

Breast feeding and the risk of childhood acute lymphoblastic leukemia in Mosul-a case control study

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ABSTRACT

Context: leukemia is the most common malignancy in childhood; many studies were conducted to explore the probable protective effect of breast feeding on childhood leukemia.

The aim of the present study is to evaluate the effect of breast on the development of childhood leukemia.

Methods: A case control design was conducted at the hematology unit; Ibn Alatheer pediatrics hospital in Mosul city. A total of 71 children diagnosed to have acute lymphoblastic leukemia and 70 children diagnosed to have diseases other than malignancy were included in the study as cases and controls respectively. SPSS and excel computer programs, chi squared test and Z test of two proportions, were used in statistical analysis.

Results: The present study observed a protective association between breast feeding and the risk of childhood leukemia (OR=0.2, P<0.05). Moreover, the study showed increased risk of leukemia among children exposed to explosions near their residency (OR= 3.9, P<0.001).

Conclusions: Breast feeding might have a vital protective effect against childhood leukemia. On the other hand, exposure to explosive materials might carry a high risk for developing leukemia.

الهدف: تهدف الدراسة إلى تقييم العلاقة بين الرضاعة الطبيعية وخطورة الإصابة بابيضاض الدم عند الأطفال في الموصل.

طريقة الدراسة: دراسة العينة والشاهد.

مكان الدراسة: وحدة أمراض الدم / مستشفى ابن الأثير للأطفال في الموصل

قياس المحصلة النهائية: تم تحليل النتائج باستخدام برنامجي SPSS و excel للحاسب الإلكتروني وقد تم استخدام اختباري X^2 و Z في التحليل الإحصائي.

النتائج: أظهرت الدراسة إن إعطاء الأطفال حليب الأم في السنة الأولى من العمر قد يحميهم من الإصابة بابيضاض الدم (OR=0.2). بالإضافة إلى ذلك أشرت الدراسة وجود علاقة قوية بين التعرض للانفجارات والإصابة بالمرض أعلاه

(OR= 3.9).

الاستنتاج: في ضوء نتائج الدراسة يمكن الاستنتاج بأن حليب الأم يحمي الطفل من الإصابة بابيضاض الدم.

Leukemia is the most common malignancy in childhood with a worldwide average annual incidence of 3.8-4.8/100000 children aged 0-14 years⁽¹⁾. Globally leukemia accounts for 30% of all childhood malignancies with 75% being diagnosed as

acute lymphoblastic leukemia (ALL)⁽¹⁻³⁾. The incidence of ALL is higher among males than females and among whites than among blacks⁽¹⁻⁴⁾. Although the etiology of childhood leukemia has been studied for more than 50 years, causal factors are largely unidentified.

Certain conditions such as Down's syndrome, genetic abnormalities, Fanconi's anemia, and exposure to ionizing radiation thought to explain a small percentage of cases of leukemia^(1,2,5).

The infectious etiology of leukemia continues, to be explored with a potential for bacterial and viral sources. After viruses were identified as the cause of some leukemias in animals, an etiological hypothesis for human leukemia has been introduced^(6,7). On the other hand, there are some epidemiological observations of geographic clusters of leukemia cases suggesting common exposures (eg: infections) may play a role⁽⁸⁾.

Current etiologic researches suggest that in utero exposure (eg: prenatal drugs and dietary exposure) are implicated in the causation of infant leukemia while infection and environmental factors after birth might play a role in the proliferation of leukemia clone⁽⁹⁻¹¹⁾.

Speculations have been focused recently on the role of breast feeding in protecting children from diseases including malignancies^(12, 13). Human milk has long been recognized as providing numerous antimicrobial, anti-inflammatory, and immunomodulating agents. Many studies have shown that breast feeding protects against infections through transmission of maternal antibodies, macrophages, and lymphocytes^(12,14,15). Human milk contains numerous immune-related compounds, and there is a comprehensive literature on the potential immune effects of human milk⁽¹⁶⁾. Several immune-related compounds are present in breast milk. Several of these components of milk offer passive protection in the upper respiratory system and the gastrointestinal tract, preventing adherence of pathogens to the mucosa, and thereby protect the infant against invasive infections. There are data suggesting that breast milk stimulates the child's own immune system as well⁽¹⁷⁾.

