RESEARCH COMMUNICATION

Breastfeeding is not Associated with Risk of Developing Childhood Leukemia in the Sultanate of Oman

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Abstract

Background: Recent case-control studies on breastfeeding and childhood leukemia risk have indicated that longer duration of breast feeding (> 6 months) is associated with decreased risk of the disease. Objective: To investigate the relationship between duration of breastfeeding and risk of childhood leukemia in Oman. Materials and Methods: In a case control study all recently diagnosed and registered cases of childhood leukemia at the National Registry during (1999- 2009), a total of 70 cases, were recruited. For each case, a gender and age matched control was selected either from the family relatives or from the neighbors of family siblings. Results: Breastfeeding is culturally favored for longer periods of time (up to 24 months) in Oman. Data of this study revealed that 21% of cases and 12 % of their gender and age matched controls were breastfed for an average duration of 6-12 months. In 75% of the cases and 81% of controls the period of breastfeeding was between 12-24 months. Only 4% of the cases and 7% of controls were breastfed for a period more than 24 months. No significant (P < 0.05) differences were observed between the cases and controls with respect to breastfeeding and the risk of childhood leukemia. Similarly the duration of breast feeding did not have any significant (P > 0.05) effect on the risk of childhood leukemia in Oman. Conclusion: This study indicated that duration of breastfeeding was not associated with risk of childhood leukemia in Oman and there may be some other environmental and genetic factors that might be responsible for the occurrence of this disease and must be explored further

Keywords: Childhood leukemia - negative risk factors - breastfeeding - Sultanate of Oman

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Introduction

Childhood cancers, primarily the leukemia and brain cancer are distinctively different from those in adults as they occur rarely in children but are one of the leading causes of childhood mortality (Jamal et al., 2003; American Cancer Society, 2010). Leukemias in Oman represents 30% of all cancers in children, and the acute lymphoblastic leukemia (ALL) is being the most common form of childhood leukemia (Silverman et al., 2001; Al-Lamki et al., 2004). Missaouti et al. (2011) reported that leukemias, lymphomas, and central nervous system (CNS) tumors were the principal cancers in the Centre of Tunisia. Although the exact etiology of childhood cancers is still not clear, the gender, age, race, in-utero ionizing radiation, and specific genetic syndromes have been consistently shown to be associated with risk of acute lymphoblastic leukemia among the children between the ages of 1 to 4 years (Cortes and Kantarjian, 1995; Eden, 2010; Kaatsch, 2010). The short period preceding the occurrence of childhood cancers provides little exposure opportunity for the assessment of nutritional factors to play a significant role in its cause or prevention. Therefore, the impact of diet on childhood leukemia during the postnatal life has been focused mainly on the role of breastfeeding in protecting children from diseases (Greaves et al., 1999; Davis 1998).

Human breast milk boosts the immunity of breastfed children by virtue of providing them with numerous antimicrobial, anti-inflammatory and immunological agents (Goldman, 1993). It also protects against different types of infections through transmission of maternal antibodies, macrophages and lymphocytes (Libster et al., 2009). Several case-control studies on breastfeeding and risk of childhood leukemia indicated that short duration (< 6 months) is associated with increased risk of the disease (Shu et al., 1995; Petridou et al., 1997; Davis et al., 1998; Hardle et al., 2001; Murray et al., 2002). Higher socioeconomic status (SES) of child's family has been considered as a risk factor for acute lymphoblastic leukemia (Greaves et al., 1993) although it has not been confirmed by other studies (Swensen et al., 1997). Higher SES mothers tend to retrospectively recall longer periods of breastfeeding than lower SES mothers (Scott et al., 1999). If the mother is better educated about the benefits of breastfeeding, she may be more inclined to breastfeed her baby, and therefore differences in education might reflects variations in breastfeeding practices (Li et al., 2002;

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Smulevich et al., 1999; Huttly et al., 1990). In addition to breastfeeding practices, early childhood dietary patterns might also play an important role in the immunologic etiology of childhood leukemia. However, only a few studies have addressed the role of early childhood feeding patterns and risk of childhood leukemia (Bener et al., 2001; Kwan et al., 2009).

