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Breast cancer in Swedish women before age 50: evidence of a dual effect of completed pregnancy

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We set out to detect a transient increase in risk of breast cancer following childbirth, the existence of which has been postulated, but for which empirical evidence is contradictory. Breast cancers and births occurring among the cohort of Swedish women born after 1939 were linked, yielding 3,439 cases and 25,140 age-matched controls with at least two children. Within three years of their last childbirth, women had an estimated rate of breast cancer of 1.21 (95 percent confidence interval [CI] = 1.02-1.44) times that of women whose last birth was 10 or more years earlier, after adjustment for parity and age at first birth. Further analyses suggested that this effect reflected, in part, a small transient increase in breast cancer risk that lasts for about three years following completed pregnancy. The effect of age at first birth on breast cancer risk appears to be confounded by time since last birth; the parity-adjusted rate ratio for having a first birth at age 35 years or more compared with under 20 years is reduced from 1.72 (CI = 1.14-2.58) to 1.36 (CI = 0.88-2.09) on additional adjustment for time since last birth. A transient increase in breast cancer risk after childbirth thus appears to account for part of the effect of age at first birth on breast cancer risk. *Cancer Causes and Control* 1995, **6**, 283-291

Key words: Age at first birth, breast cancer, females, parity, reproductive factors, Sweden.

Introduction

In 1943, Dorn[1] showed that married women with children had lower mortality from breast cancer than married women without children, as confirmed a few years later by Logan.[2] The protective effect of childbearing was challenged in 1970, when the classic study by MacMahon *et al* [3] concluded that the decline in breast cancer risk with increasing parity was due entirely to confounding by age at first birth. However, it is accepted generally now that after adjustment for age at first birth, breast cancer risk declines with increasing parity,[4] this effect being particularly marked for women of parity four or above.[5]

One intriguing feature of the effect of age at first birth is that women who have their first birth in their early thirties or later are at greater risk than nulliparous women.[3] The biological basis for the complex effects of childbearing is unclear. A dual effect of parity on breast cancer risk has been proposed,[6,7] in which there is a transient increase in risk shortly after pregnancy, which is superseded by a long-term protective effect. Evidence

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concerning the existence of such a dual effect is inconsistent. Several case-control studies have found that risk in the years shortly after childbirth is greater than in subsequent years, and therefore have concluded that there is a short-term increase in risk.[8-10] Stronger positive evidence for a transient increase in risk following childbirth comes from two similar analyses, one of linked Swedish data on nulliparous and uniparous women,[11] the other[12] a reanalysis of the original MacMahon data.[3] However, because of their analytic approach, neither study was able to provide a direct estimate of the magnitude of the effect. Set against these results, three case-control studies[13-15] have concluded that there was no evidence for such an effect.

Adequate statistical power to detect a moderate increase in breast cancer risk in the years immediately following the birth of a child requires a very large study population. We have been able to set up such a study, based on the linkage of routine data on cancer registration and births in Sweden, the results of which we now report. Unlike previous studies, we provide estimates of the magnitude of the risk of breast cancer among women of a given parity in the period shortly after the birth of another child, compared with women of the same parity who did not go on to have a further child.

Materials and methods

Records of all live- and stillbirths born in Sweden 1961-89 were linked by mothers' national identity number, with information on every birth registered to each cohort member to create a cohort of all women giving birth in Sweden during this period. This cohort then was linked to the Swedish Cancer Registry to identify breast cancers registered to the women following the birth of their first child. To simplify analysis, a nested case-control dataset was created comprised of women diagnosed with breast cancer in Sweden between 1961 and 1989 who were born after 1939, each case being matched on age with up to 10 controls, as detailed below.

Birth data

Information on births occurring between 1961 and 1972 was obtained from the Civil Birth Registry, and for births occurring between 1973 and 1989 from the Swedish Medical Birth Registry. Both registries record basic demographic data on all births in Sweden. The Medical Birth Registry also records obstetric and perinatal data for each birth. Over the period concerned, both registries were virtually complete.[16] For each birth, gender, date of birth, age of mother, singleton/multiple-birth status, and live-/stillborn status were obtained.

