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Breastfeeding Associated with Reduced Mortality in Women with Breast Cancer

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Abstract

Objective: To study whether breastfeeding affects survival from breast cancer.
Background: There are few studies on the relationship between breastfeeding, reproductive health, and breast cancer survival. This study is a follow-up of an earlier study showing no convincing associations between breastfeeding and breast cancer prognostic parameters.
Methods: From a cohort of 629 women with primary breast cancer having undergone surgery between 1988 and 1992, 341 were traced and consequently studied 20 years later regarding breastfeeding and reproductive variables, as well as for prognostic parameters such as the Nottingham histological grade, tumor size, lymph node status, and vascular invasion (VI). Multivariate Cox regression analyses were used.
Results: Increased breast cancer mortality was associated with the Nottingham prognostic index (hazard rate ratio (HR) 4.47; 95% confidence interval (CI) 2.04–9.79), VI (HR 3.44; CI 2.03–5.82), fewer pregnancies (three categories; >2, 1–2, 0) (HR per category 2.04; CI 1.34–3.11), and breastfeeding ≤6 months (HR 2.74; CI 1.41–5.35). The HRs for overall mortality were, as expected, lower for the Nottingham prognostic index (HR 1.28; CI 0.89–1.85) and VI (HR 2.09; CI 1.38–3.17), and they were slightly lower for the number of pregnancies (HR 1.61; CI 1.48–4.59), but notably similar for breastfeeding (HR 3.01;CI 1.92–4.73).
Conclusion: A total breastfeeding history >6 months and pregnancy are associated with both greater overall and breast cancer–specific survival for women diagnosed with breast cancer, having lived long enough for other causes of death to contribute substantially to mortality.

Background

Knowledge of breastfeeding and the impact on the risk of breast cancer development is substantial. The same applies to other factors (such as menarche, parity, age at first birth, number of children, and menopause.[1] Nevertheless, studies of breastfeeding and reproductive variables as prognostic markers for women already affected by breast cancer are few. The results of these studies differ considerably.

The time between the last childbirth and diagnosis is regarded as important for the prognosis and survival of breast cancer. Several studies show statistically significant associations between mortality and a short period between the last childbirth and the time of breast cancer diagnosis.[2–6]

Comparisons between studies present difficulties due to background variables, such as participant age, observation time, duration of breastfeeding, hormone use, and the presence of the BRCA mutation.[7–9] Another difficulty is that most previous studies have not adequately distinguished between breastfeeding periods in proximity of the diagnosis of breast cancer, which have been shown to be associated with lower survival, and breastfeeding periods long after the diagnosis of breast cancer, which may, indeed, be associated with greater survival. Whiteman et al.[10] found a greater overall mortality for women aged 20–45 having given birth less than 12 months before the diagnosis of breast cancer, compared with women who had not given birth at all. Breastfeeding was also investigated in this study, but no association with the prognosis was found. Trivers et al.[11] found similar results. In a study of 2640 women born between 1886 and 1928 with invasive breast cancer, Alsaker et al.[12] found a statistically nonsignificant trend ($p = 0.12$), indicating that those who had breastfed tended toward a slightly lower risk of breast cancer mortality compared with women who had never breastfed at all. Breastfeeding duration was not associated with survival. The study was adjusted for parity, with a presumably low intake of oestrogen- or progesterone-containing hormones for that period.

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Recent research has identified the importance of breastfeeding in relation to the BRCA1 mutation carriers.[13] The study shows that breastfeeding protects against the onset of breast cancer for carriers of the BRCA1 mutation. If breastfeeding history is more than 1 year, the risk is reduced by 32%.

Philips et al.[14] in a study of 3017 women, where those with a BRCA mutation 1 and 2 were excluded, approximately 10% of those with BC showed no such association between survival and breastfeeding. In 1989, Lees et al.[15] studied 1121 women, finding a significant trend for poorer survival for women who breastfed for more than two weeks compared with those who had not breastfed. Lee's study was adjusted for death from other causes, tumor stage, spreading to lymph nodes, menopause, parity, and the use of hormones and genetic influence. Time that elapsed between the last childbirth and diagnosis date was not studied.

Recent studies add to the mixed picture of knowledge about associations between reproductive factors and breast cancer prognosis (Meritt et al.,[7] Kwan et al.,[8] Song et al.[9]).

