

Breast-Feeding and Risk of Childhood Acute Leukemia

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Background: Breast-feeding is well known to have a protective effect against infection in infants. Although the long-term effects of breast-feeding on childhood cancer have not been studied extensively, a protective effect against childhood Hodgkin's disease and lymphoma has been suggested previously from small investigations. In this study, we tested the hypothesis that breast-feeding decreases the risk of childhood acute leukemia. **Methods:** A total of 1744 children with acute lymphoblastic leukemia (ALL) and 1879 matched control subjects, aged 1–14 years, and 456 children with acute myeloid leukemia (AML) and 539 matched control subjects, aged 1–17 years, were included in the analysis. Information regarding breast-feeding was obtained through telephone interviews with mothers. All leukemias combined, histologic type of leukemia (ALL versus AML), immunophenotype of ALL (early pre-B cell, pre-B cell, or T cell), and morphology of AML were assessed separately in the data analysis. **Results:** Ever having breast-fed was found to be associated with a 21% reduction in risk of childhood acute leukemias (odds ratio [OR] for all types combined = 0.79; 95% confidence interval [CI] = 0.70–0.91). A reduction in risk was seen separately for AML (OR = 0.77; 95% CI = 0.57–1.03) and ALL (OR = 0.80; 95% CI = 0.69–0.93). The inverse associations were stronger with longer duration of breast-feeding for total ALL and AML; for M0, M1, and M2 morphologic subtypes of AML; and for early pre-B-cell ALL. **Conclusion:** In this study, breast-feeding was associated with a reduced risk of childhood acute leukemia. If confirmed in additional epidemiologic studies, our findings suggest that future epidemiologic and experimental efforts should be directed at investigating the anti-infective and/or immune-stimulatory or im-

Immune-modulating effects of breast-feeding on leukemogenesis in children. [J Natl Cancer Inst 1999;91:1765–72]

Leukemia is the most common childhood malignancy in Western countries and accounts for one third of all cancers occurring in children under the age of 15 years (1). Despite studies conducted over more than four decades, the etiology of childhood leukemia remains largely unknown. Established risk factors can explain only a very small proportion of childhood leukemias (2).

Breast-feeding has long been recognized to have anti-infective and immune-modulating effects on infants (3–10). A few small studies (11–13) have suggested that breast-feeding may protect children from developing Hodgkin's disease and/or lymphoma. As part of a large, comprehensive program of study to identify risk factors for acute childhood leukemia, we examined the association between breast-feeding and the development of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in two case-control studies carried out by the Children's Cancer Group (CCG).

MATERIALS AND METHODS

Study Population

The CCG is a cooperative clinical trials group with approximately 118 member and affiliated institutions in the United States, Canada, and Australia. The CCG treats approximately 50% of all pediatric cancer patients throughout the United States (14). From 1989 through 1993, children who were newly diagnosed with acute leukemia by CCG institutions were enrolled in two large-scale epidemiologic studies to investigate the etiology of childhood AML and childhood ALL. Potential participants were identified through the registration files of the CCG, including all diagnosed with AML before age 18 years from January 1, 1989, through March 31, 1993, and with ALL before age 15 years from January 1, 1989, through June 15, 1993. Eligibility criteria for the two studies were as follows: 1) a telephone in the patient's residence; 2) availability of an English-speaking, biologic mother for interview; and 3) residence in the United States or Canada (for ALL study only). The investigations were performed with the approval of local institutional human subject review boards of the participating institutions in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Written informed consent was sought from the physician and the parents of all eligible study subjects. A total of 638 AML and 2079 ALL case subjects who met the eligibility criteria were ascertained from the CCG registration files during the study period. Of these, telephone interviews with mothers were completed for 530 eligible AML (83%) and 1914 eligible ALL (92%) case subjects and usually occurred 6–9

months after the diagnosis. The remaining case subjects were unable to be interviewed because of physician refusal (AML: 4%; ALL: 2%), parental refusal (AML: 8%; ALL: 3%), or other reasons (AML: 4%; ALL: 3%). Cell lineage of lymphoblastic leukemia case subjects was assigned at the institution and centrally evaluated with the use of a standard panel of monoclonal antibodies (15). The French-American-British classification of myeloid leukemias (16) was also assigned through central review.

