Breastfeeding Experience and Breast Cancer Risk among Postmenopausal Women

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Abstract

Results of studies of breastfeeding and postmenopausal breast cancer risk have been inconsistent, with many investigators concluding that breastfeeding does not influence risk. We examined whether breastfeeding reduces postmenopausal breast cancer risk as well as the details of this relationship, including possible modification in risk by the age that a woman first breastfed a child and the number of children she breastfed. This population-based case-control study compared 974 women who were residents of Los Angeles County and newly diagnosed with breast cancer to 973 women with no history of breast cancer who were matched to patients by age (within 3 years) and neighborhood of residence. Subjects were parous and postmenopausal. Breast cancer patients were ages 55–64 years at diagnosis. Women who breastfed at least 16 months experienced a reduced odds of breast cancer relative to women who never breastfed (odds ratio, 0.73; 95% confidence interval, 0.52–1.01). Risk decreased as the number of children breastfed increased, but the association was attenuated after accounting for lifetime duration of breastfeeding. Breast cancer risk was 30% lower among women ages 20–24 years at first breastfeeding than women who had never breastfed (odds ratio, 0.69; 95% confidence interval, 0.54–0.88), independent of the effect of age at first birth. This study provides some evidence that the protective effect of breastfeeding persists into the postmenopausal years. The potential for nondifferential error in recall of breastfeeding habits among postmenopausal patients and controls may explain the inconsistent results observed across studies and underscores the need for careful assessment of this relationship.

Introduction

The impact of breastfeeding on breast cancer risk has been of great interest over the past 30 years, as investigators have attempted to discover ways that women can actively reduce their breast cancer risk. As of 1997, more than 40 independent research studies have examined the role of breastfeeding, a potentially modifiable behavior, on breast cancer risk (1–31). The evidence is now convincing, and it is widely accepted that breastfeeding reduces the risk of premenopausal breast cancer (4, 6, 7, 13–15, 17, 19–27, 29–31), but the association of breastfeeding with risk of postmenopausal breast cancer remains controversial (4, 6, 7, 13, 15, 17, 19, 21, 22, 24–27, 30, 31). Recent studies have raised additional questions about the details of the relationship of breastfeeding on breast cancer risk, such as whether the age that a woman first breastfeeds a child or number of children she breastfeeds are independently associated with risk after accounting for the effect of lifetime duration of breastfeeding.

We examined the detailed relationship of breastfeeding on postmenopausal breast cancer risk using data from a large population-based case-control study of breast cancer risk factors in Los Angeles County, California.

Subjects and Methods

Subjects eligible to participate were English-speaking, white (and Hispanic), female residents of Los Angeles County, born in the United States, Canada, or Western Europe, with no history of breast cancer. Eligible case subjects were ages 55–64 years and were diagnosed for the first time with histologically confirmed in situ or invasive breast cancer between March 1, 1987 and December 31, 1989. Case subjects were identified by the University of Southern California Cancer Surveillance Program, the population-based cancer registry for Los Angeles County. Of 2373 eligible cases, 1579 (66%) completed the interview. Of the 794 eligible cases who were not interviewed, the physician recommended against contact for 128, 419 subjects refused to be interviewed, 230 subjects were too ill or had died, and we were unable to locate 17 subjects.

One control subject, individually matched to each case subject on birthdate (within 3 years) and neighborhood of residence, was interviewed for 1506 case subjects. We were unable to identify and interview an eligible control for the remaining 73 case subjects. We selected control subjects by canvassing housing units in the neighborhood where the case lived at the time of her diagnosis, using a predefined walk pattern (32). We canvassed each housing unit until a woman who matched the case subject on the matching criteria was located and interviewed. We made repeated attempts to obtain

Received 9/29/97; revised 2/12/98; accepted 2/23/98.

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1 This study was supported by USPHS Grant CA117054 and contract N01-CN25404 from the National Cancer Institute, NIH, Department of Health and Human Services, and by the California Public Health Foundation Subcontract 050-F-8709, which is supported by the California Department of Health Services as part of its statewide cancer-reporting program mandated by Health and Safety Code Sections 210 and 211.3. The ideas and opinions expressed herein are those of the authors, and no endorsement by the state of California, Department of Health Services, or the California Public Health Foundation is intended or should be inferred. S. M. E. was supported by funds from the California Breast Cancer Research Program of the University of California, Grant Number IFB-0341.

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the information on matching criteria by telephone or mail when no one was home. For 1205 breast cancer patients, the first identified eligible control subject participated. For 227 others, the second eligible control subject participated after the first eligible control subject refused. Three eligible control subjects were identified for 65 others, four eligible control subjects were identified for 8 others, and five eligible control subjects were identified for 1 other before an interview was obtained. The overall response rate among eligible control subjects was 80%.