Meritt et al.[7] studied the risk of breast cancer–specific and overall mortality in a cohort study of 322,972 generally healthy women aged 25–70, with a mean follow-up of 12.9 years. They were recruited from geographical areas in 10 European countries. The risk of all-cause mortality was lower in parous than in nulliparous women, in women who had breastfed versus those who had never breastfed, in users and nonusers of oral contraceptives, and in women reporting a later age at menarche. In women having had breast cancer, parity versus nonparity was strongly associated with a better prognosis, but no such association was found for breastfeeding.

Kwan et al.[8] found, in a prospective study of 1636 women in two breast cancer cohorts, that breastfeeding was associated with a decreased risk of recurrence, especially when breastfeeding for 6 months or more. Similar associations were observed for breast cancer death. Among women with luminal A subtype, breastfeeding was associated with decreased risks of recurrence and breast cancer mortality.

Song et al.[9] analyzed reproductive factors in 3430 women, including breastfeeding and number of births, as well as prognostic markers for women with breast cancer. They found that older age at menarche, having four or more children, and shorter time since the last birth were negatively associated with breast cancer–specific survival, whereas the opposite was seen for a longer duration of estrogen exposure, especially in the HR+ HER2+ subtype. No association with breastfeeding was found.

In our previous studies, there were no associations between reproductive factors and known prognostic markers except for a positive association between hormonal intake and an increased lymphovascular invasion.[16,17] This study goes a step further by investigating possible associations between breast cancer–specific mortality, lifetime breastfeeding history, and reproduction-related variables adjusted for age. By including the previously described known prognostic markers in the analysis, we sought to investigate possible differences in prognosis independent of known prognostic markers.

Methods

Study population

From 1988 to 1992, 630 women, aged 25–74, were treated for primary breast carcinoma without distance metastases, in the Counties of Kalmar and Östergötland, Sweden.[18]

Women ≤50 years at the time of diagnosis (165/629, 26%) were considered premenopausal, and older patients were considered postmenopausal (464/629, 74%). Diagnosis was made, and treatment took place between 1988 and 1992. At the beginning of this study, 275 out of 629 women had died (44%), and 10 women in terminal care were excluded (1.6%). During 2004, all living women ($n = 345$) were sent a questionnaire regarding breastfeeding and reproduction-related variables, including number of children, time of their children's births, and duration of breastfeeding[16]; 250 out of 345 women responded (72%).

A survival analysis was performed 20 years later. Forty-five of those interviewed had died.

To obtain information on reproductive variables from 380 women, from the original cohort that had not participated in the questionnaire study, we collected information on births from the Medical Birth Registry, National Board of Health and Welfare, for the number of childbirths for each woman, including the children's social security numbers. Using these numbers, we then traced the children's health records via the Child Healthcare (CHC) archives of 14 municipalities and County Councils. The records contain information on how the child was raised, and how many months the child breastfed, in whole or in part. A calculation was then made of each deceased woman's breastfeeding.

To validate the record-based data against data from the questionnaire, we succeeded in tracing 26 matching CHC records, finding that, according to our chosen categories (≤6 and >6 months), the lifetime breastfeeding histories were almost identical in all cases.

Ninety-one patient records were found. Hence, 341 women were included in the survival analysis, of whom 205 were still alive. Those with no children were assigned a breastfeeding time of zero.

The Southeastern Swedish Breast Cancer Register provided information on mortality for diagnostic groups according to the international ICD-10 classification. The C509 and 1749 were applied for breast cancer mortality.

The study was approved by the regional ethical review board of Linköping, Sweden.

Prognostic markers, reproductive and breastfeeding data

Prognostic markers. Prognostic markers and tumor properties of prognostic significance for breast cancer and reproductive data, including breastfeeding history, have been previously presented[16,18] and are merely summarized here. The Nottingham prognostic index (NPI) is a weighted sum of the following three parameters: 0.2 × tumor size (cm) + LNS (lymph node status having the value 1 with no nodes affected, 2 with 2–3 nodes affected, and 3 with >3 affected) + the Nottingham histological grade (NHG) (assessed as 1, 2, or 3). NPI is then categorized as 0 if <3.4, or otherwise as 1. Vascular invasion (VI) is defined as positive (= 1) if malignant cells within a vessel in the periphery of the tumor are present; otherwise, it is defined as negative (= 0).[16,18]

Reproductive data and breastfeeding. Number of pregnancies (including abortions and still- births) was categorized as follows: 0 = no pregnancy, 1 = one or two pregnancies

[there were only four women having either abortions only, ($n=2$), or miscarriages only ($n=2$)], and 2 = two or more pregnancies. Breastfeeding history was categorized as ≤6 months or as >6 months. Age at first child (AFC) was categorized either as 0 if <23 years or as 1. Time between the last childbirth and the cancer diagnosis is categorized as ≤26 years and >26 years (median value), and it is restricted to women with children ($n=265$).