After each case subject was interviewed, a control subject was selected with the use of a previously described random-digit-dialing procedure (17). Control subjects were individually matched to case subjects on age at diagnosis (within 25% of the age at diagnosis of the case subject), on geographic location (telephone area code and exchange), and on race (white or nonwhite). The ratio of control subjects to case subjects was generally 1:1 for both studies, except for certain rare subgroups of AML (2:1 for rare morphologic subgroups, i.e., M3 [acute promyelocytic leukemia], M6 [acute erythroleukemia], M7 [acute megakaryoblastic/megakaryocytic leukemia], and myelodysplastic syndromes) and ALL (2:1 for T-cell ALL). As with case subjects, there had to be a telephone in the control subject's residence and an English-speaking, biologic mother had to be available for interview. Telephone interviews with mothers were completed for 610 eligible control subjects matched to AML case subjects (79%) and for 1986 eligible control subjects matched to ALL case subjects (77%), which resulted in 517 matched sets for AML (426 sets of 1:1 match, 89 sets of 1:2 match, and two sets of 1:3 match) and 1842 matched sets for ALL (1704 sets of 1:1 match, 132 sets of 1:2 match, and six sets of 1:3 match), respectively. Parental refusal accounted for the majority of nonparticipation among control subjects (18% for both AML and ALL).

Accumulating evidence increasingly indicates that infant leukemia (defined as leukemia in the first year of life) arises *in utero* and that postnatal exposure(s) are unlikely to play an etiologic role (18). We, therefore, excluded from this report all subjects who were under the age of 1 year at diagnosis or reference date (defined as the date of diagnosis for

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the case subject for each matching control subject) and the corresponding matched-pair member (61 AML case subjects and 71 AML control subjects and 98 ALL case subjects and 107 ALL control subjects). A total of 456 AML and 1744 ALL case subjects and 2418 matched control subjects (539 for AML and 1879 for ALL) remained in this study. Exclusion from this analysis of children under 1 year of age also avoided the potential for misclassification of exposure if breast-feeding was prematurely discontinued because of the development of illness related to leukemia.

Exposure Assessment

Information regarding maternal exposures, both preconception and prenatal, and childhood (postnatal) exposures was collected through a telephone interview of mothers of study subjects with the use of a structured questionnaire. Information collected included maternal prenatal and perinatal exposures and breast-feeding experience; history of childhood postnatal diseases, medication use, and x-ray exposure; maternal personal habits (e.g., smoking and alcohol consumption); residential and occupational exposures (e.g., exposures to pesticides or solvents); and family history of selected diseases (e.g., history of cancer or congenital malformations). During the interview, mothers of study subjects were asked, "Was [the index child] primarily breast-fed or bottle fed?" and "If [the child was] breast-fed, how long did you breast-feed?" No definition was provided to the respondent as part of the question about whether the index child was "primarily breast-fed" during the interview. The ending date of breast-feeding was also obtained.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) derived from conditional logistic regression models were employed to assess the association between childhood leukemia and breast-feeding. Duration of breast-feeding was categorized into not primarily breast-fed, breast-fed 1–6 months, and breast-fed greater than 6 months according to categories used in earlier studies (11–13,19–21) and into shorter intervals (e.g., breast-fed 1–3 months, 4–6 months, 7–9 months, 10–12 months, or >12 months). Children who were breast-fed less than 1 month were grouped into the not primarily breast-fed group (15 for the AML study and 136 for the ALL study). Tests for linear trend of the association were evaluated by treating categorical variables as continuous in the model. All *P* values for trend tests are two-sided. Analyses were carried out for all acute leukemias combined, separately for ALL and AML, and further stratified by immunophenotype (ALL case subjects) and morphologic type (AML case subjects). Stratified analyses were conducted to evaluate the potential confounding and modifying effects of selected sociodemographic characteristics and postulated risk factors. Confounding effects were further examined in the conditional logistic regression analyses by comparing the OR of breast-feeding with and without adjustment for confounding factor(s). A confounding effect was defined if a 10% difference in the unadjusted and adjusted ORs was observed. Effects were considered to be statistically significant at *P* < .05 or if 95% CIs excluded 1.00.

RESULTS

Of the case subjects included in these analyses, 42.3% of the AML case subjects and 64.4% of the ALL case subjects were 1 through 5 years of age; 22.4% of the AML case subjects and 23.4% of the ALL case subjects were 6 through 10 years of age; the remaining 35.3% of the AML case subjects were aged 11 through 17 years, and 12.2% of the ALL case subjects were aged 11 through 14 years at diagnosis. There were more boys than girls among both AML (52.6%) and ALL (55.7%) case subjects.

