternal estrogen levels between first and second pregnancy is modest (about 15 percent) and it should not be expected to generate stronger risk contrasts. Furthermore, there are no data on levels of maternal estrogens in pregnancies of order higher than 2, and it is conceivable (although unlikely) that it is only the second pregnancy that is characterized by lower levels of maternal estrogens. In addition, it was not expected to observe the birth-order/breast-cancer association only among premenopausal women, although it is credible to assume that perinatal events would be more relevant, if at all, to breast cancer risk of younger women.

There has been only one previous study that examined birth order in relation to breast cancer risk. Janerich *et al*[18] reported no statistically significant association, but did not present actual data and they were skeptical themselves about the sensitivity of the Greenwood-Yule method they used. The association of birth order with

breast cancer also was examined briefly in the data set of the present study by Rothman *et al.*[10] In their investigation of the relation between maternal age at birth and breast cancer risk, no association was found for the total group.

If, indeed, birth order is a risk factor for breast cancer, the universally strong, positive association between birth order and maternal age at birth would generate negative mutual confounding with respect to breast cancer risk. Since the relations of both these factors to breast cancer are at most weak, a slight negative confounding could be consequential, and it could be partly responsible for the failure of some studies to demonstrate significant associations between maternal age at birth and breast cancer risk.

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References

1. Trichopoulos D. Hypothesis: does breast cancer originate *in utero*? *Lancet* 1990; **335**: 939 – 40.
2. Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE. Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. *JNCI* 1986; **76**: 1035 – 9.
3. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity, and pregnancy estrogens. *Cancer Causes and Control* 1990; **1**: 117 – 24.
4. MacMahon B, Lin TM, Lowe CR, *et al.* Lactation and cancer of the breast. *Bull World Hlth Org* 1970a; **42**: 185 – 94.
5. MacMahon B, Cole P, Lin TM, *et al.* Age at first birth and breast cancer risk. *Bull World Hlth Org* 1970b; **43**: 209 – 21.
6. Salber EJ, Trichopoulos D, MacMahon B. Lactation and reproductive histories of breast cancer patients in Boston, 1965 – 66. *JNCI* 1969; **43**: 1013 – 24.
7. Lowe CR, MacMahon B. Breast cancer and reproductive history of women in South Wales. *Lancet* 1970; **1**: 153 – 7.
8. Yuasa S, MacMahon B. Lactation and reproductive histories of breast cancer patients in Tokyo, Japan. *Bull World Hlth Org* 1970; **42**: 195 – 204.
9. Trichopoulos D, Hsieh C-C, MacMahon B, *et al.* Age at any birth and breast cancer risk. *Int J Cancer* 1983; **31**: 701 – 4.
10. Rothman KJ, MacMahon B, Lin TM, *et al.* Maternal age and birth rank of women with breast cancer. *JNCI* 1980; **65**: 719 – 22.
11. Hsieh C-C, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer* 1990; **46**: 796 – 800.
12. Hsieh C-C, Trichopoulos D. Breast size, handedness and breast cancer risk. *Euro J Cancer* (in press).
13. Breslow NE, Day NE. *Statistical Methods in Cancer Research Vol 1. The Analysis of Case-control Studies.* Lyon: International Agency for Research on Cancer, 1980; IARC Sci. Publ. No. 32: 338.
14. Kelsey JL, Hildreth NG. *Breast and Gynecologic Cancer Epidemiology.* Boca Raton: CRC Press; 1983: 5 – 70.
15. Boyle P. Epidemiology of breast cancer. In: Yorbro JW, Bornstein RS, Mastrangelo MJ, eds. *Bailliere's Clinical Oncology. Vol 2.* Eastbourne: Saunders; 1988: 1 – 57.
16. National Center for Health Statistics, US Department of Health, Education and Welfare. *Vital Statistics of the United States, 1965. Vol II—Mortality, Part A (Tables 5 – 3).* Washington, D.C.: US Government Printing Office, 1967.
17. National Center for Health Statistics, US Department of Health, Education and Welfare. *Vital Statistics of the United States, 1966. Vol II—Mortality, Part A (Tables 5 – 3).* Washington, D.C.: US Government Printing Office, 1968.
18. Janerich DT, Hayden CL, Thompson WD, *et al.* Epidemiologic evidence of perinatal influence in the etiology of adult cancers. *J Clin Epidemiol* 1989; **42**: 151 – 7.