Cancer data

Information on date of diagnosis, age at diagnosis, method of diagnosis, tumor morphology, and ICD-7[17] four-digit code was obtained for each case from the Swedish Cancer Registry. Notification of cases comes principally from diagnosing doctors. Cases identified solely from death certificates are not registered. Established in 1958, the Swedish Cancer Registry is thought to have a very high level of completeness.[18]

Case-control selection

In order for cases and controls to be selected, further linkages were made with the date of death registry, the emigration registry, and the 1992 Swedish population registry. Cases were defined as all women born after 1939 who had been registered with a first primary breast cancer (ICD-7 code 170) in the period 1961-89, who had had at least one birth in the same period that preceded the diagnosis of the breast cancer, and for whom there was no notification of emigration from Sweden prior to that date. Incidence density sampling (without replacement within each risk set)[19] was used to select controls. For each case, 10 controls were selected at random, matched on year of birth, from among women who, on the day of diagnosis of their matched case, had not died or emigrated from Sweden, had had at least one birth, and had not been registered with breast cancer. Finally, as a precaution against selection bias due to potential incompleteness of the emigration or mortality data, both cases and controls had to be listed in the Swedish National Population Register for 1992 if they had not been registered as having died or emigrated prior to 1992.

Of the 53,647 cases and controls, one was excluded because of missing information on the date of birth of a child. We also excluded women who had delivered twins or higher-order multiple births prior to the date of diagnosis of the relevant case, as it has been suggested that multiple births affect breast cancer risk.[20] In this analysis, multiple births were defined as births to the same woman where the date of birth (± 1 day) was the same.

Analysis

Parity was defined for a case as the total number of live- and stillbirths registered prior to her date of diagnosis, and for a control as the number of live- and stillbirths registered prior to the date of diagnosis of her matched case. Time since last birth was defined for controls with respect to date of diagnosis of the matched case. The four categories of time since last birth used in some of

the initial analyses were defined so as to make our results comparable with other studies.[8,9,15]

The primary objective of the analysis was to determine if breast cancer risk was increased in the period immediately following the birth of a child, independently of parity and age at first birth. For uniparous women, there is a linear dependency between age, age at first birth, and interval between birth and cancer. After matching on age at diagnosis, the effects of age at first birth and time since first birth therefore cannot be separated in these women. To avoid this difficulty, women of parity one were excluded from our initial analyses.

We also undertook a further set of analyses specifically to determine whether the risk of breast cancer in the few years following the birth of a child increased compared with parous women who had not had a further birth. For these analyses, we contrasted risk among women of parity two whose last birth was three years or more in the past, with the risk experienced by women of the same age, and age at first birth, who were of parity three and who had had their last birth more recently. Similar contrasts were estimated for women of higher consecutive parities. The transient effects of having a second child are of particular interest, not the least because far fewer women go on to have three or more children. Despite the general problem of linear dependency outlined above, we were able to contrast the risk of women of parity one having their first birth three or more years in the past, with women of parity two who had had their second birth more recently. This was possible because no attempt was made to estimate the effects of time since last birth among uniparous women; women of parity one whose first birth occurred less than three years earlier still being excluded. Women of parity six or more, and women of parity five whose last birth was three years or more in the past also were excluded from these further analyses, as their numbers were too small to be informative.

Conditional logistic regression was employed in a standard fashion,[21] using the EPICURE computer package,[22] to obtain maximum likelihood estimates of the breast cancer rate for one level of a factor relative to a baseline (rate ratio). Whether an explanatory factor had a significant effect on the rate ratio independent of any particular set of other variables was judged by comparing the deviance of regression models with and without terms representing levels of the factor. The difference in the deviance of the two models was compared to the chi-square distribution on k-1 degrees of freedom, where k was the number of levels of the factor. Tests of linear trend were carried out by fitting a continuous scored-variable whose values corresponded to the level of the factor. As the hypothesis under investigation is that there is a short-term increase in risk following childbirth, rather than a linear, progressive effect over the entire period since last birth, linear trend statistics were not considered relevant, and thus are not reported for this variable. Confidence intervals were calculated based on the standard errors of the parameter estimates.

