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Breastfeeding and Reduced Risk of Breast Cancer in an Icelandic Cohort Study

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Case-control studies on the association between breastfeeding and the subsequent risk of breast cancer have given inconsistent results. To date, only two cohort studies have been reported on this subject. The present nested case-control study uses data from an Icelandic cohort of 80,219 women visiting a Cancer Detection Clinic that offers population-based cervical and breast cancer screening, in the years 1979–1995. The 993 parous cases were aged 26–90 years at diagnosis, with 9,729 parous controls individually matched on birth year, vital status at case diagnosis, and age when giving information on several potential risk factors for breast cancer. Using conditional logistic regression and confining the analysis to the 84 cases who were <40 years at diagnosis, an inverse association was evident between total duration of breastfeeding and breast cancer, with the adjusted odds ratio = 0.77 per 6 months' increase in duration of breastfeeding (95% confidence interval: 0.59, 1.00), whereas for the remainder of the women, a much weaker trend was observed. Ever lactating was associated with decreased risk, with the adjusted odds ratio = 0.33 (95% confidence interval: 0.19 , 0.56) for women diagnosed at all ages. This is the first cohort study to indicate a negative association between breastfeeding and breast cancer. *Am J Epidemiol* 2001;154:37–42.

breast neoplasms; cohort studies; lactation

Breastfeeding is one of the few known risk factors for breast cancer that is modifiable, but research has given somewhat inconsistent results regarding whether lactation is associated with a decreased risk of breast cancer after adjusting for the effects of parity and age at first birth. The majority of case-control studies have indicated a statistically significant inverse association, with relative risk estimates ranging between 0.4 and 0.9, either confined to young or premenopausal cases (1–8) or for women diagnosed at various ages (9–17). The duration of breastfeeding was inversely related to risk in some of these (2, 3, 5–7, 9–12, 14), whereas in others the association was apparent only when comparing ever lactating with never lactating parous women (1, 4, 8, 13, 15–17). A number of case-control studies have found some evidence for an inverse association but lacking statistical significance (18–22), whereas in other studies, no association was apparent (23–32).

Only two studies with a cohort design have addressed the question previously. The results of these studies did not indicate an overall association between lactation and the occurrence of breast cancer (33–35). The authors of a recent review article (36) point out that the collective epidemiologic evidence to date, which is mainly based on case-control studies, is not conclusive.

Here we report results from a third cohort study. The data were gathered from women visiting the Cancer Detection Clinic of the Icelandic Cancer Society that offers population-based cervical and breast cancer screening, in the years 1979–1995.

MATERIALS AND METHODS

We conducted a case-control study nested in a cohort of 80,219 women who attended the nationwide screening program of the Cancer Detection Clinic of the Icelandic Cancer Society in the years 1979–1995 and gave answers to questions on reproductive and menstrual factors. The women were at ages 20– 81 years when attending the Clinic. Since 1964, information on potential risk factors for cervical and breast cancer has been collected. Between 1964 and 1987, the activities of the Cancer Detection Clinic were confined to cervical cancer screening, but in November 1987, mammography was added to the screening program. Furthermore, the Clinic also serves women who present with symptoms. The majority of information in the Databank of the Cancer Detection Clinic has been collected in association with the cervical cancer screening, both because the mammography program is relatively new and because the attendance rate for the breast cancer screening has been considerably lower than for the cervical cancer screening. The percentage of all Icelandic women who have attended the Clinic has been increasing with younger birth cohorts. Studying attendance in the years

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1964–1989 revealed that, of women born in 1900–1909 who were alive in the study period, only 45.6 percent had attended at least once, whereas 97.4 percent of women born in 1940–1949 had visited the Clinic at least once and contributed information to the Databank (37). In 1979, several new questions regarding risk factors for breast cancer were added, and that year was defined as the first year of the current study.

All Icelandic women diagnosed with first invasive breast cancer in the years 1979 –1995 were identified from the population-based Cancer Registry of Iceland, a total of 1,601 cases. Record linkage identified 85 percent of those in the Databank of the Cancer Detection Clinic. Only women who had given information at the Clinic in the years 1979–1995 were included. Only answers given before diagnosis of a first breast cancer were used. For women who had attended repeatedly, the data recorded at the last applicable visit were used. These restrictions resulted in a total of 1,120 cases, which comprise 70 percent of the women diagnosed with their first invasive breast cancer in Iceland in the study period. Of those, 993 were parous. From the Databank of the Cancer Detection Clinic, we sought 10 controls for each of the 993 cases, individually matched on birth year and age when giving information at the Clinic. They had to have been alive at least until the diagnosis-year of their matched case. The following variables from the Databank were used: age at menarche, age at first birth, number of births, number of children that were breastfed, average number of weeks spent breastfeeding each child, oral contraceptive use, height, and weight. All the variables were entered as continuous.