For the 73 breast cancer patients for whom no control interview was obtained, we were unable to locate and interview a matched control after contacting a median of 107 housing units. Among the other 1506 patients, we obtained complete walk-pattern censuses for neighborhoods of 636 cases. For the remaining 870 breast cancer patients, we were unable to obtain a census for at least one housing unit (median, 4) in the walk pattern. A median of 25 housing units was approached to obtain a complete interview for the 1506 controls.

The case and control of a matched pair were interviewed by the same interviewer. The approximately 45-min in-person interview obtained detailed information about demographic characteristics and reproductive and breastfeeding histories as well as other known or suspected breast cancer risk factors. For each case and control pair, a reference date was created that was the date 12 months before the index patient’s breast cancer diagnosis. Information obtained in the interview referred to the time before the reference date.

For each pregnancy, we obtained the following: date the pregnancy ended (month and year), outcome (current pregnancy, single live birth, multiple birth (all live), multiple birth (not all live), stillbirth, spontaneous abortion, induced abortion, tubal pregnancy, gestation (months), and duration of breastfeeding (months). A woman was considered to have a family history of breast cancer if her mother, sister, or daughter had been diagnosed with breast cancer.

Of 3085 cases and controls, 605 cases and 533 controls were excluded from the analysis for the following reasons: we determined that they were premenopausal (still menstruating and not using hormone replacement therapy: 58 cases and 51 controls); we were unable to determine their age at menopause (usually hysterectomy without oophorectomy: 352 cases and 360 controls); they had never experienced a full-term pregnancy (191 cases and 121 controls); or we had incomplete information on family history, education, alcohol consumption, or weight (4 cases and 1 control). The remaining 974 cases and 973 controls were included in the breastfeeding analyses.

ORs3 and 95% CIs were calculated using logistic regression methods. Because the matched pairs were not retained in the analyses, we included age (continuous) and socioeconomic status (five categories based on residential census tract) in all of the models. The multivariate models also included education (less than high school, high school, partial college, college or graduate/professional training), age at first full-term pregnancy (<20, 20–24, 25–29, ≥30 years), number of full-term pregnancies (1, 2, 3, ≥4), age at menarche (<12, 12, 13, ≥14 years), first-degree family history of breast cancer (yes/no), use of estrogen-only hormone-replacement therapy (0, 1–12, 13–72, 73–120, ≥121 months), use of combined estrogen and progestin hormone-replacement therapy (0, 1–12, 13–72, 73–120, ≥121 months), age at menopause (<45, 45–49, 50–54, ≥55 years), average alcohol consumption per day at the reference date (0, 1–13, 14–26, ≥27 g), and body mass index at the reference date (<21.8, 21.8–23.9, 24.0–27.3, ≥27.4 kg/m²), all as categorical variables. Inclusion of physical activity and oral contraceptive use did not materially change the results; therefore, they were not included in any of the models presented. To test for trend in effect across categories, we used the two-sided P associated with the coefficient fit to the median value of each category of the variable.

Results
Among these parous, postmenopausal women, we observed only very weak associations between age at menarche and age at first full-term pregnancy and breast cancer risk (Table 1). However, we observed a marked inverse association between number of full-term pregnancies and breast cancer risk; women who gave birth four times or more had only half the risk of women who gave birth only once. Increasing age at menopause and having at least one first-degree relative with breast cancer also substantially increased breast cancer risk in this study.

Overall, women who breastfed at least one child experienced more than a 20% reduction in breast cancer risk compared with women who did not breastfeed (Table 2). In addition, the longer that a woman breastfed her children, the greater her reduction in risk. In multivariate analysis, the reduction in risk with increased duration of breastfeeding diminished slightly (with individual category ORs achieving only borderline statistical significance), possibly due to the strong correlation between lifetime months of breastfeeding and parity.

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3 The abbreviations used are: OR, odds ratio; CI, confidence interval.
We observed that the more children a woman breastfed over the course of her lifetime, the lower her breast cancer risk, even after adjusting for parity and lifetime duration of breastfeeding (Table 2). However, the test for linear trend was not statistically significant after these adjustments, again possibly due to the high correlations among these three variables. In an attempt to separate the effects of these variables, we first evaluated whether the highly protective association of increasing parity with breast cancer risk may be due, at least in part, to breastfeeding. Adjusting for lifetime months of breastfeeding did not markedly change the association of parity with breast cancer risk. However, when we restricted the analysis to women who had never breastfed, which included roughly one-half of the women in the study, the association of parity with breast cancer risk was greatly attenuated (women with more than a 30% reduction in risk compared with women who did not breastfeed, but the reductions were small and not statistically significant. It is unlikely that the observed reduction in risk at young ages could be explained by confounding by age at first full-term pregnancy, which had a much weaker association with breast cancer risk at all ages. Nonetheless, to examine risk associated with age at first birth with no potential confounding by lactation, we assessed the association of age at first full-term pregnancy among women who had never breastfed. In this analysis, we observed virtually no association of age at first full-term pregnancy with breast cancer risk, with an OR of 0.97 (95% CI, 0.63–1.51) for women who were ages 20–24 years at their first full-term pregnancy compared with women who were under the age of 20 years. This finding also confirmed that the reduction in risk among women who were young when they first breastfed a child was not likely due to confounding by age at first full-term pregnancy.

