The purpose of this review is to critically evaluate the collective epidemiologic evidence that a history of breast-feeding may decrease the risk of breast cancer. Original data for inclusion were identified through a MEDLINE® search of the English language literature from 1966 through 1998. To date, virtually all epidemiologic data regarding breast-feeding and breast cancer risk are derived from case-control studies, which vary according to classification of breast-feeding history. Overall, the evidence with respect to “ever” breast-feeding remains inconclusive, with results indicating either no association or a rather weak protective effect against breast cancer. An inverse association between increasing cumulative duration of breast-feeding and breast cancer risk among parous women has been reported in some, but not all, studies; the failure to detect an association in some Western populations may be due to the low prevalence of prolonged breast-feeding. It appears that the protective effect, if any, of long-term breast-feeding is stronger among, or confined to, premenopausal women. It has been hypothesized that an apparently protective effect of breast-feeding may be due to elevated breast cancer risk among women who discontinue breast-feeding or who take medication to suppress lactation; however, the evidence is limited and should be interpreted with caution. The biology underlying a protective effect of breast-feeding and why this should be restricted to premenopausal women remain unknown, although several mechanisms have been postulated (hormonal changes, such as reduced estrogen; removal of estrogens through breast fluid; excretion of carcinogens from breast tissue through breast-feeding; physical changes in the mammary epithelial cells, reflecting maximal differentiation; and delay of the re-establishment of ovulation). While breast-feeding is a potentially modifiable behavior, the practical implication of reduced breast cancer risk among premenopausal women with prolonged durations of breast-feeding may be of marginal importance, particularly in Western societies. [J Natl Cancer Inst 2000;92:302–12]

More than 70 years ago, it was proposed that “the breast which has never been called upon for normal function is certainly more liable to become cancerous” (1), and a history of breast-feeding came to be considered as a protective factor for breast cancer. This hypothesis is consistent with the pattern of geographic variation in breast cancer incidence, which is markedly lower among populations in which breast-feeding is the most common and the most prolonged (2). In 1970, however, MacMahon et al. (3) reported, on the basis of a large international case-control study, that breast-feeding was unlikely to have an independent influence on breast cancer risk after adjusting for the effects of number of full-term pregnancies and age at first birth. These findings seemed, at the time, to close the issue, and many subsequent epidemiologic studies disregarded the association between breast-feeding and breast cancer.

More recently, the issue has undergone increasing scrutiny, and the attitude of the scientific community toward breast-feeding in relation to breast cancer has changed. A number of epidemiologic investigations have once again suggested that breast-feeding, particularly for extended periods of time, may be associated with a decreased risk of breast cancer, even after adjusting for potential confounders, and that this protection may be greatest among women under 50 years of age. It is difficult to summarize the magnitude of the association, if any, because of the variety of methodologies for reporting breast-feeding history; some studies report the effect of mean duration of breast-feeding for each child, others report the effect of cumulative duration following all births, and still others use different exposure measures.

The purpose of this review is to critically evaluate the existing epidemiologic evidence that history of breast-feeding may decrease the risk of breast cancer. Breast-feeding, if, in fact, it is shown to be protective against the development of breast cancer, is a potentially modifiable behavior and thus may represent one of the few opportunities for intervention at present.

**METHODS**

Original data for inclusion in this review were identified through a MEDLINE® search of the literature. All papers from 1966 through 1998 were identified by use of either the term “breast-feeding” or the term “lactation,” together with the term “breast cancer.” Moreover, all review papers addressing reproductive factors in relation to breast cancer were identified, and references were examined to supplement, if necessary, papers recovered through the initial search. For the purposes of this review, only those studies that included more than 200 cases overall and which explicitly controlled for number of full-term pregnancies and age at first birth, both of which are associated with breast cancer risk and potentially related to breast-feeding habits, were evaluated in detail. Individual results were evaluated for bias, confounding, and chance and are summarized in Tables 1–6. On the basis of the individual data, a qualitative summary of the results is presented in the text.

**EPIDEMIOLOGIC FINDINGS**

Since the publication of the large international case-control study (3), virtually all of the relevant epidemiologic data regard-
ing breast-feeding and breast cancer risk are derived from case–control studies, the majority of which have been conducted in North America or in Europe. The characteristics and results of these hospital-based and population-based, case–control studies, as well as those of the only cohort study to date (4) and two retrospective assessments of breast-feeding in the Nurses’ Health Study (5,6), are summarized in Tables 1–6. Where available, relative risk (RR) estimates are presented for women who ever breast-fed and for categories of cumulative duration of breast-feeding, average duration of breast-feeding per child, and number of children breast-fed. Clearly, even in studies with more than 200 cases overall, many of the subgroup analyses were based on smaller numbers. While several studies were designed specifically to evaluate the role of breast-feeding, they varied according to subject selection criteria and classification of breast-feeding history. Many were based on relatively small numbers of women who breast-fed for prolonged periods, making it difficult to meaningfully evaluate the role of long-term breast-feeding in the etiology of breast cancer.

