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REPRODUCTIVE FACTORS IN BREAST CANCER EPIDEMIOLOGY

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There is abundant epidemiologic evidence showing that early menarche, late menopause, low parity and late age at first birth are related to increased risk of breast cancer. However, in younger age groups, uniparous women seem to be at higher risk than nulliparous, and the effect of later pregnancies is less clear in this group. Intervals between pregnancies may modify the general protective effect. Some studies have indicated an adverse effect of late age at pregnancies after the first. Further studies are necessary to determine if the general protective effect of pregnancies after the first is preceded by a transient increase in breast cancer risk. No clear association has been established with number of abortions. Results from two large prospective studies suggest that breast feeding is not strongly related to risk of breast cancer among Western populations.

Key words: Breast cancer, epidemiology, abortion, age at first birth, age at last birth, lactation, menarche, menopause, parity, twin birth, review.

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Relationships between reproductive factors and breast cancer risk have been extensively studied. This paper is a review of particular important studies which have contributed to out present understanding of these relationships. In addition to associations with age at menarche and age at menopause, recent findings related to the effects of parity, breast feeding, age at deliveries and possible influence of multiple births on breast cancer risk will be considered.

Age at menarche and menopause

Most epidemiologic studies have described an inverse association between age at menarche and breast cancer risk. This has been observed in several prospective studies (1–4) as well as in the large international case–control study by MacMahon & Cole (5). However, some previous studies have found no relationship between age at menarche and breast cancer risk, and in a number of case–control studies, the mean age at menarche was only slightly less among women with breast cancer than among controls (6). More recent reports have not been entirely consistent. Some have indicated a general protective effect of late menarche (7–11), whereas others have not (12–14). Certain studies have shown a definite protective effect among premenopausal women only (15–18), supporting previous reports of a stronger effect premenopausally and perimenopausally than in postmenopausal women (6). However, there are also studies showing a decreased risk for postmenopausal breast cancer only (19, 20). In a Norwegian prospective study, the suggested protective effect of late menarche seemed to be independent of age at breast cancer diagnosis (4).

The failure to identify an effect of age at menache, especially in case–control studies, may be related to inaccurate recall. However, there are data suggesting that recall of age at menarche is reasonably accurate (21). Nevertheless, this problem might explain the lack of association seen in some studies, especially for older breast cancer patients. Furthermore, as the effect of age at menarche is likely to be weak, one should not expect statistically

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significant results in small studies. Thus, the cumulative evidence to date definitely suggests that early age at menarche is a risk factor for breast cancer, both in premenopausal and postmenopausal years.

There exists extensive evidence of a protective effect of low age at menopause on breast cancer risk. This has been shown in several studies (4, 6, 7, 9, 11, 15, 16, 18, 22–24). Some studies (25, 26) have indicated that this relationship may be strongest in older women, and our results (4) confirm that the protective effect lasts until old age. A study by Kampert et al. (27) indicated that nulliparous and lean women may be more protected by early menopause than parous and overweight women.

On the basis of relative risk estimates for the effect of age at menopause, it has been calculated that the increase in risk per year of increase in age at menopause is in the order of 3–6% (4). On the basis of a mathematical model, which gave a good prediction of age-specific incidence curves in different populations, Moolgavkar et al. (28) found that menopause at 52 years of age was predicted to carry a two-fold risk over menopause at 42 years of age. This estimate corresponds to an increase in risk of 7% per year increase in age at menopause. Similar calculations for age at menarche gave estimates corresponding to an increase in risk of 12% per year decrease in age at menarche. Most studies, including our own (4), have found weaker effects. If the assumptions in the model are correct, this discrepancy might indicate inaccurate recall, which would tend to weaken observed relationships, especially for menarche. Bilateral oophorectomy before the age of 40 have been reported to entail about a 50% reduced risk in relation to women with natural menopause (29).

