



# Longer breast-feeding and protection against childhood leukaemia and lymphomas

A. Bener<sup>a</sup>, S. Denic<sup>b,\*</sup>, S. Galadari<sup>c</sup>

<sup>a</sup>*Department of Community Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates*

<sup>b</sup>*Department of Internal Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates*

<sup>c</sup>*Faculty of Medicine and Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates*

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## Abstract

The role of breast-feeding in protecting against childhood acute leukaemia and lymphomas is uncertain. We investigated this issue in a case-control study comprising 117 patients, aged 2–14 years, with acute lymphocytic leukaemia (ALL), Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL), as well as 117 controls matched for age, sex and ethnicity. Information was collected via a telephone interview of the mothers. The median duration of breast-feeding among patients was significantly shorter than among controls, 7 (range 0–23) and 10 (range 0–20) months, respectively ( $P < 0.0001$ ). Breast-feeding of 0–6 months' duration, when compared with feeding of longer than 6 months, was associated with increased odds ratios (OR) for ALL (OR = 2.47, 95% confidence interval (CI) 1.17–5.25), HL (OR = 3.75, 95% CI 0.80–18.69), NHL (OR = 4.06, 95% CI 0.82–22.59), and overall (OR = 2.79, 95% CI 1.54–5.05). In the patient group, there were a significantly higher number of children and people per family, and patients were of a higher birth order than controls. In multivariate analysis, breast-feeding duration continues to be an independent predictor of lymphoid malignancies ( $P = 0.015$ ). In conclusion, breast-feeding lasting longer than 6 months may protect against childhood acute leukaemia and lymphomas. © 2001 Elsevier Science Ltd. All rights reserved.

**Keywords:** Breast-feeding; Acute lymphocytic leukaemia; Hodgkin's lymphoma; Non-Hodgkin's lymphoma; United Arab Emirates

## 1. Introduction

Whether breast-feeding is associated with a decreased incidence of the lymphoid malignancies in children is uncertain [1–7]. The hypothesis that breast-feeding provides protection against lymphoid malignancies is based on the belief that unspecified viruses can cause cancer, and that immunoglobulins from mother's milk protect the infant from infection. The hypothesis that acute leukaemia and Hodgkin's (HL) and non-Hodgkin's lymphomas (NHL) have a viral aetiology stems from two types of observations. Firstly, there is direct evidence that human T-cell leukaemia/lymphoma virus type I (HTLV-I) causes adult T-cell leukaemia/lymphoma; there is a less firm link between HTLV-II and

hairy cell leukaemia, Epstein–Barr virus and both HL and Burkitt's lymphomas, and human herpesvirus-8 and NHL in AIDS patients [8]. There is also evidence linking hepatitis C virus with the development of NHL [9]. Secondly, epidemiological observations show a positive correlation between an increased incidence of acute leukaemia and lymphomas and the factors underlying a higher level of infection [10,11]. The study that examined the incidence of childhood cancer in relation to breast-feeding found a lower incidence of cancer in children who were breast-fed longer. But the lower incidence of cancer was due to the lower incidence of lymphoma [1]. In another study, the risk of HL and NHL was reduced, but this reduction did not reach statistical significance [2]. While a recent study found a significant risk reduction for acute lymphocytic leukaemia (ALL) among children who were breast-fed for longer periods [7], other investigators have shown the same less convincingly or not at all [1–6]. At present,

\* Corresponding author. Tel.: +971 3 7039 421; fax: +971 3 7672 995.

E-mail address: s.denic@uaeu.ac.ae (S. Denic).

therefore, the role of breast-feeding in protecting against childhood leukaemia and lymphomas is unclear.

In a case–control study comprising a population with a strong tradition of breast-feeding, we sought to determine whether longer breast-feeding was associated with a decreased risk of lymphoid malignancies. The results show that breast-feeding for longer than 6 months may protect children against acute leukaemia and lymphomas.

