ABSTRACT. Objective. To conduct a systematic review to evaluate the evidence for the effect of breastfeeding on the risk of developing childhood leukemia.

Review Methods. We sought studies providing data regarding the association of breastfeeding and occurrence of childhood leukemia. Studies were identified by using Medline, HHS Blueprint for Action on Breastfeeding, US Department of Health and Human Services Office on Women’s Health, Cochrane Database of Systematic Reviews, National Centre for Reviews and Dissemination, reference lists, and national experts. Methodologic quality was evaluated for each study by using criteria from the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination.

Results. We reviewed 111 citations to identify 32 potentially eligible full-text articles. Of the 10 studies reviewed, only 4 were sufficient to provide at least fair-quality evidence regarding the association between maternal breastfeeding and childhood leukemia. Studies conflicted regarding the protective effect of breastfeeding on childhood leukemia. In the 2 largest and highest quality studies, breastfeeding was associated with a significant risk reduction in one study with longer breastfeeding duration, reflecting greater protection, and a nonsignificant but suggestive difference in the other. Taken together, half of the studies associated breastfeeding with a lower risk of acute lymphocytic leukemia.

Conclusions. There are few high-quality studies that examine the potential for a protective effect of breastfeeding for childhood leukemia. Furthermore, the few studies that exist disagree regarding the association. It is estimated that the United States spends $1.4 billion annually on the treatment of childhood leukemia. Patients, clinicians, and policy makers do not have the data that they need to make decisions regarding this important potential preventive measure. Pediatrics 2005;116:e724–e731. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0636; breastfeeding, human milk, leukemia, case-control studies, childhood malignancy, evidence review, evidence-based medicine, risk assessment, human, infant, female, pregnancy.

ABBREVIATIONS. ALL, acute lymphocytic leukemia; SES, socioeconomic status; OR, odds ratio; CI, confidence interval; UKCCS, United Kingdom Childhood Cancer Study; AML, acute myelogenous leukemia.

Leukemia is the most common malignancy in childhood, with an average annual incidence of 3.8 to 4.8 cases per 100 000 children aged 0 to 14 years.1 Leukemia accounts for 30% of all childhood malignancies, with 75% being diagnosed as acute lymphocytic leukemia (ALL). The incidence is slightly higher among males than females and 50% higher among white children than among black children.2 Although the etiology of childhood leukemia has been studied for a half of a century, causal factors associated with leukemia are largely unidentified. Certain conditions such as Down syndrome, other genetic abnormalities, and ionizing radiation exposures are thought to explain a small percentage of cases of leukemia.1,3

The infectious etiology of leukemia continues to be explored, with potential for bacterial and viral sources. After viruses were identified as the cause of some leukemias in animals,4 1 popular etiologic hypothesis for human leukemia, especially that occurring in childhood, has been the result of a viral infection. Two additional observations suggest that immunologic factors may play a role in the development of childhood leukemia. The first factor originates from epidemiologic observations of geographic clusters of leukemia cases, suggesting that a common exposure (such as infectious exposure) may play a role.5 The second factor arises from observations that children with leukemia are less commonly found to be exposed very early in infancy to common infections compared with children without leukemia, promoting an aberrant response to future exposures.6 Because breastfeeding is noted for providing the newborn with passive immunity, protecting from some early infections, investigators have hypothesized that breastfeeding could reduce the risk of childhood leukemia.7 This review was conducted for the US Department of Health and Human Services Office on Women’s Health to evaluate the evidence for the effect of breastfeeding on the risk of developing childhood leukemia.

METHODS

Searching
Pertinent articles were identified from a larger literature search performed by the Office on Women’s Health. Briefly, it included a Medline search from 1990 through March 2004, articles identified from the HHS Blueprint for Action on Breastfeeding,5 and additional
articles identified from experts at the Breastfeeding Experts Panel Meeting in 2003. Additionally, 1 of the investigators (C.D.M.) and a medical librarian searched Medline from 1990 to January 4, 2004, by using search terms “leukemia,” “breastfeeding,” or “human milk” to identify additional articles.