<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Study period</th>
<th>No. of case patients</th>
<th>No. of control subjects</th>
<th>Measure of lactation</th>
<th>OR 95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoo et al., 1992 (7)</td>
<td>Japan</td>
<td>1988–1989</td>
<td>430</td>
<td>455 noncancer patients</td>
<td>Ever No. of children breast-fed</td>
<td>0.62 0.37–1.04</td>
<td>Adjusted for age, family history of breast cancer, age at menarche, menstrual regularity, menopausal status, age at menopause, parity, age at first birth</td>
</tr>
<tr>
<td>Thomas and Noonan, 1993 (25)</td>
<td>Australia, Germany, Israel, Chile, China, Kenya, Colombia, Mexico, Philippines, Thailand</td>
<td>1979–1986</td>
<td>2336</td>
<td>14,900 nonobstetric/gynecologic patients</td>
<td>Total duration, mo</td>
<td>0.86 0.72–1.02</td>
<td>Adjusted for age, study center, parity, age at first birth</td>
</tr>
<tr>
<td>Negri et al., 1996 (21)</td>
<td>Italy</td>
<td>1991–1994</td>
<td>2167</td>
<td>2208, non-neoplastic, nongynecologic, non-hormone-related hospital admissions</td>
<td>Ever No. of children breast-fed</td>
<td>1.17 1.0–1.3</td>
<td>Adjusted for age, study center, education level, parity, menopausal status, age at menopause, age at first birth, family history of breast cancer, benign breast disease, body mass index, marital status</td>
</tr>
<tr>
<td>Katouyanni et al., 1996 (8)</td>
<td>Greece</td>
<td>1989–1991</td>
<td>657</td>
<td>1164 orthopedic patients and hospital visitors</td>
<td>Total duration, mo</td>
<td>0.92 0.67–1.27</td>
<td>Adjusted for age; place of birth; body mass index; age at menarche; menopausal status; age at menopause; parity; age at first birth; total daily intake; history of benign breast disease; family history of breast cancer; intake of fruit, vegetables, olive oil, and alcohol; induced abortions; menopausal estrogen use</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval.
Any History of Breast-Feeding

One measure of breast-feeding history that has been commonly used in epidemiologic studies is that of “ever versus never” breast-feeding. Overall, the evidence of an inverse association between ever breast-feeding and breast cancer risk remains limited and inconclusive, with results suggesting either no association or a definite, although modest, protective effect. Among studies (6–19) that have found a protective effect, reported RRs among parous women who have ever breast-fed...
<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Study period</th>
<th>No. of case patients</th>
<th>No. of control subjects</th>
<th>Measure of lactation</th>
<th>OR</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubin et al., 1982 (19)</td>
<td>Canada</td>
<td>1976–1977</td>
<td>489</td>
<td>731, social insurance files</td>
<td>≥2 consecutive wks</td>
<td>0.6</td>
<td>0.5–0.8</td>
<td>Adjusted for age, parity, age at first birth</td>
</tr>
<tr>
<td>Brinton et al., 1983 (9)</td>
<td>United States</td>
<td>1973–1977</td>
<td>1143</td>
<td>1056, breast cancer screening participants</td>
<td>Ever No. of children breast-fed</td>
<td>0.94</td>
<td>0.8–1.1</td>
<td>Adjusted for age at first birth, parity</td>
</tr>
<tr>
<td>Yuan et al., 1988 (27)</td>
<td>Shanghai, China</td>
<td>1984–1985</td>
<td>429</td>
<td>429, neighborhood sampling</td>
<td>Total duration, mo</td>
<td>0.64–1.72</td>
<td>Adjusted for parity, age at first birth</td>
<td></td>
</tr>
<tr>
<td>Tao et al., 1988 (26)</td>
<td>Beijing, China</td>
<td>1980–1984</td>
<td>449</td>
<td>449, neighborhood sampling</td>
<td>Total duration, mo</td>
<td>0.5–1.5</td>
<td>Adjusted for parity, age at first birth</td>
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<tr>
<td>Layde et al., 1989 (23)</td>
<td>United States</td>
<td>1980–1982</td>
<td>3830</td>
<td>3931 random-digit dialing</td>
<td>Total duration, mo</td>
<td>0.5–1.4</td>
<td>Adjusted for parity, age at first birth</td>
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<tr>
<td>Siskind et al., 1989 (10)</td>
<td>Australia</td>
<td>1981–1985</td>
<td>459</td>
<td>1091, electoral rolls</td>
<td>Total duration, wk</td>
<td>0.58–1.34</td>
<td>Adjusted for age, education level, place of birth, family history of breast cancer, parity, age at first birth, age at menarche, benign breast disease</td>
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<tr>
<td>Adami et al., 1990 (24)</td>
<td>Sweden, Norway</td>
<td>1984–1985</td>
<td>422</td>
<td>527, population register</td>
<td>Total duration, mo</td>
<td>0.68–2.00</td>
<td>Adjusted for parity, age at first birth</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 1992 (28)</td>
<td>Tianjin, China</td>
<td>1985–1986</td>
<td>246</td>
<td>246, residence files</td>
<td>Total duration, mo</td>
<td>0.3–1.4</td>
<td>Adjusted for parity, age at first birth</td>
<td></td>
</tr>
<tr>
<td>Newcomb et al., 1994 (11)</td>
<td>United States</td>
<td>1989–1991</td>
<td>5434</td>
<td>7563, driver’s licenses or Medicare</td>
<td>Total duration, mo</td>
<td>0.79–1.15</td>
<td>Adjusted for age at first birth, parity, benign breast disease, family history of breast cancer, body mass index, age at menarche, menopausal status</td>
<td></td>
</tr>
</tbody>
</table>

