Prospective assessment of breastfeeding and breast cancer incidence among 89 887 women

Karin B Michels, Walter C Willett, Bernard A Rosner, JoAnn E Manson, David J Hunter, Graham A Colditz
Susan E Hankinson, Frank E Speizer

Summary

Background The relation between breastfeeding and breast-cancer risk has been examined in many studies; some have reported no association, and others a reduced risk, particularly among premenopausal women. In the only prospective cohort study, no association was found. We have assessed prospectively the association between breastfeeding and incidence of breast cancer among 89 887 women in the US Nurses' Health Study.

Methods In 1986, participants were asked about the number of months they breastfed for all their children combined. Parous women with no history of cancer were included in this analysis. During 6 years of follow-up (513 015 person-years), 1459 invasive breast cancer cases were diagnosed.

Findings Relative to women who had never breastfed, no significant overall association was found—after adjusting for established risk factors for breast cancer—between a history of having breastfed and subsequent development of breast cancer (relative risk [RR] 0·93, 95% CI 0·83–1·03). No inverse trend was observed with duration of breastfeeding; women who breastfed for 2 years or longer had a RR of 1·11 (0·90–1·35). Among women who had given birth only once, women who had breastfed their child experienced a lower incidence of breast cancer (RR 0·68, 95% CI 0·46–1·00). Among premenopausal women, who tended to be near menopause due to the age structure of the cohort, the RR of breast cancer for those who had lactated was 1·16 (0·89–1·50). Premenopausal women who had lactated for 1 year or more had a RR of 1·10 (0·78–1·57).

Interpretation These data suggest that there is no important overall association between breastfeeding and the occurrence of breast cancer.


Introduction

The relation between reproductive factors and breast cancer risk has been studied extensively, and the influences of age at first birth, parity, age at menarche, and age at menopause have been well established.4,5 The possibility of a relation between breastfeeding and breast cancer was raised some 70 years ago when both the inability to lactate and prolonged lactation were more often noted from the medical histories of women with breast cancer.6,7 Women from Japan with unilateral breast cancer had a history of hyposecretion of milk from the affected breast.8,9 A number of other studies have assessed prospectively the association between breastfeeding and breast cancer among women from several countries.25 Among these, the largest and most recent study was that of Byers et al.,25 who found no overall relation between breastfeeding and breast cancer.7 This finding led to the belief that any relation between breastfeeding and breast cancer was spurious, due to the confounding effects of parity.5 Several studies published in the late 1960s and in the 1970s did not show convincing associations, but among women below age 50 who had breastfed a somewhat lower risk was apparent.10 In subsequent case-control studies, no association between breastfeeding and breast cancer was found in some,11,12 and an inverse (protective) association in others.13-22 In about half of the studies in which a...
protective association was observed, the apparent protection was restricted to premenopausal women and in one analysis only premenopausal women were studied. An inverse trend associated with duration of breastfeeding was reported in several studies, while the potential protection appeared independent of duration in another. The lifetime duration of breastfeeding necessary to confer a risk reduction varied considerably among populations, ranging from 4 months in a study conducted in the USA to 6–8 years in China. In the only prospective study, Kvåle and Heuch did not find an overall association between breastfeeding and breast cancer. In a retrospective analysis in the Nurses' Health Study, a large cohort of North American women, no important association between breastfeeding reported in 1986 and breast cancer incidence between 1976 and 1986 was seen.

As a cross-check against possible differential bias arising from inaccurate recollection of breastfeeding history among women with and without breast cancer we conducted a prospective analysis among women in the Nurses' Health Study who were free of cancer in 1986.

### Patients and methods

**The Nurses' Health Study cohort**

In 1976, 121 701 female nurses aged 30 to 55 years living in 11 US states completed a self-administered questionnaire that included items about risk factors for cancer and heart disease. Information was collected on demographic and reproductive factors as well as family and personal history of cancer. Every 2 years, follow-up questionnaires have been mailed to cohort members to update the information on potential risk factors and to identify newly diagnosed cases of cancer and other medical events.