Number of years of menstrual activity

A relationship between the total number of years of menstrual activity and risk of breast cancer has been reported (30, 31). It has been proposed that breast cancer risk may be directly related to the total number of sterile menstrual cycles (32) and that the effects of various reproductive factors might be explained by their contribution towards a reduction in the number of such cycles (32). Results from several epidemiologic studies are consistent with this theory. However, the protective effect of a pregnancy seems to be stronger than expected under this hypothesis. Thus, from the relative risk estimates of the effect of parity (33), we found that each new full-term pregnancy resulted in a reduction in breast cancer risk of 16%. Further, the age when a pregnancy occurs and the length of intervals between pregnancies may be important (34). There is still no general agreement on the effect of lactation on breast cancer risk (35). However, a simple relationship explained by the duration of postpartum amenorrhoea, which correlates well with the duration of lactation (36), seems unlikely. Thus, there is still a strong need to study each reproductive variable separately. Analysis of such indices as total number of sterile menstrual cycles may conceal, rather than disclose, important associations.

Number of ovulatory/anovulatory cycles

Associations with early menarche and late menopause have been previously related to a higher frequency of anovulatory cycles (37, 38). However, Wallace et al. (39) observed that women with early menarche established a pattern of regular cycle intervals more promptly than women with late menarche, and early onset of ovulatory cycles has been observed in women with early menarche (40–42). In a case–control study (43), it was found that breast cancer patients established regular cycles significantly earlier than controls. Data from a study of MacMahon et al. (44) suggested that the high breast cancer risk in women with early menarche is most likely explained both by a longer duration and by a higher level of exposure to estrogens experienced by these women.

Several studies have indicated that women with irregular or long cycles may be at reduced risk of breast cancer (4, 45–47). In a Swedish study (48), deficit of long cycles was observed among women with breast cancer. To the extent that menstrual irregularities indicate anovulatory cycles, these results are consistent with the hypothesis that regular ovulatory cycles increase breast cancer risk (49).

Parity and age at first birth

Low parity has been suspected of being a risk factor for breast cancer for more than half a century (50, 51). In the early studies (50–54), however, the effect of parity could not be adequately separated from the effects of related variables, such as age at first birth. Later, in the large multinational case–control study by MacMahon et al. (55), with special emphasis on the effect of age at first birth, it was concluded that births after the first entailed no further protection.

Since 1970, several epidemiological studies with analyses of relationships with parity and age at first birth have been published, with varying results regarding the relative importance of parity and age at first birth on breast cancer risk. Table I summarizes the number of cases in 29 studies published since 1970. The studies are grouped according to study-design and whether or not associations with parity and/or age at first birth were observed. Fifteen studies with more than 21 000 cases have shown independent associations with parity and age at first birth (9, 14, 15, 17, 33, 34, 45, 56–64). Five out of a total of six cohort-studies (33, 34, 58, 62, 63, 64) belong to this group. Six additional studies (8, 65–69) with more than 3 000 cases, 94% from population-based case–control studies, showed an inverse association with parity, but no significant association with

Table 1

Parity and age at first birth and breast cancer. A review of 29 studies since 1970[1]

Association with		Number of cases (References in brackets)			
Parity	Age at first birth	Total	Cohort studies	Case-control studies	
				Population based	Hospital based
Yes	Yes	21 294	8 589 (33, 34, 58, 62, 63, 64)	6 911 (9, 15, 45, 56, 60, 61)	5 794 (14, 17, 57, 59)
Yes	No	3 463	0	3 270 (8, 65, 67, 68, 69)	193 (66)
No	Yes	7 822	454 (71)	2 577[2] (12, 72, 74)	4 791 (55, 70, 73)
No	No	400	0	400 (89)	0

[1] Based in part on a review by La Vecchia et al. (107).
[2] Cases and controls from screening clinics.

age at first birth. In the seven studies showing an association with age at first birth (12, 55, 70–74), but not with parity, 61% of the cases were from hospital-based case–control studies (55, 70, 73). With the exception of one small cohort study (71), the remaining studies had both cases and controls selected from screening programmes (12, 72, 74). Overall, these 29 studies provide very strong evidence that parity and age at first birth have independent effects on breast cancer risk.