(Table continued)
compared with women who have never breast-fed range from 0.54 to just below 1.0 (Tables 1, 3, and 5). However, a history of ever breast-feeding may be too crude an indicator, and it may be more important to demonstrate a dose–response association with increasing duration of breast-feeding in making causal inferences.

**Number of Children Breast-Fed**

Recent studies have raised the question of whether the total number of children that a woman has breast-fed may be etiologically relevant or whether breast-feeding additional children after the first may provide incremental protection against breast cancer development. Two investigations (12,20) have reported that the more children a woman breast-fed over the course of her lifetime, the lower her breast cancer risk. Romieu et al. (12) found that, after adjustment for several other risk factors, women who breast-fed four or more children had a statistically significant 60% reduction in breast cancer risk (odds ratio [OR] = 0.39; 95% confidence interval [CI] = 0.21–0.70) compared with women who never breast-fed; women who breast-fed one or two children had an intermediate 43% reduction in breast cancer risk (Table 3). However, a number of studies (7,9,21,22) have found no such trend of decreasing risk with increasing number of breast-fed children.

**Cumulative Duration of Breast-Feeding**

In many studies to date, the summation of all breast-feeding episodes is calculated as the total duration of breast-feeding for each woman, taking into account breast-feeding after all births. Using the cumulative duration as a measure of a woman’s complete breast-feeding history allows for the examination of dose–response trends in drawing causal inferences. However, study populations have been drawn from different geographic areas and cultures, which could have important consequences with respect to the interpretation and comparison of findings from different studies. For instance, the classification of long-term breast-feeding ranged from 24 months or longer in several studies in Europe and in North America (5,6,8,10,11,14,20,21,23,24) to 100 months or longer in studies conducted in Asia and in other non-Western societies (25–28). Such diversity in the definition of exposure and nonexposure may account for the large discrepancies in the percentages of control women with extensive durations of breast-feeding. As a result, the magnitude of risk estimates could be greatly affected, and direct comparison of findings from different studies is difficult.

Among case–control studies that have found a decreasing trend in breast cancer risk with increasing duration of breast-feeding among parous women, adjusted ORs for premenopausal women who have breast-fed for at least 12 months range from 0.21 to slightly below 1.0 compared with parous women who never breast-fed (8,12,23,25–27,29) (Tables 1–4). In the Cancer and Steroid Hormone Study, breast-feeding for 25 months or longer was associated with an OR of 0.67 (23) (Table 3). Several studies (4–6,10,11,21,24,28) have failed to confirm such response trends in drawing causal inferences. However, study populations have been drawn from different geographic areas and cultures, which could have important consequences with respect to the interpretation and comparison of findings from different studies. For instance, the classification of long-term breast-feeding ranged from 24 months or longer in several studies in Europe and in North America (5,6,8,10,11,14,20,21,23,24) to 100 months or longer in studies conducted in Asia and in other non-Western societies (25–28). Such diversity in the definition of exposure and nonexposure may account for the large discrepancies in the percentages of control women with extensive durations of breast-feeding. As a result, the magnitude of risk estimates could be greatly affected, and direct comparison of findings from different studies is difficult.