Data analysis and statistics

A Kaplan–Meyer plot describing breast cancer mortality and overall mortality was created first, solely for descriptive purposes (Fig. 1). Variables were categorized for two reasons, first to make the following Cox regression analysis more robust (e.g., avoiding outliers), and second, to allow the two variables ''age at first child'' and ''lifetime breastfeeding history'' to be defined among women with no children. Nevertheless, ''time from last child to cancer diagnosis'' is, understandably, not definable for women without children, and to avoid a significant number of missing values this parameter was omitted in the Cox analyses, but is presented in the ''patient details'' table (Table 1). The 2×2 contingency tables using the categorical variables and censoring variables (overall mortality and breast cancer mortality, respectively) were analyzed using Fisher's exact test and, for 3×2 table (in one instance only; pregnancy, >2, 1–2, 0) using Chi-2 test. Continuous variables were analyzed using Mann–Whitney's U-test (Table 1). Significant variables (in either all-cause or breast cancer mortality) and age were then included in the survival analyses using a multiple Cox regression. Overall mortality and breast cancer mortality were analyzed separately. Statistica version 12 (StatSoft®, Tulsa, OK) was used, and a significance level of $p<0.05$ was regarded as statistically significant.

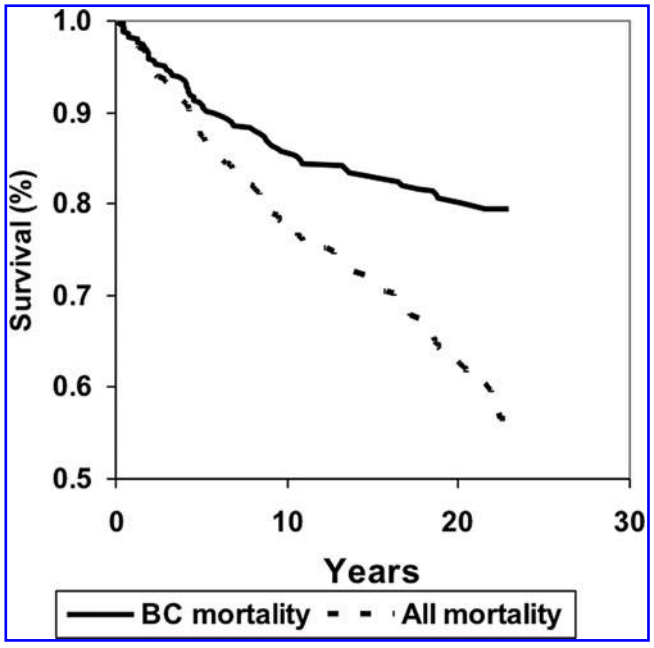

FIG. 1. Kaplan–Meyer curves calculated for breast cancer mortality and overall mortality.

Results

Breastfeeding and reproductive data were available in 341 of the original cohort of 650 (53%) operated women with breast cancer without distance metastases at the time of diagnosis. Values of the NPI were missing in three patients.

Five-year survival was: for the overall mortality group 87%, 10 years, 78%, 15 years, 71%, and 20 years, 63%. Corresponding numbers for breast cancer mortality were 91%, 85%, 83%, and 80%, respectively. Other causes of death were as follows (n): other malignant tumors (25), cardiovascular diseases (21), dementia (8), infections (5), lung/liver diseases (4), other diseases (7), and unknown causes (2). Among other malignant tumors, we found ovarian $n=5$, liver/gallbladder $n=3$, colon $n=1$, myeloma $n=1$, kidney $n=1$, pancreas $n=2$, and peritoneum $n=1$. The remainder were unknown. Eighteen percent had lobular cancer, 72% had ductal, and 10% had other types of breast cancer. Cancer type was not statistically associated with mortality in the group. Seventy-four percent were of the ductal type among the dead, and 70% were among those who were still alive. Corresponding numbers for breast cancer mortality were 86% versus 69% with borderline significance ($p=0.052$). Women who died (overall mortality) during the follow-up were, as expected, older than those who survived (mean 60 years versus 54 years) but no significant age differences were seen for breast cancer mortality (Table 1). The NPI was, as expected, significantly higher for the deceased women compared with survivors, for both overall mortality (mean 4.3 versus 3.7) and breast cancer mortality (mean 5.1 versus 3.7, Table 1). Breastfeeding history, calculated for the 265 women with children, was significantly shorter among those having died compared with survivors (overall mortality: 7.4 months versus 12.1, and for breast cancer mortality: 6.8 versus 11.2). AFC was not significantly different for the 265 women with children ($p=0.118$ for overall mortality and $p=0.074$ for breast cancer mortality), but the time between the last child and cancer diagnosis was statistically significant in both groups ($p=0.050$ for overall mortality, and $p=0.011$ for breast cancer mortality). The categorized variables used in the Cox regression analysis, where pregnancy, breastfeeding history, and AFC are defined to include all 341 patients, showed similar results, with the exception of ''age at first child'' that became highly significant as categorical compared with continuous (Table 1).

