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Dual Effect of Parity on Breast Cancer Risk

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This study examined whether breast cancer risk increased for a short period after childbirth, but decreased after a longer period of time. Data from an international case–control study on breast cancer conducted in the 1960s were used to study the modifying effect of age at enrolment on the relationship between parity and breast cancer risk, comparing first uniparous with nulliparous women, and then biparous versus uniparous women. The statistical analysis was performed by modelling through multiple logistic regression, adjusting for study site, age at menarche, menopausal status and obesity index. Comparing uniparous with nulliparous women, an early age at birth seems to be protective for all periods after birth, whereas a late age at birth imparts a higher risk than nulliparity in the period immediately after birth, which declines with the passage of time. The modification effect by age was not apparent when biparous women with different age at second birth were compared with uniparous women. The results support the hypothesis that pregnancy oestrogens impart a transient increase of maternal breast cancer risk when the full-term pregnancy occurs late in a woman's life.

Key words: breast neoplasms, age at birth, parity, case–control studies
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INTRODUCTION

IT HAS been suggested that hormonal changes associated with a full-term pregnancy exert a short-term, adverse and a long-term, beneficial influence on breast cancer risk [1]. This dual effect could be due to growth-enhancing consequences of the elevated pregnancy hormones on already initiated cells, superimposed on the long-term protective effect brought about by pregnancy-induced terminal differentiation of the susceptible mammary gland cells [2, 3].

With different approaches, various studies have examined this

issue. In case–control studies of women with two or more parities, Bruzzi and colleagues [4] and Williams and colleagues [5] observed transient increases in breast cancer risk lasting 3 to 9 years since last full-term pregnancy. In addition, recent findings, indicating age at last birth as an independent predictor of breast cancer risk [6, 7], have linked it to the postulated short-term adverse effect of pregnancy [8]. Furthermore, several studies have reported a "cross-over" effect, i.e. an increased breast cancer risk in parous women during childbearing years followed by a decreased risk in older ages [9–14]. Taken together, these findings appear compatible with animal studies [2], as well as with theoretical models of breast carcinogenesis [15, 16], suggesting that pregnancy not only prevents the initiation of a breast tumour (long-term risk reduction), but may also promote the later stages of the process (short-term risk increase). We have developed an alternative approach in order to examine this issue.

The terminal differentiation effect of a full-term pregnancy, if it exists, would be in operation after the first birth, and would tend to mask the short-term promoting effect of subsequent parities for women with two or more children. Thus, it is unsatisfactory to group women with different parities together. Therefore, we have focused our examination on the comparison between uniparous and nulliparous women.

However, case–control studies which matched on or adjusted for age could not easily assess the effect of time since delivery independent of age at first birth. For uniparous women, the period following pregnancy is the complement of age at first birth for a given age at diagnosis or interview. Therefore, conditional on age, the effect of age at birth and year since delivery can not be distinguished. This has been pointed out by Bruzzi and colleagues [4]. Our approach assesses the effect of time since delivery indirectly by examining whether the relationship between age at birth and breast cancer risk varies with age.

If the effect of parity on breast cancer development varies over different periods after childbirth, the risk would be expected to differ over age categories for a given age at birth. When comparing uniparous with nulliparous women, one can predict that the relative risk observed for the younger age categories could be larger than one (short-term increase of breast cancer risk after pregnancy), whereas the relative risk for older age categories could be smaller than one (long-term reduction of risk). In other words, age can be considered as an effect modifier in the comparison between nulliparous women and uniparous women with a particular age at birth.

The hypothesis can be examined further comparing biparous women with uniparous women, adjusting for age at first birth. With the differentiation initiated by the first pregnancy already under way, the modification effect by age in this comparison should be less evident than that in the comparison between uniparous and nulliparous women.

To our knowledge, this analytical approach, which examines two adjacent parities at a time and evaluates age as effect modifier after each birth, has not been previously attempted.

SUBJECTS AND METHODS

The study was conducted with a similar protocol in seven areas with low (Taipei, Taiwan; Tokyo, Japan), intermediate (Athens, Greece; São Paulo, Brazil; Slovenia, then part of Yugoslavia), and high (Boston, U.S.A.; Glamorgan, U.K.) incidence of breast cancer [17]. Except in Tokyo and São Paulo, where the cases represented about 50 and 70% of all incident cases, most of the female residents of the study areas who were hospitalised for a first diagnosis of breast cancer during the study period were included [17]. For each case who was interviewed, 3 eligible patients in the hospital beds closest to that of the index case were interviewed as controls. To be eligible, a control had to be a resident of the study area, to have never had cancer of the breast, and to be over 35 years of age (except when the index case was under 35, in which event controls were age-matched within 2 years). Details about study design and collective results concerning lactation, age at first birth, parity, age at any birth and several other variables have been published [17–19].