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<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Study period</th>
<th>No. of case patients</th>
<th>No. of control subjects</th>
<th>Measure of lactation</th>
<th>OR 95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byers et al., 1985 (13)</td>
<td>New York state</td>
<td>1957–1965</td>
<td>107</td>
<td>440, household sampling</td>
<td>Total duration, mo</td>
<td>0.78</td>
<td>Adjusted for age, parity, age at menarche, age at first birth, education level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Per 6 mo</td>
<td>0.60</td>
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<tr>
<td>McTiernan et al., 1986 (33)</td>
<td>Washington state</td>
<td>1981–1982</td>
<td>163</td>
<td>146, random-digit dialing</td>
<td>Total duration, mo</td>
<td>0.66</td>
<td>Adjusted for age, parity, age at first birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–3</td>
<td>0.35–1.20</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>4–12</td>
<td>0.24–0.87</td>
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<tr>
<td></td>
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<td>≥13</td>
<td>0.21–0.96</td>
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<tr>
<td>Siskind et al., 1989 (10)</td>
<td>Australia</td>
<td>1981–1985</td>
<td>136</td>
<td>397, electoral rolls</td>
<td>Ever Total duration, wk</td>
<td>0.93†</td>
<td>Adjusted for age, education level, place of birth, family history of breast cancer, age at first birth, age at menarche, benign breast disease</td>
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<td></td>
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<td>0</td>
<td>0.48–1.80</td>
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<td></td>
<td>1–13</td>
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<td>14–52</td>
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<td>&gt;104</td>
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<td>Duration per child, wk</td>
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<tr>
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<td>&lt;1</td>
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<td>≥39</td>
<td>0.46–3.20</td>
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<td>Yang et al., 1993 (14)</td>
<td>British Columbia</td>
<td>1988–1989</td>
<td>271</td>
<td>286, random-digit dialing</td>
<td>Breast-fed ≥2 mo</td>
<td>1.0</td>
<td>Adjusted for age at parity, age at first birth</td>
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<tr>
<td></td>
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<td>Breast-fed &lt;1 mo</td>
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<td>1.3–2.5</td>
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<tr>
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<td></td>
<td>Never breast-fed</td>
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<td></td>
<td></td>
<td>Total duration, mo</td>
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<td>2–3</td>
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<td>4–6</td>
<td>0.4–1.3</td>
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<td>7–12</td>
<td>0.5–1.7</td>
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<td>13–24</td>
<td>0.3–1.2</td>
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<td></td>
<td></td>
<td>≥25</td>
<td>0.2–1.2</td>
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<td>U.K. National Case–Control Study Group, 1993 (20)</td>
<td>Britain</td>
<td>1982–1985</td>
<td>755</td>
<td>755, random sampling from general practitioner attending the case patient</td>
<td>Total duration, mo</td>
<td>0.83</td>
<td>Adjusted for parity, age at menarche, family history of breast cancer, benign breast disease, age at first birth, oral contraceptive use</td>
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<tr>
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<td></td>
<td>1–3</td>
<td>0.83</td>
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<td>4–9</td>
<td>0.77</td>
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<td>10–15</td>
<td>0.53</td>
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<td>16–21</td>
<td>0.68</td>
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<td>≥22</td>
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<td>No. of children breast-fed</td>
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<td>2</td>
<td>0.62</td>
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<td></td>
<td></td>
<td></td>
<td>≥3</td>
<td>0.79</td>
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</tr>
<tr>
<td>Newcomb et al., 1994 (11)</td>
<td>United States</td>
<td>1989–1991</td>
<td>1180</td>
<td>2185, driver’s licenses or Medicare</td>
<td>Ever Total duration, mo</td>
<td>0.78</td>
<td>Adjusted for age at first birth, parity, benign breast disease, family history of breast cancer, body mass index, age at menarche</td>
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<tr>
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<td></td>
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<td>4–12</td>
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<td>&gt;24</td>
<td>0.50–0.87</td>
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<tr>
<td>Brinton et al., 1995 (15)</td>
<td>United States</td>
<td>1990–1992</td>
<td>1211</td>
<td>1120, random-digit dialing</td>
<td>Ever Total duration, mo</td>
<td>0.87</td>
<td>Adjusted for site, age, race, parity, age at first birth, oral contraceptive use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>0.8–1.2</td>
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<td></td>
<td>12–17</td>
<td>0.7–1.2</td>
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<td></td>
<td></td>
<td></td>
<td>≥18</td>
<td>0.6–1.1</td>
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<td>Duration per child, wk</td>
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<td>24–35</td>
<td>0.6–1.1</td>
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<td></td>
<td></td>
<td></td>
<td>≥36</td>
<td>0.6–1.1</td>
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</tr>
</tbody>
</table>

(Table continues)
population breast-fed for at least 12 months, only 17% of the women in the Nurses’ Health Study due to the low prevalence of prolonged breast-feeding; for in-

teresting in Western populations. A prolonged duration of breast-feeding is an important risk factor for breast cancer in some non-Western societies, also found a statistically significant reduction in breast cancer risk (OR = 0.72) among women with a prolonged duration (73–107 months) of breast-feeding (Table 1). Although it is difficult to speculate at this stage that long-term breast-feeding has substantial incremental benefit in all populations, there appears to be evidence for a protective influence on breast cancer risk among women in non-Western societies with extensive cumulative durations of breast-feeding. However, the potential for confounding by numerous factors, including low body weight and height, low socioeconomic status, poor nutritional status and possibly associated amenorrhea, or age at any pregnancy (30), cannot be ruled out.

### Average Duration of Breast-Feeding Per Child

Average months of breast-feeding per child has been used as a measure of breast-feeding history in a number of studies, based

0.86 for fewer than 3 months of breast-feeding, 1.02 for 406 months, 0.95 for 7–11 months, 0.86 for 12–23 months, and 1.11 for 24 months or longer (Table 5). The only prospective study (4) of breast-feeding to date found no association among either premenopausal or postmenopausal Norwegian women (Table 5), despite the fact that it included a high percentage of women with long durations of breast-feeding compared with studies in other Western populations.