## 2. Patients and methods

The patient group included children with acute lymphocytic leukaemia (ALL), HL and NHL who were seen in the hospital over a 15-year period (1 January 1983–31 December 1997). The cases were identified from the hospital Medical and Pathology Department records. The hospital, which is the cancer centre of the United Arab Emirates (UAE), is the main teaching hospital of the medical school and provides free care to all persons with cancer. The patients selected, between 1 and 15 years of age, dead and alive, were all native-born UAE nationals. The patients whose parents were not born in the UAE and UAE nationals of other ethnic extraction were excluded; our cases thus represent a population of Bedouin Arabs. For each case, one non-cancer control was randomly selected and matched by sex, nationality and year of birth. The controls were healthy subjects who visited the general practitioner or paediatric well-baby clinic in the hospital for immunisation, periodic follow-up of healthy children or minor medical problems; children with chronic diseases were excluded. Selection along ethnic lines was the same as for the cases and was done to decrease the environmental and genetic influences that have been said to affect the incidence of childhood lymphoid malignancies and because the local population is made up of highly diverse, often newly arrived ethnic groups [12,13]. Information from the patients and controls was obtained by standardised telephone interviews with the mothers, who were asked whether they had breast-fed their children and if so, for how long. The cases and controls were interviewed at the same time, interviews being completed within a 4-month period. The time between diagnosis and interview was up to 15 years. Information on the factors that may lead to increased levels of infection was also collected, as were data on other variables previously reported to be associated with lymphoid malignancies (Table 1). Birth weight was obtained from the medical records. The parents' age refer to the time of child's birth. The parents' years of education, number of children per family, number of bedrooms, number of people per household and family income refer to the time at diagnosis. Smoking history was not obtained, as the women native to this area do not smoke [14]. Breast-feeding duration was classified

into intervals of 0–6 months and >6 months to make analysis comparable to past studies.

The statistical analysis was performed using the Statistical Packages for Social Sciences (SPSS). Data are expressed as means with 95% confidence intervals. The Student *t*-test and the Mann–Whitney test were used to ascertain the significance of differences between mean values of two continuous variables. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated by using the Mantel–Haenszel Chi-Square test. Stepwise logistic regression analysis was performed to find the best predictors of malignancy as dependent variables. A two-tailed *P*-value of <0.05 was considered significant.

## 3. Results

4 patients and 3 controls could not be traced after they had been identified. All mothers of both the patients and controls responded to the questionnaire. The mean age of 117 patients was 4.7 (range: 2–14 years); 64% were males and 36% were females. The duration of breast-feeding ranged from 0 to 23 months in patients, and from 0 to 20 months in controls; 4 patients and 1 control received artificial feeding (breast-feeding of 0 month duration). Patients with lymphoid malignancies (ALL, 69 (59%); HL, 22 (19%); NHL, 26 (22%)) had significantly fewer median and mean months of breast-feeding than did their matched controls (Table 1). Zero to 6 months breast-feeding duration, compared with breast-feeding of longer than 6 months, was associated with increased odds of all lymphoid neoplasms. Shorter periods of breast-feeding were associated with an increased risk of ALL, HL and NHL (Table 2).

The patients had significantly more brothers and sisters, more people per household, higher number of bedrooms, higher birth order and higher family income than controls. The birth weight, parents' age and education were not significantly different between the patients and controls (Table 1). In multivariate analysis, breast-feeding again showed an independent protective effect on the risk for all lymphoid malignancies. The number of people per household, number of children per family, and birth order were also independent predictors of childhood lymphoid malignancies in multivariate analysis. The numbers of bedrooms and family income were not significant variables (Table 3).

## 4. Discussion

Breast-feeding for longer than 6 months was associated with a decreased risk of developing ALL, HL and NHL. The evidence of a protective effect against lymphoid malignancies from longer breast-feeding

Table 1  
Breast-feeding and other variables in patients and controls

	Mean (95% CI)		<i>P</i> value
	Patients ( <i>n</i> = 117)	Controls ( <i>n</i> = 117)	
Breast-feeding duration (months)			
Median (range)	7 (0–23)	10 (0–20)	< 0.0001
Mean	8.8 (7.6–9.9)	12.0 (10.9–13.1)	< 0.0001
Birth weight (kg)	3.2 (3.1–3.3)	3.3 (3.1–3.4)	0.11
Mother's age (years)	26.9 (25.9–27.9)	27.9 (27.0–28.8)	0.11
Father's age (years)	33.5 (31.6–35.3)	35.1 (34.0–36.2)	0.08
Education (years)			
Mother	8.0 (6.9–9.2)	8.0 (7.0–9.1)	0.79
Father	5.7 (4.8–6.5)	6.4 (5.3–7.5)	0.39
Children per family	5.1 (4.6–5.7)	3.5 (3.1–3.9)	< 0.0001
Birth order	4.1 (3.60–4.5)	2.9 (2.6–3.2)	< 0.0001
Number of bedrooms	5.3 (4.8–5.8)	3.3 (3.1–3.5)	< 0.0001
People per household	10.4 (9.6–11.1)	7.1 (6.5–7.7)	< 0.0001
Family income (USD per month)	2222 (2025–2420)	1918 (1666–2172)	0.01

USD, U.S. dollars; 95% CI, 95% confidence interval.