Most of the studies investigating the association between breastfeeding and risk of childhood leukemia have been conducted in the West and their matched controls were not selected from the same family relatives of the studied cases (Bener et al., 2001; Guise et al., 2005; Martin et al., 2005; Flores-Lujano, et al, 2009) and therefore had little consideration for socioeconomic and genetic causes of disease. In the Sultanate of Oman breast feeding is culturally and religiously favored and is normally carried out for much longer periods of time (up to 3 years). To our knowledge so far no studies have been conducted in Oman to investigate the association between the duration of breastfeeding, childhood dietary patterns and risk of childhood leukemia. The present study was therefore conducted to investigate the impact of breastfeeding duration and childhood dietary patterns on the acute lymphoblastic leukemia (ALL) risk among children in the Sultanate of Oman.

Materials and Methods

Study Setting and Design

The study was carried out at the Sultan Qaboos University Hospital (SQUH), which manages the National Registry for childhood leukemia cases in Oman, starting from 1999 to present. The study was approved by the Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University (EC, No: 80). A hospital-based case-control study design was used to evaluate the impact of breastfeeding on the risk of childhood acute lymphoblastic leukemia (ALL).

Target Population

The study comprised of all recently diagnosed ALL cases including the registered cases at the Sultan Qaboos University Hospital (SQUH) during the years 2008-2010. A total of 274 ALL cases were registered and targeted for this study. Out of this 124 ALL cases died because of their original disease or one of its complications. The families of these cases could not be traced out as there has always been an emotional barrier for the mothers to share their views and answer the study questionnaire. We were however able to recruit 70 out of 150 alive cases. The others could not be included in the study due to either (1) Loss of contact track of the family, change their residence, close their phones; or (2) refusal of some families to consent for the study or (3) there was only one child in the family and no matching controls were available from the immediate relatives or neighborhood. The ratio of cases to controls was 1:1. As per our study criteria, for each case, one control was selected from the same family relatives (subject to be free from any blood disease and other type of cancer or any chronic diseases), so that the cases and controls are shared almost the same socioeconomic and genetic background, as well as dietary and environmental exposure.

For all study participants (cases and controls), the mothers were personally interviewed at the Nutrition Clinic of SQUH for the completion of study questionnaire. The questionnaire included the following: (1) Personal data: Name, age, sex, residence, mothers educational level, and occupation and family monthly income. (2) Risk factors related to childhood ALL; example family history of cancer, chromosomal breakage syndromes (Dawn's-Bloom's), exposure to radiation..etc. (3) History of breast feeding during infancy, including duration of breast feeding, pattern of breast feeding (solely or with weaning diets) and other nutritional supplements in non-breast fed cases. (4) Diet History Questionnaire (DHQ) developed by National Cancer Institute (Millen et al., 2006; Subar et al., 2001) and was appropriately modified for this study and tested for its validity and reliability.

The DHQ included 28 food items following the U.S. Department of Agriculture (USDA) Food Guide Pyramid food groups. The Cereals and grains group included whole grains, non-whole grains e.g. white bread, rice, pasta, all type of cereals. The vegetables group included dark green leafy and non-leafy vegetables, deep yellow vegetables, potatoes (fried and cooked), tomatoes, cabbage, cauliflower, brussel sprouts and other vegetables available in the local market). The fruits group included all types of available fruits. The dairy group included milk, yogurt, cheese and other dairy products. The meat group included beef, lamb, processed meats, organ meats, fish, poultry, seafood, eggs, meat substitutes, legumes, lentils, soybean and its products and nuts. The questions were also asked about sweets and added sugar (sugars added during processing) and discretionary fat (i.e. excess fat in foods and fat added to foods).

Statistical Analysis

The collected data was reviewed for its completeness and accuracy and was statistically analyzed using the statistical software, GraphPad Prism version 5. The results are expressed as mean + standard deviation (S.D.) or as percentage (%) of the different qualitative variables. Comparison between the cases and controls was made using unpaired t-test and Chi-square Pearson's ($\chi 2$), at 95% confidence intervals (95% CIs) and $P < 0.05$ was considered as statistically significant.

Results

General Characteristics of the study participants

The socio-demographic characteristics of the studied groups are given in Table 1. The gender ratio among study participants was similar (30 males and 40 females for cases and 30 males and 40 females for controls). The average mean age of the studied population was the almost the same (12.9 years ± 2.72 and 13.51 years ± 2.85, for cases and controls respectively), t= 1.29, P = 0. 19.