The failure to detect an association in some studies may be due to the low prevalence of prolonged breast-feeding; for instance, only 17% of the women in the Nurses’ Health Study population breast-fed for at least 12 months (6). Thus, it is difficult in Western studies to evaluate the influence of the extensive durations of breast-feeding experienced by the majority of parous women in many non-Western populations. For example, in China, where more than half of the women breast-feed for at least 3 years, a 64% reduction in risk has been found among mainly premenopausal women who breast-fed for at least 10 years compared with women who never breast-fed (26). Breast-feeding for 3–5 years was associated with little decrease in risk. In this study, more than 15% of the parous control subjects had breast-fed for more than 6 years. Similarly, Yuan et al. (27) reported adjusted ORs of 0.35 and 0.37 after 73–108 months and greater than 109 total months of breast-feeding, respectively, among Chinese women (Table 3). Another large study (25) conducted in 10 countries, the majority of which are non-Western societies, also found a statistically significant reduction in breast cancer risk (OR = 0.72) among women with a prolonged duration (73–107 months) of breast-feeding (Table 1). Although it is difficult to speculate at this stage that long-term breast-feeding has substantial incremental benefit in all populations, there appears to be evidence for a protective influence on breast cancer risk among women in non-Western societies with extensive cumulative durations of breast-feeding. However, the potential for confounding by numerous factors, including low body weight and height, low socioeconomic status, poor nutritional status and possibly associated amenorrhea, or age at any pregnancy (30), cannot be ruled out.

### Average Duration of Breast-Feeding Per Child

Average months of breast-feeding per child has been used as a measure of breast-feeding history in a number of studies, based

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**Table 4 (continued), Population-based, case–control studies of breast-feeding and breast cancer among premenopausal parous women**

<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Study period</th>
<th>No. of case patients</th>
<th>No. of control subjects</th>
<th>Measure of lactation</th>
<th>OR  95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romieu et al., 1996 (12)</td>
<td>Mexico</td>
<td>1990–1992</td>
<td>112</td>
<td>513, household sampling</td>
<td>Total duration, mo</td>
<td>0.58</td>
<td>0.30–1.11</td>
</tr>
<tr>
<td>Enger et al., 1997 (22)</td>
<td>Los Angeles, CA</td>
<td>1983–1988</td>
<td>452</td>
<td>452, neighborhood</td>
<td>Total duration, mo</td>
<td>0.93</td>
<td>0.69–1.26</td>
</tr>
<tr>
<td>Freudenheim et al., 1997 (17)</td>
<td>New York state</td>
<td>1986–1991</td>
<td>253</td>
<td>266, driver’s licenses or Health Care Financing Agency</td>
<td>Total duration, mo</td>
<td>0.80</td>
<td>0.54–1.17</td>
</tr>
<tr>
<td>Gilliland et al., 1998 (29)</td>
<td>New Mexico</td>
<td>1992–1994</td>
<td>231</td>
<td>326, random-digit dialing</td>
<td>Total duration, mo</td>
<td>0.74</td>
<td>0.39–1.42</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval.
†Studies in which reference groups include nulliparous women.
given circumstances such as returning to work are among other reasons while breast infections, cracked nipples, and nonmedical cir-

cumstances as returning to work are among other reasons given (13,15).

Byers et al. (13) reported a twofold increase in risk of breast cancer among premenopausal women who cited insufficient milk as the reason for having stopped breast-feeding compared with women who cited all other reasons combined. While adjusting for insufficient milk eliminated the increased risk observed among women in the category of shortest cumulative breast-feeding duration, it did not markedly reduce the overall strength of the inverse association between breast-feeding duration and breast cancer. These findings suggest that there may still be a protective effect of breast-feeding independent of those factors that lead women to cease breast-feeding because of a perception of insufficient milk (13). A population-based, case–control study conducted in British Columbia (14) reported significantly elevated risks of breast cancer among premenopausal women who tried to breast-feed for more than 1 month but were unsuccessful because of either “insufficient milk” (OR = 3.1) or other reasons (OR = 3.0) compared with women who breast-fed for at least 2 months. In both studies (13,14), the association between breast cancer and “insufficient milk” was less pronounced among postmenopausal women. In a number of other studies (10,11,15,17), however, there was no evidence that women who reported stopping breast-feeding because of a perception

on the hypothesis that a higher average duration of breast-feeding per child may confer greater protection against breast cancer. However, four studies (4,7,10,25) have failed to show any significant association between breast cancer risk and this measure of breast-feeding, while only one study (15) reported a statistically significant trend of decreasing risk with increasing average length of breast-feeding per child (Table 4).

### Reasons for Cessation of Breast-Feeding

It has been hypothesized that the apparently protective effect of breast-feeding against breast cancer may be due to an elevated risk among women who either have difficulties in starting breast-feeding or who discontinue breast-feeding after a short interval (13), perhaps as a result of abnormalities in estrogen levels or other endocrine or psychosocial factors. A common reason for stopping breast-feeding, particularly among women who cease within the first month, is “insufficient milk supply,” while breast infections, cracked nipples, and nonmedical circumstances such as returning to work are among other reasons given (13,15).

