Breastfeeding and Childhood Leukemia Incidence
A Meta-analysis and Systematic Review

Efrat L. Amitay, PhD, MPH; Lital Keinan-Boker, MD, PhD, MPH

IMPORTANCE  Childhood cancer is a leading cause of mortality among children and adolescents in the developed world and the incidence increases by 0.9% each year. Leukemia accounts for about 30% of all childhood cancer but its etiology is still mostly unknown.

OBJECTIVE  To conduct a meta-analysis of available scientific evidence on the association between breastfeeding and childhood leukemia.

DATA SOURCES  A thorough search for articles published between January 1960 and December 2014 researching the association between breastfeeding and childhood leukemia was conducted on PubMed, the Cochrane Library, and Scopus (performed in July and December 2014), supplemented by manual searches of reference lists.

STUDY SELECTION  To be included in the meta-analyses, studies had to be case control; include breastfeeding as a measured exposure and leukemia as a measured outcome; include data on breastfeeding duration in months; and be published in a peer-reviewed journal with full text available in English.

DATA EXTRACTION AND SYNTHESIS  The search identified 24 relevant studies, 17 of which met all inclusion criteria. No publication bias or significant heterogeneity among these 17 studies were detected. The quality of each study that met the inclusion criteria was assessed using the Newcastle-Ottawa Scale. Multiple meta-analyses were conducted using the random effect model on raw data in the StatsDirect statistical program.

MAIN OUTCOMES AND MEASURES  No or short duration of breastfeeding and the incidence of childhood leukemia.

RESULTS  The meta-analysis of all 17 studies indicated that compared with no or shorter breastfeeding, any breastfeeding for 6 months or longer was associated with a 20% lower risk for childhood leukemia (odds ratio, 0.80; 95% CI, 0.72-0.90). A separate meta-analysis of 15 studies indicated that ever breastfed compared with never breastfed was associated with a 9% lower risk for childhood leukemia (odds ratio, 0.91; 95% CI, 0.80-1.04), although the definition of never breastfed differed between studies. All meta-analyses of subgroups of the 17 studies showed similar associations. Based on current meta-analyses results, 14% to 20% of all childhood leukemia cases may be prevented by breastfeeding for 6 months or more.

CONCLUSIONS AND RELEVANCE  Breastfeeding is a highly accessible, low-cost public health measure. This meta-analysis that included studies not featured in previous meta-analyses on the subject indicates that promoting breastfeeding for 6 months or more may help lower childhood leukemia incidence, in addition to its other health benefits for children and mothers.
Approximately 175,000 cancer cases are diagnosed annually in children younger than age 15 years worldwide, with an annual increase of around 0.9% in incidence rate in the developed world, only partly explained by improved diagnosis and reporting. Childhood cancer is rare and its survival rate has increased significantly over the years owing to advancement in treatment technologies; however, it still is a leading cause of death among children and adolescents in developed countries, ranking second among children aged 1 to 14 years in the United States, surpassed only by accidents. Childhood cancer is also emerging as a major cause of death in the last few years in Asia, Central and South America, NorthWest Africa, and the Middle East, where death rates from preventable communicable diseases are declining.

Leukemia, a cancer of the bone marrow that damages the normal formation of blood cells, is the most common childhood cancer, accounting for about 30% of all childhood malignancies. Among children, both acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) are usually diagnosed in their acute form. From 1975 to 2011, the incidence rate of leukemia increased in the United States by an annual average of 0.7% for children and adolescents aged 0 to 19 years, while in the European Union, the yearly increase in leukemia incidence between 1978 and 1997 averaged 0.6%.

Still, very little is known of its etiology. Some risk factors for childhood cancers, including leukemia, have been identified, such as Down syndrome and exposure to ionizing radiation and viruses such as Epstein-Barr virus. However, in most children diagnosed as having cancer, none of these defined risk factors are found. Greaves’ hypothesis, the Infective Agent Theory, outlines a 2-stage oncogenic process for childhood leukemia—an in-utero genetic mutation causing a genetic predisposition to cancer followed by a delayed exposure (known also as the Hygiene Hypothesis) to an infective agent that brings into effect the genetic tendency.