To be able to detect possible different effects according to age at diagnosis (or menopausal status), we analyzed three subgroups with respect to age at diagnosis: <40 years, 40–55 years, and >55 years. Those groups represent very young or premenopausal, perimenopausal, and postmenopausal women, respectively. We tried two models with included interaction terms between total duration of breastfeeding (entered as a continous variable) and age at diagnosis as a categorical variable. Two different cutpoints were entered, <40 years versus older and <56 years versus older, testing whether the interaction term between those variables would attain statistical significance when added to either of the models.

Conditional multiple logistic regression (38) was applied for the multivariate analysis of these matched data, using the statistical package STATA (39).

RESULTS

For some of the 993 cases, fewer than 10 controls fulfilled the inclusion criteria; thus, a total of 9,729 women contributed information as controls. In table 1, details are given on the cases and their matched controls. The matching was successful, with the age when giving information and year of birth being almost identical in both groups. The controls had longer average duration of lactation in all age groups. The young group of 84 cases diagnosed at ages <40 years was also youngest when giving information (medium age, 32 years), on average 3 years before diagnosis. With increasing age at diagnosis, there was a trend toward a higher average number of children and an increasing total duration of lactation. Contributing to this are both the fact that the younger women were still at reproductive ages when giving the information and a tendency to decreasing birth rate among more recent birth cohorts of Icelandic women (40). On the other hand, a downward trend in the average duration of breastfeeding per child was apparent when we studied successive birth cohorts in the control group. This trend seemed to be reversing in the most recent birth cohorts, with the mean duration of breastfeeding per child being 17.2, 14.3, 11.5, and 14.6 weeks for women born in 1903–1919, 1920–1929, 1930–1949, and 1950–1967, respectively. The average total duration of breastfeeding in controls (all groups combined) was 45 weeks.

The study group consisted of 70 percent of all women diagnosed with their first invasive breast cancer in Iceland

TABLE 1. Characteristics of the cases and their matched controls according to age at diagnosis, parous women, Iceland, 1979–1995

	No. of cases	No. of controls	Age at diagnosis (years)		Age of cases and controls when giving information (years)	
			Median	Range	Median	Range
Total group	993	9,729	55	26–90	51	20–81
Age at diagnosis						
<40 years	84	857	35	26–39	32	20–39
40–55 years	399	4,052	48	40–55	42	28–59
>55 years	510	4,820	63	56–90	59	44–81

	Year of birth of cases and controls		Average no. of births		Average duration of breastfeeding (weeks)	
	Median	Range	Cases	Controls	Cases	Controls
Total group	1933	1903–1967	3.2	3.6	38.9	45.1
Age at diagnosis						
<40 years	1951	1941–1967	2.2	2.3	23.4	31.6
40–55 years	1940	1924–1955	3.1	3.3	33.0	36.8
>55 years	1924	1903–1939	3.5	4.0	46.0	54.6

TABLE 2. Effects of lifetime duration of breastfeeding in the total study group, in comparison with women who had lactated for less than 5 weeks,* parous women, Iceland, 1979–1995

Weeks of breastfeeding	Cases (n = 973)		Controls (n = 9,449)		Odd ratio	95% Confidence interval	p value
	No.	%	No.	%			
0	24	2.5	66	0.7			
1–4	56	5.7	417	4.4			
0–4	80	8.2	483	5.1	1		
5–26	373	38.3	3,606	38.1	0.67	0.51, 0.89	0.005
27–52	292	29.7	2,688	28.4	0.79	0.59, 1.05	0.106
53–104	180	18.3	1,917	20.3	0.70	0.51, 0.97	0.030
≥105	48	4.9	755	8.0	0.48	0.31, 0.74	0.001

* Multivariate analysis, taking into account the effects of age at menarche, age at first birth, number of births, oral contraceptive use, height, and weight. All variables entered as continuous.

in the study period. The remaining 30 percent of cases did not fulfill the criteria of having contributed information to the Databank of the Cancer Detection Clinic during the study period, at least 1 year before diagnosis. These cases belonged to birth cohorts older than the study group (median year of birth, 1912; range, 1890–1967).