#### Ascertainment of exposures

The baseline questionnaire in 1976 included items on parity, age at menarche, personal and family history of breast cancer, history of benign breast disease, weight, height, oral contraceptive use, menopausal status, and postmenopausal hormone use. On follow-up biennial questionnaires, information about menopausal status, weight, and benign breast disease was updated along with a number of other exposures and outcome measures. Data on parity and oral contraceptive use were updated until 1984, family history of breast cancer in 1982 and 1988, and age at first birth was assessed in 1976 and derived in 1978 through 1984. Detailed information about physical activity was recorded in 1986. Diet, including intake of alcohol and vitamins, was assessed in 1980, 1984, and 1986 with a semiquantitative food-frequency questionnaire.

Data on breastfeeding were collected in 1986. On the 1986 questionnaire, the total number of months of breastfeeding for all births combined was asked (i.e., never, <1 month, 1–2 months, 3–6 months, 7–11 months, 12–23 months, ≥24 months).

### Population for analysis

In 1976, 121 701 nurses responded to the questionnaire. From this baseline population, 118 405 reported no previous diagnosis of cancer (excluding non-melanoma skin cancer). Of these women, 28 518 were excluded from this analysis for the following reasons: they had died before 1986; reported any type of cancer (other than non-melanoma skin cancer) between 1978 and 1986; were nulliparous in 1984 or their parity status was unknown; or did not report their breastfeeding history. Also excluded were women with in-situ breast cancer. Cohort members were mailed up to four times and attempts to interview nonrespondents by telephone were made. The remaining 89 887 women accrued 512 015 person-years of follow-up from the return of the 1986 questionnaire to a diagnosis of breast cancer, death, or June 1, 1992, whichever occurred first.

#### Identification of cases

On each biennial follow-up, information was requested about breast cancer diagnosed during the previous 2 years. For nonrespondents, records were searched for in the computerised National Death Index. Invasive breast cancer cases reported in 1992 were included in this analysis. For each reported case of breast cancer, we requested permission to obtain hospital records and pathology reports (from next of kin for dead people). Since medical records confirmed almost all self-reported cases of breast cancer, cases of disease were also included when records were not available. Pathology records were obtained for 94% of breast cancer cases included in this study.

#### Data analysis

Age-adjusted stratified analysis was conducted with person-time denominators. During each of the three time intervals (1986–88, 1988–90, 1990–92) person-time—equal to the number of months between the return of the previous questionnaire and the return of the subsequent questionnaire—was allocated to every participant. For the initial follow-up interval, person-time was allocated according to each participant's breastfeeding status (information on breastfeeding history was collected only in 1986) and to levels of other covariates reported in 1986 or before 1986. For subsequent 2-year intervals, person-time was similarly assigned according to covariates which, when available, were updated at the beginning of each 2-year interval. Information on age at menarche was used from the baseline questionnaire in 1976, history of oral contraceptive use from the 1982 questionnaire, parity and age at first birth were derived from the 1984 questionnaire, and alcohol and vitamin A intake (including supplements) as well as physical activity were obtained from the 1986 questionnaire. Data about family history of breast cancer were derived from the 1976 and 1982 questionnaires and updated in 1988; history of benign disease, body mass index (BMI), menopausal status, age at menopause, and postmenopausal hormone use were updated on each questionnaire through 1990. If a given questionnaire was not returned, the most recently updated covariate status was used to assign person-time for the subsequent interval. Women who reported breast cancer between 1986 and 1992 contributed

### Table 1: Relative risk of breast cancer in relation to lifetime duration of breastfeeding among 89 887 parous women, US Nurses' Health Study, 1986 to 1992

