Cancer Causes Control
DOI 10.1007/s10552-012-0097-5

ORIGINAL PAPER

Nutrition in early life and risk of childhood leukemia: a case–control study in Greece

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Received: 24 August 2012 / Accepted: 3 November 2012

Abstract
Purpose There is a paucity of findings concerning the role of diet in childhood leukemogenesis, whereas the results are equivocal and the studies heterogeneous with regard to food items examined. This case–control study investigates the association of childhood leukemia with food groups, macronutrient consumption, total energy intake and adherence to Mediterranean diet among children aged 5–14 years in Greece.
Methods A total of 139 consecutive, incident leukemia cases out of which 121 were acute lymphoblastic leukemia were derived from the Nationwide Registry for Childhood Hematological Malignancies along with one : one age- and gender-matched hospital controls. Information on sociodemographic, maternal and child variables and dietary habits was obtained through in-person interviews with the guardians/children. Multiple logistic regression was performed with adjustment for birth weight and possible confounding variables.
Results Higher consumption of added lipids was associated with an increased risk of childhood leukemia, whereas consumption of milk and dairy products with reduced risk. From the macronutrient analysis, a borderline trend linking high protein intake with reduced childhood leukemia risk was observed.
Conclusion Consumption of milk and dairy products in the first year of life may protect against childhood leukemia possibly through vitamin D actions, while added lipids may increase the risk through various mechanisms. These results offer a holistic evaluation of children's nutrition and suggest that dietary habits in the early years of life may contribute to the prevention of childhood leukemia.

Keywords Food group · Diet · Nutrition · Macronutrients · Child · Leukemia

Electronic supplementary material The online version of this article (doi:10.1007/s10552-012-0097-5) contains supplementary material, which is available to authorized users.

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Published online: 21 November 2012

Introduction

Leukemia is the most frequent form of cancer in children less than 14 years. Two major types characterize leukemia, namely acute lymphoblastic leukemia (ALL), which is the most common type, and acute myeloblastic leukemia (AML). Both genetic and environmental risk factors have been implicated in the pathogenesis of this cancer of the hematopoietic system, but their implications have not been fully understood and appreciated [1]. Some of the environmental factors that have been examined so far include ionizing radiation, electromagnetic fields, chemicals, infections, parental smoking and maternal dietary habits, but only ionizing radiation has been consistently associated with childhood leukemia [2].

Although diet has been linked with many types of cancer [3], the association between food groups, macronutrients and childhood leukemia is yet ambiguous. Previous studies that have examined either maternal diet during pregnancy [4–6] or childhood diet [7–10] in relation to leukemia have yielded equivocal results. Maternal consumption of vegetables, protein sources, fruit and legume food groups has been inversely associated with childhood leukemia risk [4–6]; on the other hand, increased maternal intake of sugars and syrups, as well as meat products, seems to be a risk factor for ALL in the offspring [6]. Similarly, regarding childhood diet, regular consumption of oranges (or orange juice) and bananas [7], vegetables and bean curd [8] may confer protection in terms of risk; on the contrary, increased consumption of cured/smoked meat products has been highlighted as a detrimental factor, associated with increased childhood leukemia risk [8–10].

During the recent years, nutritional epidemiology has turned to the study of dietary patterns, instead of isolated food groups and nutrients. The Mediterranean diet is one of the most studied dietary patterns and has shown a consistent protective association against coronary heart disease, mental disorders [11] and some types of cancer [12], mainly due to its anti-inflammatory and anti-oxidant effects. In brief, the typical Mediterranean diet includes high intake of vegetables, fruits and nuts, legumes, cereals, pulses, fish and monounsaturated fat, with olive oil as the primary source; relatively low intake of meat, poultry and dairy products; and moderate consumption of alcohol [13].

To our knowledge, despite the multifaceted beneficial effects mediated by Mediterranean diet, its association with childhood leukemia has not yet been studied. Thus, the aim of the present work was to evaluate the association between childhood leukemia and childhood diet, in terms of food groups and macronutrients, as well as in terms of the Mediterranean dietary pattern, through a case–control study of 139 children, 5–14 years old, with leukemia, selected from a nationwide registry in Greece, and 139 controls matched by age and sex.