The model is supported by several observations: peak incidence of both childhood leukemia and common childhood infections occur among children aged 2 to 5 years and a viral etiology documented in some animal and human cancers (eg, Epstein-Barr virus for Burkitt lymphoma). It was also suggested that there is a statistically significant seasonal variation in the onset dates of childhood leukemia, similar to outbreaks of communicable diseases. Further support is drawn from the population-mixing theory that an excess of childhood leukemia has been found in rural, potentially immunologically naive, populations that have undergone an influx of permanent residents.

Breast milk is a total food meant to exclusively supply all the nutritional needs of infants. Current recommendations of leading health organizations, including the American Academy of Pediatrics and the World Health Organization, state that “infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to two years of age or beyond.” Therefore, breastfeeding is an infant’s first food and a substantial early-life exposure. The aim of this systematic review and meta-analysis was to examine a possible relationship between being breastfed and childhood leukemia.

Three meta-analyses were published previously on leukemia and breastfeeding. The first was published in 2004 by Kwan et al and included 14 case-control studies. Ten of those studies are also included in the current analysis. The other 4 studies did not meet the selection criteria for this analysis. Kwan et al found that breastfeeding is negatively associated with ALL risk, both for breastfeeding of less than 6 months (odds ratio [OR], 0.89; 95% CI, 0.80-0.98) and for longer than 6 months (OR, 0.76; 95% CI, 0.68-0.86) compared with no breastfeeding at all. For the association between breastfeeding and AML, the researchers analyzed 8 studies and found a statistically significant inverse association between breastfeeding for longer than 6 months and AML risk (OR, 0.85; 95% CI, 0.73-0.98), although there was no significant association for breastfeeding for less than 6 months.

Martin et al published in 2005 an analysis consisting of 26 studies on breastfeeding and different types of childhood cancer—all but 1 were case-control studies. Twelve studies, contributing 7596 childhood leukemia cases, were included in the analysis of breastfeeding and childhood leukemia and the authors found a moderate effect of between-study heterogeneity that was eliminated when they removed the study by Smulevich et al. The calculated pooled OR of the 12 studies indicated a statistically significant inverse association between ever breastfed compared with never breastfed and childhood leukemia (OR, 0.87; 95% CI, 0.77-0.99). Calculated without the study by Smulevich et al, the pooled OR was 0.89 (95% CI, 0.83-0.94).

A third meta-analysis was published in 2007 by Ip et al. The researchers combined socioeconomic status-adjusted ORs of only 3 studies that were determined by the systematic review by Guise et al and published in 2005 to be of good or fair quality: the UK Childhood Cancer Study, Shu
et al,20 and Dockerty et al.19 Based on their analyses, they concluded that breastfeeding for more than 6 months was associated with a 20% lower risk for ALL (OR, 0.8; 95% CI, 0.71-0.91).

Methods

Original research articles on the association between breastfeeding and childhood leukemia published between January 1960 and December 2014 were searched on PubMed, the Cochrane Library, and Scopus in July and December 2014. The search keywords used included leukemia and breastfeeding, childhood cancer and breastfeeding, leukaemia, breast-feeding, and breast feeding. In addition, we searched the bibliographies of the articles found and of previous systematic reviews and meta-analyses on the subject.15,30-33

Selection Criteria

Selection criteria for the present meta-analysis included articles researching the association between breastfeeding and childhood leukemia (Figure 1). Studies had to be case control for the purpose of the statistical analysis; have breastfeeding as a measured exposure and leukemia as a measured outcome; include data on breastfeeding duration in months, including but not limited to, 6 months or more (where relevant data were unavailable in the publication, the authors of the studies were contacted); and been published in peer-reviewed journals with full text available in English. Two investigators (E.L.A. and L.K.-B.) independently searched the literature, reviewed and assessed the articles, and decided on inclusion. We identified 24 case-control studies16-29,34-44 examining the relationship between breastfeeding and childhood leukemia risk, 6 of them were not included in any previous meta-analysis.38-43

Results

All Qualifying Studies

The 17 studies included in the meta-analysis provided a total of 9650 leukemia cases and 16 526 control individuals for which there were breastfeeding data that could be analyzed. The main characteristics of the studies are outlined in Table 2. When comparing any breastfeeding for 6 months and beyond with no or any breastfeeding for less than 6 months, the calculated ORs of each study separately ranged between 0.34 and 1.25. The meta-analysis of all 17 studies indicated a statistically significant inverse association between any breastfeeding for 6 months or longer and childhood leukemia (OR, 0.80; 95% CI, 0.72-0.90) (Figure 3).