<table>
<thead>
<tr>
<th>History of breastfeeding</th>
<th>Lifetime duration (months)</th>
<th>No of cases</th>
<th>Person-years of observation</th>
<th>RR (95% CI) age-adjusted</th>
<th>RR (95% CI) multivariate$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td></td>
<td></td>
<td>191 434</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td></td>
<td>321 581</td>
<td>0.95 [0.86–1.00]</td>
<td>0.93 [0.83–1.03]</td>
</tr>
<tr>
<td>&lt; 3</td>
<td></td>
<td></td>
<td>116 194</td>
<td>0.91 [0.79–1.04]</td>
<td>0.86 [0.75–0.99]</td>
</tr>
<tr>
<td>4–6</td>
<td></td>
<td></td>
<td>60 896</td>
<td>1.03 [0.87–1.21]</td>
<td>1.02 [0.87–1.21]</td>
</tr>
<tr>
<td>7–11</td>
<td></td>
<td></td>
<td>49 092</td>
<td>0.98 [0.82–1.18]</td>
<td>0.95 [0.79–1.14]</td>
</tr>
<tr>
<td>12–23</td>
<td></td>
<td></td>
<td>61 458</td>
<td>0.87 [0.73–1.04]</td>
<td>0.86 [0.72–1.03]</td>
</tr>
<tr>
<td>≥24</td>
<td></td>
<td></td>
<td>33 941</td>
<td>1.10 [0.90–1.36]</td>
<td>1.11 [0.90–1.38]</td>
</tr>
</tbody>
</table>

*p value for trend*

$^a$Multivariate model includes age, parity, age at first birth, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, body mass index, age at menopause, postmenopausal hormone use, alcohol intake, vitamin A intake (including supplements), and physical activity. Includes women who never breastfed.

---

432 Vol 347 • February 17, 1996
Women with uncertain menopausal status were excluded from this analysis. Multivariate model includes age, parity, age at first birth, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, body mass index, alcohol intake, vitamin A intake (including supplements), and physical activity. Multivariate model includes all terms indicated above and in addition age at menopause and postmenopausal hormone use. Includes women who never breastfed.

Table 2: Relative risk of breast cancer in relation to lifetime duration of breastfeeding, by menopausal status, among 89 887 parous women, US Nurses' Health Study, 1986 to 1992

<table>
<thead>
<tr>
<th>History of breastfeeding</th>
<th>Lifelong duration (months)</th>
<th>Premenopausal women</th>
<th>Postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>Person-years of observation</td>
<td>RR (95% CI) age-adjusted</td>
<td>RR (95% CI) multivariate</td>
</tr>
<tr>
<td>Never</td>
<td>78</td>
<td>43 003</td>
<td>1:00</td>
</tr>
<tr>
<td>Ever</td>
<td>178</td>
<td>84 479</td>
<td>1:16 (0-89-1-50)</td>
</tr>
<tr>
<td>&lt;=3</td>
<td>53</td>
<td>23 676</td>
<td>1:21 (0-85-1-70)</td>
</tr>
<tr>
<td>4-6</td>
<td>35</td>
<td>15 125</td>
<td>1:27 (0-86-1-89)</td>
</tr>
<tr>
<td>7-11</td>
<td>30</td>
<td>14 501</td>
<td>1:14 (0-75-1-73)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>42</td>
<td>19 396</td>
<td>1:20 (0-82-1-74)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>18</td>
<td>11 781</td>
<td>0-85 (0-51-1-41)</td>
</tr>
<tr>
<td>p value for trend</td>
<td></td>
<td>0-65</td>
<td>0-98</td>
</tr>
</tbody>
</table>

Results
Among the 89 887 parous women who reported on breastfeeding history in 1986, 37% reported no breastfeeding, 11% less than 1 month, 12% between 1 and 3 months, 12% between 4 and 6 months 10% between 7 and 11 months, 12% between 12 and 23 months, 5% between 24 and 47 months, and 1% 48 months or more. Between 1986 and 1992, 1459 incident cases of invasive breast cancer were identified among the women included in this analysis.