Table 2 shows the survival analysis for overall and breast cancer–specific mortality assessed by Cox multivariate regression. Not surprisingly, the two prognostic markers for breast cancer survival, NPI and VI showed statistically significant hazard rate ratios (HR) for breast cancer mortality and VI also showed the same for overall mortality. Although not significant in every instant, mortality was adjusted for both NPI and age.

Regarding reproductive data, lifetime breastfeeding and/or number of pregnancies were statistically associated with both overall and breast cancer–specific mortality. Note that the multivariate analysis showed that these reproductive variables, at least partly, were independent of each other, and of NPI, VI, and age at diagnosis. By contrast, the significance of age at first birth >23 years vanished in the multivariate analyses.

Table 1. Patient Details for Overall Mortality and Breast Cancer Mortality

		Overall mortality			*Breast cancer mortality*		
	N *total*	*No (205)*	*Yes (136)*	p-*Value*	*No (277)*	*Yes (64)*	p-*Value*
Age at diagnosis	341						
Mean (SD)		54.3 (9.8)	60.2 (11.6)		57.1 (10.5)	55.1 (12.8)	
Median (range)		54 (31–74)	64 (32–75)	<0.001	58 (31–75)	55 (32–75)	0.272
≤50 years		74 (70%)	32 (30%)		80 (75%)	26 (25%)	
>50 years		131 (56%)	104 (44%)	**0.017**	197 (84%)	38 (16%)	0.073
NPI	338						
Mean (SD)		3.7 (1.1)	4.3 (1.5)		3.7 (1.2)	5.1 (1.3)	
Median (range)		3.4 (2.1–6.6)	4.3 (2.1–7.9)	**0.001**	3.4 (2.1–6.6)	5.2 (2.2–7.9)	**<0.001**
<3.4		98 (67%)	49 (33%)		140 (95%)	7 (5%)	
≥3.4		107 (56%)	84 (44%)	0.056	135 (71%)	56 (29%)	**<0.001**
Vascular invasion	341						
No		176 (63%)	103 (37%)		242 (87%)	37 (13%)	
Yes		29 (47%)	33 (53%)	**0.022**	35 (56%)	27 (44%)	**<0.001**
Pregnancy number	341						
>2		88 (73%)	32 (27%)		108 (90%)	12 (10%)	
1–2		97 (65%)	52 (35%)		123 (83%)	26 (17%)	
0		20 (28%)	52 (72%)	**<0.001**	46 (64%)	26 (36%)	**<0.001**
Lifetime BF history	341[a]						
Mean (SD)		12.1 (11.6)	7.4 (8.5)		11.2 (11.3)	6.8 (6.6)	
Median (range)		10 (0–96)	4 (0–45)	**<0.001**	9 (0–96)	4 (0–28)	**0.011**
>6 months		131 (80%)	32 (20%)		149 (91%)	14 (9%)	
≤6 months		74 (42%)	104 (58%)	**<0.001**	128 (72%)	50 (28%)	**<0.001**
Age at first child	341[a]						
Mean (SD)		24.8 (4.8)	25.9 (5.4)		24.9 (5.0)	26.2 (4.9)	
Median (range)		24 (16–41)	25 (18–42)	0.118	24 (16–41)	26 (18–42)	0.074
<23 years		75 (72%)	29 (28%)		94 (90%)	10 (10%)	
≥23 years		130 (55%)	107 (45%)	**0.003**	183 (77%)	54 (23%)	**0.004**
Last child to cancer	265						
Mean (SD)		25.4 (11.8)	28.7 (13.5)		27.2 (12.1)	21.8 (13.3)	
Median (range)		24 (0–57)	31 (2–62)	**0.050**	26 (0–62)	20 (2–56)	**0.011**
≤26 years		104 (76%)	32 (24%)		113 (83%)	23 (17%)	
>26 years		78 (60%)	51 (40%)	**0.005**	115 (89%)	14 (11%)	0.214

Pregnancy including abortions and stillbirths. Statistical analyses for continuous variables with Mann–Whitney's U-test and for categorical variables with Chi-2 test for pregnancy, otherwise Fisher's exact test. *p*-values <0.05 are indicated in bold.