Selection
We sought studies providing data regarding the association of breastfeeding and occurrence of childhood leukemia. Inclusion criteria were established by the Office on Women’s Health. For inclusion, a study must have been in full text, been published after 1990, contained >100 participants, had concurrent comparison groups, been conducted in a developed country, and been published in the English language. Two investigators (J.-M.G. and C.D.M.) independently reviewed all titles and abstracts for inclusion; there were no disagreements on inclusion. Full-text articles were then reviewed for eligibility. A study was considered relevant if it met all inclusion criteria and contained data for both breastfeeding exposure and outcome of childhood ALL or all childhood leukemias.

Validity Assessment
Three investigators independently rated study quality by using criteria from the US Preventive Services Task Force9 and the National Health Service Centre for Reviews and Dissemination.9 Studies received a poor rating if the cases were not assessed reliably (potentially unreliable method for diagnosing disease), if the groups assembled were not comparable, if there was considerable attrition or differences in nonrespondents between cases and controls, or if there was not adequate consideration given to confounding. Studies were rated as poor if their case definition included infants diagnosed under the age of 6 months and did not allow for separate analysis for children older than 6 months of age, because the time from exposure to breastfeeding and diagnosis of leukemia is crucial for biological plausibility of association. Regarding accurate ascertainment of cases and controls, studies were examined for the response rate within first-choice controls and were rated as poor if there was potentially biased ascertainment of second- or higher-order controls. Additionally, studies that used hospital or nonconcurrent controls were considered inferior to studies that used population-based controls. Regarding consideration of confounders, examining the role of socioeconomic status (SES) was considered important, because it is associated with both leukemia and the likelihood of breastfeeding.

Data Abstraction
From each study, 3 reviewers independently abstracted study design, setting, demographics, leukemia definition, breastfeeding initiation and duration methods of assessment and results, and methods for assessing or adjusting for confounders.

RESULTS
Quality Assessment and Study Characteristics
We identified 111 citations and reviewed 32 full-text articles. Ten studies10–19 met all eligibility criteria and were reviewed for study quality to identify 2 good-quality case-control studies,10,17 2 fair-quality studies,11,16 and 6 poor-quality studies.12–15,18,19 Three case-control studies met all inclusion criteria except that they were conducted in developing countries: Russia, United Arab Emirates, and China.20–22 Table 1 describes the population and study characteristics of all case-control studies of breastfeeding and childhood leukemia. The presented results focus on details and findings of the 2 good-quality studies,10,17 comparisons to the 2 fair-quality studies,11,16 factors that distinguish them from studies rated as “poor” in quality, and implications for future research. The descriptions of the studies included in this systematic review are shown in Table 1. Of the 10 studies, 6 were conducted in European countries. All studies but 1 focused solely on childhood leukemia. The majority included <1000 cases. Notably, 6 of the studies explicitly sought to characterize the relationship between breastfeeding and leukemia as the primary objective, whereas the others included breastfeeding measures from the perspective of measuring broader characteristics of the immune system and early infections in the etiology.

The quality ratings of the studies are shown in Table 1. The 3 reviewers varied minimally in their ratings: at least 2 reviewers were in complete agreement 100% of the time, and all 3 reviewers were in agreement after discussion. Of the 10 studies, 2 received a consensus rating of “good,” 2 “fair,” and 6 “poor.” Two of the largest studies with the largest number of cases included, from the United Kingdom Childhood Cancer Study (UKCCS) and the Children’s Cancer Group, were both rated as good.10,17 Both studies satisfactorily met all criteria for accurate assessment of cases, response rate of cases and controls, and accurate measurement of exposure. The 2 studies rated as fair were smaller in size; cases were assembled from national or regional cancer registries in New Zealand and Quebec, Canada.11,13 Both merited fair ratings because each included infants diagnosed with ALL at <1 year of age without subanalysis. In all but 2 of the 10 case-control studies,12,15 there was a potentially important difference in response rate between cases and all controls or first-choice controls as noted. Both articles that were rated as good, however, attempted to identify the degree of response bias associated with replacement controls and adjusted for resulting bias in the analysis.