No important overall association was found for a history of ever having breastfed and breast cancer incidence (age-adjusted RR=0.95, 95% CI 0.86-1.06) (table 1). This association did not subsequently change.
when adjusting for parity, age at first birth, age at menarche, age at menopause, postmenopausal hormone use, family history of breast cancer, history of benign breast disease, BMI, use of oral contraceptives, alcohol intake, vitamin A intake (including supplements), and physical activity in a multivariate logistic regression model (RR 0·93, 0·83–1·03) (table 1). Adjusting for age in 1-year categories did not change the estimates.

When cumulative duration of breastfeeding for all births was considered, no important trend emerged (test for trend: z=0·45, p=0·65). The adjusted RR for women who reported to have breastfed for 24 months or more compared with parous women who never lactated was 1·11 (0·90–1·38) (table 1). Women who breastfed for 48 months or more had a RR for breast cancer of 1·39 (0·90–2·17).

Among premenopausal women, the RR associated with a history of ever having breastfed, adjusted for known determinants of breast cancer, was 1·14 (0·87–1·50), and among postmenopausal women the RR was 0·89 (0·79–1·00). Risk did not vary appreciably by duration of breastfeeding among either premenopausal or postmenopausal women (table 2).

The association between breastfeeding and breast cancer incidence varied by parity. When the analysis was restricted to women who had given birth to only one child, the RR was 0·68 (0·46–1·00) for women who ever lactated compared with those who did not (table 3). Among these lactating women, the duration of breastfeeding gave no clear trend. Among those with single parity, premenopausal women showed a stronger protective association than postmenopausal women (premenopausal OR 0·38, 0·14–1·08; postmenopausal OR 0·74, 0·48–1·15). Compared with women of the same parity who never breastfed, RRs associated with having breastfed increased with every level of parity, increasing from 0·68 for women with one child to 1·15 (0·91–1·46) for women who had given birth four times or more (p for trend=0·02) (table 3).

Among women who had one child only, breastfeeding seemed slightly more protective among women with a later age at first pregnancy, but the difference was not statistically significant (p for interaction=0·32).

**Discussion**

This prospective analysis in a large cohort of middle-aged women does not support an overall association between breastfeeding and breast cancer incidence. This finding is in agreement with a number of previous studies. We also could not detect the general protective effect previously described among premenopausal women. A lower risk of breast cancer was, however, seen among women who had one child only and who had breastfed that child. The protective association found among these women relates primarily to premenopausal breast cancer risk. No association with duration of breastfeeding was observed.

A previous, retrospective assessment of data from the same cohort yielded similar results; no difference, however, was seen for women with different parity and no protective association emerged for women with one child only. When the data from the Nurses' Health Study were compared with the subsequently published results from a large case-control study conducted by Newcomb et al, London speculated that differences in the results between this cohort and Newcomb et al might account for differences observed in the two studies. In two US studies of women with age structures similar to those in this cohort, no association between breastfeeding and breast cancer was found, whereas an inverse association was seen in one study.

Breastfeeding patterns have changed considerably throughout this century. At the beginning of this century, more than half of the infants in the USA were breastfed beyond 1 year. Frequency of breastfeeding declined over the following decades, reaching its low in the early 1970s when only about 25% of all infants were breastfed at all. The women in our cohort gave birth during the 1940s, 1950s, and 1960s, when breastfeeding declined to about 30% of parous. We found that 64% of women in our cohort had breastfed at some point in their life; however, generally for a shorter duration than earlier birth cohorts.