Methods

Study sample

The Nationwide Registry for Childhood Hematological Malignancies (NaReCHeM) [14] comprises all six Childhood Hematology–Oncology Departments across Greece located in "A. Sophia" and "A. Kyriakou" Children's hospitals of Athens (three Departments), the "American Hellenic Educational Progressive Association Hospital" (AHEPA) and Hippokrateion Hospital in Thessaloniki, as well as the University Hospital in Heraklion, Crete, which treat the bulk of morbidity in Greece. A total of 175 incident cases aged 5–14 years suffering acute leukemia were enrolled between January 1999 and June 2003; out of them, all 23 cases diagnosed in Hippokrateion had to be excluded due to administrative inability of the Department to implement the dietary questionnaire. Of the remaining 152, nine were excluded due to incomplete data and four children died soon after their admission before the scheduled date of interview leading to a response rate of 92 %. For each case, a control subject of the same gender and similar age (±six months) was selected from the same institution concurrently hospitalized for minor conditions and negative history of cancer or overt nutritional or metabolic disorders. Specifically, 62 controls were hospitalized for mild viral respiratory conditions or other infections, 12 for allergy, 29 for gastrointestinal or genitourinary conditions, 11 for nervous system conditions or mild psychiatric disorders and another 25 for various other reasons. The Ethics Committee of the University of Athens Medical School approved the study protocol, and all procedures were in accordance with the Helsinki declaration for human rights.

Measurements

Trained interviewers, the same for each case–control pair, interviewed face-to-face the guardian in the presence of the child in the respective health care settings at the time of diagnosis for the cases and at the time of hospitalization for the controls on the basis of a precoded questionnaire covering socio-demographic variables, maternal medical history during the index pregnancy as well as detailed medical history of the index child. Due to the length of the questionnaire, dietary habits of the child have been recorded in NARECHEM only during the 4.5-year period of the study and were evaluated using a validated, semi-quantitative food-frequency questionnaire that included the frequency of consumption of 157 food items [15] during the interview for the cases and the controls. To avoid overestimation of energy and nutrients intake, the respondents determined their portion size by selecting one photo out of three that depicted a specific quantity of the given food (small, medium and large portion).

Furthermore, the MedDietScore [13] was calculated from the dietary questionnaire to evaluate the level of adherence to the Mediterranean diet. MedDietScore assigns scores from 0 for rare/no consumption to five for daily consumption of items presumed to be close to the Mediterranean dietary pattern (e.g., vegetables), while items presumed to be away from this diet were assigned a 0 for daily consumption and five for rare/no consumption. In each of the 11 main food categories of the Mediterranean diet pyramid (i.e., non-refined cereals, potatoes, fruits, legumes, fish, red meat and products, poultry, full fat dairy products, use of olive oil in cooking), higher values of the reliable and repeatable MedDietScore tool suggest better adherence to the Mediterranean diet [13].

Statistical analysis

The frequency of consumption of various food items was quantified on a monthly basis, by multiplying the daily intake by 30 and the weekly by four and by assigning 0 to the food items that were rarely or never consumed. Food items were thereafter combined in nine basic food groups, namely cereal and starchy roots; sugars and syrups; pulses, nuts and seeds; vegetables; fruits; meats and meat products, fish and shellfish; milk and dairy products; and added lipids (Table 1). This distribution into food groups is a variation of the scheme proposed by Davidson and Passmore [16], regularly used in nutritional epidemiology in Greece [6] in order to accommodate it to the Greek dietary habits and include specific Greek foods. Total energy and macronutrient intake (proteins, carbohydrates and total fats) as well as intake of three subgroups of total fats (saturated, monounsaturated, polyunsaturated) were calculated using food composition tables based on the methodology that has been previously reported [17]. For the statistical analysis, intakes of energy (in kcal/day) and intakes of each of the nine food groups were then distinguished into quintiles based on the respective distributions of the cases and controls combined. Categorical variables are presented by frequencies (Table 2), while continuous variables by mean and standard deviation (SD) (Table 3), separately for cases and controls, and the chi-square test and the t test were used for the calculation of p value, respectively. Consequently, conditional logistic regression was performed, adjusting in the core model for birth weight (500 g increment), birth order (one child more), maternal age (three-year increment), maternal education (one level more) and tobacco smoking during pregnancy (yes vs. no) as well as for breastfeeding (yes vs. no). Results are reported as odds ratios (OR) and 95 % confidence intervals (95 % CI). To measure the degree of association between specific food groups and likelihood of leukemogenesis, each food group was added alternatively (one at a time) to the core model, controlling for total energy intake (Model 1); alternatively, all food groups were mutually adjusted, apart from “Sugar and syrups” and “Fruits” to avoid colinearity (Model 2). Respectively, each fraction of macronutrients per one SD increase in total energy intake was alternatively introduced (Model 3). Lastly, the role of MedDietScore [13] (1/55 units increase) and total energy intake were studied with the variables alternatively introduced into the core model (Models 4 and 5, respectively). SAS software version 9 for Windows 9 was used in all analyses (SAS Institute Inc., Cary, NC, USA).