The monthly income of the families for cases and controls was (550.12 ± 23.64 versus 555.23± 24.12 Omani

Table 1. Socio-demographic Characteristics of Childhood Leukemia Cases and Their Controls

Characteristic	Cases* No.	%	Controls* No.	%	Statistical Analysis
Age in years[1]	12.1±2.72		13.5±2.85		P=0.19
Monthly Family Income (Omani Riyals)	550±23.6		555±24.1		P = 0.21
Family Size					$\chi2$= 0.04;
<4	9	13	9	13	P = 0.98
5 - 10	39	56	40	57	
>10	22	31	21	30	
Mothers Marital status					$\chi2$= 0.69;
Married	67	96	65	93	P = 0.71
Divorced	1	1	1	1	
Widowed	2	3	4	6	
Mothers Education					$\chi2$= 0.16;
Illiterate	11	15.7	10	14.3	P = 0.98
Secondary	49	70	50	71.4	
Diploma	3	4.3	3	4.3	
University	7	10	7	10	

*n=70; [1] Mean ±S.D

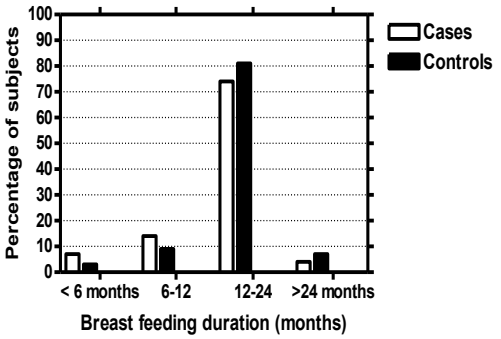

Figure 1. Distribution of subjects by Duration of Breastfeeding

Riyals respectively). The difference was not statistically significant, t= 1.27, P = 0.21. There was no significant difference in the family size between the cases and control groups, $\chi2$=0.04, P=0.98. Thirty one percent of cases had more than 10 family members, whereas 56% of cases had 5-10 family members. Only 13% of the cases had less than 4 family members. The same family size pattern was observed for the controls (30%, 57% and 13% respectively).

As regard the mothers' marital status, 96% of mothers for cases were married and only 4% was either widowed or divorced. However, no statistically significant difference was observed among the cases and controls regarding mothers' marital status, $\chi2$ =0.69, P=0.71. The educational status indicated that majority of the mothers (70%) had secondary school education in both cases and control groups. Almost 16% of cases and 14% for controls were Illiterate mothers. Those with higher education (diploma and university) constituted 14%. There was no statistically significance difference in the mother's educational status in cases and control, $\chi2$= 0.16, P=0.98.

Occupational status of the mothers of both cases and controls groups was similar, the majority (87 %) of the mothers were not working (house workers) as compared to working group (13%), for both cases and controls. Most of the mothers were involved in non technical administrative occupations.

Breastfeeding practice

The data on the frequency of breastfeeding is shown in Figure 1. The results indicated that 75% of the cases were breastfed for 12 to 24 months; 14% between 6-12 months, and 8% for less than six months. Only 4 % of children in cases group were breastfed for > 24 months. Almost similar patterns of breastfeeding were observed in the control group; 81% were breastfed for 12 to 24 months; 9% between 6-12 months, and 3% for less than six months. Only 7% children in control group were breastfed for more than 24 months. No statistically significant difference were observed among the studied groups, $\chi2$= 3.816, P=0.282.

Frequency of food consumption of the studied subjects

The frequency of consumption of carbohydrate rich foods from the cereals and grains group was the highest (60%) mainly the bread and different types of cooked rice. There was no statistically significant difference between cases and controls group, P<0.05, with regard to the consumption pattern of foods from cereal group. Meanwhile, regarding the utilization of fats and oils, it was revealed that that 69% of both the cases and controls consumed vegetable oils for their cooking and there was no statistically significant difference between the cases and controls, $\chi2$= 1.352, P=0.716.

The frequency of consumption of protein from different sources (animals, plants and dairy products) indicated that majority of the studied population cases (40% cases versus 43% controls) were consuming milk daily and there was no statistically significant difference in the cases and controls, $\chi2$= 0.916, P=0.8214. The weekly consumption of red meat (67%), fish (71%), poultry (71%) and eggs (65%) for cases was comparable with that of controls group (69%, 79%, 79% and 66% respectively) with no statistically significant difference. The consumption of plant protein, legumes and pulses (daily, weekly and monthly) was also comparable for both the cases and controls, $\chi2$= 2.44, P=0.485. There was no significant difference between the daily, weekly and monthly consumption of fresh vegetables and fruits between the cases and controls group ($\chi2$= 0.91, P=0.82, $\chi2$= 0.98, P=0.99, $\chi2$= 5.98, P=0.112 respectively). Regarding cooked vegetables, 26% of the cases were not consuming cooked vegetables versus 17% for controls group. However, the daily, weekly and monthly consumption of these foods was comparable for both groups with no statistically significant differences $\chi2$= 4.8, P=0.185.