Studies Including Only Children Diagnosed at Age 1 Year or Older

Leukemia diagnosed before age 1 year is usually attributed to prenatal risk factors; thus, cancer onset may have preceded breastfeeding or affected its duration.46,47 Therefore, a separate meta-analysis was conducted for studies that excluded such cases (Figure 4). This analysis including 7 studies20,23,25,37-39,42 showed that any breastfeeding for more than 6 months compared with a shorter duration was associated with a 17% decreased risk for childhood leukemia (OR, 0.83; 95% CI, 0.72-0.96).

Studies With High NOS Scores

The quality of a meta-analysis is dependent on the quality of the studies it includes. In the review published by Guise et al in 2005, the authors classified only 2 of the 10 studies as being of good quality. To ensure good-quality data, we conducted a

Validity Assessment

Seventeen articles met all selection criteria and were included in this study.16-25,37-43 We read the articles independently and assessed their quality using the Newcastle-Ottawa Scale (NOS).44 Results of the validity assessment were discussed until agreement was reached. Quality ratings of the studies are shown in Table 1, where each asterisk denotes 1 point and the NOS score is the sum of the points.

Data Analysis

Data analysis was done using StatsDirect Statistical software. Crude ORs were calculated in the program, thus avoiding biases that may have arisen from adjustments to different confounders done in each study. Noncombinability of the 17 selected studies was assessed using Cochran-Q test (Q = 29.7) (P = .02) and between-study heterogeneity was assessed with I² = 46.2% (95% CI, 0%-68%), indicating moderate heterogeneity between studies. Publication bias was assessed using the Egger bias test (bias = −0.69; 95% CI, −2.01 to 0.687; P = .3) and a bias-assessment funnel plot (Figure 2). Both tests showed no signs of a publication bias. Since moderate heterogeneity between the studies included in this meta-analysis was demonstrated, the more conservative option of the random effects model (DerSimonian-Laird) was chosen.

Table 1. Case-Control Studies Considering All Diagnoses

<table>
<thead>
<tr>
<th>Study</th>
<th>NOS Score</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A</td>
<td>7</td>
<td>High</td>
</tr>
<tr>
<td>Study B</td>
<td>6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Study C</td>
<td>5</td>
<td>Low</td>
</tr>
</tbody>
</table>

Figure 1. Flow Diagram of Study Selection

![Flow Diagram of Study Selection](https://example.com/flow-diagram.png)

Table 2. Characteristics of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A</td>
<td>Case-control</td>
<td>1000 cases, 1000 controls</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Study B</td>
<td>Case-control</td>
<td>500 cases, 500 controls</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Study C</td>
<td>Case-control</td>
<td>250 cases, 250 controls</td>
<td>Case-control study</td>
</tr>
</tbody>
</table>

Figure 2. Bias-Assessment Funnel Plot

![Bias-Assessment Funnel Plot](https://example.com/bias-plot.png)

Figure 3. Forest Plot of Studies

![Forest Plot of Studies](https://example.com/forest-plot.png)

Figure 4. Forest Plot of Studies Excluding Cases Diagnosed at Age 1 Year or Older

![Forest Plot of Studies Excluding Cases](https://example.com/forest-plot-excluding.png)
meta-analysis including only the 8 studies that received a NOS grade of 8 or higher of a possible 10. Tests for heterogeneity showed no noncombinability or heterogeneity between these studies (Cochran-$Q = 5.01; P = .65; I^2 = 0\%$; 95\% CI, 0\%-56.3\%). This meta-analysis also indicated a protective association between breastfeeding and childhood leukemia risk (OR, 0.86; 95\% CI, 0.78-0.95).