Table 1 Classification into food groups of the food items evaluated in the food-frequency questionnaire

Food group	Food item
Cereals and starchy roots	White bread, brown bread, traditional bread, rice, pasta, various breakfast cereals, trahana, cheese pie (1/2), meat pie (1/2), vegetable pie (1/2), pizza (1/2), pasticcio (1/2) potatoes
Sugars and syrups	Sugar, cookies, chocolate bars, wafers, baklava, kataifi and other Greek sweets with syrup, spoonful sweets (Greek delicacies), jellies, glaze fruits, cream pastries, pancakes with syrup, bonbons, honey, compote (1/2)
Pulses, nuts and seeds	Dry beans, chick peas, peas, lentils, fava beans, dry broad beans, nuts
Vegetables	Raw tomatoes, cooked tomatoes, cucumbers, peppers, raw cabbage, cooked cabbage, lettuce, raw carrots, cooked carrots, zucchini, onions, green beans, eggplants, spinach, leeks, okra, dandelions, artichokes, fresh broad beans, cauliflower, broccoli, beets, mushrooms, courgette, vegetable pie (1/2), mousaka (1/2),
Fruits	Watermelon, melon, mandarins, oranges, apples, peaches, pears, grapes, apricots, cherries, strawberries, bananas, figs, pineapple, grapefruit, fresh fruit juice, dried fruits, compote (1/2)
Meats and meat products	Pork, veal, beef, lamb, goat, chicken, turkey, ham, salami and sausages, liver and other entrails, eggs, meat pie (1/2), mousaka (1/2), pasticcio (1/2)
Fish and shellfish	Fish, shellfish
Milk and dairy products	Feta cheese, kasseri cheese, other cheese, whole milk, skimmed milk, full fat yogurt, reduced fat yogurt, milk pudding, rice milk pudding, ice cream, cheese pie (1/2) pizza (1/2)
Added lipids	Butter on bread, butter for cooking, margarine on bread, margarine for cooking, seed oils, olive oils, olives

“1/2” indicates the cooked meals that were allocated to two food groups (one half in each)

Table 2 Distribution of 121 ALL cases aged 5–14 years and their age- and gender-matched controls, by demographic and maternal characteristics

Variable	Cases [*n* (%)]	Controls [*n* (%)]	*p* value
Age (years)		Matched variable	
5–7	59 (48.8)	59 (48.8)	
8–10	29 (24.0)	29 (24.0)	
11–14	33 (27.2)	33 (27.2)	
Gender		Matched variable	
Male	73 (60.3)	73 (60.3)	
Female	48 (39.7)	48 (39.7)	
Birth weight (g)			0.02
<3,000	23 (19.0)	29 (24.0)	
3,000–3,499	46 (38.0)	58 (47.9)	
3,500–3,999	36 (29.8)	27 (22.3)	
≥4,000	16 (13.2)	7 (5.8)	
Birth order			0.30
1st	52 (43.0)	43 (35.5)	
2nd	47 (38.8)	53 (43.8)	
≥3rd	22 (18.2)	25 (20.7)	
Maternal age at time of delivery (years)			0.60
<20	7 (5.8)	9 (7.4)	
20–22	23 (19.0)	13 (10.7)	
23–25	23 (19.0)	34 (28.1)	
26–28	28 (23.1)	22 (18.2)	
29–31	19 (15.7)	17 (14.1)	
32–34	10 (8.3)	12 (9.9)	
≥35	11 (9.1)	14 (11.6)	
Maternal education (years)			0.54
<12	50 (41.3)	41 (33.9)	
12	47 (38.9)	58 (47.9)	
≥13	24 (19.8)	22 (18.2)	
Maternal smoking during pregnancy			0.40
No	102 (84.3)	97 (80.2)	
Yes	19 (15.7)	24 (19.8)	
Breastfeeding			0.65
No	29 (24.0)	26 (21.5)	
Yes	92 (76.0)	95 (78.5)	

Results

As expected, in this age group, 121 out of the 139 childhood leukemia cases were acute lymphoblastic (ALL; 102 B cell ALL, 19 T cell ALL) and 18 acute myeloblastic leukemias (AML); the domination of ALL cases (87.1 %) essentially drove the results to the same direction, as when both ALL and AML were considered in total. Consequently, the findings on ALL are presented in the manuscript, whereas the results on total leukemia cases are provided in Supplemental Tables 1 to 3.