Changing practices have affected not only the likelihood of breastfeeding but also its duration and frequency. Token breastfeeding—adhering to a regular schedule and restricting frequency of breastfeeding—was popular in the first half of this century, whereas feeding on demand became popular only later. London has suggested that even with the same total duration women who breastfed less frequently would have an earlier return of ovulation and therefore less protection, provided lack of ovulation is the mechanism by which breastfeeding lowers breast cancer risk. Thus, the breastfeeding experience among the Nurses' Health Study participants, which largely occurred earlier during this century than among the women studied by Newcomb et al, might account for differences observed in the two studies. In two US studies of women with age structures similar to those in this cohort, no association between breastfeeding and breast cancer was found, whereas an inverse association was seen in one study.

During the observation period of this cohort (1986–1992), the ages of the population ranged between 40 and 65 years at the beginning of follow-up and 46 to 71 years at the end. Among all cases, 95% were 46 years of age or older at diagnosis, and of all cases 84% were 50 years or older. Given this age structure, the majority of cases were postmenopausal, while the premenopausal cases tended to be close to menopause. If there was a true protective association between breastfeeding and breast cancer restricted to premenopausal women, we might not be able to detect it in this cohort. The relative risk for premenopausal breast cancer among women who had breastfed in this population was, however, slightly raised and the lower boundary of the 95% confidence interval for ever having breastfed (0·87) is greater than the odds ratio of 0·78 reported by Newcomb et al in their case-control study.

The inverse association with breastfeeding apparent among women in our cohort who had given birth only once parallels previous findings. In this analysis, women who had given birth once reported a mean duration of breastfeeding of 4·7 months; those who had two, three, or four or more children reported a mean duration of 7·3, 9·6, and 13·2 months of breastfeeding, respectively, indicating a decrease in duration of breastfeeding with every birth. Women who bear only one child possibly remember their duration of breastfeeding more accurately than women who have more than one child. The duration of breastfeeding, however, did not affect the associations observed in this cohort. Women are likely to remember whether they breastfed their individual children and thus the comparison of ever having breastfed versus never having breastfed should not have been appreciably affected by recall bias.

A plausible biological hypothesis of the observed
have observed no protection distinctly conferred by pregnancy at an early age—when breast cells are protective, with and without lactation: no permanent lactation beyond the effect of pregnancy itself in animal risk modulation has been derived from animal models; risk of breast cancer. The relevance of age at first birth to reproductive life—is the primary determinant of reduced tissues of rats that had lactated and parous rats that did not lactate (the latter were not given hormonal blockade).

Newcomb et al, in their retrospective case-control study, found that the inverse association among premenopausal women was most profound in women lactating at younger age. The association between breastfeeding and cancer risk was not modified appreciably by age at first birth for women in our study.

In some analyses, the inverse association between breastfeeding and breast cancer was found to be dependent on the duration of breastfeeding. These associations have been stronger in studies from Asian countries, where about half the children are breastfed for 3 years or more. Other investigators found a protective effect of short duration of breastfeeding. In our study, no important trend emerged with duration of breastfeeding, but the total duration was far less than in countries with high parity and long duration of breastfeeding per child. If duration of breastfeeding were important for breast cancer risk such an effect would likely be mediated through a lower number of lifetime ovulations. The importance of an interruption of cyclic ovarian activity in breast cancer etiology has been previously questioned. Factors influencing the choice and duration of breastfeeding deserve consideration. Some women are unable to breastfeed because of inadequate milk supply. Women who have difficulty lactating may have less differentiated breast tissue. Byers et al found that women with breast cancer reported insufficient lactation more often than women free of the disease. A protective association seen between breastfeeding and cancer could therefore be due to the morphologic structure of the breast in those contracting the disease rather than to a directly protective effect of lactation among disease-free controls. Another confounding factor may be premature birth, which is correlated with impaired lactation. Women who give birth prematurely may not achieve full differentiation of their breast cells, and may have a slightly increased cancer risk. Finally, initiation and duration of breastfeeding are strongly related to cultural heritage, socioeconomic status, education of the mother, the mother's marital status, and employment outside the home. However, McTiernan did not detect any confounding by these demographic variables.

