

Evaluation of diet as a risk factor in the development of childhood leukaemia: a case control study

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Abstract

Objective: To evaluate probable association of dietary risk factors with childhood leukaemia.

Methods: The case-control study was conducted at the Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from January to December 2017, and comprised children of either gender aged 2-12 years with recently diagnosed acute lymphocytic or acute myelocytic leukaemia. An age and gender matched equal group of healthy children was taken as controls. Dietary-intake data was collected for six food groups, namely raw vegetables, fresh fruits, packed fruit juices, caffeinated drinks, junk foods, and processed/precooked food items. Frequency of the selected food group consumption was summarised in six categories: rarely/never, 1-3 days/week, 4-6 days/week, once daily, twice daily and thrice daily. Data was collected through interviews with the mothers using a pre-designed questionnaire, and was analysed using SPSS 21.

Results: Of the 90 subjects, 45(50%) were in each of the two groups. There were no differences in baseline characteristics between the two groups ($p>0.05$). Consumption of caffeinated drinks and junk food was significantly higher in cases ($p=0.001$) while controls showed significantly higher consumption of fresh fruits ($p=0.0012$). No significant difference was noted for consumption of vegetables, packed fruit juices and processed food between the groups ($p>0.05$).

Conclusion: Higher consumption of caffeinated drinks and junk food was observed in cases compared to controls.

Keywords: Acute lymphoblastic leukaemia, Childhood leukaemia, Diet. (JPMA 70: 404; 2020).

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Introduction

Leukaemia, an un-regulated clonal proliferation of haematopoietic stem cell, is the number one childhood cancer responsible for 30% of under-15-year childhood cancer burden. A 78:22 ratio between acute lymphocytic leukaemia (ALL) or acute myelocytic leukaemia (AML) varieties exists.^{1,2} Leukaemias are the second largest cause of childhood mortality after accidents and the incidence is increasing by 0.9% every year. The exact cause of leukaemia remains unknown.³ Recently, substantial literature considering genetic, infectious and

environmental risk factors in childhood-cancer aetiology has emerged.^{4,5} Only a few factors like ionizing radiation and benzene exposure have definite proven association.^{6,7,8} Leukemogenic translocations and gene fusions may explain some cases of childhood ALL originating in-utero. In addition, siblings and close relatives of a leukaemia child are more likely to develop leukaemia compared with the general population.⁹ Most children with leukaemia are now cured but many suffer long-term complications. The cost of leukaemia treatment, hence, extends beyond the patient, affected family, friends and the community. So developing primary prevention activities for childhood leukaemia is the need of the hour.¹⁰ Lifestyle risk factors associated with many solid tumours have received little attention in the context of leukaemia. Dietary management is a part and parcel of leukaemia treatment.¹¹ Eating sensibly and doing exercise may have a preventive role as well. The possible relation between

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child's diet and risk of childhood leukaemia remains largely unexplored. Some studies have described possible association of childhood leukaemia with nutrition in early life, carcinogens in cooked meat, and increased consumption of hotdogs etc.^{12,13} Others have demonstrated a link between childhood leukaemia and breastfeeding practices;^{14,15} formula feeding alone or in combination with breastfeeding.¹⁶ Besides, data is inconsistent regarding the consumption of fruits, fruit juices and meat.¹⁷ Data on this subject is minimal in Pakistan. A recent cancer registry data from 19 centres in Pakistan demonstrated that the most common childhood cancer, both in males (3.6%) and females (2.2%), was leukaemia.¹⁸ These patients presented with higher risk features than those reported from the developed countries and almost a quarter of them failed to complete induction chemotherapy.¹⁹ The reported outcomes were inferior with high rates of infections and relapse.²⁰ The current study was planned to explore the association of dietary factors with childhood leukaemia in Pakistani population.

Subjects and Methods

The case-control study was conducted at the Paediatric Medical Ward of the Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from January to December 2017, and comprised children of either gender aged 2-12 years with recently diagnosed ALL or AML, and an equal number of age- and gender-matched controls. After approval from the institutional ethics review board, the sample size was calculated using World Health Organisation (WHO) calculator²¹ by taking level of significance 5%, power of test 90%, exclusive breastfeeding for the first six months of life in cases (P1) 59.7% and exclusive breastfeeding for the first six months of life in controls (P2) 89.6%.²² Children with other co-morbid conditions were excluded, and the sample was raised using non-probability consecutive sampling. Dietary intake data was collected using a customised food frequency questionnaire (FFQ) through face-to-face interviews with mothers of the children (Annexure). The FFQ comprised a food list keeping in view the dietary patterns of children in our society. The data comprised demographic information along with pattern of intake of six food groups, including raw vegetables, fresh fruits, packed fruit juices, caffeinated drinks, junk foods and pre-cooked food items. Mothers were asked to recall the dietary history of their