Results

Excluding women who had a history of multiple births, the distribution of cases and controls according to parity, age at first birth, and time since last birth is shown in Table 1. When analyses were restricted to women of parity two or more (Tables 2-4), the data comprised 3,439 case-control sets with at least one control, of which 171 had fewer than five controls, 2,666 having eight or more controls.

Table 2 shows the breast cancer rate ratios by parity, with and without adjustment, for age at first birth and time since last birth. Whereas adjustment for age at first birth has the effect of reducing the strength of the parity association, adjustment for time since last birth strengthens it. When adjusted for both age at first birth and time since last birth simultaneously, these opposing effects almost cancel out, the fully adjusted

Table 1. Distribution of breast cancer cases and controls who had had singleton births only, by parity, age at first birth, and time since last birth, Sweden

	Cases		Controls	
	No.	%	No.	%
Parity				
1	1,285	27.2	11,046	24.4
2	2,319	49.1	22,204	49.1
3	926	19.6	9,290	20.5
4	162	3.4	2,134	4.7
5+	34	0.7	575	1.3
Age at first birth (yrs)				
<20	606	12.8	6,790	15.0
20-24	2,112	44.7	21,396	47.3
25-29	1,417	30.0	12,599	27.8
30-34	474	10.0	3,579	7.9
35+	117	2.5	885	2.0
Time since last birth (yrs)				
<3	634	13.4	5,103	11.3
3-6	902	19.1	8,023	17.7
7-9	678	14.4	6,871	15.2
10+	2,512	53.2	25,252	55.8
Total	4,726	100.0	45,249	100.0

Table 2. Unadjusted and adjusted rate ratios for breast cancer by parity, for women aged less than 50, of parity 2+ with no multiple births, Sweden

Parity	No. of cases	Rate ratios (CI)[a] adjusted for			
		Unadjusted	Age at first birth[b]	Time since last birth[c]	Age at first birth and time since last birth[b,c]
2 (Baseline)	2,317	1.00	1.00	1.00	1.00
	—	—	—	—	—
3	926	0.97	1.03	0.92	1.00
		(0.89-1.05)	(0.94-1.12)	(0.85-1.00)	(0.91-1.09)
4	162	0.72	0.80	0.66	0.75
		(0.61-0.85)	(0.67-0.94)	(0.56-0.78)	(0.63-0.90)
5+	34	0.60	0.67	0.52	0.62
		(0.42-0.85)	(0.47-0.96)	(0.36-0.74)	(0.43-0.89)
χ^2 heterogeneity (3 df)[d]		24.2 ($P < 0.001$)	13.5 ($P = 0.004$)	38.2 ($P < 0.001$)	16.6 ($P < 0.001$)
χ^2 trend (scored)		17.4 ($P < 0.001$)	5.1 ($P = 0.024$)	31.3 ($P < 0.001$)	8.2 ($P = 0.004$)

[a] CI = 95% confidence interval.
[b] Age at first birth (in yrs) fitted as a factor with 18 levels (<19,19,20 ... 35+).
[c] Time since last birth (in yrs) fitted as a factor with 11 levels (0,1,2 ... 10+).
[d] df = degrees of freedom.

rate ratios being very similar to the unadjusted ones. For all models, the declining trend in the rate ratio with increasing parity is significant.