Of the 6 studies rated as poor, 4 had unclear or biased selection of cases or controls. These studies used nonconcurrent controls,18 2 used hospital-based controls,15,19 and another had an unclear case or control definition including only fatal leukemia.14 Two studies12,16 failed to account for potential important confounding in their analysis. Two of these articles failed to record how mothers were asked about breastfeeding. Because of the potential bias introduced by selection of cases and controls, the lack of control of confounding, and the potential misclassification introduced by the lack of specificity in exposure definition, these studies will not be discussed further.

Study Findings
The 2 good-quality studies present conflicting results regarding the association between breastfeeding and leukemia. As 1 of the 2 studies rated as good, the Children’s Cancer Group17 included 1914 children with ALL as cases from the United States, Canada, and Australia; controls were recruited by random-digit dialing. These patients were participating in cooperative cancer treatment trials at cancer centers. After adjustment for maternal race, education, and family income, breastfeeding was associated with a significantly reduced risk of ALL (odds ratio [OR]: 0.80; 95% confidence interval [CI]: 0.69–0.93). When considering duration, there was a graded effect, with breastfeeding ≤6 months conferring some-
<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Years of study</th>
<th>Study size</th>
<th>Study intent</th>
<th>Country</th>
<th>Population</th>
<th>Ages included</th>
<th>Important exclusions</th>
<th>Cases included</th>
<th>Confirmation of case diagnosis</th>
<th>Controls</th>
<th>Case-control matching</th>
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<tbody>
<tr>
<td>Beral et al (2001)</td>
<td>Good</td>
<td>1992–1996 (England and Wales) and 1991–1994 (Scotland)</td>
<td>1627 leukemia cases, 6964 controls (7629 eligible)</td>
<td>Study of all childhood cancers; lymphoid cancers were selected to look for an association between any BF and childhood leukemia or lymphoma but not other cancers</td>
<td>United Kingdom (UKCCS)</td>
<td>Population-based case-control study of all children (aged 0–14 y) diagnosed with cancer in England, Wales, and Scotland; controls from health boards or family health services authorities</td>
<td>0–14 y at diagnosis</td>
<td>Excluded diagnosis &lt;1 y and if BF history not reported by biological mother</td>
<td>Diagnosed with lymphatic malignancy (including AML, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, and ALL), analyzed separately</td>
<td>Histopathology confirmed, also identified for subtype</td>
<td>2 controls for every case randomly selected from family health services authorities and health boards rosters</td>
<td>Matched on gender, month, year of birth, and region of residence</td>
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<tr>
<td>Shu et al (1999)</td>
<td>Good</td>
<td>1989–1993</td>
<td>1914 (92%) of 2079 patients with ALL; 1986 (77%) matched patients</td>
<td>To test whether BF reduces the risk of childhood leukemia</td>
<td>118 affiliated institutions in Canada, US (50% of pediatric cancer in US), and Australia (Children’s Cancer Group)</td>
<td>ALL diagnosed before age of 15 y within registry of clinical trials</td>
<td>&lt;15 y</td>
<td>All cases diagnosed before 1 y of age</td>
<td>All eligible identified from cooperative clinical trials group</td>
<td>Cases confirmed by histopathology; also identified by subtype</td>
<td>Random-digit dialing, matched for age at diagnosis (within 25% of age), area code, race (white versus non-white); all considered cases more likely nonwhite and less educated than controls, adjusted for maternal age, education, and income, birth weight and birth order, and number of siblings</td>
<td>Controlled for SES by maternal education, race, and family income because they were found to be confounding</td>
</tr>
<tr>
<td>Dockerty et al (1999)*</td>
<td>Fair</td>
<td>1990–1993</td>
<td>121 (of 131) cases, 121 NZ resident controls, plus 303 controls with solid tumors</td>
<td>To examine the viral and late infection exposure etiology for childhood leukemia</td>
<td>Nationwide case-control study in NZ</td>
<td>Newly diagnosed leukemia in NZ-born residents; controls randomly selected from national birth records; children with solid tumors were also used as controls</td>
<td>0–14 y at diagnosis</td>
<td>Non-NZ residents</td>
<td>Newly diagnosed with childhood leukemia</td>
<td>Reviewed histopathology</td>
<td>Randomly selected from NZ-born and resident childhood population using national birth records, registered in same quarter of same year as case; solid-tumor cases were also used as controls</td>
<td>Matched on gender and age (within quarter of year of birth)</td>
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<td>Table 1: Continued</td>
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| Participation | 92% of cases; 74% of first-choice controls |
|BF assessment | Maternal interviews in homes from 1991–1995 with standard questionnaire (adapted from McKinney) |
|Association | ALL (not adjusted): ever BF, OR: 1.10 (95% CI: 0.47–2.56). Age of child at last BF: 2 days–6 mo, OR: 1.35 (95% CI: 0.56–3.27); >6–12 mo, OR: 0.88 (95% CI: 0.35–2.25); >12 mo, OR: 0.73 (95% CI: 0.27–1.98); test of trend: increased risk of leukemia with increasing BF duration; lower risk with lower BF duration |
|Comments | Included 0–1 y of age, significant difference in number of prior residences (more in cases) probably reflects replacement in controls |