<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Period of follow-up</th>
<th>Population</th>
<th>No. of case patients</th>
<th>Measure of lactation</th>
<th>RR</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kvale and Heuch, 1987 (4)</td>
<td>Norway</td>
<td>1961–1980</td>
<td>50,274 parous women</td>
<td>1136</td>
<td>Total duration, mo: per 6 mo</td>
<td>1.01</td>
<td>0.97–1.05</td>
<td>Adjusted for age, place of residence, parity, age at first birth</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Duration per child, mo: per 2 mo</td>
<td>1.01</td>
<td>0.98–1.05</td>
<td></td>
</tr>
<tr>
<td>London et al., 1990 (5)</td>
<td>United States</td>
<td>1976–1986</td>
<td>89,413 parous nurses</td>
<td>1262</td>
<td>Total duration, mo</td>
<td>0.94</td>
<td>0.82–1.06</td>
<td>Adjusted for age, parity, age at first birth, age at menarche, family history of breast cancer, benign breast disease, oral contraceptives, menopausal status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;7</td>
<td>0.83</td>
<td>0.67–1.03</td>
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<td></td>
<td></td>
<td></td>
<td>7–11</td>
<td>0.90</td>
<td>0.74–1.09</td>
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<td></td>
<td></td>
<td>12–23</td>
<td>0.95</td>
<td>0.73–1.23</td>
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<td></td>
<td></td>
<td>≥24</td>
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<tr>
<td>Michels et al., 1996 (6)</td>
<td>United States</td>
<td>1986–1992</td>
<td>89,887 parous nurses</td>
<td>1459</td>
<td>Ever</td>
<td>0.93</td>
<td>0.83–1.03</td>
<td>Adjusted for age, parity, age at first birth, age at menarche, family history of breast cancer, benign breast disease, oral contraceptives, body mass index, age at menopause, postmenopausal hormone use, alcohol intake, vitamin A, physical activity</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Total duration, mo</td>
<td>0.86</td>
<td>0.75–0.99</td>
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<td></td>
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<td>&lt;3</td>
<td>1.02</td>
<td>0.87–1.21</td>
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<td>4–6</td>
<td>0.95</td>
<td>0.79–1.14</td>
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<td></td>
<td>7–11</td>
<td>0.86</td>
<td>0.72–1.03</td>
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<td>12–23</td>
<td>1.11</td>
<td>0.90–1.38</td>
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<td></td>
<td></td>
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<td></td>
<td>≥24</td>
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</tr>
</tbody>
</table>

*RR = relative risk; CI = confidence interval.

<table>
<thead>
<tr>
<th>Authors, year (reference No.)</th>
<th>Location</th>
<th>Period of follow-up</th>
<th>Population</th>
<th>No. of case patients</th>
<th>Measure of lactation</th>
<th>RR</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>London et al., 1990 (5)</td>
<td>United States</td>
<td>1976–1986</td>
<td>89,413 parous nurses, age 30–55 y</td>
<td>624</td>
<td>Total duration, mo</td>
<td>1.00</td>
<td>0.83–1.20</td>
<td>Adjusted for age, parity, age at first birth, age at menarche, family history of breast cancer, benign breast disease, oral contraceptives</td>
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<td></td>
<td>&lt;7</td>
<td>0.85</td>
<td>0.63–1.14</td>
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<td>0.90</td>
<td>0.69–1.18</td>
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<td>12–23</td>
<td>1.06</td>
<td>0.75–1.50</td>
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<td>≥24</td>
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</tr>
<tr>
<td>Michels et al., 1996 (6)</td>
<td>United States</td>
<td>1986–1992</td>
<td>89,887 parous nurses</td>
<td>256</td>
<td>Ever</td>
<td>1.14</td>
<td>0.87–1.50</td>
<td>Adjusted for age, parity, age at first birth, age at menarche, family history of breast cancer, benign breast disease, oral contraceptives, body mass index, alcohol, vitamin A, physical activity</td>
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<td></td>
<td></td>
<td></td>
<td>Total duration, mo</td>
<td>1.10</td>
<td>0.77–1.56</td>
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<td>&lt;3</td>
<td>1.12</td>
<td>0.73–1.71</td>
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<td>4–6</td>
<td>1.21</td>
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<td>1.31</td>
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<td>12–23</td>
<td>0.90</td>
<td>0.53–1.54</td>
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<td>≥24</td>
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</tbody>
</table>

*RR = relative risk; CI = confidence interval.
of insufficient milk were at markedly elevated risk of breast cancer.

It has also been suggested that breast cancer risk may be increased among women who do not breast-feed as a result of exposure to lactation suppressants. In a number of studies (11,15), a substantial proportion of women, often as many as 44%, reported having been given treatment to induce cessation of lactation after one or more births. However, the use of hormonal medication to suppress breast-feeding has not been consistently linked with an increased risk of breast cancer, either before or after adjustment for duration of breast-feeding (11,14,15,17,20,22,25).