[a]$n = 265$ for continuous variables and $n = 341$ for categorical variables.

NPI, Nottingham prognostic index; Lifetime BF history, lifetime breastfeeding history.

Discussion

Women with primary breast cancer had a better survival rate if total breastfeeding was longer than 6 months and/or if they had at least one pregnancy. Intriguingly, these reproductive parameters are virtually independent of whether death was due to breast cancer or other causes. Our results differ from earlier studies,[7,9–11] and it is, therefore, important to start the discussion with methodological issues.

Methodological discussion

Although breastfeeding time is shown to have important associations with breast cancer incidence and prognosis, it is an incomplete measure of breastfeeding intensity. The fact that we have no data on the respective proportions of breastfeeding and other methods of feeding is an obvious limitation of our data, as it is in the data of other studies within the field we have partaken of. Breastfeeding per child is another aspect of breastfeeding intensity. However, no significant prognostic information was added when we made a new multivariate analysis exclusively with the three variables: ''Duration of breastfeeding,'' ''Number of parities,'' and ''Duration of BF divided by parity.'' Future research on associations between reproductive factors and breast cancer incidence and prognosis would strongly benefit from including accurate estimations of breastfeeding intensity.

Selection bias. Our material is, in some respect, selected, since there is an overrepresentation of surviving patients, that is, the interviewed women. If reproductive data were randomly spread among all 629 women in the primary cohort, any sample, selected for longevity or not, would have had the same random and nonsignificant coupling of, for example, breastfeeding time or time to the first child to death. Our data have shown that this is not the case, that is, a coupling exists, with high statistical significance, between mortality and reproductive data as shown in Table 2. A hypothetical selection bias occurs if the traced women (not interviewed), for some reason, should have had shorter breastfeeding time, or

Table 2. Survival Analysis of Overall and Breast Cancer–Specific Mortality Using Multivariate Cox Regression

		Overall mortality		*Multivariate Cox regression*		*Breast cancer mortality*		*Multivariate Cox regression*	
Parameter	*Total*	n	*(%)*	*HR (95% CI)*	p	n	*(%)*	*HR (95% CI)*	p
Age at diagnosis									
≤50 years	106	32	30	1.00		26	25	1.00	
>50 years	235	104	44	1.45 (0.97–2.17)	0.072	38	16	0.74 (0.44–1.23)	0.240
NPI									
<3.4	147	49	33	1.00		7	5	1.00	
≥3.4	191	84	44	1.28 (0.89–1.85)	0.185	56	29	4.47 (2.04–9.79)	<0.001
Vascular invasion									
No	279	103	37	1.00		37	13	1.00	
Yes	62	33	53	2.09 (1.38–3.17)	<0.001	27	44	3.44 (2.03–5.82)	<0.001
Pregnancy (number)									
>2	120	32	27	1.00		12	10	1.00	
1–2	149	52	35	1.61 (1.22–2.14)		26	17	2.04 (1.34–3.11)	
0	72	52	72	2.61 (1.48–4.59)	<0.001	26	36	4.15 (1.78–9.64)	<0.001
Lifetime BF history									
>6 months	163	32	20	1.00		14	9	1.00	
≤6 months	178	104	58	3.01 (1.92–4.73)	<0.001	50	28	2.74 (1.41–5.35)	0.003
Age at first child[a]									
<23 years	104	29	28			10	10		
≥23 years	237	107	45	–	0.320	54	23	–	0.169

HR is hazard rate ratio, and 95% CI is 95% confidence interval.
[a]Age at first child is not included in the final analysis, but significant values (*p*-values) at the last step before deletion are shown.

different reproductive data, than those we were not able to trace, but we can see no cause for this.

We compared included (interviewed) and nonincluded (interviewed) women regarding age at diagnosis, parity, Nottingham score, and VI, and found that the nonincluded women mirrored the selection. As expected, mortality was lower in the included group and might be explained by lower age at diagnosis and lower frequency of VI, but NPI did not show any significant difference. Pregnancies were only partly traced (158 out of 288), and mean or median numbers are not significantly different but categorization unveils fewer 0-parieties among the nonincluded. As 0-pariety is a distinct variable in the multivariate analysis, this difference does not affect the result.