**Rosenbaum et al** (2000)
- **Quality**: Fair
- **Years of study**: 1980–1991
- **Study size**: 80% of 400 cases
- **Study intent**: To examine the role of early child care on childhood ALL
- **Country**: US: hospitals in New York, cases identified from hospital registries and pediatric hematology/oncology records; 88% reported to New York state cancer registry
- **Population**: Cases from referral centers, controls randomly selected from live births in 31 counties served by the 4 referral centers
- **Ages included**: <15 y
- **Important exclusions**: Adopted children, physician refusal
- **Cases included**: Cases diagnosed with ALL in 4 treatment (referral) centers for 31-county area
- **Controls**: Controls randomly selected from birth certificates
- **Case-control matching**: Matched for gender, race, and birth year
- **Participation**: 71% of cases; 55% of controls
- **Association**: BF at birth: 47% cases, 51% controls (OR: 1.20 NS); mean BF duration: cases, 25.6 wk (SD: 21 wk); controls, 27.5 wk (SD: 27 wk)
- **Comments**: Poor participation of cases and controls; under1yo fa g eincluded; hospital based; BF measured in weeks but not used in analysis; demonstrated bias with regard to race and maternal education

**Hardell and Dreifaldt** (2001)
- **Quality**: Poor
- **Years of study**: 1988–1991
- **Study size**: 204 ALL; 202 controls
- **Study intent**: To evaluate childhood cancer in relation to BF duration
- **Country**: Nationwide case-control study in Sweden
- **Population**: Population-based cases from national cancer registry
- **Ages included**: 0–14 y at diagnosis
- **Important exclusions**: None
- **Cases included**: Recorded in cancer registry as cancer
- **Controls**: Children entered in Swedish Birth Register adjacent to cases
- **Case-control matching**: Matched on gender and age
- **Participation**: NA: 84% of data found in medical records
- **BF assessment**: BF duration recorded from regular medical-examination records
- **Association**: ALL: adjusted OR (gestational age, birth order, birth weight, maternal age, and smoking): 1–<6 mo, OR: 1.0 (95% CI: 0.5–2.0); >6–12 mo, OR: 0.9 (95% CI: 0.5–1.8)
- **Comments**: Included up to 1 y of age, although excluding children under 1 y of age yielded similar results