Table 3 shows the breast-cancer rate ratios by age at first birth, with and without adjustment for parity and time since last birth. The unadjusted estimates show the well-known increase in risk with increasing age at first birth, the increase being smooth and statistically significant. The rate ratios were reduced to the greatest extent on simultaneous adjustment for both parity and time since last birth, although the χ^2 for linear trend remains highly significant. In the unadjusted model, the rate of breast cancer is estimated to increase by a factor of 1.21 (95 percent confidence interval [CI] = 1.15-1.26)

Table 3. Unadjusted and adjusted rate ratios for breast cancer by age at first birth (in years), for women aged less than 50, of parity 2+ with no multiple births, Sweden

Age at first birth in years	No. of cases	Rate ratios (CI [a]) adjusted for			
		Unadjusted	Parity[b]	Time since last birth[c]	Parity and time since last birth[b,c]
<20 (Baseline)	503	1.00	1.00	1.00	1.00
	—	—	—	—	—
20-24	1,694	1.14	1.11	1.12	1.07
		(1.02-1.27)	(1.00-1.24)	(1.01-1.25)	(0.96-1.20)
25-29	1,003	1.35	1.30	1.31	1.20
		(1.20-1.52)	(1.16-1.47)	(1.16-1.48)	(1.05-1.37)
30–34	209	1.47	1.42	1.39	1.22
		(1.24-1.76)	(1.19-1.70)	(1.15-1.68)	(0.99-1.49)
35+	30	1.79	1.72	1.62	1.36
		(1.19-2.68)	(1.14-2.58)	(1.06-2.46)	(0.88-2.09)
χ^2 heterogeneity (4 df)[d]		40.7 ($P < 0.001$)	31.7 ($P < 0.001$)	25.5 ($P < 0.001$)	9.4 ($P = 0.052$)
χ^2 trend (scored)		40.1 ($P < 0.001$)	31.0 ($P < 0.001$)	24.6 ($P < 0.001$)	8.5 ($P = 0.004$)

[a] CI = 95% confidence interval.
[b] Parity fitted as a factor with 4 levels (2,3,4,5+).
[c] Time since last birth (in yrs) fitted as a factor with 11 levels (0,1,2 ... 10+).
[d] df = degrees of freedom.

Table 4. Unadjusted and adjusted rate ratios for breast cancer by time since last birth (in years), for women aged less than 50, of parity 2+ with no multiple births, Sweden

Time since last birth in years	No. of cases	Rate ratios (CI [a]) adjusted for							
		Unadjusted		Parity[b]		Age at first birth[c]		Parity and age at first birth[b,c]	
0	119	1.17 (0.94-1.45)	1.36 (1.19-1.56)	1.31 (1.05-1.64)	1.51 (1.31-1.74)	0.93 (0.74-1.17)	1.10 (0.94-1.28)	1.04 (0.81-1.33)	1.21 (1.02-1.44)
1	173	1.52 (1.26-1.84)		1.69 (1.39-2.05)		1.22 (0.99-1.50)		1.35 (1.09-1.69)	
2	169	1.40 (1.16-1.68)		1.54 (1.27-1.86)		1.14 (0.93-1.39)		1.26 (1.02-1.55)	
3	145	1.09 (0.90-1.33)	1.16 (1.04-1.30)	1.19 (0.98-1.45)	1.25 (1.12-1.40)	0.91 (0.74-1.12)	1.00 (0.88-1.13)	0.99 (0.80-1.23)	1.07 (0.94-1.22)
4	176	1.30 (1.09-1.55)		1.41 (1.18-1.69)		1.11 (0.92-1.33)		1.20 (0.98-1.45)	
5	203	1.39 (1.18-1.64)		1.49 (1.26-1.77)		1.19 (1.00-1.42)		1.28 (1.07-1.54)	
6	161	0.93 (0.78-1.11)		0.99 (0.83-1.18)		0.81 (0.68-0.99)		0.86 (0.72-1.05)	
7	164	1.03 (0.86-1.23)	1.03 (0.92-1.15)	1.09 (0.91-1.30)	1.08 (0.96-1.20)	0.92 (0.77-1.10)	0.93 (0.83-1.04)	0.97 (0.81-1.17)	0.97 (0.86-1.10)
8	187	1.08 (0.91-1.27)		1.13 (0.96-1.34)		0.97 (0.82-1.15)		1.02 (0.86-1.21)	
9	180	0.99 (0.84-1.17)		1.02 (0.86-1.21)		0.90 (0.76-1.07)		0.93 (0.77-1.11)	
10+ (Baseline)	1,762	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
χ^2 heterogeneity (10 df)[d]		41.8 ($P < 0.001$)	21.7 ($P < 0.001$)	55.8 ($P < 0.001$)	35.2 ($P < 0.001$)	24.4 ($P = 0.007$)	5.2 ($P = 0.1577$)	27.5 ($P = 0.002$)	8.0 ($P = 0.046$)