Table 1 presents selected characteristics of case and control subjects that have been linked to breast-feeding and/or childhood leukemia risk in some studies. Mothers of case subjects were more likely to be nonwhite and, on average, were less educated than mothers of control subjects in both the AML and the ALL studies. In addition, there were more ALL case subjects from lower income families or with birth weight greater than 4000 g compared with the control subjects. Mothers of AML case subjects were less likely than mothers of control subjects to drink alcohol during pregnancy. AML risk was higher among children whose birth order was fourth or higher compared with the firstborn child. No statistically significant differences were found between case and control subjects with regard to maternal age at birth of the index child, smoking during pregnancy, employment during infancy of the index child, or sibship size.

Ever having been primarily breast-fed among control subjects in the CCG studies was positively and statistically significantly associated with maternal education, family income, maternal age, birth weight, birth order of the index child, and number of siblings (for the last three characteristics, among the control subjects in the ALL study only) (data not shown). Primarily having been breast-fed (ever versus never) was also statistically significantly more frequent among whites (ALL control subjects only), nonsmokers, and those mothers who drank alcohol during the index pregnancy (data not shown). To control for any potential confounding from the socioeconomic differences between case and control subjects, we adjusted for maternal education, race, and family income throughout the remaining analyses. None of the other characteristics listed in Table 1 were found to confound the relationship between breast-feeding and acute leukemia in multivariate analy-

ses (data not shown) or in stratified analyses (data shown in Table 2), and we found no other potential confounders (examined factors included diagnostic x-ray exposure, parental occupational exposures, and day care, etc. [data not shown]).

Overall, children who were ever primarily breast-fed had a reduced risk of childhood acute leukemia, both AML and ALL combined (OR = 0.79; 95% CI = 0.70–0.91) (Table 3). An inverse association was also observed for AML (OR = 0.77; 95% CI = 0.57–1.03) and ALL (OR = 0.80; 95% CI = 0.69–0.93); an even larger reduction in leukemia risk was seen for children breast-fed for more than 6 months (AML: OR = 0.57 [95% CI = 0.39–0.84]; ALL: OR = 0.72 [95% CI = 0.60–0.87]). When the duration of breast-feeding was further categorized into shorter intervals (i.e., 0, 1–3 months, 4–6 months, 7–9 months, 10–12 months, and >12 months), leukemia risk tended to decrease with increasing duration of breast-feeding up to 12 months for ALL and 9 months for AML. The risk of leukemia was also lower, although not statistically significantly reduced, for children who were breast-fed for more than 12 months (AML: OR = 0.58 [95% CI = 0.31–1.08]; ALL: OR = 0.85 [95% CI = 0.66–1.11]). Breast-feeding for 1 month was not associated with risk of acute childhood leukemia (data not shown).

The association with breast-feeding was further evaluated according to the morphologic subtype (French–American–British classification) of AML and the immunophenotype of ALL case subjects (Table 4). Children breast-fed for more than 6 months had an OR lower than 1 for all morphologic subgroups of AML. The ORs, however, were statistically significant only for the AML morphologic subtypes M0 (myeloblastic with no maturation), M1 (myeloblastic with minimal maturation), and M2 (myeloblastic with maturation).

Breast-feeding for more than 6 months was associated with a statistically significantly or marginally significantly lower risk of early pre-B-cell ALL (B-lineage markers positive, cytoplasmic immunoglobulin negative) (OR = 0.70; 95% CI = 0.54–0.92) and pre-B-cell ALL (B-lineage markers positive, cytoplasmic immunoglobulin positive) (OR = 0.59; 95% CI = 0.35–1.01), but there was a weaker and statistically nonsignificant reduction in risk of T-cell ALL (Table 4).

Table 1. Risk of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) associated with demographic, maternal, and birth-related characteristics*