**Infante-Rivard et al** (2000)
- **Quality**: Poor
- **Years of study**: 1989–1995
- **Study size**: 491 (96%) of 510 eligible cases; 493 (84%) of 588 eligible controls (65% first-choice controls)
- **Study intent**: To assess the relationship between childhood ALL and prenatal and postnatal markers of infection and BF
- **Country**: Canada
- **Population**: Cases identified through tertiary care centers: hospitals, province discharge files, lists from hematology-oncology labs, and pediatric center (they consider this to be equivalent to a population-based study because of universal insurance)
- **Ages included**: 0–10 y at diagnosis
- **Important exclusions**: Adopted children or those in foster families; families not speaking either French or English; those not residents of Canada; neither parent available for interview; 2 regions without cases excluded
- **Cases included**: Diagnosed ALL, defined by ICD-9 code 204.0
- **Confirmation of case diagnosis**: No
- **Controls**: 1:1, matched on age within 24 mo, gender, and region of residence at diagnosis; a list of 10 potential controls randomly chosen from list according to expected distribution of cases
- **Case-control matching**: Matched on age (±24 mo), gender, and region of residence at the time of diagnosis
- **Participation**: 96% of cases; 84% of controls
- **BF assessment**: Telephone interview using structured questionnaire
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<th>Study</th>
<th>Quality</th>
<th>Years of study</th>
<th>Study size</th>
<th>Study intent</th>
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<th>Cases included</th>
<th>Confirmation of case diagnosis</th>
<th>Controls</th>
<th>Case-control matching</th>
<th>Participation</th>
<th>BF assessment</th>
<th>Association</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancashire et al\textsuperscript{14} (2003)</td>
<td>Poor</td>
<td>1972–1981</td>
<td>3376 parents of 4288 deceased cases, with matched controls</td>
<td>To use old study data to examine BF effect on risk of leukemia deaths</td>
<td>United Kingdom: Oxford Survey of Childhood Cancers related to UKCCS but separate data</td>
<td>England, Wales, and Scotland, 1953–1984 deaths from cancer before the child’s 16th birthday</td>
<td>0–14 y</td>
<td>Interviewed parents of children dying before the age of 16 y</td>
<td>56% of eligible families interviewed</td>
<td>Consistency with medical records only</td>
<td>Selected from local health authority in which child died; 54% first-choice controls</td>
<td>6 controls per case matched for gender and date of birth</td>
<td>Initial case participation was 56% (63% of those approached), but 11% more were dropped because of no matching control; control participation was 48% of first choice, 16% of second choice, 25% of third through sixth choice, and 11% none</td>
<td>No association for ALL, other leukemia, or total</td>
<td>Decreased risk seen; dose response with BF: 1 mo of BF, no reduced risk; 6 mo, reduced risk of ALL and AML (minor discrepancies in numbers in text)</td>
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<tr>
<td>Petridou et al\textsuperscript{15} (1997)</td>
<td>Poor</td>
<td>1993–1994</td>
<td>136 ALL</td>
<td>To ascertain risk factors for childhood leukemia in Greece</td>
<td>Greece, nationwide</td>
<td>Cases reported by a national network of childhood hematologists/oncologists, believed to be complete for the country</td>
<td>0–14 y</td>
<td>Any children treated abroad or not of Greek nationality</td>
<td>Diagnosed with leukemia</td>
<td>Bone marrow–confirmed cases</td>
<td>Matched for gender, age (≥6 mo &lt;3 y; ≥12 mo for children &gt;3 y), and residence</td>
<td>100% of cases; 96% of controls</td>
<td>No details on the questions for BF in interviewer-administered questionnaire</td>
<td>BF yes/no: adjusted OR: 0.85 (95% CI: 0.52–1.41); ( P = .54 )</td>
<td>No association for ALL, other leukemia, or total</td>
<td>Decreased risk seen; dose response with BF: 1 mo of BF, no reduced risk; &gt;6 mo, reduced risk of ALL and AML (minor discrepancies in numbers in text)</td>
</tr>
<tr>
<td>Schuz et al\textsuperscript{18} (1999)</td>
<td>Poor</td>
<td>1980–1994</td>
<td>1184 leukemia cases of 2588 controls</td>
<td>To study the relationship between factors relating to childhood immunity and leukemia</td>
<td>Germany (German Childhood Cancer Registry)</td>
<td>2 different phases, 1 embedded study addressed proximity to nuclear installations</td>
<td>&lt;14 y</td>
<td></td>
<td></td>
<td>Hospital controls and those hospitalized at the same time for acute diseases</td>
<td>Matched for gender, age (≥6 mo &lt;3 y; ≥12 mo for children &gt;3 y), and residence</td>
<td>100% of cases; 96% of controls</td>
<td>No details on the questions for BF in interviewer-administered questionnaire</td>
<td>BF ORs: 6-mo ORs: acute leukemias, 1.0; common leukemias, 1.0; 2- to 6-mo ORs: acute, 1.2 (NS); common, 1.2; &lt;1-mo ORs: acute, 1.2 (NS); common, 1.3 (95% CI: 1.0–1.7)</td>
<td>Large discrepancies between numbers in text and tables (eg, 588 cases in text, 680 in table); demonstrated bias, issue with controls; could only select current controls, but cases were from up to 14 y previously</td>
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what less protection against ALL (OR: 0.86; 95% CI: 0.73–1.01) than >6 months of breastfeeding (OR: 0.72; 95% CI: 0.60–0.87), as compared with no breastfeeding. Considering durations from none to >12 months, there was a statistically significant trend for decreased risk for ALL with increasing duration of breastfeeding (P = .0034).