Table 2  
Duration of breast-feeding and the risk of childhood leukaemia and lymphoma

	Patients <i>n</i> (%)	Controls <i>n</i> (%)	Odds ratio (95% CI)	<i>P</i> value
Overall				
Breast-fed 0–6 months	56 (48)	29 (25)	2.79 (1.54–5.05)	0.0002
Breast-fed > 6 months	61 (52)	88 (75)	1.0 <sup>a</sup>	
Acute lymphocytic leukaemia				
Breast-fed 0–6 months	37 (54)	22 (32)	2.47 (1.17–5.25)	0.01
Breast-fed > 6 months	32 (46)	47 (68)	1.0 <sup>a</sup>	
Hodgkin's lymphoma				
Breast-fed 0–6 months	10 (45)	4 (18)	3.75 (0.80–18.69)	0.055
Breast-fed > 6 months	12 (55)	18 (82)	1.0 <sup>a</sup>	
Non-Hodgkin's lymphoma				
Breast-fed 0–6 months	9 (35)	3 (12)	4.06 (0.82–22.59)	0.050
Breast-fed > 6 months	17 (65)	23 (88)	1.0 <sup>a</sup>	

95% CI, 95% confidence interval.

<sup>a</sup> Referent.

comes from a population with a strong and continuing tradition of breast-feeding.

The effect of breast-feeding on risk reduction for childhood ALL was examined in several studies [1–7]. One large recent case-control study showed that breast-feeding for longer than 6 months significantly reduced the risk of ALL [7]. Two other studies also found reduced risks for ALL, though they were non-significant [1,6]. Other studies, however, did not show a protective effect of breast-feeding against childhood ALL [3–5]. Our findings of a decreased risk of HL and NHL in children who were breast-fed for longer than 6 months are of borderline significance and are similar to previously published reports. One of those reports found significantly decreased odds of NHL [1] and the other showed non-significantly decreased odds of HL and NHL [2] in children who were breast-fed longer.

Table 3  
Risk factors for childhood lymphoid malignancies by multivariate analysis

	Odds ratio (95% CI)	<i>P</i> value
Breast-feeding duration	2.26 (1.17–4.35)	0.015
Birth weight	1.23 (0.81–1.85)	0.315
Mother's age	1.03 (0.98–1.10)	0.234
Father's age	1.00 (0.92–1.04)	0.18
Education		
Mother	1.00 (0.95–1.06)	0.784
Father	0.99 (0.92–1.05)	0.813
Children per family	1.63 (1.55–1.71)	< 0.0001
Birth order	1.80 (1.13–2.86)	0.012
Number of bedrooms	0.89 (0.67–1.17)	0.195
People per household	2.51 (1.48–4.25)	< 0.0001
Family income	1.14 (0.59–2.22)	0.69

95% CI, 95% confidence interval.

However, another small study detected no risk reduction for NHL in breast-fed children [4]. A 1988 review of breast-feeding and lymphoid malignancies concluded that the evidence points towards a protective effect of breast-feeding against HL, but not against NHL or ALL [15]. Therefore our results need to be interpreted in view of all findings.

In our study of 69 ALL cases, 68% of controls had been breast-fed by their mothers for more than 6 months. In another positive report that reached statistical significance and which involved 1744 cases [7], 44% of controls had been breast-fed for more than 6 months. In the two ALL positive reports that did not reach statistical significance [1,6], breast-feeding for more than 6 months in controls was 35 and 17%, respectively. The first of these two studies had 52 matched ALL patients and the second 1001 patients. In two other negative reports, however, longer breast-feeding was the case in only 8 and 9%, respectively [3,4]. Another study did not take the duration of breast-feeding into consideration [5]. Additionally, the overall prevalence of breast-feeding in our population was higher (control group = 99%) than in all other studies (ALL control groups range: 41–73%) [1–7]. This suggests a ‘dosing effect’ i.e. that low prevalence of prolonged breast-feeding together with a lower overall prevalence of breast-feeding may obscure its protective effect against childhood leukaemia. The high prevalence of breast-feeding in our study is not a chance finding, as others have also found a high prevalence of breast-feeding in this part of the world [16].