Several lines of evidence support the hypothesis that the child's own immune system is influenced by breast milk. The thymus plays an important role in the maturation of the immune system. Ultrasound measures of thymus size in healthy Danish infants at 4

months of age revealed that the thymus of breast-fed infants is twice the size of that in formula-fed infants⁽¹⁸⁾.

In conclusion, the most important short-term benefit of breast-feeding is the protection against infectious diseases, which can be explained by the immune factors in human milk, of which the most important are IgA antibodies. There is also evidence that breast-feeding influences the development of the infant's own immune system, which could be the reason that some immune-related diseases such as inflammatory bowel diseases, childhood cancers, and type I diabetes seem to be less prevalent in breast-fed infants. The effect on atopic diseases is not so clear. There seems to be a protective effect against asthma, but the effect on atopic dermatitis is more doubtful, especially in infants without a family history of atopic disease⁽¹⁷⁾.

Based on these facts, investigators hypothesized that breast feeding could reduce the risk of childhood leukemia, and many studies all over the world suggest that breast feeding protects children from developing childhood leukemia^(7, 12, 19-21).

The aim of the present study is to evaluate the probable protective effect of breast feeding on the development of childhood leukemia in Mosul.

Patients and Methods:

The study was conducted over 1 year period from the 1st of April 2007 to the 1st of April 2008. In order to achieve the aim of the present study, case control design has been adopted. The study sample includes 71 children aged ≤ 15 years, and diagnosed to have ALL who consult hematology unit in Ibn Alatheer pediatrics hospital in Mosul. On the other hand, 70 children with the same age group who were consulting the same hospital and diagnosed to have any other disease than malignancy were chosen as controls. Unpaired sampling technique was used in the study; matching for age was conducted.

Every child included in the study sample was interviewed and examined by the investigators in the presence of the parents. A questionnaire form was completed for every child which includes age, sex, residency, in

addition to information regarding the probable factors than can be associated with ALL including type and duration of feeding in infancy, positive family history for leukemia, exposure to parental smoking, and history of exposure to explosion in a distance ≤ 1 km from their residency.

Data analysis was done by using SPSS and excel computer systems; odds ratio has been calculated for every factor dealt with in this study with its 95% confidence interval. Chi squared test and Z test for two proportions were used for the measurement of the statistical significance.

Results:

The present study showed that ALL was more frequent in males than in females (60.6% and 39.4% respectively) and the difference was statistically significant ($P=0.03$). Moreover, about 47% of the cases were observed in the age group 5-10 years, Table (1).

Table (2) shows the distribution of the study population according to the type of feeding during infancy. It is evident that the frequency of breast feeding for a duration ≥ 6 months (compared to those with no history of breast feeding) was higher among controls than among cases (81.4% and 73.3% respectively)

with odds ratio 0.2 and the difference between the two groups was statistically significant ($P<0.05$). In addition, the 95% confidence interval for the odds ratio was found to be 0.05-0.87.

On the other hand, Table (3) shows the distribution of the study population according to some probable risk factors for ALL. It is evident that positive family history for leukemia, and parental smoking had nearly a similar frequency among cases and controls with odds ratio 1.06 and 1.46 respectively.

Moreover, unfortified milk feeding during infancy was found to be more frequent among cases than among controls (14% and 8.6% respectively) with odds ratio 1.75; the difference was not significant ($P> 0.05$). Place of residency was found to be similarly distributed among cases and controls (35.2% and 35.7% respectively) with odds ratio 1.03.

Nevertheless, the frequency of exposure to explosions was much higher among cases than among controls (39.4% and 14.3% respectively) with a very highly significant statistical difference ($P<0.001$), odds ratio was found to be 3.9 with 95% confidence interval 1.78-8.85.

Table (1) Age and sex distribution of all cases .

Age	Male		Female		Total	
	No	%	No	%	No	%
0-<5	13	18.3	8	11.3	21	29.6
5-<10	18	25.4	15	21.1	33	46.5
10- \leq 15	12	16.9	5	7.0	17	23.9
Total	43	60.6	28	39.4	71	100

Table (2) Distribution of the study population according to type and duration of feeding during infancy.

Breast Feeding	Cases (n = 71)		Controls (n = 70)		OR	P	95% CI
	No	%	No	%			
Duration ≥ 6 months	52	73.3	57	81.4	0.2*	<0.05*	0.05-0.87
Duration < 6 months	10	14.1	11	15.7	0.2**	>0.05**	0.04-1.05
No history of breast feeding	9	12.6	2	2.9	-	-	-

*Breast feeding for Duration ≥ 6 months Vs No history of breast feeding.