	AML study			ALL study		
	No. of case subjects	No. of control subjects	OR (95% CI)†	No. of case subjects	No. of control subjects	OR (95% CI)†
Birth weight, g‡						
<3000	93	106	1.00 (reference)	305	356	1.00 (reference)
3000–3499	167	187	1.06 (0.74–1.50)	605	649	1.07 (0.88–1.29)
3500–4000	138	170	0.95 (0.65–1.39)	567	638	1.02 (0.84–1.24)
>4000	58	75	0.89 (0.57–1.38)	264	235	1.29 (1.03–1.63)
Maternal education						
≤High school	210	206	1.00 (reference)	748	725	1.00 (reference)
Some post-high school	150	185	0.78 (0.58–1.06)	561	662	0.79 (0.67–0.93)
College graduate	96	148	0.61 (0.43–0.88)	435	492	0.82 (0.69–0.98)
Family annual income						
<\$20 000	143	180	1.00 (reference)	576	519	1.00 (reference)
\$20 001–\$39 999	226	245	1.16 (0.86–1.57)	733	807	0.79 (0.67–0.93)
≥\$40 000	87	114	0.97 (0.63–1.47)	435	553	0.64 (0.53–0.78)
Maternal race						
White	368	455	1.00 (reference)	1463	1667	1.00 (reference)
Other	88	84	1.72 (1.00–2.95)	281	212	2.54 (1.84–3.50)
Mother worked during infancy of index child						
No	243	290	1.00 (reference)	854	876	1.00 (reference)
Yes	213	249	1.01 (0.78–1.31)	890	1003	0.91 (0.80–1.04)
Mother smoked during pregnancy						
No	326	392	1.00 (reference)	1232	1357	1.00 (reference)
Yes	130	147	1.05 (0.78–1.41)	512	522	1.09 (0.96–1.27)
Mother drank alcohol during pregnancy						
No	321	339	1.00 (reference)	1014	1110	1.00 (reference)
Yes	135	200	0.71 (0.53–0.93)	730	769	1.05 (0.91–1.20)
Maternal age, y‡						
<25	192	196	1.00 (reference)	606	618	1.00 (reference)
25–29	143	184	0.80 (0.60–1.06)	615	695	0.89 (0.76–1.05)
30–34	85	112	0.78 (0.54–1.13)	388	436	0.90 (0.75–1.08)
≥35	36	46	0.78 (0.47–1.28)	135	130	1.03 (0.78–1.35)
No. of siblings						
0	47	59	1.00 (reference)	263	236	1.00 (reference)
1	205	233	1.08 (0.69–1.69)	788	829	0.84 (0.68–1.04)
2	119	167	0.84 (0.52–1.35)	424	526	0.72 (0.57–0.89)
≥3	85	80	1.33 (0.80–2.22)	269	288	0.85 (0.66–1.08)
Birth order						
First	191	249	1.00 (reference)	730	813	1.00 (reference)
Second	155	186	1.09 (0.82–1.46)	634	659	1.08 (0.93–1.26)
Third	68	69	1.32 (0.88–1.97)	242	281	0.97 (0.79–1.18)
Fourth or more	42	35	1.67 (1.02–2.74)	138	126	1.26 (0.96–1.64)

*Subjects under the age of 1 year at diagnosis were excluded from the analysis. Frequencies were obtained for all case and control subjects pooled.

†Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from conditional logistic regression model.

‡Subjects in these categories do not sum to the total number of study subjects because of missing data.

Stratified analyses demonstrated no clear evidence of a modifying effect on the relationship between breast-feeding and risk of either AML or ALL by maternal race, maternal education, maternal smoking during pregnancy, maternal drinking during pregnancy, maternal employment during the infancy period, family annual income, as well as number of siblings and birth order of the index child (Table 2).

In an ancillary study, focusing mostly on residential magnetic fields and other environmental exposures in relation to ALL (22), a subgroup of participants (682

case and 768 control subjects) was specifically asked whether the index child had ever been breast-fed as opposed to “primarily breast-fed” in the main study and about the duration of breast-feeding. The overall agreement rate for ever/never breast-fed with primarily breast-fed for the two surveys among the same children was 88% (87% for case subjects and 89% for control subjects). Eighty-one percent of children reported to have ever been breast-fed in the ancillary study were classified as primarily breast-fed in the analysis of the main study of the entire population of ALL case and control sub-

jects evaluated, whereas only 1% of children reported to have never been breast-fed in the ancillary study were described as having been primarily breast-fed in the main study of ALL. For mothers who reported that they breast-fed the index child in both surveys, the correlation of the duration of breast-feeding obtained from the main study and the ancillary study of ALL was 0.93 (0.94 for case subjects and 0.92 for control subjects). For the 19% of subjects whose mothers reported that their children had not been primarily breast-fed in the main study but had ever been breast-fed in the ancillary study, 99%

Table 2. Breast-feeding and risk of childhood acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) stratified by socioeconomic and selected maternal characteristics*