The other study rated as good by all 3 reviewers included the largest population of all reviewed. In the UKCCS,10 1637 population-based leukemia cases were selected with 6964 controls selected from health services records. Considering all types of leukemia, breastfeeding had a nonsignificant relationship with risk (OR: 0.89; 95% CI: 0.80–1.00). When only cases with ALL were considered, breastfeeding conferred a nonsignificant reduction in risk (OR: 0.91; 95% CI: 0.81–1.04) after adjustment for age at diagnosis, gender, region, birth order, and a measure of SES. Duration of breastfeeding was not significantly related to risk (χ² for trend: P = .48): duration <1 month (OR: 0.96; 95% CI: 0.82–1.17), duration 1 to 6 months (OR: 0.90; 95% CI: 0.77–1.04), and duration ≥7 months (OR: 0.89; 95% CI: 0.75–1.05). Risk was also not related to subcategories of ALL.

Similarly, the 2 fair-quality studies disagreed on the protective effect of breastfeeding. In the study by Infante-Rivard et al13 conducted in the Province of Quebec, the authors recruited cases of ALL including children <1 year of age. As compared with population-based controls, breastfeeding was associated with protection from ALL comparing a duration of >3 months with a duration ≤3 months (matched OR: 0.67; 95% CI: 0.47–0.94). However, in the other study rated as fair, Dockerty et al11 similarly recruited children aged 0 to 14 years with leukemia in New Zealand and controls selected from birth records, matched on age and gender. After adjustment for relevant confounders, breastfeeding was not associated with ALL (OR: 0.98; 95% CI: 0.39–2.47).