[a] CI = 95% confidence intervals.
[b] Parity fitted as a factor with 4 levels (2,3,4,5+).
[c] Age at first birth (in years) fitted as a factor with 18 levels (<19,19,20 . . . 35+).
[d] df = degrees of freedom.

for every five-year increase in age at first birth, whereas in the fully adjusted model, it increases by a factor of 1.15 (CI = 1.08-1.22).

Table 4 shows the breast cancer rate ratios by time since last birth, with and without adjustment for parity and age at first birth. In the unadjusted data, there is evidence of a greater risk of breast cancer in the period zero to five years following the last birth compared with later periods. This effect is largest in the period zero to two years after the last birth. After simultaneous adjustment for parity and age at first birth, there remains evidence of a small but statistically significantly greater risk of breast cancer risk in the period zero to two years following the birth of the last child, compared with 10 or more years, with again the strongest effect being in the period one to two years.

The analyses presented in Table 4 demonstrate that the risk of breast cancer in the period zero to two years following the birth of a child is greater than among women of the same parity and age, whose last birth was 10 or more years ago. This is not equivalent to showing that there is a transient increase in breast cancer risk following the birth of a child. To do this, we need to compare the risk of women of parity (n) who had had their last birth some years in the past with the risk of women of the same age but of parity ($n+1$) who had had their last birth more recently. For this analysis, as explained earlier, we were able to include those women of parity one whose last birth was three or more years ago.

The results of these analyses are given in Table 5 in the form of rate ratios for categories defined according to the joint effects of parity (1,2,3,4, and 5) and time since last birth (< 3 years, 3+ years), with women of parity one whose last birth was three or more years in the past forming the baseline category. Each rate ratio

Table 5. Rate ratios (and 95% confidence intervals [CI]) for breast cancer according to simultaneous variation in parity and interval from last birth, adjusted for age at first birth, for women aged less than 50 with no multiple births, Sweden

Parity	Time since last birth (in yrs)	No. of cases	Rate ratio (CI)[a]
1 (Baseline)	3+	1,113	1.00 —
2	<3	278	1.11 (0.95-1.29)
2	3+	2,041	0.93 (0.86-1.01)
3	<3	143	1.06 (0.88-1.28)
3	3+	783	0.94 (0.85-1.05)
4	<3	30	0.73 (0.50-1.08)
4	3+	132	0.75 (0.62-0.91)
5	<3	8	0.78 (0.36-1.61)

[a] The model included 2 variables: age at first birth (in years) fitted as a factor with 18 levels (<19,19,20 ... 35+) and an 8-level factor, each level of which corresponded to a particular combination of parity and time since last birth (*e.g.*, parity 2, 3 or more years since last birth).

was estimated from a model that involved fitting an eight-level factor, corresponding to the rows of Table 5, in addition to age at first birth.

The results in Table 5 suggest that women of parity two and three do experience a transient increase in risk of breast cancer in the period zero to two years following the birth of their most recent child, although these parity-specific effects are not statistically significant. No such effect is apparent at higher parities, but it should be noted that the number of cases in each of these higher parity categories is relatively small, and thus the rate ratios are particularly subject to random error.

It has been proposed[23] that age at last birth is an independent risk factor for breast cancer. It is not possible to look at the effects of age at last birth adjusted for time since last birth, as given age at diagnosis, these two variables have a linear dependency on each other. However, compared with time since last birth, the effect of this variable upon risk was weak. After adjustment for parity and age at first birth, among women of parity two or more, the rate ratios for the categories of age at last birth of 20-24, 25-29, 30-34, 35-39, and 40+ years, relative to the category of less than 20 years, were, respectively, 0.77 (CI = 0.48-1.26), 0.80 (CI = 0.49-13.0), 0.86 (CI = 0.52-1.42), 0.91 (CI = 0.55-1.53), and 0.97 (CI = 0.53-1.78). The chi-square for heterogeneity was 5.3 on five degrees of freedom ($P = 0.39$), and for trend was 3.4 ($P = 0.07$).