Different data types. Reproductive data were obtained differently from those interviewed and the traced women, respectively, but in our validation (see study population) we found no differences after having categorized breastfeeding (≤6 and >6 months).

Confounders. We should consider the possibility of women in our study who had breastfed less, had other risk factors such as a ''negative lifestyle,'' smoking, high alcohol intake, and obesity, all of which have been shown to have a negative impact on the prognosis of breast cancer.[19–21] These lifestyle factors are less common among more highly educated women compared with those less so. In Sweden, during the period when the women in our study were breastfeeding, well-educated women gave birth later in life, and breastfed less.[22]

We, therefore, find it less probable that an unfavorable lifestyle should underlie the poorer prognosis in our study of women who spent less time breastfeeding. Many contradictory studies exist on the connection between hormones and their influence on breast cancer, but the use of hormones was not registered in this study.

Results discussion

As discussed earlier, there is a highly probable association between survival (equally for overall and breast cancer), breastfeeding time, and time to the first child. This, in turn, means that there is a selection bias in this study. The selection of our material implies that the study provides knowledge of reproductive variables and their influence on mortality at a stage where other causes begin to contribute considerably more to death.

The early deaths from breast cancer had only a slight statistical influence, and we conclude from the cohort studies referred to in the background section, all of which followed the majority of women from the time of their diagnosis, that we found no short-term associations between reproductive factors and survival corresponding to the differences of hazard ratios. Thus, we do not believe that our findings could, in fact, be ascribed to a remaining effect of an early difference in survival. Among those traced are some who had died early, but nearly half of those traced died of causes other than breast cancer. Our results are consistent with the weak, but still statistically significant, association between having breastfed and a decrease in overall mortality demonstrated in the extensive population study by Meritt et al. However, in that

study, only parity, and not breastfeeding was positively associated with survival in women with breast cancer. The specific group of women with long-term survival after a breast cancer diagnosis has not been previously studied. There are studies indicating a low risk for a number of diseases by longer breastfeeding time, for example, hypertension, type 2 diabetes, ovarian cancer, and osteoporosis.[14,15]

Whether these observations are interpreted in terms of a specific mechanism for each disease, or in terms of a ''general health effect,'' also suggested by the findings of Meritt et al.,[7] such as mediation by CNS/ neural/endocrine/immune bio-behavioral pathways, which were shown to be associated with favorable social relations,[23,24] such as experiences of being loved, valued, and cared for by family, friends, or colleagues, remains an open question. The finding that breastfeeding represents an important and general life value[25] may support the latter hypothesis. In our study, the decrease in mortality from breast cancer is equal to that of other causes. This makes it plausible that even the decrease in late deaths in breast cancer should be ascribed mainly to such a general effect rather than to specific effects on breast tissue. This idea is also supported by the fact that breastfeeding and AFC had an impact on prognosis, generally independent of the prognostic markers.

Still, findings by Kwan et al. indicate that there are breast cancer specific mechanisms. Plausible theories of how breast feeding affects cellular proliferation and differentiation of the glandular cells in the breasts, in turn affecting malignant transformation as well as the degree of differentiation of actual tumors, have been presented by Alsaker[12] and Kwan et al.[8] Our finding that not just breastfeeding, as such, but its duration as well has importance finds support in the study by Kwan et al.. The degree to which the positive association of pregnancy with prognosis is, in fact, an association with breast feeding is difficult to determine since the two are so closely intertwined. The fact that they may be distinguished statistically through multivariate regression analysis does not exclude the fact that what we measure is still an interaction.

The complexity of the picture of associations that prevails parallel to the emerging findings of the possible positive effects of breastfeeding on prognosis has been suggested to reflect the complexity of breast cancer subtypes.[8,9,12]

Conclusions

In this study, a total breastfeeding history >6 months and number of pregnancies are independent predictors for both decreased mortality in breast cancer and overall mortality, and independent of the NPI, and VI.

The clinical conclusion is that women diagnosed with breast cancer, and who have lived long enough to make other causes of death contribute substantially to mortality, have a better survival rate if they have been pregnant and breastfed longer. Our findings require more research on the associations and causal relationships between breastfeeding and all-cause mortality.

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Disclosure Statement

No competing financial interests exist.

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