Table 3 Dietary characteristics of the 121 ALL cases and their age- and gender-matched controls

Variable	Cases Mean ± (SD)	Controls Mean ± (SD)	*p* value
MedDiet Score (0–55)	28.7 ± (3.5)	28.2 ± (2.9)	0.21
Cereals and starchy roots (portions/month)	129.1 ± (63.1)	118.4 ± (55.5)	0.18
Sugars and syrups (portions/month)	73.6 ± (67.8)	68.3 ± (66)	0.42
Pulses, nuts and seeds (portions/month)	12.1 ± (12.6)	10.7 ± (8.5)	0.85
Vegetables (portions/month)	86.9 ± (50.5)	81.8 ± (50.3)	0.43
Fruits (portions/month)	135.1 ± (71.5)	130.6 ± (69.8)	0.38
Meats and meat products (portions/month)	51.5 ± (23.7)	50.7 ± (20.9)	0.90
Fish and shellfish (portions/month)	7.8 ± (4.9)	7.7 ± (4.2)	0.88
Milk and dairy products (portions/month)	90.1 ± (38.8)	92.8 ± (38.4)	0.47
Added lipids (portions/month)	16.4 ± (17.3)	11.7 ± (13.6)	0.04
Total energy intake (kcal/day)	2,015.7 ± (741.2)	1,969.1 ± (701.5)	0.53
Protein (g/day)	81.3 ± (25.1)	81 ± (24.4)	0.83
Carbohydrates (g/day)	237.1 ± (93.9)	231.6 ± (84.4)	0.63
Total fat (g/day)	96.7 ± (36.2)	94.3 ± (36.1)	0.44
Saturated fat (g/day)	31.9 ± (11.6)	32 ± (13.1)	0.80
Monounsaturated fat (g/day)	35.1 ± (13.6)	34.2 ± (13.2)	0.45
Polyunsaturated fat (g/day)	8.6 ± (4.9)	8.2 ± (4.4)	0.36

The distribution of the studied child and maternal characteristics by case–control status is shown in Table 2, whereas Table 3 presents the distribution of the dietary characteristics. The actual range of MedDietScore was 19-38 for the cases and 21–34 for the controls. Birth weight was positively related to ALL risk ($p = 0.02$, Table 2) and so was the increased consumption of added lipids ($p = 0.04$, Table 3) in these uncontrolled analyses.

Conditionally derived ORs (Table 4) confirmed the positive association of ALL with birth weight (OR 1.40, 95 % CI 1.03–1.89, core model). A statistically significant increase in risk with one quintile increase in added lipids (OR 1.31. 95 % CI 1.04–1.64 in Model 1 and OR 1.60, 95 % CI 1.16–2.20 in Model 2) was also noted. After mutual adjustment between the food groups, intake of "milk and dairy products," which comprise a principal source of proteins among children, showed a statistically significant association with ALL (OR 0.77, $p = 0.03$, Model 2) in line with the inverse association of same magnitude of borderline statistical significance with proteins found in the macronutrients analysis (OR 0.76, $p = 0.09$, Model 3). No other statistically significant association between other studied food groups or macronutrients and ALL was observed. Neither total energy intake nor MedDietScore seemed to be associated with leukemogenesis (Models 4 and 5, respectively).

Discussion

This case–control study revealed an inverse association between consumption of milk and dairy products and the likelihood of having childhood leukemia, as well as a positive association between consumption of added lipids and leukemia. No other significant associations were observed, regarding the consumption of various foods and nutrients. The presented results may convey an important public health message, implicating the role of dietary habits in the early years of life in the pathogenesis of childhood leukemia.