In our groups of 22 HL and 26 NHL cases, 82 and 88% of controls had been breast-fed for more than 6 months, respectively. In another two positive lymphoma studies, 35 and 63% of controls had been breast-fed for more than 6 months, respectively [1,2]. In a negative study, this was the case in 9% of controls and none of the 19 NHL patients were breast-fed for longer than 6 months [4]. The data for lymphomas also suggest that duration of breast-feeding may be important if children are to be protected against this neoplasm. A study size determines statistical power and in lymphoma studies [1,2,4] it varied between 14 and 68, another important factor to consider in the interpretation of the results.

A bias can influence results of a study. In our study, the dropout rate of 3% among both the patients and controls (untraceable families) was low, and the response rate in personal interviews of mothers only was 100%. Other studies had larger dropout rates, also used fathers or other guardians of children to obtain information about breast-feeding, or used mailed written questionnaires, all of which leave room for bias. Our study was also well controlled for smoking, as the women native to our region do not smoke [14]. Smoking during pregnancy has been considered an indicator of social class [4], but it should not be excluded as a possible environmental risk for childhood leukaemia and

lymphomas. The varying rates of childhood leukaemia in different parts of the world suggest a possible influence of environmental or genetic factors [12,13]. In our study the possibility of such influences was minimised because we were able to study an ethnically homogeneous population in an otherwise ethnically diverse country. The negative reports [3,4] on the benefits of longer breast-feeding did not control for this variable as strictly as we did. None the less, we could not exclude selection bias. The differences in income between cases and controls may suggest a selection bias or could be a chance finding, a result of multiple comparisons. However, in our multivariate analysis income was not an independent prognostic factor. Noteworthy is the fact that the mean family income in our population is high and uniformly distributed. Another source of bias could have been interviews despite the same recall times for cases and controls. This would be the case if mother's recall was affected by child's malignancy, a chronic illness that was an exclusion criterion in controls.

The preponderance of males over females among the patients with lymphoid malignancies was also found by others [1,5]. Among the patient group, household crowding was greater than among controls. The number of children in a family, birth order, number of bedrooms and the number of people per household are all factors favouring the transmission of infection and are all significantly higher among the patients than controls. All of those variables except the number of bedrooms were significant in multivariate analysis, suggesting that number of bedrooms is a confounding factor. These findings support the hypothesised role of unspecified viruses in the development of acute leukaemia and lymphomas. One of the negative breast-feeding studies [3] used, as supporting evidence against the hypothesis, the finding that hospital admissions for infection during the first year of life were not decreased among breast-fed children and not increased among ALL patients. Acute infant infection requiring hospitalisation, however, may not be a good surrogate for the slow viral carcinogenesis implicit in the hypothesis. In the study mentioned above, only 8% of children in the control group and 6% in the ALL group were breast-fed for longer than 6 months, suggesting that small numbers in the “intervention” group may prevent detection of benefit. We did not find maternal age, paternal age, education and birth weight to be different between the patients and controls. These parameters in the past were inconsistently correlated with childhood leukaemia and lymphoma.

Our findings could have come from the unequal distribution of some unknown prognostic factors for leukaemia and lymphomas. This is always possible in dealing with diseases whose development may be influenced by multiple environmental and hereditary factors. We believe this to be unlikely because of our moderately

large number of patients and matched control groups of the same size, and the same direction and similar magnitude of risk for each of the three lymphoid malignancies. Multiple comparisons could produce significant results by chance and could not be excluded in our study. However, the same reverse association between breast-feeding duration and risk for all three different malignancies makes it unlikely.

In conclusion, the results of our study are derived from a population with a strong and continuing tradition of prolonged breast-feeding, a practice that has generally been abandoned in developed countries. Breast-feeding for 6–24 months is recommended by the World Health Organization (WHO) [17]. We believe, in view of all evidence cited above, that the protective effect of longer breast-feeding against childhood leukaemia and lymphomas is now more firmly established.

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