** Breast feeding for Duration < 6 months Vs No history of breast feeding.

Table (3) Distribution of study population according to probable risk factors of leukemia .

Factors	Cases (n=71)		Controls (n=70)		OR	P*	95% CI
	No	%	No	%			
Positive family history for leukemia	18	25.4	17	24.3	1.06	>0.05	0.5-2.26
Parental smoking	35	49.3	28	40	1.46	>0.05	0.51-2.83
Infant feeding with unfortified milk	10	14	6	8.6	1.75	>0.05	0.62-4.92
Urban residency	28	35.2	29	35.7	1.03	>0.05	0.9-1.18
Exposure to explosions in a distance \leq 1 km	28	39.4	10	14.3	3.9	<0.001	1.78-8.85

* Chi squared test is used.

Discussion:

Leukemia is the leading cause of morbidity among children less than 15 years of age⁽²²⁾. Currently, the causes of childhood leukemia are not well known although sex, age, race, ionizing radiation, and specific genetic syndromes, have been consistently shown to be associated with increased risk of leukemia⁽²²⁾.

The present study observed that ALL was more common among males than among females, with male to female ratio 1.54:1. Similar results have been found in other studies conducted by Zack et al, Kaye et al, and Cartwright et al⁽²³⁻²⁵⁾.

The scientific evidence has been mixed regarding the association of breast feeding and childhood leukemia. A number of studies showed no association between breast feeding and leukemia risk, however, many recent studies suggest that breast feeding protects children from developing leukemia⁽¹²⁾.

The present study observed a negative association between breast feeding for a duration \geq 6 month, and the risk of childhood leukemia (OR=0.2). This result supports the theory that breast feeding protects children against leukemia.

Similar results have been observed in many other studies conducted all over the world. Van Duisu et al in Netherlands and Davis et al in USA observed a negative association between breast feeding and leukemia (OR=0.83 and 0.68 respectively)^(26,27). Moreover, similar negative association was observed in other studies conducted in

Germany and Canada 1999 (OR= 0.77 and 0.72 respectively)^(19, 28).

Nevertheless, the present study also found a negative association between shorter duration of breast feeding (< 6 months) and the risk of childhood leukemia (OR=0.2) but the difference was not significant ($p>0.05$) which might be due to the relatively small sample size. Although other studies conducted in UK 2001 observed a significant negative association between breast feeding for duration < 6 months, and the risk of leukemia (OR = 0.25)⁽²⁹⁾, Hardell et al in Sweden 2001 found no association between breast feeding <6 months and leukemia (OR = 1)⁽³⁰⁾.

A meta analysis was conducted in 2004 and reviewed 30 articles, which evaluated the association between breast feeding and childhood leukemia. The meta analysis observed a protective association between both short and long term breast feeding and childhood leukemia⁽¹²⁾.

On the other hand, the present study failed to find an association between the presence of some factors such as parental smoking, positive family history, feeding unfortified milk during infancy, and residency and the development of leukemia, although another study conducted in UK observed an association between parental smoking and leukemia⁽³¹⁾.

Nevertheless, the present study observed a very highly significant positive association between leukemia and exposure to explosions in a distance \leq 1 km. (OR=3.9, $P<0.001$). This association might be attributed to the exposure

to some carcinogenic chemicals or radioactive substance, which are products of the explosive materials, in addition to the severe psychological trauma on those children. There are many well documented cases of radiation induced cancer in human, some epidemiological studies postulated that even the exposure to small doses of radiation increase the risk of cancer significantly⁽³²⁾.

In bomb survivors and other irradiated populations the increase in risk of leukemia has appeared within 2-5 years after exposure⁽³³⁾. A cohort study conducted in Japan showed that the relative risk of leukemia at atomic bomb survivors at 1950-1985 was five⁽³⁴⁾.

Conclusions and Recommendations:

From the results of the present study, the following conclusions can be stated:

1. Breast feeding has a vital role in preventing childhood leukemia.
2. The exposure to explosions in near distance might carry a high risk for the development of childhood leukemia.
3. No association could be observed between place of residence and positive family history and the development of childhood leukemia. It is worthwhile to conduct other studies in Iraq to evaluate and observe the risk factors of childhood leukemia especially the exposure to explosive materials and to evaluate the protective effect of breast feeding.

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