	Odds ratio (95% confidence interval)†					
	AML study			ALL study		
	Never breast-fed	Breast-fed ≤6 mo	Breast-fed >6 mo	Never breast-fed	Breast-fed ≤6 mo	Breast-fed >6 mo
Maternal education						
≤High school	1.00 (reference)	0.61 (0.35–1.07)	0.47 (0.24–0.91)	1.00 (reference)	0.89 (0.69–1.14)	0.62 (0.46–0.85)
Some post-high school	0.70 (0.47–1.05)	0.72 (0.44–1.18)	0.47 (0.27–0.83)	0.89 (0.71–1.12)	0.70 (0.54–0.90)	0.63 (0.47–0.84)
College graduate	0.48 (0.28–0.82)	0.69 (0.41–1.17)	0.32 (0.17–0.59)	0.88 (0.66–1.19)	0.86 (0.65–1.14)	0.76 (0.58–1.00)
Family annual income						
<\$20 000	1.00 (reference)	0.90 (0.49–1.63)	0.70 (0.35–1.40)	1.00 (reference)	0.69 (0.51–0.92)	0.76 (0.54–1.06)
\$20 001–39 999	1.42 (0.96–2.10)	0.89 (0.53–1.51)	0.70 (0.40–1.23)	0.78 (0.62–0.98)	0.74 (0.56–0.97)	0.52 (0.39–0.69)
≥\$40 000	0.85 (0.46–1.56)	1.87 (0.95–3.67)	0.65 (0.31–1.35)	0.61 (0.45–0.81)	0.58 (0.43–0.78)	0.50 (0.35–0.70)
Maternal race						
White	1.00 (reference)	1.00 (0.69–1.45)	0.60 (0.40–0.90)	1.00 (reference)	0.84 (0.71–1.00)	0.68 (0.56–0.83)
Other	1.68 (0.88–3.21)	1.33 (0.61–2.90)	0.79 (0.25–2.44)	2.07 (1.43–3.00)	1.99 (1.27–3.12)	2.48 (1.38–4.47)
Maternal age, y						
<25	1.00 (reference)	0.79 (0.48–1.31)	0.44 (0.22–0.88)	1.00 (reference)	0.94 (0.71–1.23)	0.69 (0.49–0.97)
25–29	0.78 (0.51–1.20)	0.72 (0.43–1.21)	0.60 (0.32–1.12)	1.03 (0.81–1.31)	0.82 (0.64–1.06)	0.73 (0.54–0.97)
30–34	0.66 (0.38–1.15)	1.42 (0.69–2.94)	0.51 (0.27–0.97)	1.14 (0.86–1.52)	1.03 (0.75–1.41)	0.63 (0.46–0.87)
≥35	1.11 (0.54–2.30)	0.67 (0.26–1.72)	0.34 (0.12–0.95)	0.92 (0.59–1.42)	0.71 (0.43–1.18)	1.59 (0.97–2.62)
Maternal smoking during pregnancy						
No	1.00 (reference)	0.93 (0.64–1.37)	0.52 (0.34–0.81)	1.00 (reference)	0.83 (0.69–1.01)	0.67 (0.55–0.83)
Yes	0.88 (0.59–1.30)	0.83 (0.46–1.51)	0.68 (0.31–1.47)	0.93 (0.76–1.15)	0.85 (0.65–1.11)	0.91 (0.61–1.35)
Maternal drinking during pregnancy						
No	1.00 (reference)	1.00 (0.66–1.52)	0.67 (0.42–1.06)	1.00 (reference)	0.81 (0.66–1.01)	0.71 (0.56–0.90)
Yes	0.80 (0.54–1.17)	0.74 (0.46–1.52)	0.34 (0.19–0.63)	1.07 (0.87–1.31)	0.97 (0.77–1.21)	0.78 (0.60–1.01)
Maternal employment						
No	1.00 (reference)	1.18 (0.73–1.91)	0.62 (0.37–1.04)	1.00 (reference)	0.81 (0.63–1.03)	0.70 (0.55–0.89)
Yes	1.15 (0.81–1.65)	0.92 (0.59–1.43)	0.60 (0.35–1.03)	0.89 (0.73–1.09)	0.80 (0.64–1.00)	0.64 (0.48–0.85)
No. of siblings						
0	1.00 (reference)	0.40 (0.14–1.11)	0.19 (0.05–0.75)	1.00 (reference)	0.87 (0.57–1.34)	0.66 (0.38–1.15)
1	0.72 (0.38–1.33)	0.85 (0.43–1.68)	0.45 (0.21–0.97)	0.84 (0.63–1.12)	0.78 (0.57–1.06)	0.64 (0.45–0.89)
2	0.55 (0.28–1.05)	0.71 (0.34–1.50)	0.35 (0.16–0.76)	0.78 (0.57–1.07)	0.53 (0.38–0.75)	0.57 (0.39–0.81)
≥3	1.14 (0.54–2.40)	0.57 (0.24–1.37)	0.64 (0.28–1.46)	0.78 (0.54–1.12)	0.87 (0.58–1.32)	0.58 (0.39–0.88)
Birth order						
First	1.00 (reference)	0.91 (0.56–1.46)	0.47 (0.26–0.86)	1.00 (reference)	0.88 (0.69–1.13)	0.68 (0.51–0.89)
Second	0.99 (0.67–1.46)	1.34 (0.80–2.26)	0.59 (0.31–1.12)	1.06 (0.85–1.32)	0.86 (0.66–1.12)	0.85 (0.64–1.14)
Third	1.40 (0.79–2.47)	1.19 (0.49–2.88)	0.83 (0.41–1.67)	1.07 (0.78–1.47)	0.88 (0.62–1.25)	0.66 (0.46–0.95)
Fourth or higher	2.37 (1.14–4.93)	0.62 (0.21–1.84)	1.13 (0.41–1.67)	1.13 (0.73–1.75)	1.20 (0.72–1.99)	0.89 (0.55–1.43)