ANNEXURE-I

Data Collection Instrument

Group:	Cases ☐	Controls ☐				
	Serial Number: _____					
Name: _____	Father's Name: _____					
Age: _____	Gender: _____					
History of Breast Feeding:	Present ☐	Absent ☐				
If present, what is the duration?	_____ months					
Weaning Age:	_____ months					
Socioeconomic status of parents:						
Low: (Monthly income <PKR20000) ☐						
Low to middle: (Monthly income PKR 21 to 50000) ☐						
Middle to high (Monthly income >PKR 50000) ☐						
Education Status:						
Uneducated ☐	≤5 school years ☐	6-8 school years ☐				
9-10 school years ☐	8-12 school years ☐	11-12 school years ☐				
≥ 14 school years ☐						
Employment status:						
Employed ☐ Unemployed ☐						
Dietary pattern (FFQ)						
Dietary factors	rarely/never	1-3 days/week	4-6 days/week	daily	Twice daily	Thrice daily
Vegetables						
Fresh fruits						
Packed fruit juices						
Caffeine drinks						
Junk food						
Processed/precooked food						

children in the preceding 2-3 years before the diagnosis of leukaemia. To summarize the frequency of the selected food group consumption, six categories were created: rarely/never, 1-3 days/week, 4-6 days/week, once daily, twice daily and thrice daily. SPSS21 was used for data analysis. Consumption of each food group was compared between the groups. Box plots were created to summarise overall consumption of each food group in the cases and the controls. Independent sample student t test was used to assess the significance of observed difference in quantitative variables between the groups. Chi-square test was used for qualitative variables. $P < 0.05$ was considered significant.

Results

Of the 90 subjects, 45(50%) were in each of the two groups. Baseline characteristics were similar in both the groups ($p > 0.05$) (Table 1-2). The intake of caffeinated drinks ($p = 0.001$) and junk food ($p = 0.001$) was significantly higher

Table-1: Baseline demographic characteristics among cases and controls (quantitative variables).

Variables	mean±SD	p-value (t-test)
Age (years)		0.633
Cases	6.1±2.6	
Controls	5.8±2.6	
Brest feeding duration (months)		0.663
Cases	18.9±9.2	
Controls	18.1±9.2	
Weaning age (months)		0.901
Cases	9.4±6.2	
Controls	9.5±7.2	

in the cases, while the controls showed significantly higher consumption of fresh fruits ($p=0.012$). Consumption of processed food was higher among the cases but the difference was not statistically significant ($p>0.05$). No significant difference was noted for consumption of vegetables and packed fruit juices between the groups ($p>0.05$). Overall consumption of different food groups among cases and controls was noted (Figure), and details of dietary consumption pattern were tabulated separately (Table3).

Discussion

The study showed excessive consumption of caffeinated drinks and junk food in the cases. Several adult and childhood cancers are linked with dietary factors.²³ Micronutrients regulate cell-wall integrity, control

Table-2: Baseline demographic characteristics among cases and controls (qualitative variables).