Estrogen Receptor Status

Breast tumors that are estrogen receptor (ER) positive have been shown to be slower growing tumors, and patients with these types of tumors have fewer recurrences, longer survival, and seem to respond better to therapy than patients with ER-negative tumors (31). It has been suggested that the risk factor profiles for these breast tumor subtypes may differ, but there are limited data with respect to whether the ER status (ER positive versus ER negative) of breast tumors, as well as the actual concentration of ER protein, varies according to breast-feeding history. In an intracase analysis among parous women (32), those with ER-positive breast tumors were more likely than ER-negative cases to have breast-fed at least one child, although the results were of borderline significance. After adjustment for several known breast cancer risk factors, women who ever breast-fed were three times more likely than those who never breast-fed to have an ER-positive tumor as opposed to an ER-negative tumor (OR = 3.4; 95% CI = 1.3–8.7); similarly, a history of ever having breast-fed was significantly associated with the ER concentration of the tumor. In their case–control analysis, Hildreth et al. (32) showed that a history of ever having breast-fed was not associated with an increased risk for ER-positive breast tumors, while the association with ER-negative tumors was, if anything, inverse.

Another case–control study (33), which compared risk factors for ER-rich and ER-poor breast cancers, reported an inverse association between cumulative duration of breast-feeding and both ER-positive and ER-negative tumors. In particular, women who breast-fed for longer than 13 cumulative months had a decreased OR of 0.43 (95% CI = 0.20–0.95) for ER-positive breast cancer and 0.71 (95% CI = 0.31–1.6) for ER-negative breast cancer. To date, a plausible biologic mechanism for differential influences of breast-feeding on the ER status of a tumor has not been put forth, and the findings should be interpreted with caution until they are confirmed in other studies.

Ethnic Differences

There is striking geographic variation in breast cancer incidence rates, with the highest rates seen in North America and in Europe and the lowest rates in Asia and in Africa. While a number of studies (7,25–28) have evaluated breast cancer risk factors, including breast-feeding, among Asian and African populations, the epidemiologic data with respect to the potential association between breast-feeding and breast cancer risk among various racial and ethnic groups within the United States are substantially more limited.

Studies of migrants suggest that environmental factors are largely responsible for the international variation in breast cancer incidence rates. Patterns among migrants to the United States show that women born in countries with low breast cancer rates, such as China and Japan, experience an increase in rates above those of their country of birth but still below U.S. rates (2). Wu et al. (34) conducted a study among Asian-Americans, both American-born and migrants, to investigate if breast-feeding had a protective effect on breast cancer risk in this population. No statistically significant trend of decreasing breast cancer risk with increasing duration of breast-feeding was observed.

Mayberry et al. (35) conducted a case–control study of African-American and Caucasian women to determine if there were different breast cancer risk profiles between the two races. The multivariate analysis of breast-feeding among parous women of both races indicated that increasing total months of breast-feeding was associated with decreased breast cancer risk among both African-Americans and Caucasians. However, the magnitude of the protective effect was larger among African-American than among Caucasian women, with adjusted ORs of 0.45 and 0.76, respectively, for women who breast-fed for 16 months or longer compared with those who breast-fed for fewer than 4 months.

Similarly, a study of risk factors for breast cancer among Hispanic and non-Hispanic white women found that the protective effect of longer cumulative duration of breast-feeding varied between these two groups (29). Non-Hispanic white women who breast-fed for longer than 12 months had a statistically significant reduced OR of 0.58, while Hispanic women who breast-fed the same length of time had an OR of 0.78 that was not statistically significant.

Menopausal Status

Examination of the pattern of breast cancer risk among parous women by menopausal status has produced inconsistent results. However, in most studies (7,8,10–14,17,18,22–26,36), any apparently protective effect of breast-feeding was stronger among, or confined to, premenopausal women, despite differences in the classification of menopausal status. Adjusted ORs for premenopausal parous women who have ever breast-fed compared with those who never breast-fed ranged from 0.58 to 1.14 (Tables 2, 4, and 6). The findings of the United Kingdom National Case–Control Study (20), as well as a number of other investigations (11,14,22,36), indicate a statistically significantly decreasing risk for breast cancer among young women with increasing duration of breast-feeding or with number of children breast-fed. If, indeed, there is an inverse association between breast-feeding and breast cancer that is confined to young women, the small number of premenopausal women in the prospective study of Kvale and Heuch (4) may have reduced the statistical power to detect a modest association.

Few investigations have reported a statistically significant inverse association between breast-feeding and postmenopausal breast cancer. One case–control study in Los Angeles (16) found that postmenopausal women who breast-fed for at least 16 months had a reduced risk of breast cancer (OR = 0.73; 95% CI = 0.52–1.01) relative to postmenopausal women who never breast-fed, suggesting that a protective effect of breast-feeding may persist into the postmenopausal years. However, the collective evidence for an inverse relation between breast-feeding and postmenopausal breast cancer is limited, with numerous studies (5,7,8,10,11,13,14,25,36) reporting no such association. It is possible that postmenopausal women may have more dif-
ficulty recalling past breast-feeding habits, thereby attenuating any association with breast cancer risk.