Subjects were excluded from the present analysis when information was not available for any one of the following study variables; parity, age at respective birth examined, age at menarche, Quetelet index and menopausal status.

Cases and controls were first tabulated by age at interview and age at the relevant (first or second) birth in 5-year categories. The respective odds ratios were derived from a logistic regression analysis adjusting for study center. The log-transformed odds ratios were later pooled according to years after delivery, with weight inversely proportional to the variance of the logarithm of the odds ratio. Next, statistical analysis was performed by modelling all study variables through multiple logistic regression. The analyses were adjusted for study centre (categorically), age at menarche (as a continuous variable), menopausal status (binary), and obesity index (kg/m^2, as a continuous variable). For the comparison between uniparous and nulliparous, variables added to the model included parity (1 = uniparous, 0 = nulliparous), age at first birth (as a continuous variable, centred at 24.8), age at interview (as a continuous variable) and the interaction term between age at first birth and age at interview.

For the comparison between biparous with uniparous women, variables added to the model included age at first birth (as a continuous variable), indicator for parity 2 (1 = biparous, 0 = uniparous), age at second birth (as a continuous variable, centred at 27.4), age at interview (as a continuous variable), and the interaction term between age at second birth and age at interview.

RESULTS

The distribution of the 1688 cases and 4157 controls who were nulliparous or uniparous by 5-year categories of age at interview and age at first birth is shown in Table 1. The odds ratios, which were adjusted for study site, comparing uniparous women of different ages at first birth to nulliparous women are shown in Table 2. To assess whether the effect of parity with a specific age

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Table 1. Distribution of cases and controls who were nulliparous or uniparous, by age at first birth and age at diagnosis or interview

Age (years)		Nulliparous	Uniparous, age at first birth (years)				
			< 25	25–29	30–34	35–39	40 +
< 25	Cases	4	0	—	—	—	—
	Controls	18	6	—	—	—	—
25–29	Cases	21	3	5	—	—	—
	Controls	58	13	13	—	—	—
30–34	Cases	27	8	10	7	—	—
	Controls	75	30	30	16	—	—
35–39	Cases	78	19	16	32	9	—
	Controls	341	104	79	62	36	—
40–44	Cases	132	24	23	20	15	2
	Controls	313	102	84	46	22	4
45–49	Cases	133	26	23	8	12	4
	Controls	275	87	60	49	17	9
50–54	Cases	146	31	24	29	13	4
	Controls	265	80	65	47	21	8
55–59	Cases	142	20	27	15	18	4
	Controls	314	92	55	47	32	6
60 +	Cases	364	61	56	44	19	10
	Controls	687	184	148	86	49	22

at first birth varied over different ages, we examined column-wise the odds ratio estimates in this table. When the birth occurred before age 30, uniparous women had, in general, a lowered risk of breast cancer than nulliparous women in all age groups (Table 2), i.e. age did not modify the effect of the first parity which occurred before 30. For uniparous women with an age at birth of 30 or higher, the risk was higher than nulliparous women in the younger age categories and lower in the older age categories (Table 2). Therefore, the effect of parity which occurred after 30 was modified by age. Estimates for uniparous women with age at birth over 40 were derived from only 24 cases and 49 controls, and are considered uninformative.

To examine the risk associated with different intervals after the childbirth, odds ratios in Table 2 were further pooled according to comparable periods since delivery (Table 3). Compared to nulliparous women, uniparous women with an age at birth less than 30 had lowered odds ratios in all periods after delivery, and the longer the period after the delivery, the smaller the observed odds ratios (Table 3). Those with an age at birth over 30 had an elevated risk of breast cancer during the period

Table 2. Centre-adjusted odds ratios for categories of age at first birth for each 5-year age group

Age (years)		Nulliparous	Uniparous, age at first birth (years)			
			< 25	25–29	30–34	35–39
< 25	OR	1.00	*	—	—	—
	95% CI	—				
25–29	OR	1.00	0.82	0.83	—	—
	95% CI	—	(0.20–3.30)	(0.24–2.94)		
30–34	OR	1.00	0.64	1.07	1.56	—
	95% CI	—	(0.24–1.70)	(0.43–2.66)	(0.55–4.38)	
35–39	OR	1.00	0.83	0.93	2.47	1.10
	95% CI	—	(0.47–1.45)	(0.51–1.70)	(1.49–4.10)	(0.50–2.40)
40–44	OR	1.00	0.57	0.68	1.20	2.04
	95% CI	—	(0.34–0.94)	(0.40–1.14)	(0.67–2.14)	(1.00–4.18)
45–49	OR	1.00	0.61	0.80	0.34	1.56
	95% CI	—	(0.37–0.99)	(0.47–1.36)	(0.16–0.74)	(0.72–3.40)
50–54	OR	1.00	0.67	0.66	1.14	1.15
	95% CI	—	(0.42–1.07)	(0.40–1.11)	(0.68–1.90)	(0.55–2.37)
55–59	OR	1.00	0.47	1.12	0.72	1.33
	95% CI	—	(0.27–0.79)	(0.68–1.86)	(0.39–1.34)	(0.72–2.48)
60 +	OR	1.00	0.60	0.72	0.95	0.75
	95% CI	—	(0.44–0.83)	(0.51–1.00)	(0.64–1.40)	(0.44–1.30)