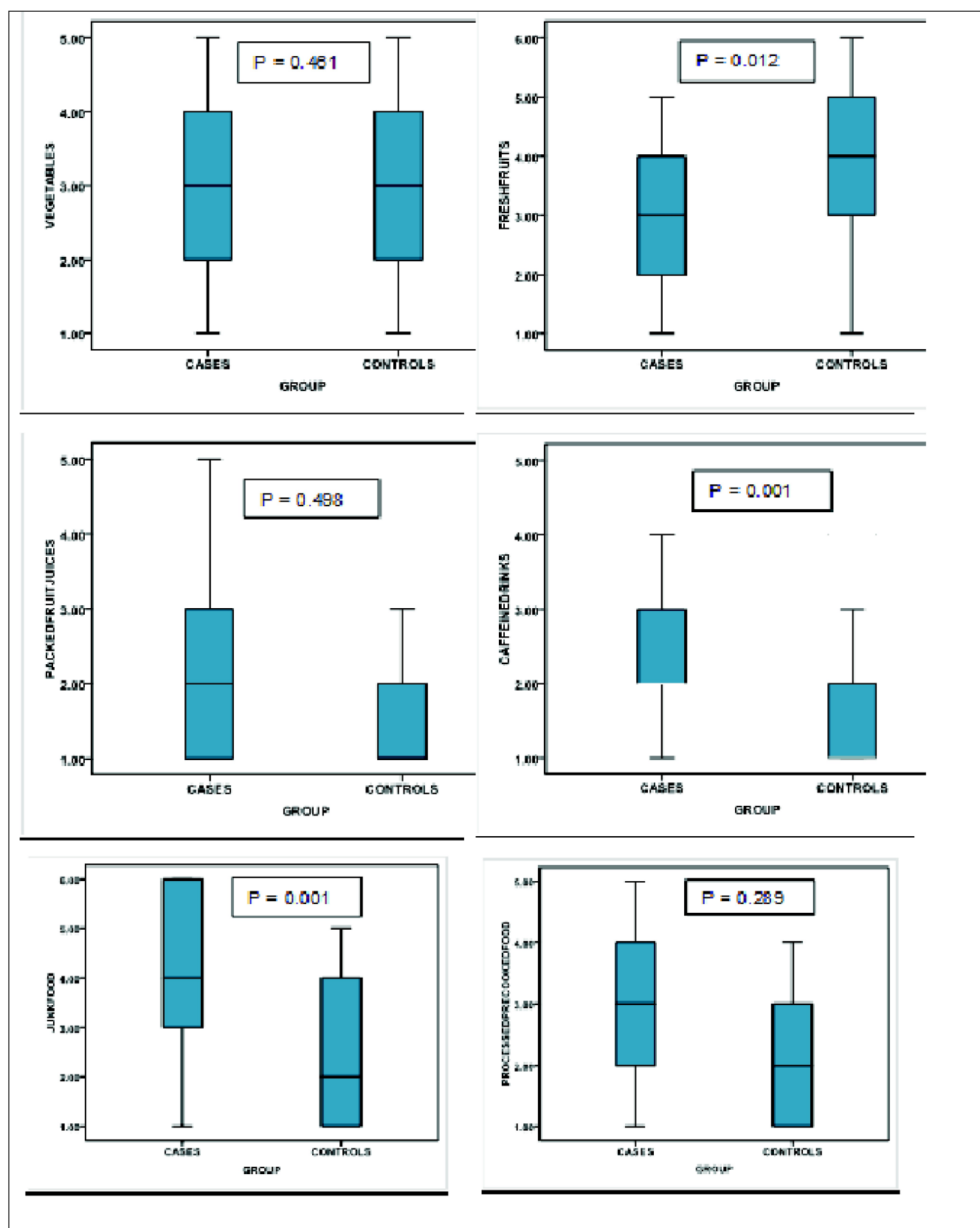
Variables	Cases n (%)	controls n (%)	p-value (chi-square)
Gender			0.506
Males	31 (68.9)	28 (62.2)	
Females	14 (31.1)	17 (37.8)	
H/o breast feeding			0.238
Present	43 (95.6)	40 (88.9)	
Absent	2 (4.4)	5 (11.1)	
SE status			0.800
Low	10 (22.2)	8 (17.8)	
Low-middle	27 (60.0)	30 (66.7)	
Middle-high	8 (17.8)	7 (15.6)	
Education status (school years)			0.156
Uneducated	16 (35.6)	13 (28.9)	
Five	16 (35.6)	8 (17.8)	
Eight	2 (4.4)	4 (8.9)	
Ten	5 (11.1)	6 (13.3)	
Twelve	5 (11.1)	8 (17.8)	
≥ Fourteen	1 (2.2)	6 (13.3)	
Employment			0.520
Employed	17 (37.8)	20 (44.4)	
Unemployed	28 (62.2)	25 (55.6)	

inflammation, and improve immune responses, and, hence, interfere with cancer development.²⁴ Various biological mechanisms such as exposure to dietary mutagens and mutagenesis due to nutrient deficiencies can explain these observations. Nutritional influence on epigenetic processes may in fact contribute to

Table-3: Consumption of different food groups among cases and controls (frequency categories analysis)

Dietary factors	rarely/never n (%)	1-3 days/week n (%)	4-6 days/week n (%)	daily n (%)	twice daily n (%)	thrice daily n (%)	p-value
Vegetables							0.461
Cases	2 (4.4)	18 (40.0)	10 (22.2)	13 (28.9)	2 (4.4)	-	
Controls	3 (6.7)	15 (33.3)	5 (11.1)	18 (40.0)	4 (8.9)	-	
Fresh fruits							0.012
Cases	4 (8.9)	18 (40.0)	4 (8.9)	17 (37.8)	2 (4.4)	-	
Controls	2 (4.4)	6 (13.3)	6 (13.3)	19 (42.2)	9 (20.0)	3 (6.7)	
Packed fruit juices		0.498					
Cases	17 (37.8)	14 (31.1)	7 (15.6)	5 (11.1)	2 (4.4)	-	
Controls	23 (51.1)	11 (24.4)	7 (15.6)	4 (8.9)	0 (0)	-	
Caffeine drinks							0.001
Cases	10 (22.2)	19 (42.2)	5 (11.1)	10 (22.2)	1 (2.2)	-	
Controls	31 (68.9)	10 (22.2)	1 (2.2)	2 (4.4)	1 (2.2)	-	
*Junk food							0.001
Cases	1 (2.2)	5 (11.1)	6 (13.3)	12 (26.7)	8 (17.8)	13 (28.9)	
Controls	14 (31.1)	9 (20.0)	3 (6.7)	16 (35.6)	3 (6.7)	-	
Processed/precooked food							0.289
Cases	43 (95.6)	2 (4.4)	-	-	-	-	
Controls	39 (86.7)	5 (11.1)	1 (2.2)	-	-	-	