Studies Conducted in Developed Countries
Because there are discernable differences in childhood leukemia rates and breastfeeding rates between developed countries with a Western lifestyle and other countries, an analysis was conducted including only the 12 studies led in developed countries. The analysis indicated a statistically significant inverse association between any breastfeeding for more than 6 months and childhood leukemia (OR, 0.84; 95\% CI, 0.78-0.91).

The 4 Largest Studies
The 4 largest studies contributed more than 1000 cases each to the breastfeeding and childhood leukemia analysis, 6161 leukemia cases, and 11 704 control individuals combined—more than half of all the cases and control individuals of the full meta-analysis. These studies differed with regards to their results. The largest study, conducted in the United States by Shu et al\textsuperscript{20} and published in 1999, provided 2199 leukemia cases and found that ever being breastfed was associated with a 21\% reduced risk for childhood acute leukemia (OR, 0.79; 95\% CI, 0.7-0.91). The UK Childhood Cancer Study investigators\textsuperscript{23} published in 2001 a study that provided 1636 leukemia cases and indicated a weak evidence of borderline statistical significance that ever (compared with never) having been breastfed was associated with a small reduction in leukemia risk (OR, 0.89; 95\% CI, 0.84-1.00).
A study conducted in the United Kingdom by Lancashire et al\(^2\) and published in 2003 was based on 1325 childhood leukemia cases who died before their 16th birthday and provided no evidence of protective association between breastfeeding and ALL (OR, 1.04; 95% CI, 0.86-1.26). Schüz et al\(^18\) published in 1999 a study including 1001 leukemia cases in Germany. It found that a breastfeeding duration of less than a month was not significantly associated with childhood leukemia when compared with breastfeeding duration of 6 months or more (OR, 1.2; 95% CI, 0.9-1.6).

The separate analysis of these 4 studies indicated a statistically significant inverse association between any breastfeeding for 6 months or more compared with a shorter duration and childhood leukemia (OR, 0.84; 95% CI, 0.75-0.94).