*Subjects under the age of 1 year at diagnosis were excluded from the analysis.

†Odds ratios and 95% confidence intervals were derived from conditional logistic regression models, adjusted for maternal race, maternal education, and family annual income.

were breast-fed for 6 months or less (70% were breast-fed for 1 month, 24% were breast-fed for 2–3 months, and 5% were breast-fed for 4–6 months), and only 1% were breast-fed for 7 months according to the information obtained from the ancillary study. With the use of data from the ancillary study, relative risks of ALL were estimated as 0.68 (95% CI = 0.54–0.85), 0.72 (95% CI = 0.56–0.92), and 0.60 (95% CI = 0.45–0.80), respectively, for ever breast-fed, breast-fed 1 through 6 months, and breast-fed more than 6 months. Furthermore, analysis from the ancillary study revealed ORs of 0.73 (95% CI = 0.57–0.92) for those breast-fed for 6 months or less, 0.69 (95% CI = 0.37–1.31) for those exclusively breast-fed for more than 6 months, and 0.60

(95% CI = 0.45–0.82) for those who were both breast-fed and bottle-fed for more than 6 months compared with those never having been breast-fed.

DISCUSSION

To date, only a limited number of studies (11,12,19–21,23–25) have specifically examined the relationship of breast-feeding with the risk of childhood leukemia, and none has found a statistically significant association. Five of these earlier studies (11,19,20,23,24) were of small size (range, 22–153 case subjects). A larger study conducted by Schwartzbaum et al. (12) included 522 ALL case subjects and 107 AML case subjects but no healthy control subjects. The breast-

feeding experience of case subjects was compared with that of 72 rhabdomyosarcoma case subjects. Breast-feeding for more than 6 months was found to be associated with a statistically nonsignificantly reduced risk of leukemia (OR = 0.83) in another two population-based studies (21,25) involving 1000 acute leukemia case subjects in Germany and 492 ALL case subjects in The Netherlands, respectively. In this study, which includes the largest case-control studies of childhood ALL and AML that evaluated the association of breast-feeding with childhood leukemia to date, we found that ever primarily breast-feeding was related to a reduced risk of ALL and AML (OR = 0.79; 95% CI = 0.69–0.90), with a greater benefit for children who were