Discussion

Our population-based study has found that in the three years following the birth of their last child, breast cancer risk in multiparous women is higher than among women whose last birth was farther in the past. This dependence of risk upon time since last birth is not explained by the effects of age, age at first birth, and parity on breast cancer risk. Time since last birth appears to confound the association of age at first birth with breast cancer, the effect of age at first birth on risk declining substantially in our dataset of women under 50 years of age on adjustment for this factor. The decline in risk with time since last birth reflects, in part at least, a transient increase in risk following the birth of a child.

Being based on the linkage of routinely collected data, the main limitation of our study is the absence of information on breast cancer risk factors such as age at menarche, menopausal status, obesity, use of exogenous hormones, and family history of breast cancer. However, it is difficult to see how such factors could provide alternative explanations for the sorts of associations we have observed, particularly with respect to time since last birth. The high level of completeness of the source registries, and the adoption of a case-control design, nested within a cohort, minimizes the probability of selection bias and misclassification of exposure or disease status.

Six published studies[8-10,13-15] have examined the effect of time since last birth on breast cancer risk in order to draw inferences about the existence of a transient increase in risk following the birth of a child. Three of these[10,13,14] included women of parity one in analyses in which age, age at first birth, and time since last birth were included simultaneously in a model. Strictly speaking, their results are not interpretable because of the linear dependency between these variables for uniparous women. The results of these studies will not be considered further. Of the three other studies, two[8,9] found time since last birth to have a strong effect, while the other[15] concluded that there was no effect on breast cancer risk. The studies that reached positive conclusions found effects that are appreciably larger than those reported here. Bruzzi *et al*[9] reported a relative risk (RR), adjusted for parity and age at first birth, of 2.66 (CI = 1.31-5.39) in the period zero to two years from the birth of the last child compared with the period 10 or more years, and Williams *et al*[8] reported

an RR of 2.92 (CI = 1.32-6.49). It has been acknowledged,[8] that these hospital-based studies may have overestimated the strength of the short-term effect because women who have given birth to a child recently are less likely to be hospitalized for nonmalignant conditions compared with similar women who last gave birth farther in the past. Our population-based design is not subject to this selection bias.

The most recent investigation to look at the effect of time since last birth was a reanalysis of the large United States population-based Cancer and Steroid Hormone (CASH) case-control study[15] involving 2,279 multiparous breast cancer cases diagnosed at age 25 to 49 years. They found an odds ratio (OR) (adjusted for age, parity, and age at first birth) of 1.16 (CI = 0.84-1.59) in the period zero to two years following the last birth, relative to women who had given birth to their last child 10 or more years before. The corresponding ORs for the periods of three to six years and seven to nine years from last birth were 1.21 (CI = 0.95-1.54) and 1.04 (CI = 0.84-1.38), respectively. These effects are slightly smaller, but consistent with the ones we have found.

All of the other studies discussed so far have focused upon whether breast cancer risk changes with time since last birth. As already discussed, even if such an effect is demonstrated, this itself is not equivalent to showing that there is a transient increase in risk following the birth of a child. However, our data suggest that in the period zero to two years following the birth of their second child, women experience an increased risk of breast cancer, a similar transient increase being seen for women following the birth of their third child (Table 5). These transient effects, if real, appear to be small, and further, yet larger, studies will be required to establish firmly their magnitude.