*No convergence.

Table 3. Weighted average of the odds ratios (ORs) from the first two, the third and the fourth or more 5-year age-group for each 5-year category of age at first birth

Midpoint of years after first birth		Nulliparous	Uniparous, age at first birth (years) < 25	25–29	30–34	35–39
5	OR	1.00	0.82	0.98	2.26	1.54
(0–9)	95% CI	—	(0.20–3.30)	(0.47–2.06)	(1.43–3.56)	(0.91–2.61)
10	OR	1.00	0.64	0.93	1.20	1.56
(6–15)	95% CI	—	(0.24–1.70)	(0.51–1.70)	(0.67–2.14)	(0.72–3.40)
15 +	OR	1.00	0.61	0.77	0.84	1.01
(11 +)	95% CI	—	(0.51–0.74)	(0.63–0.94)	(0.65–0.94)	(0.71–1.44)

The weighted odds ratios were based on the log odds ratios and their variances from Table 2 and adjusted for study centre. All of the heterogeneity tests were non-significant before pooling.

immediately after the birth (0–9 years), and the odds ratio declined in the later periods (Table 3).

Since both the age and age at first birth were in 5-year categories, the intervals after delivery, which were based on the differences between the two grouped variables, overlapped in Table 3. To study age and age at first birth in single years, we undertook a logistic regression analysis treating age, age at first birth, and their interaction as continuous variables. The model-derived (smoothed) estimates in Table 4 again showed that uniparous women who gave birth before 30 years of age had a lowered breast cancer risk throughout their life than nulliparous women of the same age. Those who gave birth at an older age had the highest risk right after the delivery and had a decreasing risk thereafter (Table 4). This pattern is plotted in Figure 1 using the corresponding year since delivery (age minus age at birth) as the time axis.

A similar model was fitted to the uniparous and biparous women to examine the modifying effect of age on the relation between age at second birth and breast cancer risk. Age at first birth was adjusted in this analysis. Figure 2 was based on the results from a full multiple logistic regression model contrasting biparous women of different ages at second birth to uniparous women. It showed an absence of an additional protective effect of the second birth as compared to the first, and indicated little variation of breast cancer risk in different periods after the second birth.

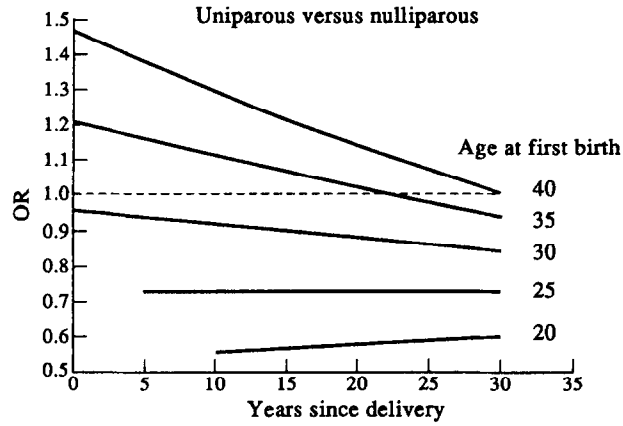

Figure 1. Logistic regression-derived odds ratios comparing uniparous women of different ages at birth with nulliparous women, by years since delivery.