Table 3. Breast-feeding and risk of childhood leukemia*

	Total sample			AML			ALL		
	No. of case subjects	No. of control subjects	OR (95% CI)†	No. of case subjects	No. of control subjects	OR (95% CI)†	No. of case subjects	No. of control subjects	OR (95% CI)†
Ever breast-fed	2200	2418							
No	1126	1096	1.00 (reference)	266	273	1.00 (reference)	860	823	1.00 (reference)
Yes	1074	1322	0.79 (0.70–0.91)	190	266	0.77 (0.57–1.03)	884	1056	0.80 (0.69–0.93)
Months breast-fed‡									
None	1126	1096	1.00 (reference)	266	273	1.00 (reference)	860	823	1.00 (reference)
≤6	623	704	0.87 (0.75–1.01)	118	135	0.95 (0.68–1.33)	505	569	0.86 (0.73–1.01)
>6	450	617	0.70 (0.59–0.82)	72	130	0.57 (0.39–0.84)	378	487	0.72 (0.60–0.87)
Trend test§			<i>P</i> = .0001			<i>P</i> = .0084			<i>P</i> = .005
Months breast-fed‡									
None	1126	1096	1.00 (reference)	266	273	1.00 (reference)	860	823	1.00 (reference)
1–3	364	394	0.88 (0.74–1.05)	60	55	1.12 (0.73–1.72)	304	339	0.85 (0.70–1.03)
4–6	259	310	0.80 (0.70–1.03)	58	80	0.81 (0.54–1.23)	201	230	0.87 (0.68–1.08)
7–9	146	214	0.65 (0.51–0.83)	25	52	0.48 (0.28–0.82)	121	162	0.70 (0.53–0.92)
10–12	138	203	0.63 (0.49–0.81)	26	38	0.69 (0.39–1.23)	112	165	0.61 (0.46–0.80)
>12	166	200	0.81 (0.64–1.03)	21	40	0.58 (0.31–1.08)	145	160	0.85 (0.66–1.11)
Trend test§			<i>P</i> = .0002			<i>P</i> = .0065			<i>P</i> = .0034

*Subjects under the age of 1 year at diagnosis and subjects with a missing value were excluded from analysis. AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia.

†Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from conditional logistic regression models, adjusted for maternal race, maternal education, and family annual income.

‡Subjects in these categories do not sum to the total number of study subjects because of missing data.

§All *P* values are two-sided; those <.05 were considered to be statistically significant.

Table 4. Breast-feeding and risk of childhood acute leukemia by morphology and immunophenotype*

	OR (95% CI)† by AML morphologic subtype		
	M0, M1, and M2‡ [No. of case/control subjects = 157/165]	M4 and M5§ [No. of case/control subjects = 135/137]	Other AML [No. of case/control subjects = 164/237]
Never breast-fed	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever breast-fed	0.73 (0.42–1.26)	0.88 (0.51–1.51)	0.72 (0.45–1.16)
Duration breast-fed			
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤6 mo	1.04 (0.55–1.96)	1.02 (0.54–1.91)	0.84 (0.49–1.43)
>6 mo	0.42 (0.20–0.88)	0.73 (0.37–1.45)	0.59 (0.32–1.10)
Trend test¶	<i>P</i> = .04	<i>P</i> = .42	<i>P</i> = .10
	OR (95% CI)† by ALL immunophenotype		
	Early pre-B-cell ALL# [No. of case/control subjects = 842/914]	Pre-B-cell ALL** [No. of case/control subjects = 218/229]	T-cell ALL [No. of case/control subjects = 177/193]
Never breast-fed	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever breast-fed	0.84 (0.68–1.04)	0.53 (0.35–0.81)	0.83 (0.49–1.39)
Duration breast-fed			
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤6 mo	0.95 (0.75–1.20)	0.50 (0.31–0.81)	0.84 (0.48–1.48)
>6 mo	0.70 (0.54–0.92)	0.59 (0.35–1.01)	0.81 (0.41–1.61)
Trend test¶	<i>P</i> = .01	<i>P</i> = .01	<i>P</i> = .50

*Subjects under the age of 1 year at diagnosis and subjects with missing values were excluded from the analysis. AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia.

†Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from conditional logistic regression models, adjusted for maternal race, maternal education, and family annual income. Case subjects (*n* = 217) with B-cell ALL (not otherwise specified) were not included in the smaller group analyses of ALL because of potentially heterogeneous disease subtypes.

‡M0 = myeloblastic with no maturation; M1 = myeloblastic with minimal maturation; M2 = myeloblastic with maturation.

§M4 = acute myelomonocytic leukemia; M5 = acute monocytic leukemia.

||Other AML include M3 (acute promyelocytic leukemia), M6 (acute erythroleukemia), and M7 (acute megakaryoblastic/megakaryocytic leukemia).

¶All *P* values are two-sided; those <.05 were considered to be statistically significant.

#Early pre-B-cell ALL = B-lineage markers positive, cytoplasmic immunoglobulin negative.