*Commercially brand potato chips and other saltish items, French fries, Sugar coated jellies, burgers, etc.



carcinogenesis.²⁵ A recent meta-analysis by the Childhood Leukaemia International Consortium has suggested a link between childhood leukaemia and breastfeeding practices.^{14,15} Majority of our cases and controls were breastfed (90%) with comparable mean duration of 18.9 vs 18.1 months. ($p>0.05$). This is in sharp contrast to reports from the Third National Health and Nutrition Examination Survey describing 54% of infants in the United States as ever being breastfed.²⁶ Except breastfeeding, there is lack of knowledge about the effect of early childhood-diet on the occurrence of leukaemias. Formula feeding alone or in combination with breastfeeding is associated with an increased incidence of leukaemia.¹⁶ A dose-response relationship has also been reported.²⁷ Serum insulin-like growth factor-1 (IGF-1) levels in top-fed infants are higher than in breastfed infants and foetal growth pathway is thought to play a role in leukaemia occurrence.²⁷ In our cohort, we tried to gather data about duration and amount of formula milk consumption, but recall problems in mothers of cases and controls posed a significant challenge. Hence, these observations were not included in the final analysis. Older age at introduction to solid food in general and older age at introduction to vegetables in particular, was associated with an increased risk of childhood ALL. A reduced risk was reported for late introduction to eggs.¹³ However, in the present cohort, the weaning age was also similar in both groups ($p>0.05$). Hence, an association could not be determined. Associations between a child's consumption of various food groups and the risk for childhood leukaemia are inconsistent, especially regarding the consumption of fruits, fruit juices and meat.¹⁷ Our results showed that higher consumption of fresh fruits is associated with reduced risk of leukaemia. These findings, in association with the consumption of oranges, bananas and orange-juice, confirm the protective role of fruits and vegetables observed recently in adults with leukaemia.²⁸ Both oranges and bananas are rich in vitamins, minerals and vitamin C. These antioxidants prevent damage to deoxyribonucleic acid (DNA) and hamper initial events in carcinogenesis.²⁹ Our study results showed that consumption of caffeinated drinks and junk food was significantly higher in cases ($p<0.05$). In a recent meta-analysis, child's consumption of caffeinated drinks was not associated with leukaemia, in contrast to maternal consumption during pregnancy.³⁰ This difference may be attributed to a different sample size as the other study enrolled 3649 cases and 5705

controls in contrast to our study with 45 cases and controls each, leading to higher than usual effect size. We suggest further studies with larger sample size to explain this association in greater detail. Overall, our observations suggest a consistently decreased risk of childhood leukaemia with regular consumption of fresh fruits. The association with hot dogs/lunch meats and leukaemia risk noted in earlier studies was not confirmed. Higher risk was associated with consumption of junk foods and caffeinated drinks. In summary, these findings suggest that fruits or fruit juices with a high content of vitamin C and/or potassium may reduce the risk of childhood leukaemia, when consumed regularly. If these results are extrapolated, a public health intervention of leukaemia prevention may ensue.

The present study has several strengths. First, the questionnaire was designed to account for the different frequency categorisation of consumption of food groups in question. Second, the list of food items was broad-spectrum to cover a typical young child's diet. Finally, selection bias among controls was probably less of a concern and paternal income and maternal education status were similar in both the groups. Overall, the role of socioeconomic status remains uncertain in the aetiology of childhood leukaemia, especially considering the difficulty in assessing socioeconomic status and disentangling the impact of bias.

The current study also has its limitations. The questionnaire asked fresh fruits and fresh fruit juices as a single entity instead of two. As a result, the independent effect of juices could not be separated in the analysis, and the observed association lacks specificity. Secondly, the sample size was small for an epidemiological study. The results, hence, cannot be extended to the population in general. We suggest a future multicentre study to deal with the problem of smaller sample size. Thirdly, in the present study we only performed univariate analyses that couldn't adjust for matching factors like age and gender. Lastly, an inherent problem of all case-control studies is the recall bias. The respondents for cases could have recalled consumption of certain foods more readily than the respondents for controls or vice versa, thus producing differential misclassification. All efforts were made to minimise the recall bias by educating the parents before the interview.

Conclusion

The consumption of caffeinated drinks and junk food was significantly higher in the cases, while the controls had significantly higher consumption of fresh fruits and fruit juices.

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