TABLE 1. Continued

<table>
<thead>
<tr>
<th>Perrillat et al19 (2002)</th>
<th>Poor</th>
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<tbody>
<tr>
<td>Quality</td>
<td>1995–1999</td>
</tr>
<tr>
<td>Years of study</td>
<td>280 (99%) of 282 cases (240 with ALL, 40 with ANLL); 287 (99%) of 291 controls</td>
</tr>
<tr>
<td>Study size</td>
<td>Investigate the role of early infections in childhood ALL</td>
</tr>
<tr>
<td>Study intent</td>
<td>France: hospital-based case-control study in Lille, Lyon, Nancy, and Paris</td>
</tr>
<tr>
<td>Country</td>
<td>Conducted in hospitals, cases diagnosed with ANLL or ALL</td>
</tr>
<tr>
<td>Population</td>
<td>&lt;15 y</td>
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<tr>
<td>Ages included</td>
<td>Children hospitalized for congenital malformation or malignancies other than leukemia</td>
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<tr>
<td>Important exclusions</td>
<td>Diagnosed with ALL or ANLL</td>
</tr>
<tr>
<td>Cases included</td>
<td>Hospital controls, mainly in orthopedics and emergency department, living in catchment area of hospital</td>
</tr>
<tr>
<td>Confirmation of case diagnosis</td>
<td>Matched on age, gender, hospital, hospital catchment area, and ethnic origin</td>
</tr>
<tr>
<td>Controls</td>
<td>Mothers interviewed in hospital when child in remission or good condition (average 2 months after diagnosis) by using standard questionnaire</td>
</tr>
<tr>
<td>Case-control matching</td>
<td>ALL: BF OR (≥6 mo), 0.5 (95% CI: 0.2–1.1); ANL (≥6 mo), 0.5 (95% CI: 0.1–2.5); both together (≥6 mo), 0.5 (95% CI: 0.2–1.0)</td>
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<tr>
<td>BF assessment</td>
<td>Hospital based; interviewed in hospital, not blinded; case was in remission in good condition</td>
</tr>
<tr>
<td>Association</td>
<td>* The questionnaire was adapted from that of Patricia McKinney, BSc, PhD, and Eve Roman, BSc, PhD.</td>
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</table>

BF indicates breastfeeding/breastfeed; NZ, New Zealand; ICD-9, International Classification of Diseases, Ninth Revision; ANLL, acute nonlymphoblastic leukemia; NS, not significant.

* The questionnaire was adapted from that of Patricia McKinney, BSc, PhD, and Eve Roman, BSc, PhD.

DISCUSSION

Of the 10 studies reviewed, only 4 were sufficient to provide at least fair-quality evidence regarding the association between maternal breastfeeding and childhood leukemia. In the 2 studies rated as good, breastfeeding was associated with a significant risk reduction in 1 study17 and a nonsignificant but suggestive difference in the other.10 Similarly, there was a relationship with duration of breastfeeding in the former study but not in the latter. In the 2 studies rated as fair, 1 was associated with risk reduction.13 Taken together, half of the studies associated breastfeeding with a lower risk of ALL.

Our review differs in methodology from previous meta-analyses performed by Beral et al10 and Kwan et al.23 Neither of these groups examined studies for quality or used quality ratings as a determinate for inclusion in analysis. The review performed by Beral et al was a meta-analysis of 15 studies regarding breastfeeding and leukemia or childhood cancer. In that analysis, having ever been breastfed was associated with a small risk reduction for childhood leukemia (OR: 0.86; 95% CI: 0.81–0.92). Breastfeeding for >6 months seemed to confer somewhat greater protection (OR: 0.78; 95% CI: 0.71–0.85) than for a duration of <6 months (OR: 0.91; 95% CI: 0.85–0.99).10 However, this protective effect was uniform for all pediatric cancers. This would either indicate a universal effect of an immunologic influence across all cancers or, more likely, an inherent bias in the control ascertainment, indicative of unresolved confounding. Although they seemed to have performed a comprehensive search, they did not report following standard steps required for a systematic review, including explicit search criteria, inclusion and exclusion criteria, and quality assessment. Their methodologic rigor and findings differ from this review. No quality rating was considered for the studies included in their meta-analysis. Of the 15 studies
included in their analysis, 8 were also included in our systematic review. Four were excluded because they were published before 1990, and 3 were conducted in developing countries. Notably, of the 8 studies that both Beral et al and our group considered eligible for review, 4 were judged of poor quality and were not included in this review.2,12,15,16,18