Discussion

The specific etiology of childhood acute lymphoblastic leukemia is still unclear. Breastfeeding has long been associated with reduced risk of acute lymphoblastic leukemia and other cancers (Davis, 1998; Bener et al., 2008) because of its anti-infection and immune-modulating effects in children (Goldman, 1993; Shu et al., 1999; McNally and Eden, 2004). No significant (P >

0.05) differences were observed in the socio-demographic characteristics of cases and controls indicating no association between these factors and risk of acute lymphoblastic leukemia in Omani children. These results are partially in line with the findings reported earlier (Hrusak et al., 2002; Kwan et al., 2009). Breastfeeding appeared to be a very common practice in Oman. The results of the present study indicated that 75% of the cases and 81% of controls were breastfed for 12 to 24 months and only 8% and 3% of cases and controls were breastfed for less than six months.

The breastfeeding as well as the duration of breastfeeding did not show any significant ($P > 0.05$) effect on the risk of acute lymphoblastic leukemia. These results contradicts several studies reported from Western countries, which have shown a protective effect of prolonged breastfeeding (> 6 months) on risk of acute lymphoblastic leukemia as previously mentioned. Of particular interest is a similar study reported from Qatar, which showed that prolonged breastfeeding reduced the risk of acute lymphoblastic leukemia malignancy (Bener et al., 2008). The authors attributed their findings mainly to the possibility of reducing the risks of early childhood infections (McNally et al., 2004; Bener et al., 2008). The major limitation of this study was that the relationship between breastfeeding and infections occurrence was only assumed and not investigated. In addition to this the study population included the mixed population (patients from mixed nationalities).

In a larger and more comprehensive meta-analysis, Guise et al. (2005) reviewed 10 recent studies evaluating the evidence for the effect of breastfeeding on the risk of developing acute lymphoblastic leukemia. They concluded that the current literature regarding the protective role of prolonged breastfeeding on acute lymphoblastic leukemia risk has substantial limitations and there is a need for more cohort studies to clarify the protective effect of breastfeeding.

Our study did not show any protective effect of prolonged breastfeeding on the risk of acute lymphoblastic leukemia in children. The study population (both cases and controls) was a homogenous group and all the children were Omani nationals and they were all coming from comparable social background, middle class income families with almost similar education level of the mothers. These factors were the main limiting confounders in the previous studies reported in literature. None of the study participants and their families was consuming processed meats. It has been reported that the consumption of processed meats during the early childhood period, which contain N-nitroso precursors could lead to the formation of carcinogenic N-nitroso compounds and subsequently lead to increasing the risk of childhood cancers including leukemia (Preston-Martin, 1994; Blot, 1999).

No supplementary milk formulas and/or cow-based milk formulas were reported to be used during the first three years of life by acute lymphoblastic leukemia cases who participated in our study. The consumption of cow-based milk or formula can potentially influence the child's immune status since the intestine of a young infant is highly permeable to macromolecules of food (Kramer et al., 2001; Kuitunen et al., 1994). Specific antibodies to individual cow's milk proteins such as casein, lactoferrin, and serum albumin have been found in serum of infants (Host, 1994). Thus, an infant who consumes cow-based milk or formula might be more likely to experience an immunological reaction that could be related to risk of childhood leukemia. In contrast, soy formula or milk is less antigenic to infants when compared to cow's milk (Wilson and Hamburger, 1988). The previously reported studies however suggest that breastfeeding protect against childhood acute lymphoblastic leukemia incidence. However, two major disadvantages were observed, (1) the number of selected cases was not relevant to the total population to the country in which the study was done and (2) the matched controls, for the noted case-control studies, were not chosen from the family relatives of the studied cases.

In conclusion, the current study revealed that longer duration of breast feeding is religiously and culturally favored in Oman as compared to Western countries. The patterns of food consumption and food varieties were the same among cases and control indicating a similar cultural and environmental exposure. The duration of breast feeding did not show any protective effect against the risk of childhood acute lymphoblastic leukemia in Oman. The major limitation of our study was high rate of drop out from the registered cases as out of a total of 276 diagnosed acute lymphoblastic leukemia cases, we were able to recruit only 70 cases. In addition to this the other risk factors (such as history of radiation during pregnancy, viral infections preceding the disease, genetic disorders predisposing to leukemia and drug ingestion) for development of acute lymphoblastic leukemia were not looked in the study.

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