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Table 2. Main Characteristics of the Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Main Study Goal</th>
<th>No. of Cases in BF Analysis</th>
<th>No. of Controls in BF Analysis</th>
<th>Age Range of Cases, y</th>
<th>Method Assessing Infant Feeding</th>
<th>BF Durations Compared in Study</th>
<th>In Subanalyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waly et al,(^{41}) 2011 (Oman)</td>
<td>Hospital based</td>
<td>BF and leukemia</td>
<td>70</td>
<td>70</td>
<td>No mention</td>
<td>Maternal interview</td>
<td>&lt;6, 6-12, and 12-24 vs &gt;24 mo</td>
<td>Developed; over 1 y; ALL; AML; ever</td>
</tr>
<tr>
<td>Rudant et al,(^{42}) 2010 (France)</td>
<td>Population based</td>
<td>Infections, allergy, and leukemia</td>
<td>718</td>
<td>1487</td>
<td>1-15</td>
<td>Maternal telephone interview</td>
<td>No vs yes; &lt;6, &gt;6; ≥2, 3-5, 6-11, and ≥12 mo</td>
<td>Developed; high NOS score; ALL; AML; ever</td>
</tr>
<tr>
<td>Bener et al,(^{41}) 2008 (UAE)</td>
<td>Hospital based</td>
<td>BF, leukemia, and lymphoma</td>
<td>103</td>
<td>98</td>
<td>0-15</td>
<td>Maternal telephone interview</td>
<td>&lt;6 vs &gt;6 mo</td>
<td>Developed; high NOS score; ALL; AML; ever</td>
</tr>
<tr>
<td>MacArthur et al,(^{40}) 2008 (Canada)</td>
<td>Population based</td>
<td>Vaccines, infections, medication use, and leukemia</td>
<td>395</td>
<td>398</td>
<td>0-14</td>
<td>Face-to-face interview with parents</td>
<td>0-3, 4-6, and 7-12 mo</td>
<td>Developed; over 1 y; ALL; AML; ever</td>
</tr>
<tr>
<td>Altinkaynak et al,(^{19}) 2006 (Turkey)</td>
<td>Population based</td>
<td>BF, leukemia, and lymphoma</td>
<td>87</td>
<td>92</td>
<td>0-16</td>
<td>Maternal interview</td>
<td>0-1, 1-3, and &gt;6 mo</td>
<td>Developed; high NOS score; ALL; AML; ever</td>
</tr>
<tr>
<td>Kwan et al,(^{18}) 2005 (US)</td>
<td>Population based</td>
<td>BF and leukemia</td>
<td>305</td>
<td>398</td>
<td>0-14</td>
<td>In-home interview + self-administered questionnaire</td>
<td>Yes vs no; ≤3, 4-6, 7-12, and &gt;13 mo</td>
<td>Developed; over 1 y; ALL; AML; ever</td>
</tr>
<tr>
<td>Jourdan-Da Silva et al,(^{20}) 2004 (France)</td>
<td>Population based</td>
<td>Infectious diseases, perinatal characteristics, and leukemia</td>
<td>445</td>
<td>515</td>
<td>1-15</td>
<td>Self-administered questionnaire to mother</td>
<td>Yes vs no; 0, &lt;3, 3-6, and &gt;6 mo</td>
<td>Developed; over 1 y; ALL; AML; ever</td>
</tr>
<tr>
<td>Lancashire and Sorehan; OSCC,(^{25}) 2003 (UK)</td>
<td>Population based</td>
<td>BF and childhood cancer</td>
<td>1325</td>
<td>1327</td>
<td>1-14</td>
<td>Interview with parents</td>
<td>Yes vs no; &lt;1, 1-6, and &gt;7 mo</td>
<td>Developed; over 1 y; 4 large studies; ALL; ever</td>
</tr>
<tr>
<td>Perrillat et al,(^{24}) 2002 (France)</td>
<td>Hospital based</td>
<td>Day care, early infections, and leukemia</td>
<td>246</td>
<td>235</td>
<td>0-15</td>
<td>Maternal interview</td>
<td>Yes vs no; never, &lt;3, 3-5, 6-11, and &gt;12 mo</td>
<td>Developed; ever</td>
</tr>
<tr>
<td>UKCCS,(^{23}) 2001 (UK)</td>
<td>Population based</td>
<td>BF and childhood cancer</td>
<td>1636</td>
<td>6959</td>
<td>1-14</td>
<td>Maternal interview</td>
<td>Yes vs no; ≤1, 1-6, and &gt;6 mo</td>
<td>Developed; over 1 y; high NOS score; 4 large studies; ALL; AML; ever</td>
</tr>
<tr>
<td>Hardell and Dreifaldt,(^{22}) 2001 (Sweden)</td>
<td>Population based</td>
<td>BF and childhood cancer</td>
<td>235</td>
<td>237</td>
<td>0-14</td>
<td>Medical records</td>
<td>0-1, 1-6, and &gt;6 mo</td>
<td>Developed; high NOS score; ALL; AML; ever</td>
</tr>
<tr>
<td>Infante-Rivard et al,(^{27}) 2000 (Canada)</td>
<td>Population based</td>
<td>Infection, BF, and leukemia</td>
<td>491</td>
<td>491</td>
<td>0-10</td>
<td>Maternal telephone interview</td>
<td>No, ≤3, &gt;3, also: none ≤1, and ≤6 mo</td>
<td>Developed; high NOS score; 4 large studies; ALL; AML; ever</td>
</tr>
<tr>
<td>Shu et al,(^{20}) 1999 (US)</td>
<td>Population based</td>
<td>BF and leukemia</td>
<td>2199</td>
<td>2417</td>
<td>1-17</td>
<td>Maternal telephone interview</td>
<td>No, &lt;1, 1-6, and &gt;6 mo</td>
<td>Developed; high NOS score; over 1 y; 4 large studies; ALL; AML; ever</td>
</tr>
<tr>
<td>Dockerty et al,(^{19}) 1999 (New Zealand)</td>
<td>Population based</td>
<td>Infections, vaccines, and ALL</td>
<td>95</td>
<td>303</td>
<td>0-14</td>
<td>At-home interview with mothers</td>
<td>No vs yes; ≤6, 6-12, and &gt;12 mo</td>
<td>Developed; high NOS score; 4 large studies; ALL; AML; ever</td>
</tr>
<tr>
<td>Schüz et al,(^{18}) 1999 (Germany)</td>
<td>Population based</td>
<td>Factors related to immune system and leukemia</td>
<td>1001</td>
<td>1001</td>
<td>0-14</td>
<td>Self-administered questionnaire + telephone interview</td>
<td>&lt;1, 2-6, and &gt;6 mo</td>
<td>Developed; high NOS score; 4 large studies; ALL; AML; ever</td>
</tr>
<tr>
<td>Smulevich et al,(^{17}) 1999 (Russia)</td>
<td>Population based</td>
<td>Family history, pregnancy, BF, and cancer</td>
<td>199</td>
<td>398</td>
<td>0-14</td>
<td>Face-to-face interview</td>
<td>&lt;1, 1-2, 3-4, 5-6, 7-12, and &gt;12 mo</td>
<td>Developed; high NOS score; ever</td>
</tr>
<tr>
<td>Shu et al,(^{16}) 1995 (China)</td>
<td>Population based</td>
<td>BF, leukemia, and lymphoma</td>
<td>100</td>
<td>100</td>
<td>0-15</td>
<td>Interview with parents</td>
<td>Never, &gt;1, and &gt;6 mo</td>
<td>Developed; high NOS score; ever</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BF, breastfeeding; NOS, Newcastle-Ottawa Scale; OR, odds ratio; OSCC, Oxford Survey of Childhood Cancers; UKCCS, UK Childhood Cancer Study.
Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia

Separate meta-analyses were also conducted for ALL and AML cases. For ALL, the analysis of 11 studies included 5745 cases and 12,764 control individuals and indicated a statistically significant inverse association between any breastfeeding for 6 months or more and ALL risk (OR, 0.82; 95% CI, 0.73-0.93). The analysis for AML only included 6 studies that supplied 854 cases and 9542 control individuals, but the association between any breastfeeding for 6 months or more and AML risk was not statistically significant. No association between any breastfeeding for 6 months or more and AML risk was found (OR, 0.74; 95% CI, 0.48-1.14).

Ever vs Never

Another analysis was conducted for ever vs never breastfed, including 14 studies because 3 studies did not have data for never breastfed. The definition of never breastfed differed among studies, with some defining never as no and some as less than 1 month; therefore, between-study heterogeneity was significantly higher (Cochran-Q = 38; P < .01; I² = 65.8%; 95% CI, 30.8%-79.2%). This analysis showed that ever breastfed was associated with a 9% lower risk for childhood leukemia (OR, 0.91; 95% CI, 0.80-1.03).

In this meta-analysis of published (1995-2011) case-control studies examining the relationship between breastfeeding and childhood leukemia, all analyses, except the sub-analysis for AML alone, which was not statistically significant, showed that being breastfed for at least 6 months compared with less than that or not at all was significantly associated with a 14% to 20% lower risk for childhood leukemia, with a 20% lower risk when all selected 17 studies were included in the analysis.

Figure 3. Meta-analysis of All 17 Qualifying Studies: Any Breastfeeding for 6 Months and Beyond Compared With Shorter Duration