Indirect evidence for the existence of a transient increase in breast cancer risk following the birth of a first child is provided by two recent, very similar studies.[11,12] The first is a Swedish study[11] based on another linkage of national routine data, the second[12] is a reanalysis of the original MacMahon multicenter case-control study.[3] Both studies mainly focused upon nulliparous and uniparous women, and argued that if there were a transient increase in risk, then among uniparous compared with nulliparous women diagnosed at a specified age, the risk of breast cancer would be greatest among those who had had their child most recently. On the basis of this logic, both studies found evidence for a transient increase in risk following a woman's first birth. The Swedish study[11] also found that a similar, but much smaller transient increase in risk existed among women of parity two following the birth of their second child. This was not found in the reanalysis of the MacMahon data.[12] The authors of both papers suggest that the existence of a more pronounced effect for first births may be because such an effect in later pregnancies is masked by the protection imparted by the first pregnancy. This suggestion is consistent with the small effects we have observed. Unlike these two other studies, our data indicate that any increase in risk following completed pregnancy persists for only a few years.

The idea that a transient increase in risk may occur in the period immediately following childbirth, in addition to childbearing being protective in the long-term, is biologically plausible. Within tissues which undergo continual renewal, such as the breast, stem cells may be regarded as "a small population with a very high capacity for self renewal that can give rise to all differentiated progeny."[24] Experimental and observational data strongly suggest that many tumors originate as a consequence of irreversible changes to stem cells, rather than from such changes in terminally differentiated cell-types which have a finite lifespan. Recently, it has been proposed that first pregnancy brings about a long-term decrease in the number of stem cells through differentiation[25,26] or a decline in sensitivity of stem cells to insults.[26] These hypotheses involve the notion that an early first birth reduces the absolute number of stem cells that may be subject to malignant transformation during a woman's life. The earlier this change occurs, the smaller the lifetime risk of cancer.

The hypothesized changes to stem cells following first pregnancy would predict that parous women would have consistently lower risk of breast cancer than the nulliparous. This is at odds with the well-known observation that women who have a first birth in their mid-thirties or older have a greater risk of breast cancer than those women who remain childless.[3] To account for this, it has been suggested that during a first full-term pregnancy there is a transient, hormonally mediated increase in the rate of cell division[26] which results in an incremental increase in the biological age of breast tissue.[27] Specifically, an increase in the rate of cell division during pregnancy may increase risk in the short-term because this leads to the rapid growth of previously occult malignancies.[7,9]

The evidence from our and other studies that risk of breast cancer is greater in the period immediately following the birth of a child than when the last birth is farther in the past, is stronger than the evidence for a transient increase in risk *per se*. We suggest that the pattern of risk associated with time since last birth may have two components: a short-term transient increase in risk, together with a protective effect of childbearing that evolves over a longer period of time. However, regardless of the balance between these two components, what is clear from our data (Table 2) is

that this time-dependent effect of parity explains part of the effect of age at first birth on breast cancer risk among women aged less than 50 years. Other studies of the effect of time since last birth have failed to look at the extent to which it may confound the association of age at first birth with breast cancer risk.

Given that time since last birth appears to be related to risk only in the first three or so years after the birth, thereafter seeming to be unrelated to risk, it might be expected that in postmenopausal women as a whole, time since last birth is unlikely to have any effect on risk. We might predict therefore that the effect of age at first birth (which in younger women appears to be confounded by the transient increase in risk associated with childbearing) might be weaker in older/postmenopausal women, where due to the absence of recent births, it would be mainly an expression of the long-term protective effect of childbearing. We have not been able to look at this directly, as our data are restricted to women aged less than 50 years. However, this interaction with age is precisely what has been observed in the literature, although until recently,[28] it has evoked little comment. Of 13 studies that provide quantitative estimates of this differential effect of age at first birth according to age at diagnosis, 10 of them[3,4,11,28-34] found that it is weakest in women aged over 50 or those who are postmenopausal, one[35] found that the effect is similar in pre- and postmenopausal women, while only two[36,37] found that the effect is strongest in older/postmenopausal women.

In conclusion, our study provides the most direct evidence to date for an association between breast cancer risk and time since last birth among women of parity two or more. This association appears to be a consequence of a small and transient increase in risk in the three years following childbirth acting in conjunction with the development of a longer-term protective effect of childbearing. The transient increase in risk may account for the greater influence of age at first birth on breast cancer risk in the pre- compared with the postmenopausal period.

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