A recent meat-analysis of eight population-based studies of breast cancer and reproductive variables in the Nordic countries is consistent with these findings (75). The combined analysis showed that women with age at first birth at age 35 or later had a 40% increased risk compared to women with first birth at age less than 20 years. An effect of age at first birth was observed in all age groups, but was strongest in women under the age of 55 years. This finding provides some support to the results in the study by Layde et al. (61) showing that the effect of age at first birth was essentially confirmed to premenopausal women. The meta-analysis (75) showed that the risk for women with 5 or more children was 69% of the risk for women with 1–2 children. Very high parity is related to a further reduction in risk. Thus, two Norwegian cohort studies showed that the risk among women with 9 or more children was about 20% of the risk among nulliparous (33, 64).

Parity as a risk factor for breast cancer in young women

Several studies have shown that incidence and mortality rates for single women compared with ever-married women diverge only after the age of 40 (76, 77). In agreement with results obtained by Logan in 1953 (76), more recent data from the New York State Cancer Registry (78) indicate that married women may actually have higher breast cancer rates under the age of 40, but increasingly lower rates at a higher age. This might indicate that a pregnancy is associated with a transient increase in breast cancer risk. Results from the Cancer and Steroid Hormone Study (61) support the contention that high parity may be associated with increased risk of breast cancer in younger women. In this study high parity was associated with increased risk in women under the age of 35, whereas the protective effect gradually became stronger from the group aged 35–39 to the group aged 50–54 years. These results are consistent with findings in some previous studies (10, 79, 80) and are in agreement with recent case–control studies from Italy (24, 81), Sweden and Norway (82). Previously, Pathak et al. (58), in a prospective study of married women aged 30–55 years, found higher breast cancer risk among uniparous women than among nulliparous, especially among the very young. However, also in this young cohort they observed a significant protective effect of increasing parity for pregnancies after the first. In our study (33) we observed higher risk in uniparous women compared with nulliparous for cancers diagnosed before the age of 60, but, similar to the findings by Pathak et al. (58), we observed a protective effect of pregnancies after the first.

Thus, there seems to be consistent evidence that uniparous women have higher breast cancer risk than nulliparous in the younger age groups. More data are needed to elucidate whether pregnancies after the first lead to a further increase in risk, or are associated with a decrease in risk, similar to what is observed in higher age groups.

Interaction between the effects of parity and age at first birth

Several epidemiologic studies have indicated that having many children late in life may constitute a risk factor for breast cancer. When examining the effect of parity within groups defined by age at first birth in our study (33) we found evidence of heterogeneity, with the strongest inverse association in groups with an early first birth. Among women aged 35 or more at first birth, a positive association was suggested. Similar observations were also noted in the study by MacMahon et al. (55) and were confirmed in a later reanalysis of the same data (83). Parallel results have also been reported from several case–control studies (15, 24, 72). Thus, taken together, these results suggest that having many children late in life is not protective, but may actually increase the risk of breast cancer also in older age groups.

Age at pregnancies after the first birth

Whereas the effects of parity and age of first birth have been extensively studied, the effects on breast cancer risk of age at births after the first have more rarely been considered. In our prospective study (34) we found no overall association with age at first birth when taking into account parity and age at last birth. However, age at last birth was positively associated with breast cancer risk in analyses adjusted for parity and age at first birth. That late age at last birth is a risk factor for breast cancer has previously been indicated by the findings of Lubin et al. (10). Furthermore, MacMahon et al. (12) found similar associations among Estonian women with two births, and in a reanalysis of the large international case–control study (55), Trichopoulos et al. (83) found an increase in risk with increasing age at any birth.

A recent study examined breast cancer risk according to time since last birth (81). This is an alternative approach to studying the effect of age at last birth in age specific analyses. However, analysis of the relationship with time since last birth restricted to women in younger age groups might be more appropriate when the aim is to detect a transient increase in breast cancer risk after a pregnancy. Bruzzi et al. (81) studied the risk of breast cancer according to years since last birth in a hospital-based case–control study of women under the age 50 with two or more children. They found that women in the first three years after a delivery had a nearly three-fold risk compared to women with a period of ten or more years since last birth. Similar results were reported from a case–control study by Williams et al. (84). These results are consistent with findings from previous epidemiologic studies on the effect of parity in younger age groups. However, a weakness of these studies might be that hospitalized controls probably represent groups which due to their disease might have few recent births. Thus, a population-based case–control study of 422 breast cancer cases less than 45 years of age in Sweden and Norway did not show any trend with years since last birth (82).