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waly et al, Oman 2011</td>
<td>0.38</td>
<td>0.04-2.45</td>
</tr>
<tr>
<td>Rudant et al, France 2010</td>
<td>0.78</td>
<td>0.58-1.04</td>
</tr>
<tr>
<td>Bener et al, UAE 2008</td>
<td>0.14</td>
<td>0.18-0.64</td>
</tr>
<tr>
<td>MacArthur et al, Canada 2008</td>
<td>0.89</td>
<td>0.62-1.28</td>
</tr>
<tr>
<td>Altinkaynak et al, Turkey 2006</td>
<td>0.36</td>
<td>0.18-0.73</td>
</tr>
<tr>
<td>Kwan et al, US 2005</td>
<td>0.85</td>
<td>0.61-1.18</td>
</tr>
<tr>
<td>Jourdan-Da Silva et al, France 2004</td>
<td>1.25</td>
<td>0.72-2.20</td>
</tr>
<tr>
<td>Lancashire and Sorahan; OSCC, UK 2003</td>
<td>1.00</td>
<td>0.73-1.37</td>
</tr>
<tr>
<td>Perrillat et al, France 2002</td>
<td>0.49</td>
<td>0.24-0.97</td>
</tr>
<tr>
<td>UKCCS, UK 2001</td>
<td>0.89</td>
<td>0.77-1.02</td>
</tr>
<tr>
<td>Hardell and Dreifaldt, Sweden 2001</td>
<td>0.92</td>
<td>0.62-1.17</td>
</tr>
<tr>
<td>Infante-Rivard et al, Canada 2000</td>
<td>1.04</td>
<td>0.69-1.58</td>
</tr>
<tr>
<td>Smulevich et al, Russia 1999</td>
<td>0.64</td>
<td>0.44-0.93</td>
</tr>
<tr>
<td>Shu et al, US 1999</td>
<td>0.75</td>
<td>0.65-0.86</td>
</tr>
<tr>
<td>Dockerty et al, New Zealand 1999</td>
<td>0.78</td>
<td>0.48-1.28</td>
</tr>
<tr>
<td>Schüz et al, Germany 1999</td>
<td>0.81</td>
<td>0.63-1.03</td>
</tr>
<tr>
<td>Shu et al, China 1995</td>
<td>1.04</td>
<td>0.58-1.88</td>
</tr>
<tr>
<td>Combined (Random)</td>
<td>0.80</td>
<td>0.72-0.90</td>
</tr>
</tbody>
</table>

OSCC indicates Oxford Survey of Childhood Cancers; UAE, United Arab Emirates; UK, United Kingdom; UKCCS, UK Childhood Cancer Study; US, United States.

Figure 4. Meta-analysis of Studies Including Only Children Diagnosed as Having Cancer at Age 1 Year or Older

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Rudant et al, France 2010</td>
<td>0.78</td>
<td>0.58-1.04</td>
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<td>Altinkaynak et al, Turkey 2006</td>
<td>0.36</td>
<td>0.18-0.73</td>
</tr>
<tr>
<td>Kwan et al, US 2005</td>
<td>0.85</td>
<td>0.61-1.18</td>
</tr>
<tr>
<td>Jourdan-Da Silva et al, France 2004</td>
<td>1.25</td>
<td>0.72-2.20</td>
</tr>
<tr>
<td>Lancashire and Sorahan; OSCC, UK 2003</td>
<td>1.00</td>
<td>0.73-1.37</td>
</tr>
<tr>
<td>UKCCS, UK 2001</td>
<td>0.89</td>
<td>0.77-1.02</td>
</tr>
<tr>
<td>Shu et al, US 1999</td>
<td>0.75</td>
<td>0.65-0.86</td>
</tr>
<tr>
<td>Combined (Random)</td>
<td>0.83</td>
<td>0.72-0.96</td>
</tr>
</tbody>
</table>

OSCC indicates Oxford Survey of Childhood Cancers; UK, United Kingdom; UKCCS, UK Childhood Cancer Study; US, United States.
Discussion

The etiology of childhood leukemia is an important epidemiological and public health question. This meta-analysis makes a significant contribution to the available evidence on this topic because it includes 6 original studies on the subject not included in previous meta-analyses.\(^{38-43}\) Moreover, to our knowledge, this is significantly the largest and most up-to-date review and analysis of current knowledge on childhood leukemia and breastfeeding.

Several biological mechanisms may explain the results of the current and previous meta-analyses. Breast milk is a live substance, containing antibodies and having a prebiotic effect that promotes a healthy microbiome in the intestines.\(^{47-50}\) Antibodies contained in breast milk may provide protection against pathogens and reduce inflammation.\(^{51}\) Lactoferrin, a protein found in breast milk, can also destroy microbes and reduce inflammation.\(^{51}\) Additional protective mechanisms include the presence of secretory IgA antibodies directed particularly against the microbial flora of the mother and her environment.\(^{51}\)

Breastfeeding provides the neonate with considerable amounts of secretory IgA antibodies directed particularly against the microbial flora of the mother and her environment. Lactoferrin in breast milk can also destroy microbes and reduce inflammatory responses as do the oligosaccharides that block attachment of microbes to the infant’s mucosa, preventing infections.\(^{51}\)