**BIOLOGIC MECHANISMS**

The biologic basis for an inverse association between breast-feeding and breast cancer risk has not been adequately elucidated, although several mechanisms have been postulated. One hypothesis is that lactation causes long-term endogenous hormonal changes, possibly reduced estrogen, and increased prolactin production, which may decrease a woman’s cumulative exposure to estrogen, thereby inhibiting the initiation or growth of breast cancer cells (13,37). This effect, if indeed it were real, would be more pronounced among premenopausal women. Another proposed mechanism is estrogen synthesis by the lactating breast and removal of estrogens through breast fluid. Breast fluid estrogen levels, independent of serum estrogen levels, were found to be lower in premenopausal parous women who were breast-feeding when compared with levels among parous women who did not breast-feed or among nulliparous women. In fact, breast fluid estrogen levels in the women who breast-fed appeared to gradually increase over a period of several years since last breast-feeding to reach levels found in nulliparous women (38). Again, this underlying mechanism could explain why an apparently protective effect of breast-feeding would be stronger among premenopausal women.

It has also been suggested that a protective effect of breast-feeding on breast cancer risk may be attributed to the excretion of carcinogetic agents from the breast ductal tissue through breast-feeding (39). For instance, there is some evidence that the level of a potential carcinogen, cholesterol-β-epoxide, is lower in the breast fluid of women during and up to 2 years after breast-feeding (40). However, it would be expected that these carcinogens would, in turn, affect the child being breast-fed, an association that has not been reported in epidemiologic studies.

Milk from unsuckled breasts has been shown to have a slightly higher pH in comparison to that from suckled breasts, which remains acidic during breast-feeding (41). Studies (39) have shown that epithelial cells in an alkaline environment undergo preneoplastic alterations, such as hyperplasia, cell atypia, and increased mitotic activity at a more frequent rate.

Alternatively, physical changes in the epithelial cells of the mammary ducts, including extended terminal differentiation induced by lactation, may directly affect risk by making the breast tissue more resistant to carcinogenesis (42). The lactational period of the mammary gland is characterized by the presence of lobule type 4, a lobular structure that represents maximal development and differentiation and which is not present among nulliparous women (42).

Finally, the effect of breast-feeding may be attributed to its role in delaying the re-establishment of ovulation (43), although the relation between cumulative number of ovulatory cycles and breast cancer risk remains controversial. Moreover, it has not been shown that breast cancer risk relates more strongly to duration of exclusive breast-feeding (until supplementation) than to duration of total breast-feeding (15), which would be expected if this were the underlying mechanism.

**DISCUSSION**

The collective epidemiologic evidence to date, while certainly not conclusive, is compatible with a protective effect of prolonged breast-feeding against breast cancer risk among premenopausal women. However, the effect, even if it were real, appears to be relatively weak and limited to a minority of women at risk of breast cancer. It is not clear why breast-feeding should reduce the risk of breast cancer at the biologic level, nor is there a convincing etiologic explanation for why this association should be restricted to premenopausal women.

Future research should address the possibility that breast-feeding delays the occurrence of breast cancer among premenopausal women and that the postponed breast cancer cases occur postmenopausally and mask a similarly generated protective effect among postmenopausal women. Moreover, if, in fact, an inverse association does exist between breast-feeding and breast cancer, it may be important to examine the joint effect on breast cancer risk of breast-feeding on the one hand and family history of breast cancer or genetic susceptibility on the other. Finally, it should be investigated whether breast-feeding from smaller breasts, representing smaller mammary gland mass, may be more protective.

Clearly, assessment of the effects of breast-feeding on breast cancer risk is complicated, and most studies have limited data on breast-feeding histories, including reasons for starting or discontinuing breast-feeding and the manner of introduction of supplemental formula. This may be of particular importance when comparing results from populations with different breast-feeding practices. For instance, in non-Western populations in which extended breast-feeding is the norm and there are relatively few women who never breast-feed, a reference group of parous women who have never breast-fed is likely to have different characteristics compared with the same reference group from a population in which breast-feeding is less common (17).

Breast-feeding is a potentially modifiable behavior, and an understanding of its contribution to the etiology of breast cancer is clearly a major research and public health priority. However, breast-feeding may not be a practical intervention for women in the United States and in other Western societies if, in fact, a protective effect of breast-feeding on breast cancer risk is apparent only after prolonged periods of breast-feeding. The choice to breast-feed is primarily determined by socioeconomic considerations and concerns for the health of the child, and only if there were convincing evidence for a strong effect of breast-feeding against breast cancer risk would a public health recommendation of breast-feeding for the benefit of the mother be justified.

**REFERENCES**


NOTES

Supported in part by Public Health Service grant CA68485 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

We thank Johnson Eyadiel for his help with literature research.

Manuscript received March 28, 1999; revised November 29, 1999; accepted December 7, 1999.