Intervals between births

It has been suggested that the protective effect of pregnancies lasting to full-term may possibly be modified by intervals between successive pregnancies (33). In our data we found that parous women with two or three full-term pregnancies with a late last birth ($\geqslant$35 years) had *higher* risk than nulliparous women if the first birth occurred *early* ($<$25 years), and *lower* risk if the first birth occurred later (Table 2). Thus, in a group of women with relatively low parity and late last birth, an adverse effect of early first birth was indicated.

Some support for these findings is given by the results presented by Negri et al. (85). Combining data from two case–control studies they were able to present results from 1 200 biparous breast cancer cases. As in our study, they observed an increase in risk with decrease in age at first birth among women with second birth at age 35 or more. Early age at first birth was protective only among women with a second birth before the age of 30.

Large population-based studies will be necessary to establish with more certainty the effect of intervals between births suggested by the results from these studies. The results which indicate that intervals between births are of importance for the protective effect of successive pregnancies, might point to other factors than hormones as the biologic explanation of the protective effect of high parity.

Multiple births

In a recent report, Jacobson et al. (86) found that risk of developing breast cancer was reduced in women having a multiple last birth. The study was based on 118 cases with multiple births. For 53 of these, the multiple birth was reported as the last birth. However, a previous study (87) based on 107 cases of breast cancer in mothers with dizygotic twins showed a relative risk of 1.1 for breast cancer in a group of mothers of dizygotic twins compared to mothers with only single births.

It has been speculated that mothers of dizygotic twins might actually experience an increased risk of breast cancer because of the elevated levels of gonadotropins in these women (88). However, it has also been shown that mothers with twins have higher sex-hormone binding globulin (SHBG) than women who have not delivered twins (89).

Further epidemiologic studies are necessary to establish whether twin births differ from single births with regard to the effect on breast cancer risk.

Number of abortions

Some authors have reported a possible risk-enhancing effect of ever having had an abortion (55, 72, 90, 91) while

Table 2

Relative risk estimates of breast cancer for combined effects of age at first and last birth in 16 400 biparous and 11 100 women with three full-term pregnancies. Results from a Norwegian prospective study (Number of cases in brackets)[1]

	Age at first birth (years)	Age at last birth (years)			
		<25	25–29	30–34	≥35
Parity 2					
	<25	0.9 (19)	1.0[2] (57)	1.1 (22)	1.8 (12)
	25–29		1.1 (37)	1.4 (96)	1.1 (26)
	30–34			1.4 (30)	1.3 (53)
	≥35				1.1 (26)
Parity 3					
	<25	0.7 (4)	1.0[2] (33)	1.0 (35)	1.8 (34)
	25–29		0.2 (1)	0.9 (35)	1.3 (56)
	30–34			1.4 (3)	1.1 (33)
	≥35				1.3 (11)

[1] Modified from Kvåle & Heuch (34).
[2] Reference category.

others have found no such effect (15, 83, 92), and some have observed a risk decreasing effect (9, 33, 93). Among studies showing a risk increasing effect, some have reported that an abortion before the first full-term pregnancy is especially important for the increase in risk (91, 94). Ewertz & Duffy (69) found increased risk in women with abortions when full-term pregnancies did not succeed the abortion. This finding has not, however, been confirmed by others (72, 82, 95).

Taken together, the epidemiologic evidence indicates that a pregnancy terminating in an abortion is not associated with a decreased risk of breast cancer, as observed for full-term pregnancies. Further studies are needed to clarify whether abortions are associated with an increased risk. Epidemiologic results are consistent with a hypothesis that both abortions and full-term pregnancies are associated with a transient increase in risk, whereas only pregnancies lasting until full-term are protective.