Table 2 shows that a long duration of breastfeeding is not common in this population, with only 8 percent of the control group lactating for 2 years or more. On the other hand, it can also be seen that it is exceptional for parous women not to breastfeed in this population. Only 0.7 percent of parous women in the control group had never lactated and 2.5 percent in the group of cases. Thus, the comparison group was very small when comparing ever lactating women with never lactating women, which could result in imprecise risk estimates. Therefore, it was decided to expand the comparison group by adding to it women who had breastfed for 4 weeks or less. Reduced risk was observed in all categories of total duration.

In table 3 the group is divided according to age at diagnosis. An overall 5 percent reduction in breast cancer risk for each 6 months' increase in duration of lactation was observed when considering the total group, but the dose-response relation in the youngest group accounted for most of this observed risk reduction. However, a slight trend was also present in the older groups. A stratified analysis (results not shown) did not indicate any systematic difference in the effects of lactation according to number of births. Here, comparing ever lactating women with the small group of never lactating women, we found the odds ratios to be lower than those shown in table 2 where the category 1–4 weeks had been added to the comparison group.

For parous women, the p values for the interaction terms between age at diagnosis and duration of breastfeeding were 0.08 and 0.28 when trying models with the cutpoints <40 years vs. older and <56 years versus older, respectively.

DISCUSSION

The results indicate an inverse dose-response relation between the duration of breastfeeding and the risk of breast cancer, mainly confined to women diagnosed before the age of 40, but with a weak trend for older patients. There is also the suggestion of decreased risk in ever lactating parous women irrespective of age at diagnosis.

The prospective design rules out information bias as an explanation for the findings, because only answers given before diagnosis were used. Using controls matched on birth year and age when giving information should minimize diluting effects due to variation in duration of breastfeeding by age and birth cohort in times of rapidly changing breastfeeding practices. The 30 percent of cases diagnosed in the study period that were not included in the study belonged to older birth cohorts as expected, because those were less

TABLE 3. Multivariate analysis* by age at diagnosis, showing effects of increasing duration of breastfeeding and of ever versus never breastfeeding, parous women, Iceland, 1979–1995

Age at diagnosis	Increasing total duration of breastfeeding (per 6 months)			Ever vs. never breastfeeding		
	Odds ratio	95% Confidence interval	p value	Odds ratio	95% Confidence interval	p value
26–90 years (993 cases)	0.95	0.91, 0.99	0.024	0.33	0.19, 0.56	<0.001
<40 years (84 cases)	0.77	0.59, 1.00	0.052	0.09	0.02, 0.45	0.003
40–55 years (399 cases)	0.94	0.86, 1.03	0.215	0.51	0.20, 1.30	0.157
>55 years (510 cases)	0.96	0.91, 1.01	0.103	0.32	0.15, 0.66	0.002

* Adjusted for age at menarche, age at first birth, number of births, oral contraceptive use, height, and weight. All variables entered as continuous.

likely to have visited the Cancer Detection Clinic. The controls were randomly drawn from the same data bank as the cases and thus subject to the same inclusion criteria. Therefore, even though the study group may not be representative of all Icelandic women, the comparisons are likely to be valid.

The present findings of an inverse dose-response relation are in accordance with results from a large number of case-control studies. On the other hand, the interpretation of the observed decreased risk associated with ever lactating is more problematic, because there the comparison group consisted of never lactating parous women, and this group was very small (only 0.7 percent of controls) and may represent women who have special reasons for not breastfeeding, such as medical problems, premature birth, and stillbirths. However, we still found decreased risk in each category of breastfeeding over 4 weeks after adding to the comparison group the category 1–4 weeks of total duration. The majority of case-control studies have also found ever breastfeeding to be associated with decreased breast cancer risk.

It is possible that differences in design, such as selection of the control group, can explain some of the inconsistencies in results from the case-control studies. Population-based controls were more often used in studies that indicated an inverse association (1–4, 6–12, 14–17), whereas hospital controls were more commonly used in the negative case-control studies (23, 29–31). Another possible explanation for discrepancies between results was mentioned in a recent review article (36), that is, the diversity of duration of breastfeeding between populations. It was suggested that the failure to detect an association in some Western populations may be due to the low prevalence of prolonged breastfeeding. This was not confirmed by the present study, in which the average cumulative duration of breastfeeding for controls was 45 weeks, and only 3.1 percent reported lactating for 36 months or more, which is low compared with most non-Western populations (36).