To examine further the role of age at first breastfeeding experience, we analyzed the association of lifetime duration of breastfeeding with breast cancer risk separately for women who were younger than 25 when they first breastfed a child and for women who were ages 25 years or older when they first breastfed a child (Table 3). In the multivariate analysis that included women who were under the age of 25 when they first breastfed a child, we observed a substantial decrease in breast cancer risk with increasing duration of breastfeeding, and the trend across categories was highly statistically significant. We observed no association of duration of breastfeeding with breast cancer risk in the analysis that included women who were 25 years or older when they first breastfed a child.

Discussion

Our findings are consistent with a modest reduction in risk of postmenopausal breast cancer among women who breastfed their infants. The high correlation of lifetime months of breastfeeding with parity raises concern about whether these effects are solely due to breastfeeding. However, the parity-breast cancer association was markedly reduced when restricted to women who had never breastfed, suggesting that, if anything, the association of parity with breast cancer was confounded by breastfeeding rather than the reverse. Our results differ from those observed in a large prospective cohort study of nurses (25). However, the nurses, all educated professionals, may have been more likely to return to work and introduce supplemental bottles to their infants than participants in other published studies, a possibility alluded to by the authors. If breast cancer risk is determined by a woman’s cumulative exposure to endogenous estrogens (33), then breastfeeding may reduce breast cancer risk by reducing the cumulative number of ovulatory menstrual cycles she experiences during her reproductive years. The nurses may not have breastfed their infants at a frequency sufficient to suppress menses and ovulation and therefore to reduce their breast cancer risk. The lack of an association among the premenopausal nurses contradicts the large body of studies of this issue and further raises concerns about possible differences in lactation practices among nurses compared with women who participated in other studies.

Nearly one-half of the published studies of breastfeeding and postmenopausal breast cancer risk reported results consistent with a weak to modest protective association. It is possible
Table 3  Association of lifetime duration of breastfeeding with breast cancer risk according to the age that a woman first breastfeeds a child (n = 1947 parous, postmenopausal women)

<table>
<thead>
<tr>
<th>Lifetime months of breastfeeding</th>
<th>Age breastfed first child</th>
<th>OR* (95% CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>504</td>
<td>433</td>
<td>1.00</td>
<td>504</td>
<td>433</td>
</tr>
<tr>
<td>1−3</td>
<td>127</td>
<td>125</td>
<td>0.86</td>
<td>0.64−1.16</td>
<td>80</td>
</tr>
<tr>
<td>4−6</td>
<td>45</td>
<td>64</td>
<td>0.62</td>
<td>0.41−0.95</td>
<td>36</td>
</tr>
<tr>
<td>7−15</td>
<td>52</td>
<td>81</td>
<td>0.58</td>
<td>0.39−0.86</td>
<td>50</td>
</tr>
<tr>
<td>≥16</td>
<td>49</td>
<td>77</td>
<td>0.54</td>
<td>0.36−0.82</td>
<td>31</td>
</tr>
<tr>
<td><strong>Trend P</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ORs adjusted for age at first full-term pregnancy, number of full-term pregnancies, age at menarche, age at menopause, family history of breast cancer, body mass index, average alcohol consumed per day during the reference year, education, use of estrogen-only hormone replacement therapy, use of combined estrogen and progesterin hormone replacement therapy, socioeconomic status, and age at reference year.