Breast feeding

There is still no general agreement about the relation between duration of lactation and breast cancer risk. Though several early reports indicated a possible inverse association, many investigators have found no overall effect after adjustment for parity (6). Most studies have been of the case–control type, with analysis based on a crude classification of breast feeding experience. Since 1985, four large case–control studies have indicated a protective effect of breast feeding (13, 19, 60, 61). The study of Layde et al. (61), based on 4 599 women with breast cancer, aged 20–55 years, found relative odds of 0.67 for women who had breast fed 25 months or more compared to women who never had breast fed. Others have not found statistically significant negative relationships (35, 68, 82, 96). Our prospective study with 1 136 cases of breast cancer suggested a non-linear relation with duration of lactation per birth (35). The highest risk was ovserved for those with intermediate duration of breast feeding, whereas lower risks were found among those with very short (<2 months/per child) or very long (>12 months/per child) duration. That very long duration of breast feeding is associated with decrease in risk is consistent with results of a case–control study from South Africa (97). In this study a strong decrease in breast cancer risk was observed among black women with average duration of breast feeding per birth of 24 months or more, both in pre- and postmenopausal women. However, parity was not adjusted for in this study. Whereas some studies have indicated a stronger protective effect in premenopausal women (13, 19), others have found similar effects in different groups defined by age and menopausal status (60, 61, 97). However. recently published results based on 1 262 cases of breast cancer diagnosed after 10 years' follow-up of 86 413 US registered nurses did not show any association with duration of lactation, neither in premenopausal nor in postmenopausal women (98).

Thus, there are divergent findings between the only prospective studies (35, 98) which found weak and non-significant associations, and some recent case–control studies (13, 19, 60, 61) which have indicated a protective effect of breast feeding. Possible selection bias in the case–control studies has been suggested as an explanation of the discrepant findings (98), and results from most previous studies (6) agree with the findings from the two prospective studies. Available evidence thus suggest that lactation of a duration most commonly observed in Western populations (<12 months per child) is probably not

protective. Further studies are needed to clarify whether very long duration of lactation, which is practised in several other countries, might be beneficial.

Biological explanations

The duration and level of exposure to female sex hormones can clearly explain associations with menarche and menopause (4, 44, 99). The observation that regular ovulatory cycles increase breast cancer risk (48, 49) indicates that high levels of estrogens *and* progesterons are related to increased risk of breast cancer (99). A transient increased risk after a pregnancy, full-term as well as pre-term, may be related to very high levels of estrogens in the first trimester of a pregnancy (100). The increase in free estradiol in the first trimester seems to be stronger in the first than in subsequent pregnancies.

The mechanisms behind the long-term protective effect are less clear. Hormonal (100) as well as immunological (34) explanations have been considered. Thus, associations between high parity and low prolactin levels have been observed both in pre- and postmenopausal women (102). Further, higher levels of sex hormone-binding globulin and lower levels of free estradiol have been found in parous compared to nulliparous women (103). Another line of evidence relates to differentiation of breast epithelial cells during a pregnancy, in particular the first. Animal experiments indicate that the hormones during a pregnancy induce differentiation of breast epithelial cells which make them less sensitive to carcinogenesis (104). The strong and long-term protective effect of high parity could thus be explained if the pool of glandular cells susceptible to carcinogenesis is reduced by each successive full-term pregnancy.

Results from epidemiologic studies have suggested that the protective effect of high parity and early age at first birth is confined to estrogen receptor positive tumours (105, 106). This may indicate that a pregnancy decreases the risk of breast cancer by causing a permanent reduction in the pool of estrogen receptor positive cells, thereby rendering the breast less sensitive to the tumour-promoting influence of estrogens. Further epidemiologic studies are needed to clarify these issues. In addition to studies relating reproductive factors to breast cancer risk in subgroups defined by receptor status, detailed descriptions of receptor status in normal breasts according to age and pregnancy history might prove to be of particular importance for our understanding of the mechanisms behind the complex associations between pregnancies and breast cancer risk in different age groups.

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