Another possible pathophysiological mechanism of the influence of breastfeeding on breast cancer risk is the elimination of carcinogens through breastmilk secretion, including highly suspect organochlorines. Breastmilk concentrations of these substances decrease with cumulative breastfeeding.

In conclusion, it remains unclear whether an association between breastfeeding and breast cancer exists. The epidemiologic evidence is inconsistent. Most of the case-control studies thus far may have biases inherent to their design. Differences in the choice of control groups may have contributed to the differing conclusions. Although Kyvale and Heuch found no relationship between breastfeeding and breast cancer, they had not stratified by menopausal status. While no significant association was detected in the Nurses' Health Study, the possibility that breastfeeding confers protection to some women, particularly before cessation of menses, cannot be ruled out. This premenopausal protective effect may be stronger, or more apparent, among women of low parity. We advocate further studies in younger cohorts of premenopausal women.

This study was supported by research grants from the National Institutes of Health (CA 40356), and the American Cancer Society Special Institutional Grant 18. KBM was supported in part by Deutsche Akademische Austauschdienst, and by the Gottlieb Daimler and Karl Benz-Stiftung, Germany. JEM is the recipient of a Merck Society for Epidemiological Research Clinical Fellowship. DJH is supported in part by a Faculty Research Award (FRA 455) from the American Cancer Society. GAC is supported in part by a Faculty Research Award (FRA 398) from the American Cancer Society.

We thank Mark Shneyder for programming assistance.

References

Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease

Joan A Barberà, Núria Roger, Josep Roca, Irene Rovira, Timothy W Higenbottam, Robert Rodriguez-Roisin

Summary

Background Inhalation of nitric oxide (NO) causes selective pulmonary vasodilatation and improves arterial oxygenation in acute respiratory distress syndrome. But some patients do not respond or gas exchange worsens when inhaling NO. We hypothesised that this detrimental effect might be related to the reversal of hypoxic vasoconstriction in those patients where this mechanism contributes to ventilation-perfusion (V/Q) matching.

Methods We studied 13 patients with advanced chronic obstructive pulmonary disease (COPD). We compared their responses to breathing room air, NO at 40 parts per million in air, and 100% O₂, in pulmonary haemodynamics, blood gases, and V/Q distributions were assessed.

Findings NO inhalation decreased the mean (SE) pulmonary artery pressure from 25-9 (2-0) to 21-5 (1-7) mm Hg (p=0-001) and PaO₂ from 56 (2) to 53 (2) mm Hg (p=0-014). The decrease in PaO₂ resulted from worsening of V/Q distributions, as shown by a greater dispersion of the blood-flow distribution (logSD Q) from 1-11 (0-1) to 1-22 (0-1) (p=0-018). O₂ breathing reduced the mean pulmonary arterial pressure to 23-4 (2-1) mm Hg and caused greater V/Q mismatch (logSD Q, 1-49 [0-1]). The intrapulmonary shunt on room air was small (2-7 [0-9]% and did not change when beathing NO or O₂.

Interpretation We conclude that in patients with COPD, in whom hypoxaemia is caused essentially by V/Q imbalance rather than by shunt, inhaled NO can worsen gas exchange because of impaired hypoxic regulation of the matching between ventilation and perfusion.

Lancet 1996; 347: 436–40

Introduction Inhaled nitric oxide (NO) is a selective pulmonary vasodilator that can improve arterial oxygenation in patients with acute respiratory distress syndrome (ARDS)3. This effect on gas exchange is attributed to a selective increase in perfusion of ventilated lung areas accessible to inhaled NO, which improves ventilation-perfusion (V/Q) imbalance. However, arterial oxygen desaturation develops in some patients with ARDS when they inhale NO.5 Furthermore, NO can decrease the partial pressure of arterial oxygen (PaO₂) in some patients with chronic obstructive pulmonary disease (COPD).81