The protective association implicating the consumption of milk and dairy products may be inscribed into the wider context of beneficial effects mediated by the consumption of dairy products during childhood [18]. The underlying biochemical mechanisms remain elusive for the time being; nevertheless, numerous possible links may well exist. Milk is a considerable source of vitamin D, the latter being capable of inhibiting the clonogenic growth of both normal and malignant lymphoid B cell progenitors [19]. Interestingly, it has been postulated that the beneficial effects of milk consumption during childhood in terms of reduced cancer risk may also apply during adulthood, as reported for instance in the case of colorectal cancer [20] but not breast cancer [21]. Comparing our findings with those of other studies, it seems worth mentioning that Kwan et al. [7] described a null effect of milk consumption upon childhood leukemia risk, whereas a significant protective association against acute myeloid leukemia has been recorded in a case–control study performed on adult women [22].

The inverse association between dairy product consumption and ALL risk may underlie the borderline trend pointing to a reduced likelihood of childhood leukemia along with increasing protein intake. However, it should be stressed that protein intake essentially integrates the consumption of various food groups, as proteins are present in high quantities elsewhere as well, especially in the meat products that were not associated with childhood leukemia in contrast with the previous case–control studies [8–10]. Regarding the potentially favorable effects of protein intake, the antioxidant tripeptide glutathione (GSH) that is contained in foods rich in protein may protect the cell from ROS-mediated DNA-damage and ROS-induced regulation of gene expression as well as may contribute to the detoxification of potential carcinogenic compounds [23]. Soy peptides, which were nevertheless not specifically addressed in our study, may additionally confer a reduced risk for several types of cancer [24].

In the present study, the consumption of added lipids was associated with increased leukemia risk. From the clinical perspective, this may represent a dilemma for the pediatrician, as lipids are essential for tissue growth, cardiovascular health, brain development and function [25]; future studies should thus focus on disentangling the contribution of specific fatty acids in the risk profiling for childhood leukemia. At any case, lipid consumption has been strongly and positively implicated in the pathogenesis of cancers of the immune system [26] and other types of cancer [27], possibly mediating its effects by modifying signaling molecules such as hedgehog proteins and by affecting the endogenous steroid synthesis [28]. Under consideration should be taken the difficulty in differentiating the effects of lipids independent of total energy intake, and for this reason in this study, adjustment for the rest of the food groups was performed.

Regarding the originality of the present study in comparison with the existing literature, only one previous study [7] examined the association between consumption of milk and dairy products with leukemia, whereas macronutrients have never been examined before in detail. The study of Kwan et al. [7] was the only one to cover a broad spectrum of a typical child's diet and found that regular consumption of oranges/bananas and orange juice during the first 2 years of life was associated with a reduced risk of leukemia. Liu et al. [8] assessed specific food groups according to the *N*-nitroso compound (NOC) hypothesis and found that the consumption of cured/meat and fish was associated with a higher risk of acute leukemia and that consumption of bean curd foods and vegetables was associated with a reduced risk. Same findings were reported by Peters et al. [9] who examined specific meat and fruit products, stating a much higher risk of childhood leukemia for children that consumed 12 or more hot dogs a month, although this result was based on only 14 exposed cases and three exposed controls. Finally, Sarasua and Savitz [10] assessed only specific meat products and reported positive association between consumption of hot dogs one or more times per week and ALL.

Among the other factors that were examined in this work, Mediterranean diet score was not associated with childhood leukemia risk, despite the well-established

Table 4 Conditional logistic regression-derived, mutually adjusted odds ratios (OR) and 95 % confidence intervals (95 % CI) for ALL among children aged 5–14 years old, by core model variables and dietary patterns