Results from the two previous large cohort studies did not suggest an overall association between breastfeeding and the occurrence of breast cancer, but one of them did not include any women diagnosed under the age of 40 (33), and the other included only seven women of this young age (35). In the present study, the inverse dose-response relation between breastfeeding and breast cancer was mainly confined to women younger than 40 years at diagnosis, with the lowest odds ratio and a p value of 0.05, even though this group was the smallest. In the group diagnosed at perimenopausal ages (40–55 years), no effect was detected, indicating that the main effect was confined to the very young cases and that the cutpoint should not be defined by menopausal status but rather by young age at diagnosis. Furthermore, when testing for effect modification by age at diagnosis, we found that the interaction term in the model approached statistical significance when the cutpoint was 40 years, whereas when we used 56 years as the cutpoint, the p value for the interaction term was 0.28.

Feeding on demand may offer stronger protection than feeding according to schedule (41). The breastfeeding habits in Iceland have been changing. Feeding according to schedule was the rule before 1980, but feeding on demand has now become the common procedure. In the group younger than 40 years at diagnosis, 84 percent had their first birth before 1980, so feeding on demand is not likely to have been predominating, although more common than in the older group in which 99 percent had their first birth before 1980. Thus, it seems unlikely that changing breastfeeding practices explain the different effects according to age.

Another possible reason for the observed shift around the age of 40 could be that the postulated protective effects lasted only for a certain period after cessation of lactation. Adverse transient effects following pregnancies are well documented (42, 43) and are believed to be due to increased cell proliferation in the breast tissue during pregnancy. It is possible that lactation has transitional protective effects. We could not address this in the present study because data on timing of births (except the first one) and breastfeeding were lacking. Still another reason for the observed shift could relate to differing etiology between young and older patients, such as a higher proportion of women with an inherited tendency to develop breast cancer in the youngest group. In Iceland, *BRCA2* mutation carriers in an unselected group of patients were 24 percent, 14 percent, and 4 percent of women diagnosed while under age 40 years, 40–49 years, and ≥50 years, respectively (44). It is possible that breastfeeding is more strongly associated with breast cancer risk in mutation carriers. This could be either because of a stronger response to breastfeeding in this group or because mutation carriers had problems with breastfeeding, with a resulting observed shorter duration in that group (45). It is of great interest to study in more detail whether the association between known risk factors and breast cancer differs between mutation carriers and other women.

Several biologic mechanisms have been pointed out that could account for the postulated protective effects of lactation. Research by Russo and Russo (46) indicates that lactation, as well as pregnancy, increases the proportion of differentiated cells in the breast (46) and, using animal models, they have demonstrated that differentiation of the cells of the mammary gland, prior to exposure to a carcinogen, protects from malignant transformation (47, 48). Long-term endogenous hormonal changes have also been suggested as a possible mechanism. Lowered estrogen levels have been observed following full-term birth and lactation (49). Decreased levels of serum prolactin have also been reported (50), but prolactin may have both some mitogen and differentiating influences on breast cells (51). Furthermore, cholesterol levels in breast fluid have been found to be low in lactating women, and cholesterol oxidation products identified in breast secretions have known carcinogenic potential (52). Another postulated mechanism relates to the delay of onset of menses during lactation. This could reduce breast cancer risk because the risk may be positively correlated with the cumulative number of ovulatory cycles, since mitotic activity is enhanced in the luteal phase of the mestrual cycle (53). It has also been suggested that lactation might reduce breast cancer risk by temporarily draining the breasts of potential chemical carcinogens (54) and, finally, the hormone oxytocin, which causes contraction of myo-

epithelial cells as a response to suction, has been reported to inhibit cell proliferation and tumor growth in animal models (55). Most of the above-mentioned mechanisms are more likely to be related to long-term breast cancer risk, which is not in accordance with the present observation that the risk reduction was mainly confined to the youngest women. The two possibilities mentioned last are perhaps the most likely to have short-term effects.

The present results, in the context of results from previous studies, indicate that breastfeeding reduces the risk of breast cancer diagnosed under the age of 40, and it may offer some protection for older cases also. Even though breast cancer is relatively rare in young women, it is a serious problem. Preventive measures are lacking both for women with an inherited tendency to develop breast cancer and for other women. Breastfeeding has various beneficial effects in addition to those reported here. However, it remains to be studied further whether the observed risk reduction applies to women with inherited susceptibility to develop breast cancer.

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