DISCUSSION

The data in the present analysis are based on the multicentre international case–control study of breast cancer undertaken more than 25 years ago by MacMahon and colleagues [17]. Although the study was reasonably large, its case–control design allowed the assessment of a possible dual effect of pregnancy

Table 4. Logistic regression-derived odds ratio estimates and 95% confidence intervals for uniparous women of different ages at first birth versus nulliparous women, by age at diagnosis or interview

Age at first birth (years)		Age (years) 30	35	40	45	50	55	60
20	OR	0.55	0.57	0.58	0.59	0.60	0.61	0.62
	95% CI	(0.45–0.69)	(0.46–0.69)	(0.48–0.69)	(0.49–0.70)	(0.51–0.71)	(0.52–0.72)	(0.53–0.74)
25	OR	0.73	0.73	0.73	0.73	0.73	0.73	0.72
	95% CI	(0.64–0.83)	(0.64–0.83)	(0.64–0.83)	(0.64–0.82)	(0.64–0.82)	(0.64–0.82)	(0.64–0.82)
30	OR	0.96	0.94	0.92	0.90	0.88	0.86	0.84
	95% CI	(0.79–1.15)	(0.79–1.10)	(0.79–1.06)	(0.79–1.03)	(0.78–1.00)	(0.76–0.97)	(0.74–0.96)
35	OR	—	1.21	1.16	1.11	1.07	1.02	0.98
	95% CI		(0.92–1.58)	(0.92–1.45)	(0.92–1.34)	(0.90–1.26)	(0.87–1.20)	(0.82–1.17)
40	OR	—	—	1.46	1.37	1.29	1.21	1.14
	95%CI			(1.06–2.02)	(1.05–1.79)	(1.03–1.62)	(0.98–1.51)	(0.90–1.45)

The odds ratios and 95% confidence intervals were derived from the logistic regression with the coefficients estimates −0.3273 parity + 0.0793 (AAFB −24.8) * parity −0.00082 age * (AAFB −24.8) * parity and were adjusted for centre, age, age at menarche, menopausal status and Quetelet index.

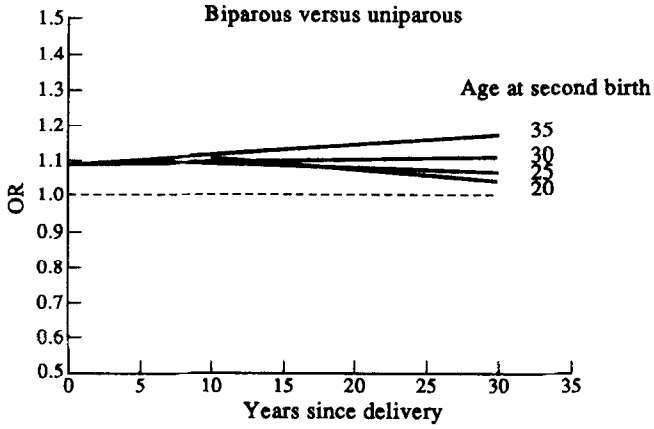

Figure 2. Logistic regression-derived odds ratios comparing biparous women of different ages at second birth with uniparous women, by years since second birth.

only in the context of an interaction term, thus limiting the available statistical power.

In a cohort follow-up design, the incidence rate of breast cancer can be estimated directly for different time periods after each pregnancy [20]. The rates in different periods can then be compared in order to assess the short-term and long-term effects of a particular pregnancy. In estimating the effect of a specific pregnancy, a woman would be eligible for inclusion until she had another pregnancy. Therefore, a cohort design can not only estimate the short-term and long-term effects of parity directly, but it is also more informative (powerful) than a case–control design. In the case–control design, the comparison is only between subsets of women whose final status on parity has been determined, and who contribute no information to the comparisons concerning periods following previous parities. Even though the power is reduced, the approach adopted in our analysis is valid in addressing the dual effect of parity in a case–control study.

Our results indicate that, with an early age at birth, uniparity seems to be protective in all periods after delivery, whereas uniparity with a late age at birth imparts a higher risk than nulliparity in the period immediately after childbirth, with the relative risk declining with advancing age. This finding would be consistent with a lower probability of initiated cells being present among younger women. With a birth at a very young age, the growth-promoting properties of pregnancy would have little effect, and only the terminal differentiation effect of the pregnancy would be expressed and sustained through the later years. However, since the number of young cases and controls in this analysis was relatively small, the findings on the short-term effect following an early age at first birth should be re-examined by studies with a larger number of young study subjects.

The comparison between biparous and uniparous women yielded, as predicted, less striking results. In this analysis, which adjusts for age at first birth, we assumed the effect of the second pregnancy to be independent of time since first pregnancy, or age at first pregnancy. However, since we have found that the effect of the first pregnancy is modified by both age at first birth and time since first birth, it is conceivable that these variables may also modify the effect of the second pregnancy. Further stratification by age at first birth may be necessary, but requires larger studies.

The implication of pregnancy oestrogens being responsible for the transient increase of maternal breast cancer risk can also provide an explanation for (i) the reported reduction of maternal breast cancer risk following pregnancy-induced hypertension [21], since this condition is associated with reduced pregnancy oestrogens [22]; and (ii) the findings that mothers of multiple births are at a slightly increased risk of breast cancer, since twin pregnancies are characterised by higher levels of oestrogens [19].

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