Variable	Increment	ALL			
		OR	95 % CI		*p* value
Core model					
Birth weight	500 g more	1.40	1.03	1.89	0.03
Birth order	One more	0.82	0.56	1.19	0.30
Maternal age at the time of delivery	3 years more	1.00	0.84	1.18	0.97
Maternal education	One level more	0.90	0.62	1.32	0.60
Maternal smoking during pregnancy	Yes versus no	0.65	0.44	1.68	0.65
Breastfeeding	Yes versus no	0.75	0.40	1.40	0.36
Additionally alternatively introduced variables					
Model 1					
Cereals and starchy roots	One quintile	1.17	0.92	1.49	0.20
Sugars and syrups	One quintile	1.10	0.88	1.38	0.38
Pulses, nuts and seeds	One quintile	0.94	0.76	1.15	0.55
Vegetables	One quintile	1.09	0.90	1.33	0.37
Fruits	One quintile	1.05	0.88	1.25	0.60
Meats and meat products	One quintile	0.96	0.78	1.18	0.69
Fish and shellfish	One quintile	1.00	0.82	1.21	0.98
Milk and dairy products	One quintile	0.94	0.77	1.14	0.53
Added lipids	One quintile	1.31	1.04	1.64	0.02
Model 2**					
Cereals and starchy roots	One quintile	1.23	0.91	1.66	0.17
Pulses, nuts and seeds	One quintile	0.85	0.67	1.08	0.18
Vegetables	One quintile	0.96	0.73	1.26	0.77
Meats and meat products	One quintile	0.90	0.71	1.13	0.35
Fish and shellfish	One quintile	0.96	0.76	1.20	0.70
Milk and dairy products	One quintile	0.77	0.60	0.98	0.03
Added lipids	One quintile	1.60	1.16	2.20	0.004
Model 3					
Protein/energy*	One SD	0.76	0.55	1.05	0.09
Carbohydrates/energy*	One SD	0.97	0.74	1.28	0.84
Total fat/energy*	One SD	1.05	0.81	1.35	0.72
Saturated fat/energy*	One SD	0.94	0.73	1.20	0.61
Monounsaturated fat/energy*	One SD	1.06	0.83	1.35	0.64
Polyunsaturated fat/energy*	One SD	1.12	0.84	1.48	0.45
Model 4					
MedDiet Score	1/55 unit	1.06	0.98	1.15	0.16
Model 5					
Total energy intake	One SD	1.08	0.81	1.44	0.60

* Fraction of macronutrient intake by total energy intake

** Food groups are also mutually adjusted. “Sugar and syrups” and “Fruits” are excluded to avoid collinearity

cancer preventing properties of Mediterranean diet [12]. This may point to the fact that dietary patterns may well necessitate longer time periods for the emergence of their favorable effects. Only birth weight was found to be positively associated with childhood leukemia, a finding that has already been reported [29]. Breastfeeding did not confer a significant protective effect against leukemia, possibly due to its high prevalence in this population (77 %). Regarding maternal smoking, although it was initially considered a risk factor, the majority of the studies on maternal smoking and childhood leukemia did not find a significant positive association, as reflected upon the most recent meta-analysis on the field [30].

There are several strengths of this study including its nationwide coverage, the smooth cooperation on the part of the children’s mothers in the hospital environment and the high comparability between cases and controls. Information for several potential confounders that have been reported from previous studies was used for adjustment including birth weight, birth order, maternal age, maternal education, maternal smoking and breastfeeding. Furthermore, the previously validated dietary questionnaire covered a broad spectrum of foods and was not focused on specific foods related to NOC, as previous studies. The study had also several limitations that should be considered, including the selection of controls from the hospital environment. Moreover, all children with leukemia diagnosis in age less than five years were excluded because the early onset of the disease is primarily attributed to other reasons (i.e., maternal diet) than child's diet, which may indeed need some years in order to have a significant influence on the hemopoietic system. The controls were selected from the same major pediatric hospitals, which treat most of childhood morbidity besides the hematological/oncological cases making selection bias less likely. The occurrence of a recall bias is less probable given that the time period of recall is relatively short as the questionnaire evaluated the frequency of consumption of foods at the time of the interview. The sample size was relatively small, but may be considered adequate, as it allowed the reproducibility of numerous statistically significant associations at the univariate and multivariate analyses. Moreover, food-frequency questionnaires are prone to overestimation of energy and nutrient intake due to miss reporting of portion sizes; however, an effort was made to avoid this by using photos of common portion sizes. An additional weakness of the study was the lack of detailed information for the estimation of the socioeconomic status that has been linked to childhood leukemia [31]. Finally, the maternal diet was not adjusted for in this study.

In summary, this study stated a research hypothesis that added lipids and foods with high fat content may confer to the risk of childhood leukemia, whereas milk and dairy products might have a protective role. The underlying mechanisms are not well understood, but the presented results may guide the scientific community to a further, in depth, investigation of the stated research hypothesis, for example, a separate investigation into the various sources of added lipids (e.g., olive oil, vegetable oil, margarine, butter).

Acknowledgments We would like to express our gratitude to the six Childhood Hematology–Oncology Departments, who kindly provided us with valuable data on their studies. This research has been funded in part by the Athens University Medical School.

Conflict of interest The authors declare that they have no conflict of interest.

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