that recall of breastfeeding history may be less accurate among older than younger women. The upper age limit of women in our study (64 years) is younger than that of studies reporting no association with breastfeeding with postmenopausal breast cancer risk (all had upper age limits of at least 74 years; Refs. 4, 7, 21, 22, 24, 25, 26, 30, and 31). Of the four other studies consistent with a weak or modest protective effect of breastfeeding in postmenopausal women, one included only women who were ages 55 years or younger (6). The other three studies were conducted outside of the United States, where, generally, a greater proportion of women breastfeed their infants (13, 17, 27) and did so for longer periods of time (27) than is typically observed in studies conducted in the United States. In contrast, five other studies conducted outside of the United States reported no association of breastfeeding with postmenopausal breast cancer, and at least 70% of the women in those studies breastfed at least one infant (7, 21, 24, 26, 31). Two studies have examined the association of number of children breastfed with postmenopausal breast cancer risk (17, 27), and one reported a protective association (27). We observed that the number of children breastfed was associated with a reduction in breast cancer risk independent of number of full-term pregnancies, but the association was not statistically significant when adjusted for lifetime duration of breastfeeding. Unfortunately, we were unable to clearly disentangle the protective effect of number of children breastfed from lifetime duration of breastfeeding using statistical methods, given the high correlation of these two measures of breastfeeding.

We found that a young age at first breastfeeding experience was associated with a decreased breast cancer risk relative to women who had never breastfed a child, and the association was independent of age at first birth. Of the two other studies that have examined this issue in postmenopausal women (22, 30), one reported no association of age at first breastfeeding experience with breast cancer risk (22), and one reported a highly protective association of a young age (<25 years) at first breastfeeding and breast cancer risk (30). However, the authors of the second study (30) were unable to rule out the possibility that their findings were confounded by age at first birth. Because the association of age at first birth with breast cancer risk is very weak in the current study and becomes essentially null when the analysis is restricted to women who have never breastfed, it is likely that the age when a woman first breastfeeds a child is independently associated with a reduction in breast cancer risk.

As in all case-control studies, we could not dismiss the possibility of bias due to nonparticipation or differential recall of exposure. The participation rate among case subjects, 66%, was somewhat low. However, the majority of nonresponse was due to reasons unlikely to be associated with breastfeeding, such as physician refusal. The response rate among eligible control subjects, 80%, was higher than among case subjects. It is not likely that the reasons for nonparticipation of cases or controls are related to breastfeeding history. It is possible that women with breast cancer may recall their breastfeeding histories differently than women without breast cancer. However, it is unlikely that the women at each end of the breastfeeding spectrum (those who never breastfed a child and those who breastfed their children for very long periods of time) would incorrectly recall the extent of their breastfeeding experiences and be misclassified in the analysis of the categorical breastfeeding variable.

Several hypotheses have been suggested as to how breastfeeding may reduce breast cancer risk. As mentioned above, one theory attributes the reduction in risk to a reduction in the cumulative number of ovulatory menstrual cycles a woman experiences during her reproductive years and, as a result, her cumulative exposure to estrogen, a hypothesized cause of breast cancer (33). Because release of prolactin during lactation directly inhibits ovulation (34), the enhanced protection of longer duration of breastfeeding or of more children breastfed would result in a reduction in the cumulative estrogen exposure.

An alternative hypothesis attributes the protection afforded by lactation to the terminal differentiation of the mammary gland during lactation, which renders breast cells less susceptible to carcinogenesis (35). Thus, breastfeeding at an earlier age may be protective because breast stem cells undergo earlier differentiation and resistance to carcinogenesis.

Elimination of carcinogenic agents through breast secretion is a third possible mechanism. Investigators examining the composition of breast fluid have found that estrogen levels are very low among lactating women and increase with time since last breastfeeding (36). These reduced levels were maintained several years following weaning of the child from the breast. The same investigators (37) also detected levels of exogenous substances such as pesticide residues in breast secretions. Breastfeeding may reduce breast cancer risk by flushing potentially carcinogenic substances out of the breast ductules (alternatively, the hypothesized association between carcinogens in breast fluids and breast cancer risk may be confounded by breastfeeding.)

This study demonstrates that the well-established protective effect of breastfeeding on breast cancer risk during the reproductive years may persist into the postmenopausal years. Although the individual risk estimates were modest, we observed a consistent dose-response trend of duration of breast-
feeding with breast cancer risk, suggesting that the longer a woman breastfeeds her children over the course of her lifetime, the lower her risk. We could not confirm statistically that the number of children that a woman breastfeeds is independently associated with breast cancer risk after accounting for the effects of lifetime duration of breastfeeding due to the collinearity issues inherent in these analyses. We observed that the protective effect of breastfeeding was restricted to women who breastfed a child for the first time at younger ages, independent of the effect of age at first full-term pregnancy. Results across studies of breastfeeding and postmenopausal breast cancer risk have been inconsistent, with many investigators concluding that breastfeeding does not influence the etiology of postmenopausal breast cancer. However, given the present findings, because the possibility that errors in recall of breastfeeding habits may increase with age and the general lack of information about supplementation in breastfeeding studies, it may be imprudent to rule out the possibility of a weak or modest protective association of breastfeeding with risk of postmenopausal breast cancer.

References

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