The meta-analysis by Kwan et al23 used similar methods to include 14 case-control studies. These authors concluded that short-term (≤6 months) and long-term (>6 months) breastfeeding was associated with a reduced odds of both ALL (OR: 0.76; 95% CI: 0.68–0.84) and acute myelogenous leukemia (AML) (OR: 0.85; 95% CI: 0.73–0.98). No quality rating of studies was included. This lack of a relationship specific to ALL and the lack of a duration effect of breastfeeding may be indicative of bias, particularly confounding by SES. Many included studies that failed to adjust for SES, and the imbalance in this factor between cases and controls as well as participation bias may be contributory given the strong relationship with breastfeeding. Mothers who breastfeed ≥6 months differ from those who breastfeed less, in more ways than just having a different SES. Taveras et al24 report that mothers who feed their infants longer have less restrictive behavior regarding child feeding at 1 year. These groups of mothers also differ significantly by age, prepregnancy BMI, income, education, race, and gravidity. Risk for ALL may be associated with ≥1 of these factors, and the effect may not be removed entirely by adjusting for SES.

The certainty that one has in making clinical recommendations is guided by the confidence that the effect observed in the literature is likely to be true. Leading organizations agree on the importance of explicitly evaluating the quality of the evidence to provide guidance regarding the certainty of recommendations.8,25–35

This is the first review of the literature to evaluate the quality of each study and use it to guide the analysis and presentation of results. All peer-reviewed full-text studies mentioned in each of the prior reviews were evaluated in this review; however, after formal quality assessment, only 4 were rated as at least fair in quality and they form the foundation for our results.

The primary findings of our review indicate that there are few high-quality studies to inform an important question for parents as to whether it is possible to reduce the risk of childhood leukemia by breastfeeding, and those few studies disagree. The studies frequently failed to measure important factors such as breastfeeding exclusivity (reporting ever breastfed rather than quantifying breastfeeding by exclusivity combined with duration) and consideration of other important confounders such as SES and other infectious exposures (such as household or school contacts). Because childhood leukemia is a rare disease, a case-control study is the only study design that will allow calculation of the risk that breastfeeding plays in the development of this disease. However, case-control studies are notoriously among the most difficult to conduct given the influence of bias and confounding. None of the studies included in this systematic review were without flaw. An optimal study might be conducted within the framework of a large population-based registry or cohort with full access to medical records, pathology, and demographic data that would be able to accurately identify all cases of ALL diagnosed (with pathologic confirmation) at >1 year of age within a defined time period. Access to original records, pathology, and clinical examination is essential to ascertain diagnostic accuracy. Ideally, this same registry or cohort would allow for identification of controls on the basis of the same sampling frame, with equal access to medical care and the ability to accurately match for important influential factors. Breastfeeding duration and exclusivity would be measured practically by maternal survey, and ideally, duration and cessation would be confirmed with infant health records. This would eliminate a strong influence of recall bias given the ability to verify the answers for the principal risk factor in the context of an interview of mothers of cases and controls. Last, SES remains an important confounder and should be assessed by multiple measures such as parental education, employment, and income, if possible.

Childhood leukemia remains the most common type of cancer diagnosed in children. It is estimated that the United States spends $1.4 billion dollars annually for the treatment of childhood leukemia.1 There are ∼2400 children diagnosed annually with ALL in the United States.36 An ability to prevent 10% to 20% of these cases through breastfeeding would constitute an obvious health and fiscal benefit. Despite the public health importance of identifying potential interventions that could prevent the onset of childhood leukemia, the current literature regarding the preventive role of breastfeeding has substantial limitations. Given the burden of disease and potential cost-effectiveness, conducting high-quality research should be a high priority.

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