**Pre-B-cell ALL = B-lineage markers positive, cytoplasmic immunoglobulin positive.

breast-fed for more than 6 months (OR = 0.7). The reduced risks were observed for M0, M1, and M2 morphologic subtypes of AML and early pre-B-cell ALL. The inconsistency between current and earlier studies may be due to the fact that none of the early studies had adequate statistical power to detect the inverse association of breast-feeding with the risk of childhood acute leukemia as reported in the current study. Differences in the type, source, or characteristics of the control group, particularly in relation to breast-feeding, could explain some of the inconsistent findings (26).

Alternative explanations must be considered. The observed inverse association with breast-feeding may reflect a potential selection bias due to the source of control subjects (random-digit-dialing) and different participation rates among control and case subjects. The difference between case and control subjects in maternal education and family income may also suggest the possibility of selection bias (27). On the other hand, the breast-feeding rate among control subjects in our study (i.e., 56% of control children who were born during 1984–1992 and were 1–5 years of age at interview had ever been primarily breast-fed) was similar to that in the general U.S. population. For example, 52% of U.S. mothers surveyed in 1989 and 60% surveyed in 1995 indicated that they had breast-fed their newborns (28). Thus, while selection bias cannot be completely excluded, it appears unlikely to be the sole explanation for the inverse associations found in our study. The similar inverse association with breast-feeding observed for both AML and ALL may raise some concerns about bias, particularly recall bias, although other exposures (including high-dose ionizing radiation, use of chloramphenicol, and paternal preconception x-ray exposure) have been found to be associated with both AML and ALL in children (29–31). Comparing breast-feeding data collected during two separate interviews among a subgroup of study participants, we found that women can fairly consistently report long-term breast-feeding (>6 months) experience. We, however, were not able to evaluate the validity of the self-reported breast-feeding information compared with the actual practice. The inverse association found in our study, therefore, could have resulted from differential misclassification if mothers of control subjects overreported breast-feeding

their offspring and/or mothers of case subjects underreported breast-feeding their children. Finally, the large number of analyses performed raises the possibility of a chance finding. The consistency across both ALL and AML subtypes, however, makes this less likely.

Biologically plausible mechanisms that may underlie the relationship between breast-feeding and risk of childhood acute leukemia include anti-infective and/or immune-stimulatory and immune-modulating effects (26). Breast-feeding can reduce risk of enteric infectious diseases, otitis media, and respiratory infections in infants (3,4,6–10) through transmission of maternal antibodies and macrophages and lymphocytes via colostrum and human milk (3,4). Breast-feeding also can stimulate or modulate the development of the immune system of infants (3,26), with breast-fed infants demonstrating enhanced vaccine responses (32) and larger thymus size (5). In addition, various growth factors and cytokines (e.g., transforming growth factor- α , tumor necrosis factor- α , insulin-like growth factor, and interleukins 10 and 8) have also been isolated from human milk (3). All of these mechanisms may potentially influence leukemogenesis.

Although the leukemogenic effects of feline and bovine viruses are well documented in animal studies (33), various infections, organisms, and/or unusual manifestations of infections have been proposed to play a role in childhood ALL (33–40), but epidemiologic studies have provided only circumstantial evidence. This evidence includes the following: 1) the emergence of an ALL incidence peak at ages 2–4 years among white children in the United States and the U.K. between 1920 and 1940 and among black children during the latter part of the 1960s (34,35); 2) a positive association between the ALL age peak and socioeconomic status (in some but not all studies) (34,35); 3) an inverse association between early infection, day care, and risk of childhood leukemia (34,36); 4) a statistically significant increase in the incidence of ALL in the peak age group after an unusual degree of population mixing (37); and 5) association of childhood leukemia risk with influenza outbreaks and other maternal common infections during pregnancy (e.g., varicella, influenza, or rubella) (2,39), as well as postnatal *Mycoplasma pneumoniae* (40). In contrast to childhood ALL, the relationship between infection

and the occurrence of childhood AML has not been extensively studied. The international variation in the incidence pattern for childhood AML, with higher risks observed in populations from Asian and African countries, may suggest the involvement of certain infectious agents in the development of AML (1). The specific or nonspecific anti-infectious effect and early immune-stimulating effects of breast-feeding may work either independently or synergistically to protect children against acute leukemia.

In summary, findings from the large CCG epidemiologic studies of childhood AML and ALL show a reduction in risk among breast-fed infants, particularly those breast-fed for more than 6 months. To eliminate the possibility that the findings are due to potential forms of bias or chance, confirmation is needed from other large and more detailed investigations. If our findings are confirmed, they may provide further support for the recommendation of the American Academy of Pediatrics (41) for longer term breast-feeding of infants.

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