The introduction of infant formula to babies’ diets changes the infants’ gut microbiome, thus affecting the response of the infant immune system to pathogens.\(^{47-51}\) A greater amount of natural-killer cells, suggesting a more mature immune system, have been found in breastfed infants than in formula-fed infants.\(^{52}\) In addition, pH levels in the stomach of breastfed children are better for the promotion of the protein-lipid α-lactalbumin (termed HAMLET), which induces apoptosis-like death in tumor cells.\(^{51,53}\)

A discovery was made that breast milk contains stem cells with multilineage properties similar to human embryonic stem cells. The breastfed infant ingests thousands to millions of those cells daily. Based on animal models, including a primate model, it is hypothesized that the cells remain unharmful in the digestive tract of the infant then enter the bloodstream, migrate to different organs, and there provide active immunity.\(^{54}\)

All these biological mechanisms may contribute to the protective effect of breastfeeding against childhood leukemia. Infant formulas cannot mimic the array of protective properties of breast milk, which fits the infant both species-wise (eg, human milk vs cow milk) and individually owing to the dyadic connection between a mother and her baby.

An important potential limitation of this analysis was that it was based solely on case-control observational studies, as most studies looking at the effects of breastfeeding vs not breastfeeding are. These studies are at risk for selection bias of cases and of control individuals and their results might be influenced by potential confounders such as other health behaviors that may be independently associated both with breastfeeding and childhood leukemia risk, although this is of course not limited to case-control studies. Moreover, data for exposures in almost all studies were based only on maternal recall, sometimes some years after the exposures, although studies have shown that mothers remember breastfeeding durations many years after breastfeeding has stopped.\(^{55-57}\) Furthermore, research shows that mothers of sick children sometimes remember early exposures of their children in greater detail compared with mothers of healthy children, especially when the exposures are publicly perceived to be associated with the outcome studied. Because there is no public perception of an influence of breastfeeding on childhood leukemia risk, this recall bias might not heavily affect the validity of the data in the studies included in this analysis.\(^{58}\)

Another limitation was the response rate of study participants. Thirteen of the 17 included studies reported response rates for cases ranging between 47% and 98%, and 10 studies reported response rates for control individuals ranging from 71% to 95%. There is a concern that participating control individuals have a higher socioeconomic status than nonparticipating control individuals,\(^{19}\) and in developed countries, maternal socioeconomic status plays a role in the decision to breastfeed and its duration.\(^{59,60}\) If indeed the control individuals have higher socioeconomic status and therefore higher breastfeeding rates, it constitutes a differential misclassification that might lead to overestimation of the association between breastfeeding and leukemia. Nonetheless, the submeta-analysis of studies from developed countries had a similar OR to the overall OR and the other subanalyses.

Other limitations of the included studies were that some studies lacked the distinction between exclusive breastfeeding, defined by the World Health Organization as “the infant has received only breast milk from his/her mother or a wet nurse, or expressed breast milk, and no other liquids or solids, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines,” and partial breastfeeding, defined by the World Health Organization as “a situation where the baby is receiving some breastfeeds but is also being given other food or food-based fluids, such as formula milk or weaning foods.”\(^{61}\) The distinction between exclusive breastfeeding and partial breastfeeding in the analyses of the association between breastfeeding and the risk for childhood leukemia is essential given that the addition of infant formula, together with breast milk or instead of it, changes the infant’s gut microbiota, affecting the immunology of the infant.\(^{62,63}\) Thus, misclassification might weaken the association between breastfeeding and lower risk for childhood leukemia.

Conclusions

Based on the current meta-analysis, 14% to 20% of all childhood leukemia cases may be prevented by breastfeeding for 6 months or more, a highly accessible and low-cost public health measure. This finding is added to other health and social benefits associated with breastfeeding. Because the primary goal of public health is prevention of morbidity, health care professionals should be taught the potential health ben-
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Conflict of Interest Disclosures: None reported.

Correction: This article was corrected online November 2, 2015, for errors in the Abstract, text, references, tables, and figures and on August 3, 2015, for incorrect and misleading data in Table 2.

REFERENCES


